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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
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Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioassay of 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 environmental chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of parathion was conducted by Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by Drs. J. H. Weisburger (1,2) and R. R. Bates (1,3); the doses were selected by Drs. T. E. Shellenberger (4,5), J. H. Weisburger, and R. R. Bates. Administration of the chemical and observation of the animals were supervised by Drs. T. E. Shellenberger and H. P. Burchfield (4), with the technical assistance of Ms. D. H. Monceaux (4) and Mr. D. Broussard (4). Histopathology was performed by Dr. T. E. Murchison (6), and the diagnoses included in this report represent his interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (7). Statistical analyses were performed by Dr. J. R. Joiner (8) and Ms. P. L. Yong (8), using methods selected for the bioassay program by Dr. J. J. Gart (9). Chemicals used in this bioassay were analyzed under the direction of Dr. H. P. Burchfield, and the analytical results were reviewed by Dr. S. S. Olin (8).

This report was prepared at Tracor Jitco (8) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Drs. J. F. Robens and C. H. Williams, toxicologists; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. Y. E. Presley, and Mr. W. D. Reichardt, technical writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. P. J. Graboske.

The following scientists at NCI (1) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Dawn G. Goodman (10), Dr. Richard A. Griesemer, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire (11), Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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

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

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

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

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

(6) Dawson Research Corporation, P.O. Box 8272, Orlando, Florida.

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

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

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

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

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

SUMMARY

A bioassay for possible carcinogenicity of technical-grade parathion was conducted by administering the test chemical in the diet to Osborne-Mendel rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered parathion at one of two doses for 80 weeks, then observed for 32 or 33 weeks. Time-weighted average doses for males were 32 or 63 ppm; for females, they were 23 or 45 ppm. All surviving rats were killed at 112 or 113 weeks. Groups of 50 mice of each sex were administered parathion at one of two doses, either 80 or 160 ppm. The low-dose males were administered parathion for 71 weeks; the high-dose males for 62 weeks; and the low- and high-dose females for 80 weeks. The animals were then maintained for observation and all surviving mice were killed at 89 or 90 weeks. Matched controls consisted of groups of 10 untreated rats or mice of each sex; pooled controls of rats or mice taken from similar bioassays of other test chemicals were also used.

Mean body weights of high-dose male and female rats and of high- and low-dose male mice were generally lower than those of the matched controls during the period of administration of the chemical. Mean body weights of the other groups of dosed rats and mice did not differ appreciably from those of the matched controls. Since body weights and survival of the female mice were not affected, female mice may have been able to tolerate a higher dose. Sufficient numbers of male and female animals of both species were at risk for the development of late-appearing tumors.

In both male and female rats, the incidences of cortical adenomas or carcinomas of the adrenal showed dose-related trends (P less than 0.001) using pooled controls and, in direct comparisons, were higher in the high-dose groups (P less than 0.001) than in the pooled controls (males: pooled controls 3/80, matched controls 0/9, low-dose 7/49, high-dose 11/46; females: pooled controls 4/78, matched controls 1/10, low-dose 6/47, high-dose 13/42). Most of the tumors were adenomas. When the matched controls were used, dose-related trends in incidences of the adrenal tumors were significant (males, P = 0.048; females, P = 0.028); in direct comparisons, however, the incidences of the tumors in the individual groups did not differ significantly from those in corresponding matched controls. The incidences of the

tumors in the dosed male and female rats were higher than those in corresponding historical controls (males 8/148, females 5/180).

In mice, no tumors occurred in either sex at incidences that were signficiantly higher in the dosed groups than in the corresponding control groups.

It is concluded that under the conditions of this bioassay, parathion was not carcinogenic to B6C3F1 mice. In the male and female Osborne-Mendel rats receiving parathion in their diet, there was a higher incidence of cortical tumors of the adrenal than in pooled or historical controls, suggesting that parathion is carcinogenic to this strain of rat.

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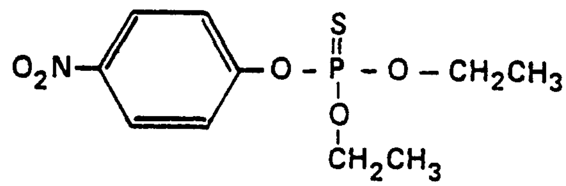

Parathion

Parathion (CAS 56-38-2; NCI C00226) is an organophosphorus pesticide that is relatively nonpersistent in the environment, with high activity against insects and mites (Benke and Murphy, 1975; Hayes, 1975). It is highly toxic to mammals, because of its rapid metabolic conversion in the liver to paraoxon, its oxygen analog (Benke and Murphy, 1975; Hayes, 1975). Paraoxon is the active form that accounts for toxicological and pharmacological effects of parathion (Koelle, 1975).

Parathion is an inhibitor of cholinesterase, as shown by a marked decrease in the concentration of enzyme in the erythrocytes of Osborne-Mendel rats fed 5 or 25 ppm of the chemical in the diet (Frawley et al., 1952). Parathion has a high acute oral toxicity in Osborne-Mendel rats (LD_{50}: 30 mg/kg in males, 3 mg/kg in females).

Parathion is used as an insecticide and acaricide on a wide variety of fruit and nut trees, berries, vegetables, field crops, and ornamental plants. Tolerances have been established for residues of parathion on many food crops (EPA Compendium of Registered Pesticides, 1973).

Parathion was selected for study in the Carcinogenesis Testing Program because of its extensive use on food and feed crops.

II. MATERIALS AND METHODS

A. Chemical

Parathion, which is the generic name for 0,0-diethyl-0-4-nitrophenylphosphorothioate, was obtained as a technical-grade material from the manufacturer, Monsanto Chemical Co., St. Louis, Missouri. According to the manufacturer, the purity of the lot used for the chronic studies (Lot No. AA1142) was 99.5%. The chemical was stored at $4^{o}C$ in the original container until used.

The identity of the chemical was confirmed by analyses at Gulf South Research Institute (infrared, ultraviolet, and nuclear magnetic resonance spectra; isobutane chemical ionization mass spectrum). Gas-liquid chromatography showed a single homogeneous peak, consistent with the manufacturer's assay. Elemental analysis was consistent with $C_{10}H_{14}NO_5PS$, the molecular formula for parathion.

The term parathion is used in the remainder of the report to designate the technical-grade material.

B. Dietary Preparation

All diets containing parathion were formulated once per week using Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of parathion for each dietary concentration. The test chemical was first dissolved in a small amount of acetone (Mallinckrodt, Inc., St. Louis, Mo.), which was then added to the feed. Corn oil (LouAna®, Opelousas Refinery Co., Opelousas, La.) was also added to the feed at 2% of the final feed weight, primarily as a dust suppressant, and the diets were mixed mechanically in a Hobart blender to assure homogeneity of the mixtures and evaporation of the acetone. Diets for the control groups of animals also contained corn oil equal to 2% of the final weight of feed. The diets were stored at room temperature until used, but no longer than 1 week before use.

The stability of parathion in feed was tested by determining the concentration of the chemical in formulated diets at intervals over a 7-day period. Diets containing 80 or 160 ppm parathion showed no significant change in concentration on standing at ambient temperature for this period.

As a quality control test on the accuracy of preparation of the diets, the concentration of parathion was determined in different batches of formulated diets during the chronic studies. The results are summarized in Appendix G. At each dietary concentration, the mean of the analytical concentrations for the checked samples was within 2.0% of the theoretical concentration, and the coefficient of variation was never more than 6.5%.

C. Animals

Rats and mice of each sex, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these bioassays. The rats were of the Osborne-Mendel strain obtained from Battelle Memorial Institute, Columbus, Ohio, and the mice were B6C3F1 hybrids obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. On arrival at the laboratory, all animals were quarantined (rats for 10 days, mice for 12 days), then assigned to control or dosed groups.

D. Animal Maintenance

All animals were housed in rooms in which the temperature ranged from 22 to 24°C, and the relative humidity from 40 to 70%. The air in each room was changed 10 to 12 times per hour. Fluorescent light provided illumination 10 hours per day. Food and water were provided *ad libitum*.

The rats were housed individually in hanging galvanized steel mesh cages, and the mice were housed in plastic cages with filter bonnets, five animals per cage for females, or two or three animals per cage for males. Initially, rats were transferred every week to clean cages; later in the study, cages were changed every 2 weeks. Absorbent sheets under the rat cages were changed three times per week. Mouse cages were provided with Absorb-dri® bedding (Lab Products, Inc., Garfield, N. J.), and the mice were transferred to clean cages every week. Feeder jars and water bottles were changed and sterilized three times per week.

Cages of control and dosed mice were placed on separate racks in the same room. Animal racks for both species were rotated laterally every week; at the same time, each cage was changed to a different position within the same column. Rats were housed in a room by themselves. Mice were maintained in the same room as mice in the following feed studies:

(CAS 60-51-5) dimethoate
(CAS 13171-21-6) phosphamidon

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses of parathion, on the basis of which two concentrations (hereinafter referred to as "low" and "high" doses) were determined for administration in the chronic studies. Groups of five rats and five mice of each sex were administered feed containing parathion at one of several doses, and groups of five animals of each sex and species were administered basal diet only. The dosed groups were fed the test diets for 6 weeks, followed by 2 weeks of observation.

Table 1 shows the doses used and the mean body weights of dosed animals at week 6 expressed as percentages of the mean weights of controls; it also shows the number of animals that died in each dosed group during the course of administration and the week on study when the last death occurred.

On the basis of these results, the initial low and high doses for the chronic studies were set at 40 and 80 ppm for male rats and

Table 1. Parathion Subchronic Feeding Studies in Rats and Mice

Dose (ppm)	Male: Mortality: Number Dead	Male: Mortality: Week on Study	Male: Mean Weight at Week 6 as % of Control	Female: Mortality: Number Dead	Female: Mortality: Week on Study	Female: Mean Weight at Week 6 as % of Control
RATS						
5			101			101
10			96			96
20			97			94
40			97			99
80			92	2	1	76
160	2	2	80	5	2	
320	5	2		5	1	
MICE						
First Study						
5			102			121
10			103			113
20			99			116
40			106			106
80			94			104
160			88			111
Second Study						
160			86			100
320	5	2		4	3	85
640	5	2		5	2	
1,280	5	1		5	1	

20 and 40 ppm for female rats; the low and high doses were set at 80 and 160 ppm for male and female mice.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3.

Since the numbers of animals in the matched-control groups were small, pooled-control groups also were used for statistical comparisons. In rats, the matched controls from the current bioassay of parathion were combined with matched controls from bioassays of azinphosmethyl (CAS 86-50-0), captan (CAS 133-06-2), chloramben (CAS 133-90-4), chlordane (CAS 57-74-9), dimethoate, heptachlor (CAS 76-44-8), malathion (CAS 121-75-5), and picloram (CAS 1918-02-1). The pooled-control groups for statistical tests using rats consisted of 90 males and 90 females.

In mice, the matched controls from the current bioassay of parathion were combined with matched controls from bioassays of azinphosmethyl, chlordane, dieldrin (CAS 60-57-1), dimethoate, heptachlor, lindane (CAS 58-89-9), malathion, phosphamidon, photodieldrin (CAS 13366-73-9), and tetrachlorvinphos (CAS

Table 2. Parathion Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Parathion in Diet(b) (ppm)	Time on Study: Dosed (weeks)	Time on Study: Observed(c) (weeks)	Time-Weighted Average Dose(b) (ppm)
Male					
Matched-Control	10	0		112	
Low-Dose	50	40	13		32
		30	67		
		0		32	
High-Dose	50	80	13		63
		60	67		
		0		32	
Female					
Matched-Control	10	0	112		
Low-Dose	50	20	13		23
		30	21		
		20	46		
		0		32	
High-Dose	50	40	13		45
		60	21		
		40	46		
		0		32-33	

(a) Animals were 5 weeks of age when placed on study.

(b) After 13 weeks, doses for males and females were made uniform for both sexes of rats. After 33 weeks, doses for females were lowered, due to generalized tremors among the high-dose females.

(c) When diets containing parathion were discontinued, dosed rats and their matched controls were fed control diets without corn oil for 1 week, then control diets (2% corn oil added) for an additional 31 or 32 weeks.

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

Table 3. Parathion Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals(a)	Parathion in Diet (ppm)	Time on Study Dosed (weeks)	Time on Study Observed(b) (weeks)
Male				
Matched-Control	10	0		90
Low-Dose	50	80	71	
		0		18
High-Dose	50	160	62	
		0		28
Female				
Matched-Control	10	0		90
Low-Dose	50	80	80	
		0		9
High-Dose	50	160	80	
		0		10

(a) Animals were 5 weeks of age when placed on study.

(b) When diets containing parathion were discontinued, high-dose males received control diets without corn oil for 8 weeks, then control diets (2% corn oil added) for an additional 20 weeks. Low-dose males and all females received control diets until termination of the study.

961-11-5). The pooled-control groups for statistical tests using mice consisted of 140 males and 130 females.

The bioassays of the test chemicals other than parathion were also conducted at Gulf South Research Institute, and the pooled controls used for statistical evaluation were started no more than 3 months apart from the matched controls of parathion. The matched-control groups of rats and mice for the different test chemicals that were used in the pool were of the same strain and obtained from the same supplier; they were diagnosed by different pathologists but the diagnoses were reviewed by NCI pathologists.

G. Clinical and Pathologic Examinations

All animals were observed twice per day. Animals were weighed at approximately every 2 weeks for the first 3 months, then monthly thereafter, and palpated for masses at each weighing. Moribund animals and animals that survived to the end of the bioassay were killed using ether and necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally, additional tissues were also examined microscopically. Special staining techniques were utilized when indicated for more definitive diagnosis.

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

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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

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

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

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

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to 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 lowerlimit 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 high-dose male and high-dose female rats were generally lower than those of the matched controls during the period of administration of the chemical, particularly for females during weeks 14 through 35, at which time the dose was increased. After administration was discontinued, the mean body weights of dosed and control animals were more nearly comparable (figure 1). Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation.

During the first 6 months of the bioassay, the dosed animals were generally comparable to the controls in appearance and behavior. One high-dose male and two high-dose females had body tremors during this period. During the second 6 months, 1/50 high-dose males, 1/50 low-dose females, and 25/50 high-dose females had generalized body tremors. During this same period, 1/50 high-dose males, 1/50 low-dose females, and 5/50 high-dose females had diarrhea. At week 32, a few animals in both control and dosed groups developed exophthalmos and corneal opacity, accompanied in

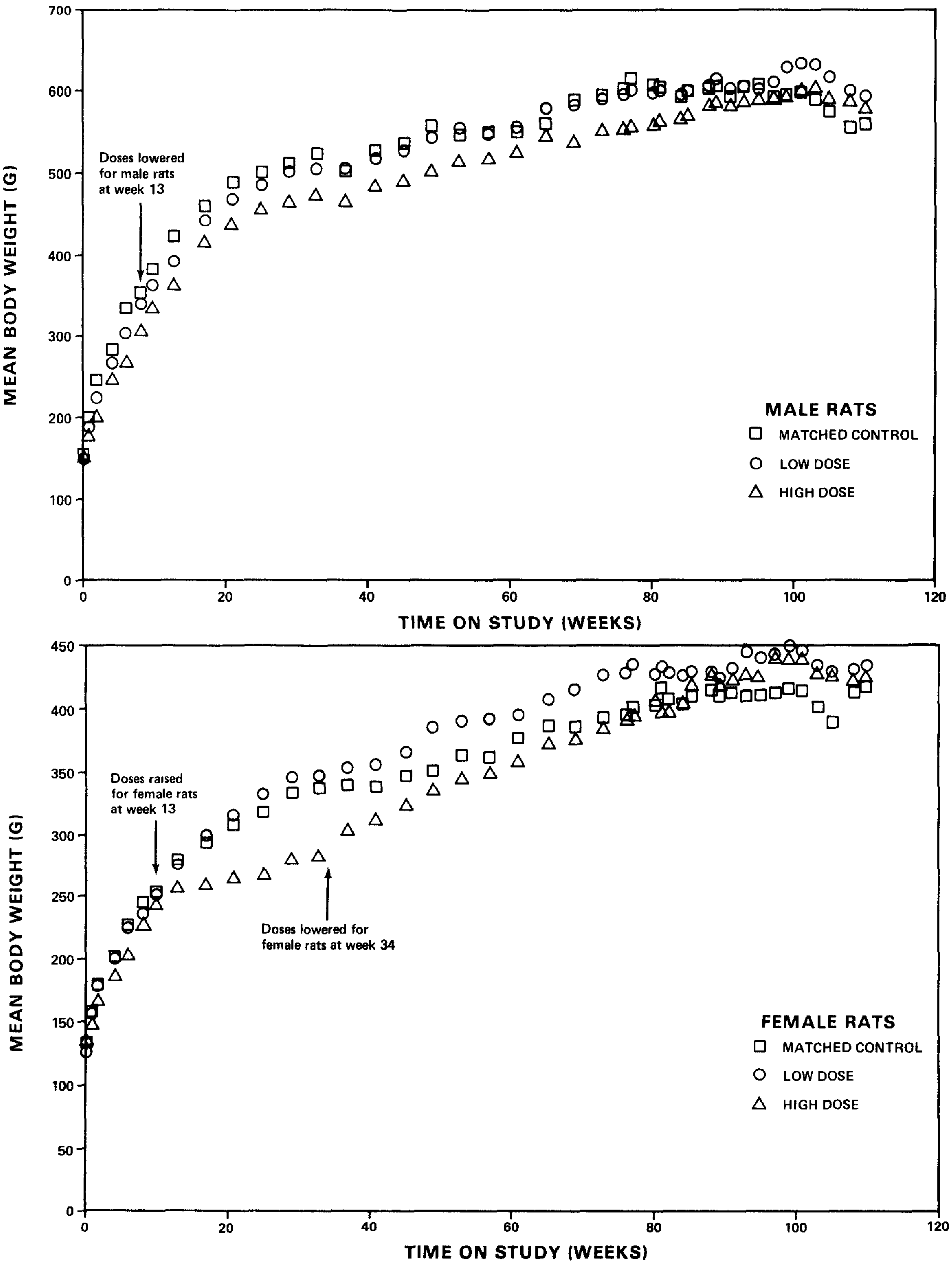

Figure 1. Growth Curves for Rats Fed Parathion in the Diet

some cases by thickening of the palpebral conjunctival membranes. This was diagnosed as viral conjunctivitis by the pathologists at the laboratory.

During the first half of the second year, clinical signs among the dosed animals were noted at a low or moderate incidence, and during the second half of the year they increased. These signs were characteristic of aging, but also included hyperactivity and hyperexcitability generally associated with organophosphorus pesticide exposure.

B. Survival (Rats)

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

In male rats, 36/50 (72%) of the high-dose group, 31/50 (62%) of the low-dose group, and 7/10 (70%) of the matched controls lived to the end of the study. In female rats, 34/50 (68%) of the

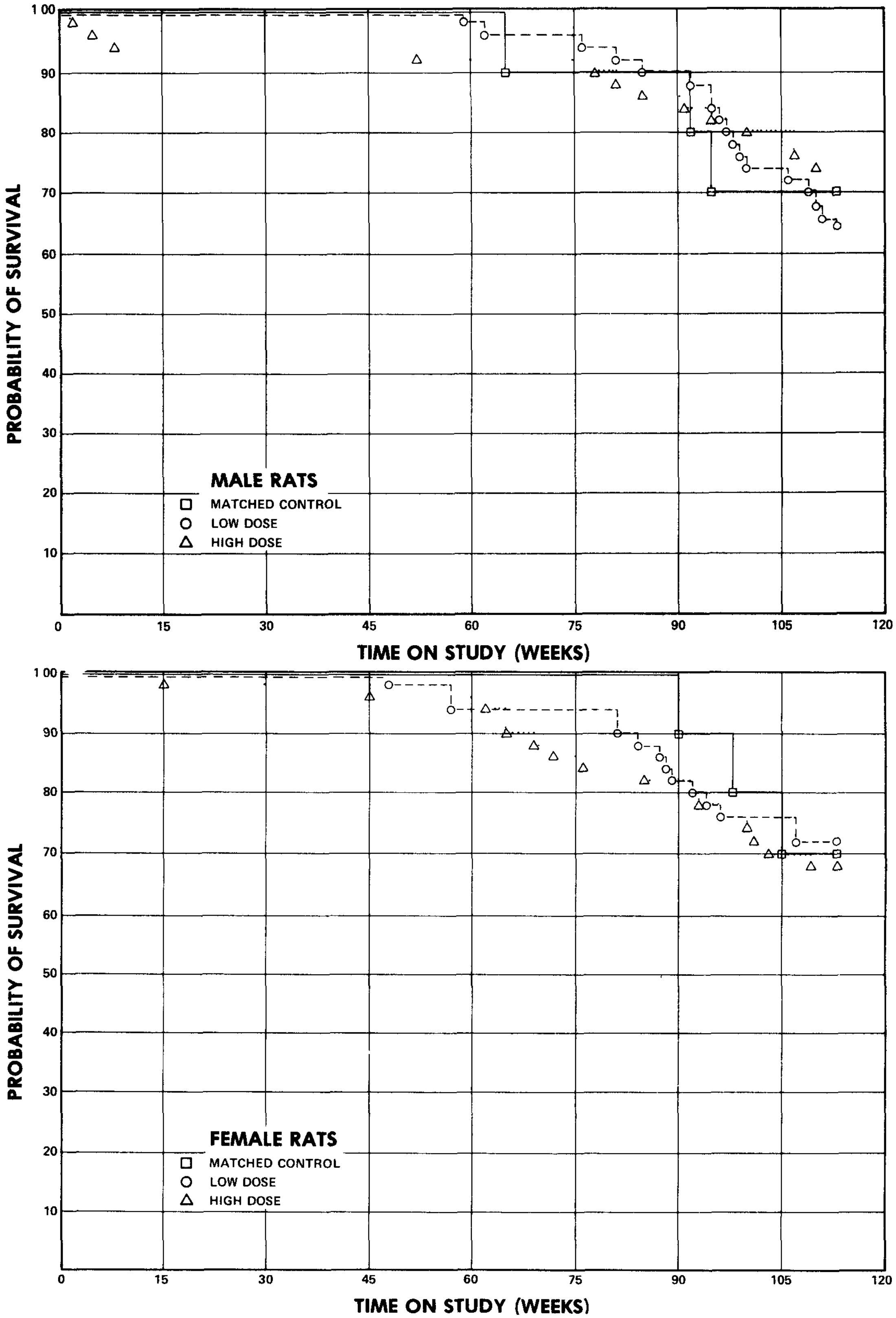

Figure 2. Survival Curves For Rats Fed Parathion In The Diet

high-dose group, 36/50 (72%) of the low-dose group, and 7/10 (70%) of the matched controls lived to the end of the study. Sufficient numbers of animals in dosed and control groups 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.

The variety of neoplasms represented among both dosed and control rats was not unusual, with the exception of a pituitary tumor in one low-dose male rat. This was a solitary tumor that consisted of an area of solid adenoma, as commonly encountered in laboratory rats, and a second component that was made up of small, rounded glandular spaces lined by a single layer of mucin-secreting cells somewhat suggestive of goblet cells. Whether these areas represented two independent tumors of the pituitary or a mixed tumor or adenoma of the pituitary is uncertain. Each of the other types of tumors represented has been encountered previously as a spontaneous lesion in the Osborne-Mendel rat.

The incidence of adrenal cortical adenomas and carcinomas was increased in high-dose male (11/46) and female (13/42) rats, as compared with matched controls (male 1/9, female 0/10). However, since the number of matched-control rats was small, this finding could not necessarily be attributed to administration of the chemical.

A variety of nonneoplastic lesions were represented among both control and dosed animals. Such lesions have been encountered previously as spontaneous occurrences in laboratory rats and are considered as such in these animals.

Based on the pathologic examination, parathion did not appear to be carcinogenic in Osborne-Mendel rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

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

In male rats, the result of the Cochran-Armitage test on the incidence of animals with cortical adenomas or carcinomas of the adrenal is significant (P less than 0.001) when the pooled-control group is used, and the results of the Fisher exact test show that the incidence in the high-dose group is significantly higher (P less than 0.001) than that in the pooled-control group. The Fisher exact comparison of incidences in the low-dose and pooled-control groups indicates a probability level of 0.035, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The adenomas were the principal lesions contributing to the significance of the combined neoplasms. When the incidences of cortical adenomas alone are tested, the results of the statistical tests are P = 0.001 in the Cochran-Armitage test using the pooled-control group and P = 0.002 in the Fisher exact test between the high-dose group and the pooled controls. In females, the Cochran-Armitage probability levels for the incidence of adrenal cortical adenomas or carcinomas are P less than 0.001 and P = 0.028, respectively, when the pooled and matched controls are used. The results of the Fisher exact test show that the incidence in the high-dose female rats is significantly higher (P less than 0.001) than that in the pooled controls. Historical records of the Carcinogenesis Testing Program at this laboratory indicate that in the male rats, cortical adenomas, cortical carcinomas, or adenomas, NOS, were observed in 8/178 (4.5%) of the controls. In female rats there were 5/180 (2.7%) cortical adenomas or adenomas, NOS, of the adrenal.

In male rats, the result of the Cochran-Armitage test for dose-related trend in the incidence of islet-cell carcinomas of the pancreas shows a significant dose-related trend (P = 0.024) when the pooled-control group is used, but the results of the Fisher exact test for comparison of the incidences of tumors in the high-dose and pooled-control groups indicate a probability level of 0.048, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The results of the tests using the matched controls are not significant.

In female rats, the Cochran-Armitage test for dose-related trend in the incidence of fibroadenomas of the mammary gland is not significant, but an indicated departure from linear trend is observed (P = 0.004) when the pooled-control group is used, since the incidence in the low-dose group is higher than that in the high-dose group. The results of the Fisher exact test show that the incidence in the low-dose group is significantly higher than that in the pooled controls (P = 0.002); however, this positive result is not confirmed by the incidence in the high-dose group. The matched controls have an incidence of 2/10 (20%) compared with 8/50 (16%) in the high-dose group, and the results of the tests using the matched controls are not significant.

In male rats, the result of the Cochran-Armitage test for dose-related trend in the incidence of follicular-cell adenoma of the thyroid is significant (P = 0.037) when the pooled-control group is used. The Fisher exact comparison of incidences in the high-dose and pooled-control groups indicates a P value of 0.046, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The Fisher exact comparison between the low-dose and the matched-control groups indicates a P value of 0.035 in the negative direction.

In summary, the incidence of the adrenal tumors in male and female rats may be associated with the administration of parathion.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male mice were lower than those of the controls during the period of administration of the chemical, but were comparable when administration was discontinued (figure 3). Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation. Mean body weights of dosed females were unaffected by the parathion when compared with controls.

During the first year of the bioassay, the dosed animals were generally comparable to the controls in appearance and behavior. Wounds from fighting were noted on the mice during the second half of the first year and continuing until termination of the bioassay.

Clinical signs in both male and female animals of the dosed groups noted with increasing frequency during the second year of the bioassay included tremors and alopecia; abdominal distention was noted in all dosed males, and most dosed females. Rough hair coats were observed beginning at week 52 in the low-dose male

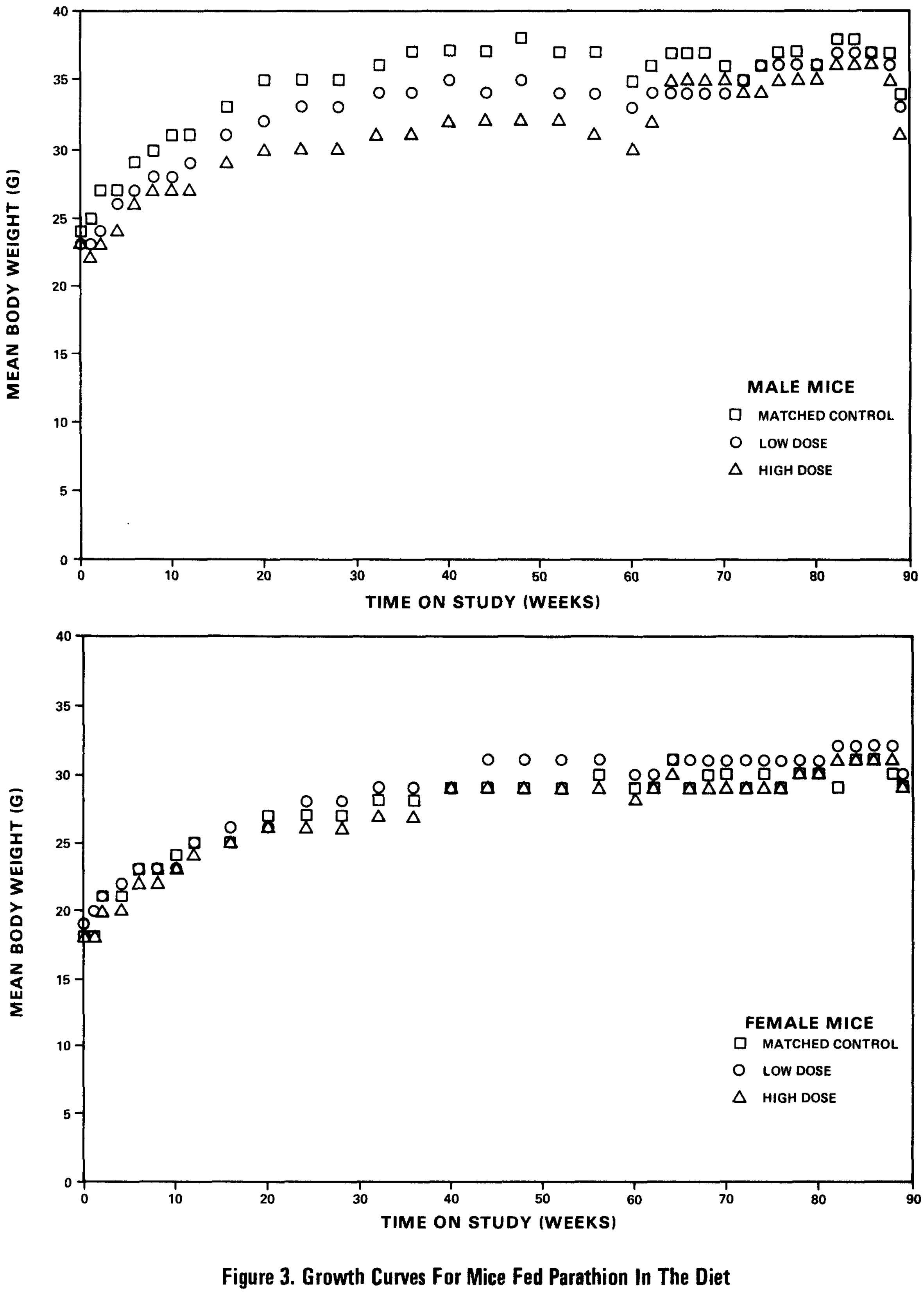

Figure 3. Growth Curves For Mice Fed Parathion In The Diet

group and at week 75 in the high-dose male group. All low-dose males had diarrhea by week 64 and all high-dose males were showing signs of hyperexcitability by week 60.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed parathion in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. In male mice, the result of the Tarone test shows a positive dose-related trend in mortality (P = 0.029) over the bioassay. In female mice, the result of the Tarone test does not show any significant dose-related trend in mortality; in fact, the controls showed a lower survival than the dosed groups.

There were 40/50 (80%) of the high-dose males, 46/50 (92%) of the low-dose males, and all 10 of the matched controls still alive at week 89. Forty-six out of 50 (92%) of the high-dose females, 46/50 (92%) of the low-dose females, and 8/10 (80%) of the matched controls were still alive at week 89. Sufficient numbers of animals in dosed and control groups were at risk for the development of late-appearing tumors.

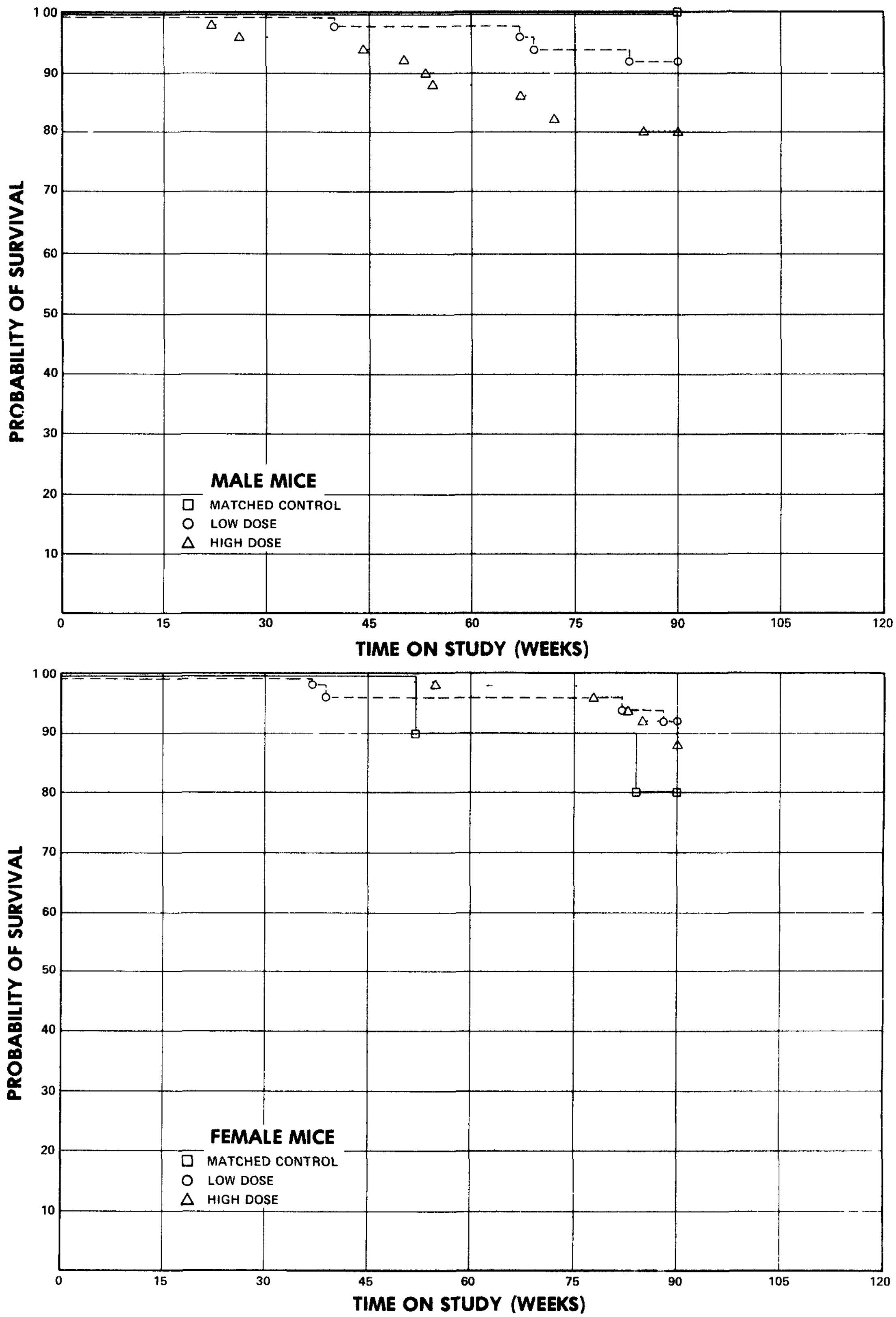

Figure 4. Survival Curves For Mice Fed Parathion In The Diet

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 neoplastic and nonneoplastic lesions are represented among both control and dosed animals. Both neoplastic and nonneoplastic lesions are judged to be distributed without any relationship to administration of the chemical.

Based on the pathologic examination, parathion was not carcinogenic in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group. In mice, the incidences of tumors at any site cannot be related in a positive direction to administration of the chemical. Significant results in the negative trend are observed in the incidence of hepatocellular carcinoma in male mice when the pooled-control group is used.

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

V. DISCUSSION

Parathion was toxic to both rats and mice at the doses administered in this bioassay, as shown by decreased mean body weights of the dosed male and female rats and male mice, and by the presence of such clinical signs as tremors, hyperactivity, and hyperexcitability associated with intoxication by parathion and other cholinesterase inhibitors (Radeleff, 1970). Since mean body weights and survival of the female mice were not affected, female mice may have been able to tolerate a higher dose. Sufficient numbers of male and female animals of both species were at risk for the possible development of late-appearing tumors.

In both male and female rats, the incidences of cortical adenomas or carcinomas of the adrenal showed dose-related trends (P less than 0.001) using pooled controls and, in direct comparisons, were higher in the high-dose groups (P less than 0.001) than in the pooled controls (males: pooled controls 3/80, matched controls 0/9, low-dose 4/49, high-dose 11/46; females: pooled controls 3/80, matched controls 0/9, low-dose 6/47, high-dose 13/42). The principle contribution to the significance of these tumors is made by the incidence of adenomas. When the matched controls were used, dose-related trends in incidences of the tumors were significant (males, P = 0.048; females, P = 0.028); in direct comparisons, however, the incidences of the tumors in the individual dosed groups did not differ significantly from those in corresponding matched controls. The incidences of the tumors in the dosed male and female rats were higher than those in corresponding historical controls (males 8/148, females 5/180).

Because of the statistical significance of the comparison of the incidence of adrenal tumors in dosed animals with that of pooled controls and the relatively low incidences observed among historical controls (even taking into account group variation), it is considered that the incidence of adrenal tumors in male and female rats may be associated with the administration of parathion.

In mice, no tumors occurred in either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

Chronic toxicity of parathion has previously been investigated in rats by Hazleton and Holland (1950), by Barnes and Denz (1951), and by the Food and Drug Administration (Lehman, 1965). In the Hazleton and Holland study, male albino rats were administered 0, 10, 25, 50, or 100 ppm of parathion in the diet for 2 years, and females albino rats were given 0, 10, or 50 ppm for 64 weeks or 100 ppm for an unstated period. At 100 ppm, peripheral tremors and irritability were noted in the males, but only for the first several weeks; females were more susceptible than the males at this dose. No neoplasms were reported in the tissues examined, which included the liver and adrenal gland. Barnes and Denz (1951) fed parathion in the diet for periods of up to 1 year to male and female albino rats at 10, 20, 50, 75, or 100 ppm. Typical cholinergic signs were observed in the groups receiving 50, 75, or 100 ppm. Survival was low at 50 ppm and above, but was high at 10 and 20 ppm, with no toxic signs observed. Lesions of the submaxillary gland and the pancreas and hypoplasia of the spleen and thymus, associated with acute poisoning in other studies by these authors, were found in animals dosed with 50 or 75 ppm but not in those dosed with 10 or 20 ppm. No neoplasms were reported. In the work carried out at the FDA (Lehman, 1965), male and female rats were fed parathion in the diet for 2 years at concentrations of 2, 5, 10, 25, 50, or 100 ppm. There was no significant effect on mortality, no histologic changes attributable to the administration of parathion were noted, and the incidence of tumors was not increased in the dosed animals.

It is concluded that under the conditions of this bioassay, parathion was not carcinogenic to B6C3F1 mice. In the male and female Osborne-Mendel rats receiving parathion in their diet, there was a higher incidence of cortical tumors of the adrenal than in pooled or historical controls, suggesting that parathion is carcinogenic to this strain of rat.

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APPENDIX A

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

TABLE A1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(49)
KERATOACANTHOMA		1 (2%)	
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(10)	(50)	(49)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA		2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(10)	(50)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
#SPLEEN	(10)	(50)	(47)
FIBROSARCOMA			2 (4%)
HAMARTOMA			1 (2%)
#LYMPH NODE	(9)	(39)	(34)
HEMANGIOSARCOMA		1 (3%)	
#MESENTERIC L. NODE	(9)	(39)	(34)
HEMANGIOSARCOMA		1 (3%)	
#FEMORAL LYMPH NODE	(9)	(39)	(34)
SARCOMA, NOS, METASTATIC			1 (3%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*HEART	(10)	(50)	(48)
FIBROSARCOMA, METASTATIC			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(48)	(44)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(10)	(50)	(49)
NEOPLASTIC NODULE			3 (6%)
HEPATOCELLULAR CARCINOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(42)	(43)
ADENOMA, NOS	4 (44%)	10 (24%)	13 (30%)
MIXED TUMOR, BENIGN		1 (2%)	
#ADRENAL	(9)	(49)	(46)
CORTICAL ADENOMA		5 (10%)	9 (20%)
CORTICAL CARCINOMA		2 (4%)	2 (4%)
PHEOCHROMOCYTOMA			2 (4%)
#THYROID	(10)	(46)	(43)
FOLLICULAR-CELL ADENOMA	3 (30%)	2 (4%)	8 (19%)
C-CELL CARCINOMA		1 (2%)	1 (2%)
#PARATHYROID	(5)	(34)	(29)
ADENOMA, NOS	1 (20%)		
#PANCREATIC ISLETS	(9)	(49)	(46)
ISLET-CELL CARCINOMA		1 (2%)	3 (7%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(49)
FIBROMA		2 (4%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(10)	(50)	(49)
SARCOMA, NOS			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		9	6
MORIBUND SACRIFICE	3	10	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	7	31	36
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	25	34
TOTAL PRIMARY TUMORS	8	33	51
TOTAL ANIMALS WITH BENIGN TUMORS	5	17	26
TOTAL BENIGN TUMORS	8	23	33
TOTAL ANIMALS WITH MALIGNANT TUMORS		9	15
TOTAL MALIGNANT TUMORS		10	15
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	2
TOTAL SECONDARY TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			3
TOTAL UNCERTAIN TUMORS			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED PARATHION IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(50)
NEOPLASM, NOS, MALIGNANT			1 (2%)
*SUBCUT TISSUE	(10)	(50)	(50)
C-CELL CARCINOMA, METASTATIC			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
C-CELL CARCINOMA, METASTATIC	1 (10%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(50)	(50)
LYMPHOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(10)	(50)	(49)
SARCOMA, NOS			1 (2%)
#LYMPH NODE	(10)	(41)	(41)
HEMANGIOMA	1 (10%)	1 (2%)	
#CERVICAL LYMPH NODE	(10)	(41)	(41)
C-CELL CARCINOMA, METASTATIC	1 (10%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(49)	(48)
HEPATOCELLULAR ADENOMA			1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NEOPLASTIC NODULE		1 (2%)	2 (4%)
*BILE DUCT	(10)	(50)	(50)
BILE DUCT ADENOMA	1 (10%)		
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(48)
† HAMARTOMA	1 (10%)		
ENDOCRINE SYSTEM			
#PITUITARY	(8)	(38)	(39)
ADENOMA, NOS	2 (25%)	11 (29%)	13 (33%)
#ADRENAL	(10)	(47)	(42)
CORTICAL ADENOMA	1 (10%)	4 (9%)	11 (26%)
CORTICAL CARCINOMA		2 (4%)	2 (5%)
C-CELL CARCINOMA, METASTATIC			1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (10%)		
#THYROID	(10)	(45)	(43)
FOLLICULAR-CELL ADENOMA	1 (10%)	4 (9%)	1 (2%)
C-CELL CARCINOMA	2 (20%)	2 (4%)	3 (7%)
#PANCREATIC ISLETS	(10)	(48)	(49)
ISLET-CELL ADENOMA	1 (10%)		1 (2%)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(50)
ADENOMA, NOS	1 (10%)	1 (2%)	
PAPILLARY ADENOCARCINOMA		1 (2%)	
FIBROMA		1 (2%)	1 (2%)
FIBROADENOMA	2 (20%)	16 (32%)	8 (16%)
#UTERUS	(10)	(49)	(45)
ADENOCA IN ADENOMATOUS POLYP		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (10%)	4 (8%)	5 (11%)
#OVARY	(10)	(45)	(45)
CYSTADENOCARCINOMA, NOS			1 (2%)

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
† This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of lipocytes, tubular structures, and fibroblasts in varying proportions.

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(10)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		2	5
MORIBUND SACRIFICE	3	12	11
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	7	36	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	34	32
TOTAL PRIMARY TUMORS	15	54	53
TOTAL ANIMALS WITH BENIGN TUMORS	8	31	25
TOTAL BENIGN TUMORS	12	44	42
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	9	8
TOTAL MALIGNANT TUMORS	3	9	9
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	2		3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

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

TABLE B1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(49)	(49)
MALIGNANT MELANOMA		1 (2%)	
*SUBCUT TISSUE	(10)	(49)	(49)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(9)	(49)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (6%)	5 (11%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(8)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#MESENTERIC L. NODE	(10)	(35)	(37)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	
#SMALL INTESTINE	(10)	(48)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(48)	(47)
NEOPLASTIC NODULE	1 (10%)	3 (6%)	8 (17%)
HEPATOCELLULAR CARCINOMA	1 (10%)	3 (6%)	1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(10)	(40)	(42)
CARCINOMA,NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		1	4
MORIBUND SACRIFICE		3	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	10	46	40
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	14	12
TOTAL PRIMARY TUMORS	2	15	14
TOTAL ANIMALS WITH BENIGN TUMORS		3	5
TOTAL BENIGN TUMORS		3	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	8	1
TOTAL MALIGNANT TUMORS	1	9	1
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3	8
TOTAL UNCERTAIN TUMORS	1	3	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED PARATHION IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	8	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	8	48	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(8)	(48)	(49)
HEMANGIOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(9)	(47)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (11%)		2 (4%)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(8)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (13%)	4 (8%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
LEUKEMIA,NOS			1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#BONE MARROW		(4)	
HEMANGIOSARCOMA		1 (25%)	
#SPLEEN	(9)	(45)	(49)
HEMANGIOMA			1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#KIDNEY	(9)	(46)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*LIVER	(9)	(47)	(49)
NEOPLASTIC NODULE	1 (11%)	1 (2%)	1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(6)	(30)	(30)
ADENOMA, NOS		1 (3%)	
#THYROID	(7)	(43)	(47)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(8)	(48)	(49)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS		1 (2%)	
HEMANGIOSARCOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	2	4	3
MORIBUND SACRIFICE			3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	46	44
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	12	9
TOTAL PRIMARY TUMORS	3	12	12
TOTAL ANIMALS WITH BENIGN TUMORS	1	1	4
TOTAL BENIGN TUMORS	1	1	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	10	5
TOTAL MALIGNANT TUMORS	1	10	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	1	1	1
TOTAL UNCERTAIN TUMORS	1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN RATS FED PARATHION IN THE DIET

TABLE C1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAIS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(49)
ULCER, NOS	1 (10%)		
*SUBCUT TISSUE	(10)	(50)	(49)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(10)	(50)	(48)
ATELECTASIS			1 (2%)
CONGESTION, NOS		3 (6%)	
EDEMA, NOS		1 (2%)	
LIPOIDOSIS			1 (2%)
ALVEOLAR MACROPHAGES			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW		(1)	(1)
ATROPHY, NOS		1 (100%)	
HYPERPLASIA, NOS			1 (100%
#SPLEEN	(10)	(50)	(47)
ACCESSORY SPLEEN		1 (2%)	
THROMBOSIS, NOS		1 (2%)	
CONGESTION, NOS		1 (2%)	
INFARCT, NOS			3 (6%)
ATROPHY, NOS		1 (2%)	
MYELOID METAPLASIA			3 (6%)
#LYMPH NODE	(9)	(39)	(34)
INFLAMMATION, ACUTE/CHRONIC			1 (3%)
#MANDIBULAR L. NODE	(9)	(39)	(34)
MELANIN			1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(10)	(50)	(48)
SCAR		1 (2%)	
#MYOCARDIUM	(10)	(50)	(48)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL			3 (6%)
*AORTA	(10)	(50)	(49)
ARTERIOSCLEROSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(10)	(50)	(49)
CONGESTION, NOS		1 (2%)	1 (2%)
HEMORRHAGE		1 (2%)	
SCAR		1 (2%)	
CIRRHOSIS, BILIARY	1 (10%)		
METAMORPHOSIS FATTY		2 (4%)	3 (6%)
FOCAL CELLULAR CHANGE		1 (2%)	2 (4%)
HEPATOCYTOMEGALY		1 (2%)	
ANGIECTASIS		1 (2%)	5 (10%)
*BILE DUCT	(10)	(50)	(49)
HYPERPLASIA, NOS	1 (10%)		
#PANCREAS	(9)	(49)	(46)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
PERIARTERITIS			4 (9%)
ATROPHY, NOS	1 (11%)		1 (2%)
#STOMACH	(10)	(42)	(46)
MINERALIZATION			1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(48)
INFLAMMATION, CHRONIC	6 (60%)	7 (15%)	9 (19%)
#KIDNEY/PELVIS	(10)	(48)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#URINARY BLADDER	(9)	(42)	(41)
CALCULUS, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(42)	(43)
CYST, NOS		1 (2%)	
MULTIPLE CYSTS			1 (2%)
#ADRENAL	(9)	(49)	(46)
THROMBOSIS, NOS		1 (2%)	
ANGIECTASIS		1 (2%)	
#PARATHYROID	(5)	(34)	(29)
HYPERPLASIA, NOS			2 (7%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(10)	(44)	(46)
INFLAMMATION, CHRONIC		3 (7%)	1 (2%)
#TESTIS	(10)	(47)	(48)
EDEMA, NOS		9 (19%)	2 (4%)
ATROPHY, NOS	1 (10%)	4 (9%)	2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(10)	(50)	(49)
EXOSTOSIS	1 (10%)		
*PALATINE BONE	(10)	(50)	(49)
FRACTURE, NOS	1 (10%)		
BODY CAVITIES			
*MESENTERY	(10)	(50)	(49)
PERIARTERITIS	1 (10%)		2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*TUNICA VAGINALIS	(10)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	10	4
AUTOLYSIS/NO NECROPSY			1

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

TABLE C2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(50)
ULCER, NOS		1 (2%)	1 (2%)
ULCER, FOCAL		2 (4%)	
FIBROSIS		3 (6%)	
ACANTHOSIS		2 (4%)	
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#BONE MARROW		(2)	(2)
HYPOPLASIA, NOS		1 (50%)	
HYPERPLASIA, NOS		1 (50%)	1 (50%)
HYPERPLASIA, ERYTHROID			1 (50%)
#SPLEEN	(10)	(50)	(49)
HYPERPLASIA, FOCAL			2 (4%)
#THYMUS		(13)	(5)
ULTIMOBRANCHIAL CYST		2 (15%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(10)	(50)	(49)
INFLAMMATION, CHRONIC			2 (4%)
DIGESTIVE SYSTEM			
#LIVER	(10)	(49)	(48)
METAMORPHOSIS FATTY		3 (6%)	3 (6%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
*BILE DUCT	(10)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#STOMACH	(10)	(48)	(47)
MINERALIZATION			1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(48)	(48)
INFLAMMATION, CHRONIC	1 (10%)	2 (4%)	4 (8%)
INFARCT, NOS		1 (2%)	
#KIDNEY/PELVIS	(10)	(48)	(48)
INFLAMMATION, SUPPURATIVE	1 (10%)		
ENDOCRINE SYSTEM			
#ADRENAL	(10)	(47)	(42)
ANGIECTASIS	1 (10%)	2 (4%)	
#THYROID	(10)	(45)	(43)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(50)
NECROSIS, CENTRAL		1 (2%)	
#UTERUS	(10)	(49)	(45)
HYDROMETRA		1 (2%)	
CYST, NOS		2 (4%)	
#UTERUS/ENDOMETRIUM	(10)	(49)	(45)
HYPERPLASIA, CYSTIC		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
GASTROSPLENIC LIGAME			
NECROSIS, FAT			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		13	14
AUTO/NECROPSY/NO HISTO			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN MICE FED PARATHION IN THE DIET

TABLE D1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(49)	(49)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (10%)		
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#BONE MARROW		(2)	(1)
HYPERPLASIA, HEMATOPOIETIC			1 (100%)
#MESENTERIC L. NODE	(10)	(35)	(37)
HEMORRHAGE		2 (6%)	
INFLAMMATION, GRANULOMATOUS		1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(48)	(47)
NECROSIS, FOCAL		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	
ANGIECTASIS		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY/PELVIS	(10)	(49)	(48)
INFLAMMATION, SUPPURATIVE			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#URINARY BLADDER	(1)	(41)	(45)
INFLAMMATION, SUPPURATIVE			2 (4%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(10)	(49)	(49)
CYST, NOS			1 (2%)
#PROSTATE	(9)	(42)	(43)
INFLAMMATION, SUPPURATIVE			2 (5%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	7	31	31
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY		1	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED PARATHION IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	8	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	8	48	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(9)	(47)	(49)
GRANULOMA, PYOGENIC			1 (2%)
METAPLASIA, OSSEOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
*BONE MARROW		(4)	
HYPERPLASIA, HEMATOPOIETIC		3 (75%)	
#SPLEEN	(9)	(45)	(49)
INFARCT, NOS			1 (2%)
MYELOID METAPLASIA			1 (2%)
#LYMPH NODE	(6)	(42)	(47)
ABSCESS, NOS			1 (2%)
#CERVICAL LYMPH NODE	(6)	(42)	(47)
INFLAMMATION, SUPPURATIVE			1 (2%)
#MEDIASTINAL L.NODE	(6)	(42)	(47)
GRANULOMA, PYOGENIC			1 (2%)
#MESENTERIC L. NODE	(6)	(42)	(47)
GRANULOMA, PYOGENIC			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(9)	(47)	(49)
BASOPHILIC CYTO CHANGE		3 (6%)	
#PANCREAS	(7)	(47)	(48)
CYST, NOS	1 (14%)		1 (2%)
ATROPHY, NOS	1 (14%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(9)	(46)	(49)
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)	
#URINARY BLADDER		(34)	(40)
INFLAMMATION, CHRONIC		1 (3%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(8)	(48)	(49)
METAPLASIA, OSSEOUS			1 (2%)
#UTERUS	(7)	(46)	(47)
INFLAMMATION, SUPPURATIVE		1 (2%)	
PYOMETRA		2 (4%)	
ABSCESS, NOS		1 (2%)	2 (4%)
#OVARY	(6)	(42)	(45)
INFLAMMATION, SUPPURATIVE		1 (2%)	
ABSCESS, NOS		9 (21%)	4 (9%)
INFLAMMATION, CHRONIC	1 (17%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	21	32
AUTOLYSIS/NO NECROPSY	2	2	1

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

APPENDIX E

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

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

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma, Hepatocellular Adenoma, or Neoplastic Nodule (b)	3/85 (4)	0/10 (0)	0/50 (0)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.000	2.313
Lower Limit			0.000	0.406
Upper Limit			2.833	15.125
Relative Risk (Matched Control) (f)			--	Infinite
Lower Limit			--	0.211
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	112
Pituitary: Chromophobe Adenoma or Adenoma, NOS (b)	21/72 (29)	4/9 (44)	10/42 (24)	13/43 (30)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.816	1.037
Lower Limit			0.377	0.529
Upper Limit			1.612	1.914
Relative Risk (Matched Control) (f)			0.536	0.680
Lower Limit			0.230	0.312
Upper Limit			1.988	2.420
Weeks to First Observed Tumor		92	100	112

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Cortical Adenoma (b)	2/80 (3)	0/9 (0)	5/49 (10)	9/46 (20)
P Values (c,d)	P = 0.001	N.S.	N.S.	P = 0.002**
Relative Risk (Pooled Control) (f)			4.082	7.826
Lower Limit			0.696	1.707
Upper Limit			41.364	71.374
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.262	0.584
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	112	91
Adrenal: Cortical Adenoma or Carcinoma (b)	3/80 (4)	0/9 (0)	7/49 (14)	11/46 (24)
P Values (c,d)	P less than 0.001	P = 0.048	P = 0.035**	P less than 0.001**
Relative Risk (Pooled Control) (f)			3.810	6.377
Lower Limit			0.914	1.789
Upper Limit			21.780	33.667
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.404	0.738
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	85	91

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma (b)	5/76 (7)	3/10 (30)	2/46 (4)	8/43 (19)
P Values (c,d)	P = 0.037	N.S.	P = 0.035* (N)	P = 0.046**
Departure from Linear Trend (e)		P = 0.010		
Relative Risk (Pooled Control) (f)			0.661	2.828
Lower Limit			0.065	0.868
Upper Limit			3.830	10.237
Relative Risk (Matched Control) (f)			0.145	0.620
Lower Limit			0.015	0.201
Upper Limit			1.150	3.239
Weeks to First Observed Tumor		95	112	95
Pancreatic Islets: Islet-Cell Carcinoma (b)	0/79 (0)	0/9 (0)	1/49 (2)	3/46 (7)
P Values (c,d)	P = 0.024	N.S.	N.S.	P = 0.048**
Relative Risk (Pooled Control) (f)			Infinite	Infinite
Lower Limit			0.086	1.024
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.011	0.133
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	112	95

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

(continued)

(a) Dosed groups received time-weighted average doses of 32 or 63 ppm.

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

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

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

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

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

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

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule or Hepatocellular Adenoma (b)	5/84 (6)	0/10 (0)	1/49 (2)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.343	1.050
Lower Limit			0.007	0.169
Upper Limit			2.929	5.121
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.012	0.139
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	112	109
Pituitary: Chromophobe Adenoma or Adenoma, NOS (b)	25/75 (33)	2/8 (25)	11/38 (29)	13/39 (33)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.868	1.000
Lower Limit			0.429	0.526
Upper Limit			1.601	1.766
Relative Risk (Matched Control) (f)			1.158	1.333
Lower Limit			0.355	0.424
Upper Limit			9.741	11.002
Weeks to First Observed Tumor	--	105	89	93

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Cortical Adenoma (b)	4/78 (5)	1/10 (10)	4/47 (9)	11/42 (26)
P Values (c,d)	P = 0.001	P = 0.037	N.S.	P = 0.001**
Relative Risk (Pooled Control) (f)			1.660	5.107
Lower Limit			0.322	1.620
Upper Limit			8.460	20.469
Relative Risk (Matched Control) (f)			0.851	2.619
Lower Limit			0.103	0.479
Upper Limit			41.020	109.307
Weeks to First Observed Tumor		98	112	65
Adrenal: Cortical Adenoma or Carcinoma (b)	4/78 (5)	1/10 (10)	6/47 (13)	13/42 (31)
P Values (c,d)	P less than 0.001	P = 0.028	N.S.	P less than 0.001**
Relative Risk (Pooled Control) (f)			2.489	6.036
Lower Limit			0.621	2.005
Upper Limit			11.349	23.541
Relative Risk (Matched Control) (f)			1.277	3.095
Lower Limit			0.192	0.587
Upper Limit			57.405	127.253
Weeks to First Observed Tumor		98	112	65

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma (b)	3/80 (4)	1/10 (10)	4/45 (9)	1/43 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			2.370	0.620
Lower Limit			0.417	0.012
Upper Limit			15.439	7.400
Relative Risk (Matched Control) (f)			0.889	0.233
Lower Limit			0.108	0.003
Upper Limit			42.792	17.864
Weeks to First Observed Tumor		112	84	113
Thyroid: C-cell Carcinoma (b)	7/80 (9)	2/10 (20)	2/45 (4)	3/43 (7)
P Values (c,d)	N.S.	N.S.	N.S	N.S.
Relative Risk (Pooled Control) (f)			0.508	0.797
Lower Limit			0.053	0.138
Upper Limit			2.517	3.274
Relative Risk (Matched Control) (f)			0.222	0.349
Lower Limit			0.019	0.050
Upper Limit			2.871	3.897
Weeks to First Observed Tumor		98	84	103

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	9/85 (11)	2/10 (20)	16/50 (32)	8/50 (16)
P Values (c,d)	N.S.	N.S.	P = 0.002**	N.S.
Departure from Linear Trend (e)	P = 0.004			
Relative Risk (Pooled Control) (f)			3.002	1.511
Lower Limit			1.362	0.539
Upper Limit			7.077	4.098
Relative Risk (Matched Control) (f)			1.600	0.800
Lower Limit			0.493	0.207
Upper Limit			13.259	7.210
Weeks to First Observed Tumor		90	57	80
Uterus: Endometrial Stromal Polyp (b)	9/82 (11)	1/10 (10)	4/49 (8)	5/45 (11)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.744	1.012
Lower Limit			0.175	0.280
Upper Limit			2.497	3.126
Relative Risk (Matched Control) (f)			0.816	1.111
Lower Limit			0.099	0.154
Upper Limit			39.389	51.348
Weeks to First Observed Tumor		98	112	112

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

(continued)

(a) Dosed groups received time-weighted average doses of 23 or 45 ppm.

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

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

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

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

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

APPENDIX F

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

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

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	10/126 (8)	0/9 (0)	3/49 (6)	5/47 (11)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.771	1.340
Lower Limit			0.140	0.374
Upper Limit			2.828	4.026
Relative Risk (Matched Control) (f)			Infinite	Infinite
Lower Limit			0.125	0.274
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	89	90
Liver: Hepatocellular Carcinoma (b)	21/127 (17)	1/10 (10)	3/48 (6)	1/47 (2)
P Values (c,d)	P = 0.003 (N)	N.S.	N.S.	P = 0.006** (N)
Relative Risk (Pooled Control) (f)			0.378	0.129
Lower Limit			0.074	0.003
Upper Limit			1.184	0.758
Relative Risk (Matched Control) (f)			0.625	0.213
Lower Limit			0.061	0.003
Upper Limit			32.146	16.378
Weeks to First Observed Tumor		90	67	85

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma, Hepatocellular Adenoma, or Neoplastic Nodule (b)	27/127 (21)	2/10 (20)	6/48 (13)	9/47 (19)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.588	0.901
Lower Limit			0.209	0.397
Upper Limit			1.340	1.796
Relative Risk (Matched Control) (f)			0.625	0.957
Lower Limit			0.144	0.258
Upper Limit			5.907	8.460
Weeks to First Observed Tumor		90	67	85
Hematopoietic System: Lymphoma (b)	3/133 (2)	0/10 (0)	3/49 (6)	0/48 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			2.714	0.000
Lower Limit			0.373	0.000
Upper Limit			19.485	4.617
Relative Risk (Matched Control) (f)			Infinite	--
Lower Limit			0.136	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	89	--

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

(continued)

(a) Dosed groups received 80 or 160 ppm.

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

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

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

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

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

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

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/128 (2)	1/9 (11)	0/47 (0)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.000	1.742
Lower Limit			0.000	0.148
Upper Limit			4.535	14.637
Relative Risk (Matched Control) (f)			0.000	0.367
Lower Limit			0.000	0.023
Upper Limit			3.585	21.260
Weeks to First Observed Tumor		90	--	90
Liver: Neoplastic Nodule or Hepatocellular Adenoma (b)	3/126 (2)	1/9 (11)	1/47 (2)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			0.894	0.857
Lower Limit			0.017	0.016
Upper Limit			10.722	10.298
Relative Risk (Matched Control) (f)			0.191	0.184
Lower Limit			0.003	0.003
Upper Limit			14.743	14.153
Weeks to First Observed Tumor		90	89	90

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

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma (b)	13/128 (10)	1/9 (11)	7/48 (15)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.436	0.603
Lower Limit			0.510	0.113
Upper Limit			3.592	2.065
Relative Risk (Matched Control) (f)			1.313	0.551
Lower Limit			0.215	0.055
Upper Limit			57.828	28.360
Weeks to First Observed Tumor		90	89	85
Hematopoietic System: Lymphoma or Leukemia (b)	14/128 (11)	1/9 (11)	8/48 (17)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control) (f)			1.524	0.746
Lower Limit			0.585	0.185
Upper Limit			3.595	2.226
Relative Risk (Matched Control) (f)			1.500	0.735
Lower Limit			0.258	0.091
Upper Limit			65.028	35.451
Weeks to First Observed Tumor		90	88	85

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

(continued)

(a) Dosed groups received 80 or 160 ppm.

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

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

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

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

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

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR

CONCENTRATIONS OF PARATHION

APPENDIX G

Analysis of Formulated Diets for

Concentrations of Parathion

A 10-g sample of the formulated diet was shaken with 125 ml hexane for 16 hours at ambient temperature. The mixture was then filtered through Celite with hexane washes, and the combined filtrates were reduced in volume to 10 ml. After appropriate dilutions, the solution was analyzed quantitatively for parathion by gas-liquid chromatography (electron capture detector, 5% QF-1 on Chromosorb W column). Recoveries were determined with spiked samples, and external standards were used for calibration.

Theoretical Concentrations in Diet (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
20	16	20.1	5.9%	17.2-21.6
30	11	29.7	4.7%	27.1-32.0
40	14	39.2	3.6%	37.5-41.8
60	10	59.0	6.5%	55.2-65.1
80	21	79.6	5.1%	75.0-89.0
160	14	160.8	4.5%	150.0-171.0

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

August 31, 1978

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

A toxicologist with Monsanto Company presented a public statement regarding the bioassay of Parathion. He noted that Monsanto is the major producer of Parathion, an agent used for the control of insects and mites on food and fiber crops. He said that Parathion does not pose an undue hazard if used in accordance with prescribed precautions. He made the following points: 1) the high spontaneous incidence of adrenal cortical tumors in the Osborne-Mendel rat should be given due consideration in evaluating the significance of this tumor type among treated animals; 2) pathological examination of treated rats failed to detect non-tumorigenic adrenal lesions which would indicate an insult to the organ; and 3) results from the NCI bioassay are inconsistent with those from three other reported studies, indicating no treatment-related histological changes in animals fed Parathion. He urged that the overall conclusion in the report reiterate the statement from the pathology section that "Paration did not appear to be carcinogenic in Osborne-Mendel rats under the conditions of this bioassay."

The primary reviewer said that the report noted an elevated incidence of adrenal tumors in treated rats. No treatment-related tumors were observed in mice. Although the study was marred by the use of a small number of matched control animals, the deficiency was compensated for by using pooled controls in the statistical analysis of the study. He pointed out that the toxicity of Parathion inhibited the levels of the compound that could be administered. He further stated that the increased incidence of adrenal neoplasms in treated rats should not be taken as conclusive evidence for the carcinogenicity of Parathion. The primary reviewer recommended that consideration be given to a retest of the compound, possibly in a different species. He added that it would be premature to assess the possible human risk posed by Parathion.

The secondary reviewer indicated that the evidence was insufficient to conclude that Parathion was carcinogenic in treated rats or mice, under the conditions of test. He suggested that the conclusion in the report be reworded as follows: "There were more adrenal cortical adenomas and carcinomas among the treated rats than among pooled and historical controls, suggesting a carcinogenic effect that requires further study." He opined that the increase in adrenal neoplasms may have been associated with the stress of the animals. Although he agreed with the shortcomings noted by the primary reviewer, he still considered the study valid for the purpose for which it was undertaken. Based on the results of the study, he concluded that Parathion did not pose a carcinogenic risk to man.

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

Members present were:

Arnold Brown (Chairman), University of Wisconsin School of Medicine
Joseph Highland, Environmental Defense Fund
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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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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