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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 azinphosmethyl 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 animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of azinphosmethyl was conducted by Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to the 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 test chemical and observation of 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 of tissues from animals dosed with azinphosmethyl and their matched controls was performed by Dr. D. A. Willigan[6] at Donald A. Willigan, Inc., 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 results of the analyses 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. Marshall Steinberg, Director of the Bioassay Program; Dr. L. A. Campbell, 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, bioscience writers; and Dr. E. W. Gunberg, technical editor.

The following other 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. Dawn G. Goodman[10], Dr. Richard A. Griesemer, 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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SUMMARY

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

Groups of 50 rats of each sex were administered azinphosmethyl at one of two doses for 80 weeks, then observed for 34 or 35 weeks. Time-weighted average doses of either 78 or 156 ppm were used for the males. Initial doses of 62.5 or 125 ppm used for the females were maintained throughout the bioassay. Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls consisted of the matched controls combined with 95 male and 95 female untreated rats from similar bioassays of 10 other test chemicals. All surviving rats were killed at 114 or 115 weeks.

Groups of 50 mice of each sex were administered azinphosmethyl at one of two doses for 80 weeks, then observed for 12 or 13 weeks. The doses were either 31.3 or 62.5 ppm for the males and either 62.5 or 125 ppm for the females. Matched controls consisted of groups of 10 untreated mice of each sex; pooled controls consisted of the matched controls combined with 130 male and 120 female untreated mice from similar bioassays of 11 other test chemicals. All surviving mice were killed at 92 or 93 weeks.

High- and low-dose male rats and mice and high-dose female rats and mice had lower mean body weights than corresponding matched controls throughout the bioassay. Typical signs of organophosphate intoxication were observed in a few animals of both species, and included hyperactivity, tremors, and dyspnea. Sufficient numbers of animals were at risk in each species for development of late-appearing tumors.

A great many tumors of the endocrine organs were observed in both dosed male and dosed female rats. Those of the adrenal in dosed males and females, the follicular cells of the thyroid in dosed

females, the anterior pituitary in dosed males, and the parathyroid in dosed males occurred at statistically significant incidences when compared with pooled controls, but not with matched controls, and they were not considered to be related to administration of the test compound. The incidences of tumors of the pancreatic islets and of the follicular cells of the thyroid in the male rats suggest, but do not clearly implicate, azinphosmethyl as a carcinogen in these animals.

In mice of each sex there were no increased incidences of tumors that could be related to administration of the test chemical.

It is concluded that under the conditions of this bioassay, neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for the carcinogenicity of azinphosmethyl in male Osborne-Mendel rats. Azinphosmethyl was not shown to be carcinogenic in female Osborne-Mendel rats or in B6C3F1 mice of either sex.

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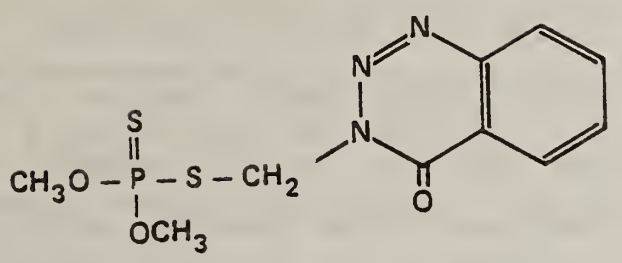
I. INTRODUCTION



Azinphosmethyl

Azinphosmethyl (CAS 86-50-0; NCI C00066) is a broad-spectrum, organophosphorus insecticide that was first produced in 1953 by Farbenfabriken Bayer AG and is used solely for agricultural purposes. In 1974, 3.1 million pounds were estimated to have been used in the United States on the following crops: alfalfa, cotton, deciduous fruits and nuts, tobacco, vegetables and some miscellaneous items (Ayers and Johnson, 1976). Azinphosmethyl is toxic both on contact and by ingestion (Cremlyn, 1974) and it has prolonged residual activity (Metcalf, 1965). The LD_{50}'s for azinphosmethyl have been reported to be 16.4 mg/kg in adult female Sprague-Dawley rats (Dubois et al., 1957), 4.0 mg/kg in adult male CF_1 mice and 8.7 mg/kg in adult female Holtzman rats

(Dubois and Kinoshita, 1968) by the oral route, and 24 mg/kg orally and 90 mg/kg percutaneously in adult female Charles River CD rats (Pasquet et al., 1976).

Azinphosmethyl is one of a series of pesticides selected for study in the Carcinogenesis Testing Program because it was produced in large quantities and the potential existed for long-term human exposure to the chemical during agricultural application or to residues of the chemical in food products.

II. MATERIALS AND METHODS

A. Chemical

Azinphosmethyl is the generic name for 0,0-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3-(4H)-yl)methyl]phosphorodithioate. It was obtained in a single batch for the chronic studies from Mobay Chemical Corp., Chemagro Agricultural Division, Kansas City, Missouri. The manufacturer's specification for this technical product (Guthion®) was 90% azinphosmethyl. Throughout the report the term azinphosmethyl is used to refer to the technical-grade material. Analyses at Gulf South Research Institute confirmed the identity of the chemical and were consistent with the manufacturer's specification (elemental analyses of C, H, N, P, S for $C_{10}H_{12}N_3O_3PS_2$; infrared, ultraviolet, and nuclear magnetic resonance spectra; thin-layer and gas-liquid chromatography). No attempt was made to identify or quantitate impurities.

The chemical was stored at 4°C in the original container.

B. Dietary Preparation

All test diets were formulated once per week using Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of azinphosmethyl 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, primarily as a dust suppressant, and the diets were mixed mechanically to assure homogeneity of the mixtures and evaporation of the acetone. Final diets, including those for the control groups of animals, contained corn oil equal to 2% of the final weight of feed. The diets were stored at approximately 17°C until used, but no longer than 1 week.

As a quality control test on the accuracy of preparation of the diets, the concentration of azinphosmethyl was determined in different batches of formulated diets during the chronic study. The results are summarized in Appendix G. At each dietary concentration, the mean of the analytical concentrations for the checked samples was within 2% of the theoretical concentration, and the coefficient of variation was never more than 6.4%. Thus, the evidence indicates that the formulated diets were prepared accurately.

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 8 days, mice for 14 days) and were then assigned to control or dosed groups.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 20-24°C and the relative humidity was maintained at 40-70%. The air in each room was changed 10-12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and water were available 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 per cage for females, and two or three 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® (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 for 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 receiving azinphosmethyl, along with their matched controls, were housed in a room by themselves. Mice fed azinphosmethyl were maintained in the same room as mice fed the following chemicals:

(CAS 61-82-5) amitrole
(CAS 76-44-8) heptachlor

Dosed mice were housed with their respective matched controls.

E. Subchronic Studies

Subchronic feeding studies were conducted with rats and mice to estimate maximum tolerated doses of azinphosmethyl, on the basis of which two concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration in the chronic studies. In these subchronic studies, azinphosmethyl was added to the animal feed in twofold increasing concentrations, ranging from 7.8 to 62.5 ppm for rats and from 7.8 to 125 for mice. Dosed and control groups each consisted of five males and of five females. The chemical was provided in feed to

dosed groups for 6 weeks, followed by 2 weeks of observation. Because there were no deaths and no effects on mean body weights in rats at 7.8 to 62.5 ppm or in female mice at 7.8 to 125 ppm, a second study was performed on rats and female mice using doses ranging from 62.5 to 1,000 ppm.

During the first weeks of the second study, depression of mean body weight was evident in the male rats administered 125 or 250 ppm and in the female rats administered 62.5 or 125 ppm. Later, these animals appeared to adapt, and mean body weight gains of dosed groups approached those of the controls; in the females, the mean body weight gains of dosed groups often surpassed those of the controls. There were no deaths at these concentrations; however, at concentrations of 500 ppm for males and 250 ppm for females, all animals were dead by week 2. The low and high doses for the chronic studies were set at 125 and 250 ppm for male rats and at 62.5 and 125 ppm for female rats.

In mice, males receiving 62.5 ppm initially lost weight, while males receiving 31.3 ppm gained weight. Female mice receiving 62.5 ppm or 125 ppm initially lost weight, but in later weeks the gain in mean body weight approached that of the controls. No deaths occurred in males at 31.3 or 62.5 ppm or in females at 62.5 or 125 ppm, but deaths occurred in males receiving 125 ppm and in females receiving 250 ppm. The low and high doses for the

chronic studies were set at 31.3 and 62.5 for male mice and at 62.5 and 125 ppm for female mice.

F. Designs of Chronic Studies

The designs of the chronic studies are shown in tables 1 and 2.

Since the numbers of animals in the matched-control groups were small, other control groups subject to study in this laboratory were used for additional statistical comparisons. For rats, matched controls from the current bioassay of azinphosmethyl were combined with matched controls from the bioassays of toxaphene (CAS 8001-35-2), lindane (CAS 58-89-9), captan (CAS 133-06-2), chloramben (CAS 133-90-4), picloram (CAS 1918-02-1), heptachlor (CAS 76-44-8), chlordane (CAS 57-74-9), dimethoate (CAS 60-51-5), parathion (CAS 56-38-2), and malathion (CAS 121-75-5). The pooled controls for statistical tests using rats consisted of 105 males and 105 females.

The pooled controls of mice were similarly combined. The controls from the bioassay of azinphosmethyl were combined with those from the bioassays of phosphamidon (CAS 13171-21-6), parathion, heptachlor, lindane, chlordane, dimethoate, tetrachlorvinphos (CAS 961-11-5), malathion, dieldrin (CAS 60-57-1), photodieldrin (CAS 13366-73-9), and captan, constituting a total of 140 males and 130 females.

Table 1. Design of Azinphosmethyl Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals[a]	Azinphosmethyl in Diet[b] (ppm)	Time on Study: Dosed[c] (weeks)	Time on Study: Observed[d] (weeks)	Time-Weighted Average Dose[e] (ppm)
Male					
Matched-Control	10	0		115	
Low-Dose	50	125	20		
		62.5	60		78
		0		34-35	
High-Dose	50	250	20		
		125	60		156
		0		34-35	
Female					
Matched-Control	10	0		115	
Low-Dose	50	62.5	80		
		0		34-35	
High-Dose	50	125	80		
		0		35	

[a]All animals were 35 days of age when placed on study.

[b]Doses of male rats were lowered at 20 weeks on study since, based on the pattern of mortality, changes in body weight, and the general condition of the animals used in similar studies of other chemicals at Gulf South Research Institute, it was believed that excessive mortality would occur before termination of the study.

[c]All animals were started on study on the same day.

[d]When diets containing azinphosmethyl were discontinued, dosed rats and their matched controls were fed control diets without corn oil for 7.5 weeks, then control diets (2% corn oil added) for an additional 27.5 weeks.

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

Table 2. Design of Azinphosmethyl Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals[a]	Azinphosmethyl in Diet (ppm)	Time on Study: Dosed[b] (weeks)	Time on Study: Observed[c] (weeks)
Male				
Matched-Control	10	0		92
Low-Dose	50	31.3	80	
		0		12
High-Dose	50	62.5	80	
		0		13
Female				
Matched-Control	10	0		92
Low-Dose	50	62.5	80	
		0		12
High-Dose	50	125	80	
		0		12

[a]All animals were 35 days of age when placed on study.

[b]All animals were started on study on the same day.

[c]When diets containing azinphosmethyl were discontinued, mice received the control diet until termination of the study.

The studies on the chemicals indicated above other than azinphosmethyl were also conducted at Gulf South Research Institute and were started no more that 3 months earlier or later than the controls of azinphosmethyl. The control animals that were used in the pooled-control groups were of the same strains (Osborne-Mendel rats and B6C3F1 mice) and from the same supplier; tissues from the pooled-control animals were diagnosed by several different pathologists.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, weighed at regular intervals, and palpated for masses at each weighing. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. 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. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. 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 died early. Also, some animals may have been missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. 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 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 relation-

ship. 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 ($P < 0.05$, 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 ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ 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 low- and high-dose male and high-dose female rats were lower than those of matched controls throughout the study, while mean body weights of low-dose females were essentially the same as those of the controls (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 wide variation.

After 1 week on study, two high-dose males and two high-dose females had generalized body tremors. At week 34, exophthalmos was observed in dosed animals, leading to unilateral blindness in 10 high-dose females and bilateral blindness in 5 high-dose females. This was diagnosed by the pathologist at the laboratory as viral conjunctivitis.

During the second year of the study, clinical signs including alopecia, rough and discolored hair coats, dyspnea, tachypnea, pale mucous membranes, hematuria, epistaxis, vaginal bleeding, and diarrhea were observed in both dosed and control rats.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of

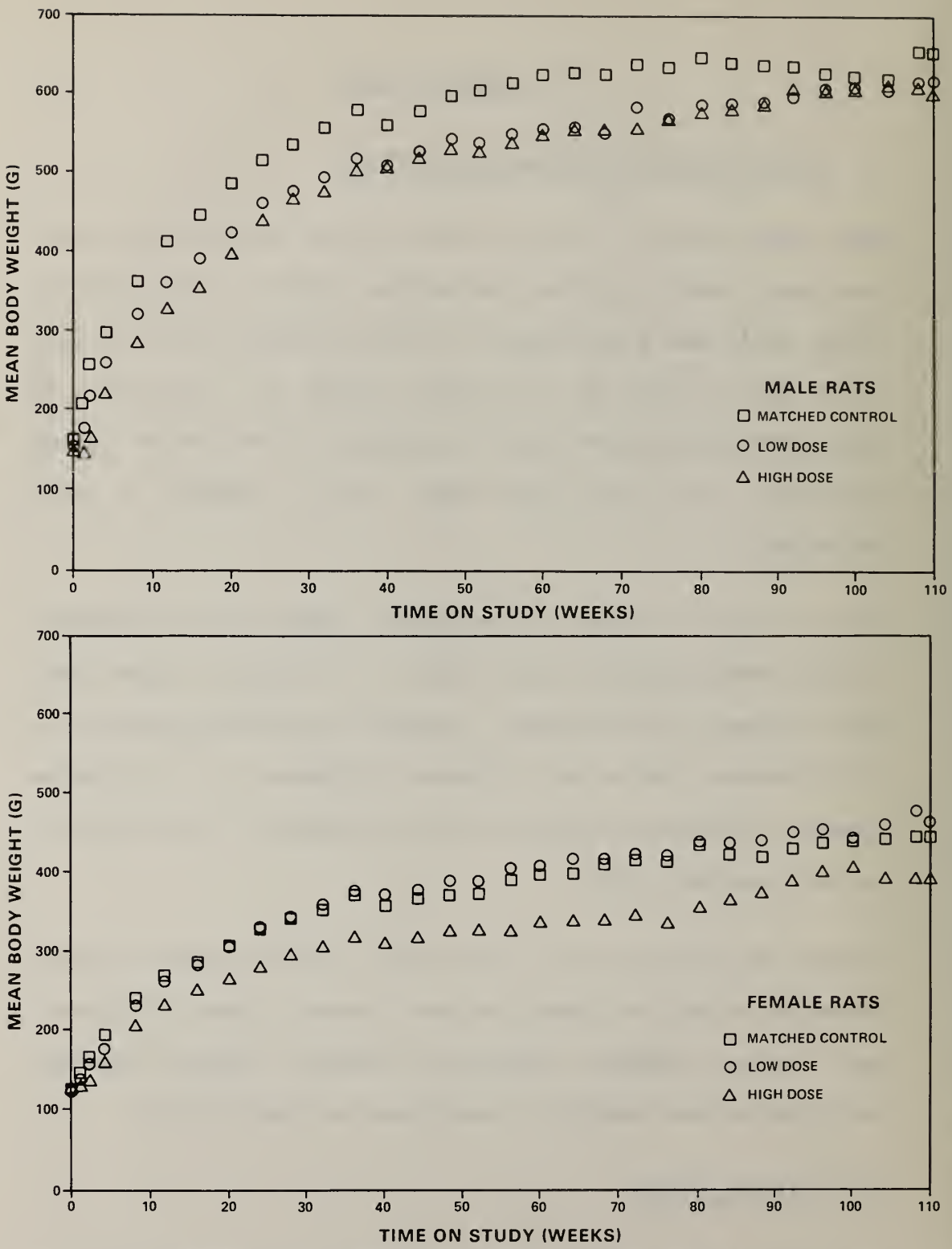


Figure 1. Growth Curves for Rats Fed Azinphosmethyl in the Diet

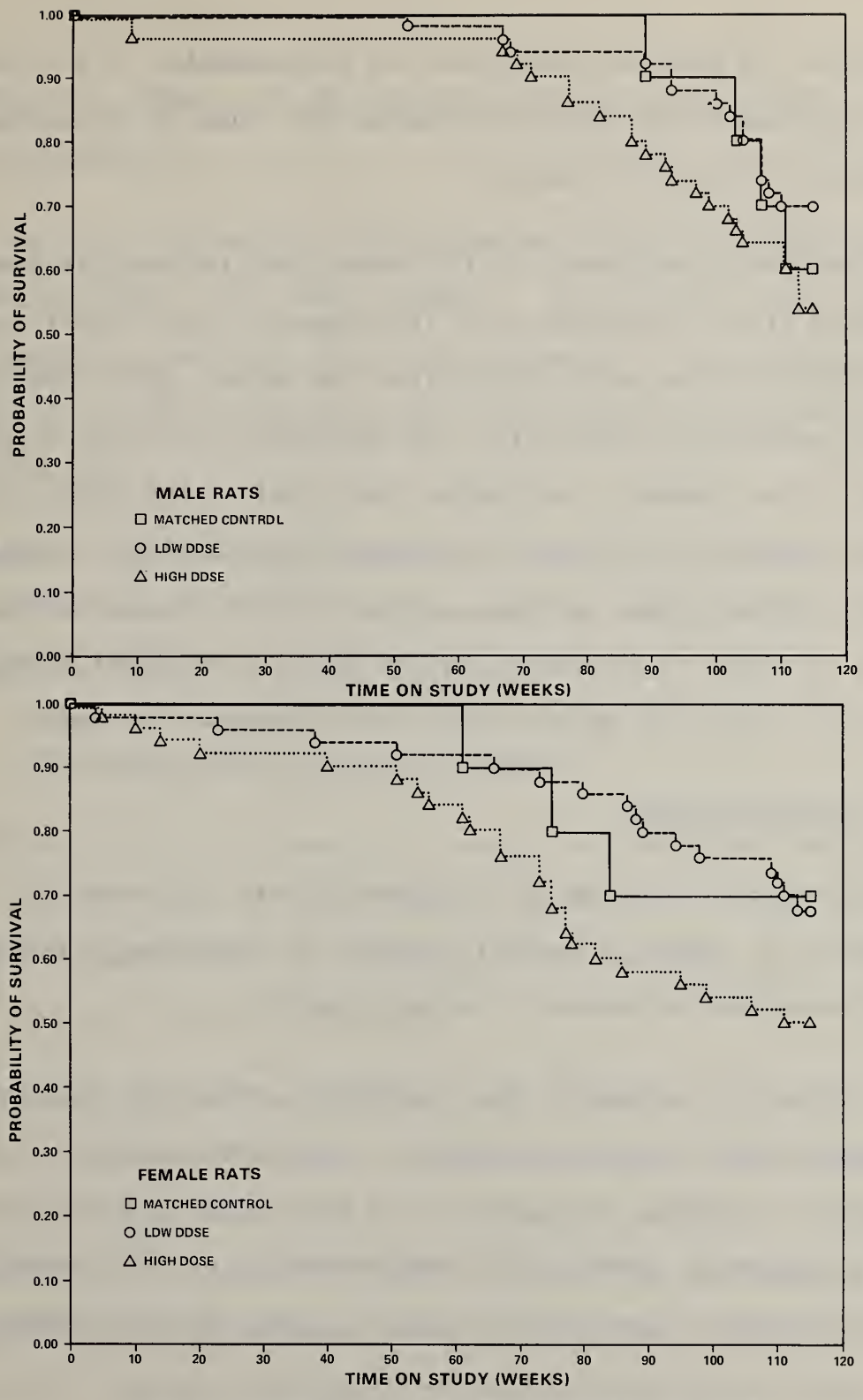


Figure 2. Survival Curves for Rats Fed Azinphosmethyl in the Diet

survival for male and female rats fed azinphosmethyl in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2.

In male rats, the result of the Tarone test for positive dose-related trend in mortality over the bioassay is not significant at the 0.05 level, with 6/10 (60%) of the control, 35/50 (70%) of the low-dose, and 27/50 (54%) of the high-dose rats living to the end of the bioassay. In females, the result of the Tarone test has a probability level of 0.041, with 7/10 (70%) of the control, 34/50 (68%) of the low-dose, and 25/50 (50%) of the high-dose rats surviving to termination of the study. Sufficient numbers of rats of each sex were at risk for the development of 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 are represented among the dosed and matched-control groups of animals. Neoplasms occurred in a variety of tissues, and each type has been encountered previously as a spontaneous lesion in the Osborne-Mendel rat. The incidence of neoplasms by type and site, and by group and sex of animal,

does not appear to be related to the administration of azinphosmethyl.

A variety of nonneoplastic responses were represented among both matched-control and dosed animals. Such lesions have been encountered previously and are considered to be spontaneous events, not unlike those commonly observed in aging Osborne-Mendel rats.

Based on the histologic examination, there was no evidence for the carcinogenicity of azinphosmethyl 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 in one group and with an incidence of at least 5% in one or more than one group.

In some instances, the matched-control group had incidences of tumors significantly higher ($P < 0.05$) than those in the pooled-control group, exclusive of the matched controls. These instances are indicated in tables E1 and E2 by the symbol "g" placed beside the incidence shown for the matched controls. This test was conducted assuming a binomial distribution of spontan-

eous tumors with the parameter given by the pooled controls excluding the matched controls of the subject chemical (Fears et al., 1977). In other instances, the matched controls were not statistically different from the pooled controls, but had a higher incidence or an incidence comparable to one or more of the dosed groups. When the incidence in the matched controls either is significantly higher than that in the pooled controls or is comparable to that in the dosed groups, the significance generated by the use of the pooled controls has been discounted in the analysis.

In male rats, the result of the Cochran-Armitage test for positive dose-related trend on the combined incidence of islet-cell adenomas or carcinomas of the pancreas is significant, using either the pooled ($P = 0.008$) or matched ($P = 0.033$) controls. The result of the Fisher exact test comparing the incidence in the high-dose group with that in the pooled controls was also significant ($P = 0.015$). Time-adjusted tests, eliminating animals that died before week 52 on study, were performed on the incidences of tumors of the pancreatic islet. The time-adjusted incidences (pooled controls 2/88 [2%], matched controls 0/9, low-dose 1/47 [2%], high-dose 6/44 [14%]) resulted in essentially the same statistics as described for the non-adjusted tests.

Since, however, the spontaneous incidence of this lesion varies in male Osborne-Mendel rats at this laboratory from 0% to 22%, with a mean of 2%, the incidence found in the high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

The Cochran-Armitage analyses of the combined incidence of adenocarcinomas or cortical adenomas of the adrenal in male rats show significant results ($P < 0.001$) when the pooled-control group is used. The result is not significant using the matched-control group. The result of the Fisher exact comparison of the incidence in the high-dose group with that in the pooled controls indicates a probability level of 0.001; however, the results of the Fisher exact test are not significant when the incidence in the matched-control group is compared with that in each dosed group. In the incidence of adenocarcinoma of the adrenal alone, the result of the Cochran-Armitage test is significant ($P = 0.015$) using the pooled-control group, but not so when the matched-control group is used. The Fisher exact test comparing the incidence in the high-dose group with that in the pooled-control group indicates a P value of 0.033, which is above the 0.25 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. Therefore,

statistically, the association of the tumors in the adrenal is not well established. No such tumor is observed in female rats.

In male rats, the results of statistical tests using the pooled-control animals on the incidences of benign thyroid tumors (follicular-cell adenomas, adenomas, or cystadenomas), malignant thyroid tumors (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas), or the combined follicular-cell tumors are all significant. In each analysis, the result of the Cochran-Armitage test is significant ($P \leq 0.008$) using the pooled controls, and the results of the Fisher exact comparisons of the incidences in any of the dosed groups with the pooled-control group show probability levels less than 0.025. The results of the Fisher exact test comparing the incidence in the matched-control group with that in each dosed group are not significant. Time-adjusted analyses, eliminating animals that died before week 52 on study, were performed on the incidences of thyroid tumors. The analysis of time-adjusted data of 7/82 (9%) in the pooled-control group, 1/9 (11%) in the matched-control group, 14/44 (32%) in the low-dose group, and 14/43 (33%) in the high-dose group resulted in essentially the same statistics as those of the non-adjusted analysis. Since, however, the spontaneous incidence of these neoplasms varies in male Osborne-Mendel rats at this laboratory from 0% to 43%, with a

mean of 7%, the incidences found in low-dose or high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

In females, the results of the statistical tests on the combined incidence of the malignant thyroid tumors (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas) are not significant. The incidence in the matched controls does not differ statistically from that in the pooled controls. When the benign thyroid tumors are combined with the malignant tumors, the result of the Cochran-Armitage test on the combined incidence in female rats, using the pooled controls, is significant ($P = 0.008$), and the results of the Fisher exact test show that the incidences in the dosed groups are significantly higher (low-dose $P = 0.002$; high-dose $P = 0.021$) than that in the pooled controls. However, the incidence of 2/9 (22%) in the matched controls, higher than that of either dosed group, makes the significance seen in the use of the pooled controls questionable. Although the results of the statistical tests of the combined incidence of cystadenomas and adenomas in the thyroid are significant, the incidence seen in the matched controls is comparable to those in the dosed groups.

When the the number of female rats with some type of pituitary tumor (chromophobe adenomas, adenocarcinomas, adenomas, or

cystadenomas) are analyzed, the results of the Cochran-Armitage test are not significant, and the Fisher exact comparison of incidences in the low-dose and pooled-control groups indicates a probability level of 0.040, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The incidence in the high-dose group is not significant.

In female rats, when hemangiomas and hemangiosarcomas are grouped for analysis, the results of the Cochran-Armitage test are not significant, but an indicated departure from linear trend is observed (P = 0.018), using the pooled controls, since the incidence in the low-dose group is greater than that in the high-dose group. The Fisher exact comparison of the incidences in the low-dose and pooled-control groups indicates a probability level of 0.036, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The incidence in the high-dose group is not significant. The incidence of these tumors in the male rats is not significant.

Some incidences at specific tumor sites indicate a higher incidence in the matched controls than in the pooled controls (marked "g" in the tables) or a comparable or higher incidence in the matched controls than in the dosed groups. Under these

circumstances, the significance generated by the use of the pooled controls is questionable. The tumors which are not said to be dose associated, because of these reasons, are the pituitary tumors, the parathyroid tumors, and hemangiomas or hemangiosarcomas in male rats; along with the liver tumors, cortical adenomas in the adrenal, fibroadenomas of the mammary gland, tumors of the uterus, and tumors of the pancreatic islet in female rats.

In summary, the statistical tests suggest that the incidences of thyroid and pancreatic islet-cell tumors in male rats are associated with administration of azinphosmethyl. None of the tumors in females could be associated with the test chemical.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the high-dose female mice were lower than those of the matched controls throughout most of the study, while mean body weights of the low-dose females and both the high- and low-dose males were essentially the same as those of the controls (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 wide variation.

During the first year on study, the dosed animals were generally comparable to the controls in appearance and behavior. At week 49, all dosed females appeared to be hyperactive.

During the second year of the study, clinical signs, including rough hair coats, alopecia, abdominal distention, and hyperactivity (in a few incidences hyperactivity alternated with hypoactivity), were noted in both dosed and control animals. Rough hair coats were observed in high-dose males beginning at week 60 and in low-dose males beginning at week 74. Convulsions in one high-dose female, in one high-dose male, and in one control male were periodically observed during the second year of the study.

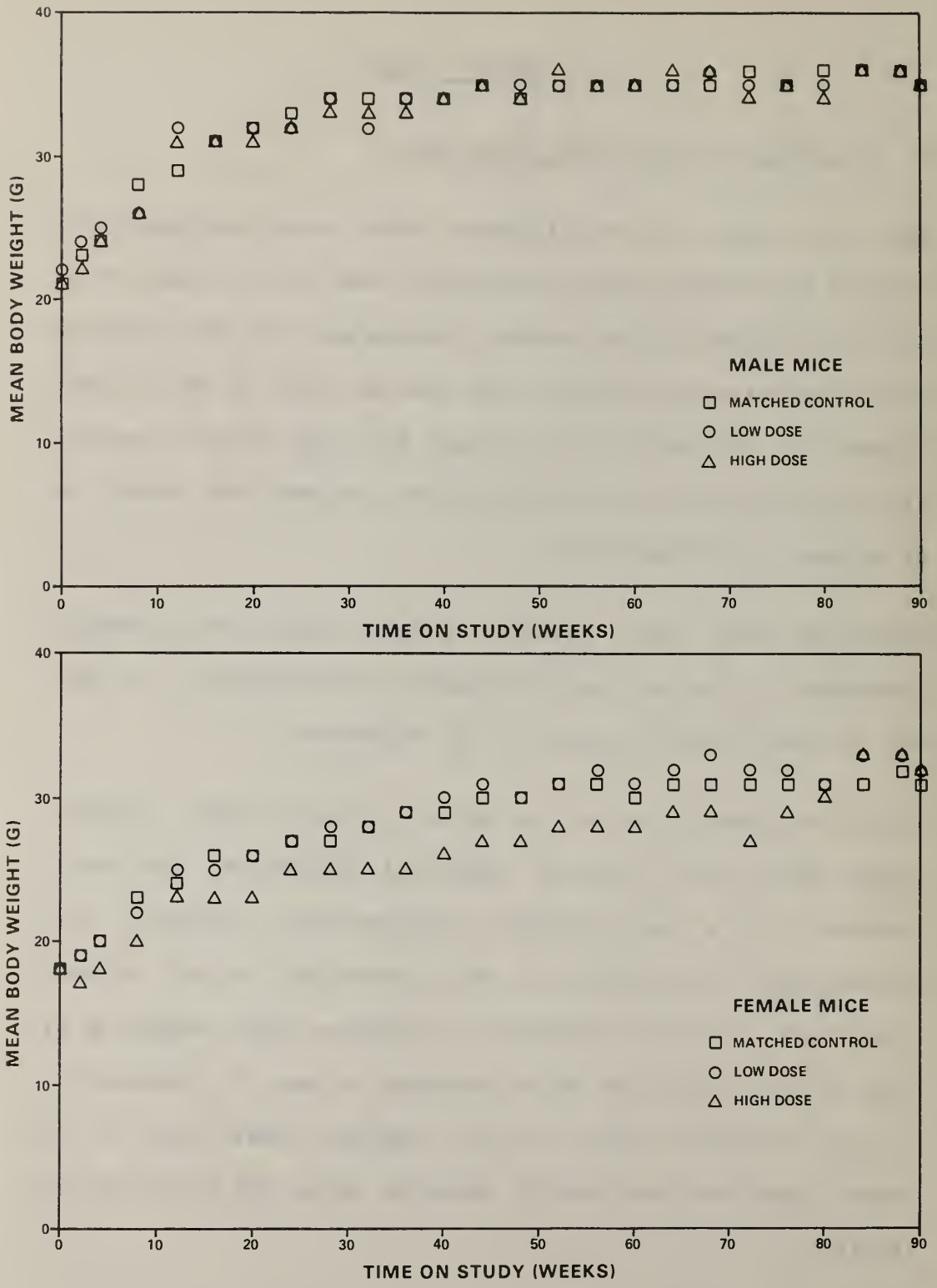


Figure 3. Growth Curves for Mice Fed Azinphosmethyl in the Diet

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed azinphosmethyl in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4.

The results of the Tarone test for positive dose-related trend in mortality over the bioassay are not significant at the 0.05 level in either sex. At least 74% of the male mice (controls 8/10 [80%], low-dose 45/50 [90%], high-dose 42/50 [84%]) and at least 70% of the female mice (controls 7/10 [70%], low-dose 44/50 [88%], high-dose 42/50 [84%]) lived to the end of the study. Sufficient numbers of dosed mice of each sex were at risk for the development of 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 are represented among the dosed and matched-control animals. Benign and malignant neoplasms occurred in a variety of tissues, and each type has been encountered previously as a spontaneous lesion in the B6C3F1 mouse. It is

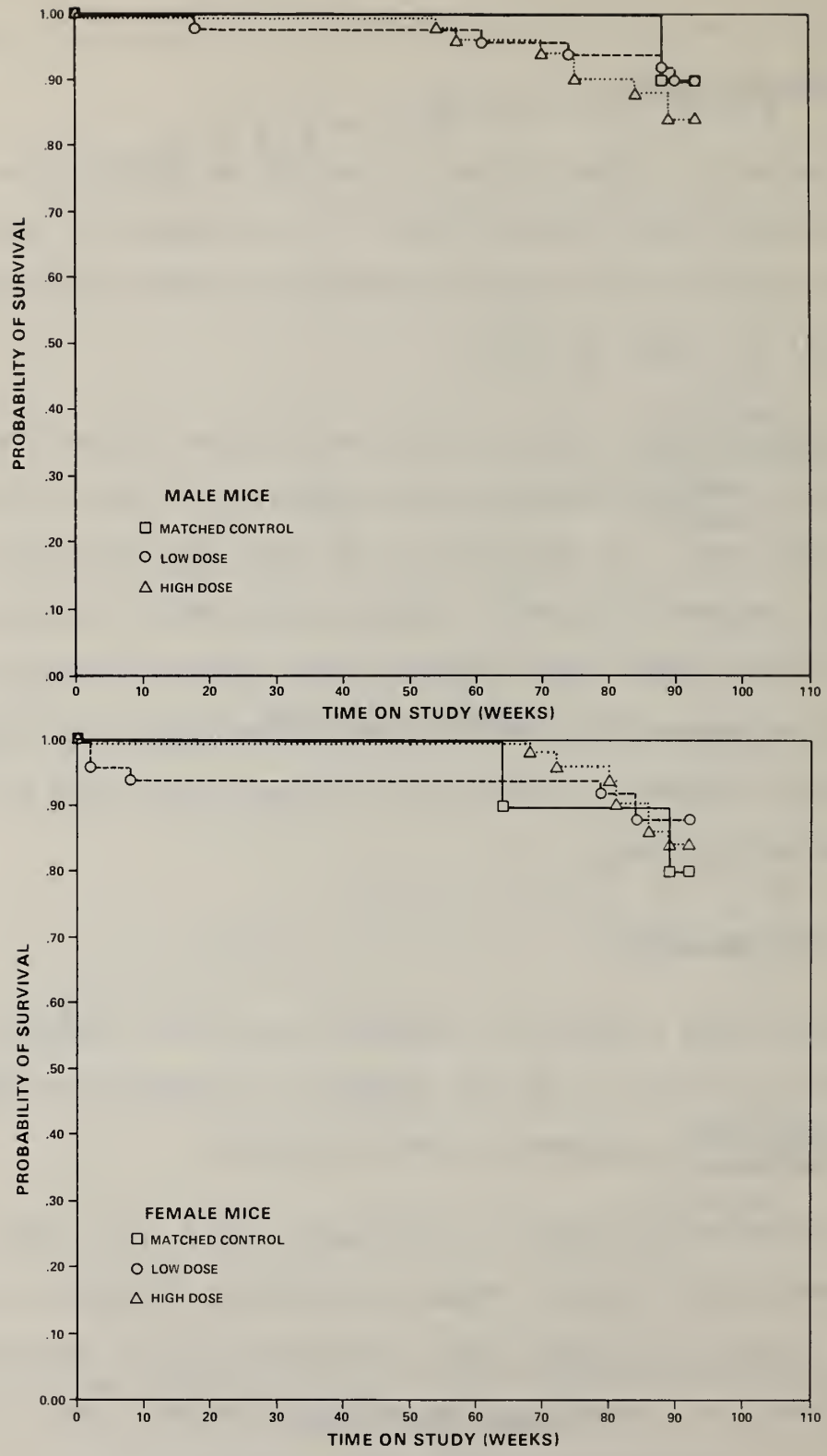


Figure 4. Survival Curves for Mice Fed Azinphosmethyl in the Diet

apparent that the incidence of neoplasms by type and site, and also by group and sex of animals, is without relationship; hence, it is unattributable to chemical exposure. The significance of hepatocellular carcinomas or adenomas in male mice is equivocal (controls 2/8 [25%], low-dose 11/49 [22%], high-dose 19/50 [38%]).

A variety of nonneoplastic responses are represented among both control and dosed animals. Such lesions have been encountered previously and are considered spontaneous events, not unlike those commonly observed in aging B6C3F1 mice. There was an apparent increase in the incidence of cystic endometrial hyperplasia in females (controls 2/7 [29%], low-dose 32/48 [67%], high-dose 32/48 [67%]). Endometrial stromal polyps occurred only in dosed females of the low-dose group (4%).

Based on the histologic examination, there was no evidence for the carcinogenicity of azinphosmethyl 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 in one group and with an incidence of at least 5% in one or more than one group.

In male mice, the incidence of hepatocellular carcinomas indicates a significant linear trend (P = 0.006) when the matched-control group is used in the Cochran-Armitage test, but none of the results of the Fisher exact test using either matched or pooled control groups have significance in the positive direction. When the numbers of male mice with hepatocellular adenomas or carcinomas or neoplastic nodules are tested, the results of the Cochran-Armitage test using the pooled-control group are significant (P = 0.048), but the Fisher exact comparison of incidences of the high-dose and pooled-control groups indicates a probability level of 0.040, which is above the 0.025 level required by the Bonferroni inequality criterion when multiple comparison is considered. The overall analysis is that the association of these tumors with the administration of the chemical is not established.

The incidence of hemangiosarcomas of all sites in male mice is significant when the incidence in the low-dose group (P = 0.020) is compared with that in the pooled controls; however, dose association is not apparent, because the results of the Cochran-Armitage test and the incidence in the high-dose group are not significant. The incidence of hemangiomas in the matched controls (1/10 [10%]) exceeds the incidence of hemangiomas or

hemangiosarcomas in either dosed group. Thus, the dose association of these tumors is questionable.

In female mice, there is no incidence of tumors with significant statistical results.

In summary, there is no conclusive statistical evidence of the association of tumors with the administration of azinphosmethyl in B6C3F1 mice of either sex.

V. DISCUSSION

In this bioassay, azinphosmethyl had a toxic effect on both rats and mice, as demonstrated by depressed mean body weights, clinical signs, and/or lower survival. High- and low-dose male rats, high-dose female rats, and high-dose female mice had lower mean body weights than their corresponding controls throughout the study. Typical signs of organophosphorus intoxication were present in a few animals of both species and included hyperactivity, tremors, and dyspnea. Convulsions in the mice may have been related to organophosphorus intoxication, although they were also seen in one control male mouse. In male rats and in both male and female mice, tests for dose-related trends in mortality over the bioassay were not significant at the 0.05 level. In female rats, 50% of the high-dose animals survived until the end of the bioassay, compared with 68% of the low-dose animals and 70% of the controls. Sufficient numbers of animals were at risk in each species for development of late-appearing tumors.

A great many tumors of the endocrine organs were observed in both dosed male and female rats but the small size of the matched control groups made interpretation difficult. Those of the adrenal in dosed males and females, the follicular cells of the thyroid in dosed males and females, the anterior pituitary in dosed males, and the parathyroid in dosed males occurred at

statistically significant incidences when compared with pooled controls, but not with matched controls. Since the pathologist examining the dosed and matched-control animals did not examine the pooled controls, and since the incidences of the pituitary and parathyroid in males, and of the thyroid in females were significantly higher in the matched controls than in the pooled controls, these neoplasms cannot be clearly related to administration of azinphosmethyl. The incidence of adenocarcinoma of the pituitary in female rats cannot be clearly associated with administration of the test chemical, since the dose-related trend and the incidence of tumors in the high-dose group were not significant; also, the combined benign and malignant tumors of the pituitary occurred at a lower level of significance than the adenocarcinoma alone. Although the incidence of tumors of the liver showed a dose-related trend in the male rats, the incidences in the dosed groups were not significantly higher than those in the controls, and these tumors cannot, therefore, be clearly related to administration of the test chemical.

In male rats, islet-cell adenomas or carcinomas of the pancreas occurred at a significant incidence ($P = 0.015$) in the high-dose male rats when compared with pooled controls (pooled controls 2/92, matched controls 0/9, low-dose 1/47, high-dose 6/45), and

the incidences showed a dose-related trend ($P = 0.008$), using the pooled controls. Two of the high-dose males had carcinomas, while the remaining four had adenomas. Since, however, the spontaneous incidence of this lesion varies in male Osborne-Mendel rats at this laboratory from 0% to 22%, with a mean of 2%, the incidence found in the high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

Follicular-cell tumors of the thyroid, either benign (adenomas, follicular-cell adenomas, or cystadenomas), malignant (adenocarcinomas, cystadenocarcinomas, or papillary cystadenocarcinomas), or combined benign and malignant occurred at significant incidences in dosed male rats when compared with pooled controls; the combined tumors occurred at significant incidences ($P = 0.001$) in both low- and high-dose groups when compared with pooled controls (pooled controls 7/86, matched controls 1/9, low-dose 14/44, high-dose 14/43), and the incidences showed a dose-related trend ($P < 0.001$), using the pooled controls. Since, however, the spontaneous incidence of these neoplasms varies in male Osborne-Mendel rats at this laboratory from 0% to 43%, with a mean of 7%, the incidences found in low-dose or high-dose male rats in this study can not be clearly implicated as a chemically induced effect.

In mice, hepatocellular adenomas or carcinomas occurred at a significant incidence (P = 0.040) in the high-dose male mice when compared with pooled controls (pooled controls 30/128, matched controls 2/8, low-dose 11/49, high-dose 19/50), and the incidences showed a dose-related trend (P = 0.048). Hepatocellular adenomas and carcinomas were diagnosed among the dosed and matched-control groups, and neoplastic nodules of the liver were diagnosed in addition in animals of the pooled-control group. The probability level of the liver tumors in the high-dose group is above that required for significance using the Bonferroni inequality criterion for multiple comparisons, and similar high incidences have been noted in other groups of controls at the same laboratory; thus, these liver tumors in male mice are not considered to be related to administration of the test chemical.

Azinphosmethyl is an organophosphorus chemical with a primary biological action of inhibiting acetylcholinesterase. This activity was very low when serum, homogenized brain, or submaxillary gland were tested in vitro; however, the chemical is rapidly oxidized in vivo to the active chemical (DuBois et al., 1957). In a 2-year feeding study using Wistar rats, there was no indication that administration of the chemical at concentrations up to 50-100 ppm induced tumors (Worden et al., 1973). This

concentration was comparable to that fed to the low-dose rats in the present study.

It is concluded that under the conditions of this bioassay, neoplasms of the thyroid and pancreatic islets suggest but do not provide sufficient evidence for carcinogenicity of azinphosmethyl in male Osborne-Mendel rats. Azinphosmethyl was not shown to be carcinogenic in female Osborne-Mendel rats or in B6C3F1 mice of either sex.

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APPENDIX A

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

TABLE A1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (2%)	
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(10)	(50)	(49)
LIPOSARCOMA	1 (10%)		
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*SKIN	(10)	(50)	(49)
MAST-CELL SARCOMA			1 (2%)
#BONE MARROW	(10)	(49)	(46)
LYMPHOMA METASTATIC		1 (2%)	
#SPLEEN	(9)	(49)	(47)
LEIOMYOMA		1 (2%)	
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA	2 (22%)		4 (9%)
MALIGNANT LYMPHOMA, NOS		2 (4%)	1 (2%)
#LYMPH NODE	(8)	(49)	(44)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
*SKELETAL MUSCLE	(10)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (10%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LUNG	(10)	(49)	(48)
LYMPHOMA METASTATIC			1 (2%)
#HEART	(10)	(48)	(47)
LYMPHOMA METASTATIC			1 (2%)
#LIVER	(9)	(49)	(46)
LYMPHOMA METASTATIC		1 (2%)	1 (2%)
#PANCREAS	(9)	(47)	(45)
LYMPHOMA METASTATIC		1 (2%)	
#ADRENAL	(9)	(45)	(46)
LYMPHOMA METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(10)	(48)	(47)
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(9)	(49)	(46)
ADENOMA, NOS		1 (2%)	
HEPATOCELLULAR ADENOMA	1 (11%)	3 (6%)	5 (11%)
#PANCREAS	(9)	(47)	(45)
ACINAR-CELL ADENOMA		1 (2%)	
LIPOSARCOMA, METASTATIC		1 (2%)	
#STOMACH	(9)	(47)	(47)
LEIOMYOSARCOMA			1 (2%)
#SMALL INTESTINE	(9)	(47)	(48)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
URINARY SYSTEM			
#KIDNEY	(10)	(49)	(47)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
LIPOSARCOMA		2 (4%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(46)	(43)
ADENOMA, NOS			3 (7%)
CHROMOPHOBE ADENOMA	4 (44%)	21 (46%)	13 (30%)
CHROMOPHOBE CARCINOMA			2 (5%)
CYSTADENOMA, NOS			2 (5%)
#ADRENAL	(9)	(45)	(46)
ADENOCARCINOMA, NOS		1 (2%)	3 (7%)
CORTICAL ADENOMA	1 (11%)	3 (7%)	7 (15%)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(9)	(44)	(43)
ADENOMA, NOS		2 (5%)	2 (5%)
ADENOCARCINOMA, NOS		3 (7%)	3 (7%)
FOLLICULAR-CELL ADENOMA	1 (11%)	1 (2%)	
CYSTADENOMA, NOS		7 (16%)	10 (23%)
CYSTADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)
#PARATHYROID	(5)	(26)	(24)
ADENOMA, NOS	1 (20%)		4 (17%)
#PANCREATIC ISLETS	(9)	(47)	(45)
ISLET-CELL ADENOMA		1 (2%)	4 (9%)
ISLET-CELL CARCINOMA			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(49)
CYSTADENOCARCINOMA, NOS			1 (2%)
FIBROMA			2 (4%)
CYSTIFIBROADENOMA	1 (10%)		
#PROSTATE	(10)	(47)	(45)
PAPILLARY ADENOMA		1 (2%)	
#TESTIS	(10)	(49)	(48)
INTERSTITIAL-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(10)	(49)	(48)
GLIOBLASTOMA MULTIFORME		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*RIB	(10)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)
*SKELETAL MUSCLE	(10)	(50)	(49)
RHABDOMYOSARCOMA		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(10)	(50)	(49)
HEMANGIOMA			1 (2%)
*PARIETAL PERITONEUM	(10)	(50)	(49)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
*TUNICA VAGINALIS	(10)	(50)	(49)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(10)	(50)	(49)
LIPOSARCOMA, METASTATIC	1 (10%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	2	4	9
MORIBUND SACRIFICE	2	11	14
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	6	35	27
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*	7	40	41
TOTAL PRIMARY TUMORS	13	61	76
TOTAL ANIMALS WITH BENIGN TUMORS	6	32	33
TOTAL BENIGN TUMORS	8	45	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	15	15
TOTAL MALIGNANT TUMORS	4	15	21
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3	3
TOTAL SECONDARY TUMORS	1	5	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	
TOTAL UNCERTAIN TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	@49	50
ANIMALS NECROPSIED	10	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	48	46
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(49)	(49)
KERATOACANTHOMA			1 (2%)
LIPOSARCOMA	1 (10%)		
RESPIRATORY SYSTEM			
#LUNG	(9)	(48)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(9)	(43)	(41)
HEMANGIOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(9)	(47)	(45)
ADENOCARCINOMA, NOS			1 (2%)
HEPATOCELLULAR ADENOMA	2 (22%)	2 (4%)	4 (9%)
HEPATOCELLULAR CARCINOMA			1 (2%)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
#STOMACH	(9)	(46)	(44)
HEMANGIOSARCOMA		1 (2%)	

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

@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT 1 ANIMAL WAS FOUND TO BE A MALE ANIMAL IN A FEMALE GROUP.

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(9)	(48)	(45)
MULTIPLE POLYPOSIS	1 (11%)		
ENDOCRINE SYSTEM			
#PITUITARY	(8)	(44)	(41)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS		8 (18%)	1 (2%)
CHROMOPHOBE ADENOMA	2 (25%)	14 (32%)	12 (29%)
CYSTADENOMA, NOS			1 (2%)
#ADRENAL	(9)	(45)	(41)
CORTICAL ADENOMA	1 (11%)	4 (9%)	8 (20%)
PHEOCHROMOCYTOMA			2 (5%)
#THYROID	(9)	(45)	(38)
ADENOMA, NOS	1 (11%)	2 (4%)	1 (3%)
ADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY ADENOCARCINOMA			1 (3%)
CYSTADENOMA, NOS		4 (9%)	3 (8%)
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (11%)	1 (2%)	1 (3%)
#PARATHYROID	(7)	(31)	(19)
ADENOMA, NOS			1 (5%)
#PANCREATIC ISLETS	(7)	(41)	(39)
ISLET-CELL ADENOMA	2 (29%)	1 (2%)	1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(49)	(49)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS		2 (4%)	
CYSTADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)
LIPOMA		1 (2%)	
LEIOMYOSARCOMA		1 (2%)	
FIBROADENOMA	2 (20%)	9 (18%)	9 (18%)
#UTERUS	(9)	(43)	(41)
ENDOMETRIAL STROMAL POLYP	1 (11%)	3 (7%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOMA		1 (2%)	
#OVARY	(9)	(47)	(42)
ADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY ADENOCARCINOMA		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	1	5	9
MORIBUND SACRIFICE	2	10	16
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	7	34	25
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*	7	37	26
TOTAL PRIMARY TUMORS	14	62	51
TOTAL ANIMALS WITH BENIGN TUMORS	7	32	24
TOTAL BENIGN TUMORS	12	44	45
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	13	6
TOTAL MALIGNANT TUMORS	2	18	6
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

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

TABLE B1

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(50)
FIBROSARCOMA			1 (2%)
LEIOMYOSARCOMA		1 (2%)	
*SUBCUT TISSUE	(10)	(50)	(50)
FIBROSARCOMA			1 (2%)
LEIOMYOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (10%)	6 (12%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (10%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(10)	(49)	(50)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
#SPLEEN	(8)	(46)	(46)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#LYMPH NODE	(9)	(46)	(46)
HEMANGIOMA	1 (11%)		
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(9)	(46)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(8)	(49)	(50)
HEPATOCELLULAR ADENOMA	2 (25%)	8 (16%)	7 (14%)
HEPATOCELLULAR CARCINOMA		3 (6%)	12 (24%)
HEMANGIOSARCOMA		2 (4%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(10)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS	1 (10%)		
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	1	1
MORIBUND SACRIFICE	1	4	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	45	42
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	23	23
TOTAL PRIMARY TUMORS	6	26	28
TOTAL ANIMALS WITH BENIGN TUMORS	4	16	10
TOTAL BENIGN TUMORS	5	16	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	8	15
TOTAL MALIGNANT TUMORS	1	10	17
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10.	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(10)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	3 (6%)
PAPILLARY CYSTADENOCARCINOMA,MET	1 (10%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (10%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
LYMPHOMA LYMPHOCYTIC METASTATIC			1 (2%)
MALIG.LYMPHOMA HISTIO-TYPE METAS		1 (2%)	
GRANULOCYTIC LEUKEMIA			1 (2%)
*SUBCUT TISSUE	(10)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
*MAMMARY GLAND	(10)	(50)	(50)
LYMPHOMA METASTATIC			1 (2%)
#BONE MARROW	(10)	(47)	(50)
LYMPHOMA METASTATIC	1 (10%)		
#SPLEEN	(9)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, NOS	1 (11%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
#LYMPH NODE	(9)	(40)	(45)
MALIGNANT LYMPHOMA, NOS		1 (3%)	2 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
LYMPHOMA METASTATIC	1 (11%)		
LYMPHOMA LYMPHOCYTIC METASTATIC			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
#LUNG	(10)	(50)	(50)
LYMPHOMA METASTATIC	1 (10%)		1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#LIVER	(10)	(49)	(50)
LYMPHOMA METASTATIC	1 (10%)		1 (2%)
LYMPHOMA LYMPHOCYTIC METASTATIC			1 (2%)
#SMALL INTESTINE	(10)	(48)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (10%)		
LYMPHOMA LYMPHOCYTIC METASTATIC			1 (2%)
#KIDNEY	(10)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA HISTIO-TYPE METAS		1 (2%)	
#KIDNEY/CORTEX	(10)	(49)	(50)
LYMPHOMA METASTATIC	1 (10%)		
#ADRENAL	(10)	(47)	(49)
LYMPHOMA METASTATIC	1 (10%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND CAPSU	(10)	(49)	(49)
HEMANGIOMA		1 (2%)	
#LIVER	(10)	(49)	(50)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA	1 (10%)		
URINARY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(7)	(39)	(40)
CHROMOPHOBE ADENOMA		1 (3%)	
#THYROID	(9)	(42)	(46)
CYSTADENCMA, NOS	1 (11%)		
PAPILLARY CYSTADENOMA, NOS			1 (2%)
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (11%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(50)
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)
FIBRCADENOMA			1 (2%)
#UTERUS	(7)	(48)	(48)
LEICMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		2 (4%)	
#CERVIX UTERI	(7)	(48)	(48)
LEICMYOSARCOMA		1 (2%)	
#OVARY	(9)	(47)	(41)
GRANULOSA-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NCNE			
SPECIAL SENSE CRGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PELVIS	(10)	(50)	(50)
LIPCSARCOMA			1 (2%)

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			
*MULTIPLE ORGANS	(10)	(50)	(50)
LIPOSARCOMA, METASTATIC			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		3	2
MORIBUND SACRIFICE	3	3	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	7	44	42
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	10	17
TOTAL PRIMARY TUMORS	6	13	19
TOTAL ANIMALS WITH BENIGN TUMORS	1	5	6
TOTAL BENIGN TUMORS	1	5	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	7	11
TOTAL MALIGNANT TUMORS	5	8	12
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	2	4
TOTAL SECONDARY TUMORS	7	2	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED AZINPHOSMETHYL IN THE DIET

TABLE C1

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(10)	(50)	(49)
ULCER, CHRONIC	2 (20%)		
*SUBCUT TISSUE	(10)	(50)	(49)
FIBROSIS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(48)
CONGESTION, NOS	1 (10%)	3 (6%)	7 (15%)
EDEMA, NOS	1 (10%)	1 (2%)	1 (2%)
HEMORRHAGE		2 (4%)	1 (2%)
INFLAMMATION, NOS	3 (30%)	12 (24%)	9 (19%)
INFLAMMATION, FOCAL	1 (10%)		2 (4%)
#LUNG/ALVEOLI	(10)	(49)	(48)
MINERALIZATION			1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(10)	(49)	(46)
CONGESTION, NOS			2 (4%)
EDEMA, NOS			1 (2%)
HEMORRHAGE			1 (2%)
HYPERPLASIA, HEMATOPOIETIC	1 (10%)		6 (13%)
HYPOPLASIA, HEMATOPOIETIC			2 (4%)
APLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(9)	(49)	(47)
CONGESTION, NOS		3 (6%)	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
HEMORRHAGE		1 (2%)	
MYELOID METAPLASIA		1 (2%)	6 (13%)
#LYMPH NODE	(8)	(49)	(44)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
PLASMA-CELL INFILTRATE		1 (2%)	
PLASMACYTOSIS	2 (25%)		
HYPERPLASIA, RETICULUM CELL	1 (13%)	2 (4%)	1 (2%)
HYPERPLASIA, LYMPHOID		8 (16%)	
CIRCULATORY SYSTEM			
#HEART	(10)	(48)	(47)
FIBROSIS, DIFFUSE	2 (20%)	2 (4%)	9 (19%)
#APEX OF HEART	(10)	(48)	(47)
FIBROSIS, DIFFUSE			1 (2%)
#HEART/VENTRICLE	(10)	(48)	(47)
FIBROSIS, DIFFUSE	1 (10%)	1 (2%)	5 (11%)
#MYOCARDIUM	(10)	(48)	(47)
FIBROSIS		5 (10%)	
FIBROSIS, DIFFUSE		2 (4%)	
#ENDOCARDIUM	(10)	(48)	(47)
FIBROSIS	1 (10%)		
*AORTA	(10)	(50)	(49)
MEDIAL CALCIFICATION	1 (10%)		1 (2%)
*PULMONARY ARTERY	(10)	(50)	(49)
MINERALIZATION			1 (2%)
HYPERPLASIA, NOS			1 (2%)
*MESENTERIC ARTERY	(10)	(50)	(49)
THROMBOSIS, NOS			3 (6%)
INFLAMMATION, CHRONIC			1 (2%)
PERIARTERITIS		1 (2%)	3 (6%)
MEDIAL CALCIFICATION			1 (2%)
*TESTICULAR ARTERY	(10)	(50)	(49)
PERIARTERITIS			1 (2%)
#HEPATIC SINUSOID	(9)	(49)	(46)
CONGESTION, NOS			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
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(10)	(48)	(47)
INFLAMMATION, CHRONIC			1 (2%)
ATROPHY, NOS			1 (2%)
#LIVER	(9)	(49)	(46)
CONGESTION, NOS	1 (11%)	3 (6%)	5 (11%)
NECROSIS, FOCAL			2 (4%)
METAMORPHOSIS FATTY	1 (11%)	1 (2%)	2 (4%)
CYTOPLASMIC CHANGE, NOS			3 (7%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
HYPERTROPHY, NOS	1 (11%)	5 (10%)	5 (11%)
HYPERTROPHY, FOCAL		8 (16%)	2 (4%)
HYPERPLASIA, NOS		3 (6%)	2 (4%)
HYPERPLASIA, FOCAL		5 (10%)	
ANGIECTASIS	1 (11%)	6 (12%)	9 (20%)
HEMATOPOIESIS			1 (2%)
#HEPATIC CAPSULE	(9)	(49)	(46)
CONGESTION, NOS	2 (22%)	7 (14%)	6 (13%)
ANGIECTASIS		5 (10%)	1 (2%)
#LIVER/PERIPORTAL	(9)	(49)	(46)
METAMORPHOSIS FATTY	1 (11%)		
CYTOPLASMIC CHANGE, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION		2 (4%)	
*BILE DUCT	(10)	(50)	(49)
INFLAMMATION, FOCAL			1 (2%)
HYPERPLASIA, NOS	4 (40%)	9 (18%)	3 (6%)
#PANCREAS	(9)	(47)	(45)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC NECROTIZIN			1 (2%)
FIBROSIS, DIFFUSE	1 (11%)	1 (2%)	4 (9%)
PERIARTERITIS		2 (4%)	1 (2%)
#PANCREATIC DUCT	(9)	(47)	(45)
HYPERPLASIA, NOS	1 (11%)	2 (4%)	5 (11%)
#PANCREATIC ACINUS	(9)	(47)	(45)
ATROPHY, NOS	1 (11%)	2 (4%)	3 (7%)
#STOMACH	(9)	(47)	(47)
INFLAMMATION, ACUTE			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
ULCER, ACUTE		2 (4%)	1 (2%)
#GASTRIC MUCOSA	(9)	(47)	(47)
MINERALIZATION			1 (2%)
CYST, NOS	1 (11%)		
#DUODENUM	(9)	(47)	(48)
ULCER, ACUTE			1 (2%)
#COLONIC SUBMUCOSA	(5)	(24)	(39)
HYPERPLASIA, LYMPHOID		1 (4%)	
URINARY SYSTEM			
#KIDNEY	(10)	(49)	(47)
MINERALIZATION	2 (20%)		2 (4%)
HYDRONEPHROSIS		1 (2%)	2 (4%)
CONGESTION, NOS			1 (2%)
INFLAMMATION, CHRONIC	4 (40%)	38 (78%)	32 (68%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
INFLAMMATION CHRONIC CYSTIC			1 (2%)
#KIDNEY/CORTEX	(10)	(49)	(47)
CYST, NOS			1 (2%)
#KIDNEY/MEDULLA	(10)	(49)	(47)
HYPERPLASIA, EPITHELIAL	1 (10%)		
#URINARY BLADDER	(9)	(49)	(44)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE HEMORRHAGIC		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(46)	(43)
CYST, NOS	1 (11%)	7 (15%)	10 (23%)
MULTILOCULAR CYST		1 (2%)	
MULTIPLE CYSTS	3 (33%)	1 (2%)	4 (9%)
HEMORRHAGIC CYST		1 (2%)	1 (2%)
#ADRENAL	(9)	(45)	(46)
HEMORRHAGIC CYST		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
ANGIECTASIS		1 (2%)	1 (2%)
#ADRENAL CORTEX	(9)	(45)	(46)
LIPCIDOSIS	2 (22%)	31 (69%)	23 (50%)
HYPERTROPHY, NOS		1 (2%)	
ANGIECTASIS			1 (2%)
#THYROID	(9)	(44)	(43)
CYST, NOS	1 (11%)		4 (9%)
FCLLICULAR CYST, NOS		3 (7%)	
HYPERPLASIA, NOS	1 (11%)	1 (2%)	
#PARATHYROID	(5)	(26)	(24)
HYPERPLASIA, NOS	2 (40%)	6 (23%)	3 (13%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(10)	(47)	(45)
INFLAMMATION, ACUTE		5 (11%)	2 (4%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE HEMORRHAGIC		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	2 (20%)		2 (4%)
INFLAMMATION, CHRONIC	1 (10%)	9 (19%)	3 (7%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	1 (2%)
FIBROSIS, DIFFUSE			2 (4%)
PERIARTERITIS			1 (2%)
HYPERPLASIA, NOS	1 (10%)		1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#TESTIS	(10)	(49)	(48)
EDEMA, NOS	2 (20%)		4 (8%)
PERIARTERITIS	1 (10%)	3 (6%)	2 (4%)
ATROPHY, NOS	2 (20%)	11 (22%)	16 (33%)
ATROPHY, FOCAL	3 (30%)	9 (18%)	14 (29%)
ASPERMATOGENESIS		1 (2%)	2 (4%)
#TESTIS/TUBULE	(10)	(49)	(48)
DEGENERATION, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(10)	(49)	(48)
INFLAMMATION, NOS		1 (2%)	
#BRAIN	(10)	(49)	(48)
HEMORRHAGE		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
ATROPHY, NOS		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(10)	(50)	(49)
OSTEOPOROSIS	1 (10%)		1 (2%)
*SKULL	(10)	(50)	(49)
EXOSTOSIS	1 (10%)		
BODY CAVITIES			
*MESENTERY	(10)	(50)	(49)
PERIARTERITIS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED		1	
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 AZINPHOSMETHYL IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	@49	50
ANIMALS NECROPSIED	10	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	48	46
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(10)	(49)	(49)
HEMATOMA, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(9)	(48)	(46)
CONGESTION, NOS		4 (8%)	7 (15%)
EDEMA, NOS			2 (4%)
INFLAMMATION, NOS	7 (78%)	16 (33%)	21 (46%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(9)	(46)	(40)
CONGESTION, NOS		1 (2%)	2 (5%)
HEMORRHAGE		1 (2%)	1 (3%)
HYPOPLASIA, NOS		1 (2%)	1 (3%)
#SPLEEN	(9)	(43)	(41)
ATROPHY, NOS			1 (2%)
MYELOID METAPLASIA	1 (11%)	1 (2%)	1 (2%)
#LYMPH NODE	(9)	(44)	(40)
HYPERPLASIA, RETICULUM CELL		2 (5%)	1 (3%)
HYPERPLASIA, LYMPHOID	1 (11%)	3 (7%)	1 (3%)
CIRCULATORY SYSTEM			
#HEART	(9)	(48)	(46)
FIBROSIS, DIFFUSE	2 (22%)		1 (2%)
#MYOCARDIUM	(9)	(48)	(46)
FIBROSIS, DIFFUSE			1 (2%)

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

@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT 1 ANIMAL WAS FOUND TO BE A MALE ANIMAL IN A FEMALE GROUP.

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(9)	(46)	(45)
CYST, NOS		1 (2%)	
#LIVER	(9)	(47)	(45)
CONGESTION, NOS	1 (11%)	7 (15%)	4 (9%)
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	2 (4%)
HYPERTROPHY, NOS		6 (13%)	3 (7%)
HYPERTROPHY, FOCAL	1 (11%)		1 (2%)
ANGIECTASIS	2 (22%)	2 (4%)	1 (2%)
#HEPATIC CAPSULE	(9)	(47)	(45)
CONGESTION, NOS	2 (22%)	6 (13%)	7 (16%)
#LIVER/PERIPORTAL	(9)	(47)	(45)
METAMORPHOSIS FATTY	1 (11%)	4 (9%)	4 (9%)
*BILE DUCT	(10)	(49)	(49)
CYST, NOS			2 (4%)
HYPERPLASIA, NOS	4 (40%)	10 (20%)	2 (4%)
#PANCREAS	(7)	(41)	(39)
FIBROSIS		1 (2%)	
FIBROSIS, DIFFUSE		1 (2%)	1 (3%)
ATROPHY, NOS		1 (2%)	
#PANCREATIC DUCT	(7)	(41)	(39)
HYPERPLASIA, NOS		3 (7%)	1 (3%)
#PANCREATIC ACINUS	(7)	(41)	(39)
ATROPHY, NOS		3 (7%)	1 (3%)
#STOMACH	(9)	(46)	(44)
INFLAMMATION, ACUTE			1 (2%)
ULCER, ACUTE			1 (2%)
#DUODENUM	(9)	(41)	(42)
ULCER, ACUTE		1 (2%)	
#COLONIC SUBMUCOSA	(4)	(28)	(31)
HYPERPLASIA, LYMPHOID		1 (4%)	
URINARY SYSTEM			
#KIDNEY	(9)	(48)	(45)
MINERALIZATION	3 (33%)	10 (21%)	9 (20%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYDRONEPHROSIS	1 (11%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		14 (29%)	9 (20%)
CALCIFICATION, DYSTROPHIC			1 (2%)
#KIDNEY/CORTEX	(9)	(48)	(45)
FIBROSIS		1 (2%)	
#KIDNEY/TUBULE	(9)	(48)	(45)
DILATATION, NOS		2 (4%)	2 (4%)
CAST, NOS		2 (4%)	2 (4%)
#U.BLADDER/SUBMUCOSA	(9)	(44)	(38)
HEMORRHAGE			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(8)	(44)	(41)
CYST, NOS	1 (13%)	2 (5%)	3 (7%)
HEMORRHAGIC CYST		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	1 (13%)		
#ADRENAL	(9)	(45)	(41)
CONGESTION, NOS		1 (2%)	
ANGIECTASIS	5 (56%)	17 (38%)	16 (39%)
#ADRENAL CORTEX	(9)	(45)	(41)
CYST, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	
LIPOIDOSIS	5 (56%)	11 (24%)	9 (22%)
ATROPHY, NOS		2 (4%)	
ANGIECTASIS			1 (2%)
#THYROID	(9)	(45)	(38)
CYST, NOS		2 (4%)	2 (5%)
HYPERPLASIA, NOS		1 (2%)	2 (5%)
#PARATHYROID	(7)	(31)	(19)
CYST, NOS		1 (3%)	
HYPERPLASIA, NOS	2 (29%)	2 (6%)	
#PANCREATIC ISLETS	(7)	(41)	(39)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(9)	(43)	(41)
HYDROMETRA	1 (11%)	3 (7%)	3 (7%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS/ENDOMETRIUM	(9)	(43)	(41)
CYST, NOS	3 (33%)	8 (19%)	8 (20%)
#OVARY	(9)	(47)	(42)
CYST, NOS	1 (11%)		
FOLLICULAR CYST, NOS	2 (22%)	5 (11%)	2 (5%)
NERVOUS SYSTEM			
#BRAIN	(9)	(48)	(45)
ATROPHY, NOS		2 (4%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(10)	(49)	(49)
ULCER, CHRONIC			1 (2%)
*EYE/RETINA	(10)	(49)	(49)
INFLAMMATION, CHRONIC			1 (2%)
MUSCULOSKELETAL SYSTEM			
*BONE	(10)	(49)	(49)
CYST, NOS		1 (2%)	
OSTEOPOROSIS		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	1
AUTO/NECROPSY/NO HISTO	1	1	3
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED AZINPHOSMETHYL IN THE DIET

TABLE D1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(10)	(49)	(50)
INFLAMMATION, NOS	1 (10%)		
#LUNG	(10)	(49)	(50)
EMPHYSEMA, NOS			2 (4%)
CONGESTION, NOS	1 (10%)	2 (4%)	5 (10%)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	1 (10%)	1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (10%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(10)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC	1 (10%)		
#SPLEEN	(8)	(46)	(46)
HYPERPLASIA, LYMPHOID			1 (2%)
MYELOID METAPLASIA		1 (2%)	
#LYMPH NODE	(9)	(46)	(46)
LYMPHANGIECTASIS		1 (2%)	1 (2%)
CONGESTION, NOS		1 (2%)	2 (4%)
ERYTHROPHAGOCYTOSIS			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (11%)	2 (4%)	4 (9%)
HYPERPLASIA, LYMPHOID		2 (4%)	
MYELOID METAPLASIA		1 (2%)	
#MESENTERIC L. NODE	(9)	(46)	(46)
LYMPHANGIECTASIS			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
HEMORRHAGE			1 (2%)
CIRCULATORY SYSTEM			
#HEART/VENTRICLE	(10)	(48)	(50)
FIBROSIS, FOCAL			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(8)	(49)	(50)
HEMORRHAGE		1 (2%)	
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL	1 (13%)		1 (2%)
#LIVER/CENTRILOBULAR	(8)	(49)	(50)
CYTOPLASMIC VACUOLIZATION			1 (2%)
*BILE DUCT	(10)	(50)	(50)
LYMPHOCYTIC INFILTRATE			1 (2%)
#PANCREAS	(8)	(49)	(47)
INFLAMMATION, CHRONIC	1 (13%)		1 (2%)
#SMALL INTESTINE	(7)	(48)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(9)	(49)	(50)
LYMPHOCYTIC INFILTRATE			1 (2%)
#KIDNEY/CORTEX	(9)	(49)	(50)
LYMPHOCYTIC INFILTRATE			1 (2%)
CYTOPLASMIC VACUOLIZATION			7 (14%)
#URINARY BLADDER	(7)	(48)	(49)
CALCULUS, NOS	1 (14%)		
INFLAMMATION, CHRONIC	1 (14%)		
ENDOCRINE SYSTEM			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(10)	(50)	(50)
CYST, NOS			1 (2%)
#TESTIS	(9)	(49)	(50)
CYTOLOGIC DEGENERATION			1 (2%)
ASPERMATOGENESIS			4 (8%)
#TESTIS/TUBULE	(9)	(49)	(50)
CYTOLOGIC DEGENERATION			3 (6%)
NERVOUS SYSTEM			
#BRAIN	(10)	(48)	(50)
CORPORA AMYLACEA	1 (10%)	16 (33%)	6 (12%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(10)	(50)	(50)
HEMORRHAGE		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	16	14
NECROPSY PERF/NO HISTO PERFORMED		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 AZINPHOSMETHYL IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	49	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(10)	(50)	(50)
CONGESTION, NOS	1 (10%)	6 (12%)	2 (4%)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	3 (30%)	6 (12%)	3 (6%)
LYMPHOCYTIC INFILTRATE			1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
#LUNG/ALVEOLI	(10)	(50)	(50)
HEMORRHAGE	2 (20%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(10)	(47)	(50)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(9)	(49)	(50)
INFLAMMATION, ACUTE		3 (6%)	
HYPERPLASIA, LYMPHOID	1 (11%)		1 (2%)
MYELOID METAPLASIA	2 (22%)	1 (2%)	2 (4%)
#LYMPH NODE	(9)	(40)	(45)
ERYTHROPHAGOCYTOSIS	1 (11%)		
HYPERPLASIA, RETICULUM CELL	1 (11%)	1 (3%)	
HYPERPLASIA, LYMPHOID		2 (5%)	
MYELOID METAPLASIA	1 (11%)		
#PANCREATIC L.NODE	(9)	(40)	(45)
INFLAMMATION, GRANULOMATOUS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(9)	(40)	(45)
INFLAMMATION, CHRONIC			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(10)	(49)	(49)
LYMPHOCYTIC INFILTRATE		1 (2%)	1 (2%)
#LIVER	(10)	(49)	(50)
LYMPHOCYTIC INFILTRATE		1 (2%)	1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		2 (4%)	
NECROSIS, FOCAL		2 (4%)	2 (4%)
NECROSIS, COAGULATIVE			1 (2%)
HYPERPLASIA, NODULAR			1 (2%)
HEMATOPOIESIS			1 (2%)
MYELOID METAPLASIA	2 (20%)		
#LIVER/CENTRILOBULAR	(10)	(49)	(50)
CYTOPLASMIC CHANGE, NOS	1 (10%)		
#PANCREAS	(9)	(40)	(48)
DILATATION/DUCTS			1 (2%)
CYST, NOS			1 (2%)
MULTILOCULAR CYST			1 (2%)
LYMPHOCYTIC INFILTRATE	1 (11%)		
INFLAMMATION, ACUTE/CHRONIC		1 (3%)	
#PANCREATIC ACINUS	(9)	(40)	(48)
CYTOPLASMIC VACUOLIZATION	1 (11%)		
URINARY SYSTEM			
#KIDNEY	(10)	(49)	(50)
HYDRONEPHROSIS			1 (2%)
LYMPHOCYTIC INFILTRATE	1 (10%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(7)	(39)	(40)
HEMORRHAGIC CYST			1 (3%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(9)	(42)	(46)
CYST, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
#UTERUS	(7)	(48)	(48)
HYDROMETRA			3 (6%)
#UTERUS/ENDOMETRIUM	(7)	(48)	(48)
CYST, NOS	1 (14%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE		1 (2%)	2 (4%)
INFLAMMATION, ACUTE VESICULAR		2 (4%)	2 (4%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, CYSTIC	2 (29%)	32 (67%)	32 (67%)
METAPLASIA, SQUAMOUS			1 (2%)
#UTERUS/MYOMETRIUM	(7)	(48)	(48)
INFLAMMATION, ACUTE		1 (2%)	
#OVARY	(9)	(47)	(41)
CYST, NOS		5 (11%)	3 (7%)
FOLLICULAR CYST, NOS	1 (11%)	2 (4%)	4 (10%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		3 (6%)	
DEGENERATION, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(10)	(49)	(50)
CORPORA AMYLACEA	2 (20%)	3 (6%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(10)	(50)	(50)
INFLAMMATION, NOS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	6	1
NECROPSY PERF/NO HISTO PERFORMED		1	
AUTO/NECROPSY/NO HISTO			1

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

APPENDIX E

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

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Hematopoietic System:				
Lymphoma[b]	5/101 (5)	1/10 (10)	3/50 (6)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.212	0.412
Lower Limit			0.194	0.009
Upper Limit			5.931	3.527
Relative Risk (Matched Control)[f]			0.600	0.204
Lower Limit			0.058	0.003
Upper Limit			30.890	15.723
Weeks to First Observed Tumor		115	68	113
Liver: Hepatocellular Adenoma[b]	3/99 (3)	1/9 (11)	3/49 (6)	5/46 (11)
P Values[c,d]	P = 0.044	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.020	3.587
Lower Limit			0.278	0.726
Upper Limit			14.484	22.059
Relative Risk (Matched Control)[f]			0.551	0.978
Lower Limit			0.055	0.139
Upper Limit			28.360	45.235
Weeks to First Observed Tumor		115	115	97

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	13/43 (30)
P Values[c,d]	P = 0.012	N.S.	P < 0.001**	P = 0.042**
Departure from Linear Trend[e]	P = 0.004			
Relative Risk (Pooled Control)[f]			2.985	1.977
Lower Limit			1.581	0.920
Upper Limit			5.696	4.147
Relative Risk (Matched Control)[f]			1.027	0.680
Lower Limit			0.513	0.312
Upper Limit			3.432	2.420
Weeks to First Observed Tumor		103	102	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	15/43 (35)
P Values[c,d]	P = 0.003	N.S.	P < 0.001**	P = 0.012**
Departure from Linear Trend[e]	P = 0.009			
Relative Risk (Pooled Control)[f]			2.985	2.281
Lower Limit			1.581	1.110
Upper Limit			5.696	4.634
Relative Risk (Matched Control)[f]			1.027	0.785
Lower Limit			0.513	0.371
Upper Limit			3.432	2.733
Weeks to First Observed Tumor		103	102	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, Chromophobe Adenoma, Chromophobe Carcinoma, or Cystadenoma, NOS[b]	13/85 (15)	4/9 (44)[g]	21/46 (46)	20/43 (47)
P Values[c,d]	P < 0.001	N.S.	P < 0.001**	P < 0.001**
Relaive Risk (Pooled Control)[f]			2.985	3.041
Lower Limit			1.581	1.601
Upper Limit			5.696	5.796
Relative Risk (Matched Control)[f]			1.027	1.047
Lower Limit			0.513	0.519
Upper Limit			3.432	3.493
Weeks to First Observed Tumor		103	102	77
Adrenal: Adenocarcinoma, NOS[b]	0/95 (0)	0/9 (0)	1/45 (2)	3/46 (7)
P Values[c,d]	P = 0.015	N.S.	N.S.	P = 0.033**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.112	1.228
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.133
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	104	92

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Adenocarcinoma, NOS, or Cortical Adenoma[b]	3/95 (3)	1/9 (11)	4/45 (9)	10/46 (22)
P Values[c,d]	P < 0.001	N.S.	N.S.	P = 0.001**
Relative Risk (Pooled Control)[f]			2.815	6.884
Lower Limit			0.494	1.871
Upper Limit			18.356	36.913
Relative Risk (Matched Control)[f]			0.800	1.957
Lower Limit			0.099	0.358
Upper Limit			38.517	82.720
Weeks to First Observed Tumor		115	104	92
Thyroid: Follicular-cell Adenoma, Adenoma, NOS, or Cystadenoma[b]	7/86 (8)	1/9 (11)	10/44 (23)	12/43 (28)
P Values[c,d]	P = 0.002	N.S.	P = 0.022**	P = 0.004**
Relative Risk (Pooled Control)[f]			2.792	3.429
Lower Limit			1.026	1.340
Upper Limit			7.965	9.403
Relative Risk (Matched Control)[f]			2.045	2.512
Lower Limit			0.375	0.480
Upper Limit			86.341	104.131
Weeks to First Observed Tumor		115	68	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	0/86 (0)	0/9 (0)	4/44 (9)	4/43 (9)
P Values[c,d]	P = 0.008	N.S.	P = 0.012**	P = 0.011**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.794	1.836
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.215	0.220
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	104	115
Thyroid: All Follicular-cell Tumors[b,h]	7/86 (8)	1/9 (11)	14/44 (32)	14/43 (33)
P Values[c,d]	P < 0.001	N.S.	P = 0.001**	P = 0.001**
Relative Risk (Pooled Control)[f]			3.909	4.000
Lower Limit			1.596	1.635
Upper Limit			10.434	10.649
Relative Risk (Matched Control)[f]			2.864	2.930
Lower Limit			0.564	0.577
Upper Limit			117.305	119.913
Weeks to First Observed Tumor		115	68	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Parathyroid: Adenoma, NOS[b]	1/81 (1)	1/5 (20)[g]	0/26 (0)	4/24 (17)
P Values[c,d]	P = 0.004	N.S.	N.S.	P = 0.009**
Departure from Linear Trend[e]	P = 0.039	P = 0.042		
Relative Risk (Pooled Control)[f]			0.000	13.500
Lower Limit			0.000	1.403
Upper Limit			57.066	632.360
Relative Risk (Matched Control)[f]			0.000	0.833
Lower Limit			0.000	0.130
Upper Limit			3.557	39.161
Weeks to First Observed Tumor		107	--	113
All Sites: Hemangiosarcoma[b]	5/101 (5)	2/10 (20)[g]	0/50 (0)	5/49 (10)
P Values[c,d]	N.S.	N.S.	P = 0.025*(N)	N.S.
Departure fromLinear Trend[e]	P = 0.036	P = 0.006		
Relative Risk (Pooled Control)[f]			0.000	2.061
Lower Limit			0.000	0.494
Upper Limit			1.608	8.485
Relative Risk (Matched Control)[f]			0.000	0.510
Lower Limit			0.000	0.107
Upper Limit			0.667	5.008
Weeks to First Observed Tumor		89	--	71

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma[b]	5/101 (5)	2/10 (20)[g]	1/50 (2)	6/49 (12)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.022		
Relative Risk (Pooled Control)[f]			0.404	2.473
Lower Limit			0.009	0.657
Upper Limit			3.459	9.689
Relative Risk (Matched Control)[f]			0.100	0.612
Lower Limit			0.002	0.141
Upper Limit			1.810	5.791
Weeks to First Observed Tumor		89	52	71
Pancreatic Islets: Islet-cell Adenoma[b]	2/92 (2)	0/9 (0)	1/47 (2)	4/45 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.979	4.089
Lower Limit			0.017	0.607
Upper Limit			18.203	43.556
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.210
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	115	115

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma or Carcinoma[b]	2/92 (2)	0/9 (0)	1/47 (2)	6/45 (13)
P Values[c,d]	P = 0.008	P = 0.033	N.S.	P = 0.015**
Relative Risk (Pooled Control)[f]			0.979	6.133
Lower Limit			0.017	1.144
Upper Limit			18.203	59.753
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.363
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	115	97

[a]Dosed groups received 78 or 156 ppm in feed.

[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 $P < 0.05$; 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 $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Azinphosmethyl in the Diet[a]

(continued)

[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 $P < 0.05$ for any comparison.

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

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

[h]These tumors consist of adenoma, NOS, adenocarcinoma, NOS, follicular-cell adenoma, cystadenoma, NOS, cystadenocarcinoma, NOS, and papillary cystadenocarcinoma, NOS.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	6/104 (6)	2/9 (22)	2/47 (4)	5/45 (11)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.738	1.926
Lower Limit			0.074	0.485
Upper Limit			3.918	7.118
Relative Risk (Matched Control)[f]			0.191	0.500
Lower Limit			0.017	0.108
Upper Limit			2.467	4.871
Weeks to First Observed Tumor		115	110	95
Pituitary: Chromophobe Adenoma[b]	25/89 (28)	2/8 (25)	14/44 (32)	12/41 (29)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relaitve Risk (Pooled Control)[f]			1.133	1.042
Lower Limit			0.600	0.525
Upper Limit			2.001	1.901
Relative Risk (Matched Control)[f]			1.273	1.171
Lower Limit			0.411	0.366
Upper Limit			10.504	9.792
Weeks to First Observed Tumor		84	110	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary:				
Adenocarcinoma, NOS[b]	0/89 (0)	0/8 (0)	8/44 (18)	1/41 (2)
P Values[c,d]	N.S.	N.S.	P < 0.001**	N.S.
Departure from Linear Trend[e]	P < 0.001	P = 0.019		
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			4.572	0.115
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.481	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	98	99
Pituitary: Chromophobe Adenoma, Adenocarcinoma, NOS, Adenoma, or Cystadenoma, NOS[b]	29/89 (33)	2/8 (25)	22/44 (50)	15/41 (37)
P Values[c,d]	N.S.	N.S.	P = 0.040**	N.S.
Relative Risk (Pooled Control)[f]			1.534	1.123
Lower Limit			0.952	0.624
Upper Limit			2.360	1.882
Relative Risk (Matched Control)[f]			2.000	1.463
Lower Limit			0.693	0.479
Upper Limit			15.699	11.921
Weeks to First Observed Tumor		84	98	95

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Adrenal: Cortical Adenoma[b]	2/95 (2)	1/9 (11)	4/45 (9)	8/41 (20)
P Values[c,d]	P = 0.001	N.S.	N.S.	P = 0.001**
Relative Risk (Pooled Control)[f]			4.222	9.268
Lower Limit			0.626	1.944
Upper Limit			44.978	85.579
Relative Risk (Matched Control)[f]			0.800	1.756
Lower Limit			0.099	0.302
Upper Limit			38.517	75.723
Weeks to First Observed Tumor		75	115	115
Thyroid: Cystadenoma or Adenoma, NOS[b]	1/94 (1)	1/9 (11)[g]	6/45 (13)	4/38 (11)
P Values[c,d]	P = 0.010	N.S.	P = 0.005**	P = 0.024**
Relative Risk (Pooled Control)[f]			12.533	9.895
Lower Limit			1.580	1.014
Upper Limit			562.024	473.300
Relative Risk (Matched Control)[f]			1.200	0.947
Lower Limit			0.185	0.118
Upper Limit			53.895	45.380
Weeks to First Observed Tumor		115	98	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	1/94 (1)	1/9 (11)[g]	2/45 (4)	1/38 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			4.178	2.474
Lower Limit			0.222	0.032
Upper Limit			240.910	189.044
Relative Risk (Matched Control)[f]			0.400	0.237
Lower Limit			0.025	0.003
Upper Limit			23.103	18.138
Weeks to First Observed Tumor		115	115	115
Thyroid: All Follicular-cell Tumors[b,h]	2/94 (2)	2/9 (22)[g]	8/45 (18)	5/38 (13)
P Values[c,d]	P = 0.008	N.S.	P = 0.002**	P = 0.021**
Departure from Linear Trend[e]	P = 0.039			
Relative Risk (Pooled Control)[f]			8.356	6.184
Lower Limit			1.748	1.056
Upper Limit			77.514	62.055
Relative Risk (Matched Control)[f]			0.800	0.592
Lower Limit			0.214	0.129
Upper Limit			7.147	5.728
Weeks to First Observed Tumor		115	98	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dsoe
All Sites: Hemangioma or Hemangiosarcoma[a]	1/105 (1)	0/10 (0)	4/49 (8)	1/49 (2)
P Values[c,d]	N.S.	N.S.	P = 0.036**	N.S.
Departure from Linear Trend[e]	P = 0.018			
Relative Risk (Pooled Control)[f]			8.571	2.143
Lower Limit			0.873	0.028
Upper Limit			412.952	164.796
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.211	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	51	115
Mammary Gland: Adenocarcinoma, Cystadenocarcinoma, or Papillary Cystadenocarcinoma[b]	3/105 (3)	0/10 (0)	3/49 (6)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.143	0.714
Lower Limit			0.295	0.014
Upper Limit			15.366	8.575
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.136	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	98	40

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma[b]	13/105 (12)	2/10 (20)	9/49 (18)	9/49 (18)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.484	1.484
Lower Limit			0.595	0.595
Upper Limit			3.456	3.456
Relative Risk (Matched Control)[f]			0.918	0.918
Lower Limit			0.247	0.247
Upper Limit			8.129	8.129
Weeks to First Observed Tumor		84	66	95
Uterus: Endometrial Stromal Polyp[b]	15/105 (14)	1/9 (11)	3/43 (7)	0/41 (0)
P Values[c,d]	P = 0.005(N)	N.S.	N.S.	P = 0.005**(N)
Relative Risk (Pooled Control)[f]			0.488	0.000
Lower Limit			0.094	0.000
Upper Limit			1.607	0.544
Relative Risk (Matched Control)[f]			0.628	0.000
Lower Limit			0.062	0.000
Upper Limit			32.213	4.097
Weeks to First Observed Tumor		84	80	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	5/97 (5)	2/7 (29)[g]	1/41 (2)	1/39 (3)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]		P = 0.015		
Relative Risk (Pooled Control)[f]			0.473	0.497
Lower Limit			0.010	0.011
Upper Limit			4.017	4.214
Relative Risk (Matched Control)[f]			0.085	0.090
Lower Limit			0.002	0.002
Upper Limit			1.513	1.588
Weeks to First Observed Tumor		115	115	115

[a]Dosed groups received 62.5 or 125 ppm in feed.

[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 < 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 < 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Azinphosmethyl in the Diet[a]

(continued)

[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 $P < 0.05$ for any comparison.

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

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

[h]These tumors consist of adenoma, NOS, adenocarcinoma, NOS, papillary adenocarcinoma, cystadenoma, NOS, and papillary cystadenocarcinoma, NOS.

APPENDIX F

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

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	13/129 (10)	1/10 (10)	6/49 (12)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.215	0.794
Lower Limit			0.396	0.195
Upper Limit			3.192	2.412
Relative Risk (Matched Control)[f]			1.224	0.800
Lower Limit			0.184	0.097
Upper Limit			55.127	38.616
Weeks to First Observed Tumor		92	92	93
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	14/129 (11)	2/10 (20)[g]	8/49 (16)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relaitve Risk (Pooled Control)[f]			1.504	0.737
Lower Limit			0.577	0.183
Upper Limit			3.555	2.201
Relative Risk (Matched Control)[f]			0.816	0.400
Lower Limit			0.211	0.073
Upper Limit			7.351	4.141
Weeks to First Observed Tumor		90	92	93

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma[b]	0/131 (0)	0/10 (0)	3/50 (6)	0/50 (0)
P Values[c,d]	N.S.	N.S.	P = 0.020**	N.S.
Departure from Linear Trend[e]	P = 0.002			
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			1.551	--
Upper Limit			Infinite	--
Relative Risk (Matched Control)[f]			Infinite	--
Lower Limit			0.134	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	88	--
All Sites: Hemangioma or Hemangiosarcoma[b]	1/131 (1)	1/10 (10)[g]	4/50 (8)	0/50 (0)
P Values[c,d]	N.S.	N.S.	P = 0.021**	N.S.
Departure from Linear Trend[e]	P = 0.002			
Relative Risk (Pooled Control)[f]			10.480	0.000
Lower Limit			1.064	0.000
Upper Limit			505.052	48.855
Relative Risk (Matched Control)[f]			0.800	0.000
Lower Limit			0.097	0.000
Upper Limit			38.616	3.747
Weeks to First Observed Tumor		90	88	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	27/128 (21)	0/8 (0)	3/49 (6)	12/50 (24)
P Values[c,d]	N.S.	P = 0.006	P = 0.012**(N)	N.S.
Relative Risk (Pooled Control)[f]			0.290	1.138
Lower Limit			0.058	0.564
Upper Limit			0.882	2.106
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.113	0.679
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	74	75
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	30/128 (23)	2/8 (25)	11/49 (22)	19/50 (38)
P Values[c,d]	P = 0.048	N.S.	N.S.	P = 0.040**
Relative Risk (Pooled Control)[f]			0.958	1.621
Lower Limit			0.465	0.946
Upper Limit			1.782	2.638
Relative Risk (Matched Control)[f]			0.898	1.520
Lower Limit			0.274	0.515
Upper Limit			7.665	12.264
Weeks to First Observed Tumor		92	74	57

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Azinphosmethyl in the Diet[a]

(continued)

[a]Dosed groups received 31.3 or 62.5 ppm in feed.

[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 $P < 0.05$; 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 $P < 0.05$ 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 $P < 0.05$ for any comparison.

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

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Azinphosmethyl in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	3/127 (2)	0/10 (0)	1/50 (2)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.847	2.540
Lower Limit			0.016	0.349
Upper Limit			10.179	18.245
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.134
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	92	92
Hematopoietic System: Lymphoma[b]	15/128 (12)	3/10 (30)[g]	5/50 (10)	6/50 (12)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.853	1.024
Lower Limit			0.253	0.341
Upper Limit			2.306	2.600
Relative Risk (Matched Control)[f]			0.333	0.400
Lower Limit			0.086	0.114
Upper Limit			1.939	2.229
Weeks to First Observed Tumor		64	84	86

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Azinphosmethyl in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Hematopoietic System:				
Lymphoma or Leukemia[b]	16/128 (13)	3/10 (30)	5/50 (10)	7/50 (14)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.800	1.120
Lower Limit			0.239	0.410
Upper Limit			2.132	2.668
Relative Risk (Matched Control)[f]			0.333	0.467
Lower Limit			0.086	0.143
Upper Limit			1.939	2.518
Weeks to First Observed Tumor		64	84	86

[a]Dosed groups received 62.5 or 125 ppm in feed.

[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 $P < 0.05$; 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 $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Azinphosmethyl in the Diet[a]

(continued)

[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 $P < 0.05$ for any comparison.

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

[g]The incidence in the matched-control group is significantly higher ($P < 0.05$) than that in the pooled controls (excluding the controls of the subject study).

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF AZINPHOSMETHYL

APPENDIX G

Analysis of Formulated Diets for

Concentrations of Azinphosmethyl

A 10-g sample of the diet mixture was shaken with 125 ml hexane at room temperature for 16 hours, then filtered through Celite with hexane washes, and reduced to 10 ml in volume. The solution was extracted with three successive 10-ml aliquots of acetonitrile. The combined acetonitrile extracts were evaporated nearly to dryness, diluted to 10 ml with hexane, and quantitatively analyzed for azinphosmethyl by gas-liquid chromatography (electron capture detector, 10% DC-200 on Gas Chrom Q column). Recoveries were checked 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)
31.2(5)	17	31.2	4.3%	28.3-34.6
62.5	22	61.2	5.9%	50.0-68.0
125.0	21	126.0	6.4%	114.0-148.0
250.0	5	256.0	2.0%	250.0-262.0

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

June 29, 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 Azinphosmethyl for carcinogenicity.

The reviewer noted that the compound is an organophosphorus cholinesterase inhibitor. Although the neoplasms of the thyroid and pancreatic islets in treated male rats were only suggestive evidence of carcinogenicity, she said that the experimental design was sufficiently flawed as to preclude any definite conclusions being drawn from the bioassay. The study was particularly deficient due to the small number of matched controls and limited number of organs examined. The reviewer questioned the practice used for concluding that a tumor incidence, observed in treated animals, was within the spontaneous range. Because of the inadequacies of the bioassay, she said that no conclusion could be drawn regarding the carcinogenicity of Azinphosmethyl. She suggested that the compound be tested in short-term in vitro assays and, if found to be positive, that it be

considered for retest in a long-term animal bioassay. A motion was made by the reviewer that the report on the bioassay of Azinphosmethyl be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. 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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