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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioassay of diazinon 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. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

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

The experimental design for this bioassay is based on guidelines for carcinogen bioassays in small animals that have been established by NCI (1). The doses for the chronic studies were selected by Drs. E. E. Storrs (2) and O. G. Fitzhugh (3,4). The principal investigator was Mr. R. J. Wheeler (2). Histologic examination of animal tissues was performed by Drs. E. Bernal (2) and R. A. Ball (2), and the diagnoses included in this report represent the interpretation of these pathologists.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (5). Statistical analyses were performed by Dr. J. R. Joiner (3) and Ms. P. L. Yong (3), using methods selected for the bioassay program by Dr. J. J. Gart (6).

The chemical was reanalyzed at Midwest Research Institute (7) upon completion of the bioassay. Chemicals were analyzed at GSRI by Mr. Wheeler (2) and dosed feed mixtures by Mr. S. M. Billedeau (2). The results of these analyses were reviewed by Dr. C. W. Jameson (3).

This report was prepared at Tracor Jitco (3) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Mr. W. D. Reichardt, Ms. L. A. Owen, and Ms. M. S. King, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of diazinon for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were administered diazinon at one of two doses, either 400 or 800 ppm for the rats and either 100 or 200 ppm for the mice, for 103 weeks and were then observed for an additional 1 or 2 weeks. Matched controls consisted of groups of 25 untreated rats and 25 untreated mice of each sex. All surviving animals were killed at the end of 104 or 105 weeks.

There was no appreciable effect of administration of diazinon on mean body weights of rats or mice of either sex. Mortality was not increased in any of the dosed groups of rats or mice, when related to that in the corresponding controls, and survival was 84% or greater in all dosed and control groups of animals at week 78. Some hyperactivity was noted in the dosed groups of both species; however, both the rats and mice may have been able to tolerate higher doses. Sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

No tumors occurred in any of the dosed groups of rats or mice of either sex at incidences that could clearly be related to the administration of diazinon.

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

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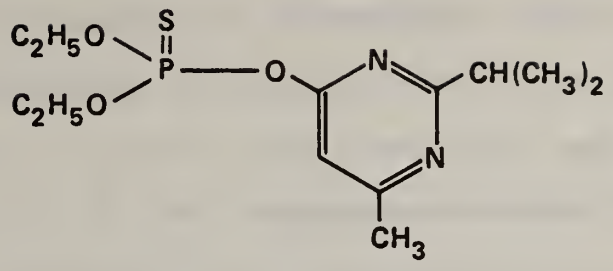
I. INTRODUCTION



Diazinon

Diazinon (CAS 333-41-5; NCI C08673) is the common name recommended by the British Standards Institution, the International Standardization Organization, and the Entomological Society of America (Martin and Worthing, 1977) for the organophosphate insecticide, O,O-diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate. It was marketed first in 1954 as an insecticide and acaricide (Bartsch, 1974) and has been used since that time as a dust or spray in agriculture, on rangeland and wasteland, in industrial establishments, and in the home (Ayers and Johnson, 1976). The EPA currently permits its use on 76 food crops, cotton, and pasture grasses (EPA, 1969-1973). Diazinon has also been applied as a livestock spray or dip and has been administered in the feed to farm and domestic animals for the control of ectoparasites (Rossoff, 1974; Mücke et al., 1970). In 1974, diazinon was the fifth most extensively used

organophosphate insecticide in the United States (Ayers and Johnson, 1976). Of the 7 million pounds estimated to have been sold that year, approximately two-thirds were expended in agriculture, and the remaining third in commercial establishments and in the home (Ayers and Johnson, 1976), by either commercial pest control operators or consumers.

The acute oral LD_{50} of diazinon is 250 mg/kg and 285 mg/kg in male and female Sherman rats, respectively (Gaines, 1969), 100-150 mg/kg in male albino rats (Bruce et al., 1955) and 82 mg/kg in male albino mice (Bruce et al., 1955). The toxic effects of diazinon are due to cholinesterase inhibition. Male albino rats administered 100 ppm diazinon in the diet for 4 weeks had reduced cholinesterase activities of the red cells, and rats administered 1,000 ppm for 4 weeks had reduced cholinesterase activity in both the red cells and the brain (Bruce et al., 1955). Toxicity is increased by metabolic conversion to the oxygen analog (Matsumura, 1975), and decreased, specifically in mammals, by hydrolysis of the pyrimidine ester of either diazinon, diazoxon, or hydroxydiazinon (Eto, 1974).

Diazinon, like other organophosphate insecticides, is rapidly degraded in the environment. It has a half-life of 2 to 4 weeks in soil depending on soil type and climate (Bartsch, 1974).

Residues may occur in food crops, and are currently established at concentrations no greater than 1 to 0.1 ppm in various crops intended for human consumption, and 60 to 10 ppm in forage crops (Code of Federal Regulations, 1976).

Diazinon was selected by the Carcinogenesis Testing Program because of its widespread use in agriculture and related industries as well as in the home and because of the possibility that residues may contaminate food.

II. MATERIALS AND METHODS

A. Chemical

Diazinon was obtained in a single batch (Lot No. F1-741306) for the chronic study from CIBA-GEIGY Corp., Greensboro, North Carolina. The identity and purity of this batch was confirmed in analysis at Gulf South Research Institute. Elemental analyses (C, H, N, P, S) were correct for $C_{12}H_{21}N_2O_3PS$, the molecular formula of diazinon. Thin-layer chromatography showed a single spot. Vapor-phase chromatography indicated an impurity of approximately 2%, which was not identified. Nuclear magnetic resonance, infrared, and ultraviolet spectra were in agreement with the structure. Reanalysis of this batch of diazinon at Midwest Research Institute after completion of the bioassay indicated that the material had not changed under the condition of storage for approximately 4 years.

B. Dietary Preparation

All diets were formulated using Wayne® Lab Blox Meal (Allied Mills, Inc. Chicago, Ill.) to which was added the required amount

of diazinon for each dietary concentration. Small amounts of acetone (Mallinckrodt Inc., St. Louis, Mo.) were used as an aid to uniform dispersion of the test compound in the feed. The diets were mixed mechanically to assure homogeneity and to allow for evaporation of the acetone. Corn oil (Louana®, Opelousas Refinery Co., Opelousas, Louisiana) equal to 2% of the final weight of feed was then added, primarily as a dust suppressant. Diets for control animals were the same as those for dosed animals, except for the absence of diazinon. Formulated diets were stored at ambient room temperature until used, but no longer than 1 week.

The stability of diazinon in feed was checked by analyzing formulated diets for the concentration of diazinon at intervals over a period of 7 days. No significant change in diazinon concentration was detected in diets containing 50 and 3,200 ppm diazinon on standing at ambient temperature for this period.

Diazinon formulated diets were checked analytically at intervals during the chronic study to assess the accuracy of the diet preparations and the homogeneity of the mixtures. Results are summarized in Appendix E. At each dietary concentration, the mean of the analytical concentrations for the checked samples was

within 97% of the theoretical concentration, and the coefficient of variation was not more than 5.7% at any level.

C. Animals

F344 (Fischer) rats and B6C3F1 hybrid mice of each sex were obtained from the NCI Frederick Cancer Research Center (Frederick, Md.). After the rats were housed within the test facility for 2 weeks and the mice for 4 weeks, they were assigned to dosed or control groups.

D. Animal Maintenance

The rats were housed individually in hanging galvanized steel mesh cages (Hoeltge, Cincinnati, Ohio), and the mice were housed five per cage in polypropylene cages (Lab Products, Inc., Garfield, N.J.). The mouse cages were covered with polyester filter bonnets (Lab Products, Inc.), and the filter bonnets were sanitized once per week. The cages for the rats were sanitized every 2 weeks, and those for the mice were sanitized twice per week. Cages and racks were washed in an industrial washer (Industrial Washing Machine Corp., Matawan, N.J.) at 82°C with

Acclaim® detergent (Economics Laboratory, Inc., St. Paul, Minn.) and then rinsed. Absorbent Kimpak® cage liners (Kimberly Clark Corp., Neenah, Wis.) were placed under the rat cages and were changed twice per week. Absorb-dri® hardwood chip bedding (Lab Products, Inc.) was used in the mouse cages and was changed twice per week. Feed jars, water bottles, sipper tubes, and stoppers were sanitized twice per week. The filter bonnets, feed jars, water bottles, sipper tubes, and stoppers were washed in a Vulcan Autosan washer (Louisville, Ky.) at 82°C, using Acclaim® detergent, and then rinsed.

Cage racks for each species were rotated to a new position in the room once per week; at the same time, each cage was moved to a different row within the same column of a rack. Rats and mice were housed in separate rooms. Control and dosed rats were housed on the same rack, whereas cages for control and dosed mice were placed in separate racks in the same room. Diazinon was the only compound on test in each room.

The animal rooms were maintained at 22 to 24°C, and the relative humidity was 40 to 70%. The air was filtered through permanent air maze filters (Air Maze Incom International, Cleveland, Ohio) and was changed 10 to 12 times per hour. Fluorescent lighting

provided illumination 10 hours per day. Food and tap water were provided ad libitum. Fresh feed was provided twice per week.

E. Subchronic Studies

Subchronic feeding studies were conducted with rats and mice to estimate the maximum tolerated doses (MTD's) of diazinon, on the basis of which concentrations (referred to in this report as "high" and "low" doses), were chosen for administration in the chronic studies. Groups of 10 rats and 10 mice of each sex were fed diets containing diazinon at one of several doses for 13 weeks, and groups of 10 control animals of each species and sex were administered basal diet only. The animals were weighed once per week. Table 1 shows the doses fed, the survivals of animals in each dosed group at the end of the study, and the mean body weights of dosed groups of animals at week 13, expressed as percentages of mean body weights of corresponding control groups. At the end of the 13 weeks, all surviving animals were killed and necropsied.

Three deaths occurred among the male rats and four among the females rats at 3,200 ppm. Mean body weight gains were appreciably decreased only in groups of males or females at doses

Table 1. Diazinon Subchronic Feeding Studies in Rats and Mice

Dose (ppm)	Male Survival(a)	Male Mean Weight at Week 13 as % of Control	Female Survival(a)	Female Mean Weight at Week 13 as % of Control
Rats(b)				
0	10/10	100	10/10	100
50	10/10	103	10/10	96
100	10/10	102	10/10	96
200	10/10	103	10/10	98
400	10/10	100	10/10	97
800	10/10	99	10/10	98
1,600	10/10	93	10/10	85
3,200	7/10	78	6/10	67
Mice(b)				
0	10/10	100	10/10	100
50	10/10	97	10/10	101
100	10/10	99	10/10	102
200	9/10	92	9/10	96
400	10/10	93	10/10	100
800	10/10	84	10/10	78
1,600	0/10		0/10	
3,200	0/10		0/10	

(a) Number surviving/number in group.

(b) No gross abnormalities were observed in necropsied animals at any dose, and microscopic examination of tissues of animals surviving the high doses showed no pathologic changes.

of 1,600 or 3,200 ppm. The diazinon was more toxic to the mice than to the rats, causing deaths of all animals at both 1,600 and 3,200 ppm, and decreases in mean body weight gain at 800 ppm.

The low and high doses for the chronic studies were set at 400 and 800 ppm for rats; and 100 and 200 ppm for mice.

F. Chronic Studies

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

G. Clinical and Pathologic Examinations

All animals were observed twice per day for signs of toxicity, weighed at 2-week intervals, and palpated for masses at each weighing. Observations of sick, tumor-bearing, and moribund animals were recorded daily. Moribund animals and animals that survived to the end of the bioassay were killed with pentobarbital and necropsied.

The pathologic evaluation consisted of gross and microscopic

Table 2. Diazinon Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Diazinon in Diet(b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	25	0		105
Low-Dose	50	400	103	2
High-Dose	50	800	103	2
Female				
Matched-Control	25	0		104-105
Low-Dose	50	400	103	1
High-Dose	50	800	103	1

(a) All rats were approximately 7 weeks of age when placed on study.

(b) Diets were provided ad libitum.

Table 3. Diazinon Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Diazinon in Diet(b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	25	0		105
Low-Dose	50	100	103	2
High-Dose	50	200	103	2
Female				
Matched-Control	25	0		106
Low-Dose	50	100	103	2
High-Dose	50	200	103	2

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

(b) Diets were provided *ad libitum*.

examination of major tissues, major organs, and all gross lesions. 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 neutral buffered 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an

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

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

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

trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be

made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

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

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

obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

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

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control

group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the dosed group than in the control.

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

III. RESULTS - RATS

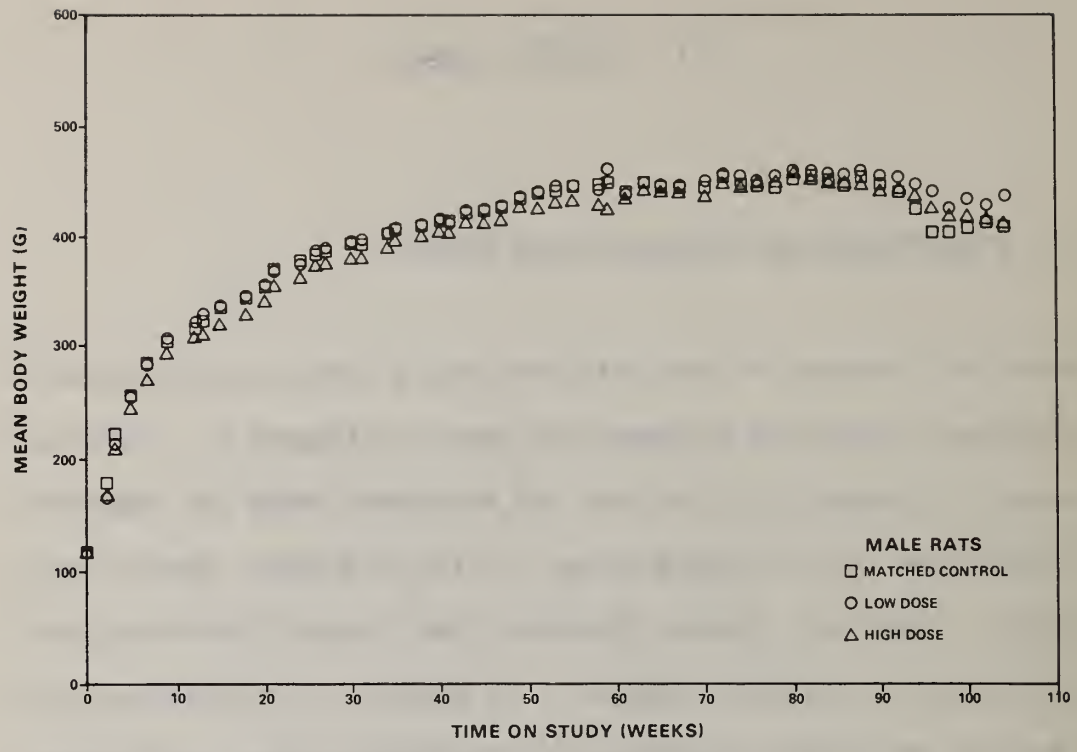
A. Body Weights and Clinical Signs (Rats)

Mean body weights of the male and female rats were essentially the same as those of corresponding controls (figure 1). Clinical signs of hyperactivity in low- and high-dose males and high-dose females and of discolored urine in the high-dose females were noted. Bloating, vaginal bleeding, and vaginal discharge also were noted in the dosed females. In addition, tissue masses were observed at highest incidences in high-dose males and low-dose females, and tachypnea was observed at a higher incidence in dosed groups than in control groups.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered diazinon in the diet at the doses of this bioassay, together with those for the matched controls, are shown by the Kaplan and Meier curves in figure 2.

In male rats, the result of the Tarone test for dose-related



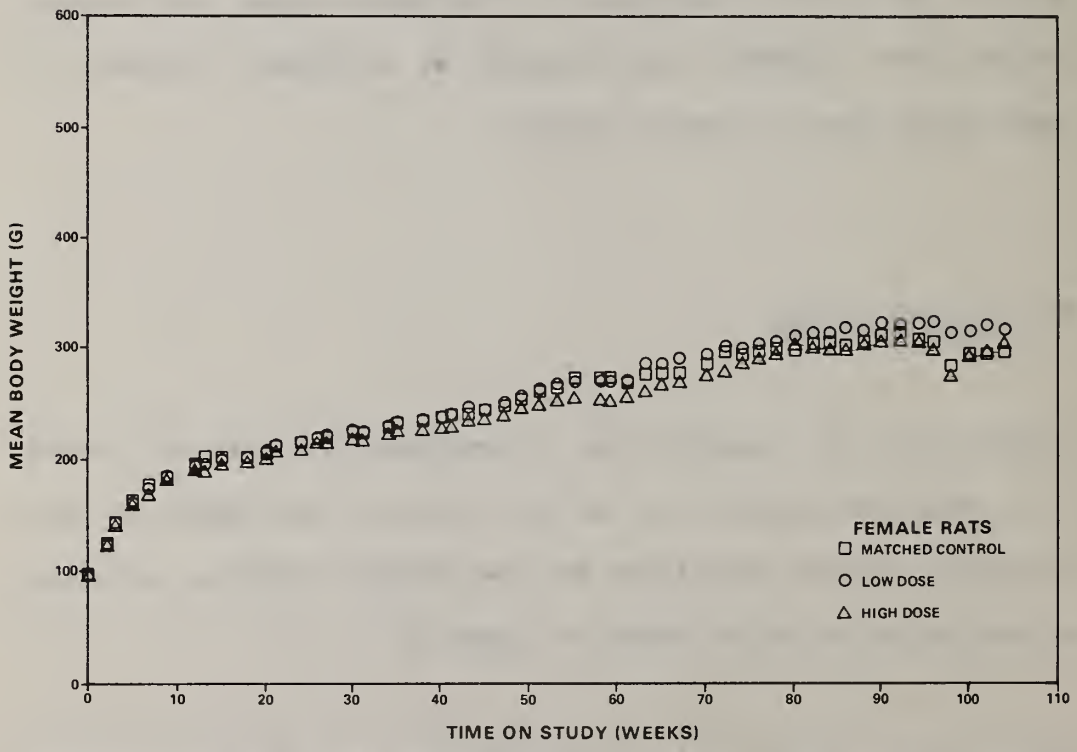


Figure 1. Growth Curves for Rats Administered Diazinon in the Diet

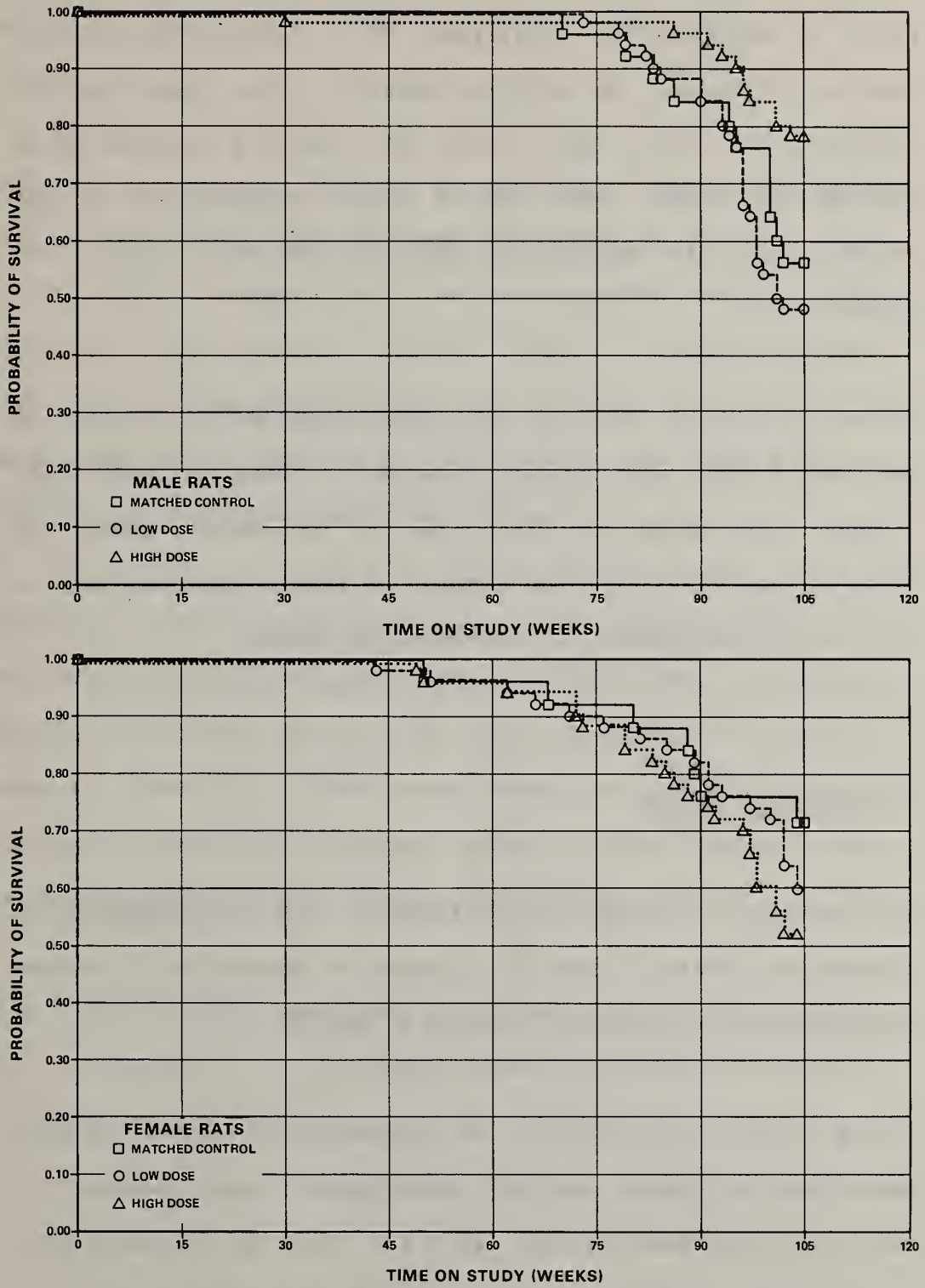


Figure 2. Survival Curves for Rats Administered Diazinon in the Diet

trend in mortality is significant (P = 0.021), but in the negative direction. An indicated departure from linear trend is observed (P = 0.033), due to the fact that the low-dose group survival was shorter than that of either the high-dose or the control group. In females, the result of the Tarone test is not significant.

In male rats 49/50 (98%) of each dosed group and 24/25 (96%) of the control group were alive at week 78. In females, 44/50 (88%) of each dosed group and 23/25 (92%) of the control group were alive at week 78. Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, tables C1 and C2.

A wide variety of neoplastic and nonneoplastic lesions occurred among male and female rats with approximately equal frequency in the control and dosed groups. In a few cases the incidence of a

particular lesion was higher in control groups than in dosed groups.

Leukemia or lymphoma occurred in dosed and control groups of rats of each sex. The increased incidence in low-dose males (25/50 (50%)), compared with the corresponding controls (5/25 (20%)) and high-dose males (12/50 (24%)), is of questionable significance. The leukemias were of the type usually seen in aging F344 rats, involving liver, spleen, and lung and were composed of neoplastic mononuclear cells.

Endometrial stromal polyps were observed at a higher incidence in the low-dose (8/43 (19%)) and high-dose (11/49 (22%)) groups than those in the control group (2/23 (9%)). However, this lesion is commonly observed in F344 rats; thus, it appears that the incidence of endometrial stromal polyps in this bioassay is not related to administration of the test chemical.

This histopathologic examination provided no convincing evidence for carcinogenicity of diazinon in F344 rats under conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables 4 and 5 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In female rats, the results of the Cochran-Armitage test for dose-related trend in the incidence of tumors and those of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group are not significant.

The result of the Fisher exact test in the incidence of lymphoma or leukemia in male rats, shows that the incidence in the low-dose group is significantly higher ($P = 0.011$) than that in the control group. However, the incidence in the high-dose group and the results of the Cochran-Armitage test are not significant.

In each of the 95% confidence intervals for relative risk, shown in the tables, except for the combined incidence of lymphoma and leukemia in the low-dose male rats, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of

the induction of tumors by diazinon, which could not be detected under the conditions of this test.

Table 4. Analyses of the Incidence of Primary Tumors in Male Rats Administered Diazinon in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	1/24 (4)	0/48 (0)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	1.959
Lower Limit		0.000	0.211
Upper Limit		9.332	94.428
Weeks to First Observed Tumor	105	--	105
Hematopoietic System: Lymphoma or Leukemia (b)	5/25 (20)	25/50 (50)	12/50 (24)
P Values (c,d)	N.S.	P = 0.011	N.S.
Departure from Linear Trend (e)	P = 0.002		
Relative Risk (f)		2.500	1.200
Lower Limit		1.107	0.454
Upper Limit		7.374	3.950
Weeks to First Observed Tumor	70	78	96

Table 4. Analyses of the Incidence of Primary Tumors in Male Rats Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Carcinoma, NOS, or Adenoma, NOS (b)	9/23 (39)	12/46 (26)	19/42 (45)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.667	1.156
Lower Limit		0.314	0.617
Upper Limit		1.555	2.440
Weeks to First Observed Tumor	79	84	91
Adrenal: Pheochromocytoma (b)	3/24 (13)	2/49(4)	2/48(4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.327	0.333
Lower Limit		0.029	0.030
Upper Limit		2.693	2.747
Weeks to First Observed Tumor	95	105	105

Table 4. Analyses of the Incidence of Primary Tumors in Male Rats Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma (b)	2/22 (9)	0/44 (0)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.220
Lower Limit		0.000	0.004
Upper Limit		1.678	4.055
Weeks to First Observed Tumor	100	--	105
Thyroid: C-cell Carcinoma or Adenoma (b)	4/22 (18)	5/44 (11)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.625	0.550
Lower Limit		0.153	0.134
Upper Limit		2.897	2.565
Weeks to First Observed Tumor	100	97	103

Table 4. Analyses of the Incidence of Primary Tumors in Male Rats Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma (b)	5/25 (20)	6/47 (13)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.638	0.612
Lower Limit		0.184	0.176
Upper Limit		2.421	2.327
Weeks to First Observed Tumor	94	90	105
Testis: Interstitial-cell Tumor (b)	20/25 (80)	46/50 (92)	45/50 (90)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.150	1.125
Lower Limit		0.937	0.913
Upper Limit		1.402	1.406
Weeks to First Observed Tumor	86	73	86

Table 4. Analyses of the Incidence of Primary Tumors in Male Rats Administered Diazinon in the Diet (a)

(continued)

(a) Dosed groups received 400 or 800 ppm.

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

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

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

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

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

Table 5. Analyses of the Incidence of Primary Tumors in Female Rats Administered Diazinon in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphoma or Leukemia (b)	2/25 (8)	6/50 (12)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.500	1.500
Lower Limit		0.297	0.297
Upper Limit		14.521	14.521
Weeks to First Observed Tumor	50	81	49
Pituitary: Carcinoma, NOS (b)	3/25 (12)	3/45 (7)	1/47 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.556	0.177
Lower Limit		0.081	0.004
Upper Limit		3.900	2.092
Weeks to First Observed Tumor	68	71	104

Table 5. Analyses of the Incidence of Primary Tumors in Female Rats Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Carcinoma, NOS, Adenoma, NOS, or Adenocarcinoma, NOS	17/28 (61)	28/45 (62)	23/47 (49)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.025	0.806
Lower Limit		0.698	0.528
Upper Limit		1.593	1.318
Weeks to First Observed Tumor	68	71	79
Thyroid: Follicular-cell Adenoma (b)	0/25 (0)	0/47 (0)	3/48 (6)
P Values (c,d)	N.S.	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.321
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	104

Table 5. Analyses of the Incidence of Primary Tumors in Female Rats Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma or Adenoma (b)	0/25 (0)	4/47 (9)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.506	0.029
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	91	91
Mammary Gland: Fibroadenoma (b)	5/25 (20)	7/50 (14)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.700	0.400
Lower Limit		0.217	0.088
Upper Limit		2.564	1.716
Weeks to First Observed Tumor	104	76	88

Table 5. Analyses of the Incidence of Primary Tumors in Female Rats Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	2/23 (9)	8/43 (19)	11/49 (22)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.140	2.582
Lower Limit		0.481	0.637
Upper Limit		19.572	22.748
Weeks to First Observed Tumor	104	62	72

(a) Dosed groups received 400 or 800 ppm.

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

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

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

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

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

IV. RESULTS - MICE

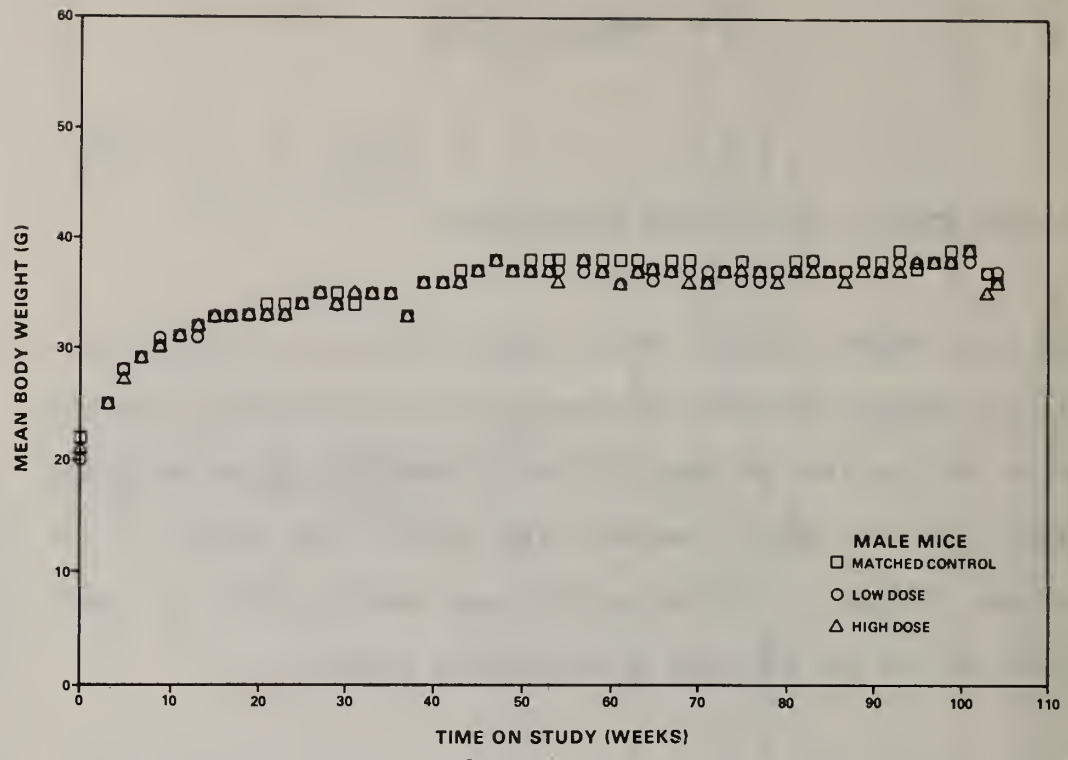
A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed groups of male and female mice were essentially the same as those of the corresponding controls except for the last 20 weeks of the bioassay, when the mean body weights of the dosed females were lower than those of the controls (figure 3). Hyperactivity was reported for the dosed groups of mice but was rare in the control groups.

B. Survival (Mice)

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

In male mice, 49/50 (98%) of the high-dose group, 45/50 (90%) of the low-dose group, and 21/25 (84%) of the control group were



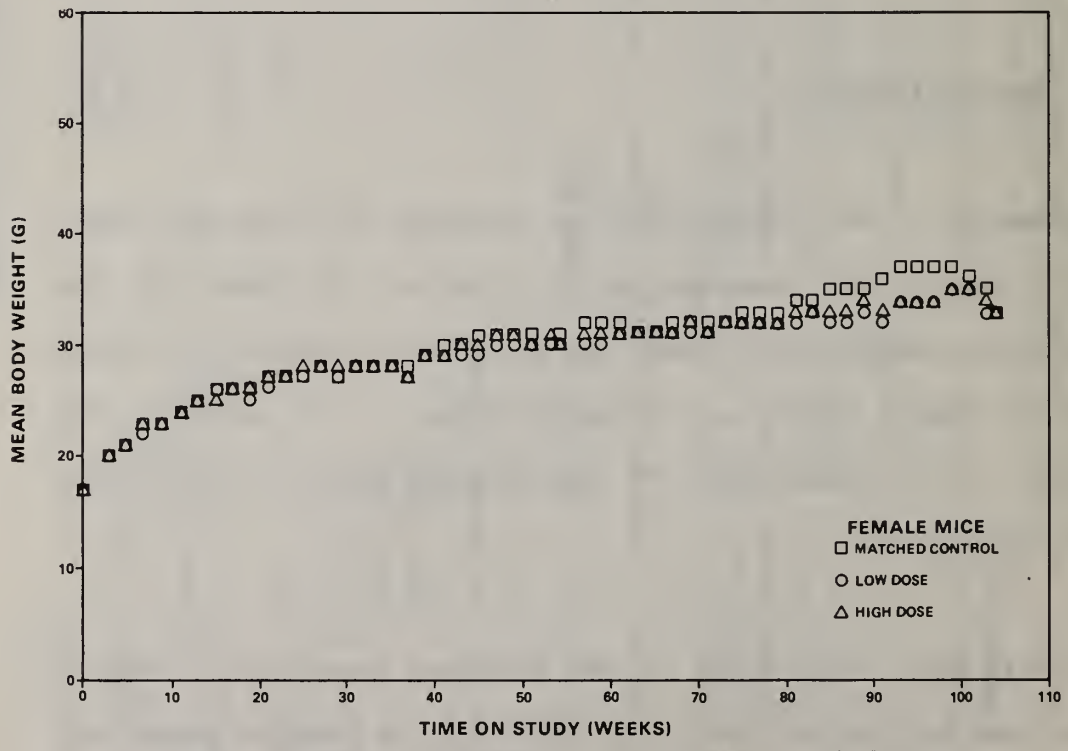
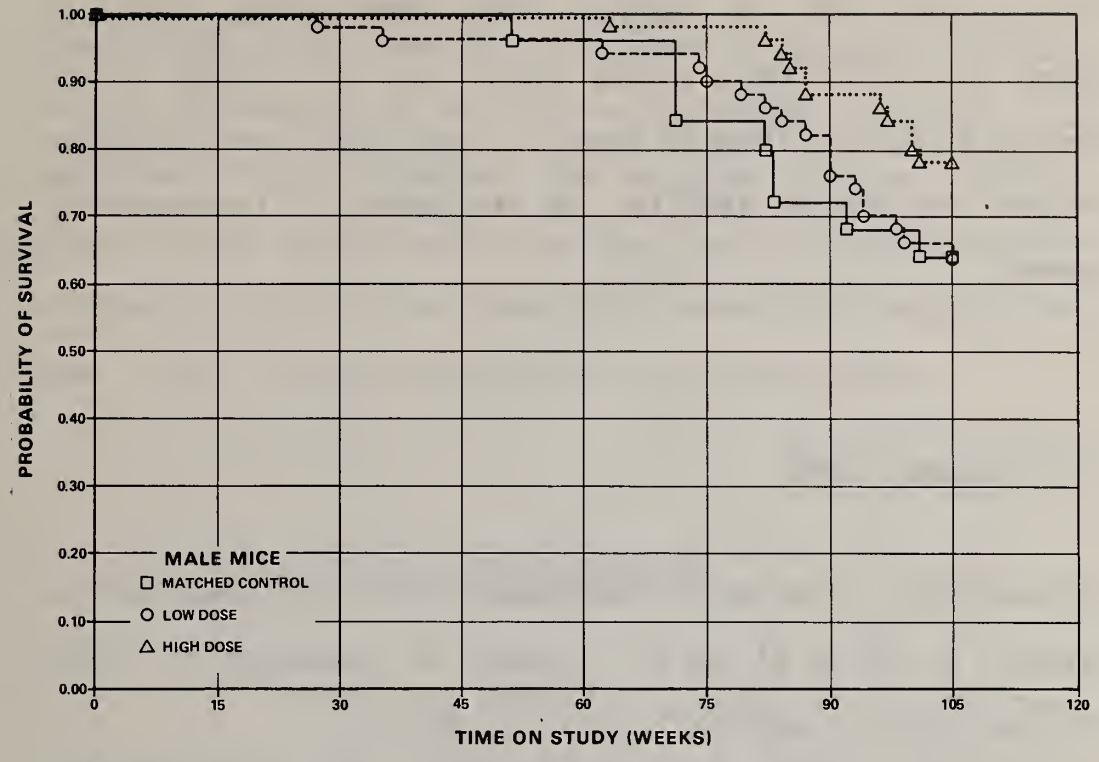


Figure 3. Growth Curves for Mice Administered Diazinon in the Diet



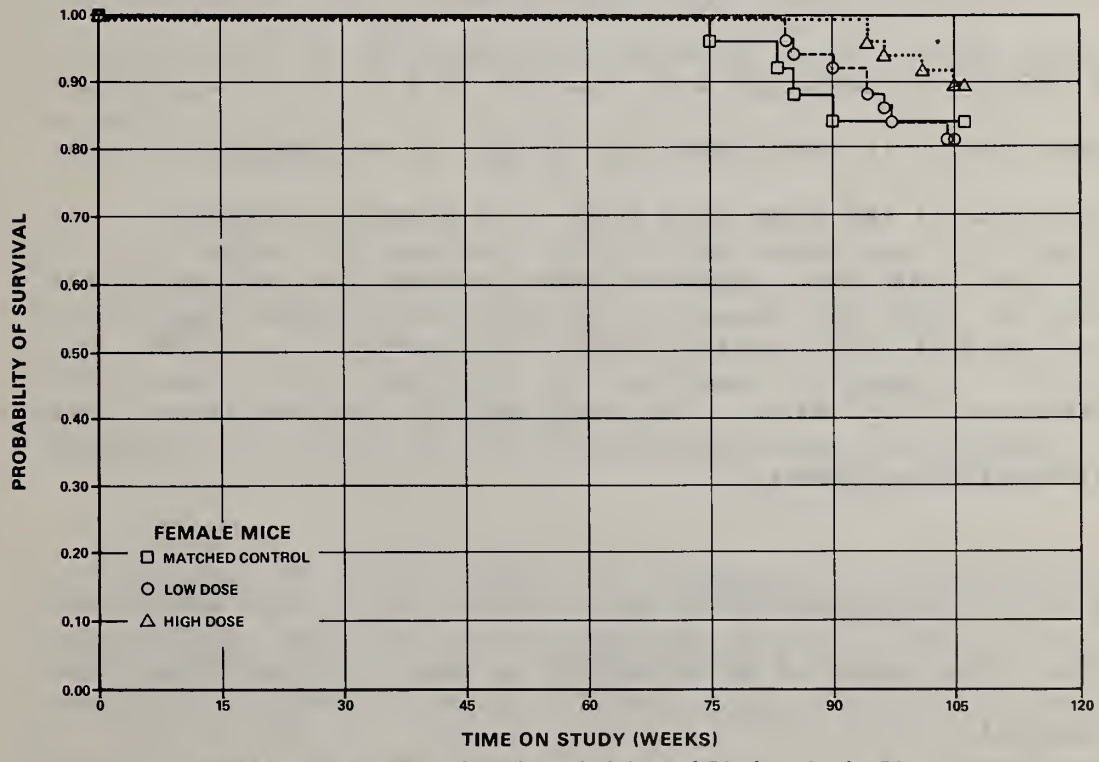


Figure 4. Survival Curves for Mice Administered Diazinon in the Diet

alive at week 78. In females, 49/50 (98%) of the high-dose group, all 50 of the low-dose group, and 24/25 (96%) of the control group were alive at week 78. Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

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

A variety of neoplasms were observed in both dosed and control mice. Most of these were not thought to be compound related. Neoplasms of the liver were seen in an elevated incidence in the low-dose male mice. Hepatocellular adenomas or carcinomas were seen in 5/21 (24%) control, 20/46 (43%) low-dose, and 13/48 (27%) high-dose male mice. The majority of the carcinomas were trabecular carcinomas.

A variety of nonneoplastic lesions were seen in dosed and control mice. None appeared to be related to administration of the test chemical.

This histopathologic examination provided no convincing evidence for the carcinogenicity of diazinon in B6C3F1 mice under the conditions of this bioassay. The elevated incidence of liver tumors in the low-dose male mice may have been associated with administration of the test chemical; however, the incidence was lower in the high-dose group than in the low-dose group.

D. Statistical Analyses of Results (Mice)

Tables 6 and 7 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In female mice, the results of the Cochran-Armitage test for dose-related trend in the incidence of tumors and those of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group are not significant.

In male mice, the Fisher exact test comparing the incidence of hepatocellular carcinomas in the low-dose group with that in the control group shows a P value of 0.046, which is above the 0.025 level required for significance when the Bonferroni inequality

criterion is used for multiple comparison. The incidence of these tumors in the high-dose group and the results of the Cochran-Armitage test are not significant. When the incidence of either hepatocellular carcinomas or adenomas in male mice is analyzed, the P values of the statistical tests are above 0.05.

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

Table 6. Analyses of the Incidence of Primary Tumors in Male Mice Administered Diazinon in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma (b)	1/22 (5)	1/47 (2)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.468	1.375
Lower Limit		0.006	0.120
Upper Limit		35.995	70.655
Weeks to First Observed Tumor	105	105	103
Lung: Alveolar/Bronchiolar Adenoma (b)	2/22 (9)	3/47 (6)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.702	0.229
Lower Limit		0.088	0.004
Upper Limit		8.025	4.219
Weeks to First Observed Tumor	105	105	105

Table 6. Analyses of the Incidence of Primary Tumors in Male Mice Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphoma or Leukemia (b)	3/22 (14)	7/47 (15)	7/48 (15)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.092	1.069
Lower Limit		0.283	0.277
Upper Limit		6.104	5.982
Weeks to First Observed Tumor	83	82	100
Liver: Hepatocellular Carcinoma (b)	4/21 (19)	20/46 (43)	10/48 (21)
P Values (c,d)	N.S.	P = 0.046	N.S.
Departure from Linear Trend (e)	P = 0.009		
Relative Risk (f)		2.283	1.094
Lower Limit		0.909	0.368
Upper Limit		8.187	4.365
Weeks to First Observed Tumor	83	74	84

Table 6. Analyses of the Incidence of Primary Tumors in Male Mice Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Adenoma (b)	5/21 (24)	20/46 (43)	13/48 (27)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.826	1.138
Lower Limit		0.800	0.452
Upper Limit		5.467	3.653
Weeks to First Observed Tumor	83	74	84

(a) Dosed groups received 100 or 200 ppm.

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

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

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

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

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

Table 7. Analyses of the Incidence of Primary Tumors in Female Mice Administered Diazinon in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphoma or Leukemia (b)	3/23 (13)	11/47 (23)	10/49 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.794	1.565
Lower Limit		0.542	0.459
Upper Limit		9.299	8.244
Weeks to First Observed Tumor	83	94	103
Liver: Hepatocellular			
Carcinoma or Adenoma (b)	2/23 (9)	0/47 (0)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.704
Lower Limit		0.000	0.880
Upper Limit		1.646	8.064
Weeks to First Observed Tumor	106	--	103

Table 7. Analyses of the Incidence of Primary Tumors in Female Mice Administered Diazinon in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	1/13 (8)	1/36 (3)	3/37 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.361	1.054
Lower Limit		0.005	0.098
Upper Limit		27.594	53.811
Weeks to First Observed Tumor	106	105	94
Mammary Gland: Fibroadenoma (b)	0/23 (0)	1/47 (2)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.027	0.449
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	94

Table 7. Analyses of the Incidence of Primary Tumors in Female Mice Administered Diazinon in the Diet (a)

(continued)

(a) Dosed groups received 100 or 200 ppm.

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

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

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

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

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

V. DISCUSSION

There was no appreciable effect of administration of diazinon on mean body weights of rats or mice of either sex. Mortality was not increased in any of the dosed groups of rats or mice, and survival was 84% or greater in all dosed and control groups at week 78. Some hyperactivity was observed in dosed groups of both species; however, both the rats and mice may have been able to tolerate higher doses. Sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

In the male rats, lymphomas or leukemias occurred in the low-dose group at an incidence that was significaltly higher ($P = 0.011$) than that in the control group; however, the incidence of the tumors in the high-dose group was not significant; (controls 5/25, low-dose 25/50, high-dose 12/50). In the male mice, hepatocellular carcinomas occurred in the low-dose group at an incidence that was significant at a level of $P = 0.046$; however, this level is above that of 0.025 required for significance when the Bonferroni inequality criterion is used for multiple comparison. In addition, the incidence of hepatocellular carcinomas in the high-dose group was not significant, (controls 4/21, low-dose 20/46, high-dose 10/48), and the incidences of

combined hepatocellular carcinomas and adenomas were not significant by any of the statistical tests used (controls 5/21, low-dose 20/46, high-dose 13/48). Thus, the occurrence of hematopoietic tumors in the male rats and of tumors of the liver in the male mice cannot clearly be related to administration of the test chemical. No tumors occurred at significant incidences by any test in either the female rats or the female mice.

In a chronic study previously carried out using diazinon (Bruce et al., 1955), diazinon was administered at 10, 100, or 1,000 ppm in the feed to Carworth Farms albino rats. At 1,000 ppm, initial growth retardation was observed in young rats; however, after 72 weeks the other concentrations had no significant effect on consumption of food, gain in body weight, or percentage of survival. The animals were to be carried on study for 2 years; however, the final results of the study are not available.

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

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED DIAZINON IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
TRICHOEPITHELIOMA		1 (2%)	
*SUBCUT TISSUE	(25)	(50)	(50)
FIBROMA	1 (4%)	1 (2%)	1 (2%)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
RESPIRATORY SYSTEM			
*NASAL MUCOSA	(25)	(50)	(50)
CARCINOMA,NOS			1 (2%)
#LUNG	(24)	(48)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(50)	(50)
LEUKEMIA,NOS	5 (20%)	16 (32%)	10 (20%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
MONOCYTIC LEUKEMIA		6 (12%)	2 (4%)
#LIVER	(24)	(49)	(49)
LEUKEMIA,NOS		1 (2%)	
#PEYERS PATCH	(22)	(44)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(25)	(49)	(50)
SARCOMA, NOS		1 (2%)	
#LIVER	(24)	(49)	(49)
NEOPLASTIC NODULE	1 (4%)	1 (2%)	
HEPATOCELLULAR CARCINOMA		1 (2%)	
#PANCREAS	(25)	(47)	(49)
ACINAR-CELL ADENOMA			2 (4%)
#SMALL INTESTINE	(22)	(44)	(48)
CARCINOMA,NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(25)	(49)	(50)
LIPOSARCOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(23)	(46)	(42)
CARCINOMA,NOS	1 (4%)		
ADENOMA, NOS	8 (35%)	12 (26%)	19 (45%)
#ADRENAL	(24)	(49)	(48)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	3 (13%)	2 (4%)	2 (4%)
GANGLIONEUROMA		2 (4%)	
#ADRENAL MEDULLA	(24)	(49)	(48)
GANGLIONEUROMA		1 (2%)	
#THYROID	(22)	(44)	(50)
FOLLICULAR-CELL ADENOMA			2 (4%)
C-CELL ADENOMA	2 (9%)	5 (11%)	4 (8%)
C-CELL CARCINOMA	2 (9%)		1 (2%)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
#PANCREATIC ISLETS	(25)	(47)	(49)
ISLET-CELL ADENOMA	5 (20%)	6 (13%)	6 (12%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
FIBROADENOMA			2 (4%)
*PREPUTIAL GLAND	(25)	(50)	(50)
ADENOMA, NOS		1 (2%)	
#TESTIS	(25)	(50)	(50)
INTERSTITIAL-CELL TUMOR	20 (80%)	46 (92%)	45 (90%)
#TUNICA ALBUGINEA	(25)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(25)	(50)	(50)
EPENDYMOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(25)	(50)	(50)
MESOTHELIOMA BENIGN		1 (2%)	
*PLEURA	(25)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
*TUNICA VAGINALIS	(25)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	2	4	1
MORIBUND SACRIFICE	9	22	10
*SCHEDULED SACRIFICE	2	2	2
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	12	22	37
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	25	49	50
TOTAL PRIMARY TUMORS	49	111	106
TOTAL ANIMALS WITH BENIGN TUMORS	24	49	49
TOTAL BENIGN TUMORS	40	78	87
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	27	16
TOTAL MALIGNANT TUMORS	8	30	18
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3	1
TOTAL UNCERTAIN TUMORS	1	3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
*SUBCUT TISSUE	(25)	(50)	(50)
FIBROMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(23)	(48)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)	2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
FIBROUS HISTIOCYTOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(50)	(50)
LEUKEMIA,NOS	1 (4%)	4 (8%)	3 (6%)
LYMPHOCYTIC LEUKEMIA			1 (2%)
MONOCYTIC LEUKEMIA		2 (4%)	1 (2%)
#SPLEEN	(25)	(47)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (4%)		
#LIVER	(24)	(48)	(50)
LEUKEMIA,NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*TONGUE	(25)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#SALIVARY GLAND	(25)	(49)	(49)
ADENOMA, NOS		1 (2%)	
#LIVER	(24)	(48)	(50)
NEOPLASTIC NODULE	1 (4%)	1 (2%)	
URINARY SYSTEM			
#KIDNEY	(25)	(50)	(50)
TUBULAR-CELL ADENOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(45)	(47)
CARCINOMA,NOS	3 (12%)	3 (7%)	1 (2%)
ADENOMA, NOS	14 (56%)	23 (51%)	22 (47%)
ADENOCARCINOMA, NOS		2 (4%)	
#ADRENAL	(25)	(50)	(49)
CORTICAL ADENOMA	1 (4%)		1 (2%)
#THYROID	(25)	(47)	(48)
FOLLICULAR-CELL ADENOMA			3 (6%)
C-CELL ADENOMA		3 (6%)	1 (2%)
C-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(25)	(48)	(50)
ISLET-CELL ADENOMA		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
ADENOMA, NOS		1 (2%)	
PAPILLARY ADENOMA		1 (2%)	
PAPILLARY ADENOCARCINOMA	1 (4%)		
INFILTRATING DUCT CARCINOMA			1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
FIBROADENOMA	5 (20%)	7 (14%)	4 (8%)
*CLITORAL GLAND	(25)	(50)	(50)
CARCINOMA,NOS		1 (2%)	1 (2%)
#UTERUS	(23)	(43)	(49)
ENDOMETRIAL STROMAL POLYP	2 (9%)	8 (19%)	11 (22%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)
#OVARY	(25)	(48)	(49)
SERTOLI-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(25)	(49)	(49)
EPENDYMOMA	1 (4%)		
OLIGODENDROGLIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*BODY CAVITIES	(25)	(50)	(50)
LIPOMA			1 (2%)
*ABDOMINAL CAVITY	(25)	(50)	(50)
LIPOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	1	2	4
MORIBUND SACRIFICE	6	18	20
*SCHEDULED SACRIFICE	2		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	30	26
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	20	44	41
TOTAL PRIMARY TUMORS	31	66	59
TOTAL ANIMALS WITH BENIGN TUMORS	16	36	35
TOTAL BENIGN TUMORS	23	50	47
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	15	12
TOTAL MALIGNANT TUMORS	7	15	12
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
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			

@ INCLUDES AUTOLYZED ANIMALS

* Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED DIAZINON IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	22	47	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	22	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(22)	(47)	(48)
BASAL-CELL CARCINOMA	1 (5%)		
FIBROSARCOMA		1 (2%)	3 (6%)
*SUBCUT TISSUE	(22)	(47)	(48)
SARCOMA, NOS		1 (2%)	
FIBROSARCOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(22)	(47)	(48)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (9%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(22)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)	3 (6%)	6 (13%)
LYMPHOCYTIC LEUKEMIA	1 (5%)		
#SPLEEN	(22)	(47)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#MESENTERIC L. NODE	(17)	(44)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		3 (7%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#STOMACH	(19)	(46)	(46)
MALIGNANT LYMPHOMA, NOS	1 (5%)		
CIRCULATORY SYSTEM			
#SPLEEN	(22)	(47)	(44)
HEMANGIOSARCOMA			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(21)	(46)	(48)
HEPATOCELLULAR ADENOMA	1 (5%)		3 (6%)
HEPATOCELLULAR CARCINOMA	4 (19%)	20 (43%)	10 (21%)
#DUODENUM	(19)	(42)	(44)
CARCINOMA-IN-SITU, NOS		1 (2%)	
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(21)	(42)	(42)
PAPILLARY ADENOMA	1 (5%)		
FOLLICULAR-CELL ADENOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(22)	(47)	(48)
ADENOMA, NOS	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	7	5	3
MORIBUND SACRIFICE	2	13	8
*SCHEDULED SACRIFICE	5	5	5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	27	34
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	12	30	24
TOTAL PRIMARY TUMORS	15	34	25
TOTAL ANIMALS WITH BENIGN TUMORS	6	3	4
TOTAL BENIGN TUMORS	6	3	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	27	21
TOTAL MALIGNANT TUMORS	9	31	21
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	23	47	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	23	47	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(23)	(47)	(49)
LEIOMYOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(23)	(46)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(23)	(47)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)	8 (17%)	7 (14%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (9%)	2 (4%)	
GRANULOCYTIC LEUKEMIA		1 (2%)	
#MESENTERIC L. NODE	(22)	(38)	(42)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#RENAL LYMPH NODE	(22)	(38)	(42)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#KIDNEY	(23)	(47)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(23)	(47)	(49)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(23)	(47)	(49)
HEMANGIOSARCOMA			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(23)	(47)	(49)
HEPATOCELLULAR ADENOMA	1 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	1 (4%)		2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(13)	(36)	(37)
ADENOMA, NOS	1 (8%)	1 (3%)	3 (8%)
#THYROID	(19)	(44)	(41)
PAPILLARY ADENOCARCINOMA			1 (2%)
#PANCREATIC ISLETS	(23)	(46)	(48)
ISLET-CELL CARCINOMA	1 (4%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(23)	(47)	(49)
FIBROADENOMA		1 (2%)	4 (8%)
#UTERUS	(22)	(44)	(46)
ENDOMETRIAL STROMAL POLYP			1 (2%)
#UTERUS/ENDOMETRIUM	(22)	(44)	(46)
ADENOMA, NOS		1 (2%)	
#OVARY	(19)	(44)	(45)
GRANULOSA-CELL TUMOR	1 (5%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(23)	(47)	(49)
ADENOMA, NOS			2 (4%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(23)	(47)	(49)
FIBROSARCOMA	1 (4%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	2	4	2
MORIBUND SACRIFICE	2	5	3
** SCHEDULED SACRIFICE	5	5	5
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	16	36	39
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

** Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	14	21
TOTAL PRIMARY TUMORS	10	16	28
TOTAL ANIMALS WITH BENIGN TUMORS	3	4	10
TOTAL BENIGN TUMORS	3	4	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	12	14
TOTAL MALIGNANT TUMORS	6	12	16
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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 ADMINISTERED DIAZINON IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(24)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
BRONCHOPNEUMONIA, ACUTE			1 (2%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(25)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#SPLEEN	(25)	(49)	(48)
CONGESTION, NOS		6 (12%)	2 (4%)
HEMORRHAGE		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LYMPH NODE	(24)	(46)	(48)
CONGESTION, NOS		1 (2%)	
#MESENTERIC L. NODE	(24)	(46)	(48)
INFLAMMATION, NOS		1 (2%)	
#PEYERS PATCH	(22)	(44)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#LYMPH NODE	(24)	(46)	(48)
LYMPHANGIECTASIS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#HEART	(25)	(50)	(50)
THROMBUS, MURAL		1 (2%)	
#AURICULAR APPENDAGE	(25)	(50)	(50)
THROMBOSIS, NOS	1 (4%)		1 (2%)
#MYOCARDIUM	(25)	(50)	(50)
INFLAMMATION, INTERSTITIAL		2 (4%)	
FIBROSIS, FOCAL		1 (2%)	
#PANCREAS	(25)	(47)	(49)
PERIARTERITIS	1 (4%)	2 (4%)	1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(25)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
#LIVER	(24)	(49)	(49)
NECROSIS, FOCAL		2 (4%)	
NECROSIS, DIFFUSE		1 (2%)	
METAMORPHOSIS FATTY	1 (4%)		1 (2%)
FOCAL CELLULAR CHANGE	1 (4%)		1 (2%)
HYPERPLASIA, NODULAR			1 (2%)
#LIVER/CENTRILOBULAR	(24)	(49)	(49)
NECROSIS, DIFFUSE		1 (2%)	
#BILE DUCT	(24)	(49)	(49)
HYPERPLASIA, NOS	1 (4%)	1 (2%)	
#PANCREAS	(25)	(47)	(49)
INFLAMMATION, NOS		1 (2%)	
ATROPHY, NOS			1 (2%)
#PANCREATIC ACINUS	(25)	(47)	(49)
ATROPHY, NOS	6 (24%)	4 (9%)	12 (24%)
ATROPHY, FOCAL		1 (2%)	
#STOMACH	(24)	(48)	(48)
CYST, NOS			1 (2%)
ULCER, NOS		2 (4%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CALCIFICATION, DYSTROPHIC		1 (2%)	
#CECUM	(22)	(45)	(46)
INFLAMMATION, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(25)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC	15 (60%)	29 (59%)	39 (78%)
CALCIFICATION, DYSTROPHIC		1 (2%)	
#URINARY BLADDER	(22)	(41)	(43)
INFLAMMATION, CHRONIC	1 (5%)		
METAPLASIA, SQUAMOUS	1 (5%)		
ENDOCRINE SYSTEM			
#PITUITARY	(23)	(46)	(42)
CYST, NOS		3 (7%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL	(24)	(49)	(48)
METAMORPHOSIS FATTY		1 (2%)	
ANGIECTASIS		1 (2%)	
#ADRENAL MEDULLA	(24)	(49)	(48)
HYPERPLASIA, NOS			1 (2%)
#THYROID	(22)	(44)	(50)
FOLLICULAR CYST, NOS		1 (2%)	
HYPERPLASIA, C-CELL		1 (2%)	1 (2%)
#PARATHYROID	(20)	(34)	(35)
HYPERPLASIA, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
#PROSTATE	(22)	(42)	(39)
MULTIPLE CYSTS		1 (2%)	
INFLAMMATION, CHRONIC	1 (5%)		
#TESTIS	(25)	(50)	(50)
ATROPHY, NOS	1 (4%)	1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTRDL	LOW DDSE	HIGH DDSE
HYPERPLASIA, INTERSTITIAL CELL	1 (4%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN	(25)	(50)	(50)
HYDROCEPHALUS, NOS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(25)	(50)	(50)
LIPOGRANULOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(25)	(50)	(50)
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(23)	(48)	(50)
BRONCHOPNEUMONIA, ACUTE			2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (4%)		
HEMATOPOIETIC SYSTEM			
*BLOOD	(25)	(50)	(50)
LEUKOCYTOSIS, NOS		3 (6%)	3 (6%)
#SPLEEN	(25)	(47)	(50)
CONGESTION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#LYMPH NODE	(22)	(43)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(22)	(43)	(47)
INFLAMMATION, NOS		1 (2%)	
CIRCULATORY SYSTEM			
#AURICULAR APPENDAGE	(24)	(48)	(50)
THROMBUS, ORGANIZED	1 (4%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(25)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
#LIVER	(24)	(48)	(50)
CYST, NOS	1 (4%)		
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
PARASITISM	1 (4%)		
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	2 (8%)	1 (2%)	2 (4%)
FOCAL CELLULAR CHANGE			1 (2%)
#BILE DUCT	(24)	(48)	(50)
HYPERPLASIA, NOS	1 (4%)	1 (2%)	
#PANCREATIC ACINUS	(25)	(48)	(50)
ATROPHY, NOS	1 (4%)	4 (8%)	1 (2%)
#STOMACH	(23)	(47)	(49)
INFLAMMATION, NOS	1 (4%)		
ULCER, NOS		4 (9%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(25)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC	6 (24%)	26 (52%)	15 (30%)
CALCIFICATION, DYSTROPHIC	1 (4%)		
#URINARY BLADDER	(24)	(45)	(48)
HYPERPLASIA, EPITHELIAL			1 (2%)
METAPLASIA, SQUAMOUS	1 (4%)		
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(45)	(47)
CYST, NOS	3 (12%)	3 (7%)	1 (2%)
MULTIPLE CYSTS		1 (2%)	2 (4%)
HEMORRHAGE			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS	3 (12%)	1 (2%)	3 (6%)
#ADRENAL	(25)	(50)	(49)
NECROSIS, NOS	1 (4%)		
ANGIECTASIS			1 (2%)
#THYROID	(25)	(47)	(48)
HYPERPLASIA, C-CELL		2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
#OVARY	(25)	(48)	(49)
CYST, NOS		1 (2%)	
FOLLICULAR CYST, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*BODY CAVITIES	(25)	(50)	(50)
LIPOGRANULOMA			1 (2%)
*ABDOMINAL CAVITY	(25)	(50)	(50)
LIPOGRANULOMA		3 (6%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	2	5

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED DIAZINON IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	22	47	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	22	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(22)	(47)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(22)	(47)	(48)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	
#SPLEEN	(22)	(47)	(44)
SCAR			1 (2%)
INFARCT, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)		
#MESENTERIC L. NODE	(17)	(44)	(48)
INFLAMMATION, GRANULOMATOUS		1 (2%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#RENAL LYMPH NODE	(17)	(44)	(48)
INFLAMMATION, ACUTE			1 (2%)
#INGUINAL LYMPH NODE	(17)	(44)	(48)
INFLAMMATION, ACUTE			1 (2%)
#LIVER	(21)	(46)	(48)
HEMATOPOIESIS	1 (5%)		
#KIDNEY	(22)	(47)	(47)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(22)	(46)	(47)
INFLAMMATION, ACUTE	1 (5%)		
#HEART/ATRIUM	(22)	(46)	(47)
THROMBOSIS, NOS	1 (5%)		
*ARTERY	(22)	(47)	(48)
PERIARTERITIS	1 (5%)		
#PANCREAS	(21)	(46)	(47)
PERIARTERITIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(21)	(46)	(48)
INFARCT, NOS		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	
FOCAL CELLULAR CHANGE	1 (5%)	1 (2%)	5 (10%)
#PANCREAS	(21)	(46)	(47)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
ATROPHY, NOS		1 (2%)	
#STOMACH	(19)	(46)	(46)
INFLAMMATION, CHRONIC			1 (2%)
#PEYERS PATCH	(19)	(42)	(44)
HYPERPLASIA, NOS			1 (2%)
URINARY SYSTEM			
#URINARY BLADDER	(20)	(42)	(45)
HYPERPLASIA, EPITHELIAL		1 (2%)	
METAPLASIA, SQUAMOUS	1 (5%)	1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(22)	(43)	(47)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL MEDULLA	(22)	(43)	(47)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(21)	(42)	(42)
COLLOID CYST	1 (5%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(22)	(47)	(48)
INFLAMMATION, ACUTE	1 (5%)		1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	12	19
AUTOLYSIS/NO NECROPSY	3	3	2

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED DIAZINON IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	23	47	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	23	47	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(23)	(46)	(49)
ATELECTASIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(23)	(47)	(49)
HYPERPLASIA, LYMPHOID	7 (30%)	6 (13%)	3 (6%)
HEMATOPOIESIS		1 (2%)	
#SPLEEN	(22)	(47)	(48)
CALCIFICATION, DYSTROPHIC			1 (2%)
HYPERPLASIA, LYMPHOID	2 (9%)	1 (2%)	
#SPLENIC SINUSOIDS	(22)	(47)	(48)
HYPERPLASIA, NOS	1 (5%)		
#LUNG	(23)	(46)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#KIDNEY	(23)	(47)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
*PULMONARY ARTERY	(23)	(47)	(49)
HYPERTROPHY, NOS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*UTERINE ARTERY	(23)	(47)	(49)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(23)	(47)	(49)
INFLAMMATION, ACUTE	1 (4%)		
GRANULOMA, NOS			1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
FOCAL CELLULAR CHANGE	1 (4%)		1 (2%)
#COLON	(22)	(45)	(45)
NEMATODIASIS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(23)	(47)	(48)
CALCIFICATION, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(13)	(36)	(37)
HYPERPLASIA, FOCAL		2 (6%)	
ANGIECTASIS			1 (3%)
REPRODUCTIVE SYSTEM			
#UTERUS	(22)	(44)	(46)
INFLAMMATION, CHRONIC	1 (5%)		
#UTERUS/ENDOMETRIUM	(22)	(44)	(46)
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, NOS	5 (23%)	7 (16%)	
HYPERPLASIA, CYSTIC		1 (2%)	22 (48%)
#OVARY	(19)	(44)	(45)
CYST, NOS		4 (9%)	2 (4%)
NERVOUS SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(23)	(47)	(49)
INFLAMMATION, GRANULOMATOUS			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	15	7
AUTOLYSIS/NO NECROPSY	2	3	1

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

APPENDIX E

ANALYSES OF FORMULATED DIETS FOR CONCENTRATIONS OF DIAZINON

APPENDIX E

Analyses of Formulated Diets for Concentration of Diazinon

A 10-gram sample of the diet mixture was shaken with 250 mls of benzene at room temperature for 16 hours. A 1-ml aliquot of the resulting benzene solution was removed for analyses. The benzene solution was quantitatively analyzed for diazinon 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 Dietary Level (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
100	15	100.19	5.0	89-110
200	11	202.54	4.7	194-220
400	11	406.12	3.3	389-433
800	11	830.47	5.7	791-966

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

December 13, 1978

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

The reviewer for the report on the bioassay of Diazinon said that the compound was not carcinogenic under the conditions of test. After a brief description of the experimental design, he said that the maximum tolerated doses probably were not tested, as indicated by the lack of weight depression among treated animals. He also noted the poor survival among certain of the animal groups. Because the study was "clearly negative," the reviewer opined that the experimental shortcomings did not invalidate the conclusion. He moved that the report on the bioassay of Diazinon be accepted as written. The motion was seconded and approved without objection.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego

Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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