National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 10
1977

BIOASSAY OF DICHLORVOS FOR POSSIBLE CARCINOGENICITY

CAS No. 62-73-7

NCI-CG-TR-10

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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DHEW Publication No. (NIH) 77-810

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CONTRIBUTORS: This report presents the results of the bioassay of dichlorvos for possible carcinogenicity, conducted by the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. This research was conducted at Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Incorporated, prime contractor for the NCI carcinogen bioassay program.

The experimental design was determined by Drs. J. H. Weisburger[1,2] and R. R. Bates[1]; the doses were selected by Drs. T. E. Shellenburger[3,4], J. H. Weisburger and R. R. Bates. Animal treatment and observations were supervised by Drs. T. E. Shellenburger, W. E. Greer[3], and H. P. Burchfield[3], with the technical assistance of Ms. D. H. Monceaux[3] and Mr. D. Broussard[3]. Necropsies were performed under the supervision of Drs. E. Bernal[3] and B. Buratto[3]. The histopathologic evaluation was conducted at Experimental Pathology Laboratories by Dr. R. A. Renne[5,9] and Dr. J. Ferrell[5], and the diagnoses included in this report represent the interpretation of these pathologists. Pathologists at NCI and Tracor Jitco have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Compilation of individual animal survival and summary tables was performed by EG&G Mason Research Institute[7]; pathology tables were compiled at Experimental Pathology Laboratories[5]; and statistical analyses were performed by Dr. J. R. Joiner[6], using methods selected for the bioassay program by Dr. J. J. Gart[8].

This report was prepared at Tracor Jitco[6] under the direction of NCI. Those responsible for the report at Tracor Jitco were the toxicologist, Dr. J. F. Robens; the chemist, Dr. S. S. Olin; the technical editor, Dr. E. W. Gunberg; and the technical writer, Mr. W. D. Reichardt. The final report was reviewed by members of the participating organizations[1,3,5,6].

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SUMMARY

A bioassay for the possible carcinogenicity of technical-grade dichlorvos was conducted using Osborne-Mendel rats and B6C3F1 mice. The test material was administered in the diet at two concentrations for 80 weeks to groups of 50 animals of each species and sex. The test animals were held for observation, and surviving rats were killed at 110-111 weeks and surviving mice at 92-94 weeks from initiation of the study. Initial doses in both species were not well tolerated and they were lowered after a few weeks. Time-weighted average doses for both males and females were 150 and 326 ppm for rats and 318 and 635 ppm for mice. The matched controls consisted of 10 rats of each sex and 10 mice of each sex; the pooled controls consisted of 60 rats of each sex, 100 male mice, and 80 female mice. All surviving rats were killed at 106 to 109 weeks; surviving mice, at 92 to 94 weeks.

After the doses were reduced, no toxic signs directly attributable to the compound were observed. However, average weights of high-dose animals were slightly depressed. Survival was not dose-related in either species. Microscopic study of the tissues of treated animals and matched and pooled controls revealed no statistically significant increase in the incidence of tumors attributable to exposure to dichlorvos in either animal species. The significance of the three esophageal tumors in male and female mice and of malignant fibrous histiocytomas in male mice is unclear and there is insufficient evidence to indicate they were associated with dichlorvos treatment. Thus under the conditions of this study, dichlorvos was not demonstrated to be carcinogenic.

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I. INTRODUCTION

Dichlorvos, 2,2-dichlorovinyl dimethylphosphate, is an organophosphate insecticide with contact and vapor action (Eto, 1974). It has been used widely for control of agricultural, industrial, and domestic pests since the 1950's. Dichlorvos is available in oil solutions, emulsifiable concentrations, and aerosol formulations; the impregnation of dichlorvos in a polyvinyl chloride base (pellets, strips, blocks, etc.) for delayed release is a widely used method for the control of pests in domestic and industrial situations (WHO/FAO, 1968; Stevenson, 1970).

Dichlorvos is registered as an anthelmintic to be administered orally in swine, dogs, horses, cats, and puppies (CFR, 1976). Topical application has been approved for beef and dairy cattle, goats, sheep, swine, and chickens to control fleas, flies, and mites. Dichlorvos has also been approved for use in barns and chicken houses (WHO/FAO, 1968; EPA, 1973). Dichlorvos may be applied in mushroom houses and in greenhouses where cucumbers, radishes, lettuce, and tomatoes are grown (EPA, 1972, 1973). Aerosols (0.5% dichlorvos) and strips are used domestically for the control of ants, bedbugs, ticks, cockroaches, flies, mosquitoes, silverfish, spiders, and wasps (WHO/FAO, 1968).

Exposure to dichlorvos occurs by the inhalation of sprays or vapors from impregnated resins, by skin contact, or orally as a residue in food. The threshold limit value in workroom air as adopted by the American Conference of Government Industrial Hygienists (1971) is 1.0 mg/m^3; the acceptable daily intake has been set at 0-0.004 mg/kg body weight (WHO/FAO, 1968). Dichlorvos was selected for testing because of extensive use and long-term human exposure.

II. MATERIALS AND METHODS

A. Chemical

The dichlorvos used for this study was the technical-grade material, Vapona®, obtained from Shell Chemical Co., Agricultural Division, San Ramon, California. Analyses at Gulf South Research Institute confirmed the manufacturer's specification of 94% minimum purity. Analytical data include infrared, ultraviolet, and nuclear magnetic resonance spectra, and thin-layer and gas-liquid chromatograms. No attempt was made to identify impurities. Dichlorvos was stored in its original container (a clear, one-quart glass bottle) in a refrigerator at 4°C.

B. Dietary Preparation

All diets were formulated weekly using Wayne® Lab-Blox animal chow (Allied Mills; Chicago, Illinois) to which was added the required amount of dichlorvos. The test compound was first dissolved in a small amount of acetone, which was then added to the feed. Corn oil was also added to the feed, primarily as a dust suppressant, and the diets were mixed mechanically to assure homogeneity and to allow for evaporation of the acetone. Final diets, including the control diet, contained corn oil equal to 2%

of the final feed weight. The corn oil was produced by Opelousas Refinery Co., Opelousas, Louisiana.

The stability of dichlorvos in feed after 1, 4, and 7 days was determined at -20°C, 4°C, and at room temperature by extraction and quantitation of the test chemical remaining in 150 ppm, 300 ppm, and 600 ppm batches. The results indicated that the stability of feed mixtures stored in sealed glass containers was satisfactory at -20°C. At 4°C, analytical concentrations were within 10% of the initial values after 7 days, but concentrations dropped to approximately 30% of the original concentration after 4 days at room temperature. Therefore, diet mixtures were stored in a glass container at 0°C or lower, and the diet mixture in the feed hoppers was changed daily.

During the chronic study, samples of the diet at each concentration were selected at intervals and analyzed for the concentration of test chemical. The analytical means and standard deviations were:

150 ppm level (24 samples) = 147.4 $\pm$ 5.4 ppm,

300 ppm level (28 samples) = 295.4 $\pm$ 11.0 ppm,

600 ppm level (25 samples) = 594.0 $\pm$ 28.4 ppm.

Water and the formulated diets were made available ad libitum to the experimental animals.

C. Animals

Rats and mice of both sexes, obtained through contracts of the Division of Cancer Treatment, NCI, were used in these tests. The rats were Osborne-Mendel strain and were approximately the third generation bred at Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts, from animals originally procured from Battelle Memorial Institute, Columbus, Ohio. All other rats used for the pooled-control group were purchased directly from Battelle Memorial. The mice were B6C3F1 hybrids obtained from Charles River Breeding Laboratories, Inc. Upon arrival at the laboratory all animals were quarantined for 6-19 days as a laboratory-acclimation period and then assigned to each test group.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. Incoming air was filtered through fiberglass air conditioner filters which were changed monthly. The total air in each room was changed 10-12 time per hour. The relative humidity of the room air was maintained between 40% and 70% and the temperature range was 22-24^{o}C. Fluorescent lighting provided

illumination 10 hours per day. Rats were housed individually in hanging galvanized steel-mesh cages, and mice were in solid-bottom and clear-sided polypropylene cages equipped with a nonwoven polyester fiber-filter bonnet. Female mice were housed five per cage, and males two or three per cage. Initially rats were transferred to clean cages weekly; later in the study clean cages were provided biweekly. Mice were transferred to clean cages with filter bonnets weekly. Cages were cleaned two days prior to use. Fresh bedding (Absorb-Dri®, Lab Products) was provided two times a week for male mice and three times a week for females. Feeder jars were changed daily, and excess feed was discarded. Water bottles were changed and sterilized three times per week. Animals racks were rotated laterally for both species at weekly intervals; at the same time, each cage was changed to a different position in the row within the same column.

Rats and mice receiving dichlorvos were housed in separate rooms with their respective controls. No other animal was housed in either room.

E. Subchronic Studies

Feeding studies were conducted to estimate the maximum tolerated doses in order to determine the high and low concentrations (hereinafter referred to as "high doses" and "low doses") to be administered in the chronic study. The low dose given in the

chronic study is 1/2 the high dose. In these subchronic studies dichlorvos was added to the animal feed at twofold increasing doses, starting with 250 ppm and ending with 4,000 ppm for rats and mice. Because there was no mortality in any treated group of mice during the entire study, a second study was performed with doses of 4,000 to 12,000 ppm. The compound was provided in feed to experimental groups of five male and five female animals of each species for 6 weeks, followed by a 2-week observation period.

At 500 ppm none of the animals died, and there was only slight reduction of weight gain. At 1,000 ppm the compound-fed animals lost weight during the first and second weeks of the study but returned to near normal weight expectation after that time. At 2,000 and 4,000 ppm all animals died during the study. The low and high doses for rats were therefore set at 500 and 1,000 ppm. Due to intense signs of toxicity observed in the high-dose rats after initiation of the chronic study, the high-dose was reduced to 300 ppm. The low-dose rats, started four weeks after the high dose due to the inavailability of animals, were therefore placed on study at 150 ppm as shown in table 1 (also see pp. 8 and 11, below).

Mice receiving 4,000 ppm lost weight during the first week of the study, and three of five female animals died; a fourth female of

this group died during week 6. At 6,000 ppm and higher, all animals died. The low and high doses for mice were set at 1,000 and 2,000 ppm.

F. Design of Chronic Studies

The design of the chronic studies, including both test aimals and their matched controls, is illustrated in tables 1 and 2.

The pooled controls consisted of the initial matched controls, 10 animals of each sex and species, for the studies of aldrin, dieldrin, chlordane, dichlorvos, dimethoate, and heptachlor. Because additional matched-control mice were started simultaneously with restarted treatment groups for some of these compounds, the numbers of mice in the pooled-control groups vary. The pooled controls for tests using rats consisted of 60 male and 60 female rats; for mice, 100 males and 80 females. Each of the matched-control groups were housed in a separate room with its respective treatment groups. All controls were placed on study at 35 days of age except the matched-control rats for dichlorvos.

Because dichlorvos was the last bioassay of this series to be started, there were slight differences in the ages of rats used in the test. Due to the inability of the supplier to provide a sufficient number of rats to start the entire test at one time, one shipment of animals (the high-dose group and five matched

Table 1. Design of Dichlorvos Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals	Dichlorvos in Diet[a] (ppm)	Time on Study Treated[b] (weeks)	Time on Study Untreated[c] (weeks)	Time-Weighted Average Dose[d] (ppm)
Male					
Matched-Control	5	0	0	110	
Low-Dose	50	150	80		150
		0	0	30	
Matched-Control	5	0	0	110	
High-Dose	50	1,000	3		326
		300	77		
		0	0	30	
Female					
Matched-Control	5	0	0	110	
Low-Dose	50	150	80		150
		0	0	30	
Matched-Control	5	0	0	110	
High-Dose	50	1,000	3	30	326
		300	77		
		0	0	30-31	

[a]Doses were lowered because of toxic response.

[b]Treatment periods at high and lowered dosages.

[c]When diets containing dichlorvos were discontinued, treated animals and their matched controls were fed control diets (2% corn oil added) until termination.

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

Table 2. Design of Dichlorvos Chronic Feeding Studies in Mice

Sex and Treatment Group	Initial No. of Animals	Dichlorvos in Diet[a] (ppm)	Time on Study: Treated[b] (weeks)	Time on Study: Untreated[c] (weeks)	Time-Weighted Average Dose[d] (ppm)
Male					
Matched-Control	10	0	0	92	
Low-Dose	50	1,000	2		318
		300	78		
		0	0	13	
High-Dose	50	2,000	2		635
		600	78		
		0	0	14	
Female					
Matched-Control	10	0	0	92	
Low-Dose	50	1,000	2		318
		300	78		
		0	0	12-13	
High-Dose	50	2,000	2		635
		600	78		
		0	0	13-14	

[a]Doses were lowered because of toxic response.

[b]Treatment periods at high and lowered dosages.

[c]When diets containing dichlorvos were discontinued, treated animals and their matched controls were fed control diets (2% corn oil added) until termination.

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

controls of each sex) was started on test at 43 days of age. Four weeks later, a second shipment of animals (the low-dose group and five additional control animals of each sex) was placed on test at 36 days of age. Both shipments were obtained from the Charles River Breeding Laboratories, Inc. and were the progeny (third generation) of a group of Osborne-Mendel rats which were purchased from the Battelle Memorial Institute, Columbus, Ohio. Thus there was probably no significant genetic drift influencing the incidence of tumors.

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. Those animals appearing moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of all major tissues, organs, or gross lesions taken from killed animals and, where feasible, from animals found dead. The following tissues were routinely subjected to microscopic examination: brain, pituitary, adrenal, thyroid, parathyroid, trachea, esophagus, thymus, salivary gland, lymph nodes, heart, lung, spleen, liver, kidney, stomach, pancreas, small intestine, large intestine, urinary bladder, prostate or uterus, testis or ovary, mammary gland, skin, and bone including marrow.

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. An occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that showed early deaths. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to precluded histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically, varies and does not necessarily represent the number of animals that were placed on experiment 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 included descriptive information on the chemicals, animals, experimental design, clinical observations, survival, animal 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.

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. Deaths due to accident or scheduled deaths are treated as censored observations, and all other deaths are uncensored. Statistical tests of differences in survival between groups are compared using the method of Cox (1972) for two groups and an extension of this method by Tarone (1975) for more than two groups.

The incidence of neoplastic or nonneoplastic lesions is given as the proportion of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals examined pathologically at that site (denominator). For the organs and tissues in which most of the lesions appeared, the denominators included only those animals for which such sites were examined histologically. For tissues that required gross observation for detection of lesions (e.g., skin or mammary tumors), for lesions that appeared at several sites (e.g., lymphomas), or for tissues that were examined histologically only when lesions were detected grossly, the denominators consisted of the numbers of animals necropsied.

Statistical analysis of the incidence of tumors was made using the Fisher exact test (Cox, 1970) to compare a control group to a group of treated animals at each dose. In addition, the Armitage

and Cochran test for linear trend in proportions, with continuity correction (Armitage, 1971), was used. This test, assuming a linear trend, determined if the slope of the dose-response curve was different from zero, at the 0.05 level of significance. The method also provided a calculation of the level of probability of departure from linear trend.

A conservative adjustment, the Bonferroni inequality (Miller, 1966), was used for simultaneous comparison of several treated groups with a control group. For the comparison of results obtained with k different test doses with those for a control, this correction requires a level of significance less than or equal to 0.05/k for the overall comparison to be significant at the 0.05 level. This adjustment was not made in the tables where the Fisher exact test results are shown but is discussed in the analysis when appropriate.

As an additional analysis, the exact 95% confidence interval for the odds ratio (Gart, 1970) between each of the dose groups and its control was calculated. The odds ratio is $p_t(1-p_c)/p_c(1-p_t)$ where p_t is the true binomial probability of tumor in a treated group of animals and p_c is the true spontaneous probability of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and that in a control group is expressed by an odds ratio of 1 (one).

Values in excess of 1 (one) represent the condition of a larger proportion in the treated group than in the control. The entries for confidence intervals in the statistical tables of this report represent the conversion of each odds ratio to the difference in probabilities, $p_t - p_c$, where $p_t - p_c = 0$ implies an odds ratio of 1 (one).

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

During the 3-week period that the high-dose animals were on test at 1,000 ppm, intense signs of toxicity were observed, i.e., tremors, rough coat, diarrhea, and poor general appearance. When the doses were reduced to 150 and 300 ppm, the appearance and behavior of the treated rats during the first year of the study generally were comparable to those of the controls.

The average weights of male and female high-dose rats were consistently lower than the low-dose and matched-control groups throughout the first year and one half of the study (see figure 1).

During the first year, adverse clinical signs were noted in both treated and control groups at low or moderate incidence, with gradually increasing frequency in treated animals during the second year. These signs included rough hair coats, epistaxis, hematuria, alopecia (generalized and/or localized), dark urine, palpable masses, and bloating or abdominal distention. These signs were evident in both treated and control groups but were predominant in the high-dose female group. At terminaton of the

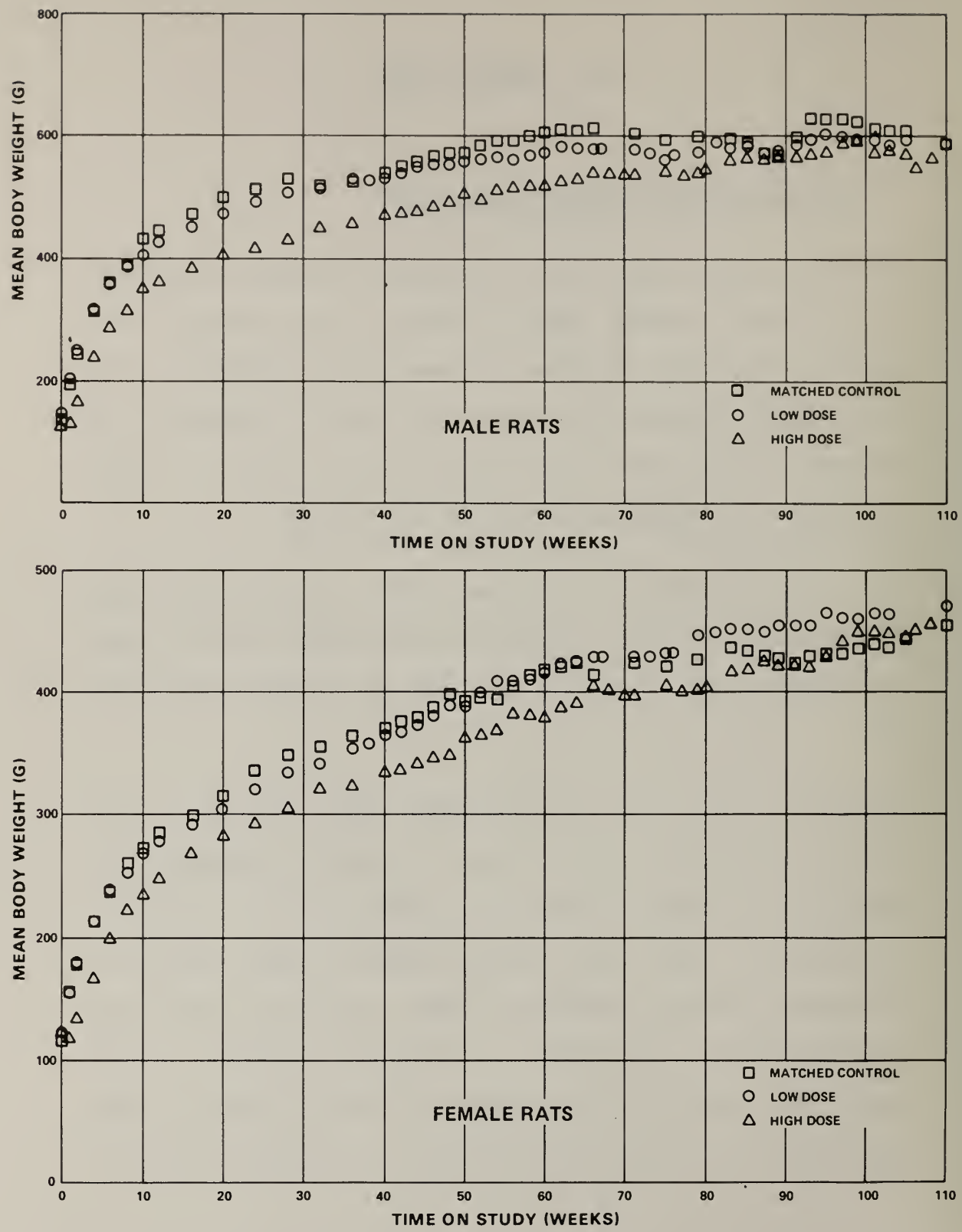


Figure 1. Growth Curves of Rats Fed Dichlorvos in the Diet

study surviving animals in both treated and control groups generally exhibited a poor physical condition.

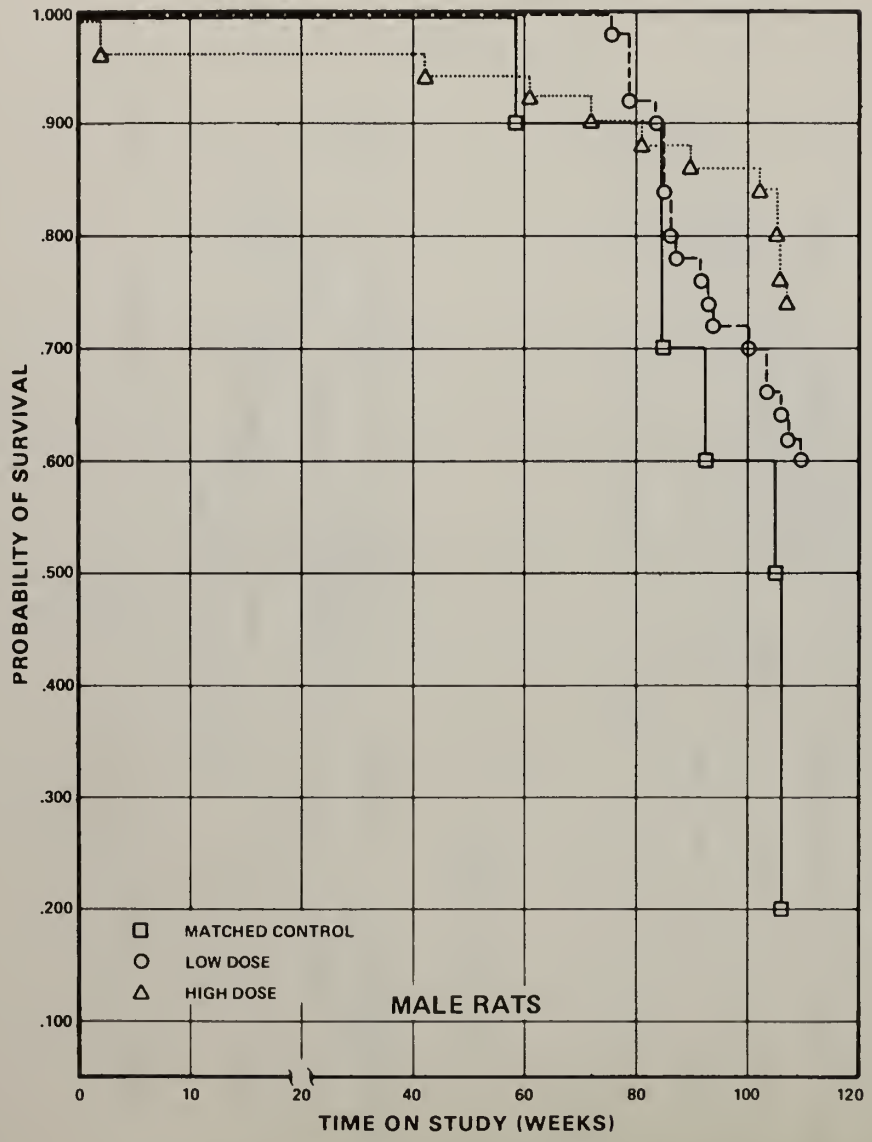
B. Survival (Rats)

There was little difference in survival between the matched-control group of male rats and the two dosed groups up to 105 weeks, at which time the matched-control group experienced a proportionally severe loss. Seventy-six percent of the high-dose males and 64% of the low-dose males survived for more than 105 weeks.

In the female rats, the matched-control group had the largest proportion of deaths prior to the terminaton of the experiment. Eighty-four percent of the high-dose females and 80% of the low-dose females survived for over 105 weeks. There is no statistical evidence of positive dose-related mortality. The Kaplan and Meier survival curves for high-dose males and females are comparable, as are those of low-dose males and females (see figure 2).

C. Pathology (Rats)

Histopathologic findings are tabulated in Appendix A, tables A1-A7, covering neoplasms and other proliferative lesions, and in Appendix C, tables C1 and C2, covering nonneoplastic lesions.



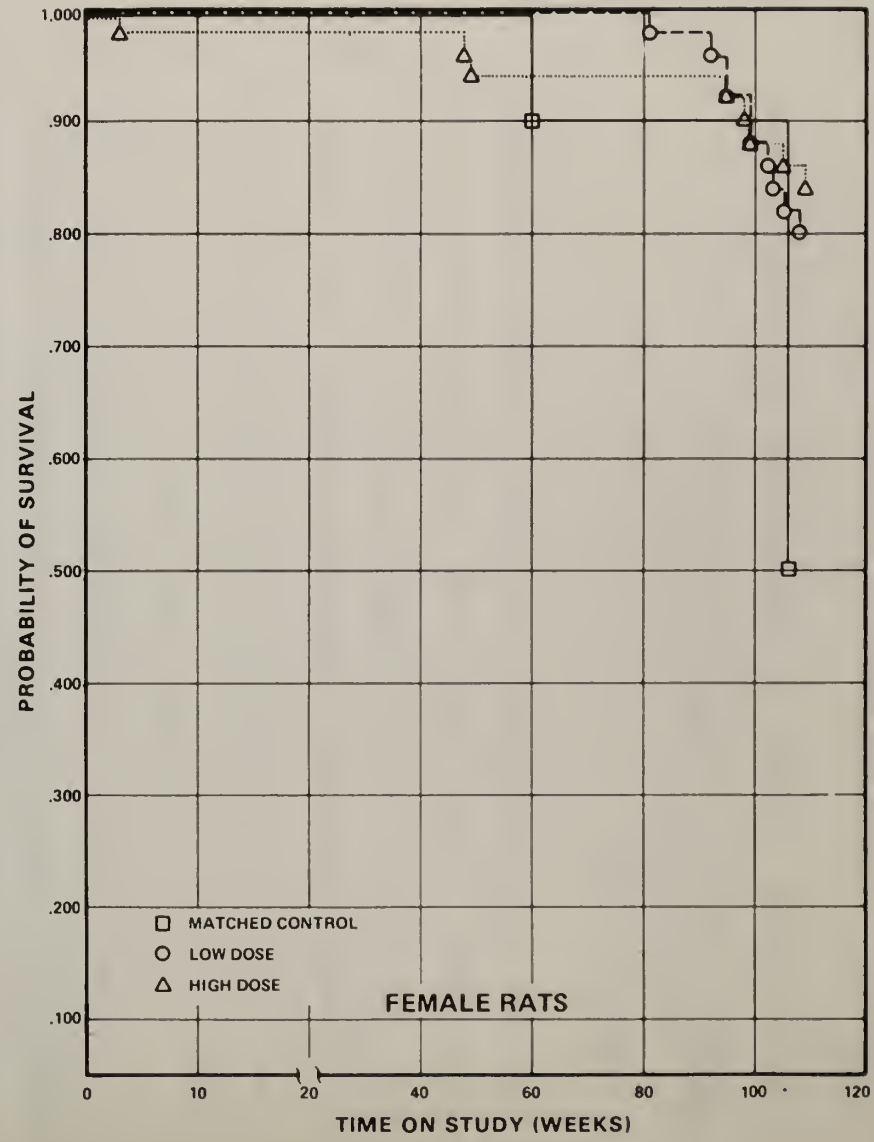


Figure 2. Survival Curves of Rats Fed Dichlorvos in the Diet

Numerous inflammatory, degenerative, and proliferative lesions commonly seen in aged rats occurred with approximately equal frequency in the dichlorvos-fed and control rats. These included focal hepatocytomegaly (table A5); chronic nephritis with scarring, tubular dilatation and regeneration, and hyperplasia of the transitional epithelium of the renal pelvis and the urinary bladder (table A6); C-cell hyperplasia of the thyroid (table A1); parathyroid hyperplasia (table A2); and endometrial hyperplasia (table A3).

Several nonneoplastic lesions occurred more frequently in the test rats than in the controls and could be related to exposure to the test compound. These included aggregates of alveolar macrophages in the lungs, interstitial fibrosis of the myocardium, and focal follicular-cell hyperplasia of the thyroid of male rats (table A1).

Benign endocrine neoplasms occurred frequently in both test and control rats (tables A1 and A2). A lesser number of malignant endocrine neoplasms were observed; pulmonary metastasis was observed of one C-cell carcinoma (low-dose male) and one pheochromocytoma (high-dose male).

Proliferative lesions of the reproductive tract are summarized in table A3. The overall incidence of tumors was low; the most frequently observed lesions were endometrial stromal polyps and

endometrial hyperplasia. The incidence of mammary neoplasms is also summarized in table A3. There was a relatively high incidence of benign mammary neoplasms in both control and test female rats. Table A4 summarizes the incidence of vascular and hematopoietic neoplasms. The most frequently occurring tumor in this category was hemangiosarcoma of the spleen, which occurred only in male rats.

The incidence of proliferative lesions of the digestive system is summarized in table A5. Lesions classified as hepatocytomegaly consisted of foci of enlarged hepatocytes, many of which contained large, vesicular nuclei and numerous fine cytoplasmic vacuoles which gave the cytoplasm a "ground glass" appearance. Distortion of lobular architecture in these foci was minimal, and trabeculae were continuous with adjacent normal hepatocytes. Lesions classified as "neoplastic nodules" had similar cytologic features, but were large and contained distinct distortion of lobular architecture. Trabeculae at the periphery of these nodules were oriented perpendicular to trabeculae in adjacent normal hepatic parenchyma. Compression of adjacent parenchyma by the nodules was evident.

Nonneoplastic proliferative lesions were observed in the squamous epithelium of the upper gastrointestinal tract of two test rats: one focus of epithelial hyperplasia of the esophagus in a low-

dose male, and one focal area of acanthosis in the squamous mucosa of the stomach in a low-dose female. No similar lesion was observed in the esophagus or stomach of the control rats.

A low incidence of various other types of neoplasms was observed in test and control rats with approximately equal frequency. These included benign and malignant primary renal tumors (table A6), malignant fibrous histiocytomas of the subcutis and of the thoracic and abdominal viscera, lipomas, and one ependymoma of the brain (table A7).

There were instances in this study, as noted above and in the appendix tables A1-A7, where neoplastic or hyperplastic lesions occurred only in test rats, or with increased frequency when compared to control groups. In the judgment of the pathologist, the nature, incidence, and severity of the lesions observed provide no evidence of carcinogenic effect. For a summary of nonneoplastic lesions in rats, see Appendix C.

D. Statistical Analyses of Results (Rats)

Appendix A, tables A8 and A9, contain the statistical analyses of the proportions of rats with tumors, as well as the analyses of those tumors which appeared in over 10% of the rats in a given treated group. Since only 10 males and 10 females were in the matched-control group for dichlorvos, matched-control groups from

studies of five other chemicals were combined for analyses and designated as pooled controls. The resulting histopathologic slides were evaluated by the same pathologist. No statistically significant differences were found between the proportions of tumors in the combined pooled-control groups and the proportions of tumors in the matched controls.

The only tumor that occurred in a statistically significant linear trend in proportions was malignant fibrous histiocytoma in male rats (P = 0.018), which was observed in 2/58 (3%) of the pooled controls, 4/48 (8%) of the low-dose, and 8/50 (16%) of the high-dose animals. In the matched controls the proportion of this neoplasm was 1/10 (10%), which exceeded that of the low-dose males and was not statistically different from the proportion seen in the high-dose males. This tumor was not observed in significant numbers in the female rats.

Tests for linear trend were negative for the proportions of tumors of the reproductive system and also for tumors of the hematopoietic system in females. In male rats the proportions of animals with some type of tumor, omitting tumors of the reproductive system, showed a departure from linear trend (P = 0.01), and the Fisher exact test between the two matched controls and the low-dose group had a probability level 0.024. This

represents a substantially larger proportion of tumors of the pituitary in the pooled controls than in the low-dose male group.

On the basis of the variability of both the incidence and type of spontaneous lesions and the lack of significant proportions of tumors in the dosed groups compared with the matched controls, no statistical significance can be attached to the incidence of the tumors seen in the dichlorvos-fed rats in this study.

As an additional statistic, the 95% confidence interval was calculated and entered in the tables. The implication of this interval is that in 95/100 (95%) of a large number of experiments, the true difference between the tumor rate for treated groups of animals and the rate for the control groups would be inside the interval calculated from the experiment. In each of the intervals shown in the tables, zero is included; this indicates the negative aspects of the results. It should also be noted that each of the intervals has a positive endpoint indicating the theoretical possibility of tumor induction by dichlorvos which could not be detected under the conditions of this test.

IV. RESULTS (MICE)

A. Body Weights and Clinical Signs (Mice)

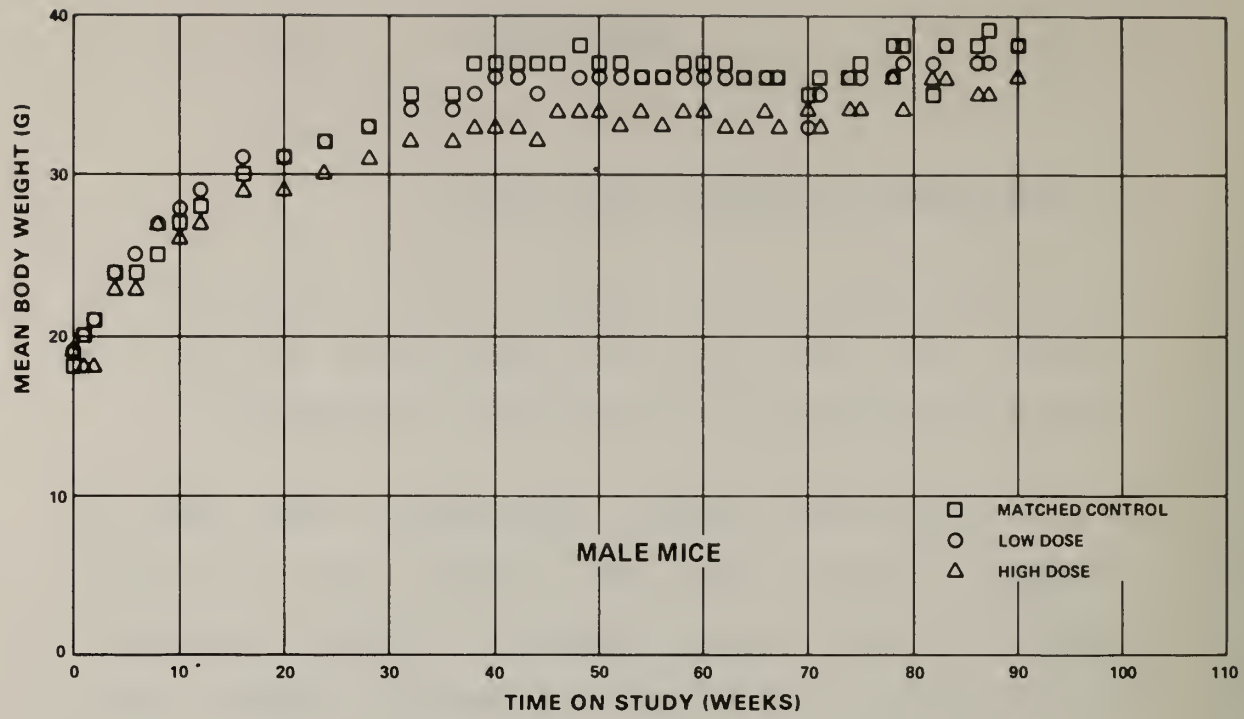
The average weights of the high-dose mice of both sexes were generally lower after the initial growth phase than were the weights of the low-dose and control groups (see figure 3).

Mice fed dichlorvos initially demonstrated severe signs of toxicity: tremors, rough coat, diarrhea, and poor general appearance. After doses were reduced the appearance and behavior of the treated and control mice were generally comparable during the first year of the study. Alopecia (generalized and/or localized) and rough hair coats were noted in many treated animals, particularly in the male groups, beginning at week 20 and persisting throughout the study.

After 50 weeks of treatment, bloating or abdominal distention was observed in both treated and control groups except high-dose females. From week 74 to termination of the study, many palpable masses were observed.

B. Survival (Mice)

In male mice the low-dose and high-dose Kaplan and Meier survival curves are comparable, whereas in female mice the curve of the



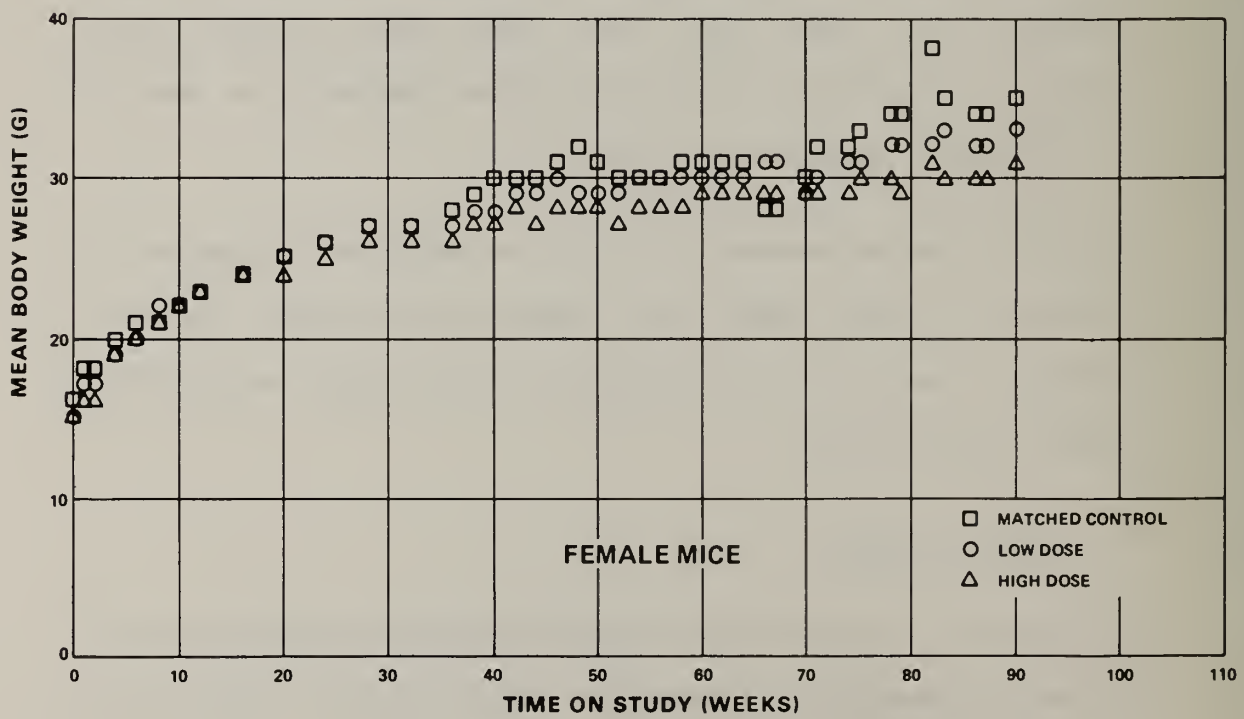


Figure 3. Growth Curves of Mice Fed Dichlorvos in the Diet

low-dose gorup shows less probability of survival than that of the high-dose group (see figure 4). There is no significant dose-related trend in either sex. In the group with the poorest survival, the low-dose female group, 74% of the animals lived to 90 weeks.

C. Pathology (Mice)

Histopathologic findings are tabulated in Appendix B, tables B1-B6, covering neoplasms and other proliferative lesions, and in Appendix D, tables D1 and D2, covering nonneoplastic lesions.

Several nonneoplastic proliferative or inflammatory lesions occurred with approximately equal frequency in control and dichlorvos-fed mice. These included a high incidence of hyperplasia of the adrenal cortex in both sexes (table B4) and cystic endometrial hyperplasia in female mice (table B5).

Proliferative lesions occurring in the digestive system are summarized in table B1. During initial microscopic examination of tissues, several rather unusual proliferative lesions were observed in the squamous epithelium of the esophagus in test mice. These included two squamous-cell carcinomas (low-dose male and high-dose female), and three cases of focal hyperplasia of esophageal epithelium (two low-dose males and one high-dose female). In addition, focal hyperplasia was observed in the

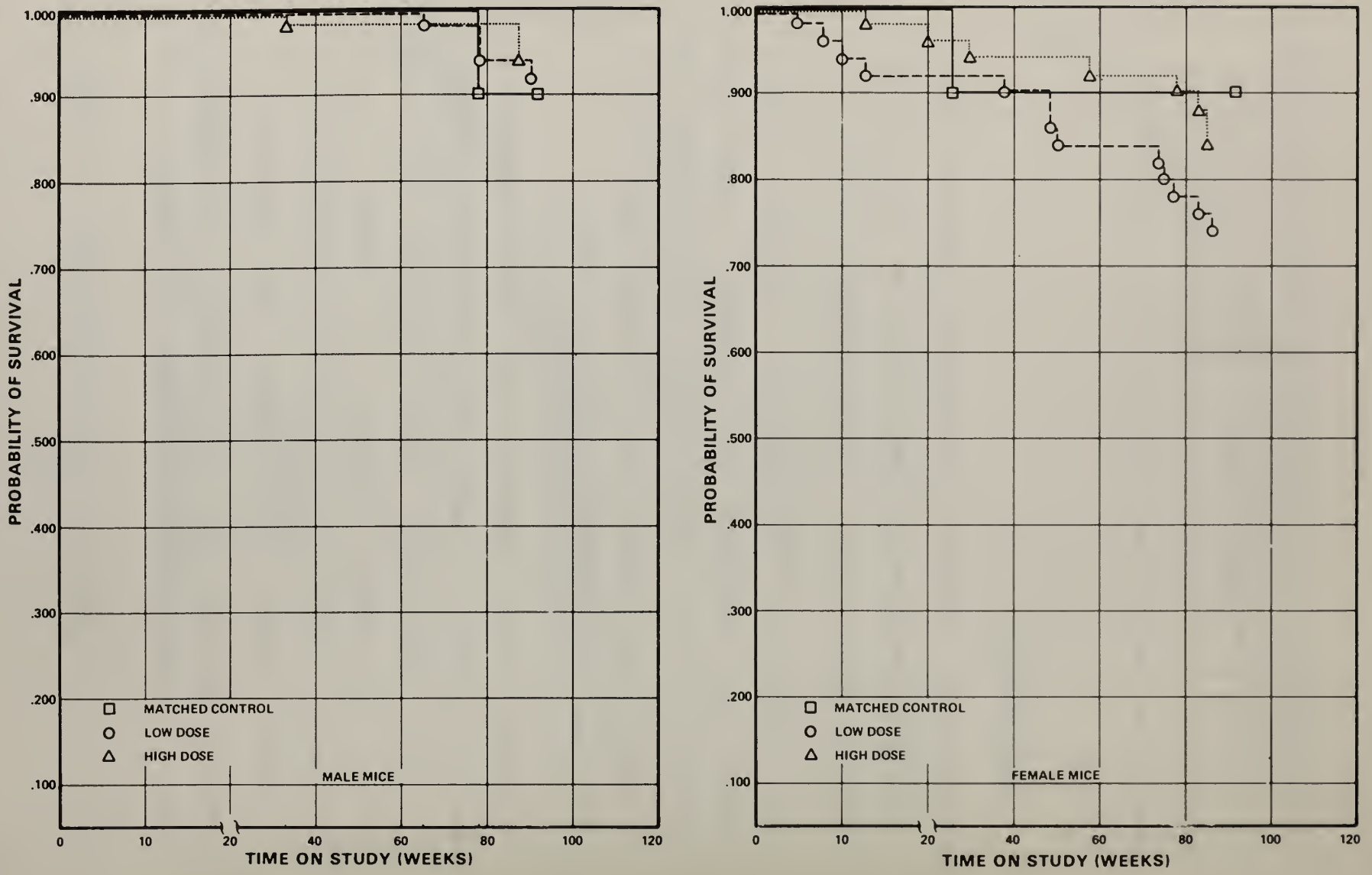


Figure 4. Survival Curves of Mice Fed Dichlorvos in the Diet

nonglandular epithelium of the stomach in a high-dose female mouse. Since these lesions are rarely observed spontaneously in laboratory mice, further examination of additional tissue sections of esophagus and stomach was carried out. This involved reexamination of all original slides from this study containing sections of esophagus and preparation and examination of additional sections of esophagus and stomach from paraffin blocks and from the remaining formalin-fixed tissues. This additional investigation, which included examination of multiple sections from many animals, revealed one additional case of focal hyperplasia of esophageal epithelium (low-dose male) and resulted in change of the diagnosis in the high-dose female from focal hyperplasia of esophageal epithelium to papilloma. The total number of sections of esophagus and nonglandular stomach examined microscopically was as follows: control males, 18; low-dose male, 186.

Morphologically, the esophageal carcinoma observed in a low-dose male was present as an uncircumscribed mass which protruded into the lumen and extended into the submucosa but did not invade adjacent muscularis or other tissues. The neoplasm was composed of rows and nests of basophilic squamous epithelial cells interspersed with small amounts of loose stroma. Numerous mitotic figures were visible, and several areas suggestive of pearl formation were visible, although there was no well-keratinized

epithelium within the interior of the lesions. The carcinoma in the high-dose female also protruded into the esophageal lumen, and had similar cellular morphology; however, because of the plane of section, the attachment of the lesion to adjacent submucosa and epithelium was not visible; thus, it was impossible to determine if the neoplasm invaded adjacent submucosa and muscularis. The esophageal papilloma observed in one high-dose female had some histologic similarities to the two carcinomas, but had a lower mitotic rate, the thickness and the architecture of the epithelium was more similar to adjacent normal epithelium, and the lesion was pedunculated with a thin band of loose stroma extending up into the protruding neoplasm. Also, no involvement of adjacent submucosa was evident. Those esophageal and gastric lesions classified as hyperplasia protruded slightly into the lumen, but were not pedunculated. The epithelium was thicker and slightly more basophilic than normal, but there were few mitotic figures, and no evidence of involvement of adjacent submucosa. In some cases, evidence of suppurative inflammation was present in and around the area of hyperplasia.

The significance of these proliferative lesions observed in the esophagus and stomach is difficult to assess. Although an esophageal carcinoma was recently diagnosed in a control mouse of the same strain in another NCI bioassay study, accurate figures for spontaneous incidence may not be available at the present

time. The esophageal tumors did not, however, occur in statistically significant proportions in the present study, and, despite the presumed rarity of such lesions in control animals, there is insufficient information to establish association of the tumors with dichlorvos treatment.

Hepatocellular carcinomas were observed rather frequently in both test and control male mice, but were rare in females (table B1). Nodular hyperplasia of hepatocytes was an infrequent lesion in both sexes.

There was a relatively low incidence of a wide variety of other neoplasms in tissues examined from mice in this study, with no obvious difference in incidence between test and control mice. These included neoplasms of the lung (table B2), vascular and hematopoietic systems (table B3), the endocrine system (table B4), the reproductive system (table B5), and the skin (table B6).

There were instances in this study, as noted above and in Appendix tables B1-B6, where neoplastic or hyperplastic lesions occurred only in test mice, or with increased frequency when compared with control groups. However, in the judgment of the pathologist, the nature, incidence, and severity of the lesions observed provide no clear evidence of carcinogenic effect.

D. Statistical Analyses of Results (Mice)

Appendix B, tables B7 and B8, contain the statistical analyses of the proportions of mice with tumor as well as the analyses of those tumors which appeared in over 10% of the mice in a given treated group. Since only 10 males and 10 females were in the control group specifically matched to dichlorvos, control groups of chlordane (20 males, 20 females), dieldrin (20 males, 20 females), aldrin (20 males, 10 females), heptachlor (20 males, 10 females) and dimethoate (10 males, 10 females) were combined with the subject control to increase the power of the test. These controls were from the same supplier, were tested concurrently over a year's span, and were evaluated by the same pathologists. Although the number of male mice with tumors in the groups added to the matched-control group to make up the pooled control was 28/81 (34%) compared with 1/10 (10%) in the matched-control group, this difference is not statistically significant. The Armitage test for linear trend in the proportions of the dosed groups compared with either the pooled-control group or the matched-control group resulted in probability levels above 0.10 for both male and female groups. In males, there was a departure from linear trend ($P = 0.028$) when the matched controls were compared with the dosed groups, and the Fisher exact test of the low dose versus the matched controls had a probability level of

0.054. This difference was not confirmed when the pooled-control group was used.

The specific tumors which had the highest incidence in male mice were alveolar/bronchiolar adenoma or carcinoma of the lung, and hepatocellular carcinoma of the liver, but the incidences of these types of tumors had no statistical significance when compared with either control group. The predominant tumor in female mice was malignant lymphoma, but this tumor appeared in comparable proportions in all groups and no statistical significance could be found. There were no significant differences between test and control groups in the age at observation of any of these tumors. There is no statistical evidence in the data that dichlorvos is carcinogenic for mice at the doses given.

As an additional statistic, the 95% confidence interval was calculated and entered in the tables. The implication of this interval is that in 95/100 (95%) of a large number of experiments, the true difference between the tumor rate for treated groups of animals and the rate for the control groups would be inside the interval calculated from the experiment. In each of the intervals shown in the tables, zero is included; this indicates the negative aspects of the results. It should also be noted that each of the intervals has a positive endpoint indica-

ting the theoretical possibility of tumor induction by dichlorvos which was not detected under the conditions of this test.

V. DISCUSSION

Dichlorvos is a member of the organophosphorous class of pesticides whose predominant mode of toxicity is inhibition of cholinesterase. No toxicity specifically characteristic of these compounds was noted except in the early weeks of the study before doses were lowered. However, general signs such as rough hair coats, epistaxis, hematuria, alopecia, and dark urine in rats were more pronounced among the treated animals in the second year of the study. The compound was toxic at least to the high-dose animals, since average weights of both high-dose rats and mice were generally lower than were the weights of the low-dose and control groups. Survival, however, was not significantly affected by the administration of dichlorvos. Thus the study was adequate under Bioassay guidelines to evaluate carcinogenicity in rats and mice.

There were instances in this study where neoplastic or hyperplastic lesions (e.g.,. malignant fibrous histiocytomas) occurred only in certain test animals, or with increased frequency in certain test animals as compared to controls. Most of these lesions, however, occurred within the expected range of variability and, in the judgment of the pathologist, were not considered to be biologically significant. The significance of

the three esophageal tumors in treated mice is uncertain because of insufficient information concerning the spontaneous incidence of these lesions in mice, and lack of statistical significance within this experiment.

It should be noted that the confidence intervals for all tumor sites in rats and mice, which were subjected to statistical analysis, include a positive value; this incidates that the possibility of tumorigenicity of dichlorvos is not precluded. However, under the conditions of this study, dichlorvos was not demonstrated to be carcinogenic in rats and mice.

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APPENDIX A

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

TABLE A1

PROLIFERATIVE LESIONS OF THE THYROID

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
Follicular-cell Adenoma	3/51 (6%)	0/10	3/45 (7%)	6/48 (12.5%)	2/59 (3%)	0/10	0/48	0/49
Follicular-cell Carcinoma	1/51 (2%)	0/10	1/45 (2%)	1/48 (2%)	1/59 (2%)	0/10	0/48	2/49 (4%)
Total Follicular-cell Neoplasms	4/51 (8%)	0/10	4/45 (9%)	7/48 (15%)	3/59 (5%)	0/10	0/48	2/49 (4%)
C-cell Adenoma	3/51 (6%)	1/10 (10%)	1/45 (2%)	4/48 (8%)	7/59 (12%)	1/10 (10%)	8/48 (17%)	6/49 (12%)
C-cell Carcinoma	1/51 (2%)	0/10	1/45 (2%)	3/48 (6%)	5/59 (8%)	0/10	0/48	2/49 (4%)
Total C-cell Neoplasms	4/51 (8%)	1/10 (10%)	2/45 (4%)	7/48 (15%)	12/59 (20%)	1/10 (10%)	8/48 (17%)	8/49 (16%)
Total Thyroid Neoplasms	8/51 (16%)	1/10 (10%)	6/45 (13%)	14/48 (29%)	15/59 (25%)	1/10 (10%)	8/48 (17%)	10/49 (20%)
Follicular-cell Hyperplasia	0/51	0/10	3/45 (7%)	5/48 (10%)	4/59 (7%)	1/10 (10%)	3/48 (6%)	3/49 (6%)
C-cell Hyperplasia	29/51 (57%)	4/10 (40%)	19/45 (42%)	15/48 (31%)	30/59 (51%)	7/10 (70%)	23/48 (48%)	26/49 (53%)

TABLE A2

OTHER PROLIFERATIVE ENDOCRINE LESIONS

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
PITUITARY								
Adenoma	14/48 (29%)	4/8 (50%)	5/44 (11%)	9/46 (20%)	23/51 (45%)	2/9 (22%)	18/45 (40%)	15/48 (31%)
Carcinoma	2/48 (4%)	0/8	0/44	0/46	0/51	0/9	1/45 (2%)	1/48 (2%)
ADRENAL								
Cortical Adenoma	2/54 (4%)	0/10	1/41 (2%)	0/45	0/56	0/10	0/46	0/49
Pheochromocytoma	1/54 (2%)	0/10	0/41	1/45 (2%)	0/56	0/10	2/46 (4%)	0/49
PANCREAS								
Islet-cell Adenoma	1/52 (2%)	0/10	3/43 (7%)	2/47 (4%)	1/60 (2%)	0/10	0/46	0/48
PARATHYROID								
Adenoma	2/39 (5%)	1/9 (11%)	0/41	0/40	0/38	0/7	0/43	0/36
Hyperplasia	5/39 (13%)	1/9 (11%)	6/41 (15%)	8/40 (20%)	3/38 (8%)	0/7	0/43	2/36 (5.5%)

TABLE A3

PROLIFERATIVE LESIONS OF THE REPRODUCTIVE SYSTEM

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
TESTIS								
Interstitial-cell Tumor	0/58	0/10	2/47 (4%)	0/50	---	---	---	---
UTERUS								
Endometrial Stromal Polyp	---	---	---	---	6/57 (11%)	2/9 (22%)	3/46 (6.5%)	2/49 (4%)
Endometrial Stromal Sarcoma	---	---	---	---	0/57	0/9	0/46	1/49 (2%)
Endometrial Hyperplasia	---	---	---	---	1/57 (2%)	0/9	4/46 (9%)	4/49 (8%)
OVARY								
Granulosa-cell Tumor	---	---	---	---	1/58 (2%)	0/10	1/48 (2%)	1/49 (2%)
CLITORAL GLAND								
Adenocarcinoma	---	---	---	---	1/60 (2%)	1/10 (10%)	0/48	0/50

TABLE A3

PROLIFERATIVE LESIONS OF THE REPRODUCTIVE SYSTEM

(continued)

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
MAMMARY GLAND								
Carcinoma	0/58	0/10	0/48	2/50 (4%)	2/60 (3%)	0/10	1/48 (2%)	0/50
Fibroma	1/58 (2%)	0/10	1/48 (2%)	0/50	1/60 (2%)	1/10 (10%)	5/48 (10%)	0/50
Fibroadenoma	0/58	0/10	0/48	0/50	8/60 (13%)	1/10 (10%)	7/48 (15%)	6/50 (12%)
Total Mammary Neoplasms	1/58 (2%)	0/10	1/48 (2%)	2/50 (4%)	11/60 (18%)	2/10 (20%)	13/48 (27%)	6/50 (12%)

TABLE A4

NEOPLASMS OF THE VASCULAR AND HEMATOPOIETIC SYSTEMS

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
Sarcoma, N.O.S., Heart	2/58 (3%)	1/10 (10%)	0/47	0/49	1/58 (2%)	0/10	0/46	0/50
Hemangiosarcoma, Spleen	3/56 (5%)	0/10	4/45 (9%)	1/48 (2%)	0/55	0/10	0/47	0/48
Malignant Lymphoma[a]	1/58 (2%)	0/10	0/48	2/50 (4%)	2/60 (3%)	1/10 (10%)	0/48	0/50

[a]For the purpose of this summary table, "malignant lymphoma" includes all types of lymphoma.

TABLE A5

PROLIFERATIVE LESIONS OF THE DIGESTIVE SYSTEM

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
LIVER NEOPLASMS								
Neoplastic Nodule	2/58 (3%)	0/10	0/47	0/50	5/60 (8%)	1/10 (10%)	3/48 (6%)	1/49 (2%)
OTHER PROLIFERATIVE LESIONS								
Hepatocytomegaly	30/58 (52%)	7/10 (70%)	24/47 (51%)	29/50 (58%)	26/60 (43%)	4/10 (40%)	14/48 (29%)	17/49 (35%)
ESOPHAGUS								
Epithelial Hyperplasia	0/20	0/6	1/37 (3%)	0/46	0/21	0/7	0/45	0/44
STOMACH								
Acanthosis	0/53	0/9	0/43	0/44	0/57	0/9	1/45 (2%)	0/47

TABLE A6

PROLIFERATIVE LESIONS OF THE URINARY TRACT

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
KIDNEY								
Hamartoma	0/57	0/10	2/47 (4%)	0/50	1/58 (2%)	1/9 (11%)	0/47	0/48
Malignant Mixed Tumor	0/57	0/10	0/47	1/50 (2%)	1/58 (2%)	0/9	0/47	1/48 (2%)
Total Renal Neoplasms	0/57	0/10	2/47 (4%)	1/50 (2%)	2/58 (3%)	1/9 (11%)	0/47	1/48 (2%)
Hyperplasia, Renal Pelvis	19/57 (33%)	2/10 (20%)	13/47 (28%)	8/50 (16%)	17/58 (29%)	1/9 (11%)	4/47 (8.5%)	1/48 (2%)
URINARY BLADDER								
Epithelial Hyperplasia	12/51 (23.5%)	5/10 (50%)	24/44 (55%)	8/41 (19.5%)	8/52 (15%)	1/8 (12.5%)	9/39 (23%)	3/46 (6.5%)

TABLE A7

MISCELLANEOUS PROLIFERATIVE LESIONS

	MALE RATS				FEMALE RATS			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
Lipoma	1/58 (2%)	0/10	0/48	0/50	2/60 (3%)	2/10 (20%)	1/48 (2%)	0/50
Malignant Fibrous Histiocytoma	2/58 (3%)	1/10 (10%)	4/48 (8%)	8/50 (16%)	1/60 (2%)	0/10	5/48 (10%)	1/50 (2%)
Ependymoma, Brain	0/57	0/10	0/47	1/49 (2%)	0/9	0/10	0/46	0/48
TUNICA VAGINALIS								
Mesothelioma	0/58	0/10	1/47 (2%)	0/50	---	---	---	---
Mesothelial Hyperplasia	0/58	0/10	2/47 (4%)	1/50 (2%)	---	---	---	---

Table A8. Analyses of the Incidence of Tumors at Specific Sites in Male Rats Fed Dichlorvos in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Total Animals: All Tumors, Omitting Reproductive System[b]	37/58(0.64)	6/10(0.60)	20/48(0.43)	33/50(0.66)
P Values[c]	N.S.	N.S.	P = 0.024*(N)	N.S.
95% Confidence Interval (matched)[d]	P = 0.010		(-0.50,0.21)	(-0.26,0.43)
95% Confidence Interval (pooled)[d]			(-0.40,0.01)	(-0.17,0.21)
Weeks to First Observed Tumor		59	76	42
Reproductive System: All Tumors[b]	2/58(0.03)	0/10(0)	3/48(0.06)	2/50(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.18,1.00)	(-0.18,1.00)
95% Confidence Interval (pooled)[d]			(-0.06,0.10)	(-0.06,0.09)
Weeks to First Observed Tumors		--	110	72

Table A8. Analyses of the Incidence of Tumors at Specific Sites in Male Rats Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	4/51(0.08)	0.10(0)	4/45(0.09)	7/48(0.15)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.19,1.00)	(-0.17,1.00)
95% Confidence Interval (pooled)[d]			(-0.10,0.12)	(-0.08,0.18)
Weeks to First Observed Tumor		--	86	110
Hematopoietic System: Malignant Lymphoma[b]	1/58(0.02)	0.10(0)	0/48(0)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]				(-0.15,1.00)
95% Confidence Interval (pooled)[d]			(-1.00,0.02)	(-0.04,0.06)
Weeks to First Observed Tumor			103	102

Table A8. Analyses of the Incidence of Tumors at Specific Sites in Male Rats Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	16/48(0.33)	4/8(0.50)	5/44(0.11)	9/46(0.20)
P Values[c]	N.S.	N.S.	P = 0.011*(N)	N.S.
Departure from Linear Trend	P = 0.045	P = 0.013	P = 0.023**(N)	N.S.
95% Confidence Interval (matched)[d]			(-0.73,-0.02)	(-0.67,0.07)
95% Confidence Interval (pooled)[d]			(-0.35,-0.03)	(-0.30,0.06)
Weeks to First Observed Tumor		80	85	110
Thyroid: C-cell Adenoma or Carcinoma[b]	4/50(0.08)	1/10(0.10)	2/45(0.04)	7/48(0.15)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.26,0.06)	(-0.29,0.16)
95% Confidence Interval (pooled)[d]			(-0.11,0.07)	(-0.08,0.18)
Weeks to First Observed Tumor		106	110	110

Table A8. Analyses of the Incidence of Tumors at Specific Sites in Male Rats Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islet: Islet-cell Adenoma[b]	1/52(0.02)	0/10(0)	3/43(0.07)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.18,1.00)	(-0.16,1.00)
95% Confidence Interval (pooled)[d]			(-0.04,0.09)	(-0.04,0.063)
Weeks to First Observed Tumors	80	--	76	110
Multiple Organs: Malignant Fibrous Histiocytoma[b]	2/58(0.03)	1/10(0.10)	4/48(0.08)	8/50(0.16)
P Values[c]	P = 0.018	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.30,0.10)	(-0.29,0.17)
95% Confidence Interval (pooled)[d]			(-0.05,0.11)	(0.00,0.19)
Weeks to First Observed Tumor	--	59	86	61

[a]Treated groups received time-weighted average doses of 150 and 327 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

Table A8. Analyses of the Incidence of Tumors at Specific Sites in Male Rats Fed Dichlorvos in the Diet[a]

(continued)

[c]Beneath the proportions for the matched- and pooled-control groups are the probability levels (P values) for the Cochran-Armitage test for dose-related trend in proportions when P is below 0.10; otherwise, N.S. (not significant is indicated. Beneath the proportions for the treated groups are the P values for the Fisher exact (conditional) test for the comparison of the treated groups with the matched-control group (*) and the pooled-control group (**) when P is below 0.05; otherwise, N.S. is indicated.
(N) A negative trend results from a lower proportion in the treated group than in the matched- or pooled-control group.

[d]95% confidence interval of the difference in proportions of treated group and matched- or pooled control group.

Table A9. Analyses of the Incidence of Tumors at Specific Sites in Female Rats Fed Dichlorvos in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Total Animals: All Tumors, Omitting Reproductive System[b]	38/60(0.63)	8/10(0.80)	34/48(0.71)	30/50(0.60)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.56,0.02)	(-0.41,0.19)
95% Confidence Interval (pooled)[d]			(-0.12,0.26)	(-0.22,0.16)
Weeks to First Observed Tumor		60	92	48
Reproductive System: All Tumors[b]	19/60(0.32)	5/10(0.50)	17/48(0.35)	10/50(0.20)
P Values[c]	N.S.	P = 0.026(N)	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.50,0.21)	(-0.63,0.05)
95% Confidence Interval (pooled)[d]			(-0.15,0.23)	(-0.28,0.07)
Weeks to First Observed Tumors		60	99	110

Table A9. Analyses of the Incidence of Tumors at Specific Sites in Female Rats Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	3/59(0.05)	0/10(0)	0/48(0)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			--	(-0.16,1.00)
95% Confidence Interval (pooled)[d]			(-1.00,0.03)	(-0.08,0.07)
Weeks to First Observed Tumor		--	--	110
Hematopoietic System: Malignant Lymphoma[b]	2/60(0.03)	1/10(0.10)	0/48(0)	0/50(0)
P Values[c]	N.S.	P = 0.034(N)	N.S.	N.S.
Departure from Linear Trend	N.S.	P = 0.020(N)	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-1.00,0.01)	(-1.00,0.05)
95% Confidence Interval (pooled)[d]			(-1.00,0.03)	(-1.00,0.03)
Weeks to First Observed Tumor		110	92	--

Table A9. Analyses of the Incidence of Tumors at Specific Sites in Female Rats Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	23/51(0.45)	2/9(0.22)	19/45(0.42)	16/48(0.33)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.22,0.42)	(-0.30,0.33)
95% Confidence Interval (pooled)[d]			(-0.24,0.19)	(-0.31,0.09)
Weeks to First Observed Tumor		106	92	105
Thyroid: C-cell Adenoma or Carcinoma[b]	12/59(0.20)	1/10(0.10)	8/48(0.17)	8/49(0.16)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.28,0.18)	(-0.28,0.18)
95% Confidence Interval (pooled)[d]			(-0.19,0.13)	(-0.19,0.12)
Weeks to First Observed Tumor		110	92	110

Table A9. Analyses of the Incidence of Tumors at Specific Sites in Female Rats Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Multiple Organs: Malignant Fibrous Histiocytoma[b]	1/60(0.02)	0/10(0)	5/48(0.10)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend	P = 0.016	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.20,1.00)	(-0.09,1.00)
95% Confidence Interval (pooled)[d]			(-0.02,0.12)	(0.03,0.04)
Weeks to First Observed Tumor	--	--	92	48

[a]Treated groups received time-weighted average doses of 150 and 327 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]Beneath the proportions for the matched- and pooled-control groups are the probability levels (P values) for the Cochran-Armitage test for dose-related trend in proportions when P is below 0.10; otherwise, N.S. (not significant) is indicated. Departure from linear trend is noted beneath the P value for dose-related trend when P is below 0.05. Beneath the proportions for the treated groups are the P values for the Fisher exact (conditional) test for the comparison of the treated groups with the matched-control group (*) and the pooled-control group (**) when P is below 0.05; otherwise, N. S. is indicated.
(N) A negative trend results from a lower proportion in the treated group than in the matched- or pooled-control group.

[d]95% confidence interval of the difference in proportions of treated group and matched- or pooled-control group.

APPENDIX B

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

TABLE B1

PROLIFERATIVE LESIONS OF THE DIGESTIVE SYSTEM

	MALE MICE				FEMALE MICE			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
LIVER								
Hepatocellular Carcinoma	17/92 (18%)	0/10	12/49 (24%)	7/50 (14%)	3/78 (4%)	0/9	0/47	0/49
Nodular Hyperplasia	3/92 (3%)	0/10	0/49	1/50 (2%)	1/78 (1%)	0/9	0/47	3/49 (6%)
STOMACH								
Squamous Epithelial Hyperplasia	0/90	0/10	0/50	0/49	0/77	0/9	0/46	1/48 (2%)
ESOPHAGUS								
Squamous-cell Carcinoma	0/27	0/10	1/47 (2%)	0/46	0/16	0/8	0/45	1/41 (2%)
Papilloma	0/27	0/10	0/47	0/46	0/16	0/8	0/45	1/41 (2%)
Epithelial Hyperplasia	0/27	0/10	3/47 (6%)	0/46	0/16	0/8	0/45	0/41

TABLE B2

PRIMARY PULMONARY NEOPLASMS

	MALE MICE				FEMALE MICE			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
Alveolar/Bronchiolar Carcinoma	0/91	0/10	1/47 (2%)	0/49	0/79	0/9	0/47	0/46
Alveolar/Bronchiolar Adenoma	6/91 (7%)	0/10	6/47 (13%)	5/49 (10%)	0/79	0/9	1/47 (2%)	1/46 (2%)
Total Primary Pulmonary Neoplasms	6/91 (7%)	0/10	7/47 (15%)	5/49 (10%)	0/79	0/9	1/47 (2%)	1/46 (2%)

TABLE B3

NEOPLASMS OF THE VASCULAR AND HEMATOPOIETIC SYSTEMS

	MALE MICE				FEMALE MICE			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
Malignant Lymphoma[a]	5/92 (5%)	1/10 (10%)	1/50 (2%)	2/50 (4%)	8/79 (10%)	1/9 (11%)	6/49 (12%)	3/50 (6%)
Hemangiosarcoma	0/92	0/10	1/50 (2%)	0/50	0/79	0/9	0/49	1/50 (2%)
Hemangioma	0/92	0/10	1/50 (2%)	0/50	0/79	0/9	0/49	0/50

[a]For purposes of this summary table, "malignant lymphoma" includes lymphosarcoma, reticulum cell sarcoma, and all "types" of malignant lymphoma.

TABLE B4

PROLIFERATIVE LESIONS OF THE ENDOCRINE SYSTEM

	MALE MICE				FEMALE MICE			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
THYROID								
C-cell Carcinoma	0/79	0/8	0/49	0/50	0/72	0/9	0/43	1/44 (2%)
Follicular-cell Adenoma	1/79 (1%)	0/8	1/49 (2%)	0/50	1/72 (1%)	0/9	1/43 (2%)	0/44
Follicular-cell Hyperplasia	0/79	0/8	1/49 (2%)	1/50 (2%)	1/72 (1%)	1/9 (11%)	3/43 (7%)	0/44
ADRENAL								
Cortical Adenoma	0/88	0/10	1/50 (2%)	0/49	0/78	0/9	0/43	0/47
Adrenocortical Hyperplasia	27/88 (31%)	7/10 (70%)	34/50 (68%)	28/49 (57%)	19/78 (24%)	9/9 (100%)	41/43 (95%)	47/47 (100%)
PITUITARY								
Chromophobe Adenoma	0/70	0/9	0/46	0/44	0/58	0/8	0/39	2/42 (5%)

TABLE B5

PROLIFERATIVE LESIONS OF THE REPRODUCTIVE SYSTEM

	MALE MICE				FEMALE MICE			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
UTERUS								
Endometrial Stromal Polyp	---	---	---	---	1/78 (1%)	0/9	1/45 (2%)	0/49
Endometrial Hyperplasia	---	---	---	---	27/78 (35%)	5/9 (55.5%)	37/45 (82%)	37/49 (75.5%)
OVARY								
Adenocarcinoma	---	---	---	---	0/73	0/8	1/40 (2.5%)	0/45

TABLE B6

NEOPLASMS OF THE INTEGUMENTARY SYSTEM

	MALE MICE				FEMALE MICE			
	Pooled Control	Matched Control	Low Dose	High Dose	Pooled Control	Matched Control	Low Dose	High Dose
SKIN								
Trichoepithelioma	0/92	0/10	0/50	0/50	0/79	0/9	1/49 (2%)	0/50

Table B7. Analyses of the Incidence of Tumors at Specific Sites in Male Mice Fed Dichlorvos in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Total Animals: All Tumors[b]	29/92(0.32)	1/10(0.10)	21/50(0.42)	14/50(0.28)
P Values[c]	N.S.	N.S.	P = 0.050**	N.S.
Departure from Linear Trend	N.S.	P = 0.028	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.06,0.44)	(-0.19,0.30)
95% Confidence Interval (pooled)[d]			(-0.02,0.32)	(-0.20,0.14)
Weeks to First Observed Tumor		78	65	33
Lung: Alveolar/Bronchiolar Adenoma or Carcinomas[b]	6/91(0.07)	0/10(0)	7/47(0.15)	5/49(0.10)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.16,1.00)	(-0.19,1.00)
95% Confidence Interval (pooled)[d]			(-0.03,0.19)	(-0.06,0.14)
Weeks to First Observed Tumors		--	65	94

Table B7. Analyses of the Incidence of Tumors at Specific Sites in Male Mice Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver:				
Hepatocellular Carcinoma[b]	17/92(0.18)	0/10(0)	12/49(0.24)	7/50(0.14)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.24,1.00)	(-0.17,1.00)
95% Confidence Interval (pooled)[d]			(-0.09,0.022)	(-0.17,0.10)
Weeks to First Observed Tumor		--	78	94
Hematopoietic System:				
Malignant Lymphoma[b]	5/92(0.05)	1/10(0.10)	1/50(0.02)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.20,0.04)	(-0.26,0.06)
95% Confidence Interval (pooled)[d]			(-0.65,0.05)	(-0.07,0.07)
Weeks to First Observed Tumor		78	90	33

[a]Treated groups received time-weighted average doses of 317 and 635 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

Table B7. Analyses of the Incidence of Tumors at Specific Sites in Male Mice Fed Dichlorvos in the Diet[a]

(continued)

[c]Beneath the proportions for the matched- and pooled-control groups are the probability levels (P values) for the Cochran-Armitage test for dose-related trend in proportions when P is below 0.10; otherwise, N.S. (not significant) is indicated. Departure from linear trend is noted beneath the P value for dose-related trend when P is below 0.05. Beneath the proportions for the treated groups are the P values for the Fisher exact (conditional) test for the comparison of the treated groups with the matched-control group (*) and the pooled-control group (**) when P is below 0.05; otherwise N.S. is indicated.
(N) A negative trend results from a lower proportion in the treated gorup than in the matched- or pooled-control group.

[d]95% confidence interval of the difference in proportions of treated group and matched- or pooled-control group.

Table B8. Analyses of the Incidence of Tumors at Specific Sites in Female Mice Fed Dichlorvos in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Total Animals: All Tumors[b]	14/79(0.18)	1/9(0.11)	11/49(0.22)	8/50(0.16)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.29,0.24)	(-0.32,0.18)
95% Confidence Interval (pooled)[d]			(-0.10,0.20)	(-0.15,0.14)
Weeks to First Observed Tumor		92	38	78
Lung: Alveolar/Bronchiolar Adenoma or Carcinomas[b]	0/79(0)	0/9(0)	1/47(0.02)	1/46(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.10,1.00)	(-0.10,1.00)
95% Confidence Interval (pooled)[d]			(-0.01,1.00)	(-0.01,1.00)
Weeks to First Observed Tumors		--	93	93

Table B8. Analyses of the Incidence of Tumors at Specific Sites in Female Mice Fed Dichlorvos in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver:				
Hepatocellular Carcinoma[b]	3/78(0.04)	0/9(0)	0/47(0)	0/49(0)
P Values[c]	P = 0.085(N)	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			--	--
95% Confidence Interval (pooled)[d]			(-1.00,0.02)	(-1.00,0.02)
Weeks to First Observed Tumor		--	--	--
Hematopoietic System:				
Malignant Lymphoma[b]	8/79(0.10)	1/9(0.11)	6/49(0.12)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.	N.S.
95% Confidence Interval (matched)[d]			(-0.34,0.14)	(-0.32,0.06)
95% Confidence Interval (pooled)[d]			(-0.09,0.14)	(-0.12,0.06)
Weeks to First Observed Tumor		92	77	78

[a]Treated groups received time-weighted average doses of 317 and 635 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

Table B8. Analyses of the Incidence of Tumors at Specific Sites in Female Mice Fed Dichlorvos in the Diet[a]

(continued)

[c]Beneath the proportions for the matched- and pooled-control groups are the probability levels (P values) for the Cochran-Armitage test for dose-related trend in proportions when P is below 0.10; otherwise, N.S. (not significant) is indicated. Departure from linear trend is noted beneath the P value for dose-related trend when P is below 0.05. Beneath the proportions for the treated groups are the P values for the Fisher exact (conditional) test for the comparison of the treated groups with the matched-control group (*) and the pooled-control group (**) when P is below 0.05; otherwise, N.S. is indicated.
(N) A negative trend results from a lower proportion in the treated group than in the matched- or pooled-control group.

[d]95% confidence interval of the difference in proportions of treated group and matched- or pooled-control group.

APPENDIX C

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

TABLE C1

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10 (100%)	48 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	47	50
ANIMALS WITH TUMORS	6 (60%)	20 (42%)	33 (66%)
INTEGUMENTARY SYSTEM			1 (2%)
SUBCUT TISSUE			1
PERIARTERITIS			1
RESPIRATORY SYSTEM	1 (10%)	21 (44%)	9 (18%)
TRACHEA		1	
INFLAMMATION CHRONIC		1	
LUNG/BRONCHIOLE			1
HYPERPLASIA EPITHELIAL			1
LUNG	1	20	8
EMPHYSEMA		1	
ATELECTASIS		1	
CONGESTION			1
INFLAMMATION INTERSTITIAL		2	
ALVEOLAR MACROPHAGES	1	14	7
HYPERPLASIA ALVEOLAR-CELL		3	
LUNG/ALVEOLI		3	1
EDEMA		1	
INFLAMMATION SUPPURATIVE		2	1
CIRCULATORY SYSTEM	3 (30%)	17 (35%)	16 (32%)
ATRIUM		1	
THROMBOSIS		1	
MYOCARDIUM	1	16	13
INFLAMMATION	1		
INFLAMMATION FOCAL			1
FIBROSIS	1	16	12
NECROSIS DIFFUSE		1	

TABLE C1 MALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCARDIUM	1	6	2
FIBROSIS	1	6	2
AORTA		3	
CALCIFICATION		3	
CORONARY ARTERY		3	
CALCIFICATION		3	
PULMONARY ARTERY		1	
HYPERPLASIA		1	
LEFT GASTRIC ARTERY	1		
CALCIFICATION	1		
MESENTERIC ARTERY	1		3
INFLAMMATION	1		
PERIARTERITIS	1		3
DIGESTIVE SYSTEM	9 (90%)	35 (73%)	43 (86%)
LIVER	7	28	32
INFLAMMATION SUPPURATIVE			1
FIBROSIS FOCAL		1	
PERIARTERITIS			1
NECROSIS FOCAL		3	
METAMORPHOSIS FATTY	1		
HEPATOCYTOMEGALY	7	24	29
ANGIECTASIS		6	2
LIVER/CENTRILOBULAR	1		
NECROSIS FOCAL	1		
BILE DUCT	1	21	22
DILATATION			2
INFLAMMATION		6	4
FIBROSIS		2	
HYPERPLASIA	1	21	22
PANCREAS	2	4	7
HEMORRHAGE			1

TABLE C1 MALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
PANCREAS (CONT.)			
FIBROSIS	1	2	3
PERIARTERITIS	1	3	4
PANCREATIC ACINUS	2	4	12
ATROPHY	2	4	12
ESOPHAGUS		1	
HYPERPLASIA EPITHELIAL		1	
GASTRIC MUCOSA	1	1	
CALCIFICATION	1	1	
GASTRIC MUSCULARIS		2	
CALCIFICATION		2	
URINARY SYSTEM	10 (100%)	42 (88%)	40 (80%)
KIDNEY	10	36	38
PYELONEPHRITIS SUPPURATIVE			1
INFLAMMATION CHRONIC	11	36	38
PERIARTERITIS			1
KIDNEY/CORTEX		1	
CYST		1	
KIDNEY/MEDULLA		1	
NECROSIS		1	
KIDNEY/PELVIS	2	13	9
DILATATION			1
INFLAMMATION SUPPURATIVE		2	1
HYPERPLASIA EPITHELIAL	2	13	8
URETER			1
HYPERPLASIA EPITHELIAL			1
URINARY BLADDER	4	24	10
CALCULUS			2
INFLAMMATION CHRONIC	2	4	5

TABLE C1 MALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY BLADDER (CONT.)			
HYPERPLASIA EPITHELIAL	4	24	8
HYPERPLASIA MESOTHELIAL			1
METAPLASIA SQUAMOUS			1
URETERA		1	1
CALCULUS		1	
HYPERPLASIA EPITHELIAL		1	1
ENDOCRINE SYSTEM	5 (50%)	31 (65%)	31 (62%)
PITUITARY		4	4
HYPERPLASIA CHROMOPHOBE-CELL		4	4
ADRENAL		2	1
NECROSIS FAT			1
CYTOMEGALY		1	
ANGIECTASIS		1	
ADRENAL CORTEX	2	4	6
CYTOMEGALY	2	3	6
HYPERPLASIA FOCAL		1	
THYROID	4	25	20
ULTIMOBRANCHIAL CYST	1	1	3
CYSTIC FOLLICLES		4	4
HYPERPLASIA		1	
HYPERPLASIA C-CELL	4	19	15
HYPERPLASIA FOLLICULAR-CELL		3	5
PARATHYROID	1	5	8
HYPERPLASIA	1	5	8
PANCREATIC ISLETS			1
HYPERPLASIA			1
HEMATOPOIETIC SYSTEM		3 (6%)	5 (10%)
SPLEEN		3	4
FIBROSIS FOCAL			1

TABLE C1 MALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
SPLEEN (CONT.)			
HYPERPLASIA RETICULUM-CELL			1
HEMATOPOIESIS		3	2
CERVICAL LYMPH NODE			1
LYMPHOID HYPERPLASIA			1
REPRODUCTIVE SYSTEM	5 (50%)	43 (90%)	40 (80%)
PROSTATE	2	5	12
INFLAMMATION SUPPURATIVE		3	11
INFLAMMATION GRANULOMATOUS		2	1
INFLAM SUPPURATIVE GRANULOMATOUS	2		
HYPERPLASIA EPITHELIAL		1	1
METAPLASIA SQUAMOUS			1
PROSTATIC DUCT	1		
DEPOSITION OF CRYSTALS	1		
TESTIS	5	41	38
PERIARTERITIS	1		4
ATROPHY	6	41	37
HYPERPLASIA MESOTHELIAL			1
TUNICA VAGINALIS		3	
HYPERPLASIA MESOTHELIAL		3	
EPIDIDYMIS			1
INFLAMMATION GRANULOMATOUS			1
NERVOUS SYSTEM		1 (2%)	2 (4%)
BRAIN		1	
HYDROCEPHALUS		1	
PINEAL BODY			2
CORPORA AMYLACEA			2

TABLE C1 MALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM		1 (2%)	
BONE		1	
FIBROUS OSTEODYSTROPHY		1	
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS	1 (10%)	1 (2%)	1 (2%)
MULTIPLE ORGANS	1	1	
ARTERIOSCLEROSIS		1	
CALCIFICATION	1	1	
ADIPOSE TISSUE			1
INFLAMMATION ACUTE			1
NO LESION REPORTED			1
AUTOLYSIS/NECROPSY PERF/NO HISTO		1	
AUTOLYSIS/NO NECROPSY PERFORMED		2	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*	1	6	6
MORIBUND SACRIFICE	7	14	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	2	30	37

*INCLUDES AUTOLYZED ANIMALS

TABLE C2

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10 (100%)	48 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	48	50
ANIMALS WITH TUMORS	8 (80%)	34 (71%)	30 (60%)
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM		23 (48%)	25 (50%)
TRACHEA			2
INFLAMMATION SUPPURATIVE			1
INFLAMMATION FOCAL CHRONIC			1
LUNG/BRONCHIOLE			2
INFLAMMATION SUPPURATIVE			2
LUNG		23	25
FOREIGN-BODY PNEUMONIA		1	3
ABSCESS		1	
INFLAM SUPPURATIVE GRANULOMATOUS			1
ALVEOLAR MACROPHAGES		22	21
HYPERPLASIA ALVEOLAR-CELL		3	3
LUNG/ALVEOLI		1	
INFLAMMATION SUPPURATIVE		1	
CIRCULATORY SYSTEM	1 (10%)	19 (40%)	16 (32%)
MYOCARDIUM	1	19	16
INFLAMMATION	1	2	1
FIBROSIS	1	19	15
ENDOCARDIUM		4	1
FIBROSIS		4	1
DIGESTIVE SYSTEM	4 (40%)	36 (75%)	41 (82%)
SALIVARY GLAND		1	
CALCULUS		1	

TABLE C2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
SALIVARY GLAND (CONT.)			
CYSTIC DUCTS		1	
FIBROSIS		1	
CALCIFICATION		1	
LIVER	4	19	26
PERIARTERITIS			1
NECROSIS FOCAL	1		
METAMORPHOSIS FATTY		4	10
HEPATOCYTOMEGALY	4	14	17
ANGIECTASIS	1	2	
BILE DUCT	2	24	25
INFLAMMATION	1	4	7
HYPERPLASIA	2	23	24
PANCREAS		2	5
ECTOPIA			1
FIBROSIS		2	4
PANCREATIC DUCT			1
DILATATION			1
INFLAMMATION GRANULOMATOUS			1
HYPERPLASIA EPITHELIAL			1
PANCREATIC ACINUS		6	11
ATROPHY		6	11
STOMACH		2	1
EPIDERMAL INCLUSION CYST		1	
ULCER			1
INFLAMMATION ACUTE			1
ACANTHOSIS		1	
LARGE INTESTINE			1
PERIARTERITIS			1
URINARY SYSTEM	9 (90%)	29 (60%)	28 (56%)
KIDNEY	8	20	27
INFLAMMATION CHRONIC	8	20	27

TABLE C2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
KIDNEY/PELVIS	2	4	2
CALCULUS	1	3	2
INFLAMMATION SUPPURATIVE		1	
HYPERPLASIA EPITHELIAL	1	4	1
URINARY BLADDER	1	9	3
HYPERPLASIA EPITHELIAL	1	9	3
ENDOCRINE SYSTEM	7 (70%)	33 (69%)	36 (72%)
PITUITARY		5	1
HYPERPLASIA CHROMOPHOBE-CELL		5	1
ADRENAL	1		1
ANGIECTASIS	1		1
ADRENAL CORTEX	2	13	14
CYTOMEGALY	1	8	6
HYPERPLASIA FOCAL		1	1
ANGIECTASIS	1	6	10
THYROID	7	25	27
ULTIMOBRANCHIAL CYST			1
CYSTIC FOLLICLES	1	1	1
ATROPHY		1	
HYPERPLASIA C-CELL	7	23	26
HYPERPLASIA FOLLICULAR-CELL	1	3	3
PARATHYROID			2
HYPERPLASIA			2
PANCREATIC ISLETS			2
HYPERPLASIA			2
HEMATOPOIETIC SYSTEM	2 (20%)	10 (21%)	7 (14%)
SPLEEN	2	10	7
FIBROSIS FOCAL		1	1

TABLE C2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
SPLEEN (CONT.)			
PERIARTERITIS			1
HEMOSIDEROSIS	2	3	2
HYPERPLASIA RETICULUM-CELL			1
HEMATOPOIESIS		6	4
REPRODUCTIVE SYSTEM	1 (10%)	6 (13%)	10 (20%)
UTERUS	1		3
HYDROMETRA	1		3
UTERUS/ENDOMETRIUM		5	4
CYST		1	
HYPERPLASIA		1	
HYPERPLASIA FOCAL		1	
HYPERPLASIA CYSTIC		2	4
OVARY		1	3
CYST		1	
FOLLICULAR CYST			2
HYPERPLASIA EPITHELIAL			1
NERVOUS SYSTEM			1 (2%)
BRAIN			1
GLIOSIS			1
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

TABLE C2 FEMALE RATS: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
NO LESION REPORTED			1
AUTOLYSIS/NO NECROPSY PERFORMED		2	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*		3	2
MORIBUND SACRIFICE	5	7	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	5	40	42
*INCLUDES AUTOLYZED ANIMALS			

APPENDIX D

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

TABLE D1

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10 (100%)	50 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	50
ANIMALS WITH TUMORS	1 (10%)	21 (42%)	14 (28%)
INTEGUMENTARY SYSTEM		1 (2%)	1 (2%)
SKIN		1	1
INFLAMMATION FOCAL CHRONIC		1	1
RESPIRATORY SYSTEM	1 (10%)	3 (6%)	3 (6%)
LUNG	1	3	3
INFLAMMATION INTERSTITIAL	1	1	3
BRONCHOPNEUMONIA SUPPURATIVE		1	
HYPERPLASIA ALVEOLAR-CELL		2	
CIRCULATORY SYSTEM	1 (10%)	1 (2%)	1 (2%)
HEART	1		1
PERIARTERITIS			1
DEGENERATION	1		
CORONARY ARTERY		1	
INFLAMMATION		1	
MESENTERIC ARTERY		1	
INFLAMMATION		1	
RENAL ARTERY		1	
INFLAMMATION		1	
DIGESTIVE SYSTEM	2 (20%)	5 (10%)	5 (10%)
LIVER	2	1	3
INFLAMMATION CHRONIC	1		
INFLAMMATION FOCAL CHRONIC	1		1
INFLAMMATION CHRONIC DIFFUSE			1

TABLE D1 MALE MICE: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
LIVER (CONT.)			
PERIVASCULAR CUFFING		1	
HYPERPLASIA NODULAR			1
ANGIECTASIS	1		
LIVER/CAUDATE LOBE		1	
NECROSIS		1	
LIVER/HEPATOCYTES		1	
HYPERTROPHY FOCAL		1	
PANCREAS			2
INFLAMMATION ACUTE			1
INFLAMMATION FOCAL CHRONIC			1
PANCREATIC ACINUS	1		
ATROPHY	1		
ESOPHAGUS		3	
HYPERPLASIA EPITHELIAL		3	
URINARY SYSTEM	1 (10%)	15 (30%)	20 (40%)
KIDNEY		15	20
INFLAMMATION CHRONIC		15	19
PERIARTERITIS			1
RENAL TUBULE	1		
CYTOPLASMIC VACUOLIZATION	1		
ENDOCRINE SYSTEM	7 (70%)	36 (72%)	30 (60%)
ADRENAL CORTEX	7	35	28
CYTOMEGALY		6	3
HYPERPLASIA	7	34	28
THYROID		2	2
INFLAMMATION ACUTE FOCAL		1	

TABLE D1 MALE MICE: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
THYROID (CONT.)			
PERIARTERITIS			1
HYPERPLASIA FOLLICULAR-CELL		1	1
PARATHYROID			1
CYST			1
HEMATOPOIETIC SYSTEM	2 (20%)	4 (8%)	4 (8%)
BONE MARROW		2	1
HYPOPLASIA		1	
HYPERPLASIA HEMATOPOIETIC		1	1
SPLEEN	2	2	2
CONGESTION	1		
HYPERPLASIA RETICULUM-CELL	1		2
HEMATOPOIESIS		2	
LYMPH NODE		2	2
HYPERPLASIA RETICULUM-CELL		1	1
LYMPHOID HYPERPLASIA			1
HEMATOPOIESIS		1	
REPRODUCTIVE SYSTEM	1 (10%)	1 (2%)	3 (6%)
TESTIS	1	1	3
SPERMATOGENIC GRANULOMA			1
ATROPHY			2
ATROPHY FOCAL	1	1	
NERVOUS SYSTEM			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

TABLE D1 MALE MICE: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS			2 (4%)
PERITONEUM			1
INFLAMMATION ACUTE			1
INFLAMMATION ACUTE NECROTIZING			1
MESENTERY			1
PERIARTERITIS			1
NO LESION REPORTED	1	3	5
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*	1		
MORIBUND SACRIFICE		4	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	46	47

*INCLUDES AUTOLYZED ANIMALS

TABLE D2

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	9 (100%)	49 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	47	49
ANIMALS WITH TUMORS	1 (11%)	11 (22%)	8 (16%)
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM		1 (2%)	1 (2%)
LUNG		1	1
INFLAMMATION INTERSTITIAL			1
HYPERPLASIA ALVEOLAR-CELL		1	
CIRCULATORY SYSTEM		2 (4%)	2 (4%)
HEART			2
PERIARTERITIS			2
MYOCARDIUM		2	1
INFLAMMATION FOCAL			1
INFLAMMATION FOCAL CHRONIC		2	
DIGESTIVE SYSTEM		9 (18%)	13 (26%)
LIVER		4	9
INFLAMMATION FOCAL		1	
INFLAMMATION SUBACUTE			2
INFLAMMATION FOCAL CHRONIC		3	4
CYTOPLASMIC VACUOLIZATION		1	1
HYPERPLASIA NODULAR			3
LIVER/HEPATOCYTES		2	
HYPERTROPHY FOCAL		2	
BILE DUCT		2	
INFLAMMATION FOCAL CHRONIC		2	
PANCREAS			1
PERIARTERITIS			1

TABLE D2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
PANCREATIC DUCT			1
CYST			1
PANCREATIC ACINUS		2	2
ATROPHY		2	2
ESOPHAGUS			1
HYPERPLASIA EPITHELIAL			1
STOMACH			1
INFLAMMATION SUBACUTE			1
HYPERPLASIA EPITHELIAL			1
S.INTESTINE/MUCOSA		1	
AMYLOIDOSIS		1	
URINARY SYSTEM	1 (11%)	7 (14%)	16 (32%)
KIDNEY	1	6	15
MINERALIZATION	1		
INFLAMMATION CHRONIC		6	14
PERIARTERITIS			1
RENAL TUBULE		1	
MINERALIZATION		1	
URINARY BLADDER			1
PERIARTERITIS			1
ENDOCRINE SYSTEM	9 (100%)	41 (84%)	47 (94%)
PITUITARY		3	
HYPERPLASIA CHROMOPHOBE-CELL		3	
ADRENAL			2
INFLAMMATION ACUTE			1
HYPERPLASIA			1

TABLE D2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
RIGHT ADRENAL GLAND			3
HYPERPLASIA			3
ADRENAL CORTEX	9	40	43
CYTOMEGALY		1	
HYPERPLASIA	9	39	43
HYPERPLASIA CYSTIC		1	
THYROID	1	3	2
CYSTIC FOLLICLES		1	1
PERIARTERITIS			1
HYPERPLASIA FOLLICULAR-CELL	1	3	
HEMATOPOIETIC SYSTEM		7 (14%)	3 (6%)
BONE MARROW		3	2
HYPERPLASIA HEMATOPOIETIC		3	2
SPLEEN		4	
HYPERPLASIA RETICULUM-CELL		2	
LYMPHOID HYPERPLASIA		2	
LYMPH NODE		2	1
LYMPHOID HYPERPLASIA		2	1
REPRODUCTIVE SYSTEM	5 (56%)	40 (82%)	40 (80%)
EXOCERVIX		1	
HYPERPLASIA		1	
UTERUS/ENDOMETRIUM	5	39	39
INFLAMMATION SUPPURATIVE		1	
INFLAMMATION ACUTE		2	2
HYPERPLASIA CYSTIC	5	37	37
OVARY		10	8
CYST			3

TABLE D2 FEMALE MICE: NONNEOPLASTIC LESIONS (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
OVARY (CONT.)			
FOLLICULAR CYST		7	3
HEMATOCYST		2	1
INFLAMMATION SUPPURATIVE		1	1
NERVOUS SYSTEM			2 (4%)
BRAIN/MENINGES			1
PERIVASCULAR CUFFING			1
BRAIN			1
INFLAMMATION FOCAL CHRONIC			1
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS			4 (8%)
PERITONEUM			2
INFLAMMATION ACUTE			2
MESENTERY			2
PERIARTERITIS			2
NO LESION REPORTED		3	1
AUTOLYSIS/NECROPSY PERF/NO HISTO		2	1
AUTOLYSIS/NO NECROPSY PERFORMED	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*	1	7	3
MORIBUND SACRIFICE		6	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	36	42
MISSING		1	

*INCLUDES AUTOLYZED ANIMALS

☆ U. S. GOVERNMENT PRINTING OFFICE : 1977 241-161/3080

DATE DUE

GAYLORD			PRINTED IN U.S.A.

DHEW Publication No. (NIH) 77-810