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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

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FOREWORD: This report presents the results of the bioassay of aldicarb 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 the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the 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 aldicarb 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., Rockville, Maryland, 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). Chemicals used in this bioassay were analyzed at Midwest Research Institute under the direction of Dr. E. Murrill (7). Chemicals and dosed food mixtures used in this bioassay were analyzed at GSRI under the direction of Mr. Wheeler. Analyses of the feed mixtures were performed by Mr. M. Billedeau (2) and Mr. J. S. Perrin (2). The results of the 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, and Ms. L. A. Owen, 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. 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 aldicarb 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 aldicarb at one of two doses, either 2 or 6 ppm, for 103 weeks and were then observed for an additional 0 to 2 weeks. Matched controls consisted of 25 untreated rats and 25 untreated mice of each sex. All surviving animals were killed at weeks 103 to 105.

Mean body weights of the dosed male and female rats were essentially the same as those of the corresponding controls. Mean body weights of the dosed male and female mice also were essentially the same as those of corresponding controls. Hyperactivity was noted in the dosed groups of mice. Survival was not affected significantly in dosed groups of either the rats or the mice and was 72% or greater in all dosed or control groups at week 90. Sufficient numbers of animals were at risk for the development of late-appearing tumors.

No tumors occurred in either the rats or mice at incidences that could clearly be related to administration of the test chemical. In both rats and mice, however, there was no indication either through weight depression or early mortality that maximum tolerated dose levels were used. Therefore, the studies may not have been conducted using maximum sensitivity for the assessment of the possible carcinogenicity of aldicarb.

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

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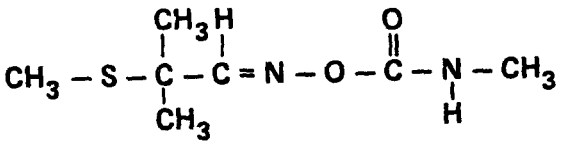
I. INTRODUCTION



Aldicarb

The carbamate pesticide aldicarb (CAS 116-06-3; NCI C08640), which is 2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)-oxime, is used for the control of insects, nematodes, and mites (Kuhr and Dorough, 1976). It is now registered for use on cotton, sugar beets, sugar cane, potatoes, peanuts, and a variety of field- and nursery-grown ornamental plants (Environmental Protection Agency, 1975). The commercial product contains from 5 to 15% of the active ingredient adsorbed to organic granules. As a systemic pesticide, it is applied below the soil surface for absorption by plant roots (Environmental Protection Agency, 1975; Kuhr and Dorough, 1976). Aldicarb ranked fourth among the carbamate insecticides in terms of the volume expended for agricultural purposes in 1974, which was 1.6 million pounds (Ayers and Johnson, 1976).

Aldicarb has a half-life of 9 to 12 days in soil under laboratory conditions, being rapidly converted to aldicarb sulfoxide. This sulfoxide derivative is the major metabolite and is more persistent than aldicarb. In one experiment, as much as 50% of radioactivity applied as S^{35} aldicarb was recovered in the sulfoxide in sand in the laboratory after 12 weeks (Coppedge et al., 1967). Under field conditions, however, aldicarb was completely metabolized within 1 week, and the sulfoxide was lost after about 4 weeks (Bull, 1968). This pattern has been confirmed in another study of the fate of aldicarb, where the half-life of aldicarb and all toxic metabolites was reported to be greater than 8 weeks in the laboratory, and less than 1 week in the field (Bull et al., 1970). Carbon dioxide is the final product of degradation (Richey et al., 1977).

Aldicarb is highly toxic to rodents by both oral and dermal routes, the acute oral LD_{50} being in the range of 0.8 mg/kg in male Sherman rats, 0.65 mg/kg in female Sherman rats (Gaines, 1969), and 1 mg/kg in female rats of an unspecified strain (Weiden et al., 1965), whereas the dermal LD_{50} is 3 and 2.5 mg/kg in male and female Sherman rats, respectively (Gaines, 1969). The acute oral LD_{50} of aldicarb for male Swiss white mice has been reported as 0.3 to 0.5 mg/kg (Black et al., 1973). Thirteen-week feeding studies indicated that a dose of 0.5 mg/kg

body weight/day in the diet increased significantly the mortality in CFE rats (Weil and Carpenter, 1969), although 2-year feeding studies indicated that a dose of 0.3 mg/kg body weight/day administered to Greenacres Laboratory Controlled Flora rats caused no adverse effects (Weil, 1975).

The mode of action of aldicarb is cholinesterase inhibition (Ryan, 1971; Koelle, 1975). Aldicarb sulfoxide, the major metabolite, has 76 times greater anticholinesterase activity than the parent compound and is believed to be the active form of the pesticide, since it is considerably more persistent in plants (Metcalf et al., 1966). Neither aldicarb nor aldicarb sulfoxide was toxic for Greenacres Laboratory Controlled Flora rats in 2-year feeding studies at a dose of 0.3 mg/kg/day; however, aldicarb sulfoxide caused some deaths in the females at a dose of 0.6 mg/kg/day (Weil, 1975). In mosquitoes, the sulfoxide was less toxic than the parent compound (Metcalf et al., 1966).

Aldicarb was one of many pesticides that were selected for study by the Carcinogenesis Bioassay Program.

II. MATERIALS AND METHODS

A. Chemical

Aldicarb was obtained in a single batch (Lot No. RDS-643-D) as the technical-grade material from Union Carbide Corporation, New York, New York. The identity and purity of this batch was confirmed in analysis at Gulf South Research Institute. The melting point was 96 to 98°C (Windholz, 1976: 99 to 100°C). Thin-layer and gas-liquid chromatography indicated no impurities and conformed to the manufacturer's specification of 99+% for the technical-grade material. Elemental analyses (C, H, N, S) were correct for $C_7H_{14}N_2O_2S$, the molecular formula of aldicarb. Nuclear magnetic resonance and infrared spectra agreed with those reported in the literature (Sadtler Standard Spectra, Sadtler Laboratories, Philadelphia, Pa.; Kieth et al., 1970). Upon completion of the bioassay this lot of aldicarb was reanalyzed by Midwest Research Institute. Analysis by gas-liquid and high-pressure liquid chromatography and infrared spectrometry indicated that this material had not changed under storage conditions 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 aldicarb for each dietary concentration. The test compound was first dissolved in a small amount of acetone (Mallinckrodt Inc., St. Louis, Mo.) which was then added to the feed. Corn oil (LouAna®, Opelousas Refinery Co., Opelousas, La.) was also added to the feed, primarily as a dust suppressant, and the diets were mixed mechanically for not less than 25 minutes to assure homogeneity and to allow for evaporation of the acetone. Final diets, including those for the control groups of animals, contained corn oil equal to 2% of the final weight of feed. Formulated diets were stored at ambient room temperature until used, but not longer than 1 week.

The stability of aldicarb in feed was tested at Midwest Research Institute by determining the concentration of the compound in formulated diets at intervals over a 7-day period. Diets containing 39 and 7 ppm aldicarb showed no significant change in aldicarb concentration on standing at ambient temperature for this period.

As a quality control check on the accuracy of preparation of the

diets, the concentration of aldicarb was measured in randomly selected batches of formulated diets at 8-week intervals during the chronic study. Results are summarized in Appendix E. At each dietary concentration, the mean of the analytical concentrations for the checked samples was within 11% of the theoretical concentration, and the coefficient of variation was never more than 0.20.

C. Animals

F344 (Fischer) rats and B6C3F1 hybrid mice of each sex were obtained from the NCI Frederick Cancer Research Center (Frederick, Md.). The rats were 8 weeks of age and the mice 6 weeks of age when placed on study.

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. Aldicarb 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, and any feed remaining from the previous day was discarded.

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of aldicarb on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were selected for administration in the chronic studies. Groups of 10 rats and 10 mice of each sex were administered diets containing aldicarb 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. Tables 1 and 2 show the doses given, the survivals of animals in each dosed group at the end of the study, and the mean body weights of the dosed groups of animals at week 13, expressed as percentages of mean body weights of corresponding controls. At the end of the 13 weeks, all surviving animals were killed and

Table 1. Aldicarb Subchronic Feeding Studies in Rats

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
0 (b,c)	10/10	100	10/10	100
5	10/10	100	10/10	101
10	10/10	100	10/10	105
20	10/10	95	10/10	97
40	10/10	84	9/10	90
80 (b)	10/10	68	10/10	81
160	0/10		0/10	
320	0/10		0/10	

(a) Number surviving/number in group.

(b) Microscopic examination was performed on tissues of 10 male and 10 female controls and on 8 male and 8 female animals dosed at 80 ppm.

(c) One female control had mild centrilobular fatty degeneration and another had mild periportal parenchymatous degeneration of the liver.

Table 2. Aldicarb Subchronic Feeding Studies in 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
0 (b)	10/10	100	10/10 (c)	100
0.5	10/10	94	10/10	97
1	10/10	91	10/10	94
2.5	10/10	91	10/10	94
5	10/10	88	10/10	94
10	10/10	91	10/10	94
20 (b)	10/10	93	10/10	96
40 (b)	10/10	95	9/10 (d)	96

(a) Number surviving/number in group.

(b) Microscopic examination was performed on 10 male and 10 female controls, on 10 males and 8 females dosed at 20 ppm, and on 8 males and 10 females dosed at 40 ppm.

(c) All control female mice showed diffuse parenchymatous degeneration of the liver, which was confirmed by a second set of microscopic sections. Sections showed a diffuse involvement of hepatocytes throughout the lobule. The cells were somewhat swollen in appearance and contained coarsely granular eosinophilic material.

One female control had benign teratoma of the ovary.

(d) The left ovary of one female dosed at 40 ppm had a large, encapsulated mass with a lobular surface, and dark-brown diffusely scattered foci on the cut surface. It was diagnosed as a benign teratoma. Another female dosed at 40 ppm showed mild diffuse fatty degeneration of the liver.

necropsied. Gross and histopathologic findings are given as footnotes in tables 1 and 2.

All rats died at doses of 160 or 320 ppm, and mean weights decreased at doses of 40 or 80 ppm. The data for the mice showed no effects clearly related to administration of aldicarb at any of the doses tested.

In a 13-week feeding study reported previously (Weil and Carpenter, 1969), mortality increased in male and female CFE rats administered aldicarb at 0.5 mg/kg body weight/day (considered by the laboratory to be about 10 ppm), but was not significantly increased in the rats administered 0.1 mg/kg body weight/day.

Doses for the chronic studies of aldicarb in both rats and mice were set at 2 and 6 ppm.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 3 and 4.

Table 3. Aldicarb Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Aldicarb Doses (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	25	0		105
Low-Dose	50	2	103	2
High-Dose	50	6	103	2
Female				
Matched-Control	25	0		105
Low-Dose	50	2	103	2
High-Dose	50	6	103	2

(a) Rats were 8 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum.

Table 4. Aldicarb Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Aldicarb Doses (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	25	0		103-104
Low-Dose	50	2	103	0-1
High-Dose	50	6	103	0-1
Female				
Matched-Control	25	0		103-104
Low-Dose	50	2	103	0-1
High-Dose	50	6	103	0-1

(a) Mice were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum.

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Clinical examination for signs of toxicity and palpation for masses were performed each month, and the animals were weighed every 2 weeks. Moribund animals and animals that survived to the end of the bioassay were killed using pentobarbitol and necropsied.

The pathologic evaluation consisted of gross and microscopic 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 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. Blood smears of all animals were routinely prepared.

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

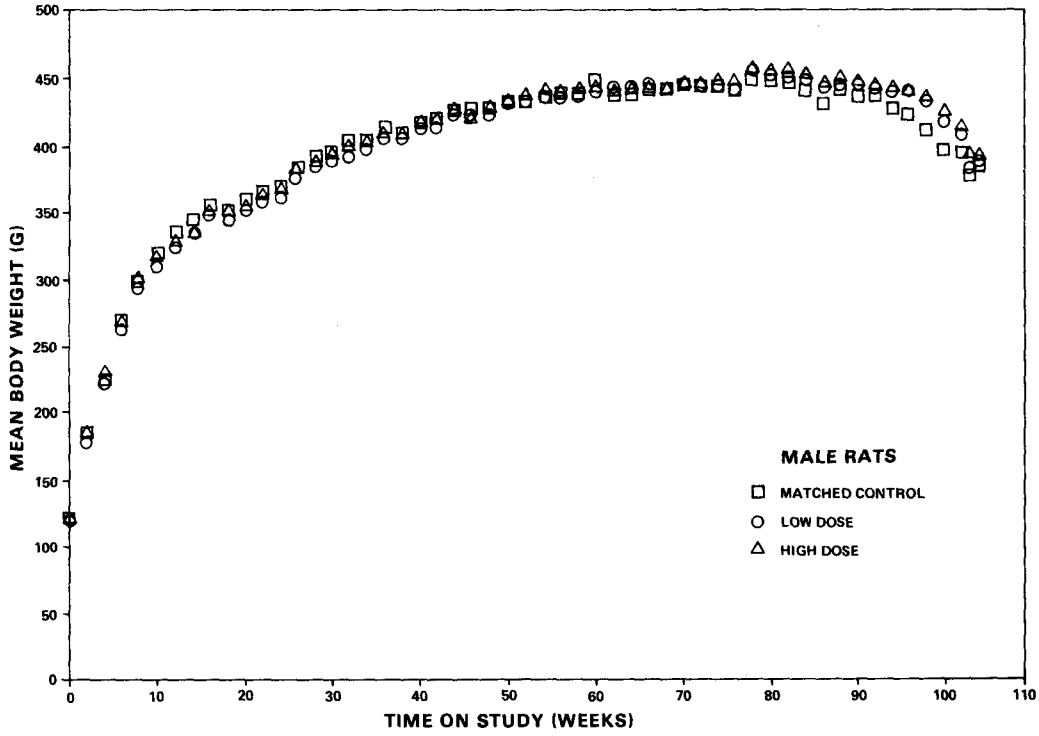
A. Body Weights and Clinical Signs (Rats)

Mean body weights of the dosed male and female rats were essentially the same as those of the corresponding controls (figure 1). Tachypnea occurred in dosed groups but not in control groups.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered aldicarb 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 each sex, the result of the Tarone test for positive dose-related trend in mortality is not significant. In male rats, an indicated departure from linear trend ($P = 0.013$) is observed because the low-dose male rats survived longer than either the high-dose or the control rats.

In male rats, 39/50 (78%) of the high-dose group, 44/50 (88%) of



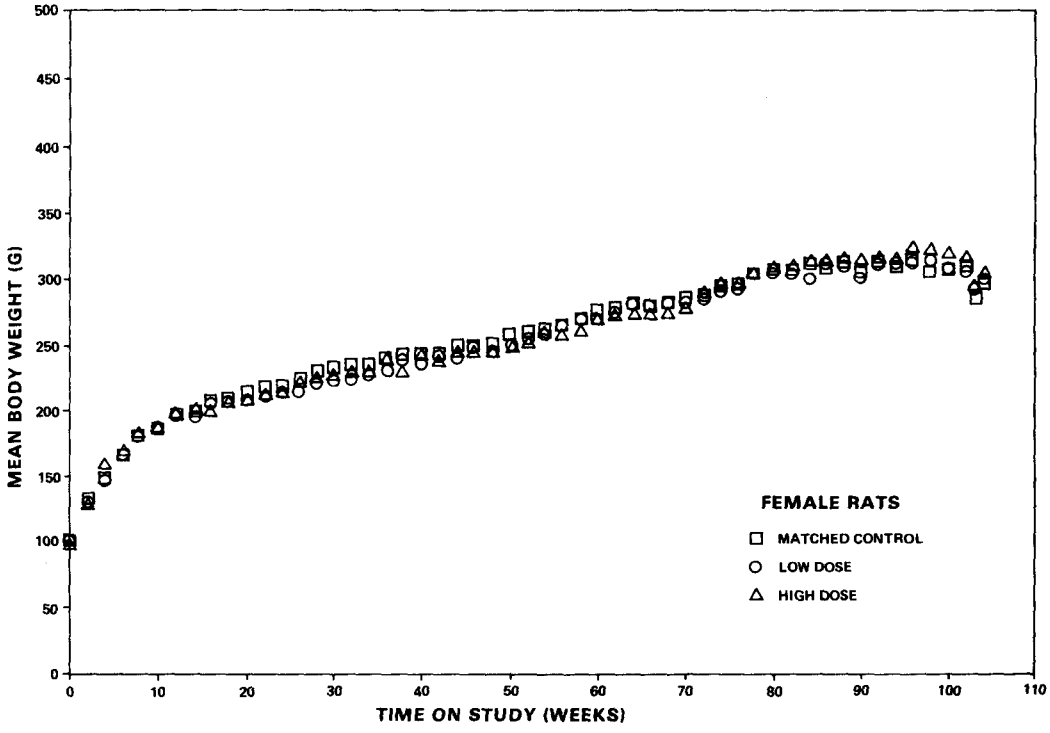


Figure 1. Growth Curves for Rats Administered Aldicarb in the Diet

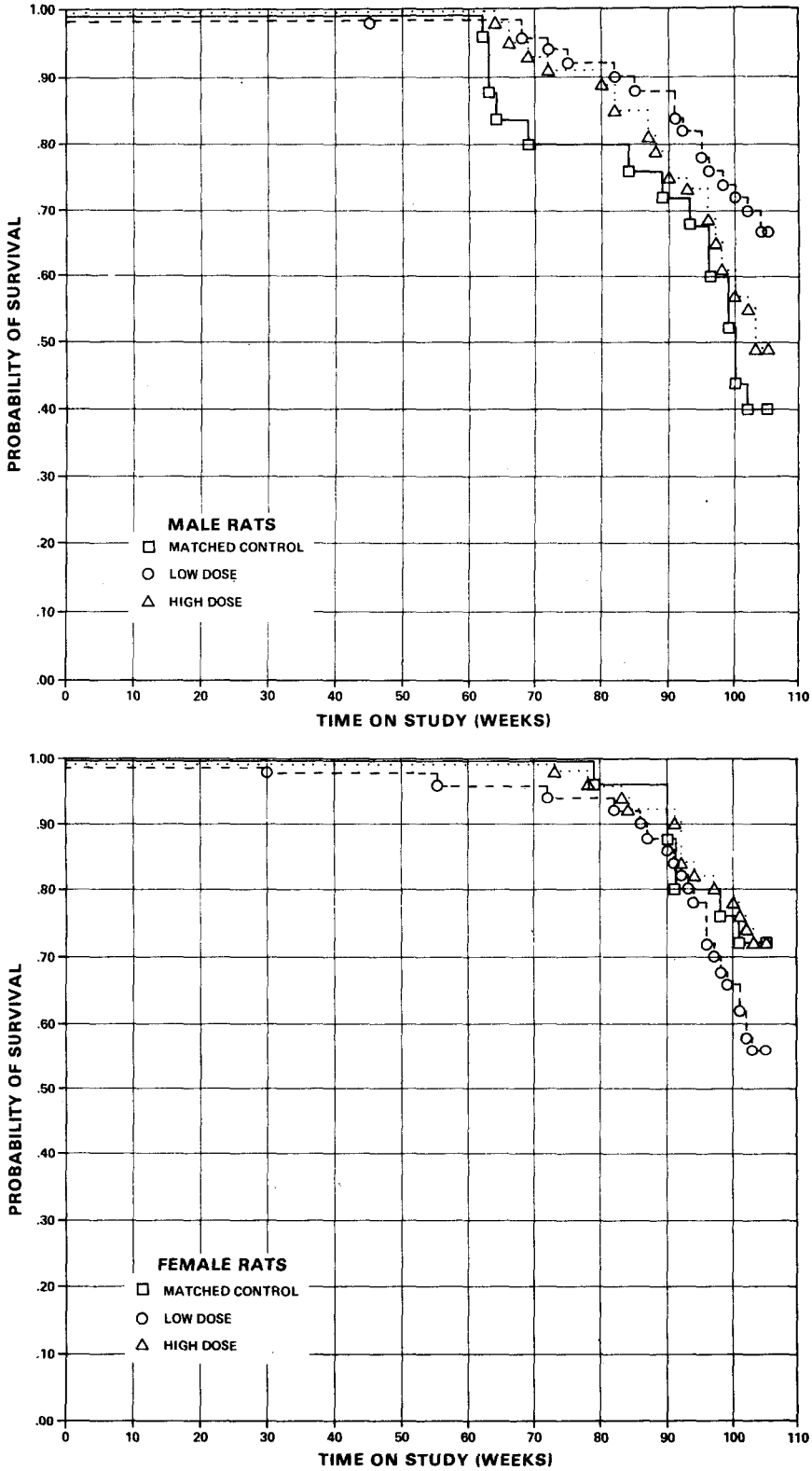


Figure 2. Survival Curves for Rats Administered Aldicarb in the Diet

the low-dose group, and 18/25 (72%) of the control group were still alive at week 90 on study. In females, 46/50 (92%) of the high-dose group, 44/50 (88%) of the low-dose group, and 24/25 (96%) of the control group were still alive at week 90 on study.

Sufficient numbers of rats of each sex were at risk for the development of tumors.

C. Pathology (Rats)

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

A variety of neoplasms occurred in both dosed and control animals. The majority were thought not to be compound related.

In the males, neoplastic nodules occurred in the livers of 1/24 (4%) controls, 1/47 (2%) low-dose animals, and 5/48 (10%) high-dose animals. One hepatocellular carcinoma was observed in the low-dose male group. No hepatic neoplasms were observed in the females. Focal cellular change was found in the livers of 2/24 (8%) of the control males, 4/47 (9%) of the low-dose males,

and 6/48 (13%) of the high-dose males. In the females, the incidences of this lesion were 4/25 (16%) in control, 4/48 (8%) in low-dose, and 5/50 (10%) in high-dose groups.

Pancreatic islet-cell adenomas occurred in dosed groups of males (low-dose 5/49 (10%); high-dose 6/48 (13%)) and females (low-dose 2/49 (4%); high-dose 2/50 (4%)), but in none of the male or female controls.

This histopathologic examination provided no conclusive evidence for the carcinogenicity of aldicarb in F344 rats under the conditions of this bioassay. However, the occurrences of hepatic neoplasms in the dosed male rats and pancreatic islet-cell adenomas in both dosed males and both females were regarded as compound related.

D. Statistical Analyses of Results (Rats)

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

In male rats, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of interstitial-cell tumor of the testis is significant (P = 0.010), and the Fisher exact test shows that the high-dose incidence is significantly (P = 0.014) higher than that in the control group. However, the incidence of this tumor in F344 control male rats of this laboratory is 220/275 (80%) compared with 18/24 (75%) in the control groups, 43/49 (88%) in the low-dose group, and 46/48 (96%) in the high-dose group of this study.

In females, the result of the Cochran-Armitage test for the incidence of animals with either adenoma or carcinoma of the pituitary is significant (P = 0.048), but the results of the Fisher exact tests are not significant. The historical records of this laboratory show an incidence of 114/273 (42%), compared with 14/25 (56%) in the control group, 33/48 (69%) in the low-dose group, and 37/48 (77%) in the high-dose group of this study.

The results of the statistical test on the incidence of islet-cell adenomas of the pancreas in male rats are not significant. The incidence of these tumors in male F344 historical-control rats at this laboratory is 23/275 (8.4.%), compared with 0/24 in the control group, 5/49 (10%) in the

low-dose group and 6/48 (13%) in the high-dose group of this study. The incidence of these tumors in the control group of male rats in this study is lower than would be expected from the historical information.

Significant results in the negative direction are observed in the incidence of pituitary tumors in male rats and in the incidence of leukemia in female rats.

In each of the 95% confidence intervals for relative risk, except that for the incidence of testis tumors in the high-dose males, 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 tumor induction by aldicarb, which could not be detected under the conditions of this bioassay.

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

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	1/22 (5)	2/49 (4)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.898	1.375
Lower Limit		0.050	0.120
Upper Limit		51.910	70.655
Weeks to First Observed Tumor	105	91	98
Hematopoietic System: Leukemia (b)	2/24 (8)	5/49 (10)	8/48 (17)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.224	2.000
Lower Limit		0.222	0.446
Upper Limit		12.283	18.398
Weeks to First Observed Tumor	100	100	97

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	1/24 (4)	1/47 (2)	5/48 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk		0.511	2.500
Lower Limit		0.007	0.306
Upper Limit		39.263	115.634
Weeks to First Observed Tumor	105	105	103
Pituitary: Adenoma or Carcinoma, NOS (b)	8/20 (40)	10/43 (23)	6/43 (14)
P Values (c,d)	P = 0.021 (N)	N.S.	P = 0.026 (N)
Relative Risk (f)		0.581	0.349
Lower Limit		0.256	0.121
Upper Limit		1.466	1.004
Weeks to First Observed Tumor	96	68	96

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma (b)	0/22 (0)	0/48 (0)	2/39 (5)
P Values (c,d)	N.S.	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.172
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	64
Thyroid: C-cell Carcinoma or Adenoma (b)	2/22 (9)	3/48 (6)	2/39 (5)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.688	0.564
Lower Limit		0.086	0.044
Upper Limit		7.863	7.391
Weeks to First Observed Tumor	105	105	64

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma (b)	0/24 (0)	5/49 (10)	6/48 (13)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.636	0.824
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	103	96
Testis: Interstitial-cell Tumor (b)	18/24 (75)	43/49 (88)	46/48 (96)
P Values (c,d)	P = 0.010	N.S.	P = 0.014
Relative Risk (f)		1.170	1.278
Lower Limit		0.915	1.020
Upper Limit		1.527	1.466
Weeks to First Observed Tumor	89	75	66

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

(continued)

(a) Dosed groups received 2 or 6 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 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Aldicarb in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Leukemia (b)	4/25 (16)	6/50 (12)	1/50 (2)
P Values (c,d)	P = 0.017 (N)	N.S.	P = 0.040 (N)
Relative Risk (f)		0.750	0.125
Lower Limit		0.200	0.003
Upper Limit		3.353	1.189
Weeks to First Observed Tumor	90	55	105
Pituitary: Carcinoma, NOS (b)	1/25 (4)	0/48 (0)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	1.563
Lower Limit		0.000	0.135
Upper Limit		9.720	80.296
Weeks to First Observed Tumor	91	--	105

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Aldicarb in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma or Carcinoma, NOS (b)	14/25 (56)	33/48 (69)	37/48 (77)
P Values (c,d)	P = 0.048	N.S.	N.S.
Relative Risk (f)		1.228	1.376
Lower Limit		0.825	0.944
Upper Limit		1.959	2.103
Weeks to First Observed Tumor	90	86	78
Thyroid: C-cell Adenoma (b)	1/24 (4)	2/44 (5)	3/47 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.091	1.532
Lower Limit		0.061	0.133
Upper Limit		62.902	78.688
Weeks to First Observed Tumor	105	105	92

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Aldicarb in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland or Mammary Duct: Carcinoma, NOS, or Adenocarcinoma, NOS (b)	0/25 (0)	2/50 (4)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.151	0.309
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	91	92
Mammary Gland: Fibroadenoma or Adenoma (b)	4/25 (16)	8/50 (16)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.000	0.625
Lower Limit		0.303	0.150
Upper Limit		4.197	2.928
Weeks to First Observed Tumor	91	82	102

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Aldicarb in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	9/24 (38)	9/47 (19)	15/49 (31)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.511	0.816
Lower Limit		0.215	0.406
Upper Limit		1.276	1.838
Weeks to First Observed Tumor	79	72	91
Adipose Tissue: Lipoma (b)	0/25 (0)	3/50 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.309	0.027
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	96	105

Table 6. Analyses of the Incidence of Primary Tumors in Female Rats Administered Aldicarb in the Diet (a)

(continued)

(a) Dosed groups received 2 or 6 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 male and female mice were essentially the same as those of corresponding controls (figure 3). Hyperactivity was reported for the dosed groups of mice.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered aldicarb 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, 45/50 (90%) of the high-dose group, 48/50 (96%) of the low-dose group, and 21/25 (84%) of the matched-control group were still alive at week 90 on study. In females, 44/50 (88%) of the high-dose group, 45/50 (90%) of the low-dose group, and 19/25

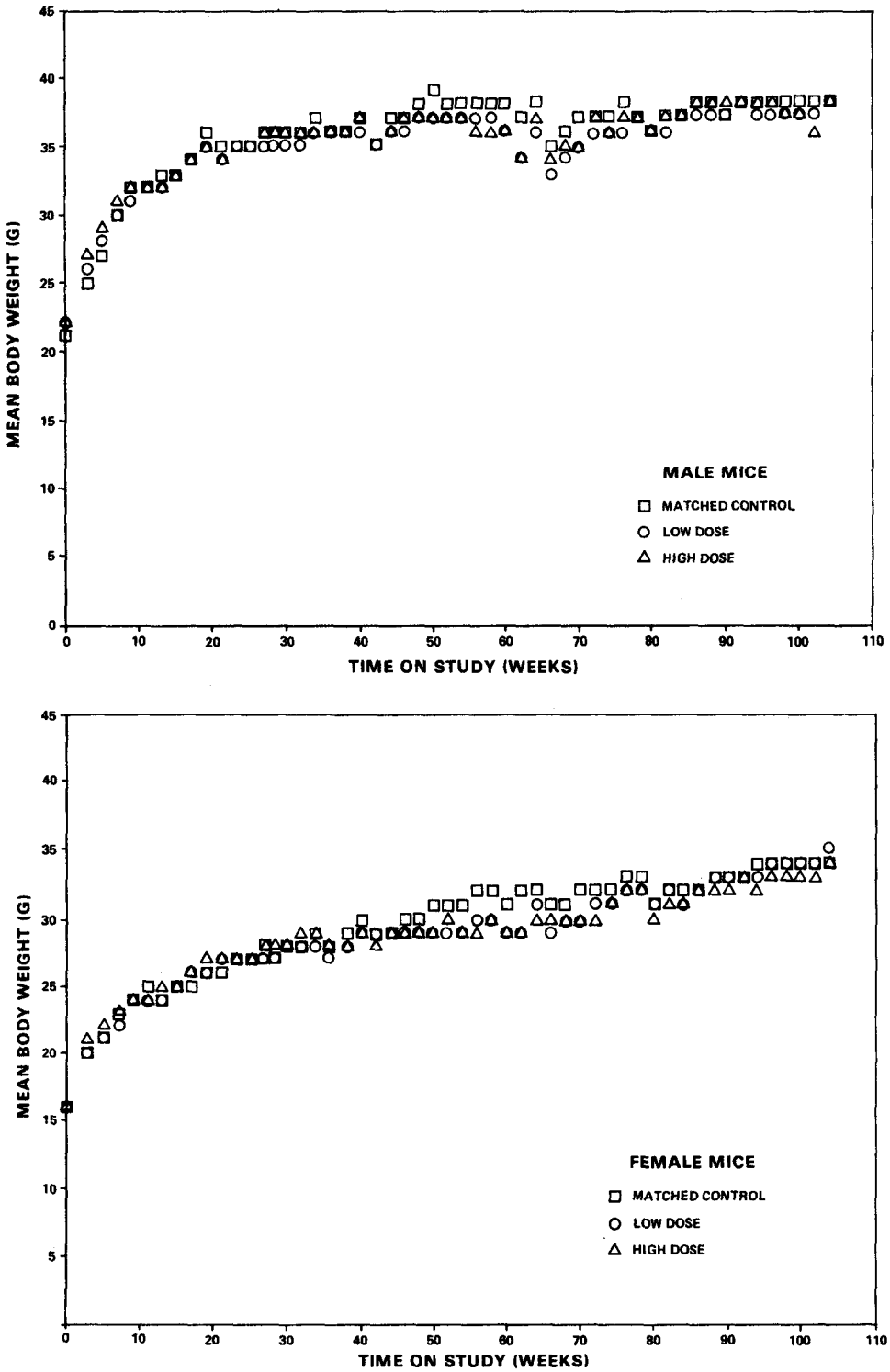


Figure 3. Growth Curves for Mice Administered Aldicarb in the Diet

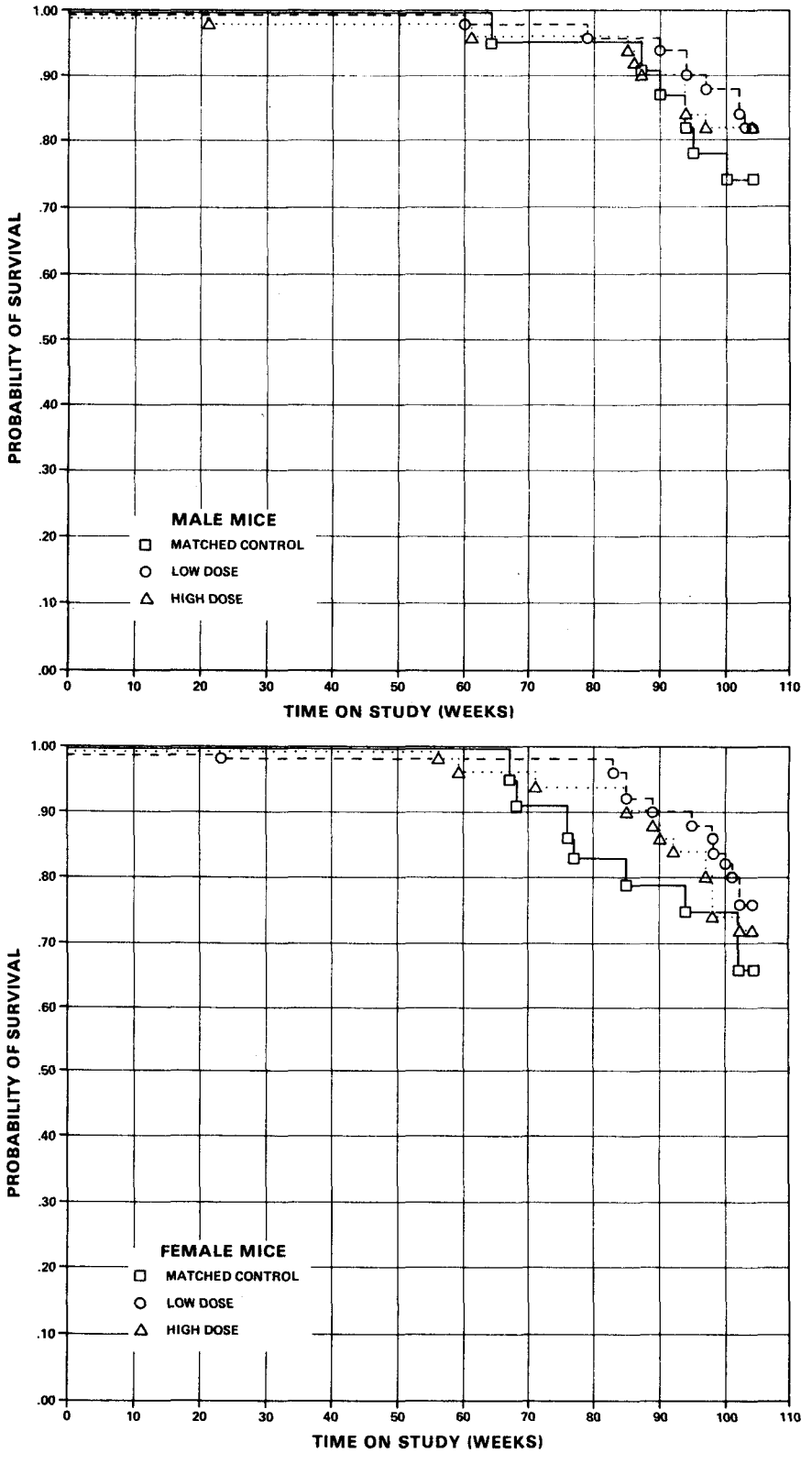


Figure 4. Survival Curves for Mice Administered Aldicarb in the Diet

(76%) of the matched-control group were still alive at week 90 on study.

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 benign and malignant tumors occurred at different anatomic sites in dosed and control mice. In general, these tumors are not unusual and occur in B6C3F1 mice independent of administration of any test chemical. The majority of neoplasms occurred at approximately the same incidence in dosed and control groups. However, the incidence of benign and malignant tumors of the liver (hepatocellular adenomas and hepatocellular carcinomas) in males, but not in females, was somewhat greater in the low- and high-dose groups that in the control group, as shown in the following table:

	Male			Female		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Animals with Tissues Examined Microscopically	24	49	49	25	49	48
Hepatocellular Carcinoma	4(17%)	10(20%)	13(27%)	3(12%)	0(0%)	4(8%)
Hepatocellular Adenoma	1(4%)	4(8%)	5(10%)	0(0%)	0(0%)	0(0%)
Animals Bearing Liver Tumors	5(21%)	14(29%)	18(37%)	3(12%)	0(0%)	4(8%)

Based on the histopathologic examination, the evidence was not sufficient to indicate a carcinogenic effect of aldicarb in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables 7 and 8 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more than one group.

In male mice, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of animals with either fibrosarcoma or sarcoma of the subcutaneous tissue in the

integumentary system is significant (P = 0.043), but the results of the Fisher exact test are not significant. In females, the results of the Cochran-Armitage test and Fisher exact test are not significant in the positive direction.

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

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

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma or Sarcoma, NOS, of the Subcutaneous Tissue (b)	0/24 (0)	1/50 (2)	4/49 (8)
P Values (c,d)	P = 0.043	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.026	0.467
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	94
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	1/24 (4)	6/49 (12)	5/48 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.939	2.500
Lower Limit		0.392	0.306
Upper Limit		132.164	115.634
Weeks to First Observed Tumor	104	103	104

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (a)	1/24 (4)	3/50 (6)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.440	0.980
Lower Limit		0.125	0.054
Upper Limit		74.077	56.627
Weeks to First Observed Tumor	95	60	104
All Sites: Hemangiosarcoma or Angiosarcoma (b)	0/24 (0)	3/50 (6)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.297	0.303
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	97	61

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	4/24 (17)	10/49 (20)	13/49 (27)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.224	1.592
Lower Limit		0.405	0.567
Upper Limit		4.919	6.133
Weeks to First Observed Tumor	64	79	85
Liver: Hepatocellular Adenoma or Carcinoma (b)	5/24 (21)	14/49 (29)	18/49 (37)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.371	1.763
Lower Limit		0.544	0.740
Upper Limit		4.389	5.436
Weeks to First Observed Tumor	64	79	85

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

(continued)

(a) Dosed groups received 2 or 6 ppm.

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

(c) Number of tumor-bearing 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 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Aldicarb in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	1/25 (4)	4/50 (8)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	0.500
Lower Limit		0.215	0.007
Upper Limit		96.452	38.493
Weeks to First Observed Tumor	103	98	104
Hematopoietic System: Lymphoma or Leukemia (b)	6/25 (24)	8/50 (16)	10/50 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.667	0.833
Lower Limit		0.233	0.318
Upper Limit		2.114	2.519
Weeks to First Observed Tumor	67	23	71

Table 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Aldicarb in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	3/25 (12)	0/49 (0)	4/48 (8)
P Values (c,d)	N.S.	P = 0.035 (N)	N.S.
Departure from Linear Trend (e)	P = 0.021		
Relative Risk (f)		0.000	0.694
Lower Limit		0.000	0.129
Upper Limit		0.843	4.461
Weeks to First Observed Tumor	104	--	98
Pituitary: Adenoma, NOS (b)	2/21 (10)	3/40 (8)	2/43 (5)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.788	0.488
Lower Limit		0.099	0.038
Upper Limit		8.941	6.417
Weeks to First Observed Tumor	94	104	104

Table 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Aldicarb in the Diet (a)

(continued)

(a) Dosed groups received 2 or 6 ppm.

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

(c) Number of tumor-bearing 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

Mean body weights of the dosed male and female rats were essentially the same as those of the corresponding controls. Mean body weights of the dosed male and female mice also were essentially the same as those of corresponding controls. Tachypnea was reported for the dosed groups of rats and hyperactivity for the dosed groups of mice. Survival was not affected significantly in dosed groups of either the rats or the mice and was 72% or greater in all dosed or control groups at week 90. These findings suggest that a maximum tolerated dose level may not have been used. Therefore, the studies may not have been conducted using maximum sensitivity for the assessment of the possible carcinogenicity of aldicarb.

In female rats, adenomas or carcinomas of the pituitary occurred at incidences that were dose related ($P = 0.048$), and in male mice, fibrosarcomas or sarcomas of the subcutaneous tissue occurred at incidences that were dose related ($P = 0.043$); however, in direct comparisons the incidences of neither tumor were significantly higher in the individual dosed groups than in the corresponding control groups (pituitary tumors: controls 14/25 (56%), low-dose 33/48 (69%), high-dose 37/48 (77%); subcutaneous tissue tumors:

controls 0/24, low-dose 1/50 (2%), high-dose 4/49 (8%)). The incidence of pituitary tumors in historical-control female F344 rats at this laboratory also was high, 114/273 (42%). Thus, the occurrence of tumors of the pituitary in the female rats and tumors of the subcutaneous tissue 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 male rats or the female mice.

In a previous 2-year feeding study using rats of unspecified strain that were administered diets containing aldicarb at doses equivalent to 0.005, 0.025, 0.05, or 0.1 mg/kg/day, the incidences of tumors in test animals were not significantly greater than those in control groups (Weil and Carpenter, 1965); body weight gain and mortality also were unaffected. No adverse effects were noted when aldicarb was fed at 0.3 mg/kg/day to Greenacres Laboratory Controlled Flora rats for 2 years (Weil, 1975). Aldicarb was not carcinogenic when administered to male C3H/HeJ mice by painting a concentration of 0.125% on the skin twice per week for a maximum period of 28 months (Weil and Carpenter, 1966).

It is concluded that under the conditions of this bioassay, technical-grade aldicarb 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 ALDICARB IN THE DIET

TABLE A1.

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

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECPOPSIED	24	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(24)	(49)	(48)
SQUAMOUS CELL CARCINOMA	1 (4%)		
FIBROMA			1 (2%)
*SUBCUT TISSUE	(24)	(49)	(48)
FIBROSARCOMA	1 (4%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(22)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	2 (4%)	3 (6%)
C-CELL CARCINOMA, METASTATIC			1 (2%)
FIBROSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(24)	(49)	(48)
LEUKEMIA,NOS	1 (4%)	2 (4%)	
UNDIFFERENTIATED LEUKEMIA	1 (4%)	3 (6%)	8 (17%)
#SPLEEN	(23)	(49)	(48)
HEMANGIOSARCOMA	1 (4%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(24)	(47)	(48)
NEOPLASTIC NODULE	1 (4%)		5 (10%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA		1 (2%)	
#DUODENUM	(24)	(46)	(47)
SARCOMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(24)	(49)	(48)
TUBULAR-CELL ADENOMA			1 (2%)
#KIDNEY/PELVIS	(24)	(49)	(48)
TRANSITIONAL-CELL CARCINOMA			1 (2%)
#URINARY BLADDER	(23)	(44)	(42)
CARCINOMA, NOS	1 (4%)		
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(43)	(43)
CARCINOMA, NOS			1 (2%)
ADENOMA, NOS	8 (40%)	10 (23%)	5 (12%)
#ADRENAL	(23)	(48)	(47)
PHEOCHROMOCYTOMA		2 (4%)	1 (2%)
#ADRENAL MEDULLA	(23)	(48)	(47)
NEUROBLASTOMA			1 (2%)
#THYROID	(22)	(48)	(39)
PAPILLARY ADENOMA			1 (3%)
C-CELL ADENOMA	2 (9%)	3 (6%)	
C-CELL CARCINOMA			2 (5%)
#PANCREATIC ISLETS	(24)	(49)	(48)
ISLET-CELL ADENOMA		5 (10%)	6 (13%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(24)	(49)	(48)
FIBROMA		1 (2%)	
FIBROADENOMA	1 (4%)	1 (2%)	1 (2%)
#TESTIS	(24)	(49)	(48)
INTERSTITIAL-CELL TUMOR	18 (75%)	43 (88%)	46 (96%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*EPIDIDYMIS	(24)	(49)	(48)
LIPOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EAR CANAL	(24)	(49)	(48)
SQUAMOUS CELL CARCINOMA			2 (4%)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(24)	(49)	(48)
LIPOMA	1 (4%)		1 (2%)
*MUSCLE HIP/THIGH	(24)	(49)	(48)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(24)	(49)	(48)
MESOTHELIOMA, NOS	1 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(24)	(49)	(48)
FIBROSARCOMA			2 (4%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	4	7	2
MORIBUND SACRIFICE	11	9	23
**SCHEDULED SACRIFICE	2	2	2
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	8	32	22
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 A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	47	47
TOTAL PRIMARY TUMORS	39	75	91
TOTAL ANIMALS WITH BENIGN TUMORS	20	47	46
TOTAL BENIGN TUMORS	31	67	67
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	7	16
TOTAL MALIGNANT TUMORS	6	7	19
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	1	5
TOTAL UNCERTAIN TUMORS	2	1	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED ALDICARB 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			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(50)	(50)
LEUKEMIA,NOS	1 (4%)	1 (2%)	
UNDIFFERENTIATED LEUKEMIA	3 (12%)	5 (10%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#HEPATIC CAPSULE	(25)	(49)	(50)
LIPOMA	1 (4%)		
URINARY SYSTEM			
#KIDNEY	(24)	(49)	(50)
TUBULAR-CELL ADENOCARCINOMA	1 (4%)		
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(48)	(48)
CARCINOMA,NOS	1 (4%)		3 (6%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ADENOMA, NOS	13 (52%)	33 (69%)	34 (71%)
#ADRENAL	(24)	(47)	(46)
CORTICAL ADENOMA	1 (4%)		
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
#THYROID	(24)	(44)	(47)
C-CELL ADENOMA	1 (4%)	2 (5%)	3 (6%)
#PANCREATIC ISLETS	(24)	(49)	(50)
ISLET-CELL ADENOMA		2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
CARCINOMA,NOS		2 (4%)	
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			2 (4%)
FIBROADENOMA	4 (16%)	7 (14%)	5 (10%)
*MAMMARY DUCT	(25)	(50)	(50)
CARCINOMA,NOS			1 (2%)
*CLITORAL GLAND	(25)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
#UTERUS	(24)	(47)	(49)
ADENOMA, NOS	1 (4%)		
SARCOMA, NOS		1 (2%)	1 (2%)
LEIOMYOSARCOMA		2 (4%)	
ENDOMETRIAL STROMAL POLYP	9 (38%)	9 (19%)	15 (31%)
NERVOUS SYSTEM			
#BRAIN	(25)	(49)	(50)
CARCINOMA, NOS, INVASIVE	1 (4%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL 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
BODY CAVITIES			
*MEDIASTINUM	(25)	(50)	(50)
ADNEXAL CARCINOMA		1 (2%)	
*ABDOMINAL CAVITY	(25)	(50)	(50)
LIPOMA			1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LIPOMA		3	1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	1	2	4
MORIBUND SACRIFICE	6	20	10
**SCHEDULED SACRIFICE	2	2	2
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	26	34
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 A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	45	46
TOTAL PRIMARY TUMORS	36	71	70
TOTAL ANIMALS WITH BENIGN TUMORS	19	40	44
TOTAL BENIGN TUMORS	30	58	62
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	13	7
TOTAL MALIGNANT TUMORS	6	13	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

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

TABLE B1.

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

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	24	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	50	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(24)	(50)	(49)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA		1 (2%)	3 (6%)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (4%)		
RESPIRATORY SYSTEM			
#LUNG	(24)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)	6 (12%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(24)	(50)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)
LEUKEMIA,NOS	1 (4%)	1 (2%)	
LYMPHOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(24)	(49)	(49)
HEMANGIOSARCOMA			2 (4%)
#LYMPH NODE	(23)	(50)	(47)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#SMALL INTESTINE	(20)	(45)	(48)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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	(24)	(49)	(49)
HEPATOCELLULAR ADENOMA	1 (4%)	4 (8%)	5 (10%)
HEPATOCELLULAR CARCINOMA	4 (17%)	10 (20%)	13 (27%)
HEMANGIOSARCOMA		2 (4%)	1 (2%)
ANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(24)	(49)	(49)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(19)	(47)	(45)
FOLLICULAR-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(24)	(50)	(49)
ADENOMA, NOS			1 (2%)
PAPILLARY ADENOMA			1 (2%)
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@	2	3	3
MORIBUND SACRIFICE	4	6	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	2		
TERMINAL SACRIFICE	17	41	41
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	27	30
TOTAL PRIMARY TUMORS	8	29	34
TOTAL ANIMALS WITH BENIGN TUMORS	2	11	10
TOTAL BENIGN TUMORS	2	12	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	16	22
TOTAL MALIGNANT TUMORS	6	17	24
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED ALDICARB 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)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(25)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	3 (12%)	2 (4%)	3 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)		1 (2%)
LEUKEMIA,NOS		2 (4%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		2 (4%)	2 (4%)
GRANULOCYTIC LEUKEMIA	2 (8%)	1 (2%)	1 (2%)
#SPLEEN	(24)	(49)	(50)
HEMANGIOMA	1 (4%)		
HEMANGIOSARCOMA		1 (2%)	
#LYMPH NODE	(20)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)
#DUODENUM	(20)	(45)	(40)
MALIGNANT LYMPHOMA, NOS			1 (3%)
CIRCULATORY SYSTEM			
NONE			

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			
#SALIVARY GLAND	(24)	(50)	(48)
FIBROSARCOMA			1 (2%)
#LIVER	(25)	(49)	(48)
HEPATOCELLULAR CARCINOMA	3 (12%)		4 (8%)
OSTEOSARCOMA, METASTATIC			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(21)	(40)	(43)
ADENOMA, NOS	2 (10%)	3 (8%)	2 (5%)
CHROMOPHOBE CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
CARCINOMA,NOS			1 (2%)
ADENOMA, NOS	1 (4%)	2 (4%)	2 (4%)
ADENOCARCINOMA, NOS			1 (2%)
#UTERUS	(25)	(50)	(49)
SARCOMA, NOS	1 (4%)	1 (2%)	1 (2%)
FIBROMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (4%)	1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(25)	(50)	(50)
ADENOMA, NOS			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
MUSCULOSKELETAL SYSTEM			
*SKULL	(25)	(50)	(50)
OSTEOSARCOMA			1 (2%)
*PELVIC BONES	(25)	(50)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(25)	(50)	(50)
SARCOMA, NOS	1 (4%)		
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	3		3
MORIBUND SACRIFICE	5	12	11
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	16	38	36
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	21	22
TOTAL PRIMARY TUMORS	17	23	28
TOTAL ANIMALS WITH BENIGN TUMORS	6	9	5
TOTAL BENIGN TUMORS	6	9	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	14	20
TOTAL MALIGNANT TUMORS	11	14	22
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED ALDICARB IN THE DIET

TABLE C1.

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

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	24	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(24)	(49)	(48)
CYST, NOS		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(22)	(49)	(48)
INFIAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(23)	(49)	(47)
FIBROUS DYSPLASIA			1 (2%)
#SPLEEN	(23)	(49)	(48)
CONGESTION, NOS		1 (2%)	2 (4%)
FIBROSIS, FOCAL		1 (2%)	2 (4%)
INFARCT, NOS	2 (9%)		
INFARCT, HEALED		1 (2%)	
LIPOIDOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS		1 (2%)	2 (4%)
#LYMPH NODE	(20)	(45)	(44)
HYPERPLASIA, NOS			1 (2%)
#MANDIBULAR L. NODE	(20)	(45)	(44)
CYST, NOS			1 (2%)
#MESENTERIC L. NODE	(20)	(45)	(44)
HYPERPLASIA, NOS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#RENAL LYMPH NODE	(20)	(45)	(44)
CYST, NOS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(24)	(49)	(48)
PERIVASCULITIS			1 (2%)
FIBROELASTOSIS ENDOCARDIAL		1 (2%)	
#HEART/ATRIUM	(24)	(49)	(48)
THROMBOSIS, NOS			1 (2%)
#AURICULAR APPENDAGE	(24)	(49)	(48)
THROMBOSIS, NOS	1 (4%)		
*SPLENIC ARTERY	(24)	(49)	(48)
THROMBOSIS, NOS		1 (2%)	
*PANCREATIC ARTERY,	(24)	(49)	(48)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(22)	(46)	(48)
INFLAMMATION, NOS	2 (9%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS	2 (9%)	1 (2%)	
#LIVER	(24)	(47)	(48)
CONGESTION, NOS	1 (4%)		
INFLAMMATION, NOS		1 (2%)	
METAMORPHOSIS FATTY	2 (8%)		
FOCAL CELLULAR CHANGE	2 (8%)	4 (9%)	6 (13%)
CYTOLOGIC DEGENERATION			1 (2%)
HEMATOPOIESIS		1 (2%)	4 (8%)
#LIVER/CENTRILOBULAR	(24)	(47)	(48)
METAMORPHOSIS FATTY		1 (2%)	
#BILE DUCT	(24)	(47)	(48)
HYPERPLASIA, NOS	5 (21%)	9 (19%)	17 (35%)
#PANCREAS	(24)	(49)	(48)
PERIARTERITIS		1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
PERIVASCULITIS			2 (4%)
ATROPHY, NOS		1 (2%)	1 (2%)
ATROPHY, FOCAL	4 (17%)	5 (10%)	4 (8%)
#STOMACH	(24)	(45)	(46)
ULCER, ACUTE			1 (2%)
INFIAMMATION, CHRONIC	2 (8%)		2 (4%)
HYPERPLASIA, NOS	1 (4%)	1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (4%)		
HYPERPLASIA, FOCAL		1 (2%)	
#DUODENUM	(24)	(46)	(47)
INFIAMMATION, CHRONIC			1 (2%)
URINARY SYSTEM			
#KIDNEY	(24)	(49)	(48)
INFIAMMATION, CHRONIC	15 (63%)	37 (76%)	38 (79%)
#KIDNEY/MEDULLA	(24)	(49)	(48)
HYPERPLASIA, EPITHELIAL			1 (2%)
#KIDNEY/PELVIS	(24)	(49)	(48)
HYPERPLASIA, EPITHELIAL			2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(43)	(43)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST	1 (5%)		2 (5%)
HYPERPLASIA, NOS	1 (5%)		
ANGIECTASIS		1 (2%)	
#ADRENAL	(23)	(48)	(47)
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(23)	(48)	(47)
HEMORRHAGE			1 (2%)
LIPOIDOSIS		2 (4%)	1 (2%)
ANGIECTASIS		1 (2%)	
METAPLASIA, OSSEOUS	1 (4%)		
#ADRENAL MEDULLA	(23)	(48)	(47)
HYPERPLASIA, NOS	2 (9%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(22)	(48)	(39)
HYPERPLASIA, C-CELL	1 (5%)	6 (13%)	2 (5%)
#PARATHYROID	(19)	(38)	(29)
HYPERPLASIA, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(24)	(49)	(48)
INFLAMMATION, ACUTE	1 (4%)		
#PROSTATE	(23)	(47)	(44)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
#TESTIS	(24)	(49)	(48)
ATROPHY, NOS	1 (4%)		
*EPIDIDYMIS	(24)	(49)	(48)
STEATITIS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(23)	(48)	(47)
HYDROCEPHALUS, NOS	2 (9%)		
GLIOSIS	1 (4%)		1 (2%)
NECROSIS, FOCAL		1 (2%)	
MALACIA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(24)	(49)	(48)
STEATITIS		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
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(24)	(49)	(48)
HEMORRHAGE		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
ACCIDENTAL DEATH			1
AUTOLYSIS/NO NECROPSY	1	1	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 ALDICARB 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)
CYST, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(25)	(45)	(49)
INFLAMMATION, ACUTE			1 (2%)
#LUNG	(25)	(48)	(50)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE			1 (2%)
INFLAMMATION, FOCAL	1 (4%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(23)	(49)	(50)
CONGESTION, NOS		2 (4%)	
HEMORRHAGE		1 (2%)	
NECROSIS, FOCAL			1 (2%)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HEMATOPOIESIS		2 (4%)	
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(25)	(50)	(50)
THROMBOSIS, NOS	1 (4%)		
#MYOCARDIUM	(25)	(50)	(50)
FIBROSIS, FOCAL		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
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(25)	(50)	(49)
INFIAMMATION, NOS		2 (4%)	2 (4%)
HYPERPLASIA, NOS		2 (4%)	2 (4%)
#LIVER	(25)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
GRANULOMA, NOS	2 (8%)	1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (4%)		
METAMORPHOSIS FATTY	1 (4%)	1 (2%)	4 (8%)
BASOPHILIC CYTO CHANGE	1 (4%)		1 (2%)
FOCAL CELLULAR CHANGE	4 (16%)	4 (8%)	5 (10%)
HEMATOPOIESIS		2 (4%)	3 (6%)
#BILE DUCT	(25)	(49)	(50)
HYPERPLASIA, NOS	3 (12%)	4 (8%)	2 (4%)
#PANCREAS	(24)	(49)	(50)
ATROPHY, NOS		1 (2%)	1 (2%)
ATROPHY, FOCAL			2 (4%)
#STOMACH	(24)	(48)	(49)
INFIAMMATION, CHRONIC		4 (8%)	2 (4%)
#CECUM	(24)	(49)	(49)
INFIAMMATION, ACUTE			1 (2%)
URINARY SYSTEM			
#KIDNEY	(24)	(49)	(50)
INFIAMMATION, CHRONIC	5 (21%)	14 (29%)	22 (44%)
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(48)	(48)
CYST, NOS	2 (8%)		1 (2%)
MULTIPLE CYSTS			1 (2%)
HEMORRHAGE	1 (4%)		
HEMORRHAGIC CYST	2 (8%)	1 (2%)	
HYPERPLASIA, NOS	1 (4%)	1 (2%)	1 (2%)
ANGIECTASIS			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
#ADRENAL CORTEX	(24)	(47)	(46)
LIPCIDOSIS			2 (4%)
#THYRCID	(24)	(44)	(47)
HYPERPLASIA, C-CELL	4 (17%)	3 (7%)	3 (6%)
#PARATHYROID	(18)	(34)	(34)
HYPERPLASIA, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
GALACTOCELE			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(24)	(47)	(49)
HYPERPLASIA, CYSTIC		4 (9%)	2 (4%)
#OVARY	(25)	(47)	(48)
STEATITIS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(25)	(49)	(50)
HYDROCEPHALUS, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, CHRONIC	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
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	2

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

APPENDIX D

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

TABLE D1.

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

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	24	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(24)	(50)	(49)
ULCER, NOS		2 (4%)	
*SUBCUT TISSUE	(24)	(50)	(49)
INFLAMMATION, FOCAL GRANULOMATOU	1 (4%)		
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(24)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
#LYMPH NODE	(23)	(50)	(47)
INFIAMMATION, NOS			2 (4%)
#MESENTERIC L. NODE	(23)	(50)	(47)
INFIAMMATION, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(24)	(49)	(49)
INFIAMMATION, MULTIFOCAL			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
INFLAMMATION, GRANULOMATOUS	1 (4%)		
NECROSIS, NOS		1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (4%)	1 (2%)	
HYPERPLASIA, NODULAR		1 (2%)	1 (2%)
NODULAR REGENERATION			1 (2%)
#BILE DUCT	(24)	(49)	(49)
DILATATION, NOS		1 (2%)	
#PEYER'S PATCH	(20)	(45)	(48)
HYPERPLASIA, LYMPHOID	1 (5%)		
#JEJUNUM	(20)	(45)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(24)	(50)	(49)
INFLAMMATION, FOCAL		1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
#URINARY BLADDER	(22)	(45)	(47)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(22)	(44)	(45)
CYST, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(24)	(50)	(49)
MULTIPLE CYSTS		1 (2%)	
INFLAMMATION, NOS		2 (4%)	
#PROSTATE	(21)	(37)	(43)
INFLAMMATION, SUPPURATIVE			1 (2%)
*SEMINAL VESICLE	(24)	(50)	(49)
HYPERPLASIA, CYSTIC	1 (4%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(24)	(50)	(47)
INFLAMMATION, ACUTE		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	13	17	13
ACCIDENTAL DEATH	1		
AUTOLYSIS/NO NECROPSY			1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED ALDICARB 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/ALVEOLI	(25)	(50)	(50)
HEMORRHAGE			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(24)	(49)	(50)
ANGIECTASIS			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
#MESENTERIC L. NODE	(20)	(47)	(48)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(25)	(49)	(48)
HEMORRHAGE		1 (2%)	
INFLAMMATION, MULTIFOCAL		1 (2%)	1 (2%)
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL			1 (2%)
#PANCREAS	(24)	(50)	(49)
DILATATION/DUCTS	1 (4%)	2 (4%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPOPLASIA, NOS		1 (2%)	
ATROPHY, NOS		1 (2%)	
#PEYERS PATCH	(20)	(45)	(40)
HYPERPLASIA, LYMPHOID			1 (3%)
#JEJUNUM	(20)	(45)	(40)
HYPERPLASIA, LYMPHOID		1 (2%)	
#ILEUM	(20)	(45)	(40)
HYPERPLASIA, LYMPHOID	1 (5%)		
URINARY SYSTEM			
#KIDNEY	(24)	(50)	(50)
HYPERPLASIA, LYMPHOID		3 (6%)	
ENDOCRINE SYSTEM			
#PITUITARY	(21)	(40)	(43)
ANGIECTASIS	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(50)
GALACTOCELE		1 (2%)	
#UTERUS	(25)	(50)	(49)
HYDROMETRA	1 (4%)		1 (2%)
#UTERUS/ENDOMETRIUM	(25)	(50)	(49)
HYPERPLASIA, CYSTIC		3 (6%)	
#OVARY	(23)	(48)	(46)
CYST, NOS		5 (10%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEAL CAVITY	(25)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	8	21	21

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

APPENDIX E

ANALYSES OF FORMULATED DIETS FOR CONCENTRATIONS OF ALDICARB

APPENDIX E

Analyses of Formulated Diets for Concentrations of Aldicarb

A 10-g sample of the diet mixture was shaken with 125 ml of acetone at room temperature for 16 hours, then filtered through Celite with acetone washes. The acetone was removed by evaporation and the residue was transferred to a 10-ml volumetric flask. After appropriate dilutions with acetone, the solution was quantitatively analyzed for aldicarb by gas-liquid chromatography (flame potentiometric detector in the sulfur mode, 20% Carbowax 20M 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)
2	9	1.77	20.1	1.14-2.35
6	9	5.76	4.94	5.41-6.18

Review of the Bioassay of Aldicarb* 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 Aldicarb.

The reviewer for the report on the bioassay of Aldicarb said that Aldicarb was not carcinogenic under the conditions of test. After a brief description of the experimental design, he said that there was no indication, either through weight depression or early mortality, that the maximum tolerated dose levels had been tested. As a result, he concluded that the chronic dosages were much too low and, therefore, the study was an inadequate bioassay for the carcinogenicity of Aldicarb.

It was moved that the report on the bioassay of Aldicarb be accepted with the notation that the results of the study do not reflect a test of the maximum tolerated doses nor one-half those amounts. The motion was seconded and approved unanimously.

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.

*U.S. GOVERNMENT PRINTING OFFICE: 1979 281-217/3157 1-3

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