National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 135
1979

BIOASSAY OF MALAOXON FOR POSSIBLE CARCINOGENICITY

CAS No. 1634-78-2

NCI-CG-TR-135

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

BIOASSAY OF

MALAOXON

FOR POSSIBLE CARCINOGENICITY

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

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

NIH Publication No. 79-1390

BIOASSAY OF
MALAOXON
FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health

FOREWORD: This report presents the results of the bioassay of malaoxon conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected environmental chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

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

The experimental design for this bioassay is based on guidelines for carcinogen bioassays in small animals that have been established by NCI (Sontag et al., 1976). The doses for the chronic studies were selected by Drs. E. E. Storrs (1) and O. G. Fitzhugh (2,3). The principal investigator was Mr. R. J. Wheeler (1). Histologic examination of rats was performed by Dr. E. Bernal (1), and histologic examination of mice was performed by Dr. B. Buratto (2). 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 (4). Statistical analyses were performed by Dr. J. R. Joiner (2) and Ms. P. L. Yong (2), using methods selected for the bioassay program by Dr. J. J. Gart (5). Chemicals

were synthesized and analyzed at GSRI by Dr. E. Green (1) and dosed feed mixtures by Mr. S. M. Billedeau (1). The results of these analyses were reviewed by Dr. C. W. Jameson (2,7).

This report was prepared at Tracor Jitco (2) 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 (8), toxicologist; Dr. R. L. Schueler, pathologist; Ms. L. A. Owen and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI (6) 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. Charles K. Grieshaber, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry Mahar, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Marcelina B. Powers, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

---

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

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

(3) 4208 Dresden Street, Kensington, Maryland.

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

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

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

(7) Now with Carcinogenesis Testing Program.

(8) Now with the Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland.

SUMMARY

A bioassay of malaoxon, the oxygen analogue of malathion (an organophosphate insecticide), 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 fed diets containing 500 or 1,000-ppm malaoxon for 103 weeks and were then observed for up to an additional 2 weeks. Matched controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed at 103 to 105 weeks.

The only effects that could be related to administration of malaoxon at the doses used were increased mortality among male mice, decreased mean body weights of female mice, gastric ulcers in male and female rats, and possibly C-cell adenomas or carcinomas of the thyroid among treated female rats. The incidence of C-cell adenomas or carcinomas among historical controls, however, precluded relating the incidence of these tumors to administration of the chemical.

It was concluded that under the conditions of this bioassay malaoxon was not carcinogenic for F344 rats or B6C3F1 mice.

TABLE OF CONTENTS

		Page
I.	Introduction	1
II.	Materials and Methods	3
	A. Chemical	3
	B. Dietary Preparation	3
	C. Animals	5
	D. Animal Maintenance	5
	E. Subchronic Studies	6
	F. Chronic Studies	10
	G. Clinical Examinations and Pathology	10
	H. Data Recording and Statistical Analyses	13
III.	Results - Rats	17
	A. Body Weights and Clinical Signs (Rats)	17
	B. Survival (Rats)	19
	C. Pathology (Rats)	21
	D. Statistical Analyses of Results (Rats)	22
IV.	Results - Mice	35
	A. Body Weights and Clinical Signs (Mice)	35
	B. Survival (Mice)	37
	C. Pathology (Mice)	39
	D. Statistical Analyses of Results (Mice)	39
V.	Discussion	47
VI.	Bibliography	51

APPENDIXES

Appendix A	Summary of the Incidence of Neoplasms in Rats Administered Malaoxon in the Diet	53
Table A1	Summary of the Incidence of Neoplasms in Male Rats Administered Malaoxon in the Diet	55
Table A2	Summary of the Incidence of Neoplasms in Female Rats Administered Malaoxon in the Diet	59

Page

Appendix B Summary of the Incidence of Neoplasms in Mice Administered Malaoxon in the Diet..... 63

Table B1 Summary of the Incidence of Neoplasms in Male Mice Administered Malaoxon in the Diet.... 65

Table B2 Summary of the Incidence of Neoplasms in Female Mice Administered Malaoxon in the Diet.. 69

Appendix C Summary of the Incidence of Nonneoplastic Lesions in Rats Administered Malaoxon in the Diet..... 73

Table C1 Summary of the Incidence of Nonneoplastic Lesions in Male Rats Administered Malaoxon in the Diet 75

Table C2 Summary of the Incidence of Nonneoplastic Lesions in Female Rats Administered Malaoxon in the Diet..... 79

Appendix D Summary of the Incidence of Nonneoplastic Lesions in Mice Administered Malaoxon in the Diet..... 83

Table D1 Summary of the Incidence of Nonneoplastic Lesions in Male Mice Administered Malaoxon in the Diet..... 85

Table D2 Summary of the Incidence of Nonneoplastic Lesions in Female Mice Administered Malaoxon in the Diet..... 88

Appendix E Analysis of Malaoxon..... 91

Appendix F Analyses of Formulated Diets for Concentrations of Malaoxon..... 97

TABLES

Table 1 Experimental Design for Subchronic Malaoxon Feeding Studies in Rats 8

Table 2 Experimental Design for Subchronic Malaoxon Feeding Studies in Mice..... 9

Page

Table 3 Experimental Design for Chronic Malaxon Feeding Studies in Rats..... 11

Table 4 Experimental Design for Chronic Malaoxon Feeding Studies in Mice..... 12

Table 5 Analyses of the Incidence of Primary Tumors in Male Rats Administered Malaoxon in the Diet..... 24

Table 6 Analyses of the Incidence of Primary Tumors in Female Rats Administered Malaoxon in the Diet..... 30

Table 7 Analyses of the Incidence of Primary Tumors in Male Mice Administered Malaoxon in the Diet..... 41

Table 8 Analyses of the Incidence of Primary Tumors in Female Mice Administered Malaoxon in the Diet..... 44

FIGURES

Figure 1 Growth Curves for Rats Administered Malaoxon in the Diet..... 18

Figure 2 Survival Curves for Rats Administered Malaoxon in the Diet..... 20

Figure 3 Growth Curves for Mice Administered Malaoxon in the Diet..... 36

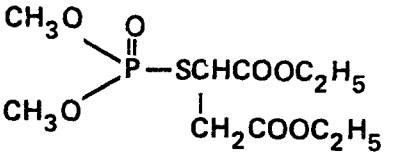
Figure 4 Survival Curves for Mice Administered Malaoxon in the Diet..... 38

Figure 5 Infrared Absorption Spectrum of Malaoxon 95

Figure 6 Nuclear Magnetic Resonance Spectrum of Malaoxon..... 96

I. INTRODUCTION

Malaoxon, O,O-dimethyl S-1,2-bis (ethoxycarbonyl)ethyl phosphorothioate (CAS 1634-78-2; NCI CO 8628), is an oxygen analogue of malathion, a widely used organophosphate insecticide. Malathion is converted to malaoxon by the substitution of oxygen for sulfur; this conversion is catalyzed *in vivo* by mixed function oxidases in mammals and insects, by peroxidases in plants, and by sunlight (Eto, 1974). This step appears to be an activation process, since malaoxon is 10^4 times more potent as a cholinesterase inhibitor than malathion (Eto, 1974) and is more toxic in acute oral doses than malathion. Malaoxon has an intraperitoneal LD_{50} in male Sprague-Dawley rats of 25 mg/kg, compared with 900 mg/kg for malathion (Brodeur and Dubois, 1967). Malaoxon is relatively nonpersistent in the environment, having a half-life of approximately 7 days in slightly acidic Illinois loam soil (Paschal and Neville, 1976).



Malaoxon

Malaoxon was selected by the Carcinogenesis Bioassay Program because

it is the active metabolite of malathion, a chemical also tested in the program (NCI, 1978; NCI, 1979).

II. MATERIALS AND METHODS

A. Chemical

Malaoxon is not available commercially. The material used for the chronic phase of the study was synthesized in one batch by Gulf South Research Institute by the method of Ailman (1965) and purified by large-scale column chromatography and/or distillation. Analysis of the malaoxon at Gulf South Research Institute included elemental analysis, thin-layer and vapor-phase chromatography, and infrared and nuclear magnetic resonance spectrometry (Appendix E). The results identified the material as malaoxon of high purity (i.e., greater than 95%). The bulk material was stored at 5°C until mixed with the feed.

B. Dietary Preparation

All diets were formulated using Wayne® Lab-Blox Meal (Allied Mills, Chicago, Illinois) to which was added the required amount of malaoxon for each dietary concentration. The test compound was first dissolved in a small amount of acetone (Mallinckrodt Chemicals, St. Louis, Mo.) which was then added to the feed. Corn

oil (Louana®, Opelousas Refinery, Opelousas, Louisiana) 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 homogenity and to allow for evaporation of the acetone. Final diets, including those for control groups of animals, contained corn oil equal to 2% of the final weight of feed. Formulated diets were stored at room temperature until used, but not longer than 1 week.

The stability of malaoxon in feed was tested by determining the concentration of the compound in formulated diets at intervals over a 7-day period. Analysis of the diets containing 500 and 1,000 ppm malaoxon showed no significant change in concentration on standing at ambient temperature for this period.

As a quality control analysis for accuracy of preparation of the diets, the concentration of malaoxon was measured in randomly selected batches of formulated diets at 8-week intervals during the chronic study. At each dietary concentration, the mean of the analytical concentration was within 2.1% of the theoretical concentration, and the coefficient of variation did not exceed 3.4% (Appendix F).

C. Animals

Male and female F344 rats and B6C3F1 mice, 4 and 5 weeks of age respectively, were obtained from the Frederick Cancer Research Center, (Frederick, Maryland). The animals were acclimated for 14 days and then assigned to control or dosed groups.

D. Animal Maintenance

Rats were housed individually in hanging galvanized steel mesh cages (Hoeltge, Inc., Cincinnati, Ohio), and mice were housed in polypropylene cages (Lab Products, Inc., Garfield, N.J.), five females or two or three males per cage. Mouse cages were covered with polyester filter bonnets (Lab Products, Inc.). Rat racks and cages were washed every 2 weeks and mouse cages each 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 changed three times per week. Absorb-dri® hardwood chip bedding (Lab Products, Inc.), used in the mouse cages, was provided two times per week for males and three times per week for females. Filter bonnets were washed each week.

Feed jars and water bottles were changed and washed three times per week; sipper tubes and stoppers were washed two times per week; the filter bonnets, feed jars, water bottles, sipper tubes, and stoppers were washed in a Vulcan Autosan washer (Vulcan Autosan, Louisville, Ky.). Cage racks for each species were rotated to a new position in the room once each week; at the same time, each cage was moved to a different row within the same column of a rack. Control and dosed rats were housed on the same rack, whereas cages for control and dosed mice were placed on separate racks in the same room. The rats and mice receiving malaoxon were housed in separate rooms with their respective controls. Malaoxon was the only compound on study in each room.

Air was maintained at 22 to 24°C, and relative humidity was 40 to 70%. Fresh air, filtered through permanent air maze filters (Air Maze Incom International, Cleveland, Ohio), was changed 10 to 12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and tap water were provided ad libitum. Twice a week excess remaining feed was discarded and fresh feed was provided.

E. Subchronic Studies

Subchronic feeding studies were conducted to determine the two

concentrations used in the chronic studies (referred to in this report as "low" and "high" doses). Groups of 10 rats and 10 mice of each sex were fed diets containing malaoxon at one of several doses for 13 weeks, and groups of 10 control animals of each species and sex were fed basal diet only. Animals were weighed each week. Tables 1 and 2 show the doses fed, the survival of animals in each dosed group at the end of the study, and the mean body weights of dosed animals at week 13, expressed as percentages of mean body weights of the corresponding controls. At the end of the 13-week period, all surviving animals were killed and necropsied. Tissues from all rats on feed containing 1,000 and 2,000 ppm and from all mice on feed containing 2,000 and 4,000 ppm were examined microscopically for pathologic change.

All rats fed 4,000 and 8,000 ppm died, and 16 of 20 mice fed 8,000 ppm died. There was no depression in weight gain compared with controls in either rats or mice in groups having no deaths. No gross or microscopic pathologic changes were observed that could be related to administration of the test chemical in the rats or the mice.

Based on the mortality data and on previous experience with the estimation of doses for chronic studies with organophosphates at

Table 1. Doses, Survival, and Mean Body Weights of Rats Fed Malaoxon for 13 Weeks

	Male		Female	
Dose(a) (ppm)	Survival (b)	Mean Weight at Week 13 as % of Control	Survival (a)	Mean Weight at Week 13 as % of Control
0(c)	10/10	100	10/10	100
125	10/10	102	10/10	103
250	10/10	100	10/10	105
500	10/10	102	10/10	104
1,000(d)	10/10	104	10/10	100
2,000(d)	10/10	99	10/10	96
4,000	0/10		0/10	
8,000	0/10		0/10	

(a) No gross pathologic changes were found at necropsy in any of the test groups.

(b) Number surviving/number in group.

(c) One male control showed mild diffuse parenchymatous hepatic degeneration.

(d) Tissues from males and females administered these doses were examined microscopically. One male in the 1,000 ppm group showed focal fatty degeneration of the liver.

Table 2. Doses, Survival, and Mean Body Weights of Mice Fed Malaoxon for 13 Weeks

	Male		Female	
Dose(a) (ppm)	Survival (b)	Mean Weight at Week 13 as % of Control	Survival (a)	Mean Weight at Week 13 as % of Control
0	10/10	100	10/10	100
125	10/10	101	10/10	93
250	10/10	102	10/10	96
500	10/10	95	10/10	101
1,000	10/10	99	10/10	100
2,000(c)	10/10	105	10/10	105
4,000(c)	10/10	101	10/10	99
8,000	3/10	98	1/10	88

(a) No gross pathologic changes were found at necropsy in any of the test groups.

(b) Number surviving/number in group.

(c) Tissues from males and females administered these doses were examined microscopically and were found to be essentially normal.

this laboratory, the low and high doses for the chronic studies were set at 500 and 1,000 ppm for both the rats and the mice.

F. Chronic Studies

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

G. Clinical Examinations and Pathology

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

Pathology consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver,

Table 3. Experimental Design for Chronic Malaoxon Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Malaoxon Doses (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	50	0	0	103-105
Low-Dose	50	500	103	0-1
High-Dose	50	1,000	103	0-1
Female				
Matched-Control	50	0	0	103-105
Low-Dose	50	500	103	0-1
High-Dose	50	1,000	103	0-2

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

(b) Test and control diets were made available ad libitum.

Table 4. Experimental Design for Chronic Malaoxon Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Malaoxon Doses (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	50	0	0	103-105
Low-Dose	50	500	103	0-2
High-Dose	50	1,000	103	0-2
Female				
Matched-Control	50	0	0	103-105
Low-Dose	50	500	103	0-1
High-Dose	50	1,000	103	0-1

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

(b) Test and control diets were made available *ad libitum*.

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 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized as necessary for more definitive diagnosis.

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

H. Data Recording and Statistical Analyses

Data on this experiment were 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).

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 two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made.

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.

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 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)

There was no appreciable effect of administration of malaoxon on mean body weights of male or female rats (figure 1).

During the first 4 months of the study, the dosed and control rats were generally comparable in appearance. One tissue mass was noted during week 2 in the high-dose male group. At week 4 the low- and high-dose males were noted as being hyperexcitable, but this condition did not persist.

During the remainder of the test, alopecia, rough discolored hair coats, discolored urine, tachypnea, loss of weight, poor food consumption, higher incidence of vaginal bleeding in the low-dose females, hyperexcitability (not general, but a few individual cases in all groups), lethargy, pale mucous membranes, abdominal distension, cyst-like growths, and palpable nodules and tissue masses were noted in the controls and dosed groups with increasing frequency. At week 78 the majority of control and dosed animals rejected their feed. This almost total rejection continued for 4 days, at which time all animals were given freshly mixed control feed containing 2%

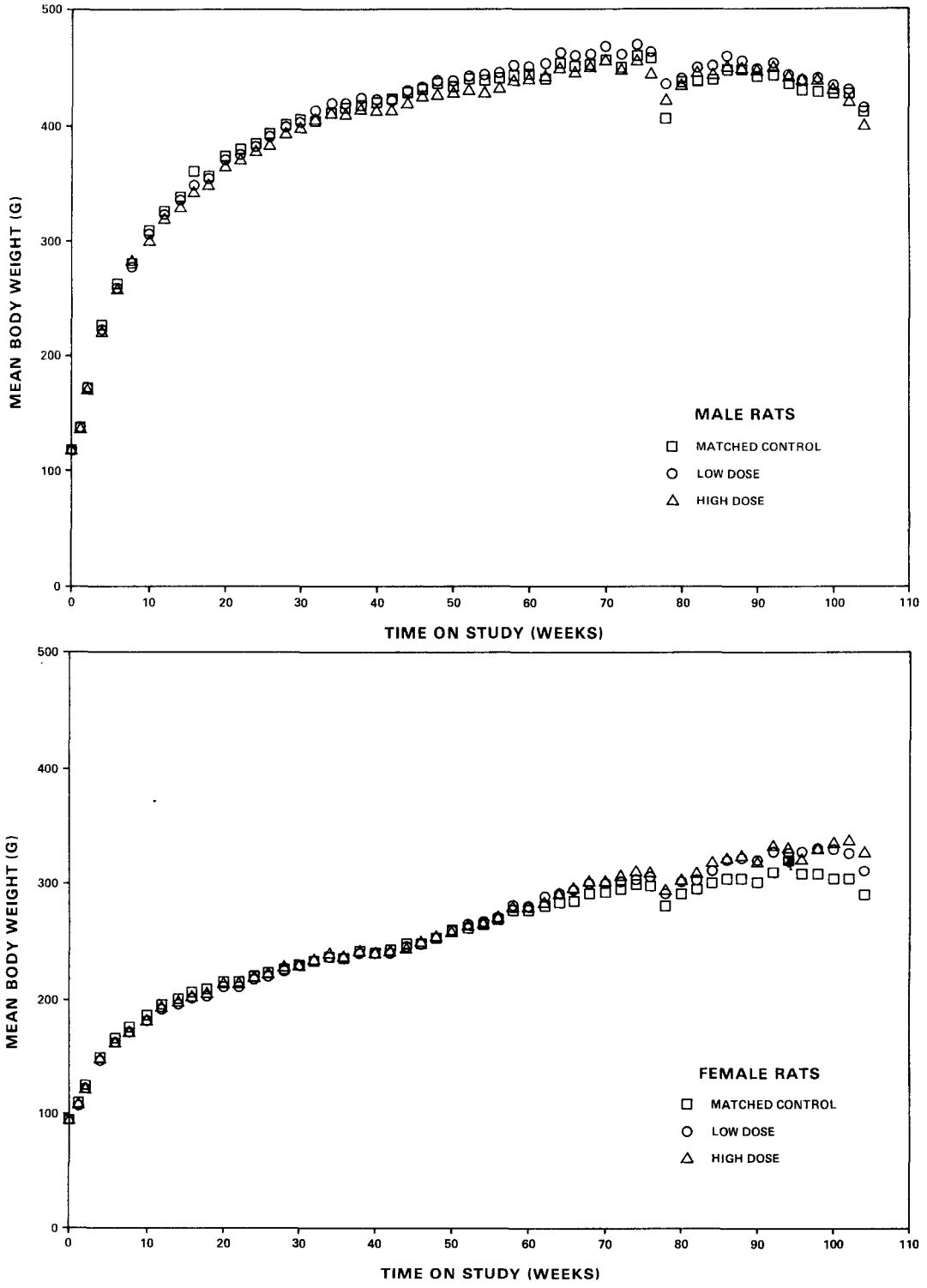


Figure 1. Growth Curves for Rats Administered Malaoxon in the Diet

corn oil. After the animals were given the control diet for 4 days, they were returned to their assigned test diets. As a result of the food rejection, mean body weight decreased in all groups, but the decrease was much greater in the males.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered malaoxon in the diet at the doses of this bioassay, together with those of the matched controls, are shown by the Kaplan and Meier curves in figure 2. The result of the Tarone test for dose-related trend in the proportions surviving is not significant in either sex. In female rats, an indicated departure from linear trend ($P = 0.041$) is observed because the control animals did not survive as long as the dosed animals. The result of the Cox test comparing the survival of the control and low-dose groups is significant ($P = 0.025$) in the negative direction.

In male rats, 37/50 (64%) of the high-dose group, 41/50 (82%) of the low-dose group, and 40/50 (80%) of the control group were alive at week 90 on study. In females, 40/50 (80%) of the high-dose group, 45/50 (90%) of the low-dose group, and 41/50 (82%) of the control group were alive at week 90 on study.

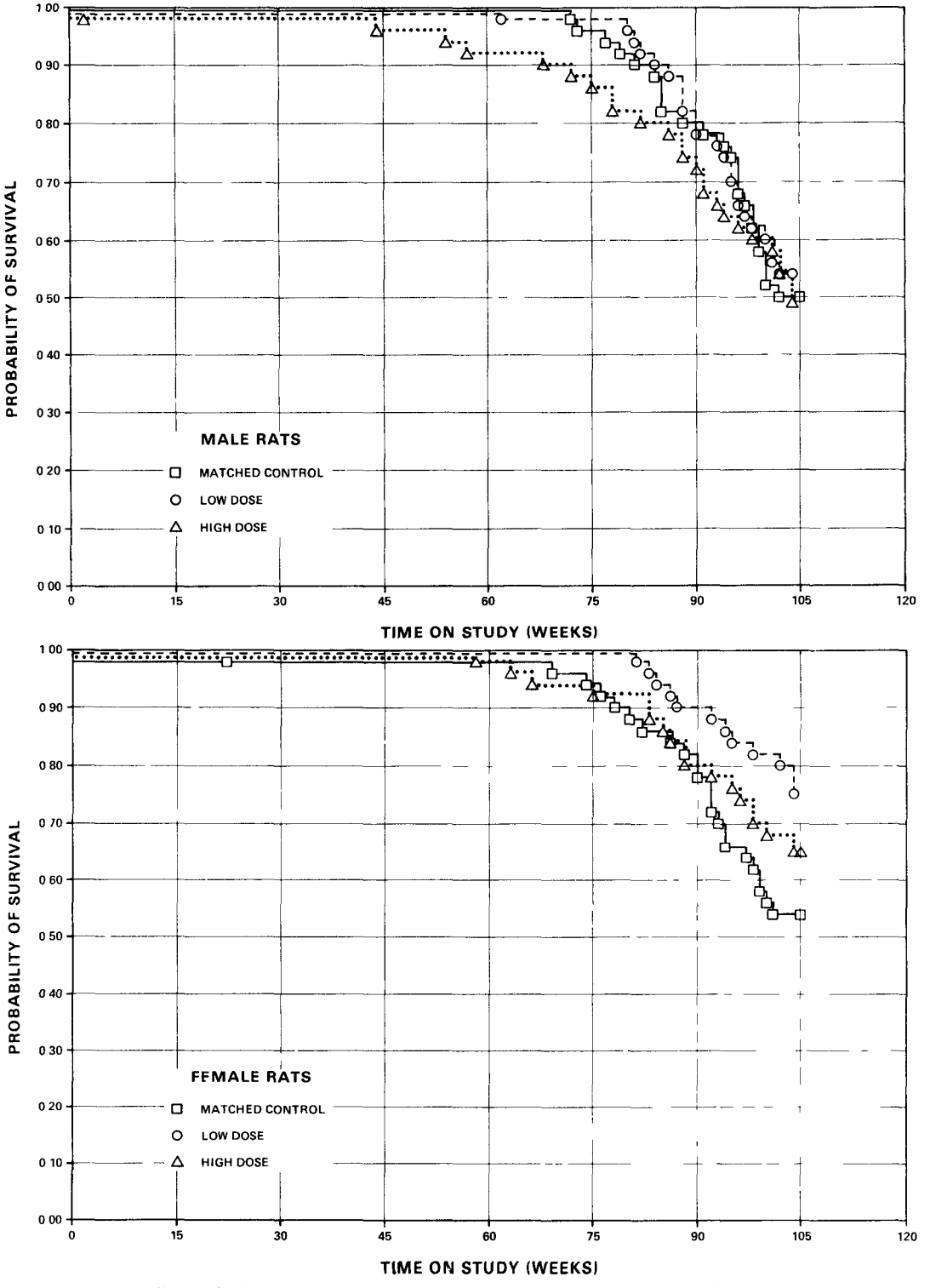


Figure 2. Survival Curves for Rats Administered Malaoxon in the Diet

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

C. Pathology (Rats)

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

A wide variety of degenerative inflammatory, proliferative, and neoplastic lesions were observed in rats of the dosed and control groups. The incidences of these lesions, with few exceptions, were approximately equal in control and dosed animals. Occasionally, a lesion occurred principally in rats of either dosed or control groups; however, the incidences of these changes were generally low (less than 5%) and were not considered to be related to the administration of the chemical.

Gastric ulcers were seen in increased incidences in dosed rats -- males: control 2/48 (4%), low-dose 6/50 (12%), high-dose 7/48 (15%); females: control 0/49 (0%), low-dose 1/49 (2%), high-dose 3/49 (6%); it was most commonly seen in the forestomach. The lesion

was usually solitary and sometimes accompanied by epithelial hyperplasia and submucosal inflammation.

The histopathologic examination provided no evidence that malaoxon was carcinogenic under the conditions of this bioassay in F344 rats.

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 of one group and at an incidence of at least 5% in one or more than one group.

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

In female rats, the result of the Cochran-Armitage test for the combined incidence of C-cell carcinomas and adenomas of the thyroid is significant (P = 0.009). The Fisher exact test shows that the incidence in the high-dose group is significantly higher (P = 0.024) than that in the control group. The historical record of this

laboratory shows an incidence of female F344 rats with C-cell adenomas or carcinomas of 16/223 (7%), compared with 0/50 in the control group, 1/49 (2%) in the low-dose group, and 5/47 (11%) in the high-dose group of this study. This indicates that the incidence of C-cell tumors of the thyroid in female rats of the present study is comparable to that usually seen in control animals.

In female rats, the Fisher exact comparison of the incidences of fibroadenomas of the mammary gland in the low-dose and control groups shows a P value of 0.026, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The result of the Cochran-Armitage test on the incidence of this tumor is not significant, and no significant incidence is observed in the high-dose group.

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

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	3/50 (6)	1/50 (2)	0/50 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.333	0.000
Lower Limit		0.007	0.000
Upper Limit		3.983	1.662
Weeks to First Observed Tumor	98	104	--
Hematopoietic System: Lymphoma or Leukemia (b)	19/50 (38)	13/50 (26)	16/50 (32)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.684	0.842
Lower Limit		0.352	0.463
Upper Limit		1.292	1.517
Weeks to First Observed Tumor	73	81	2

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Carcinoma, NOS (b)	3/45 (7)	1/45 (2)	2/45 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.333	0.667
Lower Limit		0.007	0.058
Upper Limit		3.964	5.542
Weeks to First Observed Tumor	72	98	86
Pituitary: Adenoma, NOS (b)	17/45 (38)	20/45 (44)	18/45 (40)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.176	1.059
Lower Limit		0.682	0.597
Upper Limit		2.044	1.882
Weeks to First Observed Tumor	79	62	75

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Carcinoma, NOS or Adenoma, NOS (b)	20/45 (44)	21/45 (47)	20/45 (44)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.050	1.000
Lower Limit		0.639	0.601
Upper Limit		1.728	1.664
Weeks to First Observed Tumor	72	62	75
Adrenal: Pheochromocytoma (b)	3/47 (6)	4/49 (8)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.279	1.918
Lower Limit		0.229	0.437
Upper Limit		8.316	11.263
Weeks to First Observed Tumor	105	80	68

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	3/49 (6)	0/45 (0)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.667
Lower Limit		0.000	0.058
Upper Limit		1.805	5.565
Weeks to First Observed Tumor	100	--	102
Thyroid: C-cell Adenoma or Carcinoma (b)	2/49 (4)	0/45 (0)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	2.000
Lower Limit		0.000	0.302
Upper Limit		3.671	21.298
Weeks to First Observed Tumor	100	--	72

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islet: Islet-cell Carcinoma or Adenoma (b)	5/48 (10)	6/49 (12)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.176	0.348
Lower Limit		0.321	0.038
Upper Limit		4.557	2.219
Weeks to First Observed Tumor	77	96	104
Testis: Interstitial-cell Tumor (b)	41/50 (82)	44/49 (90)	41/49 (84)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.095	1.020
Lower Limit		0.914	0.840
Upper Limit		1.268	1.231
Weeks to First Observed Tumor	73	80	68

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

(continued)

(a) Dosed groups received 500 or 1,000 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 Malaoxon in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	13/50 (26)	5/50 (10)	10/50 (20)
P Values (c,d)	N.S.	P = 0.034 (N)	N.S.
Relative Risk (f)		0.385	0.769
Lower Limit		0.116	0.334
Upper Limit		1.054	1.715
Weeks to First Observed Tumor	22	104	86
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	0/46 (0)	3/50 (6)	0/49 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.016		
Relative Risk (f)		Infinite	--
Lower Limit		0.555	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	104	--

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Carcinoma, NOS (b)	4/49 (8)	1/49 (2)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.250	1.500
Lower Limit		0.005	0.380
Upper Limit		2.409	6.811
Weeks to First Observed Tumor	69	104	63
Pituitary: Carcinoma, NOS or Adenoma, NOS (b)	35/49 (71)	34/49 (69)	32/49 (65)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.971	0.914
Lower Limit		0.737	0.686
Upper Limit		1.284	1.228
Weeks to First Observed Tumor	69	83	63

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma or Adenoma (b)	0/50 (0)	1/49 (2)	5/47 (11)
P Values (c,d)	P = 0.009	N.S.	P = 0.024
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.055	1.342
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	94	96
Mammary Gland: Fibroadenoma (b)	2/50 (4)	9/50 (18)	1/50 (2)
P Values (c,d)	N.S.	P = 0.026	N.S.
Departure from Linear Trend (e)	P = 0.002		
Relative Risk (f)		4.500	0.500
Lower Limit		0.995	0.009
Upper Limit		41.081	9.290
Weeks to First Observed Tumor	94	83	105

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	11/46 (24)	8/47 (17)	11/48 (23)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.712	0.958
Lower Limit		0.274	0.419
Upper Limit		1.760	2.194
Weeks to First Observed Tumor	93	104	86

(a) Dosed groups received 500 or 1,000 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)

There was no appreciable effect of administration of malaoxon on mean body weights of male mice (figure 3). Mean body weights of high-dose female mice were lower than those of the controls throughout most of the bioassay, and mean body weights of the low-dose females were lower than those of the controls after about week 34.

During the first year of the study, the dosed and control mice were generally comparable in appearance and behavior. At week 12 the high-dose males and females appeared hyperexcitable, but this condition did not persist. Although all male mice were observed fighting, the resulting wounds and rough or missing hair were more severe among the dosed males.

Clinical signs that were noted with increasing frequency during the second year of the study included alopecia, pale mucous membranes, abdominal distension, and palpable nodules and tissue masses. Several animals exhibited a hunched, slab-sided appearance. These signs were observed in all groups but were predominant in the dosed

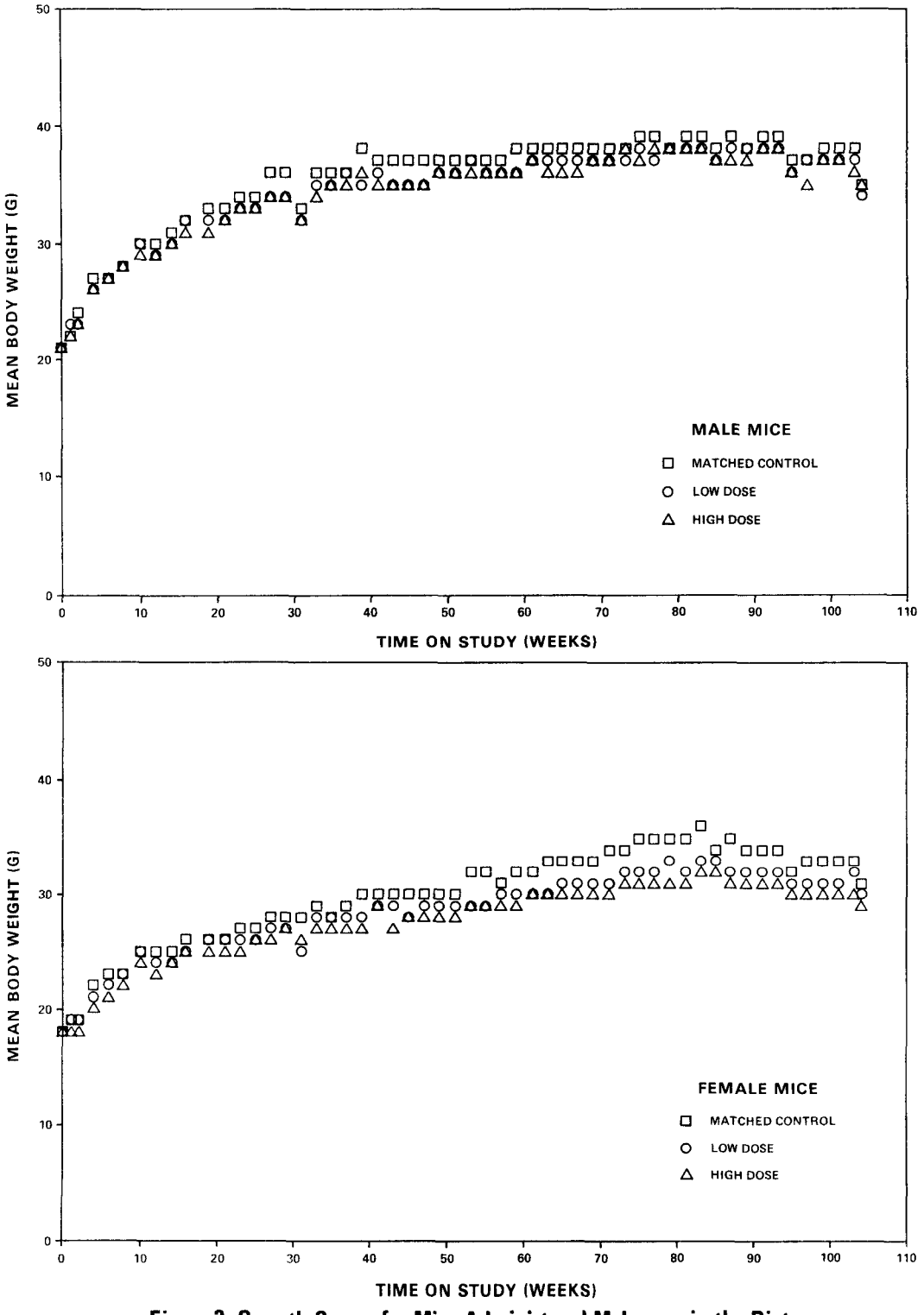


Figure 3. Growth Curves for Mice Administered Malaoxon in the Diet

males. At week 72, 10% of the high-dose females and at week 73, 30% of the low-dose females appeared hyperexcitable, but this condition did not persist.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered malaoxon in the diet at the doses of this bioassay, together with those of the matched controls, are shown by the Kaplan and Meier curves in figure 4. The result of the Tarone test for positive dose-related trend in the proportions surviving is significant (P = 0.028) in male mice but not in the females.

In male mice, 37/50 (74%) of the high-dose group, 42/50 (84%) of the low-dose group, and 45/50 (90%) of the control group were alive at week 103. In females, 45/50 (90%) of the high-dose group, 38/50 (76%) of the low-dose group, and 39/50 (78%) of the control group were alive at week 103.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

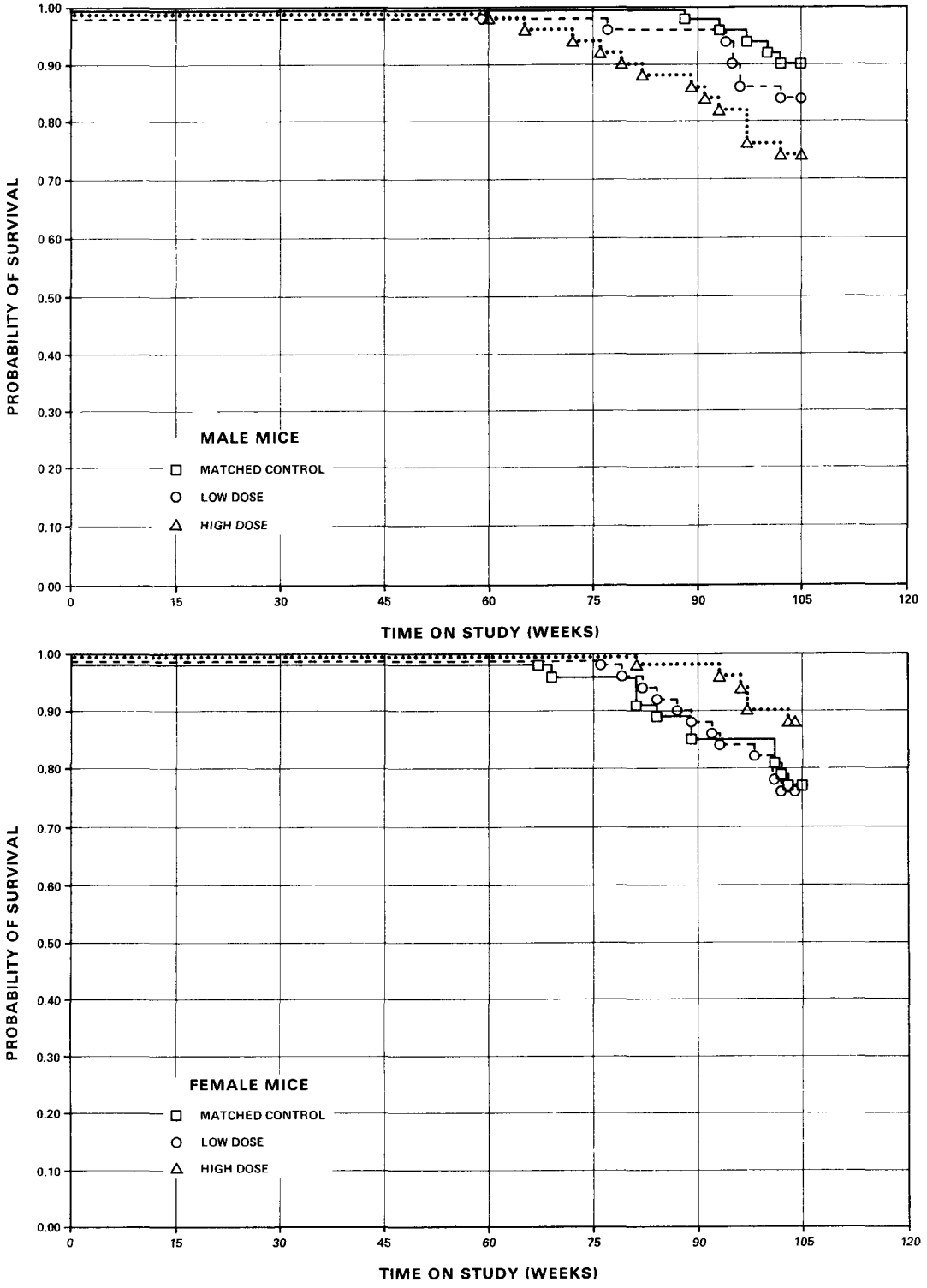


Figure 4. Survival Curves for Mice Administered Malaoxon in the Diet

C. Pathology (Mice)

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

A variety of tumors occurred in both the control and dosed groups. Some types of neoplasms occurred only, or with a slightly greater frequency, in the dosed groups; however, the incidence of tumors did not appear to be related to the administration of malaoxon.

In addition to the neoplastic lesions, a large number of degenerative, proliferative, and inflammatory changes which showed no relationship to administration of the test chemical were encountered in animals of the dosed and control groups.

The histopathologic examination provided no evidence that malaoxon was carcinogenic 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 of one group and at an incidence of at least 5% in one or more than one group.

In each sex, the results of the Cochran-Armitage test for positive dose-related trend in the incidence of tumors and the results of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group in the positive direction are not significant. Although the first observation of a hepatocellular tumor in male mice occurred at week 65 in the high-dose group, compared with week 97 in the control group and week 95 in the low-dose group, the overall comparison of the time of observation of hepatocellular tumors in the three groups by life table methods was not found to be significant. Significant results in the negative direction are observed in the incidences of liver tumors in each sex.

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

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

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma of the Subcutaneous Tissue (b)	0/50 (0)	3/49 (6)	0/50 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.013		
Relative Risk (f)		Infinite	--
Lower Limit		0.614	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	94	--
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	6/50 (12)	5/48 (10)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.868	1.000
Lower Limit		0.224	0.287
Upper Limit		3.185	3.489
Weeks to First Observed Tumor	103	96	89

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	5/50 (10)	2/49 (4)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.408	0.800
Lower Limit		0.040	0.168
Upper Limit		2.358	3.499
Weeks to First Observed Tumor	88	95	82
Liver: Hepatocellular Carcinoma (b)	12/50 (24)	2/49 (4)	13/50 (26)
P Values (c,d)	N.S.	P = 0.004 (N)	N.S.
Departure from Linear Trend (e)	P = 0.002		
Relative Risk (f)		1.701	1.083
Lower Limit		0.019	0.507
Upper Limit		0.711	2.334
Weeks to First Observed Tumor	97	95	65

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Adenoma (b)	12/50 (24)	5/49 (10)	17/50 (34)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.010		
Relative Risk (f)		0.425	1.417
Lower Limit		0.127	0.716
Upper Limit		1.190	2.892
Weeks to First Observed Tumor	97	95	65

(a) Dosed groups received 500 or 1,000 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 8. Analyses of the Incidence of Primary Tumors in Female Mice Administered Malaoxon in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	7/47 (15)	8/47 (17)	7/48 (15)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.143	0.979
Lower Limit		0.395	0.318
Upper Limit		3.404	3.019
Weeks to First Observed Tumor	81	76	93
Liver: Hepatocellular Carcinoma (b)	3/47 (6)	1/47 (2)	0/48 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.333	0.000
Lower Limit		0.007	0.000
Upper Limit		3.972	1.626
Weeks to First Observed Tumor	101	104	--

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Adenoma (b)	6/47 (13)	3/47 (6)	1/48 (2)
P Values (c,d)	P = 0.034 (N)	N.S.	N.S.
Relative Risk (f)		0.500	0.163
Lower Limit		0.085	0.004
Upper Limit		2.191	1.272
Weeks to First Observed Tumor	101	103	104
Pituitary: Carcinoma, NOS or Adenoma, NOS	1/33 (3)	1/33 (3)	3/33 (9)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.000	3.000
Lower Limit		0.013	0.257
Upper Limit		76.152	152.391
Weeks to First Observed Tumor	105	101	103

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

(continued)

(a) Dosed groups received 500 or 1,000 ppm.

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

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

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

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

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

V. DISCUSSION

Feeding of malaoxon had no appreciable effect on the mean body weights of male or female rats or male mice. Mean body weights of the high-dose female mice were lower than those of the controls throughout most of the bioassay, and mean body weights of the low-dose female mice were lower than those of the controls after about week 34. No clinical signs related to administration of the test chemical were recorded for male or female rats other than a brief period of hyperexcitability noted early in the study in dosed males. Dosed groups of male and female mice appeared hyperexcitable at times during the course of the study, but this condition did not persist. Mortality was not increased in any of the dosed groups of male or female rats or female mice. Mortality was increased in a dose-related manner in the male mice after week 65. However, survival was 74% or greater at week 103 in all groups of male and female mice. In rats, survival was 64% or greater at week 90 in both dosed and control groups. Thus, there were few clinical signs and only minimal effects on weight and survival that could be related to administration of the test chemical. Sufficient numbers of rats and mice were at risk for the development of late-appearing tumors.

Gastric ulcers were seen in increased incidences in dosed male and female rats. The lesions were most commonly seen in the forestomach and were usually solitary and sometimes accompanied by epithelial hyperplasia and submucosal inflammation. This lesion was similar to those found in male and female F344 rats administered malathion (NCI, 1979).

In female rats, C-cell adenomas or carcinomas of the thyroid occurred in the high-dose group at an incidence that was significantly higher ($P = 0.024$) than that in the control group, and the overall incidences were dose related ($P = 0.009$). However, the historical records at this laboratory show an incidence of 16/223 (7%) C-cell adenomas or carcinomas among female control rats, which suggests that the 0/50 incidence observed in the control female rats in the present study was unusually low. In a previous bioassay of malathion (NCI, 1979) using F344 rats, the incidences of C-cell adenomas of the thyroid were not significantly higher than those observed in control rats. No tumors in the present study occurred at significant incidences in the positive direction by any test in male rats and in male and female mice.

In two separate carcinogenesis bioassays of malathion, the parent compound of malaoxon, conducted previously at the same laboratory as the present study (NCI, 1978; NCI, 1979), there was no clear

evidence of the association of any tumor incidence with the dietary administration of the compound to Osborne-Mendel rats, F344 rats, or B6C3F1 mice. In the malathion study using F344 rats, it was noted that the females may have been able to tolerate higher doses. Although in the present malaoxon studies clinical signs and effects on weight and survival were limited, it is considered that the animals received approximately a maximum tolerated dose of malaoxon. In the rats, this consideration is based mainly on the development of gastric ulcers; in the mice, it is based on a decreased mean body weight gain of females and on decreased survival of males.

Under the conditions of this bioassay, malaoxon was not carcinogenic in F344 or B6C3F1 mice of either sex.

VI. BIBLIOGRAPHY

Ailman, D. E., Synthesis of O,O-dimethyl S-(1,2-dicarbethoxy)-ethyl phosphorothioate (maloxon) and related compounds from trialkyl phosphites and organic disulfieds. J. Org. Chem. 30:1074-1077, 1965.

Armitage, P., Statistical Methods in Medical Research, John Wiley & Sons, Inc., New York, 1971, pp. 362-365.

Berenblum, I., ed., Carcinogenicity Testing: A Report of the Panel of Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2, International Union Against Cancer, Geneva, 1969.

Brodeur, J. and DuBois, K. P., Studies on factors influencing the acute toxicity of malathion and malaoxon in rats. Can. J. Physiol. Pharmacol. 45:621-630, 1967.

Cox D. R., Analysis of Binary Data, Methuen & Co., Ltd., London, 1970, pp. 48-52.

Cox, D. R., Regression models and life tables. J. R. Statist. Soc. B34:187-220, 1972.

Eto, M., Metabolism. In: Organophosphorus Pesticides: Organic and Biological Chemistry, CRC Press, Inc., Cleveland, Ohio, 1974, pp. 162-163.

Gart, J. J., The comparison of proportions: a review of significance tests, confidence limits and adjustments for stratification., Rev. Int. Stat. Inst. 39:148-169, 1971.

Kaplan, E. L. and Meier, P., Nonparametric estimation from incomplete observations. J. Amer. Statist. Assoc. 53:457-481, 1958.

Keith, L., Garrison, A., and Alford, A., The high resolution NMR spectra of pesticides. I. Organophsophorus pesticides. J. Assoc. Offic. Anal. Chem. 51:1063-1094, 1968.

Linhart, M. S., Cooper, J. A., Martin, R. L., Page, N. P., and Peters, J. A., Carcinogenesis bioassay data system. Comp. and Biomed. Res. 7:230-248, 1974.

Miller, R. G., Jr., Simultaneous Statistical Inference, McGraw-Hill Book Co., New York, 1966, pp.6-10.

NCI, Technical Report No. 24, Bioassay of Malathion for Possible Carcinogenicity, DHEW Publication No. (NIH) 78-824, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1978.

NCI, Technical Report No. 192, Bioassay of Malathion for Possible Carcinogenicity, DHEW Publication No. (NIH) 79-1748, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1979.

Paschal, D. C. and Neville, M. E., Chemical and microbical degradation of malaoxon in an Illinois soil. J. Environ. Qual. 5(4):441-443, 1976.

Sontag, J. M., Page, N. P., and Saffiotti, U., Guidelines for Carcinogen Bioassay in Small Rodents, NCI Technical Report Series, No. 1, DHEW Publication No. (NIH) 76-801, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1976.

Tarone, R. E., Tests for trend in life table analysis. Biometrika 62:679-682, 1975.

APPENDIX A

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

TABLE A1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		2 (4%)	
BASAL-CELL CARCINOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	3 (6%)	1 (2%)	
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
FIBROUS HISTIOCYTOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
LEUKEMIA,NOS	13 (26%)	9 (18%)	9 (18%)
LYMPHOCYTIC LEUKEMIA			2 (4%)
MONOCYTIC LEUKEMIA	5 (10%)	4 (8%)	2 (4%)
#SPLEEN	(49)	(49)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#LIVER	(49)	(50)	(49)
LEUKEMIA,NOS	1 (2%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#PAROTID GLAND	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#LIVER	(49)	(50)	(49)
NEOPLASTIC NODULE			1 (2%)
#PANCREAS	(48)	(49)	(50)
ACINAR-CELL ADENOMA		1 (2%)	2 (4%)
#GASTRIC MUCOSA	(48)	(50)	(48)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
TUBULAR-CELL ADENOMA		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(45)	(45)
CARCINOMA,NOS	3 (7%)	1 (2%)	2 (4%)
ADENOMA, NOS	17 (38%)	20 (44%)	18 (40%)
CRANIOPHARYNGIOMA		1 (2%)	
#ADRENAL	(47)	(49)	(49)
CORTICAL ADENOMA			1 (2%)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA	2 (4%)	4 (8%)	4 (8%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		2 (4%)
#THYROID	(49)	(45)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)		1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		1 (2%)
C-CELL ADENOMA	1 (2%)		2 (4%)
C-CELL CARCINOMA	1 (2%)		2 (4%)
#PANCREATIC ISLETS	(48)	(49)	(50)
ISLET-CELL ADENOMA	4 (8%)	6 (12%)	2 (4%)
ISLET-CELL CARCINOMA	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
FIBROADENOMA			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)
#TESTIS	(50)	(49)	(49)
INTERSTITIAL-CELL TUMOR	41 (82%)	44 (90%)	41 (84%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(49)
EPENDYMOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOMA		1 (2%)	
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, NOS		2 (4%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	1	7
MORIBUND SACRIFICE	23	22	18
SCHEDULED SACRIFICE **	2		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	23	27	25
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	49	48
TOTAL PRIMARY TUMORS	104	102	101
TOTAL ANIMALS WITH BENIGN TUMORS	47	47	44
TOTAL BENIGN TUMORS	71	79	74
TOTAL ANIMALS WITH MALIGNANT TUMORS	28	19	26
TOTAL MALIGNANT TUMORS	32	20	26
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3	1
TOTAL UNCERTAIN TUMORS	1	3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

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

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

TABLE A2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	1 (2%)
FIBROSARCOMA		1 (2%)	
*MAMMARY GLAND	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA,NOS	9 (18%)	3 (6%)	9 (18%)
MONOCYTIC LEUKEMIA	3 (6%)	2 (4%)	1 (2%)
#SPLEEN	(50)	(50)	(46)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(46)	(50)	(49)
CARCINOMA, NOS, METASTATIC	1 (2%)		
NEOPLASTIC NODULE		1 (2%)	
HEPATOCELLULAR CARCINOMA		2 (4%)	
#JEJUNUM	(47)	(48)	(49)
LEIOMYOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LIPOMA	1 (2%)		
MIXED TUMOR, MALIGNANT	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(49)
CARCINOMA,NOS	4 (8%)	1 (2%)	6 (12%)
ADENOMA, NOS	31 (63%)	33 (67%)	26 (53%)
CHROMOPHOBE ADENOMA	1 (2%)		
#ADRENAL	(49)	(49)	(48)
CORTICAL ADENOMA		2 (4%)	2 (4%)
PHEOCHROMOCYTOMA	1 (2%)	2 (4%)	2 (4%)
#THYROID	(50)	(49)	(47)
FOLLICULAR-CELL ADENOMA			1 (2%)
C-CELL ADENOMA		1 (2%)	4 (9%)
C-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
PAPILLARY ADENOMA		2 (4%)	1 (2%)
FIBROADENOMA	2 (4%)	9 (18%)	1 (2%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		1 (2%)
#UTERUS	(46)	(47)	(48)
CARCINOMA,NOS	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	11 (24%)	8 (17%)	11 (23%)
#UTERUS/ENDOMETRIUM	(46)	(47)	(48)
ADENOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOMA	1 (2%)	2 (4%)	1 (2%)
ALL OTHER SYSTEMS			
LOWER LEG			
OSTEOSARCOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	3	
MORIBUND SACRIFICE	20	9	17
SCHEDULED SACRIFICE **	2		2
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	25	38	31
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)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	44	44
TOTAL PRIMARY TUMORS	70	75	70
TOTAL ANIMALS WITH BENIGN TUMORS	38	41	36
TOTAL BENIGN TUMORS	49	60	50
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	12	18
TOTAL MALIGNANT TUMORS	21	14	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

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

TABLE B1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*EAR	(50)	(49)	(50)
FIBROUS HISTIOCYTOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(50)
FIBROSARCOMA		3 (6%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	4 (8%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)		
LEUKEMIA,NOS			1 (2%)
UNDIFFERENTIATED LEUKEMIA			1 (2%)
GRANULOCYTIC LEUKEMIA	2 (4%)		
MONOCYTIC LEUKEMIA		1 (2%)	1 (2%)
*SKIN	(50)	(49)	(50)
MAST-CELL TUMOR	1 (2%)		
#LYMPH NODE	(48)	(41)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#JEJUNUM	(45)	(42)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#SPLEEN	(49)	(45)	(50)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(50)	(49)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA		3 (6%)	4 (8%)
HEPATOCELLULAR CARCINOMA	12 (24%)	2 (4%)	13 (26%)
#JEJUNUM	(45)	(42)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(35)	(24)	(30)
CARCINOMA,NOS			1 (3%)
#THYROID	(45)	(44)	(44)
FOLLICULAR-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(49)	(49)	(48)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(49)	(50)
PAPILLARY CYSTADENOMA, NOS	2 (4%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
OSTEOSARCOMA		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	4	3
MORIBUND SACRIFICE	3	4	10
SCHEDULED SACRIFICE **	5	5	5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	40	37	32
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 B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	18	26
TOTAL PRIMARY TUMORS	28	18	30
TOTAL ANIMALS WITH BENIGN TUMORS	10	8	10
TOTAL BENIGN TUMORS	10	8	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	10	19
TOTAL MALIGNANT TUMORS	17	10	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	47	47	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	47	48
INTEGUMENTARY SYSTEM			
*MULTIPLE ORGANS	(47)	(47)	(48)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(47)	(47)	(48)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(47)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	3 (6%)	
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)		2 (4%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)		1 (2%)
MONOCYTIC LEUKEMIA		2 (4%)	
#SPLEEN	(47)	(47)	(48)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#MESENTERIC L. NODE	(43)	(42)	(41)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#LIVER	(47)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#KIDNEY	(45)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#UTERUS	(45)	(46)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
#SPLEEN	(47)	(47)	(48)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(47)	(47)	(48)
HEPATOCELLULAR ADENOMA	3 (6%)	2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA	3 (6%)	1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(33)	(33)	(33)
CARCINOMA,NOS		1 (3%)	
ADENOMA, NOS	1 (3%)		3 (9%)
#ADRENAL	(45)	(45)	(46)
CORTICAL ADENOMA			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(47)	(47)	(48)
ADENOCARCINOMA, NOS			1 (2%)
#UTERUS	(45)	(46)	(46)
ADENOCARCINOMA, NOS		1 (2%)	
#OVARY	(45)	(43)	(44)
CYSTADENOMA, NOS	1 (2%)		
NERVOUS SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(47)	(47)	(48)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	5	2
MORIBUND SACRIFICE	8	7	4
SCHEDULED SACRIFICE **	5		
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	33	38	44
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	15	15
TOTAL PRIMARY TUMORS	16	16	15
TOTAL ANIMALS WITH BENIGN TUMORS	5	3	7
TOTAL BENIGN TUMORS	6	3	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	12	8
TOTAL MALIGNANT TUMORS	10	13	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	1		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 C

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

TABLE C1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
CALCIFICATION, DYSTROPHIC			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
INFLAMMATION, ACUTE			2 (4%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(49)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)
SCLEROSIS	1 (2%)		
FIBROSIS, FOCAL	1 (2%)	2 (4%)	
HYPERPLASIA, LYMPHOID	2 (4%)		
#MANDIBULAR L. NODE	(43)	(45)	(42)
CYST, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#AURICULAR APPENDAGE	(49)	(50)	(50)
THROMBOSIS, NOS	2 (4%)		2 (4%)
THROMBUS, ORGANIZED		1 (2%)	
#MYOCARDIUM	(49)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, INTERSTITIAL	1 (2%)		
#HEPATIC SINUSOID	(49)	(50)	(49)
CONGESTION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, MULTIFOCAL			1 (2%)
NECROSIS, FOCAL	1 (2%)		1 (2%)
METAMORPHOSIS FATTY	1 (2%)	3 (6%)	2 (4%)
CYTOPLASMIC CHANGE, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
ANGIECTASIS		1 (2%)	
#BILE DUCT	(49)	(50)	(49)
HYPERPLASIA, NOS	5 (10%)		1 (2%)
#PANCREATIC ACINUS	(48)	(49)	(50)
ATROPHY, NOS	2 (4%)	5 (10%)	3 (6%)
#STOMACH	(48)	(50)	(48)
ULCER, NOS	2 (4%)	6 (12%)	7 (15%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
HYDRONEPHROSIS	1 (2%)		
INFLAMMATION, CHRONIC	41 (82%)	35 (70%)	34 (69%)
#URINARY BLADDER	(48)	(45)	(48)
HEMORRHAGE		1 (2%)	
INFLAMMATION, HEMORRHAGIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(45)	(45)
CYST, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
HYPERPLASIA, FOCAL	4 (9%)	3 (7%)	2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS	1 (2%)		1 (2%)
#ADRENAL	(47)	(49)	(49)
METAMORPHOSIS FATTY	1 (2%)		
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL CORTEX	(47)	(49)	(49)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#ADRENAL MEDULLA	(47)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	3 (6%)
#THYROID	(49)	(45)	(49)
CYSTIC FOLLICLES		1 (2%)	
HYPERPLASIA, C-CELL		6 (13%)	10 (20%)
#PANCREATIC ISLETS	(48)	(49)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
#PROSTATE	(43)	(41)	(41)
INFLAMMATION, NOS	1 (2%)		
*SEMINAL VESICLE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
#TESTIS	(50)	(49)	(49)
CALCIFICATION, DYSTROPHIC		1 (2%)	
ATROPHY, NOS	4 (8%)	1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(49)
HEMATOMA, NOS			1 (2%)
GLIOSIS	1 (2%)		
#CEREBELLUM	(49)	(50)	(49)
NECROSIS, HEMORRHAGIC	2 (4%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOGRANULOMA	4 (8%)		3 (6%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1

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

TABLE C2.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
EMPHYSEMA, NOS			2 (4%)
ATELECTASIS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(46)
CONGESTION, NOS			4 (9%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LYMPH NODE	(41)	(40)	(31)
CONGESTION, NOS		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	
CIRCULATORY SYSTEM			
#AURICULAR APPENDAGE	(50)	(50)	(49)
THROMBOSIS, NOS	1 (2%)	1 (2%)	
#MYOCARDIUM	(50)	(50)	(49)
INFLAMMATION, INTERSTITIAL		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(47)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(46)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, MULTIFOCAL	3 (7%)	3 (6%)	
NECROSIS, FOCAL		1 (2%)	2 (4%)
METAMORPHOSIS FATTY	3 (7%)	7 (14%)	5 (10%)
PIGMENTATION, NOS			1 (2%)
FOCAL CELLULAR CHANGE		1 (2%)	
#PANCREATIC ACINUS	(49)	(50)	(48)
ATROPHY, NOS	1 (2%)	3 (6%)	3 (6%)
#STOMACH	(49)	(49)	(49)
ULCER, NOS		1 (2%)	3 (6%)
#DUODENUM	(47)	(48)	(49)
FIBROSIS, FOCAL		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
INFLAMMATION, CHRONIC	27 (54%)	28 (56%)	18 (36%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(49)
CYST, NOS			3 (6%)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)	2 (4%)
ANGIECTASIS	6 (12%)	11 (22%)	7 (14%)
#ADRENAL	(49)	(49)	(48)
HEMORRHAGE	1 (2%)		
METAMORPHOSIS FATTY	4 (8%)		
ANGIECTASIS	1 (2%)		1 (2%)
#ADRENAL CORTEX	(49)	(49)	(48)
DEGENERATION, NOS	3 (6%)		
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(50)	(49)	(47)
CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	6 (12%)	8 (16%)	6 (13%)
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
#UTERUS	(46)	(47)	(48)
HYDROMETRA	3 (7%)	2 (4%)	
#UTERUS/ENDOMETRIUM	(46)	(47)	(48)
DEGENERATION, CYSTIC	1 (2%)		
HYPERPLASIA, CYSTIC			1 (2%)
#OVARY	(49)	(46)	(48)
FOLLICULAR CYST, NOS		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, INTERNAL		1 (2%)	
NECROSIS, HEMORRHAGIC	3 (6%)		
CALCIFICATION, DYSTROPHIC			1 (2%)
#CEREBELLUM	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOGRANULOMA	1 (2%)		2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY	(50)	(50)	(50)
STEATITIS			1 (2%)
ALL OTHER SYSTEMS			
NONE			
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 MALAOXON IN THE DIET

TABLE D1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
EPIDERMAL INCLUSION CYST			3 (6%)
*SUBCUT TISSUE	(50)	(49)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(50)
BRONCHOPNEUMONIA, FOCAL		1 (2%)	1 (2%)
INFLAMMATION, FOCAL	8 (16%)	6 (13%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	8 (16%)	6 (13%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#LYMPH NODE	(48)	(41)	(48)
HYPERPLASIA, NOS		1 (2%)	
#MESENTERIC L. NODE	(48)	(41)	(48)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#INGUINAL LYMPH NODE	(48)	(41)	(48)
HYPERPLASIA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
ABSCESS, NOS		1 (2%)	
NECROSIS, FOCAL	1 (2%)		
INFARCT, NOS	1 (2%)		
#PANCREAS	(48)	(48)	(50)
DILATATION/DUCTS			1 (2%)
ATROPHY, NOS			1 (2%)
#PEYERS PATCH	(45)	(42)	(47)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(48)
PYELONEPHRITIS, ACUTE		1 (2%)	
#URINARY BLADDER	(50)	(43)	(49)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(35)	(24)	(30)
CYST, NOS		1 (4%)	
#ADRENAL CORTEX	(50)	(48)	(48)
INFARCT, NOS		1 (2%)	
#ADRENAL MEDULLA	(50)	(48)	(48)
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(45)	(44)	(44)
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)		1 (2%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(47)	(45)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#LEPTOMENINGES	(49)	(49)	(50)
CHOLESTEATOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(49)	(50)
PARASITISM			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	20	21	17
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 MALAOXON IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	47	47	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	47	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(47)	(47)	(48)
EDEMA, NOS			1 (2%)
HEMORRHAGE			1 (2%)
BRONCHOPNEUMONIA, FOCAL	3 (6%)		
INFLAMMATION, FOCAL	7 (15%)	6 (13%)	
BRONCHOPNEUMONIA, ACUTE	2 (4%)		1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	7 (15%)	6 (13%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MAMMARY GLAND	(47)	(47)	(48)
DYSPLASIA, NOS			1 (2%)
ADENOSIS		1 (2%)	1 (2%)
#SPLEEN	(47)	(47)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LYMPH NODE	(43)	(42)	(41)
HYPERPLASIA, NOS	1 (2%)		
#MESENTERIC L. NODE	(43)	(42)	(41)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#JEJUNUM	(45)	(45)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(47)	(47)	(48)
FOCAL CELLULAR CHANGE		1 (2%)	
#BILE DUCT	(47)	(47)	(48)
HAMARTOMA	1 (2%)		
#PANCREAS	(47)	(46)	(48)
DILATATION/DUCTS	1 (2%)		
ATROPHY, NOS		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(45)	(47)	(48)
INFARCT, NOS		1 (2%)	
#URINARY BLADDER	(41)	(43)	(44)
INFLAMMATION, CHRONIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(33)	(33)	(33)
HEMORRHAGE			1 (3%)
HYPERPLASIA, FOCAL	4 (12%)	2 (6%)	1 (3%)
#THYROID	(43)	(41)	(43)
HYPERPLASIA, FOLLICULAR-CELL			2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY LOBULE	(47)	(47)	(48)
HYPERPLASIA, NOS	1 (2%)		2 (4%)
#OVARY	(45)	(43)	(44)
CYST, NOS	2 (4%)		
HEMORRHAGE		1 (2%)	
ABSCESS, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(47)	(47)	(48)
PARASITISM		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	19	18	26
AUTOLYSIS/NO NECROPSY	3	3	2

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

APPENDIX E

ANALYSIS OF MALAOXON

APPENDIX E

Analysis of Malaoxon

A. Elemental Analysis

Element:	C	H	P	S
Theory:	38.21	6.09	9.86	10.20
Found:	37.95	6.09	9.60	10.40

B. Boiling Point

Literature: 132°C at 0.1 mm Hg (Ailman, 1965).
Found: Not determined.

C. Thin-Layer Chromatography

Plate used: Silufol (100 μ silica gel on Al foil).
Visualization: I_2 vapor.

System I	System II
Hexane, ether, acetone (10:3:1)	Hexane, ether, acetone (4:4:1)
Results: R_f 0.07, trace at 0.51	Results: R_f 0.57, trace at 0.82

D. Vapor-Phase Chromatography

Instrument: H-P 7610
Detector: EC-pulsed 150 at 280°C
Column: 10% DCZOO on GCQ, 4' x 1/4", glass at 165°C
Inlet Temp: 200°C
Results: Major peak at 6.5 minutes, with trace impurities (< 1%) at 2.0 and 5.0 minutes

E. Spectral Data

1. Infrared: The infrared absorption spectrum (figure 5) was consistant with the spectrum given in the literature (Ailman, 1965).

2. Nuclear Magnetic Resonance: The nuclear magnetic resonance spectrum (figure 6) was consistent with the spectrum given in the literature (Keith et al., 1968).

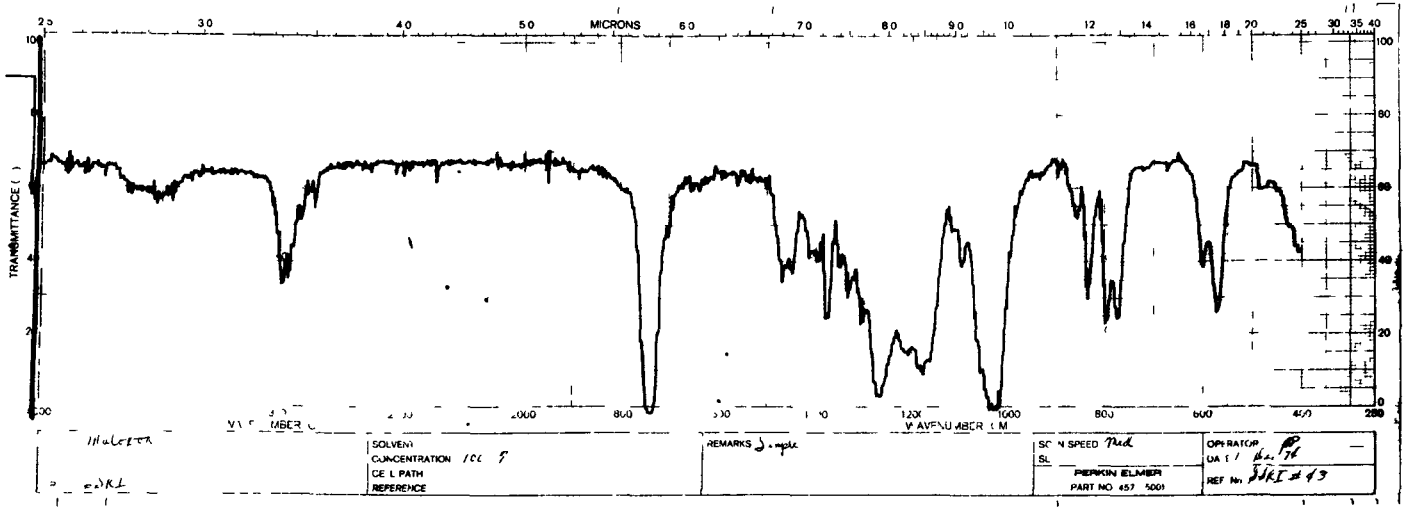


Figure 5. Infrared Absorption Spectrum of Malaoxon

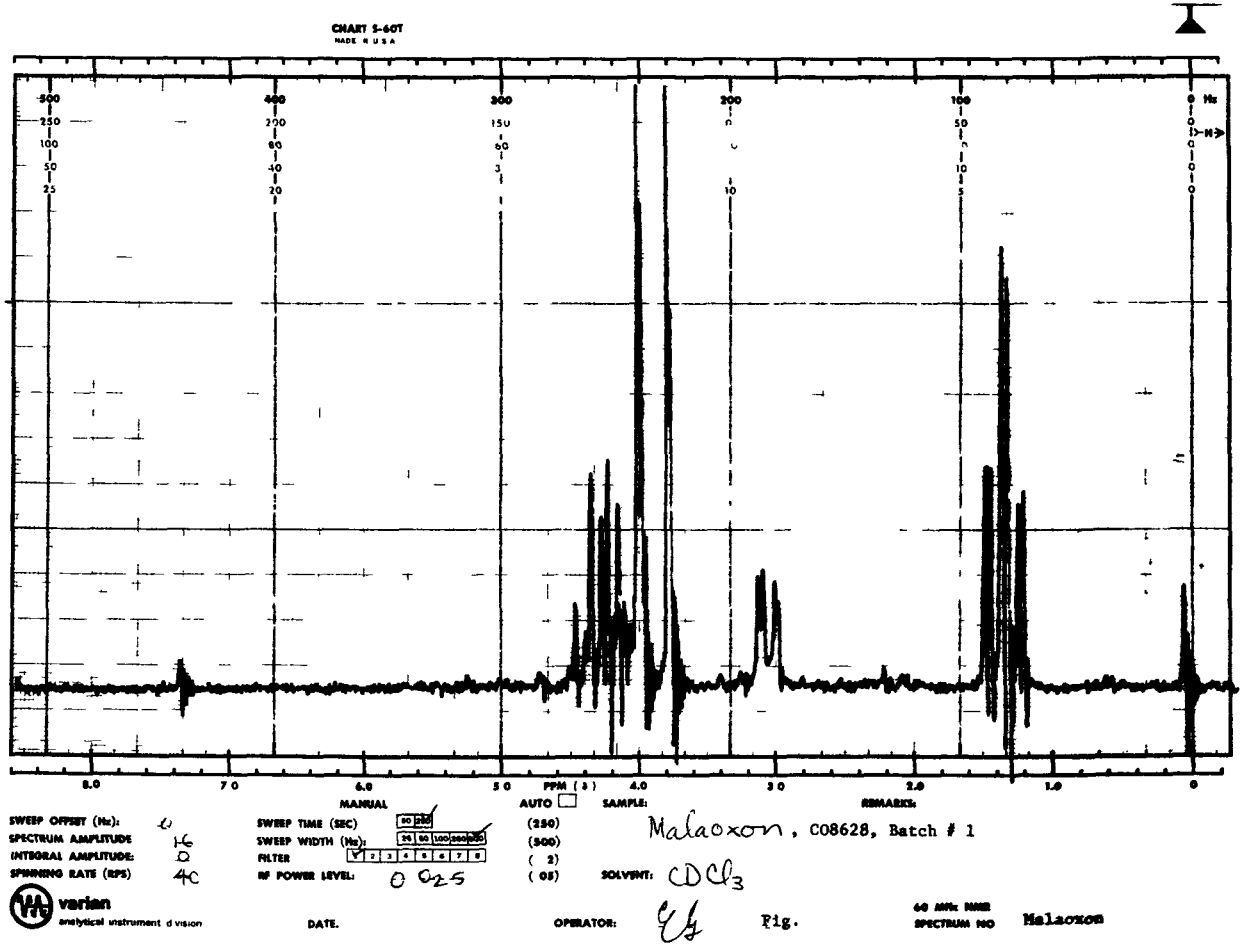


Figure 6. Nuclear Magnetic Resonance Spectrum of Malaoxon

APPENDIX F

ANALYSES OF FORMULATED DIETS FOR CONCENTRATIONS OF MALAOXON

Appendix F

Analyses of Formulated Diets for Concentrations of Malaoxon

A 10-g sample of the diet mixture containing malaoxon was extracted with 250 ml of benzene by shaking on a wrist-action shaker for 3 to 4 hours. Appropriate aliquots of the extract were taken and after appropriate dilutions, the solution was quantitatively analyzed for malaoxon by gas-liquid chromatography (flame photometric detector in phosphorus mode, 10% DC 200 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)	Coefficienct of Variation (%)	Range ppm
500	12	507.5	3.38	487-529
1000	12	979.8	3.15	923-1032
2000	11	2026.3	2.57	1934-2096

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

May 1, 1979

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 of 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 Malaoxon.

The primary reviewer for the report on the bioassay of Malaoxon said that the compound was the oxygen analogue of Malathion. The report indicated that Malaoxon was not carcinogenic in rats or mice, under the conditions of test. After briefly commenting on the experimental design, he said that the study was straightforward. He did note, however, that results from the subchronic study indicated that both rats and mice may have been able to tolerate higher chronic dose levels. The primary reviewer also pointed out the unusually high incidence of lymphomas and leukemias in control rats. A staff member commented that the incidence of these tumors are quite variable in different groups of Fischer rats.

The secondary reviewer also noted that the chronic dose levels could have been higher, as indicated from the subchronic findings. Overall, however, he thought the study was adequate.

It was moved that the report on the bioassay of Malaoxon be accepted as written. The motion was seconded and approved unanimously.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
David B. Clayson, University of Nebraska Medical Center
Joseph Highland, Environmental Defense Fund

William Lijinsky, Frederick Cancer Research Center
Sheldon Samuels, AFL-CIO
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

---

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

☆U S GOVERNMENT PRINTING OFFICE 1979—281 217 3219

NIH Publication No. 79-1390