National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 205
NTP No. 80-14
1980

BIOASSAY OF 4, 4'-OXYDIANILINE FOR POSSIBLE CARCINOGENICITY

CAS No. 101-80-4

NCI-CG-TR-205

NTP-80-14

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

BIOASSAY OF

4,4-OXYDIANALINE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205
and
National Toxicology Program
Research Triangle Park
Box 12233
North Carolina 27709

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NIH Publication No. 80-1761
August 1980

BIOASSAY OF
4,4'-OXYDIANILINE
FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
National Cancer Institute/National Toxicology Program

FOREWORD

This report presents the results of the bioassay of 4,4'-oxydianiline conducted for the Carcinogenesis Testing Program, National Cancer Institute (NCI)/National Toxicology Program (NTP). This is one of a series of experiments designed to determine whether selected 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

The bioassay of 4,4'-oxydianiline was conducted at EG&G Mason Research Institute, Worcester, Massachusetts, under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI Carcinogenesis Testing Program.

The bioassay was conducted under the supervision of Drs. A. H. Handler (1,2), H. S. Lilja (1), and E. Massaro (1,3), principal investigators, and Mr. G. Wade (1). The program manager was Ms. R. Monson (1). Ms. A. Good (1) supervised the technicians in charge of animal care, and Ms. E. Zepp (1) supervised the preparation of the feed mixtures and collected samples of the diets for analysis. Ms. D. Bouthot (1) kept all daily records of the test. Dr. A. S. Krishna Murthy (1), pathologist, directed the necropsies and performed the histopathologic examinations. The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute, Rockville, Maryland (4). The statistical analyses were performed by Dr. J. R. Joiner (5) and Ms. S. Vatsan (5), using methods selected for the bioassay program by Dr. J. J. Gart (6).

Chemicals used in this bioassay were analyzed at Midwest Research Institute (7), and dosed feed mixtures were analyzed by Dr. M. Hagopian (1).

This report was prepared at Tracor Jitco (5) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Acting Director of the Bioassay Program; Dr. S. S. Olin, Associate

Director; Dr. R. L. Schueler, pathologist; Dr. D. J. Beach, reports manager; Dr. A. C. Jacobs, bioscience writer; and Dr. W.D. Theriault and Ms. M. W. Glasser, technical editors.

The following scientists at NCI (8) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Michael P. Dieter, Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. C. W. Jameson, Dr. Y. Jack Lee, Dr. Harry Mahar, Dr. James McCoy, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Marcelina B. Powers, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

---

(1) EG&G Mason Research Institute, 57 Union Street, Worcester, Massachusetts 01608.
(2) Now with Findley Research Company, P.O. Box 375, Assonet, Massachusetts 02702.
(3) Now with Pennsylvania State University, 226 Fenske Laboratory, University Park, Pennsylvania 16802.
(4) EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland 20852.
(5) Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland 20852.
(6) 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 20205.
(7) Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri 64110.
(8) Carcinogenesis Testing Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205; National Toxicology Program, Research Triangle Park, Box 12233, North Carolina 27709.

SUMMARY

4,4'-Oxydianiline is used in the manufacture of high temperature resistant metal adhesives, molding and machine parts, and insulators. A bioassay of this chemical for possible carcinogenicity was conducted by feeding diets containing 200, 400, or 500 ppm of the test chemical to groups of 50 male or female F344 rats and 150, 300, or 800 ppm to groups of 50 male or female B6C3F1 mice for 104 weeks. Matched controls consisted of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed at 104 to 105 weeks.

A dose-related decrement in mean body weight gain was observed for all groups of dosed rats and mice. Survival was significantly shortened in the high-dose female rats and in the low- and mid-dose female mice.

In male and female rats, hepatocellular carcinomas or neoplastic nodules occurred at incidences that were dose-related, and the incidences in all dosed groups (except low-dose females) were higher than those in the controls. The occurrence of follicular-cell adenomas or carcinomas of the thyroid was dose-related. Among groups of male and female rats, the incidences in the mid- and high-dose groups of either sex were significantly higher than those of the corresponding controls.

In male and female mice, adenomas in the harderian glands occurred in all dosed groups at incidences that were significantly higher than the incidence in the matched controls.

In low-dose male mice and in high-dose female mice, hepatocellular adenomas or carcinomas occurred at incidences significantly higher than those in the matched controls.

In female mice, follicular-cell adenomas in the thyroid occurred with a positive linear trend, and in a direct comparison the incidence in the high-dose group was also significantly higher than that in the controls.

Tumors occurring among male mice at increased incidences which could not be statistically related to the chemical were adenomas in the pituitary and hemangiomas of the circulatory system.

Under the conditions of this bioassay, 4,4'-oxydianiline was carcinogenic for male and female F344 rats, inducing hepatocellular carcinomas or neoplastic nodules and follicular-cell adenomas or carcinomas of the thyroid. 4,4'-Oxydianiline was also carcinogenic for male and female B6C3F1 mice, inducing adenomas in the harderian glands, hepatocellular adenomas or carcinomas in both sexes, and follicular-cell adenomas in the thyroid of females.

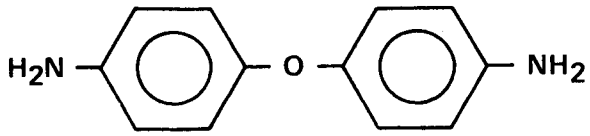
TABLE OF CONTENTS

APPENDIXES

TABLES

FIGURES

I. INTRODUCTION



4,4'-OXYDIANILINE

4,4'-Oxydianiline (CAS No. 101-80-4; NCI C50146) is a colorless powder used as a chemical intermediate in the manufacture of high temperature-resistant straight polyimide and poly(esterimide) resins (Seymour, 1968). These types of resins have wide application as insulating enamels in wire and electrical equipment, as binders in laminates for printed circuits and honeycomb structures, and in the molding of grinding wheels (International Agency for Research on Cancer, 1978). The fluorine-modified polyimide polymers are also used as adhesives in metal-to-metal bonding of airplane parts (Chemical & Engineering News, 1973). Production in 1974 was reported to be between 100,000 and 1,000,000 pounds per year (DuPont, 1974).

Lapik et al. (1968) reported the following acute toxicities for 4,4'-oxydianiline administered by different routes to white mice and albino rats (sex unspecified):

Species	Route	LD_{50} (mg/kg)
Mouse	intraperitoneal	300±20
Rat	intraperitoneal	365±25
Mouse	intragastric	685±42
Rat	intragastric	725±50

These investigators also found that administration of 68 mg/kg 4,4'-oxydianiline for 15 days to albino rats decreased hemoglobin concentration

(from 14.9 g/100 ml to 12.1 g/100 ml) and increased the weights of the adrenals and spleen.

Shimizu and Takemura (1976) reported that 4,4'-oxydianiline was mutagenic to Salmonella typhimurium.

4,4'-Oxydianiline was selected for testing by the Carcinogenesis Testing Program because of its structural relationship to 4-aminobiphenyl, a possible bladder carcinogen in man (Melick et al., 1955) and its large production, and because previous tests were considered to be inadequate.

II. MATERIALS AND METHODS

A. Chemical

Technical-grade 4,4'-oxydianiline was obtained from E. I. DuPont de Nemours and Company (Wilmington, Del.) in two batches. Lot No. 387 was used in the first and second subchronic studies and Lot No. 82/02 was used in the chronic studies. Purity and identity analyses were performed at Midwest Research Institute, Kansas City, Missouri. (Appendixes E and F). For both batches, the melting points were comparable with literature values reported by Reynolds (1951). The infrared and nuclear magnetic resonance spectra were consistent with the reference spectra (Sadtler Standard Spectra). Amine titration of Lot Nos. 387 and 82/02 indicated purities of 99.9%±0.6% and 98.9%±0.2%, respectively. Elemental analyses were consistent with the theoretical composition. Results from thin-layer chromatography indicated a trace impurity in Lot No. 387 at the origin and three trace impurities in Lot No. 82/02. Results from vapor-phase chromatography of Lot No. 387 indicated an impurity constituting 0.29% of the major peak, whereas Lot No. 82/02 contained two impurities, each with an area of 0.1% of the major peak. The nuclear magnetic resonance spectrum of Lot No. 82/02 indicated a trace impurity at 3.28 to 3.42 ppm. The impurities were not identified.

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

B. Dietary Preparation

Test diets were prepared by first mixing the chemical with an aliquot of Wayne® Lab Blox animal meal (Allied Mills, Chicago, Ill.) using a mortar and pestle. This mixture was placed in a Patterson Kelly® twin-shell blender with the remainder of the feed and mixed for 20 minutes. Test diets were sealed in labelled plastic bags and stored at 4°C for no longer than 1 week.

Analyses of the stability of 4,4'-oxydianiline in feed were performed at Midwest Research Institute by assaying dimethyl formamide extracts from samples of diet mixtures containing 100,000 ppm that had been stored at -20°,

5°, 25°, or 45°C for 2 weeks. The concentrations of the test chemical in the extracts were determined by vapor-phase chromatography under conditions given in Appendix G for system 2, except that the oven temperature was held isothermally at 200°C. 4,4'-Oxydianiline at 100,000 ppm was stable in feed for 2 weeks at 45°C.

Selected batches of the formulated diets administered during the chronic study were analyzed at EG&G Mason Research Institute for accuracy of dose level (Appendix H). The test feeds were first extracted with 95% ethanol, and concentrations of the test chemical in the extracts were determined by spectrophotometric analysis at 247 nm. The mean concentration of 12 feed samples containing a theoretical level of 200 ppm was 200±29 ppm, and the mean concentration of 14 samples measured in duplicate and containing a theoretical level of 800 ppm was 780±103 ppm.

C. Animals

Four-week-old F344 rats and 5-week old B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center (Frederick, Maryland), observed for 10 days for the presence of parasites or other diseases, and then assigned to various groups so that the average initial body weight per group was approximately the same.

D. Animal Maintenance

The rats and mice were housed in solid-bottom polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) containing Aspenbed® (aspen chips, American Excelsior, Summerville, Mass.). Rat cages were covered with a nonwoven fiber filter (Webrex). Mouse cages were covered with spun-bonded Filtek® filter bonnets (Lab Products). Rats were housed five per cage in the subchronic studies and four per cage in the chronic studies. Mice were housed five per cage.

Test and control diets and tap water were provided ad libitum. Cages, bottles, sipper tubes, and stoppers were changed twice per week. Feed hoppers were changed once per week. Stainless steel cage racks and the disposable filters were changed once every 2 weeks.

The temperature in the animal rooms was 18°-32°C, and the relative humidity was 5%-82%. Incoming air was filtered by 2-inch fiberglass Tri-dek 125-40 filters with 10 to 12 changes of room air per hour. Fluorescent lighting was provided on a 12-hour per day cycle.

Rats and mice were housed by species in separate rooms, and control animals were housed in the same room as the respective dosed animals. The rats and mice in the subchronic study were housed in the same room as rats and mice in chronic studies of cinnamyl anthranilate (CAS 87-29-6). In the chronic study, rats and mice were housed by species in rooms in which chronic studies were also being conducted on 2,6-toluenediamine dihydrochloride (CAS 15481-70-6) (feed study).

E. Range-Finding and 14-Day Repeated-Dose Studies

In the range-finding study conducted to determine the doses for the 14-day repeated-dose study, the test chemical was diluted in corn oil and administered by gavage to groups of two males and two females of each species. Doses administered and survival are shown in Table 1. The animals were observed for 7 days and then killed and necropsied. To solubilize the 4,4'-oxydianiline, the 10,000 mg/kg dose was prepared in 10% DMSO (dimethyl sulfoxide) in corn oil.

All male rats receiving the three highest doses (1,000, 3,000, and 10,000 mg/kg body weight) and all female rats receiving the two highest doses (3,000 and 10,000 mg/kg) died. No mortality occurred among the male mice, but both female mice receiving the 3,000 mg/kg dose died. Intestinal hemorrhage was observed in rats at the two highest doses. Labored respiration was observed in the rats receiving the three highest doses of 1,000, 3,000, and 10,000 mg/kg and in the mice that subsequently died after receiving the 3,000 mg/kg dose. Enlarged lymph nodes were observed in the mice at all doses.

In the fourteen-day repeated-dose studies conducted to determine the doses to be used in the 90-day subchronic studies, groups of five males and five females of each species were fed diets containing the different concentrations of the test chemical shown in Table 2. The animals were observed daily, and after 14 days, all survivors were killed and necropsied.

Table 1. Doses and Survival of Rats and Mice Administered a Single Dose of 4,4'-Oxydianiline in Corn Oil by Gavage

Dose (mg/kg)	Survival (a) Male	Female
Rats		
100	2/2	2/2
300	2/2	2/2
1,000	0/2	2/2
3,000	0/2	0/2
10,000(b)	0/2	0/2
Mice		
100	2/2	2/2
300	2/2	2/2
1,000	2/2	2/2
3,000	2/2	0/2
10,000 (b)	2/2	1/2 (c)

(a) Number surviving/number per group.
(b) At this dose, the test chemical was prepared in 10% dimethyl sulfoxide in corn oil.
(c) Death was accidental.

Table 2. Doses and Survival of Rats and Mice Administered 4,4'-Oxydianiline in the Diet for 14 Days

Dose (ppm)	Survival (a) Male	Female
Rats		
0	8/8	9/9
300	5/5	5/5
1,000	5/5	5/5
3,000	1/5	0/5
10,000	0/5	0/5
30,000	0/5	0/5
Mice		
0	9/9	8/8
300	5/5	5/5
1,000	5/5	5/5
3,000	2/5	4/5
10,000	0/5	0/5
30,000	0/5	0/5

(a) Number surviving/number per group.

All rats receiving 10,000 or 30,000 ppm 4,4'-oxydianiline and 4/5 male rats and 5/5 female rats receiving 3,000 ppm died. The LD_{50} calculated for male rats was 2,240 ppm and 1,730 ppm for females. In mice, all the animals receiving the 10,000- or 30,000-ppm dose died. Three of five male mice and 1/5 female mice receiving 3,000 ppm 4,4'-oxydianiline died. The LD_{50} calculated for male mice was 2,820 ppm and 4,470 ppm for females.

4,4'-Oxydianiline caused liver enlargement at all doses, jaundice at the two highest doses, hemorrhages of the digestive tract at the three highest doses, and hemorrhages of the renal medullae at the highest dose. Rats receiving doses greater than 1,000 ppm were emaciated because of decreased food consumption. Lymphatic enlargement was observed in all dosed mice but in only 2/9 male controls and 1/8 female controls.

F. Subchronic Studies

In 90-day subchronic feeding studies conducted to determine the concentrations of 4,4'-oxydianiline to be used in the chronic 2-year studies, groups of 10 males and 10 females of each species were fed diets containing 0, 3, 10, 30, 100, or 300 ppm for 90 days. All animals were observed twice daily for mortality. Individual animal weights, food consumption, appearance, and behavior were recorded weekly. After 13 weeks, all the animals were killed and necropsied. Representative tissues were examined microscopically as described in the section on chronic studies. Because no compound-related clinical signs, body weight changes, or pathologic changes were observed in either rats or mice, a second subchronic study was carried out using diets containing 0, 300, 600, 1,000, and 2,000 ppm. The doses administered in the second study, survival, and mean body weights of the dosed and control groups are shown in Tables 3 and 4.

Rats

A dose-related increase in mortality and decrease in weight gain were observed in both sexes of rats, and alopecia, labored respiration, and cyanosis were observed with the two highest doses (1,000 and 2,000 ppm). All rats receiving 600 ppm or more had diffuse parenchymatous goiter. In addition, pituitary hyperplasia, testicular degeneration, prostatic atrophy,

Table 3. Doses, Survival, and Mean Body Weights of Rats Administered 4,4'-Oxydianiline in the Diet for 90 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Controls (b) (Percent)
		Initial	Final	Gain	
MALE					
0	10/10	87	300	243	
300	10/10	87	302	215	-12
600	9/10	87	165	78	-68
1,000	8/10	87	121	34	-86
2,000	7/10	87	85	-2	-99
FEMALE					
0	10/10	82	204	122	
300	10/10	82	200	118	-3.2
600	10/10	82	131	49	-60
1,000	6/10	82	113	31	-75
2,000	4/10 (c)	82	88	6	-95

(a) Number surviving/number per group.

(b) Weight Change Relative to Controls = $\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$

(c) One of four survivors at 90 days was moribund.

Table 4. Doses, Survival, and Mean Body Weights of Mice Administered 4,4'-Oxydianiline in the Diet for 90 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls (b) (Percent)
MALE					
0	10/10	17.3	30.8	13.5	
300	10/10	17.3	30.0	12.7	-6
600	10/10	17.3	27.2	9.9	-27
1,000	10/10	17.3	26.2	8.9	-34
2,000	10/10	17.3	21.8	4.5	-67
FEMALE					
0	10/10	15.2	23.0	7.8	
300	9/9	15.2	23.6	8.4	+8
600	10/10	15.2	21.8	6.6	-15
1,000	10/10	15.2	19.2	4.0	-49
2,000	10/10	15.2	18.6	3.4	-56

(a) Number surviving/number per group.

(b) Weight change relative to controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

seminal vesicular atrophy, and renal microlithiasis were detected in most of the rats receiving 600 ppm or more.

Because of the weight gain depression and the thyroid effects observed in the second subchronic study, doses selected for the chronic study in rats were 200, 400, and 500 ppm. The highest dose (500 ppm) was included to enhance the possiblity of detecting a thyroid response.

Mice

None of the mice died, but a dose-associated decrease in weight gain was observed in male mice at all doses and in female mice at doses of 600 ppm and higher. Mice receiving the two highest doses were lethargic toward the end of the study. Most mice receiving 600 ppm or more had thyroid hypertrophy and hyperplasia. Hyperplastic goiter was observed in mice receiving the highest dose (2,000 ppm). Pituitary hypertrophy and hyperplasia were associated with thyroid changes in some female mice receiving 1,000 ppm and in nearly all mice receiving 2,000 ppm. Testicular degeneration was found in most male mice receiving 1,000 or 2,000 ppm.

Because of the weight gain depressions and thyroid effects observed in the second subchronic study, doses selected for the chronic study in mice were 150, 300, and 800 ppm. The highest dose (800 ppm) was included to enhance the possibility of detecting a thyroid response.

G. Design of Chronic Studies

The number of animals per group, doses administered, and durations of the chronic studies are shown in Table 5.

H. Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Mean body weights of animals by cage were recorded every 2 weeks for the first 13 weeks and monthly thereafter. Clinical signs were recorded monthly. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Table 5. Experimental Design for Chronic Feeding Studies with 4,4'-Oxydianiline in Rats and Mice

Sex, Species, and Test Group	Initial Number of Animals (a)	4,4'-Oxydianiline in Diet (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male Rats				
Matched-Control	50	0	0	104-105
Low-Dose	50	200	103	1-2
Mid-Dose	50	400	103	1-2
High-Dose	50	500	103	1-2
Female Rats				
Matched-Control	50	0	0	104-105
Low-Dose	50	200	103	1-2
Mid-Dose	50	400	103	1-2
High-Dose	50	500	103	1-2
Male Mice				
Matched-Control	50	0	0	104-105
Low-Dose	50	150	103	1-2
Mid-Dose	50	300	103	1-2
High-Dose	50	800	103	1-2
Female Mice				
Matched-Control	50	0	0	104-105
Low-Dose	50	150	103	1-2
Mid-Dose	50	300	103	1-2
High-Dose	50	800	103	1-2

(a) Rats were approximately 5 weeks old, and mice were approximately 6 weeks old when placed on chronic study.
(b) Test animals received dosed diets *ad libitum* 7 days per week.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Preparations of the following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes, ovaries/uterus, nasal cavity, brain, pituitary, eyes, and spinal cord. Special staining techniques were utilized as necessary.

Necropsies were 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.

I. Data Recording and Statistical Analyses

Data on this experiment were recorded in 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 reported only 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 (e.g., skin or mammary tumors) prior to histologic sampling, 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 three 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 Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.017. When this correction was used, it is discussed in the narrative section. It is not 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. When a linear trend is assumed, 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 relationship. This method also provides a two-tailed test of departure from linear trend.

The approximate 95% confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971).

The 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 has occurred (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). 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)

A dose-related depression in mean body weight gain was observed for all groups of dosed rats (Figure 1). Labored breathing was observed in all the female rats receiving the highest dose (500 ppm). The incidence of exophthalmia was comparable in dosed and control groups.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats fed diets containing 4-4'-oxydianiline at the doses of this bioassay, and those of the matched controls, are shown by the Kaplan and Meier curves in Figure 2. In male rats, results of the Tarone test for positive dose-related trend in mortality indicate no significant differences; however, this test indicates that there was a significantly shortened survival in the high-dose female rats (P less than 0.001) when compared with any of the other groups. Survival in the low- and mid-dose female rats and in the matched controls was comparable.

Over 90% of the male rats in each group lived to 78 weeks or more. Those surviving to the end of the study at 105 to 106 weeks included 25/50 (50%) of the matched controls, 34/50 (68%) of the low-dose, 35/50 (70%) of the mid-dose, and 30/50 (60%) of the high-dose group.

The high-dose female rats died earlier than did those in the other female groups, and only 52% of this group lived to 78 weeks, compared with over 90% in the other groups. At the end of the study (weeks 105 to 106), the survivors included 40/50 (80%) of the matched controls, 38/50 (76%) of the low-dose group, 34/50 (68%) of the mid-dose group, and 13/50 (26%) of the high-dose group.

Enough animals were at risk for the development of late appearing tumors.

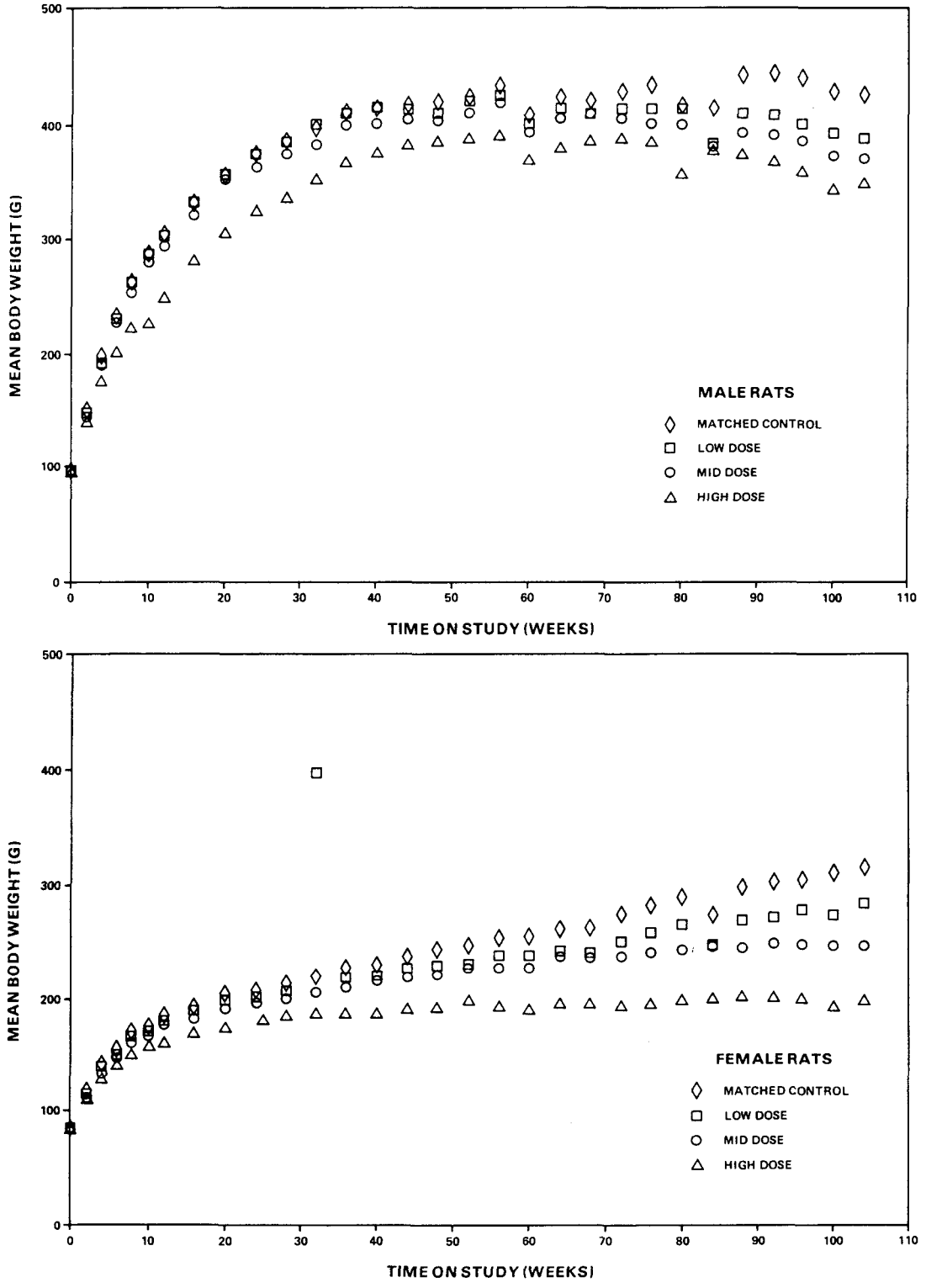


Figure 1. Growth Curves For Rats Administered 4, 4'-Oxydianiline in the Diet

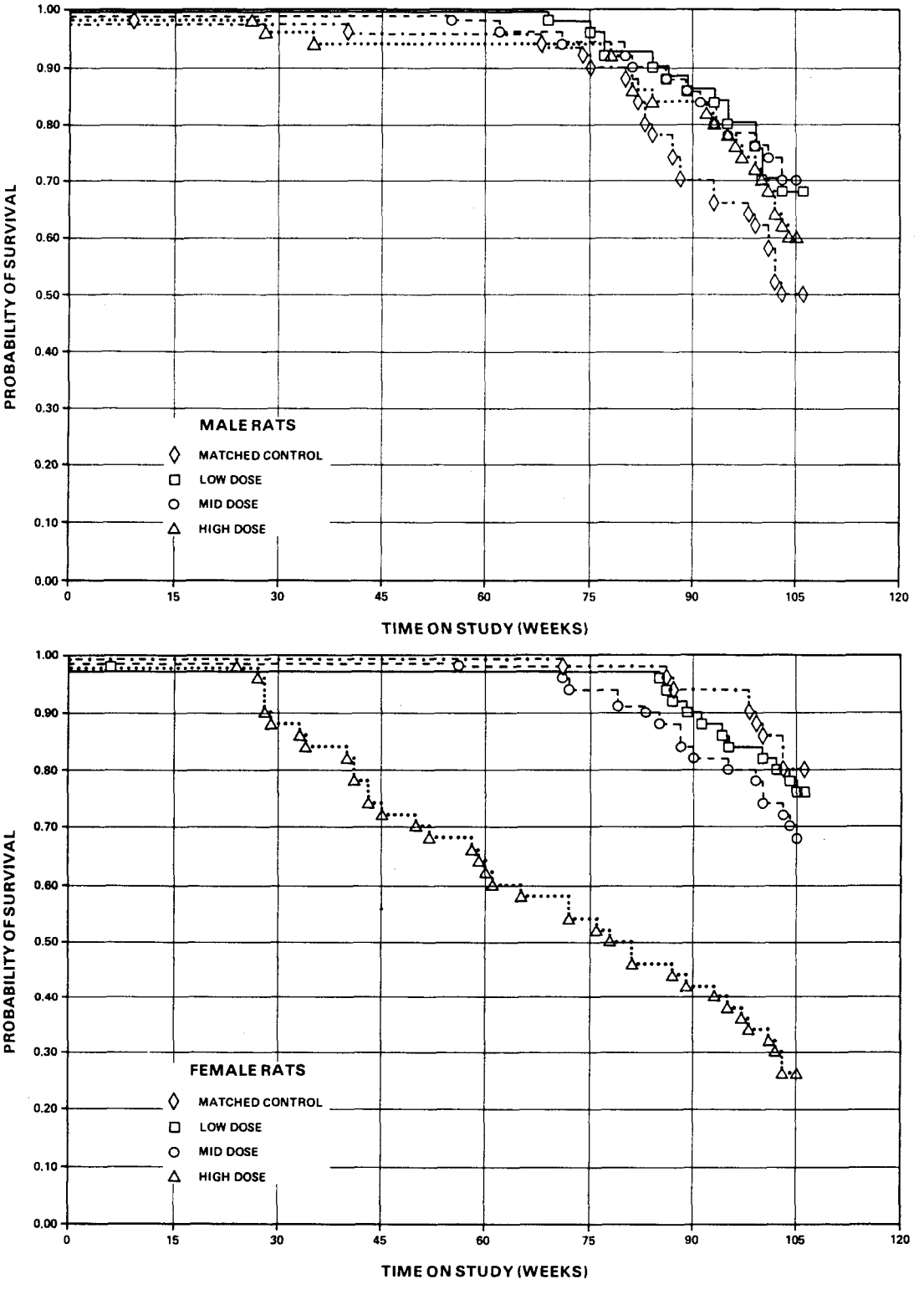


Figure 2. Survival Curves For Rats Administered 4, 4'-Oxydianiline in the Diet

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 were seen in control and dosed rats. None was associated with the test chemical except for those of the thyroid gland and liver.

The thyroid glands of most of the treated rats were grossly enlarged. Histologically, a cyst was considered to be follicular when it contained eosinophilic or pale colloid and was lined by cuboidal epithelial cells. A diffuse follicular enlargement or papillary ingrowths of the epithelium producing follicles of various sizes were characteristic features of follicular hyperplasia. The epithelial cells were either cuboidal or columnar.

Follicular neoplasms of the thyroid gland occurred in one control and in 107 treated rats (Table 6). Follicular adenomas were encapsulated and they compressed the adjacent tissue. Both macro- and micro-follicular variants were observed. Colloid was conspicuous in macrofollicular tumors. The epithelial cells were cuboidal or columnar. Cytoplasm of the cells was homogeneous and the nuclei were hyperchromatic. The infiltration of tumor cells in the capsule and/or blood vessel was considered essential for the diagnosis of follicular carcinoma. The carcinomas involved one or both lobes and compressed the trachea in a few rats. Papillary arrangement of the cells was common in many tumors. Squamous metaplasia was noted in one tumor.

Areas of necrosis were common in the large tumors. Foci of mineralization, cholesterol clefts, and golden brown pigment were additional features. Stroma was hyalinized in 20 tumors, and stromal reaction (as evidenced by presence of fibroblasts) was found in a few tumors. Follicular carcinoma had metastasized to the lung in two female rats (one mid-dose; one high-dose).

Neoplastic nodules and carcinomas occurred in the livers of some treated rats (Table 7). Multiple neoplastic nodules compressed the adjacent hepatic tissue. Cells in the nodules were larger than the normal hepatocytes. Cytoplasm of the cells was either acidophilic, basophilic, or vacuolated. Nuclei

Table 6. Numbers of Rats with Follicular or C-Cell Lesions of the Thyroid

	MALES				FEMALES			
	Control	Low-Dose	Mid-Dose	High-Dose	Control	Low-Dose	Mid-Dose	High-Dose
Number of Thyroids Examined	46	47	46	50	49	48	48	50
Follicular:								
Cyst	0	0	11	3	0	1	7	2
Hyperplasia	0	1	11	13	0	1	6	22
Adenoma	1	1	8	13	0	2	17	16
Carcinoma	0	5	9	15	0	2	12	7
C-cell:								
Hyperplasia	0	0	0	0	1	6	3	1
Adenoma	0	0	0	0	2	4	2	2
Carcinoma	0	0	0	0	0	0	1	0

Table 7. Numbers of Rats with Neoplasms of the Liver

	MALES				FEMALES			
	Control	Low-Dose	Mid-Dose	High-Dose	Control	Low-Dose	Mid-Dose	High-Dose
Number of Livers Examined	50	50	50	50	50	49[a]	50	50
Neoplastic nodule	1	9	18	17	3	0	20	11
Hepatocellular carcinoma	0	4	23	22	0	0	4	6
Neoplasm, unclassified	0	0	0	1				

(a) Tissue autolyzed

were vesicular and hyperchromatic. Hepatocellular carcinoma was well-differentiated and involved a part or an entire lobe of the liver. Fibrous tissue septa separated the tumor parenchyma into nodules of various sizes. Acinar and trabecular forms were observed in these tumors. As in the neoplastic nodules, cytoplasm of the cells was acidophilic, basophilic, or vacuolated. Nuclei were hyperchromatic, and the nucleoli were prominent. Both normal and abnormal mitotic figures were present. Multinucleate cells were found in a few tumors. Hemorrhage and necrosis occurred in the large tumors.

In some of the hepatocellular neoplasms in rats of the mid-dose and high-dose groups, the tumor cells appeared to have undergone cystic degeneration. Such areas contained a few blood cells and/or a lacy material which stained light blue.

Except for focal mineralization of the kidney and transitional cell hyperplasia of the renal pelvis in a few treated rats, there were no other chemical-related nonneoplastic lesions.

The results of the histopathologic examination indicated that, under conditions of this study, 4,4'-oxydianiline was carcinogenic to F344 rats, causing both increased incidences of follicular-cell neoplasms of the thyroid gland and liver neoplasms.

D. Statistical Analyses of Results (Rats)

Tables 8 and 9 contain the statistical analysis 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.

The Cochran-Armitage test indicates significant dose-related trends (P less than 0.001) in the incidence of animals with follicular-cell adenomas or carcinomas in the thyroid of both sexes. The incidences in the mid- and the high-dose groups of either sex are significantly higher (P less than 0.001) than in the control group. The historical incidence in the bioassay program is 25/2,230 (1.1%) in male F344 rats and 12/2,194 (less than 1%) in females as compared with the incidences of the control group (2% in male F344 rats and 4% in female F344 rats) which were observed in this study.

In male rats, the Cochran-Armitage test indicates a significant positive trend (P less than 0.001) in the incidence of animals with hepatocellular carcinomas or neoplastic nodules and a departure from linear trend due to

sharp increases in the two higher dosed groups. The incidences in all the dosed groups were significantly higher (P less than 0.001) than the incidence in the control group. The historical incidence in the bioassay program, accumulated to date, in male F344 rats with these types of tumors from all laboratories, is 26/2,230 (1.2%). This incidence is comparable with the 1/50 (2%) observed in this control group. In female rats, a significant positive trend (P less than 0.001) in the incidence of animals with neoplastic nodules or hepatocellular carcinomas was observed. The incidences in the high-dose group and mid-dose group were significantly higher (P less than 0.001) than the incidence in the controls. The historical incidence in the bioassay program, accumulated to date, in female F344 rats with these types of tumors is 25/2,194 (less than 1%).

In male rats, the incidence of leukemias occurs with a negative trend (P less than 0.001) with significantly lower incidence (P less than 0.001) in each of the dosed groups than in the control group. For male F344 rats, the historical incidence accumulated from all laboratories is lower (235/2,230 or 10%) than the incidence in the control group of male rats (23/50 or 46%) observed in this study. In females, the Cochran-Armitage test indicates a significant negative trend (P=0.019) as a result of lower incidence (P=0.028) in the high-dose group than in the control group. This may be a consequence of the early mortality observed in the high-dose group females.

A negative trend (P less than 0.001) and a significantly lower incidence (P less than 0.030) of fibroadenomas in the mammary gland of the dosed groups were observed in female rats. The control group incidence of 16/50 (32%) is almost double the historical incidence of 378/2,194 (17%) for this type of lesion.

The incidences of female rats with endometrial stromal polyps or sarcomas of the uterus and tumors of the pituitary are lower in the high-dose group than in the control group. These results may have been affected by the shortened survival in the high-dose group.

The statistical analyses indicate that the occurrence of liver and thyroid tumors in both sexes of rats is related to the administration of 4,4'-oxydianiline.

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing 4,4'-Oxydianiline (a)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Integumentary System:				
Fibroma (b)	1/50 (2)	3/50 (6)	2/50 (4)	0/50 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.000	2.000	0.000
Lower Limit		0.251	0.108	0.000
Upper Limit		154.270	115.621	18.658
Weeks to First Observed Tumor	80	93	105	—
Integumentary System:				
Fibroma or Fibrosarcoma (b)	1/50 (2)	3/50 (6)	3/50 (6)	0/50 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.000	3.000	0.000
Lower Limit		0.251	0.251	0.000
Upper Limit		154.270	154.270	18.658
Weeks to First Observed Tumor	80	93	91	—
Lung: Alveolar/Bronchiolar				
Adenoma or Carcinoma (b)	1/50 (2)	0/50 (0)	1/50 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	1.000	3.000
Lower Limit		0.000	0.013	0.251
Upper Limit		18.658	76.970	154.270
Weeks to First Observed Tumor	106	—	89	105
Hematopoietic System:				
Monocytic Leukemia (b)	23/50 (46)	3/50 (6)	3/50 (6)	2/50 (4)
P Values (c,d)	P less than 0.001(N)	P less than 0.001(N)	P less than 0.001(N)	P less than 0.001(N)
Departure from Linear Trend (f)	P=0.001			
Relative Risk (Matched Control) (e)		0.130	0.130	0.087
Lower Limit		0.027	0.027	0.011
Upper Limit		0.393	0.393	0.323
Weeks to First Observed Tumor	9	99	80	84

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System: All Leukemias (b)	23/50 (46)	3/50 (6)	3/50 (6)	2/50 (4)
P Values (c,d)	P less than 0.001(N)	P less than 0.001 (N)	P less than 0.001(N)	P less than 0.001(N)
Departure from Linear Trend (f)	P=0.001			
Relative Risk (Matched Control) (e)		0.130	0.130	0.087
Lower Limit		0.027	0.027	0.011
Upper Limit		0.393	0.393	0.323
Weeks to First Observed Tumor	9	99	80	84
Hematopoietic System: Malignant Lymphoma, NOS (b)	3/50 (6)	1/50 (2)	1/50 (2)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.333	0.333	0.333
Lower Limit		0.006	0.006	0.006
Upper Limit		3.983	3.983	3.983
Weeks to First Observed Tumor	102	69	55	105
Hematopoietic System: All Lymphomas (b)	4/50 (8)	1/50 (2)	1/50 (2)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.250	0.250	0.250
Lower Limit		0.005	0.005	0.005
Upper Limit		2.411	2.411	2.411
Weeks to First Observed Tumor	40	69	55	105
Hematopoietic System: Leukemia or Lymphoma (b)	27/50 (54)	4/50 (8)	4/50 (8)	3/50 (6)
P Values (c,d)	P less than 0.001(N)	P less than 0.001 (N)	P less than 0.001(N)	P less than 0.001(N)
Departure from Linear Trend (f)	P less than 0.001			
Relative Risk (Matched Control) (e)		0.148	0.148	0.111
Lower Limit		0.042	0.042	0.024
Upper Limit		0.382	0.382	0.327
Weeks to First Observed Tumor	9	69	55	84

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	0/50 (0)	4/50 (8)	23/50 (46)	22/50 (44)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P less than 0.001
Relative Risk (Matched Control) (e)		Infinite	Infinite	Infinite
Lower Limit		0.927	7.515	7.163
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor		93	93	95
Liver: Neoplastic Nodule (b)	1/50 (2)	9/50 (18)	18/50 (36)	17/50 (34)
P Values (c,d)	P less than 0.001	P=0.008	P less than 0.001	P less than 0.001
Relative Risk (Matched Control) (e)		9.000	18.000	17.000
Lower Limit		1.323	3.047	2.853
Upper Limit		385.071	726.973	689.570
Weeks to First Observed Tumor	88	100	81	81
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	1/50 (2)	13/50 (26)	41/50 (82)	39/50 (78)
P Values (c,d)	P less than 0.001	P less than 0.001	P less than 0.001	P less than 0.001
Departure from Linear Trend (f)	P=0.035			
Relative Risk (Matched Control) (e)		13.000	41.000	39.000
Lower Limit		2.082	7.882	7.393
Upper Limit		538.016	1478.154	1438.733
Weeks to First Observed Tumor	88	93	81	81
Pituitary: Adenoma, NOS (b)	15/44 (34)	15/43 (35)	21/41 (51)	19/43 (44)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.023	1.502	1.296
Lower Limit		0.536	0.864	0.725
Upper Limit		1.950	2.632	2.344
Weeks to First Observed Tumor	84	89	62	81

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Adrenal: Pheochromocytoma (b)	4/50 (8)	3/50 (6)	0/50 (0)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.750	0.000	1.000
Lower Limit		0.115	0.000	0.197
Upper Limit		4.206	1.079	5.083
Weeks to First Observed Tumor	106	95	--	105
Thyroid: Follicular-cell Adenoma (b)	1/46 (2)	1/47 (2)	8/46 (17)	13/50 (26)
P Values (c,d)	P less than 0.001	N.S.	P=0.015	P=0.001
Relative Risk (Matched Control) (e)		0.979	8.000	11.960
Lower Limit		0.013	1.142	1.922
Upper Limit		75.209	345.960	494.891
Weeks to First Observed Tumor	106	105	80	78
Thyroid: Follicular-cell Carcinoma (b)	0/46 (0)	5/47 (11)	9/46 (20)	15/50 (30)
P Values (c,d)	P less than 0.001	P=0.030	P=0.001	P less than 0.001
Relative Risk (Matched Control) (e)		Infinite	Infinite	Infinite
Lower Limit		1.238	2.637	4.344
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	100	93	95
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	1/46 (2)	6/47 (13)	17/46 (37)	28/50 (56)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P less than 0.001
Relative Risk (Matched Control) (e)		5.872	17.000	25.760
Lower Limit		0.755	2.872	4.642
Upper Limit		263.721	686.600	1006.470
Weeks to First Observed Tumor	106	100	80	78

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Thyroid: C-cell Adenoma (b)	3/46 (7)	4/47 (9)	2/46 (4)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.305	0.667	0.920
Lower Limit		0.234	0.058	0.129
Upper Limit		8.469	5.548	6.556
Weeks to First Observed Tumor	84	93	105	81
Thyroid: C-cell Carcinoma (b)	2/46 (4)	1/47 (2)	1/46 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.489	0.500	1.380
Lower Limit		0.008	0.009	0.166
Upper Limit		9.071	9.263	15.934
Weeks to First Observed Tumor	106	106	105	101
Thyroid: C-cell Adenoma or Carcinoma (b)	5/46 (11)	5/47 (11)	3/46 (7)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.979	0.600	1.104
Lower Limit		0.241	0.098	0.302
Upper Limit		3.976	2.895	4.280
Weeks to First Observed Tumor	84	93	105	81
Preputial Gland: Adenoma, NOS (b)	1/50 (2)	3/50 (6)	0/50 (0)	1/50 (2)
P Values (c,d)	N.S	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.000	0.000	1.000
Lower Limit		0.251	0.000	0.013
Upper Limit		154.270	18.658	76.970
Weeks to First Observed Tumor	106	106	--	105

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Testis: Interstitial-cell Tumor (b)	43/49 (88)	48/50 (96)	47/50 (94)	40/50 (80)
P Values (c,d)	N.S	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.026			
Relative Risk (Matched Control) (e)		1.094	1.071	0.912
Lower Limit		0.955	0.930	0.773
Upper Limit		1.181	1.187	1.107
Weeks to First Observed Tumor	74	69	71	81
Tunica Vaginalis: Mesothelioma (b)	1/50 (2)	3/50 (6)	2/50 (4)	1/50 (2)
P Value (c,d)	N.S	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.000	2.000	1.000
Lower Limit		0.251	0.108	0.013
Upper Limit		154.270	115.621	76.970
Weeks to First Observed Tumor	106	77	81	81

(a) Dosed groups received doses of 200, 400 or 500 ppm in the diet.
(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 the matched-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched-control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing 4,4'-Oxydianiline (a)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System: Monocytic Leukemia (b)	3/50 (6)	1/50 (2)	2/50 (4)	0/50 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.333	0.667	0.000
Lower Limit		0.006	0.058	0.000
Upper Limit		3.983	5.570	1.663
Weeks to First Observed Tumor	86	85	79	--
Hematopoietic System: Leukemia or Lymphoma (b)	5/50 (10)	2/50 (4)	2/50 (4)	0/50 (0)
P Values (c,d)	P=0.019(N)	N.S.	N.S.	P=0.028(N)
Relative Risk (Matched Control) (e)		0.400	0.400	0.000
Lower Limit		0.040	0.040	0.000
Upper Limit		2.313	2.313	0.793
Weeks to First Observed Tumor	70	6	79	--
Liver: Hepatocellular Carcinoma (b)	0/50 (0)	0/49 (0)	4/50 (8)	6/50 (12)
P Values (c,d)	P=0.002	N.S.	N.S.	P=0.013
Relative Risk (Matched Control) (e)		--	Infinite	Infinite
Lower Limit		--	0.927	1.600
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	100	101
Liver: Neoplastic Nodule (b)	3/50 (6)	0/49 (0)	20/50 (40)	11/50 (22)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P=0.020
Departure from Linear Trend (f)	P less than 0.001			
Relative Risk (Matched Control) (e)		0.000	6.667	3.667
Lower Limit		0.000	2.160	1.044
Upper Limit		1.696	32.688	19.363
Weeks to First Observed Tumor	106	—	85	89

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	3/50 (6)	0/49 (0)	24/50 (48)	17/50 (34)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P less than 0.001
Departure from Linear Trend (f)	P less than 0.001			
Relative Risk (Matched Control) (e)		0.000	8.000	5.667
Lower Limit		0.000	2.671	1.783
Upper Limit		1.696	38.375	28.309
Weeks to First Observed Tumor	106	—	85	89
Pituitary: Adenoma, NOS (b)	27/46 (59)	25/43(58)	26/43(60)	10/46 (22)
P Values (c,d)	P=0.003(N)	N.S.	N.S.	P less than 0.001(N)
Departure from Linear Trend (f)	P=0.004			
Relative Risk (Matched Control) (e)		0.991	1.030	0.370
Lower Limit		0.673	0.706	0.189
Upper Limit		1.448	1.491	0.684
Weeks to First Observed Tumor	87	86	83	76
Thyroid: Follicular-cell Adenoma (b)	0/49 (0)	2/48 (4)	17/48 (35)	16/50 (32)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P less than 0.001
Relative Risk (Matched Control) (e)		Infinite	Infinite	Infinite
Lower Limit		0.302	5.528	4.961
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	—	105	72	28
Thyroid: Follicular-cell Carcinoma (b)	0/49 (0)	2/48 (4)	12/48 (25)	7/50 (14)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P=0.007
Departure from Linear Trend (f)	P=0.035			
Relative Risk (Matched Control) (e)		Infinite	Infinite	Infinite
Lower Limit		0.302	3.747	1.903
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	—	100	104	97

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	0/49 (0)	4/48 (8)	29/48 (60)	23/50 (46)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001	P less than 0.001
Departure from Linear Trend (f)	P=0.002			
Relative Risk (Matched Control) (e)		Infinite	Infinite	Infinite
Lower Limit		0.947	9.877	7.370
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	100	72	28
Thyroid: C-cell Adenoma (b)	2/49 (4)	4/48 (8)	2/48 (4)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		2.042	1.021	0.980
Lower Limit		0.308	0.077	0.074
Upper Limit		21.726	13.585	13.058
Weeks to First Observed Tumor	106	94	105	105
Thyroid: C-cell Adenoma or Carcinoma (b)	2/49 (4)	4/48 (8)	3/48 (6)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		2.042	1.531	0.980
Lower Limit		0.308	0.183	0.074
Upper Limit		21.726	17.665	13.058
Weeks to First Observed Tumor	106	94	105	105
Mammary Gland: Fibroadenoma (b)	16/50 (32)	7/50 (14)	1/50 (2)	0/50 (0)
P Values (c,d)	P less than 0.001(N)	P=0.028 (N)	P less than 0.001(N)	P less than 0.001(N)
Relative Risk (Matched Control) (e)		0.438	0.063	0.000
Lower Limit		0.167	0.002	0.000
Upper Limit		1.018	0.376	0.198
Weeks to First Observed Tumor	87	86	103	--

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Clitoral Gland: Adenoma, NOS (b)	1/50 (2)	2/50 (4)	3/50 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		2.000	3.000	1.000
Lower Limit		0.108	0.251	0.013
Upper Limit		115.621	154.270	76.970
Weeks to First Observed Tumor	106	106	85	89
Uterus: Endometrial Stromal Polyp (b)	7/49 (14)	2/48 (4)	7/49 (14)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.	P=0.032(N)
Departure from Linear Trend (f)	P=0.048			
Relative Risk (Matched Control) (e)		0.292	1.000	0.146
Lower Limit		0.031	0.324	0.003
Upper Limit		1.438	3.091	1.072
Weeks to First Observed Tumor	100	95	88	105
Uterus: Endometrial Stromal Sarcoma (b)	0/49 (0)	3/48 (6)	1/49 (2)	0/48 (0)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.046			
Relative Risk (Matched Control) (e)		Infinite	Infinite	--
Lower Limit		0.614	0.054	--
Upper Limit		Infinite	Infinite	--
Weeks to First Observed Tumor	--	94	105	--
Uterus: Endometrial Stromal Polyp or Sarcoma (b)	7/49 (14)	5/48 (10)	7/49 (14)	1/48 (2)
P Values (c,d)	N.S.	N.S.	N.S.	P=0.032(N)
Relative Risk (Matched Control) (e)		0.729	1.000	0.146
Lower Limit		0.195	0.324	0.003
Upper Limit		2.478	3.091	1.072
Weeks to First Observed Tumor	100	94	88	105

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

(a) Dosed groups received doses of 200, 400 or 500 ppm in the diet.
(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 the matched-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched-control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

A dose-related depression in mean body weight gain was observed for all groups of dosed mice (Figure 3), and a compound-related increase in the number of mice with discharging, cloudy, or swollen eyes was also observed.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice fed diets containing 4,4'-oxydianiline at the doses of this bioassay, together with those for 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 mortality is not significant in either sex; the survival of the low- and mid-dose female groups was significantly less than that of the matched control group (P=0.028 and P=0.036, respectively).

In male mice, 35/50 (70%) of the matched-control group, 39/50 (78%) of the low-dose group, 33/49 (67%) of the mid-dose, and 34/50 (68%) of the high-dose group were alive at the end of the bioassay at 105 to 106 weeks. In females, 42/50 (82%) of the control group, 33/50 (66%) of the low-dose and mid-dose groups, and 42/50 (84%) of the high-dose group lived to the end of the bioassay.

Sufficient numbers of animals in all groups were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

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

A variety of neoplasms were seen in control and treated mice. Neoplasms or lesions associated with 4,4'-oxydianiline administration were hepatocellular neoplasms (Table 10), adenomas of the harderian gland, and proliferative lesions of the thyroid gland.

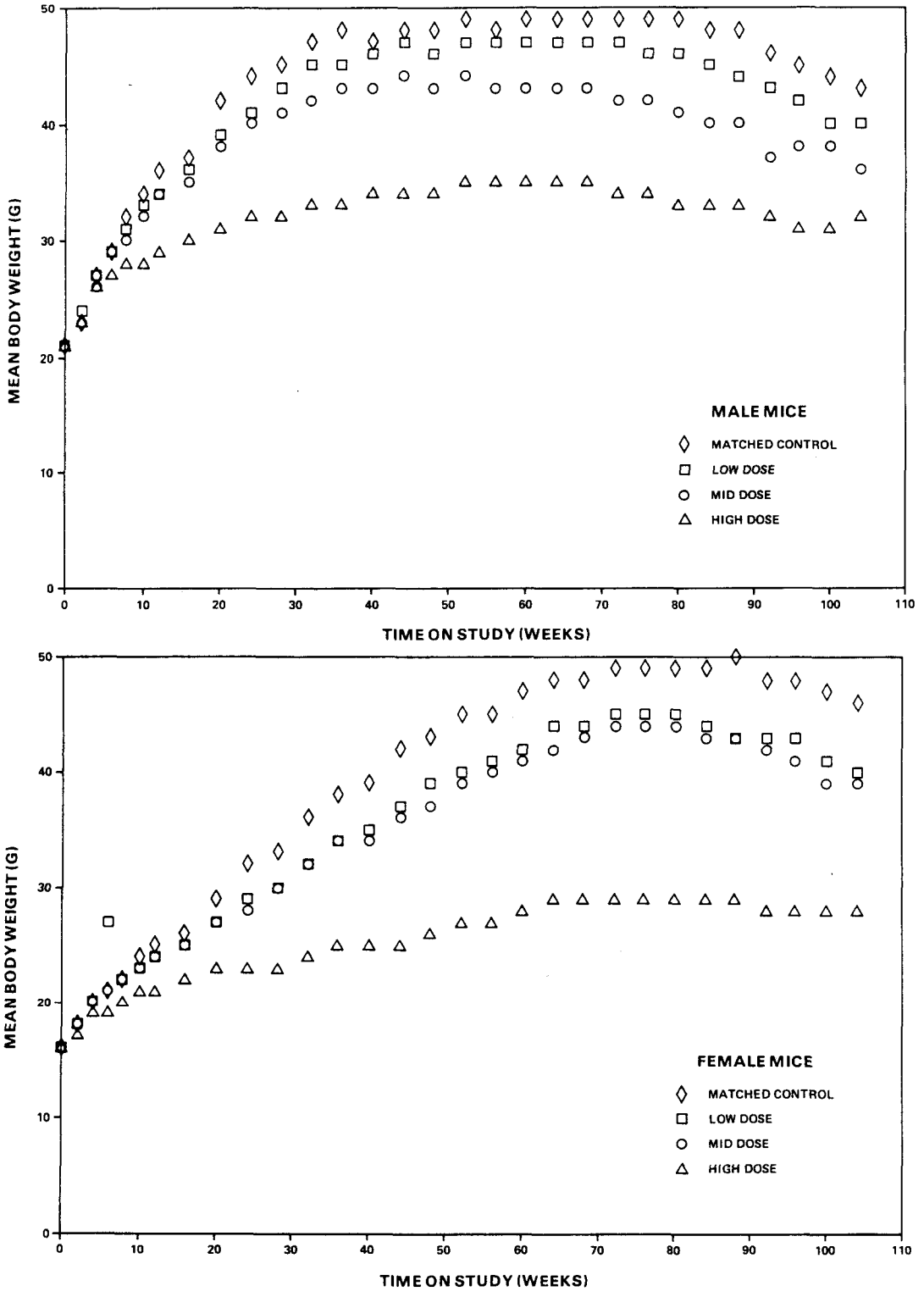


Figure 3. Growth Curves For Mice Administered 4, 4'-Oxydianiline in the Diet

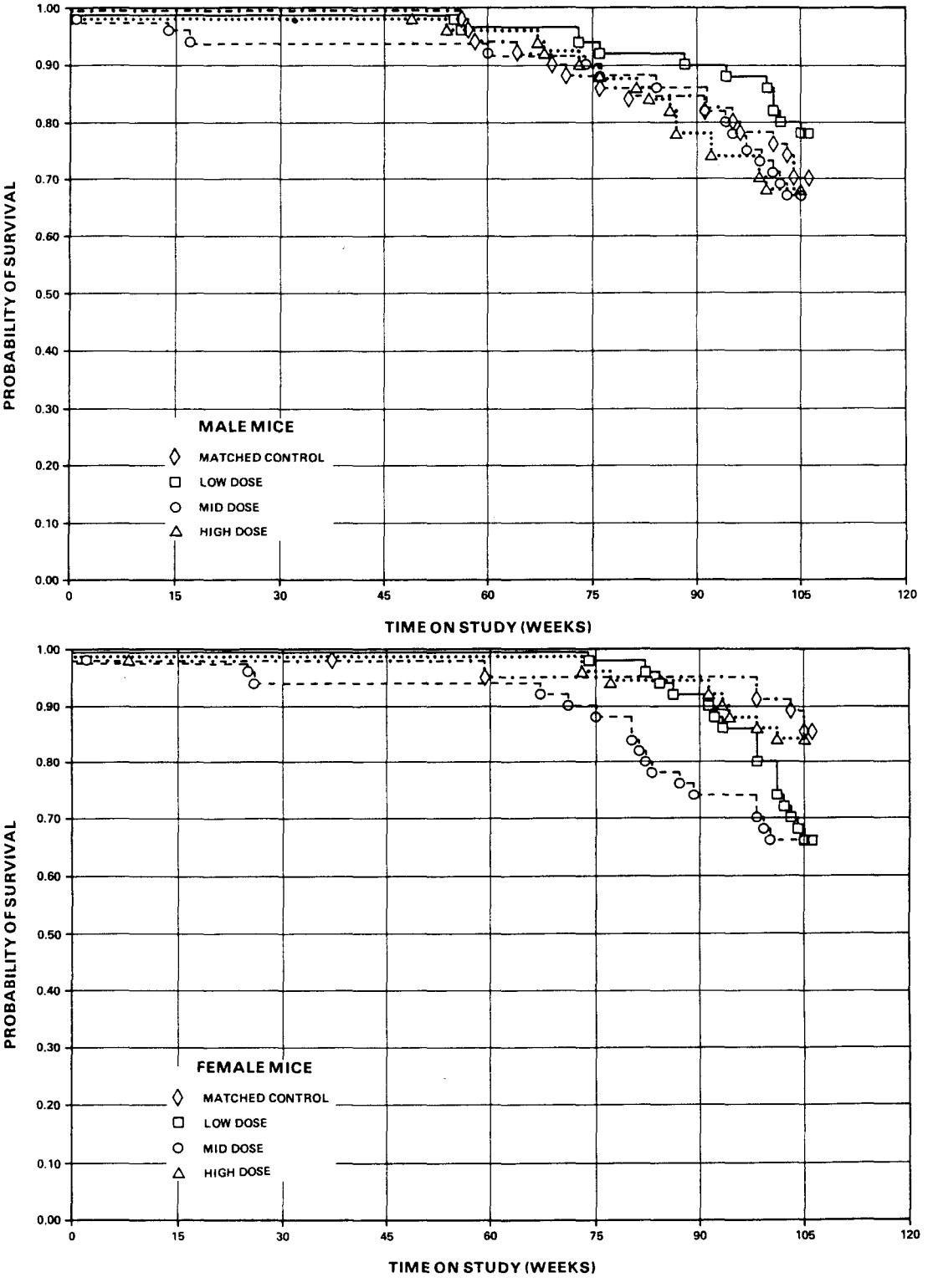


Figure 4. Survival Curves For Mice Administered 4, 4'-Oxydianiline in the Diet

Table 10. Numbers of Mice with Hepatocellular Adenomas or Carcinomas

	MALES				FEMALES			
	Control	Low-Dose	Mid-Dose	High-Dose	Control	Low-Dose	Mid-Dose	High-Dose
Number of Livers Examined	50	50	49	50	50	49	48	50
Hepatocellular:								
Adenoma	11	13	11	10	4	6	9	14
Carcinoma	18	27	23	26	4	7	6	15

Hepatocellular adenomas compressed the adjacent tissue. Cells in the adenomas were large and usually acidophilic. Nuclei were hyperchromatic. Mitotic figures were not numerous. Hepatocellular carcinomas involved a part or an entire lobe of the liver. The lobular architecture was not maintained. Cell plates were two or more cells thick. A pleomorphism in the size of cells was seen, and cytoplasmic inclusions were present in some cells. The nuclei had coarse chromatin, and nucleoli were predominant. An occasional multinucleated cell was noticed. Both normal and abnormal mitotic figures were sometimes numerous.

Markedly distended sinusoids and cavernous vascular spaces were present in a few tumors. The cells lining such vascular channels were fusiform and occasionally spherical. Cytoplasm of these cells was inconspicuous, and the nuclei were hyperchromatic. Islands of neoplastic hepatocytes were encircled by fusiform cells, and these tumors were diagnosed as hemangiomas or hemangiosarcomas.

Areas of necrosis and hemorrhage were common in the large tumors. The hepatocellular carcinomas had metastasized to the lung in 12 male mice (control, 2; low-dose, 4; mid-dose, 5; high-dose, 1) and in none of the female mice. Toxic, nonneoplastic hepatic lesions were not seen in dosed mice.

Adenomas of the harderian gland were found in 1/50 control males, 17/50 low-dose males, 13/49 mid-dose males, 17/50 high-dose males, 2/50 control

females, 15/50 low-dose females, 14/50 mid-dose females, and 12/50 high-dose females. The harderian gland was histologically evaluated only when it was enlarged. Adenomas of the harderian gland involved either a part or an entire gland and were characterized either as a papillary ingrowth of the epithelium into the lumen of the distended acini or as a solid sheet of cells. These cells were columnar, and they contrasted with the cuboidal cells in the normal gland. Cytoplasm of the cells had fine vacuoles, and nuclei were of uniform size and hyperchromatic. Mitotic figures were numerous. Porphyrin pigment was not found in any of these tumors. Clusters of inflammatory cells were scattered around the gland.

In high-dose mice, follicular-cell hyperplasia of the thyroid gland occurred in 26/49 males and 25/48 females. Adenomas were found in 2/47 mid-dose males, 2/49 high-dose males, and 7/48 high-dose females. A diffuse enlargement of the follicles or irregular papillary ingrowth of the epithelium was considered to be follicular hyperplasia. The epithelial cells were cuboidal, and the nuclei were hyperchromatic. The adenoma compressed the adjacent tissue. Follicular arrangement of the cells was maintained and cells were columnar or cuboidal. Cytoplasm of the cells was basophilic or eosinophilic, and nuclei were hyperchromatic.

Other nonneoplastic lesions occurred both in control and treated mice, but none of them appeared to be treatment related.

Under the conditions of this bioassay, 4,4'-oxydianiline was found to be carcinogenic to B6C3F1 mice, causing an increased incidence of neoplasms of liver, harderian gland, and thyroid gland.

D. Statistical Analyses of Results (Mice)

Tables 11 and 12 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 mice, the Fisher exact test shows that the combined incidence of animals with hepatocellular adenomas or carcinomas is significantly higher in the low-dose group than in the controls (P=0.015). For the bioassay program, the historical incidence of male B6C3F1 mice with these tumors is

651/2,843 (23%), which is lower than the mid- and high-dose group incidences of 34/49 (69%) and 36/50 (72%), respectively.

In female mice, a significant positive linear trend is observed (P less than 0.001) in relation to increasing dose in the incidence of animals with hepatocellular adenomas or carcinomas. The incidence in the high-dose group is also significantly higher (P less than 0.001) than that of the controls.

In male mice, a significant positive linear trend (P=0.004) was observed in the incidence of animals with adenomas, NOS (not otherwise specified), in the harderian glands. The incidences in all dosed groups were significantly higher (P less than 0.001) than the incidence in the control group. A departure from the linear trend is indicated due to a higher incidence (34%) in the low-dose group compared with the mid-dose group (27%). To date, the historical incidence from all laboratories in the bioassay program for male B6C3F1 mice with this type of tumor is 8/2,843 (0.2%).

In female mice, the Fisher exact test shows that the incidence of adenomas, NOS, in the harderian gland is significantly higher (P less than 0.005 in all dosed groups) than that in the control group. A departure from linear trend was observed due to the higher incidence in the low-dose group than in the other dosed groups. The historical incidence among female B6C3F1 mice for this kind of tumor is 9/2,917 (0.3%). This figure is lower than the 2/50 (4%) reported in the controls in this study.

In female mice, a positive linear trend (P less than 0.001) is indicated in the incidence of animals with follicular-cell adenomas in the thyroid. The incidence in the high-dose group is significantly higher (P=0.007) than in the controls. The incidence observed in the control group of this study (0%) is not significantly different from the historical incidence of 32/2,917 (1%) in the bioassay program's accumulated data.

In male mice, there is a positive linear trend (P=0.001) in the incidence of adenomas, NOS, in the pituitary. The incidence in the high-dose group is higher than that in the controls, but the P=0.023 observed is above the P=0.017 level required for significance when the Bonferroni inequality criterion is used to assess the comparison of three dosed groups with a single control group.

In male mice, the Cochran-Armitage test indicates a significant dose-related trend (P=0.011) in the incidence of hemangiomas of the circulatory

ystem. The incidences in the mid- and high-dose groups are also h
han in the control group; but the significance levels observed in t
roups do not meet the significance level required (P less than 0.017
he Bonferroni inequality criterion is applied.

In male mice, a negative trend is indicated (P=0.015) for the incid
of animals with alveolar/bronchiolar adenomas or carcinomas in the lun
egative trend with significantly lower incidence in the high-dose grou
lso observed in the incidence of malignant lymphomas in the hematopoi
ystem of both sexes.

The statistical analyses indicate that the occurrences of tumors in
arderian gland of male and female mice are related to the administratio
,4'-oxydianiline. There is also an association with liver tumors in
exes and with thyroid tumors in females.

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing 4,4'-Oxydianiline (a)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	8/50 (16)	9/50 (18)	7/49 (14)	2/49 (4)
P Values (c,d)	P=0.027(N)	N.S.	N.S.	P=0.049 (N)
Relative Risk (Matched Control) (e)		1.125	0.893	0.255
Lower Limit		0.420	0.298	0.027
Upper Limit		3.079	2.598	1.198
Weeks to First Observed Tumor	95	105	105	105
Lung: Alveolar/Bronchiolar Carcinoma (b)	6/50 (12)	1/50 (2)	1/49 (2)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.167	0.170	0.340
Lower Limit		0.004	0.004	0.035
Upper Limit		1.302	1.328	1.793
Weeks to First Observed Tumor	106	105	105	99
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	13/50 (26)	10/50 (20)	8/49 (16)	4/49 (8)
P Values (c,d)	P=0.015(N)	N.S.	N.S.	P=0.017(N)
Relative Risk (Matched Control) (e)		0.769	0.628	0.314
Lower Limit		0.334	0.248	0.080
Upper Limit		1.715	1.482	0.935
Weeks to First Observed Tumor	95	105	105	99
Hematopoietic System: Malignant Lymphoma, NOS (b)	9/50 (18)	5/50 (10)	5/49 (10)	2/50 (4)
P Values (c,d)	P=0.030(N)	N.S.	N.S.	P=0.026(N)
Relative Risk (Matched Control) (e)		0.556	0.567	0.222
Lower Limit		0.157	0.160	0.024
Upper Limit		1.708	1.741	1.005
Weeks to First Observed Tumor	80	88	91	105

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Circulatory System:				
Hemangioma (b)	0/50 (0)	0/50 (0)	5/49 (10)	5/50 (10)
P Values (c,d)	P=0.011	N.S.	P=0.027	P=0.028
Relative Risk (Matched Control) (e)		--	Infinite	Infinite
Lower Limit		--	1.287	1.261
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	17	81
Circulatory System:				
Hemangioma or Hemangiosarcoma (b)	2/50 (4)	1/50 (2)	5/49 (10)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.500	2.551	2.500
Lower Limit		0.009	0.441	0.432
Upper Limit		9.290	25.786	25.286
Weeks to First Observed Tumor	71	101	17	81
Circulatory System:				
Angiosarcoma (b)	2/50 (4)	0/50 (0)	3/49 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	1.531	0.500
Lower Limit		0.000	0.183	0.009
Upper Limit		3.381	17.671	9.290
Weeks to First Observed Tumor	106	--	105	92
Liver: Hepatocellular				
Adenoma (b)	11/50 (22)	13/50 (26)	11/49 (22)	10/50 (20)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.182	1.020	0.909
Lower Limit		0.542	0.443	0.381
Upper Limit		2.626	2.347	2.140
Weeks to First Observed Tumor	106	73	84	92

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	18/50 (36)	27/50 (54)	23/49 (47)	26/50 (52)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.500	1.304	1.444
Lower Limit		0.926	0.778	0.885
Upper Limit		2.454	2.202	2.384
Weeks to First Observed Tumor	57	76	76	73
Liver: Hepatocellular Adenoma or Carcinoma (b)	29/50 (58)	40/50 (80)	34/49 (69)	36/50 (72)
P Values (c,d)	N.S.	P=0.015	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.379	1.196	1.241
Lower Limit		1.029	0.862	0.903
Upper Limit		1.792	1.641	1.682
Weeks to First Observed Tumor	57	73	76	73
Pituitary: Adenoma, NOS (b)	1/37 (3)	0/44 (0)	0/34 (0)	7/35 (20)
P Values (c,d)	P less than 0.001	N.S.	N.S.	P=0.023
Relative Risk (Matched Control) (e)		0.000	0.000	7.400
Lower Limit		0.000	0.000	1.027
Upper Limit		15.655	20.126	321.915
Weeks to First Observed Tumor	106	--	--	87
Harderian Gland: Adenoma, NOS (b)	1/50 (2)	17/50 (34)	13/49 (27)	17/50 (34)
P Values (c,d)	P=0.004	P less than 0.001	P less than 0.001	P less than 0.001
Departure from Linear Trend (f)	P=0.004			
Relative Risk (Matched Control)(e)		17.000	13.265	17.000
Lower Limit		2.853	2.126	2.853
Upper Limit		689.570	548.394	689.570
Weeks to First Observed Tumor	106	101	91	73

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

(a) Dosed groups received doses of 150, 300, or 800 ppm in the diet.
(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 the matched-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched-control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 12. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing 4,4'-Oxydianiline (a)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	5/50 (10)	3/49 (6)	7/50 (14)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.612	1.400	0.400
Lower Limit		0.100	0.411	0.040
Upper Limit		2.967	5.236	2.313
Weeks to First Observed Tumor	105	106	80	105
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/50 (0)	2/49 (4)	3/50 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		Infinite	Infinite	Infinite
Lower Limit		0.302	0.601	0.054
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	98	98	77
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	5/50 (10)	5/49 (10)	10/50 (20)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.020	2.000	0.600
Lower Limit		0.250	0.675	0.098
Upper Limit		4.161	6.944	2.910
Weeks to First Observed Tumor	105	98	80	77
Hematopoietic System: Malignant Lymphoma (b)	14/50 (28)	7/50 (14)	13/50 (26)	2/50 (4)
P Values (c,d)	P=0.004(N)	N.S.	N.S.	P=0.001(N)
Relative Risk (Matched Control) (e)		0.500	0.929	0.143
Lower Limit		0.187	0.450	0.016
Upper Limit		1.203	1.904	0.578
Weeks to First Observed Tumor	37	98	67	93

Table 12. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System:				
All Lymphomas (b)	15/50 (30)	7/50 (14)	14/50 (28)	3/50 (6)
P Values (c,d)		P=0.045 (N)	N.S.	P=0.002 (N)
Relative Risk (Matched Control) (e)		0.467	0.933	0.200
Lower Limit		0.177	0.469	0.039
Upper Limit		1.103	1.845	0.652
Weeks to First Observed Tumor	37	98	67	93
Liver: Hepatocellular Adenoma (b)	4/50 (8)	6/49 (12)	9/48 (19)	14/50 (28)
P Values (c,d)	P=0.004	N.S.	N.S.	P=0.009
Relative Risk (Matched Control) (e)		1.531	2.344	3.500
Lower Limit		0.387	0.706	1.196
Upper Limit		6.952	9.763	13.617
Weeks to First Observed Tumor	106	106	105	77
Liver: Hepatocellular Carcinoma (b)	4/50 (8)	7/49 (14)	6/48 (13)	15/50 (30)
P Values (c,d)	P=0.002	N.S.	N.S.	P=0.005
Relative Risk (Matched Control) (e)		1.786	1.563	3.750
Lower Limit		0.486	0.396	1.302
Upper Limit		7.830	7.090	14.451
Weeks to First Observed Tumor	106	74	87	94
Liver: Hepatocellular Adenoma or Carcinoma (b)	8/50 (16)	13/49 (27)	15/48 (31)	29/50 (58)
P Values (c,d)	P less than 0.001	N.S.	N.S.	P less than 0.001
Relative Risk (Matched Control) (e)		1.658	1.953	3.625
Lower Limit		0.702	0.861	1.838
Upper Limit		4.197	4.806	7.948
Weeks to First Observed Tumor	106	74	87	77

Table 12. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing 4,4'-Oxydianiline (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Pituitary: Adenoma, NOS (b)	2/42 (5)	4/42 (10)	4/41 (10)	2/36 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		2.000	2.049	1.167
Lower Limit		0.304	0.312	0.088
Upper Limit		21.153	21.648	15.347
Weeks to First Observed Tumor	106	101	105	105
Thyroid: Follicular-cell Adenoma (b)	0/46 (0)	0/43 (0)	0/42 (0)	7/48 (15)
P Values (c,d)	P less than 0.001	N.S.	N.S.	P=0.007
Relative Risk (Matched Control) (e)		--	--	Infinite
Lower Limit		--	--	1.865
Upper Limit		--	--	Infinite
Weeks to First Observed Tumor	--	--	--	98
Harderian Gland: Adenoma, NOS (b)	2/50 (4)	15/50 (30)	14/50 (28)	12/50 (24)
P Values (c,d)	N.S.	P less than 0.001	P=0.001	P=0.004
Departure from Linear Trend (f)	P=0.005			
Relative Risk (Matched Control) (e)		7.500	7.000	6.000
Lower Limit		1.880	1.730	1.434
Upper Limit		64.479	60.610	52.834
Weeks to First Observed Tumor	106	101	80	98

(a) Dosed groups received doses of 150, 300, or 800 ppm in the diet.
(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 the matched-control group.
(e) The 95% confidence interval of the relative risk between each dosed group and the matched-control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

V. DISCUSSION

A dose-related decrement in mean body weight gain was observed for all groups of dosed rats and mice. Survival was significantly shortened in the high-dose female rats (P less than 0.001) and in the low- and mid-dose female mice (P=0.028 and P=0.036, respectively).

Hepatocellular carcinomas or neoplastic nodules occurred in male rats at incidences that were dose-related (P less than 0.001), and the incidences in all dosed groups were higher (P less than 0.01) than in the corresponding control groups. In female rats, hepatocellular carcinomas or neoplastic nodules occurred at incidences that were dose-related, and the incidences in the mid-dose and high-dose groups were significantly higher (P less than 0.001) than those in the controls. The liver was reported as a target organ by Steinoff (1977), who administered 4,4'-oxydianiline in saline to 20 male and 20 female Wistar rats subcutaneously, once per week for 670 days. Fifty rats receiving injections of saline alone for 970 days served as controls. Twenty-five percent (10/40) of the dosed rats had malignant liver tumors and 30% (12/40) had benign liver tumors as compared with 0% among the 50 control rats.

Follicular-cell adenomas or carcinomas of the thyroid occurred at dose-related incidences in male and female rats, and the incidences in the mid- and high-dose group of either sex were significantly higher (P less than 0.001) than those in the corresponding control groups.

Adenomas, NOS, in harderian glands occurred in male mice with a positive trend that was significant (P=0.004), and the incidences in all dosed groups were significantly higher (P less than 0.001) than the incidence in the control group. This same type of neoplasm occurred in all dosed groups of females at incidences that were significantly higher (P less than 0.005) than those in the controls.

Hepatocellular adenomas or carcinomas in low-dose male mice occurred with an incidence that was significantly higher (P=0.015) than that found in the controls. In female mice, these kinds of tumors occurred with a dose-related trend that was significant (P less than 0.001), and the incidence in

the high-dose group was significantly higher (P less than 0.001) than that of the controls.

Follicular-cell adenomas in the thyroid occurred with a positive linear trend (P less than 0.001) in female mice, and the incidence in the high-dose group was also significantly higher (P=0.007) than that in the controls.

Adenomas, NOS, in the pituitary occurred in male mice with a positive linear trend (P=0.001), and the incidence in the high-dose group was higher (P=0.023) than in the controls; however, P=0.023 is above the level of significance required when the Bonferroni inequality criterion is used to compare three dosed groups with a single control group.

Hemangiomas of the circulatory system occurred in male mice with a dose-related trend that was significant (P=0.011). Incidences in the mid- and high-dose groups were significantly higher (P=0.027 and P=0.028, respectively) than in the controls; however, P=0.027 and P=0.028 are above the level of significance required when the Bonferroni inequality criterion is used.

Malignant lymphomas in the hematopoietic system occurred with a negative trend in both male and female mice, and the incidences in the high-dose groups were significantly lower (P=0.026 for males and P=0.001 for females) than those in the corresponding controls.

Goitrogenic effects of 4,4'-oxydianiline were observed for rats and mice of either sex in the 90-day subchronic study. Other studies have shown that administration of antithyroid compounds to rats or mice causes enlargement of the thyroid gland and that rats or mice receiving antithyroid compounds may develop benign and cancerous tumors of the thyroid gland (Griesbach et al., 1945; Dalton et al., 1945; and Seifter et al., 1949). In the present chronic study, administration of 4,4'-oxydianiline led to increased incidence of follicular-cell adenomas or carcinomas of the thyroid in male and female rats and in female mice and to follicular-cell hyperplasias of the thyroid in male and female mice.

The goitrogenic and carcinogenic effects of 4,4'-oxydianiline may be related to the structural similarity between the test compound and thyroxin. Nuclear binding sites for thyroxin have been demonstrated in the rat liver and pituitary (Oppenheimer, 1979). The sulfur analog of 4,4'-oxydianiline, 4,4'-thiodianiline, was previously found to be carcinogenic for F344 rats

and B6C3F1 mice in another study conducted under the protocols of the Carcinogenesis Testing Program (NCI, 1978). 4,4'-Thiodianiline induced tumors in the liver, colon, and ear canal of male rats, in the thyroid, uterus, and ear canal of female rats, and in the liver and thyroid of both male and female mice.

DuPont (1978) communicated the results of a study of 4,4'- oxydianiline carried out in their Haskell Laboratory. Groups of 60 rats (unspecified strain) of each sex were fed diets containing 0, 200, or 400 ppm 4,4'-oxydianiline for 2 years. Among female rats fed 400 ppm 4,4'-oxydianiline, the incidence of uterine carcinoma was higher than that in the controls (9/59 compared with 2/58). Among male rats fed 200 or 400 ppm, the incidence of interstitial-cell testicular tumors was higher than in the controls (6/56 at 400 ppm compared with 1/55 in the controls). Uterine tumors are commonly observed in aging female F344 rats, as are testicular tumors in aging male F344 rats (Gart et al., 1979). In the tests reported here, a decreased incidence of endometrial stromal polyps or sarcomas of the uterus ($P=0.032$) was found in high-dose female rats when compared with the control group. These decreased incidences may be a consequence of the early mortality of that group.

VI. CONCLUSION

Under the conditions of this bioassay, 4,4'-oxydianiline was carcinogenic for male and female F344 rats, inducing hepatocellular carcinomas or neoplastic nodules and follicular-cell adenomas or carcinomas of the thyroid. 4,4'-Oxydianiline was also carcinogenic for male and female B6C3F1 mice, inducing adenomas, NOS, in the harderian glands and hepatocellular adenomas or carcinomas. 4,4'-Oxydianiline also induced follicular-cell adenomas of the thyroid in female mice.

VII. BIBLIOGRAPHY

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.

Chemical & Engineering News, July 30, 1973, p. 16.

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.

Dalton, A. J., Morris, H. P., and Dubnik, C. S., Morphologic changes in the organs of female C3H mice after long-term ingestion of thiourea and thiouracil. J. Natl. Cancer Inst. 9:201-223, 1945.

DuPont, Personal communication from P. M. Humanick at E. I. DuPont de Nemours & Co., Deepwater, N. J. to Tracor Jitco Inc. and other purchasers of 4,4'-oxydianiline, 13 September 1974.

DuPont, Product description, E. I. DuPont de Nemours & Co., Wilmington, Del., 13 September 1978.

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.

Gart, J., Chu, K., and Tarone, R., Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957, 1979.

Griesbach, W. E., Kennedy, T. H., and Purves, H. D., Studies on experimental goitre. VI. Thyroid adenomata in rats on Brassica seed diet. Br. J. Exp. Pathol., 26:18-24, 1945.

International Agency for Research on Cancer, 4,4'-Diaminodiphenyl ether. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Aromatic Amines and Related Nitro Compounds - Hair dyes, Colouring Agents and Miscellaneous Industrial Chemicals, Vol. 16, World Health Organization, Geneva, 1978, pp. 301-308.

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

Lapik, A. S., Makarenko, A. A. and Zimina, L. N., Toxicologic characteristics of 4,4'-diaminodiphenyl ether. Hygiene and Sanitation 33:137-138, 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.

Melick, W. J., Escue, H. M., Naryka, J. J., Mezera, R. A., and Wheeler, E. P., The first reported cases of human bladder tumors due to a new carcinogen - xenylamine. J. Urol. 74(6):760-766, 1955.

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

Midwest Research Institute, Analytical Report, 4,4'-Oxydianiline, Midwest Research Institute, Kansas City, Mo., 8 April 1975.

NCI, National Cancer Institute, Bioassay of 4,4'-Thiodianiline for Possible Carcinogenicity. TR 47, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md., 1978.

Oppenheimer, J. H., Thyroid hormone action at the cellular level. Sci. 203:971, 1979.

Reynolds, G. A., Tetramethyldiaminodiphenyl ether. J. Am. Chem. Soc. 73:4996, 1951.

Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pa., IR No. 46244.

Sadtler Standard Spectra (a), Sadtler Research Laboratories, Philadelphia, Pa., NMR No. 19057.

Seifter, J., Ehrick, W. E., and Hudyma, G. M., Effects of prolonged administration of antithyroid compounds on the thyroid and other endocrine organs of the rat. Arch. Pathol. 48:536-547, 1949.

Seymour, R. B., Plastics Technology. In: Kirk, R. E. and Othmer, D. F., eds. Encyclopedia of Chemical Technology, 2nd edition, Vol. 15, Interscience Publishers, 1968, p. 796.

Shimizu, H. and Takemura, N., Mutagenicity of some aromatic amino compounds and nitro compounds, and its relation to carcinogenicity. Sangyo Igaku 18(2):138-139, 1976.

Steinhoff, D., Cancerogene Wirkung Von 4,4'-Diamino-diphenylather bei Ratten. Naturwissenschaften 64:394, 1977.

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

Ward, J. M., Goodman, D. G., Griesemer, R. A., Hardisty, J. F., Schueler, R. L., Squire, R. A., and Strandberg, J. D., Quality assurance for pathology in rodent carcinogenesis tests. J. Environ. Pathol. Toxicol. 2:371-378, 1978.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED 4,4'-OXYDIANILINE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	2 (4%)	2 (4%)		
SQUAMOUS CELL CARCINOMA		1 (2%)		
BASAL-CELL CARCINOMA	2 (4%)	1 (2%)		
SEBACEOUS ADENOMA				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
BASAL-CELL CARCINOMA	1 (2%)			
SARCOMA, NOS	1 (2%)			1 (2%)
FIBROMA	1 (2%)	3 (6%)	2 (4%)	
FIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
NEOPLASM, NOS, METASTATIC				1 (2%)
CARCINOMA, NOS, METASTATIC			2 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
SARCOMA, NOS, METASTATIC	1 (2%)		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	3 (6%)	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)			
MONOCYTIC LEUKEMIA	23 (46%)	3 (6%)	3 (6%)	2 (4%)
#SPLEEN	(50)	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)	1 (2%)
FIBROSARCOMA, INVASIVE			1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
MALIGNANT LYMPHOMA, NOS				1 (2%)
#LYMPH NODE	(43)	(42)	(45)	(46)
SARCOMA, NOS			1 (2%)	
FIBROSARCOMA, METASTATIC			1 (2%)	
#THYMUS	(35)	(37)	(24)	(27)
THYMOMA				1 (4%)
CIRCULATORY SYSTEM				
#SPLEEN	(50)	(50)	(50)	(50)
HEMANGIOMA	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(47)	(48)	(50)
ADENOMA, NOS				1 (2%)
#LIVER	(50)	(50)	(50)	(50)
NEOPLASM, NOS				1 (2%)
NEOPLASTIC NODULE	1 (2%)	9 (18%)	18 (36%)	17 (34%)
HEPATOCELLULAR CARCINOMA		4 (8%)	23 (46%)	22 (44%)
SARCOMA, NOS, METASTATIC			1 (2%)	
FIBROSARCOMA, INVASIVE			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	1 (2%)	
SARCOMA, NOS, METASTATIC			1 (2%)	
LIPOMA	1 (2%)			
ENDOCRINE SYSTEM				
#PITUITARY	(44)	(43)	(41)	(43)
NEOPLASM, NOS	2 (5%)			
ADENOMA, NOS	15 (34%)	15 (35%)	21 (51%)	19 (44%)
#ADRENAL	(50)	(50)	(50)	(50)
PHEOCHROMOCYTOMA	4 (8%)	3 (6%)		4 (8%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#THYROID	(46)	(47)	(46)	(50)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	8 (17%)	13 (26%)
FOLLICULAR-CELL CARCINOMA		5 (11%)	9 (20%)	15 (30%)
C-CELL ADENOMA	3 (7%)	4 (9%)	2 (4%)	3 (6%)
C-CELL CARCINOMA	2 (4%)	1 (2%)	1 (2%)	3 (6%)
#PANCREATIC ISLETS	(46)	(47)	(46)	(48)
ISLET-CELL ADENOMA	2 (4%)			1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
FIBROADENOMA	1 (2%)	2 (4%)	1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)		
ADENOMA, NOS	1 (2%)	3 (6%)		1 (2%)
#TESTIS	(49)	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	43 (88%)	48 (96%)	47 (94%)	40 (80%)
NERVOUS SYSTEM				
#BRAIN	(50)	(49)	(50)	(50)
GLIOMA, NOS		2 (4%)		
SPECIAL SENSE ORGANS				
*EAR	(50)	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)			
*ZYMBAL'S GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS			2 (4%)	
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)	
BODY CAVITIES				
*PLEURA	(50)	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
*TUNICA VAGINALIS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)	2 (4%)	2 (4%)	1 (2%)
MESOTHELIOMA, INVASIVE		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)		
DIAPHRAGM				
FIBROSARCOMA, INVASIVE			1	
SITE UNKNOWN				
ADENOCARCINOMA, NOS				1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATHa	14	11	8	17
MORIBUND SACRIFICE	11	5	7	3
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	25	34	35	30
ANIMAL MISSING				

a INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	50	50	47
TOTAL PRIMARY TUMORS	114	113	147	152
TOTAL ANIMALS WITH BENIGN TUMORS	46	50	49	47
TOTAL BENIGN TUMORS	76	82	83	86
TOTAL ANIMALS WITH MALIGNANT TUMORS	31	17	34	34
TOTAL MALIGNANT TUMORS	34	19	43	47
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	4	2
TOTAL SECONDARY TUMORS	1	1	9	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	4	11	18	18
TOTAL UNCERTAIN TUMORS	4	12	21	19
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 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
NEOPLASM, NOS				1 (2%)
SARCOMA, NOS		1 (2%)	1 (2%)	1 (2%)
OSTEOSARCOMA		2 (4%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
NEOPLASM, NOS, METASTATIC				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA				1 (2%)
FOLLICULAR-CELL CARCINOMA, METAS			1 (2%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA, MET		1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
MONOCYTIC LEUKEMIA	3 (6%)	1 (2%)	2 (4%)	
#SPLEEN	(50)	(50)	(48)	(50)
OSTEOSARCOMA, METASTATIC		1 (2%)		
CIRCULATORY SYSTEM				
NONE				

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
NEOPLASTIC NODULE	3 (6%)		20 (40%)	11 (22%)
HEPATOCELLULAR CARCINOMA			4 (8%)	6 (12%)
#PANCREAS	(50)	(49)	(48)	(48)
ACINAR-CELL ADENOMA		1 (2%)		
ENDOMETRIAL STROMAL SARCOMA, INV		1 (2%)		
URINARY SYSTEM				
#KIDNEY/PELVIS	(49)	(50)	(50)	(49)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(43)	(43)	(46)
NEOPLASM, NOS			1 (2%)	1 (2%)
ADENOMA, NOS	27 (59%)	25 (58%)	26 (60%)	10 (22%)
BASOPHIL ADENOMA				1 (2%)
#ADRENAL	(50)	(50)	(50)	(50)
NEOPLASM, NOS, MALIGNANT				1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	1 (2%)	1 (2%)
OSTEOSARCOMA, METASTATIC		1 (2%)		
#THYROID	(49)	(48)	(48)	(50)
FOLLICULAR-CELL ADENOMA		2 (4%)	17 (35%)	16 (32%)
FOLLICULAR-CELL CARCINOMA		2 (4%)	12 (25%)	7 (14%)
C-CELL ADENOMA	2 (4%)	4 (8%)	2 (4%)	2 (4%)
C-CELL CARCINOMA			1 (2%)	
#THYROID FOLLICLE	(49)	(48)	(48)	(50)
NEOPLASM, NOS				1 (2%)
#PANCREATIC ISLETS	(50)	(49)	(48)	(48)
ISLET-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
FIBROADENOMA	16 (32%)	7 (14%)	1 (2%)	
*CLITORAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)	1 (2%)		
ADENOMA, NOS	1 (2%)	2 (4%)	3 (6%)	1 (2%)
*VAGINA	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	1 (2%)	
#UTERUS	(49)	(48)	(49)	(48)
ADENOMA, NOS			1 (2%)	
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)		
FIBROMA		1 (2%)		
ENDOMETRIAL STROMAL POLYP	7 (14%)	2 (4%)	7 (14%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA		3 (6%)	1 (2%)	
#OVARY	(50)	(49)	(48)	(46)
GRANULOSA-CELL TUMOR	1 (2%)			
SERTOLI-CELL TUMOR		2 (4%)		
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(49)	(50)
GLIOMA, NOS	1 (2%)			1 (2%)
SPECIAL SENSE ORGANS				
*ZYMBAL'S GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)	
ALL OTHER SYSTEMS				
DIAPHRAGM				
ENDOMETRIAL STROMAL SARCOMA, INV		1		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ADIPOSE TISSUE				
SQUAMOUS CELL PAPILLOMA	1			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATHa	2	7	8	21
MORIBUND SACRIFICE	8	5	8	16
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	40	38	34	13
ANIMAL MISSING				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	42	36	45	31
TOTAL PRIMARY TUMORS	70	60	105	63
TOTAL ANIMALS WITH BENIGN TUMORS	38	31	36	25
TOTAL BENIGN TUMORS	56	47	60	33
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	13	20	13
TOTAL MALIGNANT TUMORS	10	13	24	16
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1	2
TOTAL SECONDARY TUMORS		6	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	4		21	13
TOTAL UNCERTAIN TUMORS	4		21	14
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

a INCLUDES AUTOLYZED ANIMALS

* 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 4,4'-OXYDIANILINE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	50	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(49)	(50)
SARCOMA, NOS	1 (2%)	1 (2%)		
FIBROMA			1 (2%)	
FIBROSARCOMA		1 (2%)		
NEUROFIBROSARCOMA	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(49)	(49)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	4 (8%)	5 (10%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	8 (16%)	9 (18%)	7 (14%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (12%)	1 (2%)	1 (2%)	2 (4%)
SARCOMA, NOS, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	8 (16%)	4 (8%)	4 (8%)	1 (2%)
#SPLEEN	(49)	(50)	(47)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
#LYMPH NODE	(40)	(45)	(37)	(33)
MALIGNANT LYMPHOMA, NOS		1 (2%)		1 (3%)
#PEYER'S PATCH	(44)	(50)	(45)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
CIRCULATORY SYSTEM				
*ABDOMINAL CAVITY	(50)	(50)	(49)	(50)
HEMANGIOMA			1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
HEMANGIOSARCOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(50)	(49)	(50)
HEMANGIOMA			1 (2%)	1 (2%)
#SPLEEN	(49)	(50)	(47)	(49)
HEMANGIOMA			1 (2%)	1 (2%)
HEMANGIOSARCOMA		1 (2%)		
ANGIOSARCOMA	1 (2%)			
#LIVER	(50)	(50)	(49)	(50)
HEMANGIOMA			3 (6%)	4 (8%)
HEMANGIOSARCOMA	1 (2%)	1 (2%)		
ANGIOSARCOMA	1 (2%)		3 (6%)	1 (2%)
#PROSTATE	(42)	(47)	(44)	(44)
HEMANGIOMA			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(50)	(49)	(47)
SARCOMA, NOS		1 (2%)		
SARCOMA, NOS, METASTATIC			1 (2%)	
#LIVER	(50)	(50)	(49)	(50)
NEOPLASM, NOS			1 (2%)	
HEPATOCELLULAR ADENOMA	11 (22%)	13 (26%)	11 (22%)	10 (20%)
HEPATOCELLULAR CARCINOMA	18 (36%)	27 (54%)	23 (47%)	26 (52%)
SARCOMA, NOS		1 (2%)		
SARCOMA, NOS, METASTATIC				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(37)	(44)	(34)	(35)
ADENOMA, NOS	1 (3%)			7 (20%)
#ADRENAL	(44)	(49)	(46)	(40)
PHEOCHROMOCYTOMA			1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#THYROID	(44)	(47)	(47)	(49)
FOLLICULAR-CELL ADENOMA			2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(49)	(50)
SARCOMA, NOS			1 (2%)	
*HARDERIAN GLAND	(50)	(50)	(49)	(50)
NEOPLASM, NOS			1 (2%)	
ADENOMA, NOS	1 (2%)	17 (34%)	13 (27%)	17 (34%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(49)	(50)
SARCOMA, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATHa	13	8	16	12
MORIBUND SACRIFICE	2	3		4
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	35	39	33	34
ANIMAL MISSING			1	
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	39	45	40	42
TOTAL PRIMARY TUMORS	60	78	77	76
TOTAL ANIMALS WITH BENIGN TUMORS	17	29	29	33
TOTAL BENIGN TUMORS	21	39	42	44
TOTAL ANIMALS WITH MALIGNANT TUMORS	31	33	25	28
TOTAL MALIGNANT TUMORS	39	39	33	32
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	4	6	1
TOTAL SECONDARY TUMORS	2	4	7	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2	
TOTAL UNCERTAIN TUMORS			2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

a INCLUDES AUTOLYZED ANIMALS

* 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 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
NEOPLASM, NOS		1* (2%)		
SARCOMA, NOS	1 (2%)	2 (4%)		
FIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	3 (6%)	7 (14%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	12 (24%)	5 (10%)	12 (24%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	1 (2%)
#SPLEEN	(50)	(48)	(48)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)	
#LYMPH NODE	(42)	(40)	(45)	(40)
SARCOMA, NOS, METASTATIC		1 (3%)		
MALIGNANT LYMPHOMA, NOS	1 (2%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#PEYER'S PATCH	(47)	(46)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HEMANGIOMA				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMANGIOMA			1 (2%)	
#SPLEEN	(50)	(48)	(48)	(50)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA				1 (2%)
ANGIOSARCOMA		1 (2%)		
#LIVER	(50)	(49)	(48)	(50)
ANGIOSARCOMA		1 (2%)		
#UTERUS	(48)	(46)	(47)	(48)
HEMANGIOMA		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(48)	(50)
NEOPLASM, NOS		1 (2%)		
HEPATOCELLULAR ADENOMA	4 (8%)	6 (12%)	9 (19%)	14 (28%)
HEPATOCELLULAR CARCINOMA	4 (8%)	7 (14%)	6 (13%)	15 (30%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(42)	(41)	(36)
ADENOMA, NOS	2 (5%)	4 (10%)	4 (10%)	2 (6%)
#ADRENAL	(44)	(42)	(42)	(47)
ADENOMA, NOS			1 (2%)	
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)	1 (2%)
#THYROID	(46)	(43)	(42)	(48)
FOLLICULAR-CELL ADENOMA				7 (15%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#PANCREATIC ISLETS	(47)	(40)	(46)	(46)
ISLET-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS			2 (4%)	
#UTERUS	(48)	(46)	(47)	(48)
SARCOMA, NOS		1 (2%)		
#OVARY	(43)	(41)	(42)	(43)
GRANULOSA-CELL TUMOR				1 (2%)
TUBULAR ADENOMA	2 (5%)			
TERATOMA, NOS			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS	2 (4%)	15 (30%)	14 (28%)	12 (24%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)		
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	15	13	7
MORIBUND SACRIFICE	1	2	4	1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	1			
TERMINAL SACRIFICE	42	33	33	42
ANIMAL MISSING				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	37	40	42
TOTAL PRIMARY TUMORS	36	55	65	61
TOTAL ANIMALS WITH BENIGN TUMORS	12	23	25	32
TOTAL BENIGN TUMORS	16	31	38	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	20	22	20
TOTAL MALIGNANT TUMORS	20	22	26	20
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1	
TOTAL SECONDARY TUMORS		1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	1	1
TOTAL UNCERTAIN TUMORS		2	1	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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED 4,4'-OXYDIANILINE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
HYPERPLASIA, BASAL CELL			1 (2%)	
ACANTHOSIS		1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
METAPLASIA, OSSEOUS			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
CONGESTION, NOS				1 (2%)
HEMORRHAGE				1 (2%)
INFLAMMATION, NOS		5 (10%)	5 (10%)	8 (16%)
LIPOGRANULOMA				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
REACTION, FOREIGN BODY			1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(40)	(45)	(48)	(41)
HYPERPLASIA, NOS	1 (3%)			
HYPERPLASIA, ERYTHROID				1 (2%)
#SPLEEN	(50)	(50)	(50)	(50)
RETICULOCYTOSIS				1 (2%)
HEMATOPOIESIS	3 (6%)	8 (16%)	10 (20%)	8 (16%)
#LYMPH NODE	(43)	(42)	(45)	(46)
HEMORRHAGIC CYST				1 (2%)
REACTION, FOREIGN BODY			1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
PERIVASCULITIS				1 (2%)
*SITE UNKNOWN	(50)	(50)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
#HEART	(50)	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)			
INFLAMMATION, NECROTIZING		1 (2%)		
FIBROSIS	1 (2%)			
PERIVASCULITIS		1 (2%)		
#AURICULAR APPENDAGE	(50)	(50)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
#MYOCARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, FOCAL				1 (2%)
DEGENERATION, NOS	3 (6%)	2 (4%)	2 (4%)	
#STOMACH	(50)	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(47)	(48)	(50)
HYPERPLASIA, NOS			1 (2%)	
#LIVER	(50)	(50)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)		1 (2%)
REACTION, FOREIGN BODY			1 (2%)	
FIBROSIS			1 (2%)	
DEGENERATION, NOS			1 (2%)	
DEGENERATION, CYSTIC			4 (8%)	3 (6%)
NECROSIS, FOCAL	1 (2%)	3 (6%)		2 (4%)
METAMORPHOSIS FATTY	6 (12%)	12 (24%)	7 (14%)	5 (10%)
BASOPHILIC CYTO CHANGE	4 (8%)	3 (6%)	3 (6%)	1 (2%)
FOCAL CELLULAR CHANGE	6 (12%)	20 (40%)	1 (2%)	1 (2%)
#BILE DUCT	(50)	(50)	(50)	(50)
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	MID DOSE	HIGH DOSE
#PANCREATIC ACINUS	(46)	(47)	(46)	(48)
ATROPHY, NOS				1 (2%)
HYPERPLASIA, FOCAL		1 (2%)		
#STOMACH	(50)	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		1 (2%)	
HYPERPLASIA, BASAL CELL	1 (2%)	2 (4%)	2 (4%)	
ACANTHOSIS			2 (4%)	
#GASTRIC SUBMUCOSA	(50)	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
#CECUM	(46)	(49)	(48)	(48)
ABSCESS, NOS		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
MINERALIZATION		1 (2%)		11 (22%)
INFLAMMATION, NOS		1 (2%)		
FIBROSIS			1 (2%)	
NEPHROPATHY	32 (64%)	44 (88%)	40 (80%)	39 (78%)
NECROSIS, MEDULLARY	1 (2%)			
CALCIFICATION, FOCAL				2 (4%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)	2 (4%)	4 (8%)	7 (14%)
#URINARY BLADDER	(42)	(47)	(46)	(48)
CALCULUS, NOS				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY/BASOPHIL	(44)	(43)	(41)	(43)
HYPERPLASIA, NOS				1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)		1 (2%)
#THYROID	(46)	(47)	(46)	(50)
FOLLICULAR CYST, NOS			11 (24%)	3 (6%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
HYPERPLASIA, C-CELL	1 (2%)	2 (4%)	3 (7%)	
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	11 (24%)	13 (26%)
#PANCREATIC ISLETS	(46)	(47)	(46)	(48)
HYPERPLASIA, NOS	2 (4%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
GALACTOCELE	1 (2%)		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)			
NECROSIS, NOS		1 (2%)		
#TESTIS	(49)	(50)	(50)	(50)
MINERALIZATION		1 (2%)	2 (4%)	4 (8%)
ATROPHY, NOS	2 (4%)	1 (2%)	3 (6%)	7 (14%)
ATROPHY, FOCAL				1 (2%)
HYPOSPERMATOGENESIS	1 (2%)			
HYPERPLASIA, INTERSTITIAL CELL				3 (6%)
NERVOUS SYSTEM				
#BRAIN	(50)	(49)	(50)	(50)
MINERALIZATION	1 (2%)			
HEMORRHAGE			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT	3	9	7	3
SPECIAL MORPHOLOGY SUMMARY				
NONE				

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
EROSION		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
BRONCHOPNEUMONIA, NOS				3 (6%)
INFLAMMATION, NOS	2 (4%)	2 (4%)	6 (12%)	6 (12%)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
REACTION, FOREIGN BODY				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)		
METAPLASIA, OSSEOUS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(45)	(45)	(43)	(47)
HYPOPLASIA, NOS				1 (2%)
HYPERPLASIA, ERYTHROID				1 (2%)
#SPLEEN	(50)	(50)	(48)	(50)
HEMOSIDEROSIS				5 (10%)
HEMATOPOIESIS	16 (32%)	20 (40%)	9 (19%)	
CIRCULATORY SYSTEM				
#AURICULAR APPENDAGE	(50)	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	1 (2%)
#MYOCARDIUM	(50)	(50)	(50)	(50)
DEGENERATION, NOS			1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
DEGENERATION, CYSTIC				1 (2%)
NECROSIS, FOCAL		1 (2%)	1 (2%)	2 (4%)
METAMORPHOSIS FATTY	4 (8%)		4 (8%)	
BASOPHILIC CYTO CHANGE	30 (60%)	39 (80%)	14 (28%)	7 (14%)
FOCAL CELLULAR CHANGE	4 (8%)	7 (14%)	2 (4%)	
#LIVER/CENTRILOBULAR	(50)	(49)	(50)	(50)
NECROSIS, NOS				1 (2%)
#STOMACH	(50)	(48)	(50)	(49)
HYPERPLASIA, BASAL CELL		2 (4%)	3 (6%)	2 (4%)
ACANTHOSIS			1 (2%)	
#GASTRIC SUBMUCOSA	(50)	(48)	(50)	(49)
INFLAMMATION, NOS	1 (2%)			
#PEYER'S PATCH	(50)	(49)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)		
#CECUM	(50)	(46)	(48)	(47)
INFLAMMATION, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(49)
MINERALIZATION	3 (6%)	10 (20%)	7 (14%)	16 (33%)
FIBROSIS			1 (2%)	
NEPHROPATHY	10 (20%)	10 (20%)	8 (16%)	4 (8%)
DEGENERATION, CYSTIC			1 (2%)	
CALCIFICATION, FOCAL				14 (29%)
HYPERPLASIA, EPITHELIAL				1 (2%)
#KIDNEY/PELVIS	(49)	(50)	(50)	(49)
HYPERPLASIA, EPITHELIAL		2 (4%)	5 (10%)	4 (8%)
#URINARY BLADDER	(49)	(46)	(45)	(40)
HYPERPLASIA, EPITHELIAL	1 (2%)			
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(43)	(43)	(46)
ECTOPIA				4 (9%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
CYST, NOS				1 (2%)
HYPERPLASIA, CHROMOPHOBE-CELL				1 (2%)
#PITUITARY/BASOPHIL	(46)	(43)	(43)	(46)
HYPERPLASIA, NOS				5 (11%)
#ADRENAL CORTEX	(50)	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)			
HYPERTROPHY, NOS		2 (4%)		
HYPERTROPHY, FOCAL			1 (2%)	
HYPERPLASIA, NODULAR				1 (2%)
*THYROID	(49)	(48)	(48)	(50)
FOLLICULAR CYST, NOS		1 (2%)	7 (15%)	2 (4%)
FIBROSIS				1 (2%)
HYPERPLASIA, C-CELL	1 (2%)	6 (13%)	3 (6%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	6 (13%)	22 (44%)
METAPLASIA, SQUAMOUS			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
GALACTOCELE	4 (8%)	1 (2%)		
*CLITORAL GLAND	(50)	(50)	(50)	(50)
NECROSIS, NOS			1 (2%)	
METAPLASIA, SQUAMOUS	1 (2%)			
#UTERUS	(49)	(48)	(49)	(48)
HYDROMETRA	2 (4%)		3 (6%)	
INFLAMMATION, NOS			1 (2%)	
#UTERUS/ENDOMETRIUM	(49)	(48)	(49)	(48)
CYST, NOS		3 (6%)		
HYPERPLASIA, NOS		1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)			
#OVARY	(50)	(49)	(48)	(46)
CYST, NOS		1 (2%)		
DEGENERATION, CYSTIC	1 (2%)			
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(49)	(50)
HEMORRHAGE		1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ABSCESS, NOS				1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(50)	(50)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
*EYE/CONJUNCTIVA	(50)	(50)	(50)	(50)
DEGENERATION, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT	2	1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED 4,4'-OXYDIANILINE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	50	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(49)	(50)
INFLAMMATION, NOS			1 (2%)	
RESPIRATORY SYSTEM				
*LARYNX	(50)	(50)	(49)	(50)
INFLAMMATION, NECROTIZING			1 (2%)	
#LUNG/BRONCHUS	(50)	(50)	(49)	(49)
HYPERPLASIA, NOS			1 (2%)	
#LUNG	(50)	(50)	(49)	(49)
CONGESTION, NOS			1 (2%)	
INFLAMMATION, NOS	1 (2%)	2 (4%)	1 (2%)	3 (6%)
ABSCESS, NOS			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
HEMATOPOIESIS		1 (2%)		
#BONE MARROW	(48)	(44)	(44)	(46)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#SPLEEN	(49)	(50)	(47)	(49)
HYPERPLASIA, NOS				1 (2%)
HEMATOPOIESIS	4 (8%)	7 (14%)	9 (19%)	12 (24%)
#LYMPH NODE	(40)	(45)	(37)	(33)
HEMORRHAGIC CYST			1 (3%)	
PLASMACYTOSIS			1 (3%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIESIS		1 (2%)	1 (3%)	
#MESENTERIC L. NODE	(40)	(45)	(37)	(33)
HEMATOPOIESIS				1 (3%)
#LUNG	(50)	(50)	(49)	(49)
HISTIOCYTOSIS	1 (2%)			
#LIVER	(50)	(50)	(49)	(50)
HEMATOPOIESIS				2 (4%)
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
PERIVASCULITIS	1 (2%)			
#HEART	(50)	(50)	(49)	(49)
ABSCESS, NOS			1 (2%)	
PERIVASCULITIS		1 (2%)		
#AURICULAR APPENDAGE	(50)	(50)	(49)	(49)
THROMBOSIS, NOS		1 (2%)		
#MYOCARDIUM	(50)	(50)	(49)	(49)
INFLAMMATION, NOS	1 (2%)			1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(49)	(50)
MINERALIZATION				1 (2%)
HEMORRHAGE	1 (2%)			
ABSCESS, NOS	1 (2%)			
FIBROSIS	1 (2%)			
NECROSIS, NOS	1 (2%)		1 (2%)	1 (2%)
NECROSIS, FOCAL		2 (4%)		
METAMORPHOSIS FATTY	3 (6%)	6 (12%)		1 (2%)
#PANCREAS	(45)	(47)	(44)	(44)
INFLAMMATION, FOCAL			1 (2%)	
#PANCREATIC ACINUS	(45)	(47)	(44)	(44)
HYPERTROPHY, FOCAL		1 (2%)		
#STOMACH	(48)	(50)	(46)	(47)
INFLAMMATION, NOS		3 (6%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#PEYER'S PATCH	(44)	(50)	(45)	(49)
HYPERPLASIA, NOS		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(49)	(49)
MINERALIZATION	2 (4%)			1 (2%)
INFLAMMATION, NOS		1 (2%)		
ABSCESS, NOS			1 (2%)	2 (4%)
FIBROSIS				1 (2%)
NEPHROPATHY	2 (4%)		2 (4%)	1 (2%)
DEGENERATION, NOS		1 (2%)		
DEGENERATION, CYSTIC				1 (2%)
NECROSIS, MEDULLARY				1 (2%)
ATROPHY, NOS				1 (2%)
#URINARY BLADDER	(47)	(50)	(48)	(46)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)	
*URETHRA	(50)	(50)	(49)	(50)
CALCULUS, NOS			1 (2%)	
ENDOCRINE SYSTEM				
#ADRENAL	(44)	(49)	(46)	(40)
HYPERPLASIA, NOS	2 (5%)	1 (2%)		
#ADRENAL CORTEX	(44)	(49)	(46)	(40)
HYPERTROPHY, FOCAL		2 (4%)	1 (2%)	
#THYROID	(44)	(47)	(47)	(49)
HYPERPLASIA, FOLLICULAR-CELL				26 (53%)
#PANCREATIC ISLETS	(45)	(47)	(44)	(44)
HYPERTROPHY, NOS		1 (2%)		
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(50)	(50)	(49)	(50)
INFLAMMATION, NOS				1 (2%)
ABSCESS, NOS	1 (2%)			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
#PROSTATE	(42)	(47)	(44)	(44)
INFLAMMATION, ACUTE			1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(49)	(50)
CALCULUS, NOS			1 (2%)	
*COAGULATING GLAND	(50)	(50)	(49)	(50)
CALCULUS, NOS			1 (2%)	
#TESTIS	(50)	(50)	(49)	(49)
FIBROSIS				1 (2%)
ATROPHY, NOS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(49)	(50)
INFLAMMATION, NOS		5 (10%)	4 (8%)	6 (12%)
DEGENERATION, NOS			1 (2%)	
HYPERPLASIA, CYSTIC				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(49)	(50)
ABSCESS, NOS				2 (4%)
REACTION, FOREIGN BODY			1 (2%)	
OMENTUM				
NECROSIS, FAT		6	2	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	7	1	4	1
ANIMAL MISSING/NO NECROPSY			1	
AUTO/NECROPSY/HISTO PERF			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 4, 4'-OXYDIANILINE IN THE DIET

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
HYPERPLASIA, BASAL CELL	1 (2%)			
RESPIRATORY SYSTEM				
*LARYNX	(50)	(50)	(50)	(50)
INFLAMMATION, NECROTIZING			1 (2%)	
#LUNG	(50)	(49)	(50)	(50)
BRONCHOPNEUMONIA, NOS	1 (2%)			1 (2%)
INFLAMMATION, NOS	1 (2%)	1 (2%)	1 (2%)	4 (8%)
ABSCESS, NOS		1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(47)	(49)	(43)	(47)
HYPERPLASIA, HEMATOPOIETIC			2 (5%)	1 (2%)
#SPLEEN	(50)	(48)	(48)	(50)
NECROSIS, NOS	1 (2%)			
HYPERPLASIA, NOS		1 (2%)		
HEMATOPOIESIS	5 (10%)	9 (19%)	5 (10%)	12 (24%)
#LYMPH NODE	(42)	(40)	(45)	(40)
HEMORRHAGIC CYST	1 (2%)			
REACTION, FOREIGN BODY	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
HEMATOPOIESIS	1 (2%)			
#LIVER	(50)	(49)	(48)	(50)
HEMATOPOIESIS		1 (2%)		2 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
#HEART	(50)	(49)	(49)	(50)
CALCIFICATION, NOS	1 (2%)			
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(48)	(50)
ABSCESS, NOS			1 (2%)	2 (4%)
NECROSIS, FOCAL	1 (2%)			
NECROSIS, HEMORRHAGIC		1 (2%)		
METAMORPHOSIS FATTY	4 (8%)	1 (2%)	7 (15%)	
#STOMACH	(49)	(46)	(48)	(50)
INFLAMMATION, NOS		2 (4%)		
HYPERPLASIA, BASAL CELL		1 (2%)		
#ILEUM	(47)	(46)	(49)	(49)
GRANULOMA, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(50)	(48)	(48)	(50)
MINERALIZATION	1 (2%)	1 (2%)	1 (2%)	2 (4%)
HYDRONEPHROSIS	1 (2%)		2 (4%)	2 (4%)
ABSCESS, NOS	1 (2%)	2 (4%)	1 (2%)	1 (2%)
NEPHROPATHY	1 (2%)		3 (6%)	5 (10%)
AMYLOIDOSIS			1 (2%)	
#URINARY BLADDER	(48)	(47)	(48)	(49)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, ACUTE				1 (2%)
HYPERPLASIA, EPITHELIAL				4 (8%)
ENDOCRINE SYSTEM				
#ADRENAL	(44)	(42)	(42)	(47)
HYPERPLASIA, NOS	4 (9%)	8 (19%)	3 (7%)	2 (4%)
#THYROID	(46)	(43)	(42)	(48)
HYPERPLASIA, FOLLICULAR-CELL				25 (52%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
#UTERUS	(48)	(46)	(47)	(48)
HYDROMETRA	7 (15%)	8 (17%)	15 (32%)	15 (31%)
INFLAMMATION, NOS		1 (2%)	1 (2%)	2 (4%)
#UTERUS/ENDOMETRIUM	(48)	(46)	(47)	(48)
HYPERPLASIA, CYSTIC	17 (35%)	19 (41%)	9 (19%)	21 (44%)
#OVARY	(43)	(41)	(42)	(43)
MINERALIZATION		1 (2%)		
CYST, NOS	1 (2%)	4 (10%)	5 (12%)	5 (12%)
ABSCESS, NOS	1 (2%)			
DEGENERATION, NOS				1 (2%)
DEGENERATION, CYSTIC	2 (5%)			
NECROSIS, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(49)	(49)	(49)	(50)
ABSCESS, NOS		1 (2%)		1 (2%)
NECROSIS, NOS	1 (2%)			
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	4 (8%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
OMENTUM				
NECROSIS, FAT	1	1	2	1
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	2	1	1
AUTO/NECROPSY/HISTO PERF		1		

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

APPENDIX E

ANALYSIS OF 4,4'-OXYDIANILINE (Lot No. 387)
MIDWEST RESEARCH INSTITUTE

APPENDIX E

Analysis of Formulated Diets for Concentrations of 4,4'-Oxydianiline

Analysis of 4,4'-Oxydianiline (Lot No. 387)

Midwest Research Institute

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	71.98	6.04	13.99
Determined	71.87	6.13	14.12

B. MELTING POINT

Determined	Literature Values
191°-194°C dec (visual, evacuated capillary)	186°-187°C (cryst. from ethanol) (Reynolds, 1951)

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60 F254
Amount spotted: 100 and 300 μg
Ref. Standard: Aniline
Visualization: Ultraviolet, 254 nm

System 1: Acetronitrile, 100%
R_f: 0.60, origin (trace)
R_{st}: 0.80, origin

System 2: Ethyl acetate, 100%
R_f: 0.42, origin (trace)
R_{st}: 0.64, origin

D. VAPOR-PHASE CHROMATOGRAPHY

System 1:

Instrument: Tracor MT 220
Detector: Flame Ionization
Column: 3% OV-17, 1.5 M x 4 mm I.D.
Oven temperature program: 100°-250°C, 10°C/min
Results: One homogeneous peak, retention time-13 minutes

VAPOR-PHASE CHROMATOGRAPHY (continued)

System 2:

Instrument: Bendix 2500
Detector: Flame Ionization
Column: 3% OV-1 on chromosorb W(HP), 1.8 m x 4 mm I.D.
Oven temperature program: 100°-250°C, 10°C/min
Results: Major peak and one minor impurity

Peak	Retention Time (min)	Relative Retention Time	Relative Height
Major	12.0	1.00	1.00
Minor	12.9	1.07	0.0029

E. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12
Cell: 0.5% KBr pellet

Results: See Figure 5

Identical to literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

Instrument: Cary 118
ϵ_{max} 298 = $(3.3 \pm 0.2\ (\delta) \times 10^3$
ϵ_{max} 247 = $(1.7 \pm 0.2\ (\delta) \times 10^3$
Solvent: 95% Ethanol

No literature reference found

3. Nuclear Magnetic Resonance

Instrument: Varian A-60
Solvent: DMSO-d_6 with internal TMA
Assignments: See Figure 6
(a) 4.73 δ (b) 6.59 δ

Integration Ratios: (a) 3.58 (b) 8.00

Consistent with literature literature spectrum (Sadtler Standard Spectra (a))

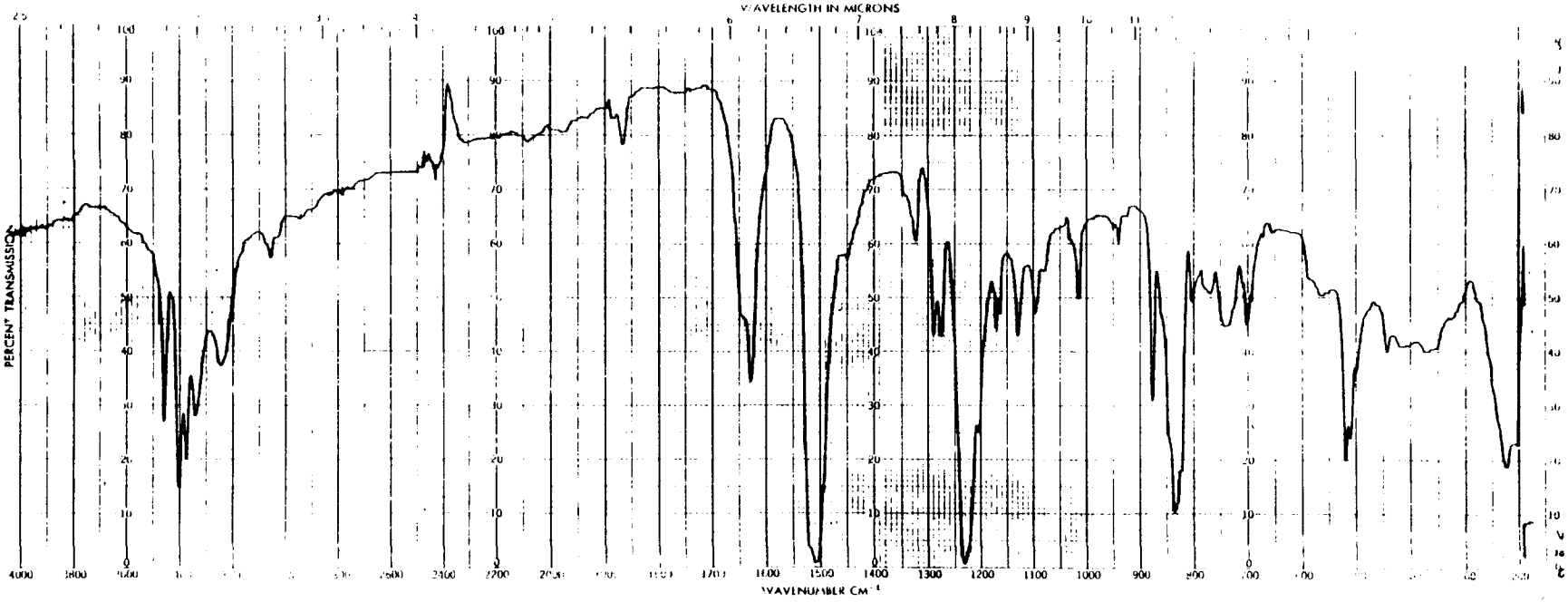


Figure 5. Infrared Absorption Spectrum of 4, 4'-Oxydianiline (Lot No. 387)

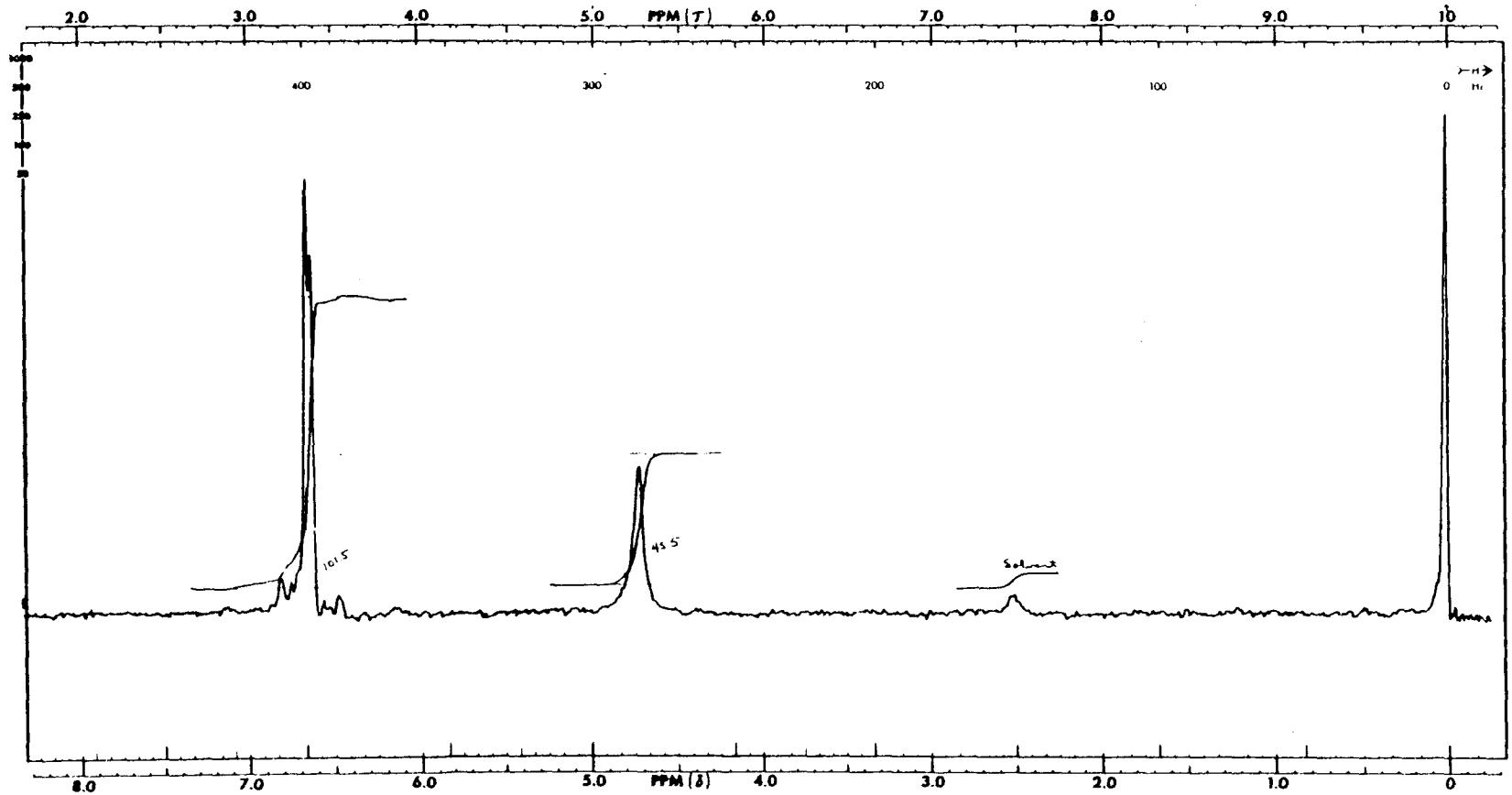


Figure 6. Nuclear Magnetic Resonance Spectrum of 4, 4'-Oxydianiline (Lot No. 387)

CONCLUSIONS

Titration of the amine groups with perchloric acid indicates 99.9±0.6 (δ)% purity. The elemental analysis agrees with the theoretical values. Thin-layer chromatography indicates only a trace impurity at the origin in addition to the spot for the major component. Vapor-phase chromatography with one system indicates one homogeneous peak. With a similar system and increased sensitivity, a very minor impurity was detected which constituted 0.29% of the major peak. The infrared, ultraviolet, and nuclear magnetic resonance spectra are consistent with the structure.

APPENDIX F

ANALYSIS OF 4,4'-OXYDIANILINE (Lot No. 82/02)
MIDWEST RESEARCH INSTITUTE

APPENDIX F

Analysis of 4,4'-Oxydianiline (Lot No. 387)

Midwest Research Institute

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	71.98	6.04	13.99
Determined	72.03	6.08	13.96

B. MELTING POINT

Determined	Literature Values
191°-198°C (visual, evacuated capillary) (DuPont 900 DTA)	186°-187°C (cryst. from C_2H_5OH (Reynolds, 1951)

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60 F-254
Amount spotted: 100 and 30 μl, 10 μg/ μl in 1,4-dioxane
System 1: Acetonitrile, dioxane (50:50)
R_f: 0.79, major

R_{st}: 0.91

Ref. Standard: Aniline
Visualization: Ultraviolet light, 254 nm and 366 nm, and 10% furfural in glacial aetic acid
System 2: Ethyl acetate (100%)
R_f: 0.82 (slight trace)
0.56 (major)
0.18 (slight trace)
origin (slight trace)
R_{st}: 0.94, 0.64, 0.21, origin

D. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT 220
Detector: Flame Ionization
Inlet temperature: 240°C
Detector temperature: 325°C

VAPOR-PHASE CHROMATOGRAPHY (continued)

System 1:

Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm I.D.
Oven temperature program: 100°-250°C, 10°C/minutes
Sample injected: 5 μl, 1 mg 4,4'-oxydianiline/ml methanol + 1 drop concentrated HCl
Results: Major peak and two impurities

Peak	Retention Time (min)	Retention Time (Relative to 4,4-Oxydianiline)	Area (Percent of 4,4'-Oxydianiline)
1	8.3	0.81	0.1
2	9.6	0.94	0.1
3	10.2	1.00	100

System 2:

Column: 3% OV-225 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 100°C, 5 minutes; 100°-250°C at 10°C/10 minutes
Sample injected: 5 μl, 5 μg/ μl N,N-dimethylformamide
Results: Single homogeneous peak, retention time 17.1 minutes

E. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12
Cell: 1% in potassium bromide
Results: See Figure 7

Consistent with literature spectrum Sadtler Standard Spectrum

2. Ultraviolet/Visible

Instrument: Cary 118

λ max	ε x 10-3
300 nm	3.8±1 (δ)
247 nm	19.1±0.7 (δ)

No literature reference found. Consistent with Lot No. 387 of this compound (MRI Anal. Report, 1975)

No absorbance in visible range (800-350 nm) at 1 mg/ml.
Solvent: 95% ethanol

3. Nuclear Magnetic Resonance

Determined	Literature Values
Instrument: Varian HA-100	Consistent with literature spectrum (Sadtler Standard Spectra, a)

Solvent: Dimethylsulfoxide-d with tetramethylsilane and $CDCl_3$ added (The $CDCl_3$ was necessary to dissolve the tetramethylsilane).
Assignments: (see Figure 8).
(a) s, δ 4.46 ppm
(b) m, δ 6.36-6.76 ppm
(c) impurity δ 3.28-3.42 ppm
Integration ratios:
(a) 3.93
(b) 8.07
(c) 0.07

CONCLUSIONS

Titration of the amino groups with perchloric acid indicates 98.9%±0.2 (δ)% purity. The elemental analyses agree with the theoretical values. Thin-layer chromatography with one system indicates three slight trace impurities. A second system indicates only the major component. Vapor-phase chromatography with one system indicates two impurities, each with an area 0.1% of that of the major peak. A second system indicates only the major peak. The infrared, ultraviolet, and nuclear magnetic resonance spectra are consistent with the structure, but the nuclear magnetic resonance spectrum indicates a trace impurity at 3.28-3.42 ppm.

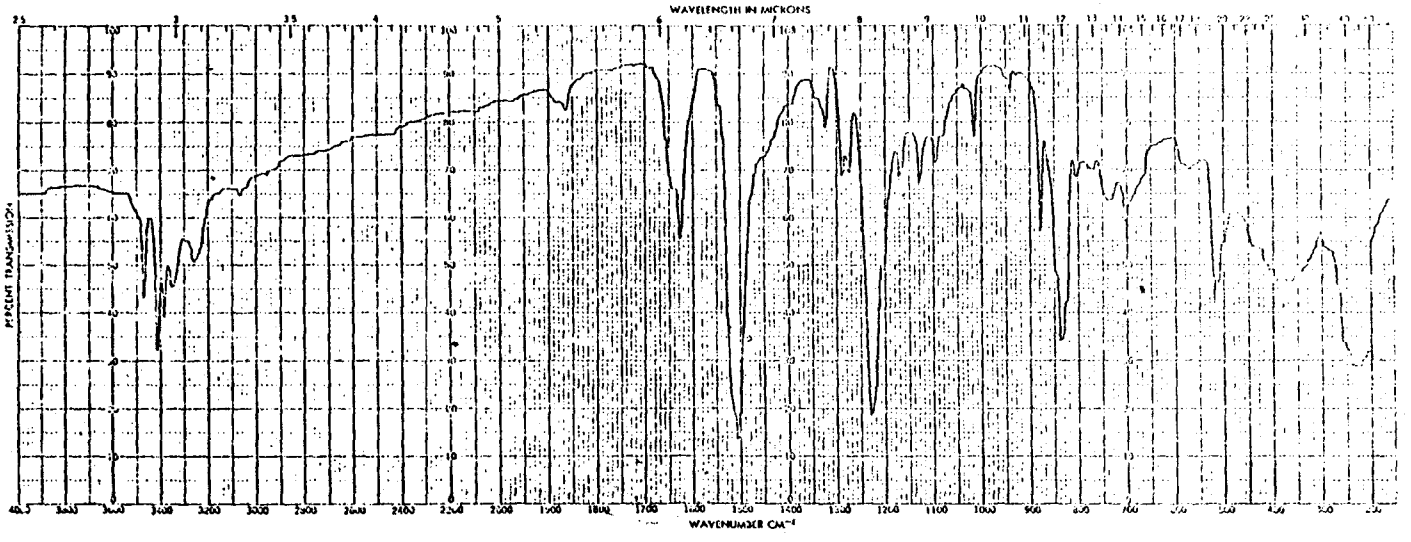


Figure 7. Infrared Absorption Spectrum of 4, 4'-Oxydianiline (Lot No. 82/02)

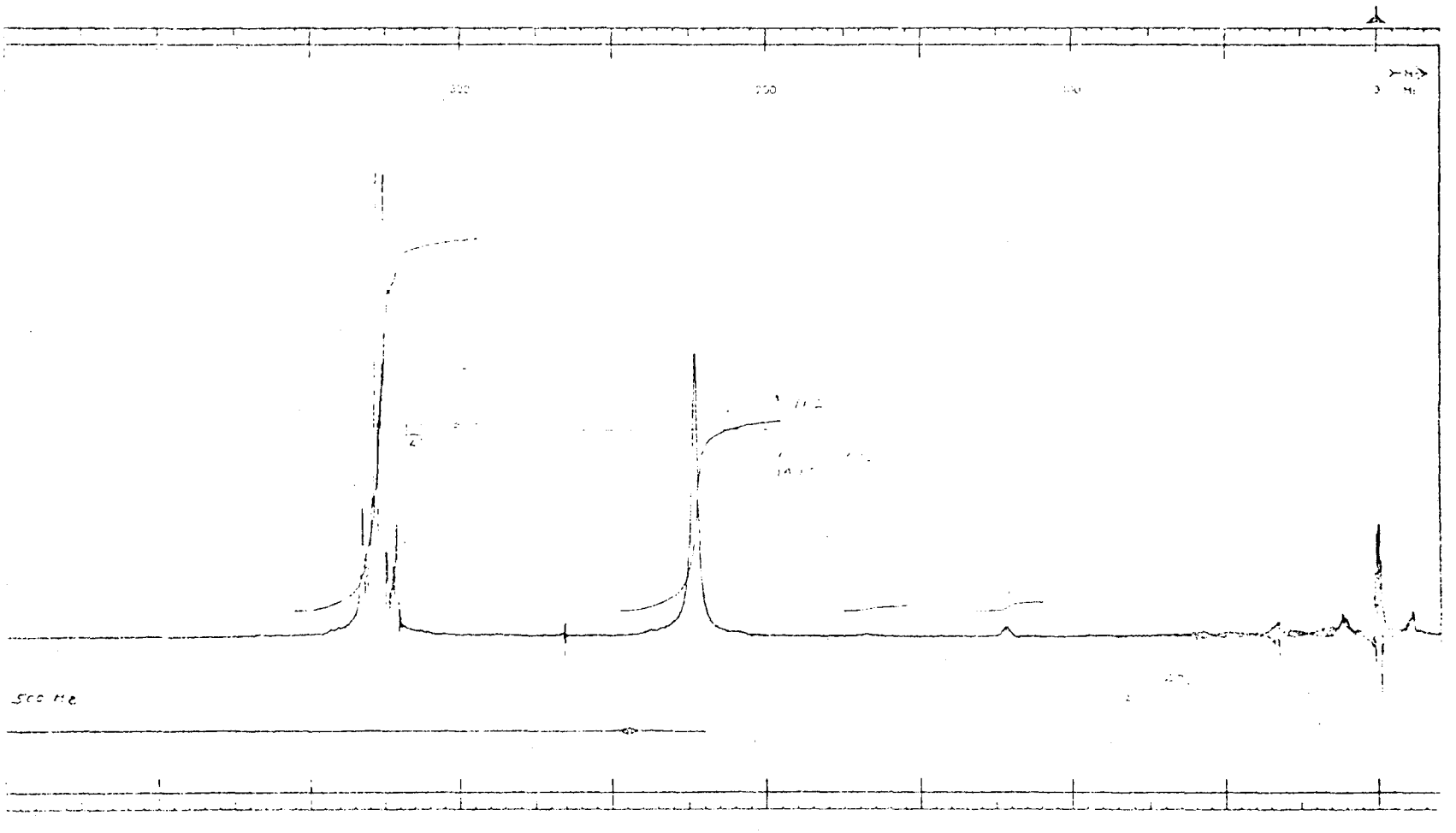


Figure 8. Nuclear Magnetic Resonance Spectrum of 4, 4'-Oxydianiline (Lot No. 82/02)

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF 4,4'-OXYDIANILINE

APPENDIX G

Analyses of Formulated Diets for Stability of 4,4'-Oxydianiline in the Diet

1. Method

Samples of diet mixtures containing 100,000 ppm (10%) 4,4'-oxydianiline were prepared and stored at -20°, 5°, 25°, and 45°C for two weeks. Samples of this mixture weighing 0.5 to 1 gram were blended with 50-ml dimethylformamide for 1 minute on a Brinkman Polytron mixer. The blended samples were centrifuged for 10 minutes and the supernatants decanted into 100-ml volumetric flasks. The centrifugates were blended with another 50 ml dimethylformamide for 1 minute on a Polytron mixer. These blended samples were centrifuged and the supernatants combined with those in the 100-ml volumetric flasks from the previous centrifugations. The resulting solutions were diluted to volume with dimethylformamide and injected on a gas chromatograph under the conditions given for System 2 (see Appendix F), except that the oven temperature was held isothermally at 200°C.

2. Results

There was no significant difference in the percent 4,4'-oxydianiline extracted from the feed based on the peak height for the major component.

Temperature (°C)	Compound on Feed (Percent)
-20	9.93±0.76
5	9.56±0.76
25	9.84±0.76
45	10.49±0.76

Percent recovery: 90.0±1.6(δ)

3. Conclusion

4,4'-Oxydianiline is stable in feed for 2 weeks at 45°C.

APPENDIX H

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATION OF 4,4'-OXYDIANILINE

APPENDIX H

Analyses of Formulated Diets for Concentrations of 4,4'-Oxydianiline

Duplicate samples of 2 g each were extracted with 50 ml of 95% ethanol in 100-ml ground glass stoppered graduated cylinders by repeated inversions of the cylinders during a 15-minute period. The feed particles were allowed to settle overnight, and the absorbance of the supernatants was measured at 247 nm in a Beckman DU Spectrophotometer after appropriate dilutions with 95% ethanol. The absorbance readings were adjusted with a "blank" extract from a 2-g feed sample from the same bag as the sample and were worked up in the same manner. Concentrations were determined by direct comparisons with standard solutions of the test compound. Recovery was determined by working up controlled feed mixtures simultaneously with the samples. The controls were prepared by spiking blank feed samples in duplicate. "Corrected" concentrations were adjusted for average recovery loss.

The results of these analyses are summarized in the following table.

Theoretical Concentration (ppm)	Number of Samples	Sample Analytical Mean	Coefficient of Variation (%)	Range (ppm)
200	12	200	14.5	160-240
800	14	780	13.2	650-1050

Review of the Bioassay of 4,4'-Oxydianiline* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

February 15, 1980

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 4,4'-Oxydianiline for carcinogenicity.

The primary reviewer for the report on the bioassay of 4,4'-oxydianiline agreed with the conclusion that the chemical was carcinogenic in rats and mice, under the conditions of test. After a brief description of the experimental design, he commented on the hepatocellular tumors and harderian gland adenomas induced in rats and hepatocellular tumors in mice. He said the study was adequate for demonstrating the carcinogenicity of 4,4'-oxydianiline.

The secondary reviewer indicated that an unrelated study had also found 4,4'-dioxyaniline to be carcinogenic. He added that the chemical has been shown to be mutagenic in Salmonella.

The primary reviewer moved that the report on the bioassay of 4,4'-dioxyaniline be accepted as written. The motion was seconded and approved unanimously.

Members present were:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
David B. Clayson, Eppley Institute for Research in Cancer
Joseph Highland, Environmental Defense Fund
William Lijinsky, Federick Cancer Research Center
Henry C. Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Louise Strong, University of Texas Health Sciences Center

---

* 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.

NIH Publication No. 80-1761
August 1980