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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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p-QUINONE DIOXIME

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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAY OF p-QUINONE DIOXIME
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of p-quinone dioxime conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of p-quinone dioxime was conducted by Litton Bionetics, Inc., Kensington, Maryland, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. N. P. Page (1,2), Dr. E. K. Weisburger (1) and Dr. J. H. Weisburger (1,3). The principal investigators for the contract were Dr. F. M. Garner (4) and Dr. B. M. Ulland (4,5). Mr. S. Johnson (4) was the coprincipal investigator for the contract. Animal treatment and observation were supervised by Mr. R. Cypher (4), Mr. D. S. Howard (4) and Mr. H. D. Thornett (4); Mr. H. Paulin (4) analyzed dosed feed mixtures. Ms. J. Blalock (4) was responsible for data collection and assembly. Chemical analysis was performed by Midwest Research Institute (6) and the analytical results were reviewed by Dr. N. Zimmerman (7).

Histopathologic examinations were performed by Dr. N. J. Wosu (4), at Litton Bionetics, Inc., the pathology narratives were written by Dr. N. J. Wosu (4), and the diagnoses included in this report represent the interpretation of this pathologist. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (8).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (9); the statistical analysis was performed by Mr. R. M. Helfand (7) and Dr. J. P. Dirkse, III (10) using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (11).

This report was prepared at METREK, a Division of The MITRE Corporation (7) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (7), task leader Ms. P. Walker (7), senior biologist Mr. M. Morse (7), biochemist Mr. S. C. Drill (7), and technical editor Ms. P. A. Miller (7). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. R. A. Griesemer (1), Dr. T. E. Hamm (1), Dr. W. V. Hartwell (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. A. R. Patel (1), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay for the possible carcinogenicity of p-quinone dioxime was conducted using Fischer 344 rats and B6C3F1 mice. p-Quinone dioxime was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls, with the exception of 18 in the control male mouse group. The high and low concentrations of p-quinone dioxime were 750 and 375 ppm for rats and 1500 and 750 ppm for mice. The compound was administered to rats and mice for 104 weeks. The period of compound administration was followed by an observation period of 1 week for both species.

There were no significant positive associations between the concentrations of p-quinone dioxime administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related mean body weight depression was observed among rats and slight mean body weight depression, relative to controls, was observed among mice, indicating that the dosages of p-quinone dioxime administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

Tumors of the urinary bladder were observed only in dosed rats. For female rats, there was a significant positive association between concentration administered and the incidences of a combination of urinary bladder neoplasms. The high dose to control Fisher exact comparison was also significant for these tumors in female rats. No compound-related neoplasms were observed in male rats or mice of either sex.

Under the conditions of this bioassay, dietary administration of p-quinone dioxime was carcinogenic to female Fischer 344 rats, causing neoplasms of the urinary bladder. The compound was not carcinogenic to male Fischer 344 rats or B6C3F1 mice of either sex.

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I. INTRODUCTION

p-Quinone dioxime (Figure 1) (NCI No. C03850), a rubber vulcanization accelerator, was selected for bioassay by the National Cancer Institute because of a lack of adequate carcinogenicity data.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is dioxime 2,5-cyclohexadiene-1,4-dione.* It is also called dioxime p-benzoquinone; p-quinonedioxime; dioxime 1,4-cyclohexadienedione; and quinone dioxime.

p-Quinone dioxime is used to accelerate the vulcanization of rubber. In conjunction with red lead, p-quinone dioxime produces a fast-curing high modulus rubber stock (Rose and Rose, 1966).

Specific production data for p-quinone dioxime are not available; however, this compound is currently produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by four U.S. companies (Stanford Research Institute, 1977). Imports of p-quinone dioxime through principal U.S. customs districts amounted to 1000 pounds in 1974 (U.S. International Trade Commission, 1976).

The potential for exposure to p-quinone dioxime is greatest for workers in the rubber and chemical manufacturing industries.

*The CAS registry number is 105-11-3.

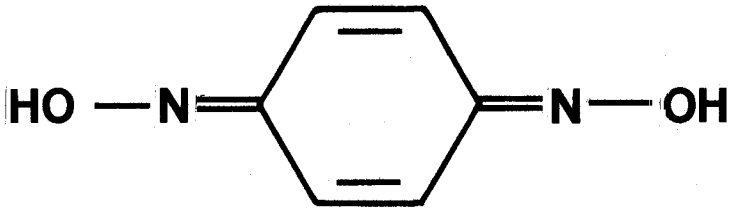


FIGURE 1
CHEMICAL STRUCTURE OF p-QUINONE DIOXIME

II. MATERIALS AND METHODS

A. Chemicals

Two batches of p-quinone dioxime were purchased as a mixture of the cis and trans isomers from Pfaltz and Bauer Chemical Company. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The experimentally determined melting point of 233° to 235°C was compared with the literature value of 240°C (Dictionary of Organic Compounds, 1965). Elemental analysis was within 5 percent of that expected on the basis of the molecular formula of p-quinone dioxime, $C_6H_6O_2N_2$. Thin-layer chromatography was performed utilizing two solvent systems (i.e., benzene:methanol and n-butanol:isopropanol:ammonium hydroxide). Visualization with ultraviolet light and ferricyanide-ferric chloride revealed the major spot and one small spot at the origin on the plate developed with the first solvent system and the major spot and two minor spots on the plate developed with the second solvent system. High pressure liquid chromatography showed the presence of one impurity. The results of infrared (IR) and nuclear magnetic resonance (NMR) analyses were consistent with the structure of the compound. Ultraviolet/visible analysis revealed λ_{max} at 323 and 414 nm with molar extinction coefficients (ϵ) of 26.2×10^3 and 1.2×10^2, respectively. This was compared with a literature λ_{max} of 323 nm and ϵ of 19.3×10^3 (Bayer, 1957).

The second batch of the compound was also analyzed by Midwest Research Institute. The results of elemental analysis were similar to

those for the first batch except that the determined nitrogen content was 10 percent less than the theoretical. Thin-layer chromatography was performed utilizing two solvent systems (i.e., ethyl acetate: methanol and 1,4-dioxane:benzene). Visualization with ultraviolet light and iodine vapor revealed the major spot and two impurities on the plate developed with the first solvent system and the major spot and three impurities on the plate developed with the second system. High pressure liquid chromatography showed one homogeneous peak. The results of IR and NMR analyses were consistent with the structure. Ultraviolet/visible analysis revealed λ_{max} at 319 and 407 nm with ϵ of 2.5×10^3 and 10.6×20^2, respectively.

Throughout this report, the term p-quinone dioxime is used to represent this material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois). p-Quinone dioxime was administered to the dosed animals as a component of the diet.

The chemical was removed from its container and a proper amount was blended with an aliquot of the feed using a mortar and pestle. Once visual homogeneity was attained, the mixture was placed in a 6 kg capacity Patterson-Kelley standard model twin-shell stainless steel V-blender along with the remainder of the feed to be prepared. After 20 minutes of blending, the mixtures were placed in double

plastic bags and stored in the dark at 4°C. The mixture was prepared once weekly.

Dosed feed preparations containing 1500 and 375 ppm of p-quinone dioxime were analyzed spectrophotometrically. The mean result immediately after preparation was 97 percent of theoretical (ranging from 96 to 98 percent). After 10 days at ambient room temperature the mean result was 78 percent of theoretical (ranging from 73 to 82 percent).

C. Animals

The two animal species, Fischer 344 rats and B6C3F1 mice, used in the carcinogenicity bioassay were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. Rats were supplied by A. R. Schmidt, Madison, Wisconsin, and Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Mice were supplied by Charles River Breeding Laboratories, Inc.

Rats and mice, approximately 4 weeks old when received, were examined and any obviously ill or runted animals were killed. After 2 weeks of quarantine, animals which did not manifest clinical signs of disease were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given species and sex.

D. Animal Maintenance

Animals were housed by species in rooms maintained at 22° to 26°C and 45 to 55 percent relative humidity. Incoming air was

filtered through HEPA filters (Flanders Filters, McLean, Virginia) at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided 8 hours per day (9:00 a.m. to 5:00 p.m.).

Rats and mice were housed by sex in groups of four or five, respectively, in polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) suspended from aluminum racks. Racks were fitted with a continuous piece of stainless steel mesh over which a sheet of filter paper was firmly secured. Filter paper was changed at 2-week intervals, when the racks were sanitized. Clean cages and bedding (Ab-sorb-dri® hardwood chip bedding [Wilner Wood Products Company, Norway, Maine]) were provided twice weekly.

Acidulated water (pH 2.5) was supplied to animals in water bottles which were changed and washed twice weekly. Sipper tubes were washed at weekly intervals. During the period of chemical administration, dosed and control animals received treated or untreated Wayne Lab-Blox® meal as appropriate. The feed was supplied in hanging stainless steel hoppers which were refilled three times per week and sanitized weekly. Food and water were available ad libitum for both species.

All dosed and control rats were housed in a room with other rats receiving diets containing* Michler's ketone (90-94-8); p-chloroaniline (106-47-8); and p-nitrosodiphenylamine (156-10-5).

*CAS registry numbers are given in parentheses.

All dosed and control mice were housed in a room with mice receiving diets containing Michler's ketone (90-94-8); 4,4'-methylene-bis(N,N-dimethyl)benzenamine (101-61-1); p-chloroaniline (106-47-8); 5-chloro-o-toluidine (95-79-4); N-phenyl-p-phenylenediamine hydrochloride (2198-59-6); 1-phenyl-2-thiourea (103-85-5); 2-nitro-p-phenylenediamine (5307-14-2); dibutyltin diacetate (1067-33-0); and 3-chloro-p-toluidine (95-74-9).

E. Selection of Initial Concentrations

To establish the concentrations of p-quinone dioxime for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Rats were distributed among ten groups, each consisting of five males and five females. p-Quinone dioxime was incorporated into the basal laboratory diet and supplied ad libitum to eight of the ten rat groups in concentrations of 680, 1000, 1470, 2160, 3150, 4600, 6800 and 10,000 ppm. The two remaining rat groups served as control groups, receiving only the basal laboratory diet.

Mice were distributed among ten groups, each consisting of five males and five females. p-Quinone dioxime was incorporated into the basal laboratory diet and supplied ad libitum to eight of the ten mouse groups in concentrations of 680, 1000, 1470, 3150, 4600, 6800, 10,000 and 14,700 ppm. The two remaining mouse groups served as control groups, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 7 weeks, followed by a 1-week observation period during which all animals were fed the basal laboratory diet. Individual body weights and food consumption data were recorded twice weekly throughout the study. Upon termination of the study all survivors were euthanized and necropsied.

The following table indicates the mean body weight gain relative to controls, survival, and incidence of convulsive attacks observed in each of the rat groups at the end of the subchronic test.

RAT SUBCHRONIC STUDY RESULTS

ppm	Mean Body Weight Gain (%)*		Survival**		Observation of Convulsive Attacks**	
	Males	Females	Males	Females	Males	Females
10,000	-137	--	1/5	0/5	0/5	0/5
6,800	-114	-66	3/5	1/5	0/5	0/5
4,600	- 99	-43	5/5	5/5	0/5	5/5
3,150	- 59	-27	5/5	5/5	0/5	0/5
2,160	- 19	-18	5/5	5/5	0/5	0/5
1,470	- 6	-17	5/5	5/5	0/5	0/5
1,000	- 18	-13	5/5	5/5	0/5	0/5
680	- 26	- 2	5/5	5/5	0/5	0/5
0	--	--	5/5	5/5	0/5	0/5

The high concentration selected for administration to dosed rats in the chronic bioassay was 750 ppm.

The following table indicates the mean body weight gain relative to controls, and survival observed in each of the mouse groups at the end of the subchronic test.

*- is indicative of mean body weight gain less than that of controls.

**Number of animals observed/number of animals originally in group.

MOUSE SUBCHRONIC STUDY RESULTS

ppm	Mean Body Weight Gain (%)* Males	Females	Survival** Males	Females
14,700	-34	--	5/5	0/5
10,000	-22	-12	5/5	3/5
6,800	- 5	- 5	5/5	5/5
4,600	- 9	- 7	5/5	5/5
3,150	+ 1	- 4	5/5	5/5
1,470	- 9	-12	5/5	5/5
1,000	+ 2	- 6	5/5	5/5
680	- 4	- 1	5/5	5/5
0	--	--	5/5	5/5

No other clinical abnormalities which could be attributed to administration of the compound were observed. The high concentration selected for administration to dosed mice in the chronic bioassay was 1500 ppm.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, concentrations administered, and duration of treated and untreated observation periods) are summarized in Tables 1 and 2.

All rats were approximately 6 weeks old at the time the test was initiated and were placed on test on the same day. Dosed rats were supplied diets containing 750 and 375 ppm p-quinone dioxime for 104 weeks followed by a 1-week observation period, when no test chemicals were used. Throughout this report those rats receiving

*+ is indicative of mean body weight gain greater than that of controls.
- is indicative of mean body weight gain less than that of controls.

**Number of animals observed/number of animals originally i9 group.

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
p-QUINONE DIOXIME FEEDING EXPERIMENT

	INITIAL GROUP SIZE	p-QUINONE DIOXIME CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	105
LOW DOSE	50	375	104	
		0		1
HIGH DOSE	50	750	104	
		0		1
FEMALE				
CONTROL	20	0	0	105
LOW DOSE	50[b]	375	104	
		0		1
HIGH DOSE	50	750	104	
		0		1

[a]Concentrations given in parts per million.
[b]One of the animals in this group was subsequently determined to be a male.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
p-QUINONE DIOXIME FEEDING EXPERIMENT

	INITIAL GROUP SIZE	p-QUINONE DIOXIME CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
CONTROL	18	0	0	105
LOW DOSE	50	750	104	
		0		1
HIGH DOSE	50	1500	104	
		0		1
FEMALE				
CONTROL	20	0	0	105
LOW DOSE	50	750	104	
		0		1
HIGH DOSE	50	1500	104	
		0		1

[a]Concentrations given in parts per million.

the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to as the low dose groups.

All mice were approximately 6 weeks old at the time the test was initiated and were placed on test on the same day. Dosed mice were supplied diets containing 1500 and 750 ppm p-quinone dioxime for 104 weeks followed by a 1-week observation period, when no test chemicals were used. Throughout this report those mice receiving the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to as the low dose groups.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment and body weights were recorded once a week for the first 6 weeks, every 2 weeks for the next 4 weeks, and at monthly intervals thereafter. All animals were inspected twice daily. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group.

All moribund animals, animals that developed large, palpable masses that jeopardized their health, or animals that survived until the end of the bioassay were euthanized using carbon dioxide inhalation. Necropsies were immediately performed on these animals and on all animals found dead during the bioassay. Gross and microscopic examinations were performed on all major tissues, organs, and gross

lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in a 10 percent neutral buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were recorded in each group at the time that the test was initiated.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical

observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined

histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined 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 was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

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

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

relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated 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 (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity,

the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

Distinct and consistent dose-related mean body weight depression was apparent in both male and female rats throughout the bioassay (Figure 2).

No other clinical signs were recorded.

B. Survival

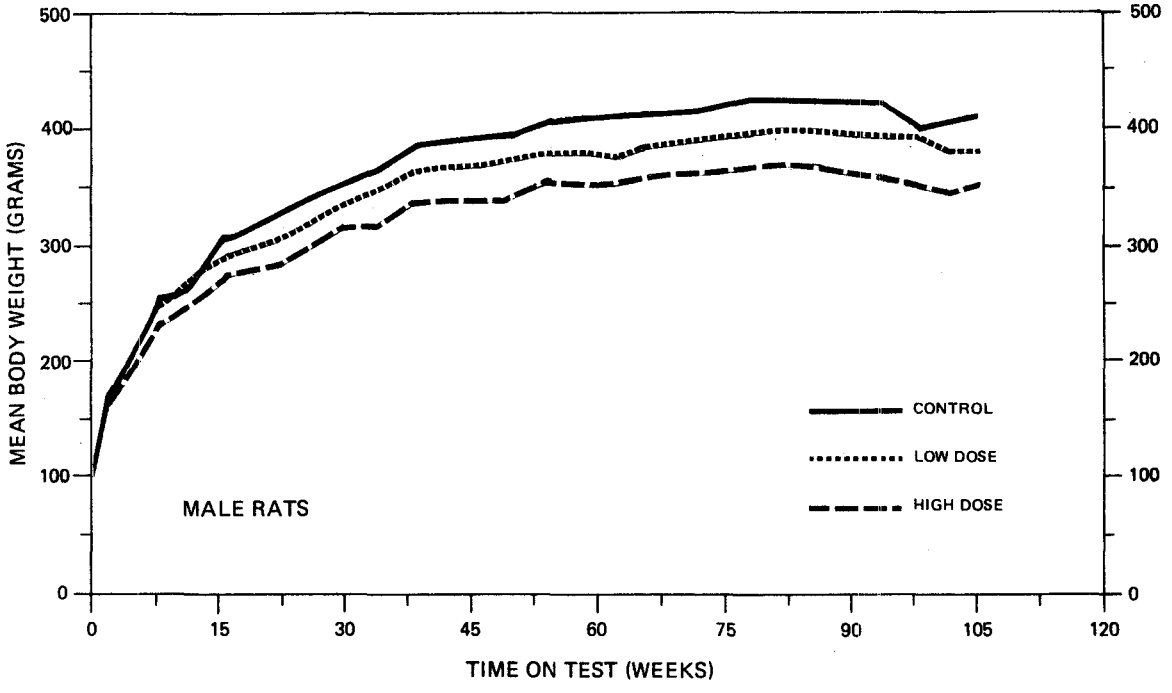
The estimated probabilities of survival for male and female rats in the control and p-quinone dioxime-dosed groups are shown in Figure 3. The Tarone test for association between dosage and mortality was not significant for either males or females.

There were adequate numbers of male rats at risk from late-developing tumors, as 70 percent (35/50) of the high dose, 78 percent (39/50) of the low dose, and 85 percent (17/20) of the controls survived on test until the termination of the study.

There were adequate numbers of female rats at risk from late-developing tumors, as 78 percent (39/50) of the high dose, 78 percent (38/49) of the low dose, and 90 percent (18/20) of the controls survived on test until the termination of the study.

C. Pathology

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).



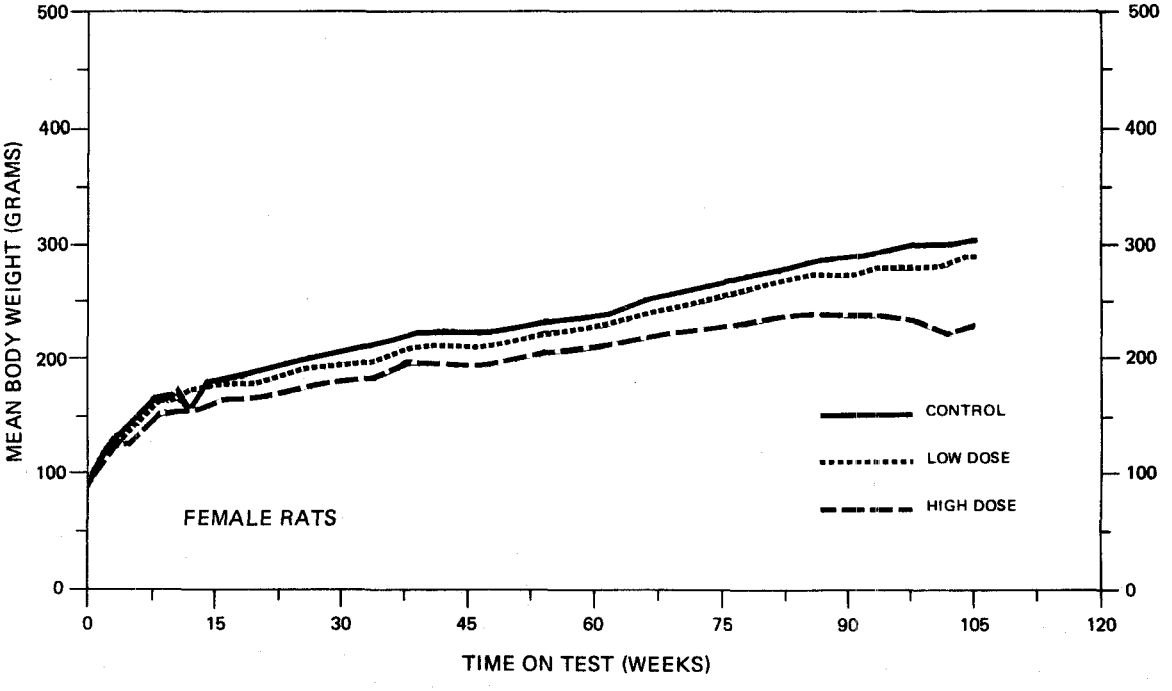
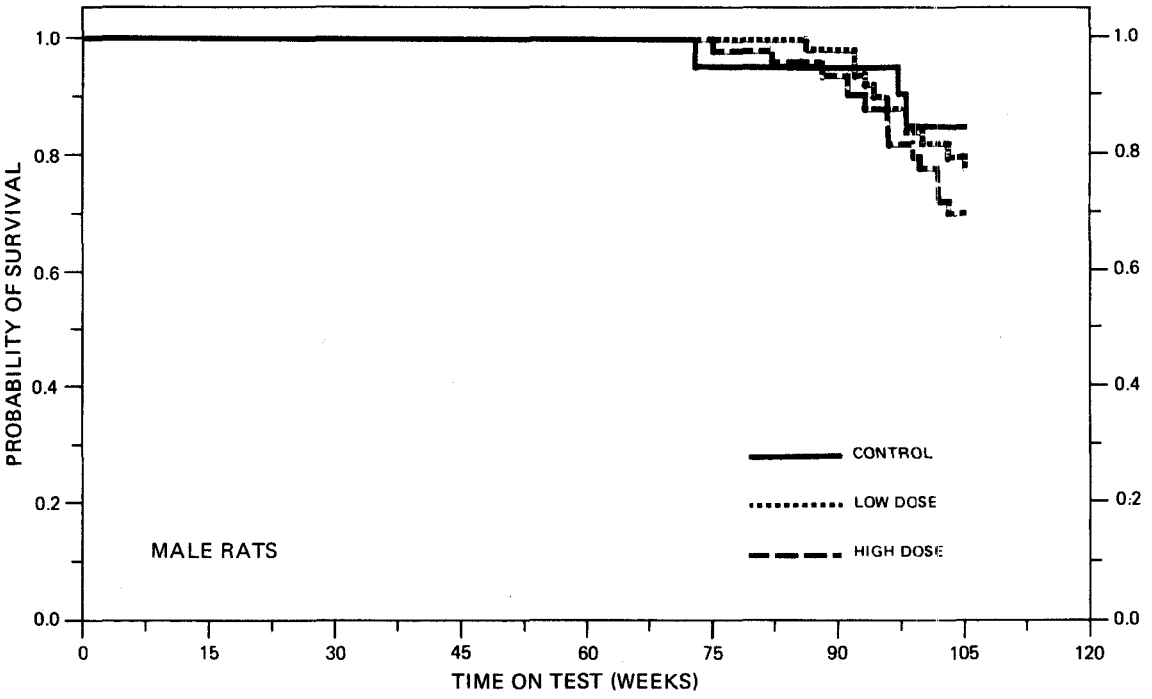


FIGURE 2
GROWTH CURVES FOR p-QUINONE DIOXIME CHRONIC STUDY RATS



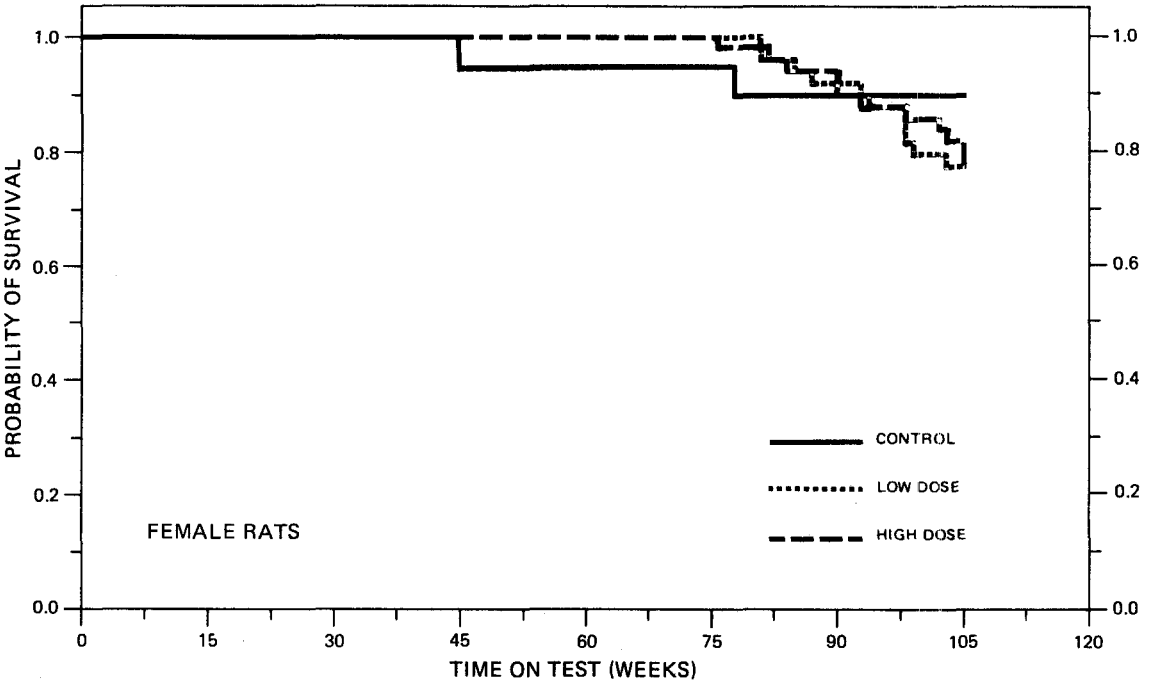


FIGURE 3
SURVIVAL COMPARISONS OF p-QUINONE DIOXIME CHRONIC STUDY RATS

Microscopic examination revealed a variety of neoplasms in male and female rats with the highest incidence in the urinary, endocrine and reproductive systems. Except for the urinary system the distribution of neoplasms was judged to be random among dosed and control animals, and the neoplasms observed were of the type commonly observed in aging Fischer 344 rats.

The neoplasms of the urinary tract, which are summarized in the following table, were observed only in dosed animals.

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
URINARY BLADDER						
No. of Animals with Tissues Examined Histopathologically	(16)	(45)	(46)	(19)	(43)	(44)
Transitional-Cell Papilloma	0	0	2(4%)	0	1(2%)	4(9%)
Squamous-Cell Carcinoma	0	0	0	0	1(2%)	0
Transitional-Cell Carcinoma	0	0	0	0	1(2%)	7(16%)
KIDNEY						
No. of Animals with Tissues Examined Histopathologically	(20)	(49)	(50)	(20)	(48)	(49)
Transitional-Cell Papilloma	0	1(2%)	0	0	0	0
Tubular-Cell Adenoma	0	0	2(4%)	0	0	0
Tubular-Cell Adenocarcinoma	0	0	1(2%)	0	0	0

Bladder neoplasms occurred predominantly in females. The papillomas generally projected into the bladder lumen as sessile or short pedunculated polyps supported on mature organized connective

tissue core and covered by well-differentiated transitional epithelium. The transitional-cell carcinomas showed variable degrees of cellular anaplasia, deviation from normal tinctorial characteristics, disarray, and loss of normal polarity to the subepithelial tissues. The mitotic index was generally high and bizarre mitotic figures were not uncommon. Subepithelial invasion present in many was not considered as the exclusive basis for malignancy especially because such invasion, if focal, could be missed in a single plane of sectioning. The squamous-cell carcinoma was massive, projected into, and nearly occluded the bladder lumen and diffusely invaded the markedly thickened scirrhous bladder wall as irregular acini trabeculae and ductules of anaplastic pleomorphic epidermoid cells. There was abundant keratin formation especially on the luminal surface. Adjoining this was a well-differentiated transitional-cell carcinoma from which the former may have arisen.

Kidney tumors were found only in males. There was one transitional-cell papilloma of the renal pelvis in a low dose male and one tubular-cell adenocarcinoma and two tubular-cell adenomas in the high dose animals. The papilloma of the renal pelvis was unilateral and well-differentiated. The tubular neoplasms were well-delineated from surrounding tissue and showed a compact glandular arrangement of plump, tubular epithelial cells. None of the neoplasms of the urinary system showed metastasis from their primary sites.

Pituitary and adrenal neoplasms were relatively more frequent in this study than expected in comparison with the spontaneous incidence of these neoplasms observed in this strain of rat at this laboratory. However, their incidence among control animals in this study was as high or even higher than among dosed animals. Other endocrine tumors were few and random.

Endometrial stromal polyps and interstitial-cell tumors were frequent but did not exceed the number expected for aged Fischer 344 rats. Tumors of other organs occurred randomly and sporadically.

A variety of nonneoplastic lesions was observed and are summarized in Appendix C, Tables C1 and C2. Geriatric progressive kidney changes were present which appeared generally more severe in dosed animals, especially males. The principal lesion was tubular nephropathy resulting in concomitant regenerative changes. Hyperplasia of the transitional epithelium lining the renal pelvis was observed in 14 high dose males and 4 high dose females. These varied in appearance from moderately rugous folds of normal appearing transitional cells to irregular villous projections and maintained normal tinctorical and cytologic characteristics. Other nonneoplastic lesions appeared randomly in dosed and control animals and were well within the expected incidence occurring spontaneously in Fischer 344 rats.

Based on the results of this pathology examination, p-quinone dioxime caused urinary bladder tumors in female Fischer 344 rats at the doses administered in this bioassay. In addition, administration

of the compound appeared to be associated with an increase in the incidence of kidney tumors in the males and with the severity of kidney tubular degeneration in both sexes.

D. Statistical Analysis of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or p-quinone dioxime-dosed groups and where such tumors were observed in at least 5 percent of the group.

In female rats the Cochran-Armitage test indicated a significant ($P = 0.003$) positive association between dose and the combined incidence of transitional-cell carcinomas, transitional-cell papillomas or squamous-cell carcinomas of the urinary bladder. This was supported by the Fisher exact test comparing the high dose group to the control group with a significant probability level of $P = 0.012$. For transitional-cell carcinomas alone, the Cochran-Armitage test indicated a significant ($P = 0.011$) positive association between dose and incidence but neither of the Fisher exact tests was significant. Based upon these statistical results there is sufficient evidence that p-quinone dioxime was a carcinogen in female Fischer 344 rats under the conditions of this bioassay.

None of the statistical tests for any site in male rats indicated a significant positive association between chemical administration and tumor incidence.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH p-QUINONE DIOXIME[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malginant Lymphoma[b]	2/20(0.10)	3/50(0.06)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.600	1.200
Lower Limit	---	0.076	0.243
Upper Limit	---	6.860	11.574
Weeks to First Observed Tumor	97	92	82
Pituitary: Chromophobe Adenoma[b]	2/18(0.11)	5/45(0.11)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.000	1.080
Lower Limit	---	0.187	0.221
Upper Limit	---	9.949	10.396
Weeks to First Observed Tumor	105	105	105
Adrenal: Adenoma NOS[b]	3/20(0.15)	3/49(0.06)	1/48(0.02)
P Values[c]	P = 0.044(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.408	0.139
Lower Limit	---	0.061	0.003
Upper Limit	---	2.857	1.631
Weeks to First Observed Tumor	105	92	105

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Carcinoma NOS or Adenoma NOS[b]	2/19(0.11)	5/45(0.11)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.056	0.388
Lower Limit	---	0.196	0.031
Upper Limit	---	10.513	5.108
Weeks to First Observed Tumor	105	98	105
Testis: Interstitial-Cell Tumor[b]	18/20(0.90)	48/49(0.98)	36/48(0.75)
P Values[c]	P = 0.012(N)	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.017	---	---
Relative Risk (Control)[d]	---	1.088	0.833
Lower Limit	---	0.959	0.723
Upper Limit	---	1.174	1.137
Weeks to First Observed Tumor	97	86	96

[a]Treated groups received doses of 375 or 750 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH p-QUINONE DIOXIME[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroadenoma[b]	2/20(0.10)	4/49(0.08)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.816	0.400
Lower Limit	---	0.131	0.032
Upper Limit	---	8.603	5.277
Weeks to First Observed Tumor	105	103	105
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	0/20(0.00)	2/49(0.04)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.125	0.250
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	85	105
Urinary Bladder: Transitional-Cell Carcinoma[b]	0/19(0.00)	1/43(0.02)	7/44(0.16)
P Values[c]	P = 0.011	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.024	0.878
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	105

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Urinary Bladder: Transitional-Cell Carcinoma, Transitional-Cell Papilloma or Squamous-Cell Carcinoma[b]	0/19(0.00)	3/43(0.07)	11/44(0.25)
P Values[c]	P = 0.003	N.S.	P = 0.012
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.277	1.502
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	81	82
Pituitary: Chromophobe Adenoma[b]	10/20(0.50)	20/46(0.43)	11/47(0.23)
P Values[c]	P = 0.014(N)	N.S.	P = 0.033(N)
Relative Risk (Control)[d]	---	0.870	0.468
Lower Limit	---	0.503	0.232
Upper Limit	---	1.728	1.048
Weeks to First Observed Tumor	105	81	103
Mammary Gland: Adenoma NOS or Fibroadenoma[b]	1/20(0.05)	0/49(0.00)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	1.200
Lower Limit	---	0.000	0.106
Upper Limit	---	7.624	61.724
Weeks to First Observed Tumor	105	---	76

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	4/20(0.20)	6/48(0.13)	1/47(0.02)
P Values[c]	P = 0.014(N)	N.S.	P = 0.025(N)
Relative Risk (Control)[d]	---	0.625	0.106
Lower Limit	---	0.171	0.002
Upper Limit	---	2.764	1.003
Weeks to First Observed Tumor	105	105	105

[a]Treated groups received doses of 375 or 750 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

In male rats the Cochran-Armitage test did indicate a significant negative association between adenomas NOS of the adrenal and also for interstitial-cell tumors. In the latter case the test for departure from linear trend was also significant.

The Cochran-Armitage test indicated a significant negative association in females for chromophobe adenomas of the pituitary and also for endometrial stromal polyps. The high dose to control Fisher exact test was not significant for chromophobe adenomas under the Bonferroni criterion, but it was significant for endometrial stromal polyps.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by p-quinone dioxime that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

While no distinct or consistent dose-related mean body weight depression was apparent in either male or female mice, dosed groups of both sexes did weigh slightly less than their controls throughout a major portion of the bioassay (Figure 4).

No other clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female mice in the control and p-quinone dioxime-dosed groups are shown in Figure 5. The Tarone test for association between dosage and mortality was not significant for either male or female mice.

There were adequate numbers of male mice at risk from late-developing tumors. Although 4 high dose, 1 low dose, and 3 control males were missing in week 21 and 1 control male was accidentally killed in week 92, 86 percent (43/50) of the high dose, 88 percent (44/50) of the low dose and 67 percent (12/18) of the controls survived on test until termination of the study.

Nine low dose females were missing, 3 in week 16, 5 in week 22, and 1 in week 105. There were adequate numbers of female mice at risk from late-developing tumors, as 78 percent (39/50) of the high dose, 64 percent (32/50) of the low dose and 80 percent (16/20) of the controls survived on test until the termination of the study.

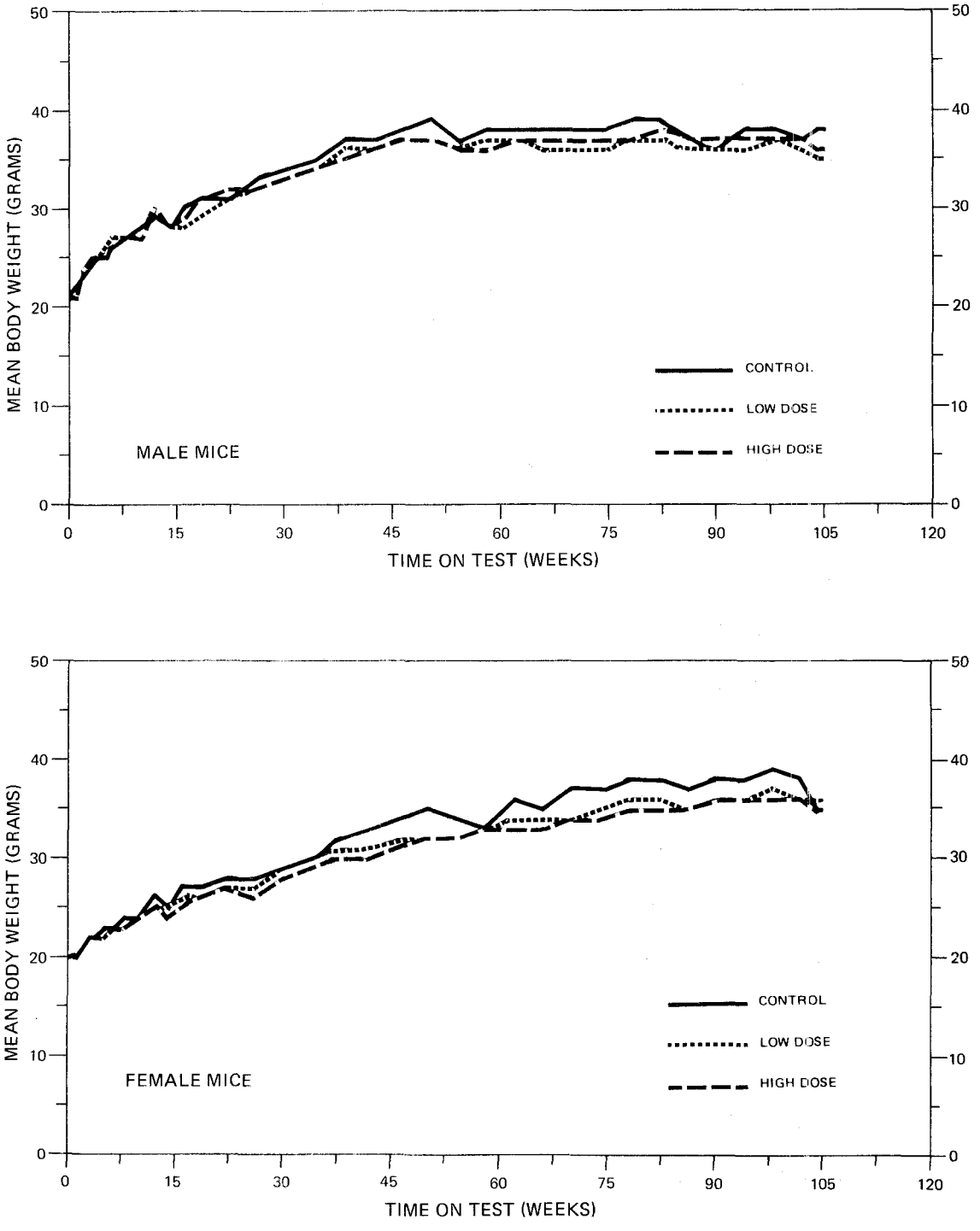
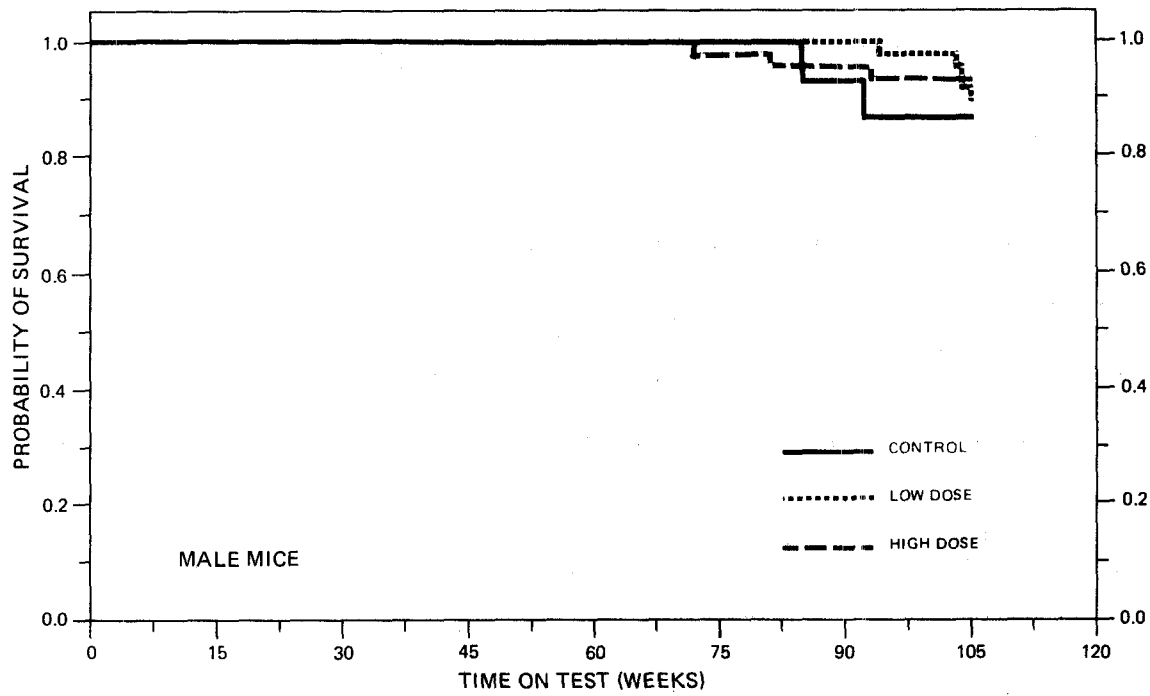


FIGURE 4
GROWTH CURVES FOR p-QUINONE DIOXIME CHRONIC STUDY MICE



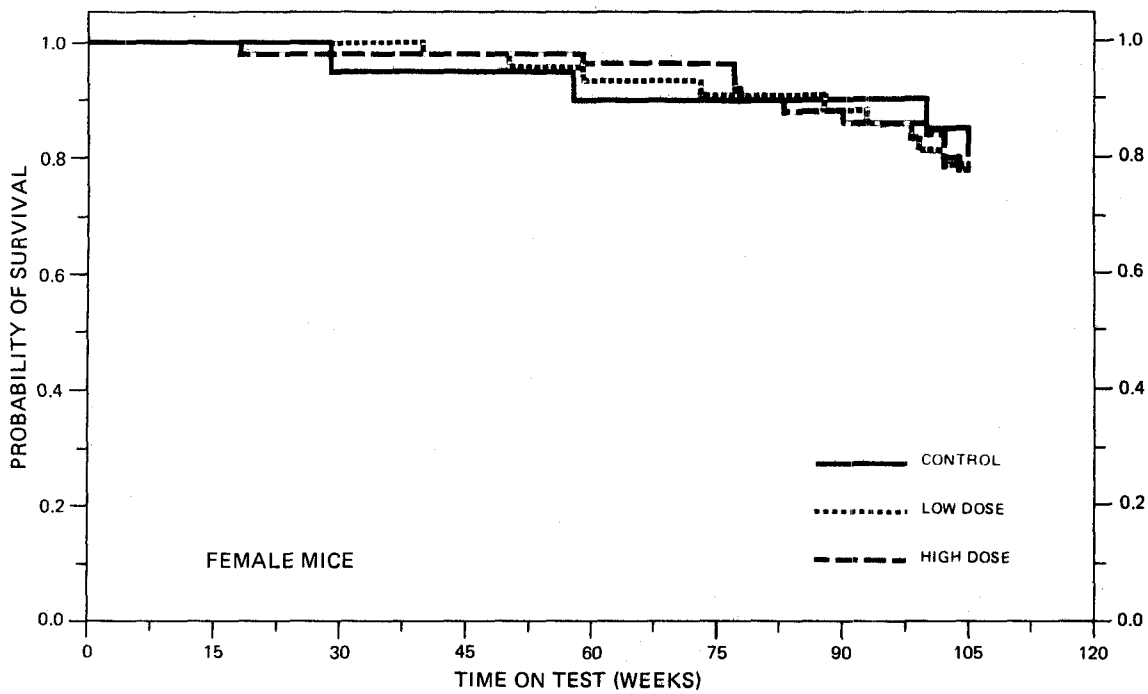


FIGURE 5
SURVIVAL COMPARISONS OF p-QUINONE DIOXIME CHRONIC STUDY MICE

C. Pathology

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).

The most commonly observed neoplasms were of the lungs and liver. Both benign and malignant alveolar/bronchiolar and hepatocellular neoplasms were present in dosed and control animals of each sex. Pulmonary metastasis of a hepatocellular carcinoma was observed in one control male. Vascular neoplasms of the spleen were observed only in dosed animals. These included hemangioma (in 1 low dose male, 3 high dose males, 2 low dose females and 1 high dose female) and hemangiosarcoma (in 2 low dose males). No metastasis was observed. Although there were instances of tumor involvement of only dosed animals, the overall data failed to give conclusive evidence of carcinogenicity for p-quinone dioxime administered at the given doses in B6C3F1 mice.

A variety of nonneoplastic lesions occurred in dosed and control animals with the incidence and intensity seen in aged B6C3F1 mice.

Based on the results of this pathology examination, p-quinone dioxime did not induce neoplastic or nonneoplastic lesions in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analysis of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH p-QUINONE DIOXIME[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/15(0.07)	3/49(0.06)	5/45(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.918	1.667
Lower Limit	---	0.083	0.215
Upper Limit	---	47.230	76.964
Weeks to First Observed Tumor	92	105	105
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	2/15(0.13)	7/49(0.14)	6/45(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.071	1.000
Lower Limit	---	0.241	0.211
Upper Limit	---	9.985	9.548
Weeks to First Observed Tumor	92	105	105
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	0/15(0.00)	7/49(0.14)	2/46(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.032	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.634	0.102
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	94	105

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangioma or Hemangiosarcoma[b]	0/15(0.00)	4/49(0.08)	3/46(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.302	0.208
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	93
Liver: Hepatocellular Carcinoma[b]	4/15(0.27)	5/49(0.10)	11/46(0.24)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.383	0.897
Lower Limit	---	0.100	0.331
Upper Limit	---	1.749	3.449
Weeks to First Observed Tumor	85	105	81
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	5/15(0.33)	6/49(0.12)	12/46(0.26)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.037	---	---
Relative Risk (Control)[d]	---	0.367	0.783
Lower Limit	---	0.117	0.327
Upper Limit	---	1.355	2.483
Weeks to First Observed Tumor	85	105	81

TABLE 5 (CONCLUDED)

[a]Treated groups received doses of 750 or 1500 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH p-QUINONE DIOXIME[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	1/19(0.05)	2/41(0.05)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.927	1.140
Lower Limit	---	0.052	0.101
Upper Limit	---	53.355	58.635
Weeks to First Observed Tumor	105	105	105
Hematopoietic System: Leukemia or Malignant Lumphoma[b]	2/20(0.10)	3/41(0.07)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.732	1.200
Lower Limit	---	0.093	0.243
Upper Limit	---	8.309	11.574
Weeks to First Observed Tumor	105	99	100
Circulatory System: Hemangioma or Hemangiosarcoma[b]	1/20(0.05)	3/41(0.07)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.463	0.800
Lower Limit	---	0.129	0.045
Upper Limit	---	74.895	46.273
Weeks to First Observed Tumor	105	102	105

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	3/41(0.07)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.305	0.525
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	73	90
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	0/20(0.00)	3/41(0.07)	8/50(0.16)
P Values[c]	P = 0.027	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.305	0.952
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	73	90
Pituitary: Chromophobe Adenoma[b]	0/13(0.00)	2/27(0.07)	1/29(0.03)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.153	0.025
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	98	105

TABLE 6 (CONCLUDED)

[a]Treated groups received doses of 750 or 1500 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or p-quinone dioxime-dosed groups and where such tumors were observed in at least 5 percent of the group.

The Cochran-Armitage test indicated a significant (P = 0.027) positive association between dose and the combined incidence of hepatocelluar carcinomas or neoplastic nodules in female mice. However, this was not supported by either of the Fisher exact tests. For female B6C3F1 mice maintained at this laboratory for the NCI Carcinogenesis Testing Program, the combined historical incidence for hepatocellular carcinomas or neoplastic nodules is 9/207 (4 percent). The historical incidences for hepatocellular carcinomas range from 0 to 6 percent and for the neoplastic nodules, the range is from 0 to 11 percent. None of the statistical tests indicated a significant positive association between dose and incidence in male mice at any site. The test for departure from linear trend was significant in male mice for hepatocellular carcinomas or neoplastic nodules.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than

one, indicating the theoretical possibility of tumor induction in mice by p-quinone dioxime that could not be established under the conditions of this test.

V. DISCUSSION

There were no significant positive associations between the concentrations of p-quinone dioxime administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related mean body weight depression was observed among rats, indicating that the dosages of p-quinone dioxime administered to the animals in this bioassay may have approximated the maximum tolerated concentrations. Since no distinct mean body weight depression relative to controls, no significantly accelerated mortality, and no other manifestations of chronic toxicity were associated with administration of p-quinone dioxime to male or female mice, it is possible that these animals may have been able to tolerate a higher dietary concentration.

Tumors of the urinary bladder occurred only in dosed rats and primarily in females (i.e., transitional-cell papilloma 0/45, 2/46, 1/43, and 4/44 in the low dose males, high dose males, low dose females, and high dose females, respectively; transitional-cell carcinoma 0/45, 0/46, 1/43, and 7/44 in the low dose males, high dose males, low dose females, and high dose females, respectively; squamous-cell carcinomas 0/45, 0/46, 1/43, and 0/44 in the low dose males, high dose males, low dose females, and high dose females, respectively). The Cochran-Armitage test for the female

rats indicated a significant positive association between the concentrations administered and the incidences of these tumors when combined. The high dose to control Fisher exact comparison for females was also significant. No statistical tests for tumors at any site in male rats or at any other site in female rats indicated a significant positive association between compound administration and tumor incidence.

In female mice there was a significant positive association between chemical administration and the incidence of hepatocellular neoplasms. However, the Fisher exact comparisons were not significant. The historical control incidence for this combination of liver neoplasms in female B6C3F1 mice maintained by this laboratory for the NCI Carcinogenesis Testing Program is 4 percent with incidences as high as 17 percent, while 8/50 (16 percent) of the high dose female mice in this bioassay had one of these tumors. The difference between the historical data and the results obtained in this bioassay, do not support an association between the administration of p-quinone dioxime and the incidence of a combination of neoplastic nodules and hepatocellular carcinomas. There were no other statistical tests for tumors at any site in mice of either sex that indicated a significant positive association between compound administration and tumor incidence.

Under the conditions of this bioassay, dietary administration of p-quinone dioxime was carcinogenic to female Fischer 344 rats,

causing neoplasms of the urinary bladder. The compound was not carcinogenic to male Fischer 344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH p-QUINONE DIOXIME

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH p-QUINONE DIOXIME

	CONTROL(UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
KERATOACANTHOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
SARCOMA, NOS	1 (5%)		
FIBROMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
C-CELL CARCINOMA, METASTATIC		1 (2%)	
HEPATOBLASTOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMIA,NOS	2 (10%)	2 (4%)	5 (10%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
NEOPLASTIC NODULE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
HEPATOBLASTOMA			1 (2%)
#SMALL INTESTINE	(20)	(50)	(49)
LEIOMYOSARCOMA			1 (2%)
#DUODENUM	(20)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	
TUBULAR-CELL ADENOMA			2 (4%)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
#URINARY BLADDER	(16)	(45)	(46)
TRANSITIONAL-CELL PAPILLOMA			2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(45)	(50)
CHROMOPHOBE ADENOMA	2 (11%)	5 (11%)	6 (12%)
#ADRENAL	(20)	(49)	(48)
ADENOMA, NOS	3 (15%)	3 (6%)	1 (2%)
PHEOCHROMOCYTOMA		2 (4%)	
#THYROID	(19)	(45)	(49)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS	2 (11%)	4 (9%)	2 (4%)
C-CELL CARCINOMA	1 (5%)	1 (2%)	
#PANCREATIC ISLETS	(19)	(50)	(48)
ISLET-CELL ADENOMA		1 (2%)	
ISLET-CELL CARCINOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(20)	(50)	(50)
ADENOMA, NOS		1 (2%)	1 (2%)
CYSTADENOMA, NOS			1 (2%)
#TESTIS	(20)	(49)	(48)
INTERSTITIAL-CELL TUMOR	18 (90%)	48 (98%)	36 (75%)

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

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*BODY CAVITIES	(20)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
FIBROSARCOMA	1 (5%)		
MESOTHELIOMA, MALIGNANT	1 (5%)	1 (2%)	
THORAX			
FIBROADENOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	6	10
MORIBUND SACRIFICE	2	5	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	39	35
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL(UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	49	41
TOTAL PRIMARY TUMORS	33	77	64
TOTAL ANIMALS WITH BENIGN TUMORS	18	48	37
TOTAL BENIGN TUMORS	26	68	54
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	8	9
TOTAL MALIGNANT TUMORS	7	8	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* 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 TREATED WITH p-QUINONE DIOXIME

	CONTROL(UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(50)
SEBACEOUS ADENOMA			1 (2%)
LIPOMA		1 (2%)	
FIBROADENOMA	2 (10%)	4 (8%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(48)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
#CEREBRUM	(19)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
LEUKEMIA,NOS		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEPATOCELLULAR ADENOMA		2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
URINARY SYSTEM			
#URINARY BLADDER	(19)	(43)	(44)
SQUAMOUS CELL CARCINOMA		1 (2%)	
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	4 (9%)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	7 (16%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(46)	(47)
CHROMOPHOBE ADENOMA	10 (50%)	20 (43%)	11 (23%)
#ADRENAL	(20)	(49)	(49)
ADENOMA, NOS	1 (5%)		1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(20)	(45)	(46)
ADENOMA, NOS		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
ADENOMA, NOS			1 (2%)
INFILTRATING DUCT CARCINOMA	1 (5%)		
FIBROADENOMA	1 (5%)		2 (4%)
#UTERUS	(20)	(48)	(47)
PAPILLARY ADENOMA			1 (2%)
MYXOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	4 (20%)	6 (13%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(19)	(48)	(48)
GLIOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A2 (CONCLUDED)

	CONTROL(UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	4	7
MORIBUND SACRIFICE	1	7	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	38	39
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	31	28
TOTAL PRIMARY TUMORS	20	43	37
TOTAL ANIMALS WITH BENIGN TUMORS	13	25	23
TOTAL BENIGN TUMORS	19	38	27
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	5	9
TOTAL MALIGNANT TUMORS	1	5	10
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH p-QUINONE DIOXIME

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH p-QUINONE DIOXIME

	CONTROL(UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	3	1	4
ANIMALS NECROPSIED	15	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	15	49	46
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(49)	(46)
CYSTADENOMA, NOS			1 (2%)
HEMANGIOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(15)	(49)	(45)
CARCINOMA,NOS			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (7%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (7%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (7%)	3 (6%)	5 (11%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(15)	(49)	(46)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	1 (2%)
#SPLEEN	(15)	(47)	(45)
HEMANGIOMA		1 (2%)	3 (7%)
HEMANGIOSARCOMA		2 (4%)	
#MANDIBULAR L. NODE	(15)	(41)	(39)
HEPATOCELLULAR CARCINOMA, METAST	1 (7%)		
#MEDIASTINAL L.NODE	(15)	(41)	(39)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (7%)		
#MESENTERIC L. NODE	(15)	(41)	(39)
PLASMA-CELL TUMOR			1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
#SMALL INTESTINE	(15)	(47)	(44)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(15)	(49)	(46)
NEOPLASTIC NODULE	1 (7%)	1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	4 (27%)	5 (10%)	11 (24%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL(UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
BODY CAVITIES			
*MESENTERY	(15)	(49)	(46)
HEMANGIOSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	5	3
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	12	44	43
ANIMAL MISSING	3	1	4
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	20	22
TOTAL PRIMARY TUMORS	7	24	27
TOTAL ANIMALS WITH BENIGN TUMORS	1	5	4
TOTAL BENIGN TUMORS	1	5	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	16	18
TOTAL MALIGNANT TUMORS	5	18	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		
TOTAL SECONDARY TUMORS	3		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	2
TOTAL UNCERTAIN TUMORS	1	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH *p*-QUINONE DIOXIME

	CONTROL(UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		9	
ANIMALS NECROPSIED	20	41	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	41	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(41)	(50)
NEUROFIBROSARCOMA	1 (5%)		
*SUBCUT TISSUE	(20)	(41)	(50)
HEMANGIOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(41)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	1 (2%)	
SARCOMA, NOS, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(41)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
MALIGNANT LYMPHOMA, MIXED TYPE		2 (5%)	1 (2%)
#SPLEEN	(20)	(40)	(48)
HEMANGIOMA		2 (5%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (5%)	1 (3%)	2 (4%)
#LUNG	(19)	(41)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#SMALL INTESTINE	(20)	(41)	(47)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
DIGESTIVE SYSTEM			
#LIVER	(20)	(41)	(50)
NEOPLASTIC NODULE			3 (6%)
HEPATOCELLULAR CARCINOMA		3 (7%)	5 (10%)
#DUODENUM	(20)	(41)	(47)
SARCOMA, NOS	1 (5%)		
#COLON	(11)	(33)	(39)
NEUROFIBROSARCOMA	1 (9%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(13)	(27)	(29)
CHROMOPHOBE ADENOMA		2 (7%)	1 (3%)
#ADRENAL	(17)	(36)	(43)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
CORTICAL CARCINOMA		1 (3%)	
#PARATHYROID	(5)	(12)	(17)
ADENOMA, NOS			1 (6%)
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(41)	(49)
ADENOCARCINOMA, NOS	1 (5%)		
#OVARY	(13)	(28)	(30)
PAPILLARY CYSTADENOMA, NOS		1 (4%)	
TERATOMA, NOS		1 (4%)	
HEMANGIOMA		1 (4%)	
#OVARY/RETE OVARII	(13)	(28)	(30)
NEOPLASM, NOS		1 (4%)	

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
NERVOUS SYSTEM			
#BRAIN	(19)	(40)	(47)
SARCOMA, NOS		1 (3%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(41)	(50)
HEMANGIOSARCOMA	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	6	9
MORIBUND SACRIFICE	1	3	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	32	39
ANIMAL MISSING		9	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL(UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	14	17
TOTAL PRIMARY TUMORS	8	18	21
TOTAL ANIMALS WITH BENIGN TUMORS		7	10
TOTAL BENIGN TUMORS		7	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	9	10
TOTAL MALIGNANT TUMORS	8	9	11
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	
TOTAL UNCERTAIN TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH p-QUINONE DIOXIME

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH p-QUINONE DIOXIME

	CONTROL (UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
VERRUCA		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(48)	(50)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
#LUNG	(19)	(50)	(50)
BRONCHOPNEUMONIA, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (5%)	2 (4%)	1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, ADENOMATOUS		2 (4%)	2 (4%)
LEUKOCYTOSIS, NOS		1 (2%)	
LEUKEMOID REACTION		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(10)	(19)	(38)
HYPERPLASIA, GRANULOCYTIC		1 (5%)	
#SPLEEN	(20)	(50)	(49)
CONGESTION, NOS			1 (2%)
FIBROSIS			1 (2%)
SCAR			1 (2%)
INFARCT, NOS		1 (2%)	
HEMOSIDEROSIS			1 (2%)
HEMATOPOIESIS	1 (5%)		2 (4%)
#LYMPH NODE	(20)	(50)	(47)
LYMPHANGIECTASIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
#MESENTERIC L. NODE	(20)	(50)	(47)
DEGENERATION, CYSTIC			2 (4%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(48)	(49)
FIBROSIS	6 (30%)	12 (25%)	9 (18%)
#ENDOCARDIUM	(20)	(48)	(49)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(19)	(48)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LIVER	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)
FIBROSIS			1 (2%)
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	1 (2%)
HYPERPLASIA, NOS		2 (4%)	3 (6%)
HYPERPLASIA, FOCAL			1 (2%)
LEUKEMOID REACTION		1 (2%)	
HEMATOPOIESIS		1 (2%)	
#BILE DUCT	(20)	(50)	(49)
DILATATION, NOS	1 (5%)		
FIBROSIS			1 (2%)
#PANCREATIC ACINUS	(19)	(50)	(48)
ATROPHY, NOS			1 (2%)
#STOMACH	(20)	(50)	(50)
ULCER, NOS		1 (2%)	
#DUODENUM	(20)	(50)	(49)
HYPERPLASIA, NOS			1 (2%)
#LARGE INTESTINE	(20)	(48)	(49)
NEMATODIASIS	7 (35%)	12 (25%)	5 (10%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
#COLON	(20)	(48)	(49)
NEMATODIASIS			2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
INFLAMMATION, CHRONIC	8 (40%)	40 (82%)	46 (92%)
HYPERPLASIA, TUBULAR CELL			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (5%)		14 (28%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(45)	(50)
CYST, NOS			2 (4%)
#ADRENAL	(20)	(49)	(48)
HEMORRHAGIC CYST		1 (2%)	
#ADRENAL CORTEX	(20)	(49)	(48)
HEMORRHAGE		1 (2%)	
METAMORPHOSIS FATTY	1 (5%)		
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(19)	(45)	(49)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#PARATHYROID	(16)	(41)	(45)
HYPERPLASIA, NOS		2 (5%)	
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(20)	(50)	(50)
DILATATION/DUCTS			1 (2%)
#TESTIS	(20)	(49)	(48)
ATROPHY, NOS	2 (10%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN	(19)	(50)	(50)
HYDROCEPHALUS, NOS	1 (5%)		

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 11-1405	LOW DOSE 11-1403	HIGH DOSE 11-1401
PERIVASCULAR CUFFING		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(20)	(50)	(50)
INFLAMMATION, CHRONIC	1 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMOID REACTION			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF			1

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH p-QUINONE DIOXIME

	CONTROL(UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(48)	(50)
CONGESTION, NOS			1 (2%)
EDEMA, NOS		1 (2%)	1 (2%)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (5%)	3 (6%)	4 (8%)
PNEUMONIA, CHRONIC MURINE			1 (2%)
GRANULOMA, NOS			1 (2%)
LEUKOCYTOSIS, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(13)	(21)	(23)
HYPERPLASIA, GRANULOCYTIC		1 (5%)	
#SPLEEN	(20)	(49)	(49)
CONGESTION, NOS			1 (2%)
CONGESTION, CHRONIC	1 (5%)		
HEMORRHAGE			1 (2%)
FIBROSIS, FOCAL		1 (2%)	
HEMOSIDEROSIS	1 (5%)	9 (18%)	8 (16%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HEMATOPOIESIS	3 (15%)	5 (10%)	3 (6%)
ERYTHROPOIESIS	1 (5%)		
#LYMPH NODE	(20)	(48)	(47)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#MANDIBULAR L. NODE	(20)	(48)	(47)
INFLAMMATION, CHRONIC		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(20)	(48)	(47)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMUS		(1)	
HYPERPLASIA, NOS		1 (100%)	
CIRCULATORY SYSTEM			
#HEART	(19)	(47)	(50)
PERIARTERITIS			1 (2%)
DEGENERATION, HYALINE			1 (2%)
NECROSIS, NOS			1 (2%)
#MYOCARDIUM	(19)	(47)	(50)
INFLAMMATION, NOS			1 (2%)
FIBROSIS	1 (5%)	6 (13%)	5 (10%)
*AORTA	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
GRANULOMA, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
BASOPHILIC CYTO CHANGE	4 (20%)	4 (8%)	2 (4%)
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, NOS	8 (40%)	14 (29%)	1 (2%)
HYPERPLASIA, FOCAL	1 (5%)	1 (2%)	
HEMATOPOIESIS	1 (5%)		
#LIVER/PERIPORTAL	(20)	(49)	(50)
NECROSIS, COAGULATIVE			1 (2%)
#PANCREATIC ACINUS	(20)	(47)	(49)
ATROPHY, NOS		1 (2%)	3 (6%)
#STOMACH	(20)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
ABSCESS, NOS			1 (2%)
#PEYERS PATCH	(20)	(48)	(48)
HYPERPLASIA, RETICULUM CELL			1 (2%)
#LARGE INTESTINE	(20)	(48)	(47)
NEMATODIASIS	1 (5%)	8 (17%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(48)	(49)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, CHRONIC	2 (10%)	5 (10%)	40 (82%)
NEPHROSIS, CHOLEMIC			1 (2%)
NECROSIS, MEDULLARY		2 (4%)	
INFARCT, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			4 (8%)
#URINARY BLADDER	(19)	(43)	(44)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(46)	(47)
CYST, NOS	1 (5%)	1 (2%)	1 (2%)
HEMORRHAGIC CYST		1 (2%)	
#ADRENAL	(20)	(49)	(49)
HEMORRHAGIC CYST	1 (5%)		
NECROSIS, NOS			1 (2%)
NECROSIS, CORTICAL		2 (4%)	2 (4%)
METAMORPHOSIS FATTY	1 (5%)		
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS			1 (2%)
#ADRENAL CORTEX	(20)	(49)	(49)
METAMORPHOSIS FATTY	1 (5%)		1 (2%)
HYPERPLASIA, NOS	1 (5%)		1 (2%)
#THYROID	(20)	(45)	(46)
HYPERPLASIA, NOS	1 (5%)		

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, CYSTIC	1 (5%)		
HYPERPLASIA, C-CELL			1 (2%)
#PARATHYROID	(17)	(34)	(37)
HYPERPLASIA, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
HYPERPLASIA, CYSTIC		1 (2%)	
*PREPUTIAL GLAND	(20)	(49)	(50)
ABSCESS, NOS	1 (5%)		
#UTERUS	(20)	(48)	(47)
CYST, NOS	1 (5%)		1 (2%)
PYOMETRA	1 (5%)		
#UTERUS/ENDOMETRIUM	(20)	(48)	(47)
CYST, NOS	1 (5%)		1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, CYSTIC		1 (2%)	
#OVARY	(19)	(48)	(46)
CYST, NOS	2 (11%)	1 (2%)	
PAROVARIAN CYST		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(19)	(48)	(48)
HYDROCEPHALUS, INTERNAL		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 11-1406	LOW DOSE 11-1404	HIGH DOSE 11-1402
BODY CAVITIES			
*PLEURA	(20)	(49)	(50)
INFLAMMATION, FOCAL		2 (4%)	
*EPICARDIUM	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
*MESENTERY	(20)	(49)	(50)
GRANULOMA, NOS		1 (2%)	
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
LEUKEMOID REACTION			1 (2%)
ADIPOSE TISSUE			
CONGESTION, NOS		1	
HEMORRHAGE		1	
NECROSIS, FAT			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	4	3
AUTO/NECROPSY/HISTO PERF	1		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH p-QUINONE DIOXIME

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH p-QUINONE DIOXIME

	CONTROL(UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	3	1	4
ANIMALS NECROPSIED	15	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	49	46
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(15)	(49)	(46)
ABSCESS, NOS		2 (4%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(15)	(49)	(45)
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC		4 (8%)	3 (7%)
#LUNG	(15)	(49)	(45)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
PERIVASCULITIS	1 (7%)	10 (20%)	7 (16%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	1 (2%)
HISTIOCYTOSIS			1 (2%)
#LUNG/ALVEOLI	(15)	(49)	(45)
HISTIOCYTOSIS		2 (4%)	3 (7%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(10)	(45)	(43)
MYELOFIBROSIS		1 (2%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC		2 (4%)	2 (5%)
#SPLEEN	(15)	(47)	(45)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HEMATOPOIESIS	1 (7%)	5 (11%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
#LYMPH NODE	(15)	(41)	(39)
INFLAMMATION, NOS		1 (2%)	
ABSCESS, NOS		1 (2%)	
HYPERPLASIA, NOS			1 (3%)
PLASMACYTOSIS	1 (7%)		1 (3%)
#MANDIBULAR L. NODE	(15)	(41)	(39)
HYPERPLASIA, NOS		1 (2%)	3 (8%)
PLASMACYTOSIS	1 (7%)		1 (3%)
HYPERPLASIA, LYMPHOID	1 (7%)		
MASTOCYTOSIS			1 (3%)
#BRONCHIAL LYMPH NODE	(15)	(41)	(39)
HYPERPLASIA, NOS			1 (3%)
#MESENTERIC L. NODE	(15)	(41)	(39)
HEMORRHAGE			2 (5%)
INFLAMMATION ACUTE AND CHRONIC			1 (3%)
HEMOSIDEROSIS			1 (3%)
HYPERPLASIA, NOS		1 (2%)	1 (3%)
HISTIOCYTOSIS			1 (3%)
PLASMACYTOSIS		1 (2%)	1 (3%)
ERYTHROPHAGOCYTOSIS			1 (3%)
HYPERPLASIA, RETICULUM CELL			1 (3%)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS		1 (2%)	
#THYMUS	(2)	(10)	(7)
ULTIMOBRANCHIAL CYST			1 (14%)
CYST, NOS		1 (10%)	
CYSTIC DUCTS		1 (10%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(15)	(48)	(46)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
*ARTERY	(15)	(49)	(46)
THROMBUS, ORGANIZED			1 (2%)
*PULMONARY ARTERY	(15)	(49)	(46)
MEDIAL CALCIFICATION		1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
*HEPATIC ARTERY	(15)	(49)	(46)
EMBOLISM, NOS	1 (7%)		
*PULMONARY VEIN	(15)	(49)	(46)
EMBOLISM, NOS		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(15)	(48)	(44)
PERIVASCULITIS		8 (17%)	3 (7%)
#LIVER	(15)	(49)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, NECROTIZING	1 (7%)		
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)
DEGENERATION, HYDROPIC			1 (2%)
NECROSIS, FOCAL		1 (2%)	3 (7%)
METAMORPHOSIS FATTY			1 (2%)
HEPATOCYTOMEGALY		1 (2%)	1 (2%)
ANGIECTASIS			1 (2%)
#LIVER/CENTRILOBULAR	(15)	(49)	(46)
DEGENERATION, HYDROPIC		1 (2%)	
NECROSIS, NOS		1 (2%)	
#BILE DUCT	(15)	(49)	(46)
INFLAMMATION, CHRONIC FOCAL	1 (7%)		
HYPERPLASIA, FOCAL			1 (2%)
#PANCREAS	(14)	(47)	(45)
CYSTIC DUCTS	1 (7%)		
INFLAMMATION, INTERSTITIAL		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	
AMYLOIDOSIS			1 (2%)
ATROPHY, FOCAL			1 (2%)
#PANCREATIC ACINUS	(14)	(47)	(45)
ATROPHY, NOS	1 (7%)		
#STOMACH	(15)	(48)	(46)
INFLAMMATION, ACUTE FOCAL			1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL(UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
#SMALL INTESTINE	(15)	(47)	(44)
FOREIGN BODY, NOS			1 (2%)
GRANULOMA, NOS			1 (2%)
NECROSIS, NOS			1 (2%)
#PEYERS PATCH	(15)	(47)	(44)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
HYPERPLASIA, NOS		9 (19%)	7 (16%)
#COLON	(14)	(35)	(38)
NEMATODIASIS	1 (7%)	8 (23%)	10 (26%)
URINARY SYSTEM			
#KIDNEY	(15)	(49)	(46)
HYDRONEPHROSIS		3 (6%)	4 (9%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (7%)	3 (6%)	2 (4%)
INFLAMMATION, CHRONIC	1 (7%)		
PERIVASCULITIS	7 (47%)	13 (27%)	8 (17%)
DEGENERATION, HYALINE		1 (2%)	
INFARCT, HEALED		1 (2%)	
CALCIFICATION, FOCAL		1 (2%)	
#KIDNEY/CORTEX	(15)	(49)	(46)
SCAR			1 (2%)
#KIDNEY/TUBULE	(15)	(49)	(46)
DEGENERATION, NOS			1 (2%)
#KIDNEY/PELVIS	(15)	(49)	(46)
INFLAMMATION, CHRONIC	1 (7%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)
#URINARY BLADDER	(13)	(45)	(35)
PERIVASCULITIS		2 (4%)	2 (6%)
ENDOCRINE SYSTEM			
#THYROID	(12)	(42)	(44)
FOLLICULAR CYST, NOS		3 (7%)	
HYPERPLASIA, FOCAL		1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
HYPERPLASIA, ADENOMATOUS			1 (2%)
HYPERPLASIA, C-CELL		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#THYROID FOLLICLE	(12)	(42)	(44)
CRYSTALS, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(15)	(49)	(46)
INFLAMMATION, INTERSTITIAL		1 (2%)	
*DUCT OF EPIDIDYMIS	(15)	(49)	(46)
INFLAMMATION, CHRONIC		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(15)	(47)	(46)
HYDROCEPHALUS, NOS			1 (2%)
CALCIFICATION, FOCAL	3 (20%)	20 (43%)	21 (46%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(15)	(49)	(46)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	4	6

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

TABLE D1 (CONCLUDED)

	CONTROL(UNTR) 22-2405	LOW DOSE 22-2403	HIGH DOSE 22-2401
ANIMAL MISSING/NO NECROPSY	3	1	4

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH p-QUINONE DIOXIME

	CONTROL (UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		9	
ANIMALS NECROPSIED	20	41	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	41	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(41)	(50)
EDEMA, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(19)	(41)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	3 (16%)	2 (5%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
CRYSTALS, NOS		1 (2%)	
#LUNG	(19)	(41)	(50)
INFLAMMATION, NOS		2 (5%)	
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
INFLAMMATION, CHRONIC		3 (7%)	3 (6%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
PERIVASCULITIS	6 (32%)	15 (37%)	15 (30%)
CHOLESTEROL DEPOSIT		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, ADENOMATOUS			3 (6%)
#LUNG/ALVEOLI	(19)	(41)	(50)
HISTIOCYTOSIS		2 (5%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(17)	(38)	(39)
HYPERPLASIA, HEMATOPOIETIC		2 (5%)	1 (3%)
#SPLEEN	(20)	(40)	(48)
CONGESTION, NOS	1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
DEGENERATION, HYALINE	1 (5%)		
ATROPHY, NOS		1 (3%)	
LEUKEMOID REACTION		1 (3%)	
PLASMACYTOSIS		2 (5%)	1 (2%)
HYPERPLASIA, PLASMA CELL			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (5%)	1 (3%)	1 (2%)
HYPERPLASIA, LYMPHOID		2 (5%)	2 (4%)
HEMATOPOIESIS	2 (10%)	4 (10%)	6 (13%)
#LYMPH NODE	(15)	(33)	(40)
INFLAMMATION, ACUTE		1 (3%)	
HYPERPLASIA, NOS			1 (3%)
PLASMACYTOSIS		1 (3%)	
HYPERPLASIA, RETICULUM CELL			1 (3%)
#MANDIBULAR L. NODE	(15)	(33)	(40)
HYPERPLASIA, NOS	1 (7%)	1 (3%)	2 (5%)
PLASMACYTOSIS	1 (7%)		
HYPERPLASIA, RETICULUM CELL		1 (3%)	1 (3%)
#BRONCHIAL LYMPH NODE	(15)	(33)	(40)
PLASMACYTOSIS		1 (3%)	1 (3%)
#MEDIASTINAL L.NODE	(15)	(33)	(40)
INFLAMMATION, ACUTE		1 (3%)	
PLASMACYTOSIS		1 (3%)	
#MESENTERIC L. NODE	(15)	(33)	(40)
INFLAMMATION, SUPPURATIVE	1 (7%)		
INFLAMMATION, ACUTE	1 (7%)		
INFLAMMATION, GRANULOMATOUS			1 (3%)
PLASMACYTOSIS	1 (7%)		
HEMATOPOIESIS		1 (3%)	
#INGUINAL LYMPH NODE	(15)	(33)	(40)
PLASMACYTOSIS			1 (3%)
#THYMUS	(4)	(6)	(5)
ULTIMOBRANCHIAL CYST			1 (20%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(40)	(50)
INFLAMMATION, SUPPURATIVE	1 (5%)		

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
*BLOOD VESSEL	(20)	(41)	(50)
AMYLOIDOSIS		1 (2%)	
*ARTERY	(20)	(41)	(50)
INFLAMMATION ACUTE AND CHRONIC	1 (5%)		
*AORTA	(20)	(41)	(50)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
*VEIN	(20)	(41)	(50)
INFLAMMATION, ACUTE			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(18)	(36)	(45)
INFLAMMATION, CHRONIC			1 (2%)
PERIVASCULITIS	7 (39%)	5 (14%)	11 (24%)
#LIVER	(20)	(41)	(50)
CONGESTION, NOS	1 (5%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL		2 (5%)	
PERIVASCULITIS		1 (2%)	
DEGENERATION, HYDROPIC		1 (2%)	
METAMORPHOSIS FATTY		2 (5%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
HYPERPLASTIC NODULE			1 (2%)
HEMATOPOIESIS			1 (2%)
*GALLBLADDER	(20)	(41)	(50)
CRYSTALS, NOS			1 (2%)
#BILE DUCT	(20)	(41)	(50)
INFLAMMATION, CHRONIC	2 (10%)	2 (5%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (5%)	1 (2%)	4 (8%)
HYPERPLASIA, FOCAL	1 (5%)	1 (2%)	
#PANCREAS	(18)	(38)	(47)
INFLAMMATION, INTERSTITIAL	1 (6%)		
#GASTRIC MUCOSA	(19)	(39)	(47)
CYST, NOS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
#PEYERS PATCH	(20)	(41)	(47)
INFLAMMATION, ACUTE	1 (5%)		
GRANULOMA, NOS			1 (2%)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	5 (11%)
#COLON	(11)	(33)	(39)
NEMATODIASIS		1 (3%)	3 (8%)
URINARY SYSTEM			
#KIDNEY	(20)	(41)	(50)
GLOMERULONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL		2 (5%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	2 (4%)
PERIVASCULITIS	4 (20%)	8 (20%)	10 (20%)
INFARCT, HEALED	1 (5%)		
AMYLOIDOSIS		1 (2%)	
HYPERPLASIA, TUBULAR CELL		1 (2%)	
#KIDNEY/PELVIS	(20)	(41)	(50)
INFLAMMATION, SUPPURATIVE	1 (5%)		
INFLAMMATION, CHRONIC		6 (15%)	1 (2%)
#URINARY BLADDER	(17)	(34)	(43)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (6%)	2 (6%)	
PERIVASCULITIS	3 (18%)	9 (26%)	4 (9%)
ENDOCRINE SYSTEM			
#PITUITARY	(13)	(27)	(29)
CYST, NOS		1 (4%)	
#ADRENAL	(17)	(36)	(43)
HYPERPLASTIC NODULE			1 (2%)
#THYROID	(18)	(32)	(45)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS		1 (3%)	
INFLAMMATION, FOCAL	1 (6%)		
INFLAMMATION, CHRONIC			1 (2%)
#THYROID FOLLICLE	(18)	(32)	(45)
ABSCESS, NOS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(41)	(50)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#UTERUS	(19)	(41)	(49)
HYDROMETRA		3 (7%)	1 (2%)
CYST, NOS		4 (10%)	1 (2%)
INFLAMMATION, SUPPURATIVE		3 (7%)	1 (2%)
PYOMETRA	1 (5%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
ABSCESS, NOS		2 (5%)	3 (6%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (5%)		1 (2%)
GRANULOMA, NOS			1 (2%)
SCLEROSIS			1 (2%)
PERIVASCULITIS			1 (2%)
#CERVIX UTERI	(19)	(41)	(49)
CHOLESTEROL DEPOSIT	1 (5%)		
#UTERUS/ENDOMETRIUM	(19)	(41)	(49)
CYST, NOS	1 (5%)	1 (2%)	10 (20%)
EDEMA, NOS			1 (2%)
INFLAMMATION, ACUTE	1 (5%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
HYPERPLASIA, CYSTIC	5 (26%)	9 (22%)	7 (14%)
METAPLASIA, SQUAMOUS			1 (2%)
#UTERUS/MYOMETRIUM	(19)	(41)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
#OVARY	(13)	(28)	(30)
CYST, NOS	3 (23%)	2 (7%)	7 (23%)
MULTILOCULAR CYST	1 (8%)	2 (7%)	
MULTIPLE CYSTS			1 (3%)
PAROVARIAN CYST			3 (10%)
HEMORRHAGIC CYST		2 (7%)	2 (7%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(19)	(40)	(47)
INFLAMMATION, SUPPURATIVE	1 (5%)		

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

TABLE D2 (CONCLUDED)

	CONTROL(UNTR) 22-2406	LOW DOSE 22-2404	HIGH DOSE 22-2402
INFLAMMATION, CHRONIC		1 (3%)	
PERIVASCULITIS			1 (2%)
#BRAIN	(19)	(40)	(47)
PERIVASCULITIS		1 (3%)	
CORPORA AMYLACEA	1 (5%)		
CALCIFICATION, NOS			1 (2%)
CALCIFICATION, FOCAL	4 (21%)	7 (18%)	17 (36%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(41)	(50)
FIBROUS OSTEODYSTROPHY	10 (50%)	25 (61%)	22 (44%)
OSTEOSCLEROSIS	1 (5%)	1 (2%)	
*SKELETAL MUSCLE	(20)	(41)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
BODY CAVITIES			
*MEDIASTINUM	(20)	(41)	(50)
ABSCESS, NOS	1 (5%)		
*PERITONEUM	(20)	(41)	(50)
INFLAMMATION, GRANULOMATOUS	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			2
ANIMAL MISSING/NO NECROPSY		9	
AUTO/NECROPSY/HISTO PERF		1	1

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

Review of the Bioassay of *p*-Quinone Dioxime* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

October 25, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (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, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of *p*-Quinone Dioxime for carcinogenicity.

The reviewer for the report on the bioassay of *p*-Quinone Dioxime said that the compound was found to induce urinary bladder carcinomas in treated female rats. After briefly describing the experimental design, he noted that analysis of *p*-Quinone dioxime showed the presence of impurities. The finding raised the question regarding the role of the impurities in the carcinogenic response. Based on the results of the study, the reviewer concluded that the compound may pose a possible human risk.

A Program staff pathologist pointed out two bladder tumors and four kidney tumors observed among treated male rats. Although they were not statistically significant, he said that they may be biologically important and lend additional significance to the findings in female rats.

There was no objection to a recommendation that the report on the bioassay of *p*-Quinone dioxime be accepted as written.

Clearinghouse Members Present

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center

Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Kenneth Wilcox, Michigan State Health Department

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

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