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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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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 1-PHENYL-3-METHYL-5-PYRAZOLONE 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 1-phenyl-3-methyl-5-pyrazolone 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 1-phenyl-3-methyl-5-pyrazolone was conducted by Litton Bionetics, Inc., Bethesda, 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. S. M. Garner (4,5) 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. P. K. Hildebrandt (4) at Litton Bionetics, Inc., the pathology narratives were written by Dr. P. K. Hildebrandt (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. W. W. Belew (7,10) and Mr. R. M. Helfand (7), 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. D. G. Goodman (1,12), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,13), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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

2. Now with the U.S. Environmental Protection Agency, 401 M Street S.W., Washington, D.C.

3. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

4. Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, Maryland.

5. Now with Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia.

6. Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.

7. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

8. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

9. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

10. Now with the Solar Energy Research Institute, Cole Boulevard, Golden, Colorado.

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

12. Now with Clement Associates, Inc., 1010 Wisconsin Avenue, N.W., Washington, D.C.

13. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay of 1-phenyl-3-methyl-5-pyrazolone for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 1-Phenyl-3-methyl-5-pyrazolone was administered in the feed, at either of two concentrations, to groups of 49 or 50 male and 50 female animals of each species. The high and low concentrations of 1-phenyl-3-methyl-5-pyrazolone utilized were, respectively, 5000 and 2500 ppm for rats and 15,000 and 7500 ppm for mice. Twenty animals of each species and sex were placed on test as controls. After a 103-week period of chemical administration, there was an additional observation period of 2 weeks for rats. A 102-week period of chemical administration was followed by an additional 2-week observation period for mice.

In both species adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors. Compound-related mean body weight depression was observed in mice, but not in rats. In addition, no significant accelerated mortality or other signs of toxicity were associated with the dietary administration of 1-phenyl-3-methyl-5-pyrazolone to rats; therefore, it is possible that the compound was not administered to rats at the maximum tolerated concentration.

There were no tumors in either sex of rats or mice for which a significant positive association could be established between chemical administration and incidence.

Under the conditions of this bioassay, there was no evidence for the carcinogenicity of 1-phenyl-3-methyl-5-pyrazolone to Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

1-Phenyl-3-methyl-5-pyrazolone (Figure 1) (NCI No. C03952), an aromatic heterocycle and widely used dye intermediate, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer observed among workers in the dye manufacturing industry (Anthony and Thomas, 1970; Wynder et al., 1963).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one.* It is also called 3-methyl-1-phenyl-2-pyrazolin-5-one; phenyl-3-methylpyrazolone; 1-phenyl-3-methyl-5-oxo-2-pyrazoline; 1-phenyl-5-(3-methylpyrazolone); Norphenazone; Developer Z; and C.I. (Colour Index) Developer 1.

1-Phenyl-3-methyl-5-pyrazolone is an intermediate in the synthesis of at least 36 dyes and pigments, 10 of which are produced in commercially significant quantities in the United States: C.I. Solvent Yellow 16, C.I. Solvent Red 8, C.I. Mordant Yellow 30, C.I. Acid Orange 74, C.I. Solvent Orange 5, C.I. Mordant Red 7, C.I. Pigment Orange 13, C.I. Pigment Red 41, C.I. Acid Yellow 42, and C.I. Acid Orange 56 (Society of Dyers and Colourists, 1956). 1-Phenyl-3-methyl-5-pyrazolone is also used as an intermediate in the synthesis of drugs and is an extremely sensitive reagent for the detection of cyanide (Rose and Rose, 1966).

*The CAS registry number is 89-25-8.

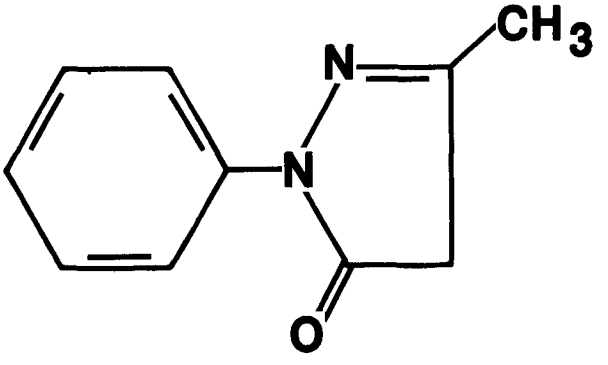


FIGURE 1
CHEMICAL STRUCTURE OF 1-PHENYL-3-METHYL-5-PYRAZOLONE

The U.S. produced 17,000 pounds of 1-phenyl-3-methyl-5-pyrazolone and sold 14,000 pounds in 1975 (U.S. International Trade Commission, 1977). Production data in 1975 are also available for the following dyes and pigments for which 1-phenyl-3-methyl-5-pyrazolone is an intermediate: C.I. Acid Orange 74 (20,000 pounds), C.I. Pigment Orange 13 (209,000 pounds), and C.I. Acid Yellow 42 (26,000 pounds) (U.S. International Trade Commission, 1977).

The potential for exposure to 1-phenyl-3-methyl-5-pyrazolone is greatest for laboratory workers and for workers in the dye, pharmaceutical, and chemical manufacturing industries.

II. MATERIALS AND METHODS

A. Chemicals

1-Phenyl-3-methyl-5-pyrazolone, a light yellow powder, was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. Analysis was performed by Midwest Research Institute, Kansas City, Missouri. The observed melting point (128° to 130°C) conformed with that found in the literature (129° to 130°C) (Jones et al., 1963) and suggested a compound of high purity. Elemental analysis was consistent with $C_{10}H_{10}N_2O$, the molecular formula for this compound. However, thin-layer chromatographic (TLC) plates utilizing two solvent systems (chloroform:methanol and ethyl acetate) indicated five and two impurities, respectively, of lower mobility than the major compound. Each plate was visualized by 254 and 356 nm light, dichromate, and heat. High-pressure liquid chromatography (HPLC) showed one homogeneous peak. Infrared and nuclear magnetic resonance analyses were consistent with the structure of the compound. Ultraviolet (UV) analysis showed a λ_{max} of 246 nm with a molar extinction coefficient (ϵ) of 13×10^3. The literature value was λ_{max} = 245 nm with ϵ = 18×10^3 (Katritsky and Maine, 1964).

A second batch of the compound was purchased five months later from the same supplier. TLC utilizing the same solvent systems described above showed the presence, respectively, of two and one impurities of lower mobility. HPLC again showed one homogeneous peak,

and the melting point and elemental analyses were similar to those observed with the first batch. UV analysis (λ_{max} = 246 with ϵ = 1.22×10^4) observed in 0.1n NaOH was almost identical with that reported in the literature (λ_{max} = 246 with ϵ = 1.17×10^4) (Katritsky and Maine, 1964).

Throughout this report, the term 1-phenyl-3-methyl-5-pyrazolone will be used to refer to this material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 1-Phenyl-3-methyl-5-pyrazolone 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 ground 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 2500 and 5000 ppm of 1-phenyl-3-methyl-5-pyrazolone were analyzed spectrophotometrically. The results immediately after preparation ranged from 92.8 to 97.9 percent with a mean of 95.7 percent of theoretical, including correction for

analytical method of recovery used. Data were not corrected for any loss which may have been due to chemical instability or reactivity.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. All rats were supplied by the Frederick Cancer Research Center, Frederick, Maryland. All mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts.

Rats and mice were approximately 4 weeks old when received. Upon receipt, animals were examined for visible signs of disease or parasites. Obviously ill or runted animals were culled. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals which did not manifest clinical signs of disease were placed on test at this time. Animals 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

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 22° to 26°C and the relative humidity was maintained between 45 and 55 percent. 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.).

All rats were housed four per cage by sex and all mice five per cage by sex. Throughout the study dosed and control animals of both species were housed in polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) suspended from aluminum racks. Racks were fitted with a continuous stainless steel mesh lid 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 were provided twice weekly. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used in polycarbonate cages for the entire bioassay.

Acidulated water (pH 2.5) was supplied to animals in water bottles filled by an automated metering device that was checked daily for diluting accuracy. Water bottles were changed twice weekly, and 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* N,N'-diethylthiourea (105-55-5) and

*CAS registry numbers are given in parentheses.

4-nitro-o-phenylenediamine (99-56-9); and other rats intubated with dosed solutions of 3-(chloromethyl)pyridine hydrochloride (3099-31-8).

All dosed and control mice were housed in a room with other mice receiving diets containing 2,4-dimethoxyaniline hydrochloride (54150-69-5); 4'-(chloroacetyl)-acetanilide (140-49-8); p-phenylenediamine dihydrochloride (624-18-0); 4-nitro-o-phenylenediamine (99-56-9); and nithiazide (139-94-6); and other mice intubated with dosed solutions of trimethylphosphate (512-56-1); 2-(chloromethyl) pyridine hydrochloride (6959-47-3); 3-(chloromethyl)pyridine hydrochloride (3099-31-8); and pivalolactone (1955-45-9).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 1-phenyl-3-methyl-5-pyrazolone for administration to dosed animals in the chronic study, subchronic toxicity tests were conducted with both rats and mice. Rats were distributed among nine groups, each consisting of five males and five females. 1-Phenyl-3-methyl-5-pyrazolone was incorporated into the basal laboratory diet of seven of the nine groups of rats in concentrations of 2150, 3160, 4600, 6800, 10,000, 14,700, and 21,600 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. 1-Phenyl-3-methyl-5-pyrazolone was incorporated into the basal laboratory diet of eight of the ten groups of mice in concentrations of 2160, 3150, 4600, 6800, 10,000, 14,700,

21,500, and 31,600 ppm. The remaining two 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 observation period, all survivors were sacrificed and necropsied.

At the end of the subchronic test, mean body weight gain among male rats receiving a dietary concentration of 4600 ppm was 4 percent less than the mean body weight gain of their controls, while female rats receiving the same concentration displayed a mean body weight gain 4 percent greater than that of their controls. At a dietary concentration of 6800 ppm, the mean body weight gain of male rats was 9 percent less than the mean body weight gain of their controls, while the mean body weight gain of female rats receiving the same concentration was 1 percent less than that of their controls. No deaths occurred in any dosed group; one female control died. The high concentration selected for administration to dosed rats in the chronic bioassay was 5000 ppm.

At the end of the subchronic test, mean body weight gain among male mice receiving a dietary concentration of 14,700 ppm was 12 percent less than the mean body weight gain of their controls, while female mice receiving the same concentration displayed a mean body

weight gain which was 11 percent less than that of their controls. At a dietary concentration of 21,500 ppm, the mean body weight gain of male mice was 17 percent less than that of their controls, while female mice receiving the same concentration displayed a mean body weight gain 19 percent less than that of their controls. No deaths occurred in any group. The high concentration selected for administration to dosed mice in the chronic bioassay was 15,000 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 simultaneously. The dietary concentrations of 1-phenyl-3-methyl-5-pyrazolone utilized were 5000 and 2500 ppm. Throughout this report those rats 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. Dosed rats were supplied with feed containing 1-phenyl-3-methyl-5-pyrazolone for 103 weeks followed by an additional 2-week observation period.

All mice were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The dietary concentrations of 1-phenyl-3-methyl-5-pyrazolone utilized were 15,000

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
1-PHENYL-3-METHYL-5-PYRAZOLONE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	1-PHENYL-3-METHYL-5-PYRAZOLONE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	105
LOW DOSE	49	2500	103	
		0		2
HIGH DOSE	50	5000	103	
		0		2
FEMALE				
CONTROL	20	0	0	105
LOW DOSE	50	2500	103	
		0		2
HIGH DOSE	50	5000	103	
		0		2

[a]Concentrations given in parts per million.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1-PHENYL-3-METHYL-5-PYRAZOLONE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	1-PHENYL-3-METHYL-5-PYRAZOLONE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	104
LOW DOSE	50	7,500	102	
		0		2
HIGH DOSE	50	15,000	102	
		0		2
FEMALE				
CONTROL	20	0	0	104
LOW DOSE	50	7,500	102	
		0		2
HIGH DOSE	50	15,000	102	
		0		2

[a]Concentrations given in parts per million.

and 7500 ppm. 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. Dosed mice were supplied with feed containing 1-phenyl-3-methyl-5-pyrazolone for 102 weeks followed by an additional 2-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice daily for mortality. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group. Body weights were recorded once monthly throughout the bioassay.

All moribund animals or animals that developed large, palpable masses that jeopardized their health were sacrificed. A necropsy was performed on each animal regardless of whether it died, was sacrificed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide asphyxiation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of 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, tunica vaginalis, 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

No distinct mean body weight depression was associated with compound administration in either male or female rats (Figure 2).

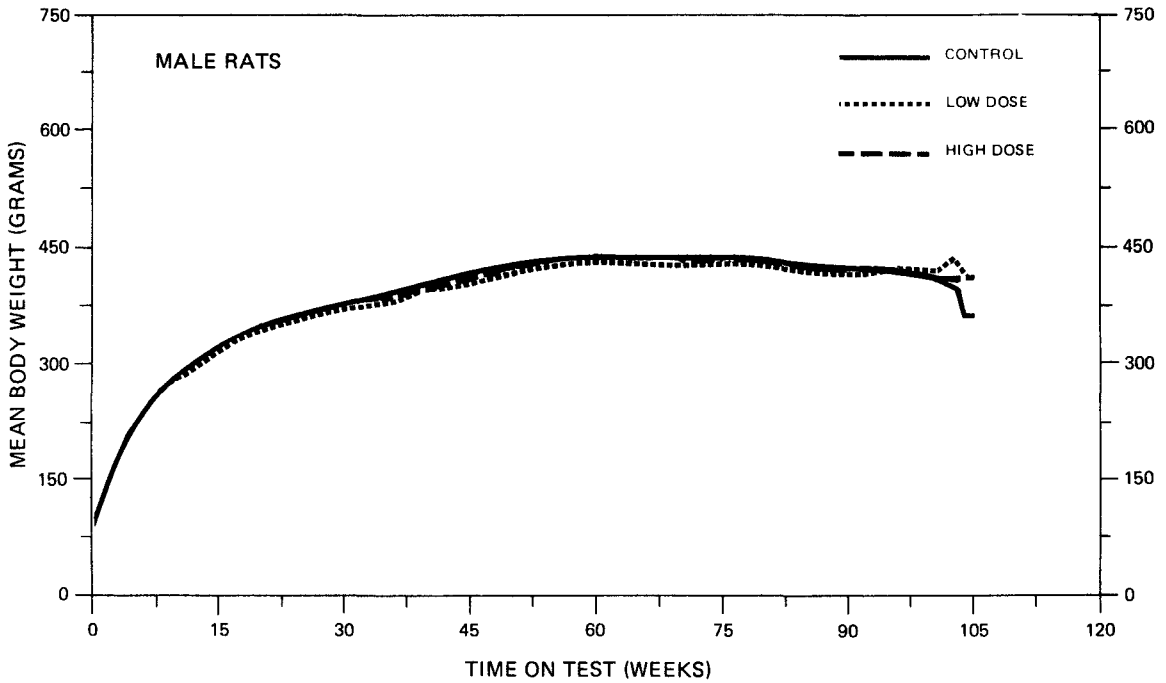
No abnormal clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 1-phenyl-3-methyl-5-pyrazolone-dosed groups are shown in Figure 3. The Tarone tests for positive association between dosage and mortality were not significant for either male or female rats. Due to the relatively high mortality of control female rats beginning with week 76, a significant ($P = 0.003$) negative association between dose and mortality and a significant ($P = 0.006$) departure from linear trend were indicated by the Tarone test.

For male rats, 74 percent (37/50) of the high dose, 59 percent (29/49) of the low dose, and 65 percent (13/20) of the control were alive at the termination of the study. Thus, adequate numbers of males were at risk from late-developing tumors.

For female rats, 88 percent (44/50) of the high dose, 88 percent (44/50) of the low dose, and 55 percent (11/20) of the control group survived on test until the termination of the study. Thus, adequate numbers of females survived sufficiently long to be at risk from late-developing tumors.



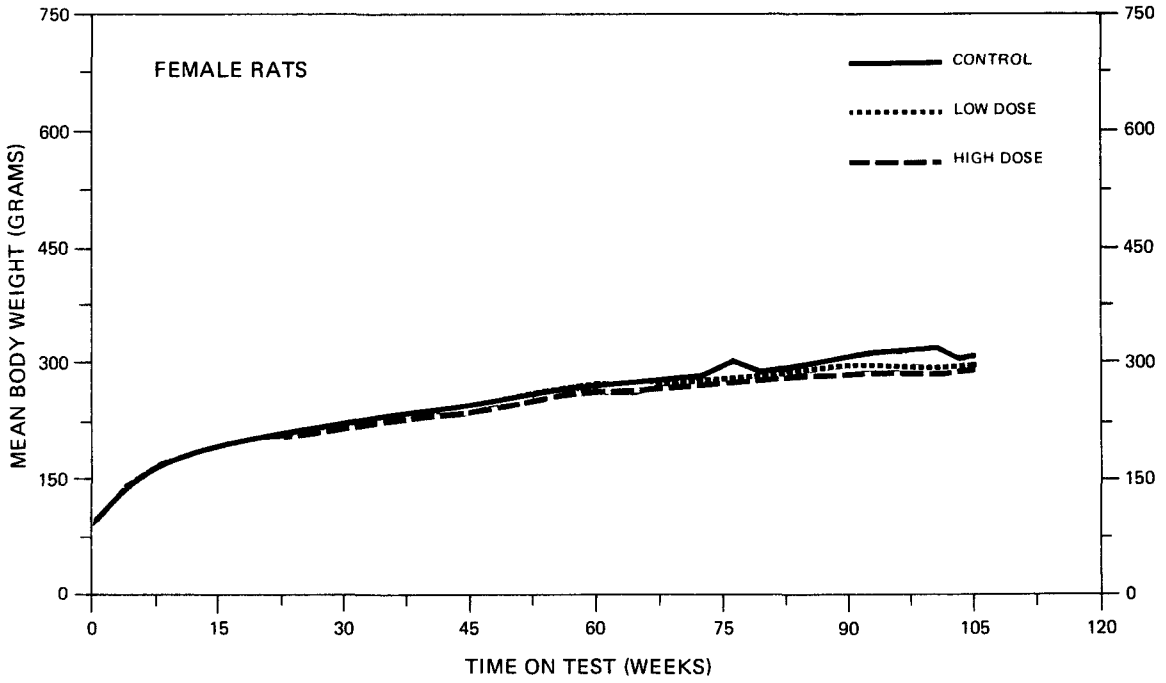
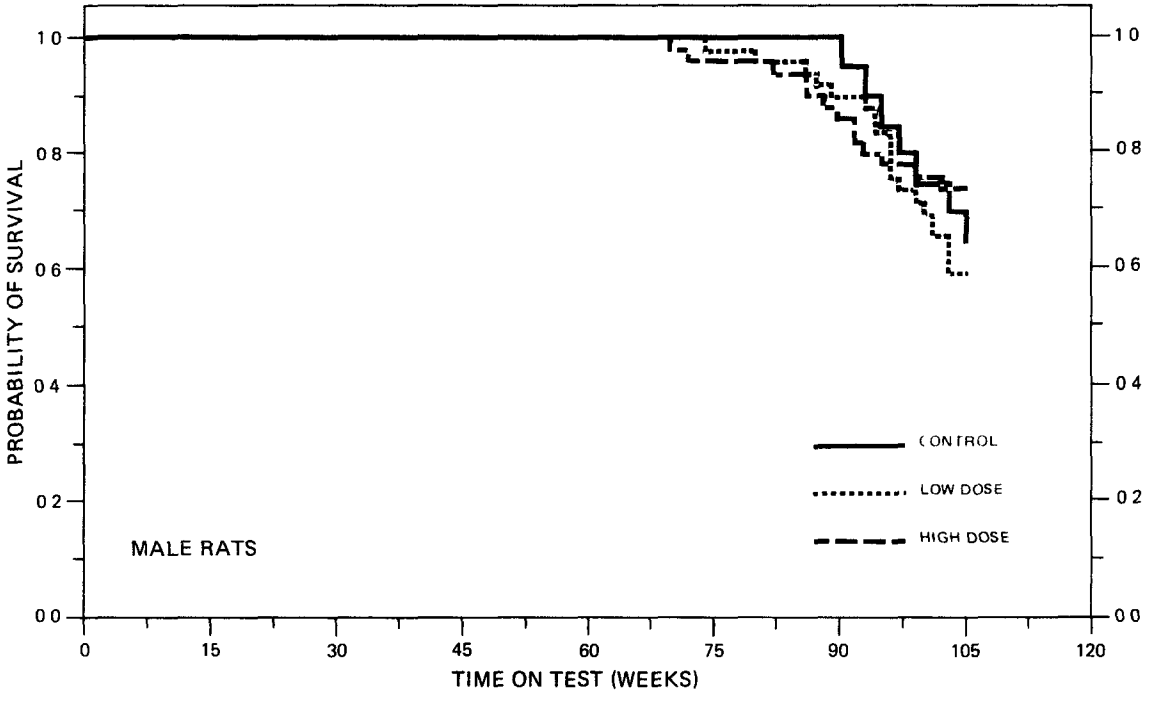


FIGURE 2
GROWTH CURVES FOR 1-PHENYL-3-METHYL-5-PYRAZOLONE CHRONIC STUDY RATS



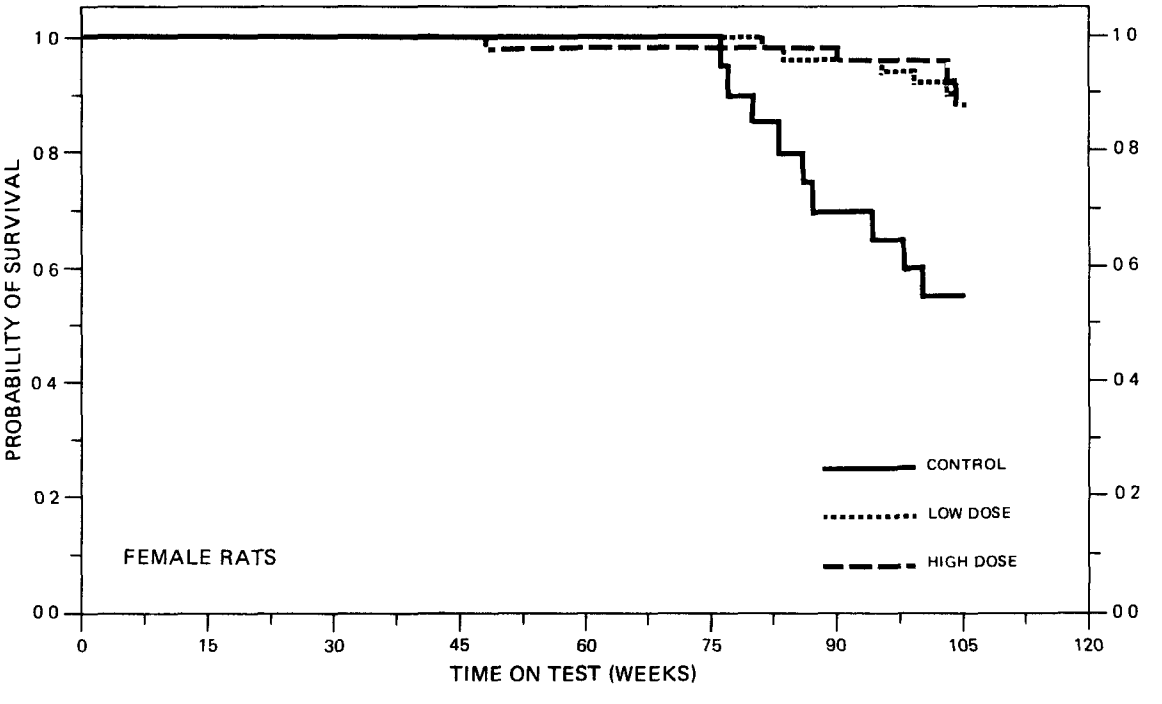


FIGURE 3
SURVIVAL COMPARISONS OF 1-PHENYL-3-METHYL-5-PYRAZOLONE CHRONIC STUDY RATS

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).

A variety of tumors was observed in both the control and dosed groups. The spontaneous occurrence of these lesions, however, is not uncommon in this strain of rats.

The incidence and variety of nonneoplastic degenerative, proliferative, and inflammatory lesions were similar in dosed and control rats (Appendix C).

The results of this pathologic examination indicate that under the conditions of this bioassay the administration of 1-phenyl-3-methyl-5-pyrazolone did not induce any toxicologic or neoplastic lesions in Fischer 344 rats.

D. Statistical Analyses 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 tumor in either sex where at least two such tumors were observed in at least one of the control or 1-phenyl-3-methyl-5-pyrazolone-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between chemical administration and an increased tumor incidence. Thus, at the dose levels

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/20(0.15)	10/49(0.20)	8/50(0.16)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.361	1.067
Lower Limit	---	0.406	0.295
Upper Limit	---	7.138	5.813
Weeks to First Observed Tumor	95	89	86
Pituitary: Chromophobe Adenoma[b]	6/18(0.33)	16/45(0.36)	16/44(0.36)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.067	1.091
Lower Limit	---	0.495	0.506
Upper Limit	---	2.880	2.939
Weeks to First Observed Tumor	97	80	82
Adrenal: Cortical Adenoma or Adenoma NOS[b]	1/19(0.05)	3/48(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.187	0.000
Lower Limit	---	0.105	0.000
Upper Limit	---	61.031	7.102
Weeks to First Observed Tumor	105	89	---

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	4/19(0.21)	8/48(0.17)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.792	0.570
Lower Limit	---	0.250	0.158
Upper Limit	---	3.278	2.520
Weeks to First Observed Tumor	103	96	88
Pancreatic Islets: Islet-Cell Adenoma[b]	0/18(0.00)	4/49(0.08)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.026	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.357	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	89	---
Testis: Interstitial-Cell Tumor[b]	15/19(0.79)	36/49(0.73)	43/49(0.88)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.931	1.112
Lower Limit	---	0.728	0.884
Upper Limit	---	1.368	1.497
Weeks to First Observed Tumor	90	87	86

TABLE 3 (CONCLUDED)

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[a]Treated groups received doses of 2500 or 5000 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 1-PHENYL-3-METHYL-5-PYRAZOLONE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	0/20(0.00)	3/50(0.06)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.250	0.250
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	99	105
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/20(0.15)	2/50(0.04)	1/50(0.02)
P Values[c]	P = 0.041(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.267	0.133
Lower Limit	---	0.024	0.003
Upper Limit	---	2.190	1.568
Weeks to First Observed Tumor	94	103	103
Pituitary: Chromophobe Adenoma or Acidophil Adenoma[b]	11/18(0.61)	23/46(0.50)	19/45(0.42)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.818	0.691
Lower Limit	---	0.525	0.429
Upper Limit	---	1.494	1.304
Weeks to First Observed Tumor	76	83	90

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/17(0.06)	4/45(0.09)	1/44(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.511	0.386
Lower Limit	---	0.168	0.005
Upper Limit	---	72.703	29.672
Weeks to First Observed Tumor	105	105	105
Mammary Gland: Fibroadenoma[b]	1/20(0.05)	3/50(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.200	0.400
Lower Limit	---	0.106	0.005
Upper Limit	---	61.724	30.802
Weeks to First Observed Tumor	100	95	105
Uterus: Endometrial Stromal Polyp[b]	2/19(0.11)	3/48(0.06)	7/50(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.594	1.330
Lower Limit	---	0.076	0.289
Upper Limit	---	6.774	12.469
Weeks to First Observed Tumor	94	105	103

TABLE 4 (CONCLUDED)

[a]Treated groups received doses of 2500 or 5000 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.

used and under the conditions of the test, there was no evidence that 1-phenyl-3-methyl-5-pyrazolone was carcinogenic in Fischer 344 rats.

In female rats the Cochran-Armitage test indicated a significant negative association between dose and the incidence of leukemia or malignant lymphoma. The Fisher exact tests, however, were not significant.

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 all 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 all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by 1-phenyl-3-methyl-5-pyrazolone that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

There was mean body weight depression in dosed male and female mice when compared with controls (Figure 4).

No abnormal clinical signs were recorded.

B. Survival

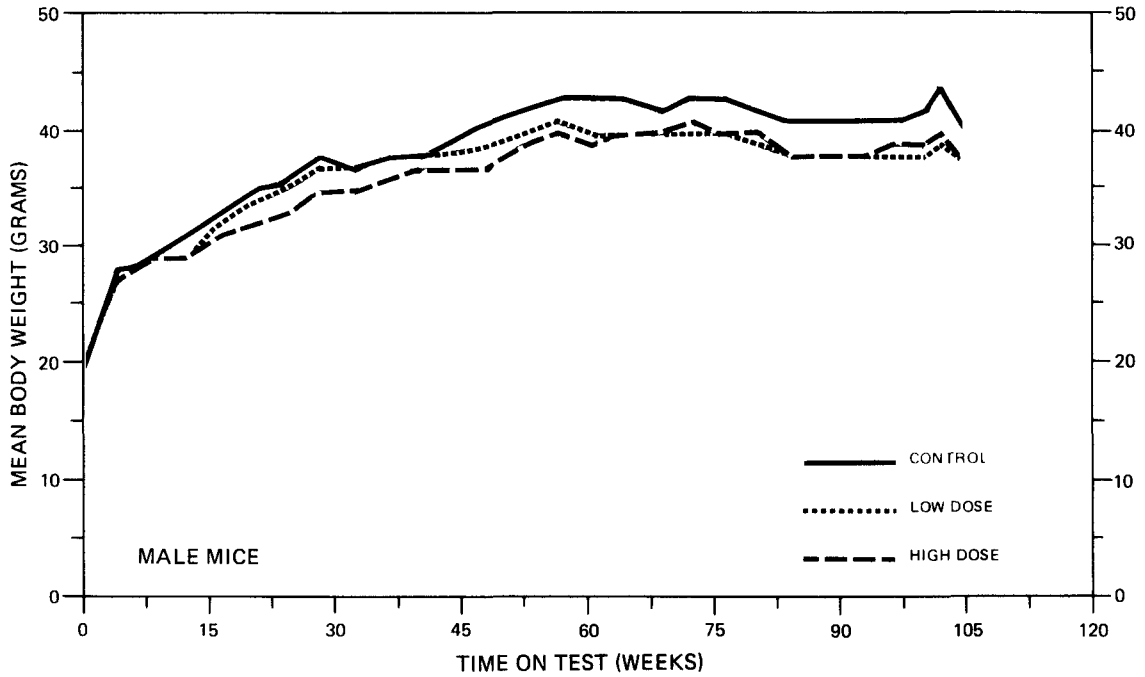
The estimated probabilities of survival for male and female mice in the control and 1-phenyl-3-methyl-5-pyrazolone-dosed groups are shown in Figure 5. The Tarone tests for positive association between dosage and mortality were not significant for either male or female mice.

Adequate numbers of male mice were at risk from late-developing tumors, as 86 percent (43/50) of the high dose, 80 percent (40/50) of the low dose, and 80 percent (16/20) of the control group survived on test until the end of the study. Two control males were missing starting with week 11.

For female mice, 68 percent (34/50) of the high dose, 76 percent (38/50) of the low dose, and 90 percent (18/20) of the control group survived on test until the end of the study, thus providing adequate numbers of mice at risk from late-developing tumors. Three high dose females were missing starting with week 8.

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).



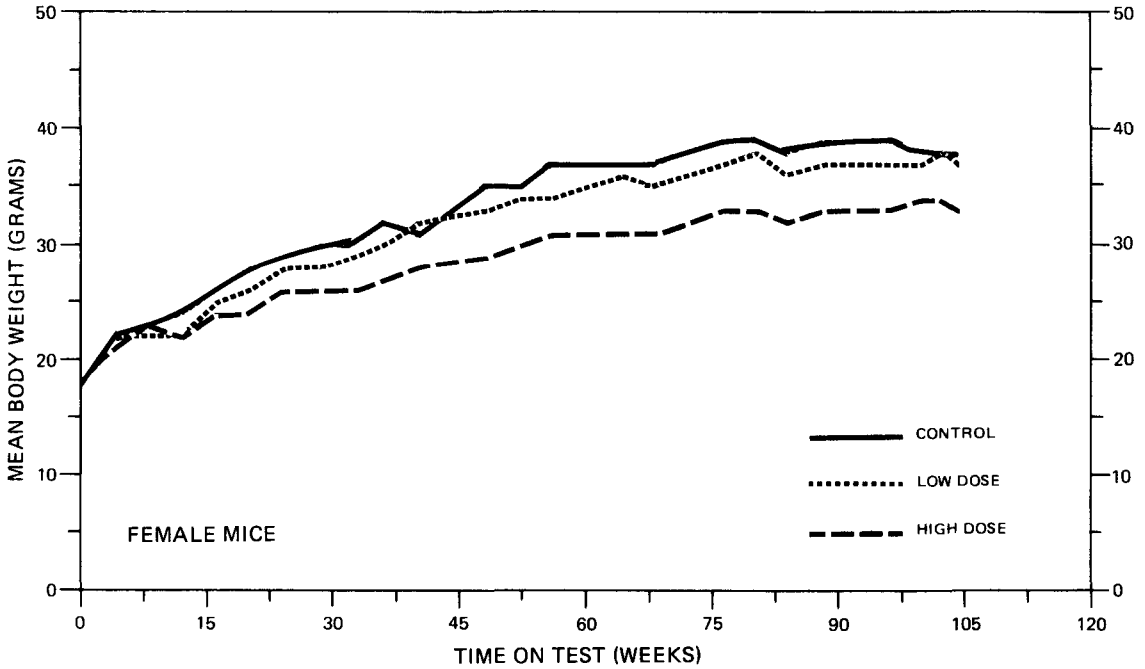
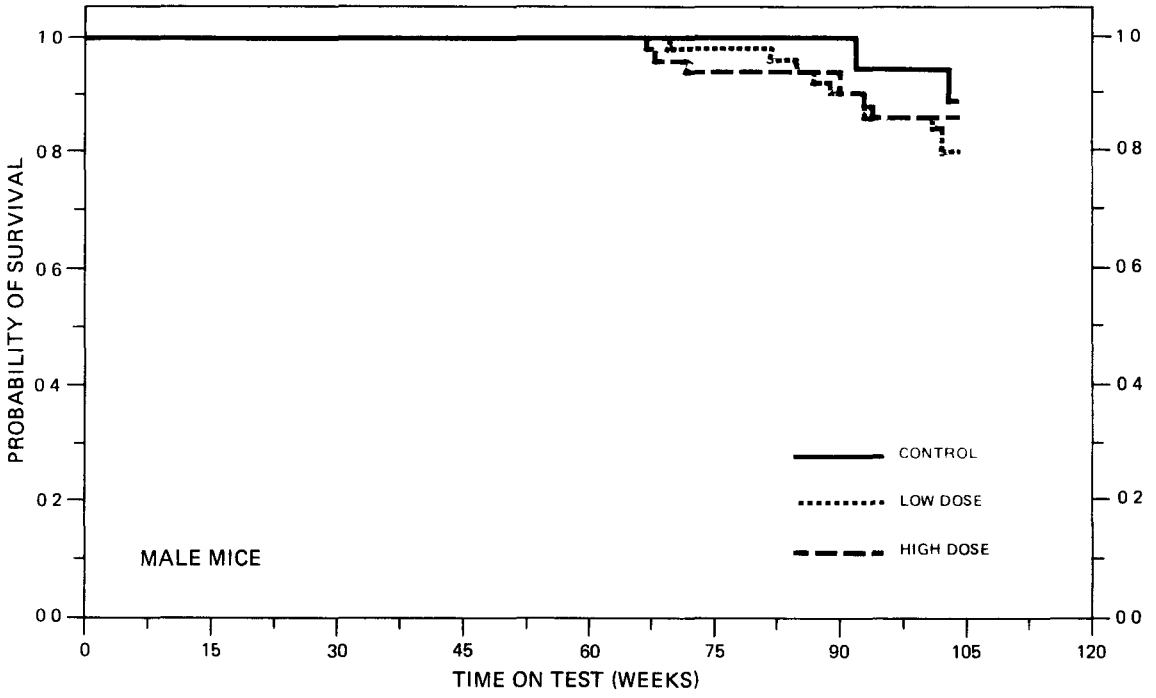


FIGURE 4
GROWTH CURVES FOR 1-PHENYL-3-METHYL-5-PYRAZOLONE CHRONIC STUDY MICE



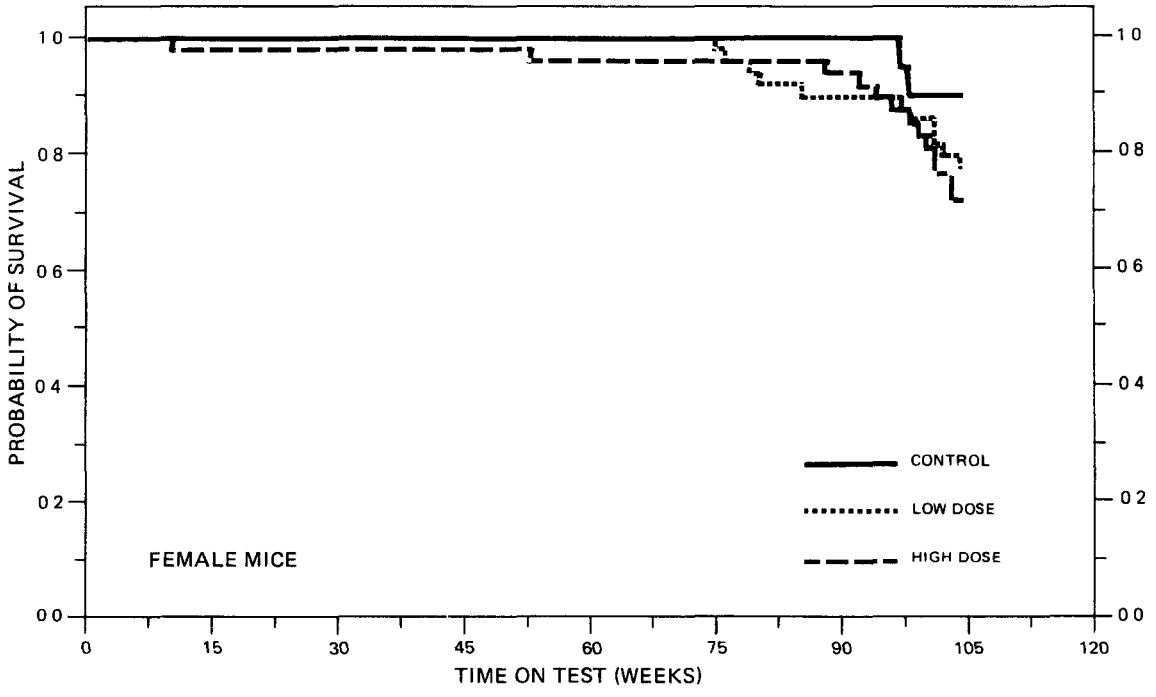


FIGURE 5
SURVIVAL COMPARISONS OF 1-PHENYL-3-METHYL-5-PYRAZOLONE CHRONIC STUDY MICE

There was an increased incidence of lymphoreticular neoplasms in low dose male mice. These are, however, common spontaneous neoplasms in mice. Lymphoreticular neoplasms occurred with approximately the same frequency in dosed and control female mice.

The incidence of follicular cysts of the ovary was slightly elevated in dosed female mice compared to controls. However, this lesion is frequently seen in aged B6C3F1 female mice. A variety of other nonneoplastic lesions was seen and did not appear to be related to compound administration.

The results of this pathologic examination indicate that under the conditions of this bioassay, the administration of 1-phenyl-3-methyl-5-pyrazolone was not carcinogenic to B6C3F1 mice.

D. Statistical Analyses 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 every type of tumor in either sex where at least two such tumors were observed in at least one of the control or 1-phenyl-3-methyl-5-pyrazolone-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site in mice of either sex indicated a significant positive association between chemical administration and an increased tumor incidence. Thus, at the dose levels used in this experiment, there was no evidence that 1-phenyl-3-methyl-5-pyrazolone was carcinogenic in B6C3F1 mice.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	3/17(0.18)	3/47(0.06)	0/49(0.00)
P Values[c]	P = 0.007(N)	N.S.	P = 0.015(N)
Relative Risk (Control)[d]	---	0.362	0.000
Lower Limit	---	0.055	0.000
Upper Limit	---	2.514	0.570
Weeks to First Observed Tumor	104	104	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/18(0.11)	11/50(0.22)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.980	0.720
Lower Limit	---	0.502	0.117
Upper Limit	---	17.385	7.578
Weeks to First Observed Tumor	104	70	68
Liver: Hepatocellular Carcinoma[b]	2/18(0.11)	3/48(0.06)	1/49(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.563	0.184
Lower Limit	---	0.072	0.003
Upper Limit	---	6.411	3.372
Weeks to First Observed Tumor	104	93	90

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Adenoma or Neoplastic Nodule or Hepatocellular Carcinoma[b]	8/18(0.44)	8/48(0.17)	6/49(0.12)
P Values[c]	P = 0.007(N)	P = 0.024(N)	P = 0.007(N)
Relative Risk (Control)[d]	---	0.375	0.276
Lower Limit	---	0.156	0.099
Upper Limit	---	0.994	0.791
Weeks to First Observed Tumor	92	93	90

[a]Treated groups received doses of 7500 or 15,000 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.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	1/20(0.05)	3/46(0.07)	1/46(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.304	0.435
Lower Limit	---	0.115	0.006
Upper Limit	---	66.966	33.420
Weeks to First Observed Tumor	104	104	101
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/20(0.25)	8/49(0.16)	12/47(0.26)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.653	1.021
Lower Limit	---	0.222	0.400
Upper Limit	---	2.293	3.310
Weeks to First Observed Tumor	97	85	53
Liver: Hepatocellular Adenoma[b]	2/20(0.10)	2/47(0.04)	0/46(0.00)
P Values[c]	P = 0.046(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.426	0.000
Lower Limit	---	0.034	0.000
Upper Limit	---	5.603	1.459
Weeks to First Observed Tumor	104	104	---

TABLE 6 (CONCLUDED)

---

[a]Treated groups received doses of 7500 or 15,000 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.

For male mice the possibility of a negative association between dose and the incidence of liver neoplasms and of lung neoplasms was observed. For female mice the Cochran-Armitage test indicated a significant negative association between dose and the incidence of hepatocellular adenomas. The Fisher exact tests, however, were not significant.

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 1-phenyl-3-methyl-5-pyrazolone that could not be established under the conditions of this test.

V. DISCUSSION

Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. A moderate depression of mean body weight gain relative to controls was observed in dosed male and female mice, but not in any rat group. In addition, no significant accelerated mortality or other signs of toxicity were associated with the dietary administration of 1-phenyl-3-methyl-5-pyrazolone to rats; therefore, it is possible that the compound was not administered at the maximum tolerated concentrations.

No neoplasms in either sex of either species occurred for which a significant positive association between chemical administration and incidence could be established. All observed neoplasms were of types and incidences known to occur spontaneously in Fischer 344 rats or B6C3F1 mice.

Under the conditions of this bioassay, there was no evidence for the carcinogenicity of 1-phenyl-3-methyl-5-pyrazolone in Fischer 344 rats or B6C3F1 mice.

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Review of the Bioassay of 1-Phenyl-3-Methyl-5-Pyrazolone*
for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

June 29, 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, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 1-Phenyl-3-Methyl-5-Pyrazolone for carcinogenicity.

The reviewer agreed with the conclusion given in the report that 1-Phenyl-3-Methyl-5-Pyrazolone was not carcinogenic in rats or mice, under the conditions of test. He said that the study was "straightforward" and moved that the report be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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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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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH
1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
ANIMALS INITIALLY IN STUDY	20	@50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
FIBROMA		1 (2%)	
*SUBCUT TISSUE	(20)	(49)	(50)
UNDIFFERENTIATED CARCINOMA			1 (2%)
BASAL-CELL CARCINOMA	1 (5%)		
SARCOMA, NOS			1 (2%)
FIBROSARCOMA		1 (2%)	
MYXOMA			1 (2%)
RHABDOMYOSARCOMA			1 (2%)
HEMANGIOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(18)	(47)	(49)
CARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (6%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
RHABDOMYOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
#BRAIN	(19)	(48)	(50)
MALIGNANT RETICULOSIS		1 (2%)	
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIGNANT LYMPHOMA, NOS			3 (6%)
LEUKEMIA,NOS	3 (15%)	9 (18%)	5 (10%)
#SPLEEN	(19)	(49)	(49)
SARCOMA, NOS	1 (5%)		
LEUKEMIA,NOS		1 (2%)	

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN STUDY BUT ONE WAS DELETED WHEN FOUND TO BE A FEMALE ANIMAL IN A MALE GROUP.

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
CIRCULATORY SYSTEM			
#HEART	(18)	(46)	(49)
ADENOCARCINOMA, NOS	1 (6%)		
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(48)
NEOPLASTIC NODULE			1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(45)	(44)
CHROMOPHOBE ADENOMA	6 (33%)	16 (36%)	16 (36%)
#ADRENAL	(19)	(48)	(50)
ADENOMA, NOS	1 (5%)		
CORTICAL ADENOMA		3 (6%)	
PHEOCHROMOCYTOMA	4 (21%)	6 (13%)	5 (10%)
PHEOCHROMOCYTOMA, MALIGNANT		2 (4%)	1 (2%)
#THYROID	(14)	(46)	(46)
CARCINOMA,NOS			1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
C-CELL ADENOMA		2 (4%)	2 (4%)
#PANCREATIC ISLETS	(18)	(49)	(47)
ISLET-CELL ADENOMA		4 (8%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
ADENOMA, NOS			1 (2%)
FIBROMA			1 (2%)
FIBROADENOMA	1 (5%)	1 (2%)	1 (2%)
*PREPUTIAL GLAND	(20)	(49)	(50)
ADENOSQUAMOUS CARCINOMA		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
#TESTIS	(19)	(49)	(49)
INTERSTITIAL-CELL TUMOR	15 (79%)	36 (73%)	43 (88%)
NERVOUS SYSTEM			
#BRAIN	(19)	(48)	(50)
GLIOMA, NOS	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(50)
MESOTHELIOMA, NOS		1 (2%)	
*TUNICA VAGINALIS	(20)	(49)	(50)
MESOTHELIOMA, NOS			2 (4%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	8	2
MORIBUND SACRIFICE	4	12	11
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	29	37
ANIMAL MISSING			
ANIMAL DELETED/WRONG SEX		1	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	49	49
TOTAL PRIMARY TUMORS	35	88	88
TOTAL ANIMALS WITH BENIGN TUMORS	18	45	47
TOTAL BENIGN TUMORS	28	70	72
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	15	13
TOTAL MALIGNANT TUMORS	7	17	13
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	2
TOTAL SECONDARY TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	3
TOTAL UNCERTAIN TUMORS		1	3
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
1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
KERATOACANTHOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
ADENOSQUAMOUS CARCINOMA		1 (2%)	
FIBROADENOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (6%)	3 (6%)
GRANULOSA-CELL CARCINOMA, METAST			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
#BRAIN	(20)	(49)	(50)
MALIGNANT RETICULOSIS	1 (5%)		
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)		
LEUKEMIA,NOS	2 (10%)	2 (4%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
NONE			

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(46)	(45)
CHROMOPHOBE ADENOMA	11 (61%)	22 (48%)	19 (42%)
CHROMOPHOBE CARCINOMA		1 (2%)	
ACIDOPHIL ADENOMA		1 (2%)	
HEMANGIOMA			1 (2%)
#ADRENAL	(20)	(50)	(47)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA		2 (4%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(17)	(45)	(44)
FOLLICULAR-CELL CARCINOMA			2 (5%)
C-CELL ADENOMA	1 (6%)	3 (7%)	1 (2%)
C-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(20)	(49)	(50)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS			1 (2%)
CYSTADENOMA, NOS		1 (2%)	1 (2%)
FIBROADENOMA	1 (5%)	3 (6%)	1 (2%)
*VAGINA	(20)	(50)	(50)
FIBROSARCOMA		1 (2%)	
#UTERUS	(19)	(48)	(50)
ADENOCARCINOMA, NOS			1 (2%)
LIPOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	2 (11%)	3 (6%)	7 (14%)
CHORIOCARCINOMA			1 (2%)
#OVARY	(19)	(48)	(50)
GRANULOSA-CELL CARCINOMA			1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKULL	(20)	(50)	(50)
OSTEOSARCOMA	1 (5%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	7	4	1
MORIBUND SACRIFICE	2	2	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	44	44
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	36	25
TOTAL PRIMARY TUMORS	20	47	46
TOTAL ANIMALS WITH BENIGN TUMORS	11	32	24
TOTAL BENIGN TUMORS	15	41	38
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	5	7
TOTAL MALIGNANT TUMORS	5	6	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH
1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	18	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(17)	(47)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (12%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (6%)		
SARCOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(18)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	1 (2%)
LEUKEMIA,NOS	1 (6%)	1 (2%)	2 (4%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(17)	(44)	(48)
FIBROSARCOMA			1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
#LYMPH NODE	(16)	(39)	(45)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
#MESENTERIC L. NODE	(16)	(39)	(45)
MALIGNANT LYMPHOMA, NOS	1 (6%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (5%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
DIGESTIVE SYSTEM			
#LIVER	(18)	(48)	(49)
HEPATOCELLULAR ADENOMA	5 (28%)	6 (13%)	5 (10%)
NEOPLASTIC NODULE	1 (6%)		
HEPATOCELLULAR CARCINOMA	2 (11%)	3 (6%)	1 (2%)
SARCOMA, NOS			1 (2%)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(16)	(43)	(45)
ADENOCARCINOMA, NOS		1 (2%)	
PHEOCHROMOCYTOMA	1 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	10	7
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	40	43
ANIMAL MISSING	2		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	20	14
TOTAL PRIMARY TUMORS	14	25	14
TOTAL ANIMALS WITH BENIGN TUMORS	7	9	6
TOTAL BENIGN TUMORS	8	10	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	15	8
TOTAL MALIGNANT TUMORS	5	15	8
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH
1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	46
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(47)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(46)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	3 (7%)	1 (2%)
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(47)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	2 (10%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)	3 (6%)	3 (6%)
LEUKEMIA,NOS			2 (4%)
UNDIFFERENTIATED LEUKEMIA			1 (2%)
ERYTHROCYTIC LEUKEMIA		1 (2%)	
GRANULOCYTIC LEUKEMIA			1 (2%)
#BONE MARROW	(19)	(45)	(40)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#SPLEEN	(19)	(45)	(42)
HEMANGIOMA		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
#LYMPH NODE	(17)	(40)	(39)
ADENOCARCINOMA, NOS			1 (3%)
#MESENTERIC L. NODE	(17)	(40)	(39)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
#LIVER	(20)	(47)	(46)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(47)	(46)
HEPATOCELLULAR ADENOMA	2 (10%)	2 (4%)	
#STOMACH	(20)	(46)	(45)
KERATOACANTHOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(6)	(30)	(22)
FOLLICULAR-CELL ADENOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(46)	(45)
LEIOMYOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	1 (5%)	2 (4%)	1 (2%)
HEMANGIOMA		1 (2%)	
#OVARY	(16)	(42)	(38)
PAPILLARY ADENOMA	1 (6%)		1 (3%)
GRANULOSA-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	8	13
MORIBUND SACRIFICE		3	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	38	34
ANIMAL MISSING		1	3
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	19	15
TOTAL PRIMARY TUMORS	10	20	18
TOTAL ANIMALS WITH BENIGN TUMORS	5	10	4
TOTAL BENIGN TUMORS	5	10	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	9	13
TOTAL MALIGNANT TUMORS	5	9	13
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
ANIMALS INITIALLY IN STUDY	20	@50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(18)	(47)	(49)
MINERALIZATION	1 (6%)		
ATELECTASIS		1 (2%)	
THROMBOSIS, NOS			1 (2%)
CONGESTION, NOS		7 (15%)	2 (4%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		2 (4%)	1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
PNEUMONIA, CHRONIC MURINE	4 (22%)	4 (9%)	5 (10%)
HYPERPLASIA, ADENOMATOUS	1 (6%)	2 (4%)	1 (2%)
HISTIOCYTOSIS	1 (6%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(49)	(49)
INFARCT, NOS			1 (2%)
HEMOSIDEROSIS			1 (2%)
HYPERTROPHY, NOS			1 (2%)
HYPERPLASIA, DIFFUSE		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
HEMATOPOIESIS			2 (4%)
#MESENTERIC L. NODE	(19)	(48)	(47)
LYMPHANGIECTASIS	1 (5%)	1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(18)	(46)	(49)
THROMBOSIS, NOS		2 (4%)	

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN STUDY BUT ONE WAS DELETED WHEN FOUND TO BE A FEMALE ANIMAL IN A MALE GROUP.

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
#MYOCARDIUM	(18)	(46)	(49)
FIBROSIS	9 (50%)	10 (22%)	15 (31%)
#ENDOCARDIUM	(18)	(46)	(49)
THROMBOSIS, NOS			1 (2%)
*ARTERY	(20)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
*AORTA	(20)	(49)	(50)
MINERALIZATION		1 (2%)	
*PULMONARY ARTERY	(20)	(49)	(50)
MINERALIZATION		1 (2%)	1 (2%)
*MESENTERIC ARTERY	(20)	(49)	(50)
MINERALIZATION		1 (2%)	
FIBROSIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(48)
CONGESTION, NOS			1 (2%)
CHOLANGIOFIBROSIS	4 (21%)		2 (4%)
HEPATITIS, TOXIC			1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	5 (10%)
BASOPHILIC CYTO CHANGE	1 (5%)	1 (2%)	1 (2%)
FOCAL CELLULAR CHANGE		2 (4%)	2 (4%)
#LIVER/CENTRILOBULAR	(19)	(49)	(48)
NECROSIS, NOS		2 (4%)	
#LIVER/HEPATOCYTES	(19)	(49)	(48)
HYPERPLASIA, DIFFUSE	1 (5%)		
*BILE DUCT	(20)	(49)	(50)
HYPERPLASIA, NOS	1 (5%)	2 (4%)	1 (2%)
HYPERPLASIA, FOCAL	1 (5%)		
#PANCREATIC ACINUS	(18)	(49)	(47)
ATROPHY, NOS	1 (6%)	1 (2%)	2 (4%)
#STOMACH	(18)	(47)	(49)
MINERALIZATION			1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
ULCER, FOCAL			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)
#LARGE INTESTINE	(19)	(48)	(50)
NEMATODIASIS	5 (26%)	18 (38%)	21 (42%)
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(50)
MINERALIZATION		1 (2%)	1 (2%)
CONGESTION, NOS		1 (2%)	1 (2%)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS		1 (2%)	1 (2%)
PYELONEPHRITIS, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	14 (74%)	21 (43%)	37 (74%)
DEGENERATION, HYALINE		1 (2%)	1 (2%)
#KIDNEY/TUBULE	(19)	(49)	(50)
DILATATION, NOS		1 (2%)	1 (2%)
#URINARY BLADDER	(11)	(37)	(39)
OBSTRUCTION, NOS			1 (3%)
INFLAMMATION, ACUTE		1 (3%)	
*URETHRA	(20)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(45)	(44)
HEMORRHAGE			1 (2%)
HEMORRHAGIC CYST	1 (6%)		1 (2%)
ANGIECTASIS	1 (6%)		
#ADRENAL	(19)	(48)	(50)
CONGESTION, NOS		1 (2%)	
#ADRENAL CORTEX	(19)	(48)	(50)
DEGENERATION, LIPOID		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
#ADRENAL MEDULLA	(19)	(48)	(50)
HYPERPLASIA, FOCAL		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
#THYROID	(14)	(46)	(46)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	1 (7%)		2 (4%)
#PANCREATIC ISLETS	(18)	(49)	(47)
HYPERPLASIA, FOCAL		1 (2%)	
REPRODUCTIVE SYSTEM			
#PROSTATE	(9)	(42)	(40)
INFLAMMATION, NOS		2 (5%)	
INFLAMMATION, SUPPURATIVE	1 (11%)		
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC			1 (3%)
#TESTIS	(19)	(49)	(49)
MINERALIZATION	1 (5%)	1 (2%)	1 (2%)
ATROPHY, NOS		3 (6%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(19)	(48)	(50)
HYDROCEPHALUS, INTERNAL		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*CHOROID	(20)	(49)	(50)
THROMBOSIS, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(49)	(50)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
BODY CAVITIES			
*MESENTERY	(20)	(49)	(50)
PERIARTERITIS		2 (4%)	1 (2%)
NECROSIS, FAT		4 (8%)	

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

TABLE C1 (CONCLUDED)

	CONTROL(UNTR) 11-1475	LOW DOSE 11-1473	HIGH DOSE 11-1471
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS	2	1	
NECROSIS, FAT			1
SPECIAL PATHOLOGY SUMMARY			
AUTO/NECROPSY/NO HISTO	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 1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
DILATATION, NOS	1 (5%)		
ATELECTASIS		1 (2%)	
CONGESTION, NOS	1 (5%)	4 (8%)	1 (2%)
EDEMA, NOS	1 (5%)		
HEMORRHAGE		5 (10%)	1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
PNEUMONIA, CHRONIC MURINE		6 (12%)	3 (6%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
FIBROSIS		1 (2%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (4%)	
HISTIOCYTOSIS	1 (5%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(48)	(46)
MYELOSCLEROSIS		1 (2%)	
#SPLEEN	(20)	(49)	(50)
FIBROSIS		1 (2%)	
HEMOSIDEROSIS	1 (5%)	1 (2%)	
#CERVICAL LYMPH NODE	(19)	(48)	(50)
ANGIECTASIS			2 (4%)
#MESENTERIC L. NODE	(19)	(48)	(50)
INFLAMMATION, CHRONIC		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
INFLAMMATION, GRANULOMATOUS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(48)	(50)
INFLAMMATION, FOCAL		1 (2%)	
FIBROSIS	1 (5%)	9 (19%)	7 (14%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU		2 (4%)	
NECROSIS, FOCAL	1 (5%)	1 (2%)	
METAMORPHOSIS FATTY	1 (5%)		5 (10%)
BASOPHILIC CYTO CHANGE	5 (25%)	21 (43%)	14 (28%)
FOCAL CELLULAR CHANGE		4 (8%)	2 (4%)
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PANCREAS	(20)	(49)	(50)
NECROSIS, FAT	1 (5%)		
#PANCREATIC ACINUS	(20)	(49)	(50)
ATROPHY, NOS	1 (5%)		1 (2%)
ATROPHY, FOCAL		1 (2%)	
#STOMACH	(20)	(50)	(49)
ULCER, FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (5%)		
#GASTRIC SUBMUCOSA	(20)	(50)	(49)
EDEMA, NOS	1 (5%)		
FIBROSIS	1 (5%)	1 (2%)	
#SMALL INTESTINE	(20)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LARGE INTESTINE	(20)	(50)	(50)
NEMATODIASIS	8 (40%)	27 (54%)	24 (48%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
MINERALIZATION		4 (8%)	3 (6%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
INFLAMMATION, CHRONIC	3 (15%)	7 (14%)	4 (8%)
NECROSIS, MEDULLARY	1 (5%)		
HYPERPLASIA, TUBULAR CELL			1 (2%)
#KIDNEY/PELVIS	(20)	(50)	(50)
INFLAMMATION, ACUTE	1 (5%)		
#URINARY BLADDER	(17)	(44)	(37)
HEMORRHAGE	1 (6%)		
INFLAMMATION, FOCAL	1 (6%)		
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(46)	(45)
CYST, NOS		2 (4%)	
HEMORRHAGIC CYST		6 (13%)	2 (4%)
ANGIECTASIS	1 (6%)	1 (2%)	1 (2%)
#ADRENAL CORTEX	(20)	(50)	(47)
NECROSIS, FOCAL	1 (5%)		
METAMORPHOSIS FATTY		1 (2%)	
CYTOLOGIC DEGENERATION	1 (5%)		
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(17)	(45)	(44)
HYPERPLASIA, C-CELL		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS		1 (2%)	
*VAGINA	(20)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
#UTERUS	(19)	(48)	(50)
CYST, NOS			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
FIBROSIS			1 (2%)
#CERVIX UTERI	(19)	(48)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#UTERUS/ENDOMETRIUM	(19)	(48)	(50)
CYST, NOS		2 (4%)	2 (4%)

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 11-1476	LOW DOSE 11-1474	HIGH DOSE 11-1472
INFLAMMATION, NOS		1 (2%)	
#OVARY	(19)	(48)	(50)
CYST, NOS		2 (4%)	2 (4%)
PAROVARIAN CYST		1 (2%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(50)
HYDROCEPHALUS, INTERNAL			2 (4%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(20)	(50)	(50)
OSTEOSCLEROSIS		1 (2%)	
BODY CAVITIES			
*MEDIASTINUM	(20)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
*MESENTERY	(20)	(50)	(50)
MINERALIZATION		1 (2%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	
NECROSIS, FAT	2 (10%)	2 (4%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			4
AUTO/NECROPSY/HISTO PERF	1	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 1-PHENYL-3-METHYL-5-PYRAZOLONE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	18	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(18)	(50)	(50)
FIBROSIS, FOCAL	1 (6%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(17)	(47)	(49)
INFLAMMATION, NOS		2 (4%)	
#LUNG	(17)	(47)	(49)
ATELECTASIS			2 (4%)
THROMBUS, ORGANIZED		1 (2%)	
CONGESTION, NOS		1 (2%)	8 (16%)
HEMORRHAGE		2 (4%)	4 (8%)
INFLAMMATION, INTERSTITIAL	3 (18%)	3 (6%)	10 (20%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
PERIVASCULAR CUFFING		1 (2%)	
CYTOMEGALY		1 (2%)	
FOAM-CELL		2 (4%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(18)	(48)	(47)
HYPERPLASIA, GRANULOCYTIC			1 (2%)
MYELOPOIESIS		1 (2%)	
#SPLEEN	(17)	(44)	(48)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (6%)	1 (2%)	2 (4%)
#SPLENIC RED PULP	(17)	(44)	(48)
HEMORRHAGE			1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
#MANDIBULAR L. NODE	(16)	(39)	(45)
HYPERPLASIA, RETICULUM CELL			1 (2%)
#MESENTERIC L. NODE	(16)	(39)	(45)
CONGESTION, NOS		1 (3%)	
CONGESTION, CHRONIC			1 (2%)
HEMORRHAGE	1 (6%)		
INFLAMMATION, CHRONIC		1 (3%)	
DEGENERATION, CYSTIC			1 (2%)
HYPERPLASIA, PLASMA CELL	1 (6%)		
HYPERPLASIA, RETICULUM CELL		1 (3%)	
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS		1 (3%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(17)	(46)	(48)
INFLAMMATION, CHRONIC			1 (2%)
#MYOCARDIUM	(17)	(46)	(48)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*TESTICULAR ARTERY	(18)	(50)	(50)
SCLEROSIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(18)	(48)	(49)
FIBROSIS, FOCAL			1 (2%)
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	
HEPATOCYTOMEGALY		1 (2%)	1 (2%)
HYPERPLASIA, DIFFUSE			2 (4%)
FOLLICULOID HYPERPLASIA		1 (2%)	
#LIVER/PERIPORTAL	(18)	(48)	(49)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
#LIVER/HEPATOCYTES	(18)	(48)	(49)
HYPERPLASIA, DIFFUSE		1 (2%)	1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
#PANCREAS	(16)	(48)	(48)
DILATATION/DUCTS		1 (2%)	
INFLAMMATION, ACUTE			1 (2%)
ATROPHY, NOS		1 (2%)	
#LARGE INTESTINE	(17)	(49)	(48)
NEMATODIASIS			5 (10%)
URINARY SYSTEM			
#KIDNEY	(18)	(48)	(50)
HYDRONEPHROSIS		1 (2%)	
CONGESTION, NOS		1 (2%)	
INFLAMMATION, CHRONIC	3 (17%)	3 (6%)	1 (2%)
PERIVASCULAR CUFFING		1 (2%)	
INFARCT, HEALED		2 (4%)	
HYPERPLASIA, TUBULAR CELL		1 (2%)	
#URINARY BLADDER	(13)	(38)	(37)
INFLAMMATION, CHRONIC		1 (3%)	
NODULE		1 (3%)	
HYPERPLASIA, EPITHELIAL			1 (3%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(16)	(43)	(45)
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(7)	(34)	(23)
HYPERPLASIA, FOLLICULAR-CELL	1 (14%)		
#PANCREATIC ISLETS	(16)	(48)	(48)
HYPERTROPHY, NOS			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(18)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*TESTIS/TUBULE	(17)	(47)	(48)
DEGENERATION, NOS		1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 22-2475	LOW DOSE 22-2473	HIGH DOSE 22-2471
NERVOUS SYSTEM			
*BRAIN	(18)	(49)	(50)
MINERALIZATION	2 (11%)	17 (35%)	7 (14%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(18)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION ACTIVE CHRONIC			1 (2%)
GRANULOMA, NOS			2 (4%)
FOAM-CELL		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(18)	(50)	(50)
PERIVASCULAR CUFFING		1 (2%)	
AMYLOIDOSIS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	9	13
ANIMAL MISSING/NO NECROPSY	2		
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO		1	

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 1-PHENYL-3-METHYL-5-PYRAZOLONE

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	49	46
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(46)	(46)
ATELECTASIS	2 (10%)		
CONGESTION, NOS	2 (10%)	1 (2%)	2 (4%)
HYPEREMIA	1 (5%)		
HEMORRHAGE	2 (10%)	2 (4%)	1 (2%)
BRONCHOPNEUMONIA, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL	8 (40%)	10 (22%)	6 (13%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
GRANULOMA, NOS		1 (2%)	
PERIVASCULAR CUFFING	1 (5%)	3 (7%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (5%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(45)	(40)
HEMOSIDEROSIS	1 (5%)	1 (2%)	1 (3%)
HYPERPLASIA, GRANULOCYTIC		2 (4%)	
#SPLEEN	(19)	(45)	(42)
HEMORRHAGE		1 (2%)	
PERIVASCULITIS			1 (2%)
NECROSIS, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	1 (2%)
HEMATOPOIESIS			1 (2%)
#MESENTERIC L. NODE	(17)	(40)	(39)
CONGESTION, NOS			1 (3%)
INFLAMMATION, GRANULOMATOUS		1 (3%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, RETICULUM CELL			1 (3%)
HYPERPLASIA, LYMPHOID		2 (5%)	1 (3%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(18)	(45)	(42)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
*PULMONARY ARTERY	(20)	(49)	(47)
HYPERTROPHY, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(47)	(46)
HEMORRHAGE	1 (5%)		
INFLAMMATION, FOCAL	1 (5%)		2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	2 (10%)		2 (4%)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
ABSCESS, CHRONIC		1 (2%)	
GRANULOMA, NOS		1 (2%)	
FIBROSIS	1 (5%)		
PERIVASCULITIS			1 (2%)
PERIVASCULAR CUFFING	2 (10%)	6 (13%)	
NECROSIS, NOS	1 (5%)		1 (2%)
NECROSIS, FOCAL	1 (5%)	2 (4%)	
NECROSIS, COAGULATIVE			1 (2%)
INFARCT, NOS			1 (2%)
HEPATOCYTOMEGALY		1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (5%)		
#LIVER/PERIPORTAL	(20)	(47)	(46)
INFLAMMATION, CHRONIC			1 (2%)
GRANULOMA, NOS			1 (2%)
#LIVER/HEPATOCYTES	(20)	(47)	(46)
DEGENERATION, NOS	1 (5%)		
HYPERPLASIA, NOS		2 (4%)	
HYPERPLASIA, DIFFUSE		1 (2%)	
#PANCREAS	(19)	(42)	(45)
INFLAMMATION, FIBRINOUS		1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
NECROSIS, NOS			1 (2%)
ATROPHY, NOS	1 (5%)		
#PEYERS PATCH	(20)	(45)	(43)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LARGE INTESTINE	(20)	(45)	(43)
NEMATODIASIS	1 (5%)	1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(46)	(44)
HYDRONEPHROSIS			1 (2%)
INFLAMMATION, CHRONIC	5 (26%)	7 (15%)	4 (9%)
PERIVASCULAR CUFFING	1 (5%)	4 (9%)	
INFARCT, HEALED	1 (5%)		
HYPERPLASIA, TUBULAR CELL		1 (2%)	
#KIDNEY/MEDULLA	(19)	(46)	(44)
CYST, NOS			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(42)	(41)
AMYLOIDOSIS		1 (2%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(46)	(45)
HEMORRHAGE			1 (2%)
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, NOS		1 (2%)	
PYOMETRA			1 (2%)
INFLAMMATION, NECROTIZING			1 (2%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
#CERVIX UTERI	(19)	(46)	(45)
INFLAMMATION, NOS			1 (2%)
#UTERUS/ENDOMETRIUM	(19)	(46)	(45)
CYST, NOS			2 (4%)
INFLAMMATION, NOS	2 (11%)	3 (7%)	2 (4%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
INFLAMMATION, SUPPURATIVE	1 (5%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE	2 (11%)	2 (4%)	2 (4%)
FIBROSIS			1 (2%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	8 (42%)	15 (33%)	19 (42%)
HYPERPLASIA, STROMAL		1 (2%)	
*OVARY	(16)	(42)	(38)
CYST, NOS		1 (2%)	1 (3%)
FOLLICULAR CYST, NOS	1 (6%)	3 (7%)	6 (16%)
CORPUS LUTEUM CYST		1 (2%)	
PAROVARIAN CYST			1 (3%)
THROMBOSIS, NOS			1 (3%)
HEMORRHAGE			1 (3%)
HEMORRHAGIC CYST			1 (3%)
ABSCESS, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(47)	(43)
INFLAMMATION, NOS			1 (2%)
#BRAIN	(20)	(47)	(43)
MINERALIZATION	4 (20%)	17 (36%)	14 (33%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(47)
INFLAMMATION, NECROTIZING			1 (2%)
*PLEURA	(20)	(49)	(47)
NODULE		1 (2%)	
*MESENTERY	(20)	(49)	(47)
NECROSIS, FAT			1 (2%)

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

TABLE D2 (CONCLUDED)

	CONTROL(UNTR) 22-2476	LOW DOSE 22-2474	HIGH DOSE 22-2472
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(47)
PERIVASCULAR CUFFING	1 (5%)		1 (2%)
AMYLOIDOSIS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		5	4
ANIMAL MISSING/NO NECROPSY		1	3
AUTO/NECROPSY/NO HISTO			1

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

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