National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 111
1978

# BIOASSAY OF 1-AMINO-2-METHYLANTHRAQUINONE FOR POSSIBLE CARCINOGENICITY

## CAS No. 82-28-0

## NCI-CG-TR-111

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

# BIOASSAY OF

# 1-AMINO-2-METHYLANTHRAQUINONE

# FOR POSSIBLE CARCINOGENICITY

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

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DHEW Publication No. (NIH) 78-1366

# REPORT ON THE BIOASSAY OF 1-AMINO-2-METHYLANTHRAQUINONE 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-amino-2-methylanthraquinone 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-amino-2-methylanthraquinone was conducted by Mason Research Institute, Worcester, Massachusetts, 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. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. R. W. Fleischman (3), Dr. D. W. Hayden (3), and Dr. A. S. Krishna Murthy (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Mr. W. W. Belew (5,8), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

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## SUMMARY

A bioassay for possible carcinogenicity of technical-grade 1-amino-2-methylanthraquinone was conducted using Fischer 344 rats and B6C3F1 mice. 1-Amino-2-methylanthraquinone was administered in the feed, at either of two concentrations, to groups of 45 to 50 males and females of each species. The high and low time-weighted average concentrations of 1-amino-2-methylanthraquinone were 0.20 and 0.10 percent, respectively, for male and female rats. For mice, two dosage regimens (designated A and B) were used, but the time-weighted average concentrations were the same, 0.06 percent. For each species, 50 animals of each sex were placed on test as controls. The period of compound administration was 78 weeks for rats followed by 26 to 28 additional weeks of observation, and 73 weeks for mice followed by 24 to 25 additional weeks of observation.

A statistically significant positive association between compound administration and mortality was established for the male and female dose A mice. Dose A mice did not survive sufficiently long to be at risk from late-developing tumors. Survival in all other groups was adequate.

The incidence of hepatocellular carcinomas was statistically significant among dosed rats of both sexes. Kidney neoplasms (the combined incidence of tubular-cell adenomas, tubular-cell adenocarcinomas, and adenocarcinomas NOS) were significantly increased among dosed male rats.

Administration of the compound was associated with a significant increase in the combined incidence of hepatocellular carcinomas and neoplastic liver nodules in female mice. No other neoplasms occurred in statistically significant positive incidences in male or female mice. 1-Amino-2-methylanthraquinone demonstrated nephrotoxic properties in mice of both sexes.

Under the conditions of this bioassay, 1-amino-2-methylanthraquinone was carcinogenic in Fischer 344 rats, inducing hepatocellular carcinomas in rats of both sexes, and kidney tumors in male rats. The compound was carcinogenic in female B6C3F1 mice, producing an increased combined incidence of hepatocellular carcinomas and neoplastic nodules.

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# I. INTRODUCTION

1-Amino-2-methylanthraquinone (Figure 1) (NCI No. C01901), an intermediate in the synthesis of anthraquinone dyes and a dye itself, was selected for bioassay by the National Cancer Institute in an attempt to elucidate those chemicals which may be responsible for the increased incidence of bladder cancer observed among workers in the dye manufacturing industry (Wynder et al., 1963; Anthony and Thomas, 1970). Aromatic amines are one of several classes of chemicals thought to contribute to the increased cancer risk in this industry (Wynder et al., 1963).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 1-amino-2-methyl-9,10-anthracenedione.* It is also known as 2-methyl-1-anthraquinonylamine and as Disperse Orange 11 (C.I. [Colour Index] No. 60700).

1-Amino-2-methylanthraquinone is used as a dye for a variety of synthetic fibers as well as wool, sheepskins and furs, and additionally, for the surface dyeing of thermoplastics (Society of Dyers and Colourists, 1971a). It may also be used as an intermediate for the production of a variety of dyes including Acid Blue 47, Acid Blue 49, and Solvent Blue 13 (Urso, 1977; Society of Dyers and Colourists, 1971b); however, none of these is currently produced commercially in the United States (U.S. International Trade Commission, 1977).

*The CAS registry number is 82-28-0.

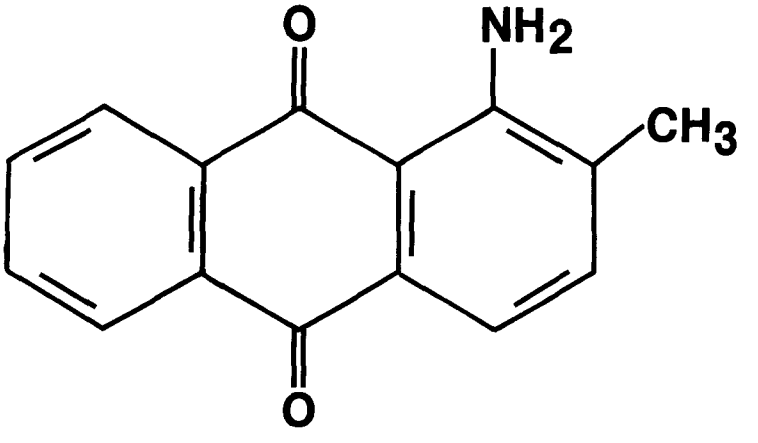



FIGURE 1
CHEMICAL STRUCTURE OF 1-AMINO-2-METHYLANTHRAQUINONE

Although 1-amino-2-methylanthraquinone has not been produced in this country in commercial quantities since 1970, significant quantities of the chemical are imported annually (Bouchard, 1977). In this country the greatest potential for exposure to 1-amino-2-methylanthraquinone would be among workers engaged in the dying of textiles. An increased incidence of bladder cancer has been observed among textile workers in Leeds, England (Anthony and Thomas, 1970).

## II. MATERIALS AND METHODS

### A. Chemicals

Technical-grade 1-amino-2-methylanthraquinone was purchased from Carroll Products, Wood River Junction, Rhode Island. Analysis was performed by Midwest Research Institute, Kansas City, Missouri. The melting point (192° to 208°C) suggested the presence of impurities due to its wide range. The value reported in the literature was 205°C (Pollock and Stevens, 1965). Thin-layer chromatography (TLC) showed the presence of at least two impurities. The infrared spectrum was consistent with that reported in the literature (Pouchert, 1975). The nuclear magnetic resonance spectrum was consistent with the structure except for an extra peak in the aromatic region that matched the chemical shift of benzene. The extra peak indicated a possible impurity. Spectra in the ultraviolet and visible range showed $\lambda_{max}$ at 245, 280 (shoulder), 305 and 475 nm for a methanol solution of the chemical. The reference spectra showed $\lambda_{max}$ at 246.5 and 305.0 for 1-amino-2-methylanthraquinone in methanol with molar extinction coefficients ($\epsilon$) of $36.9 \times 10^3$ and $6.4 \times 10^3$, respectively (Sadtler Standard Spectra). The shoulder at 280 was present in the literature spectra but no extinction coefficient was reported. The extraneous peak at 475 nm suggested the presence of impurities. The observed $\epsilon$ values for the two peaks (246.5 and 305 nm) were, respectively, $35.2 \times 10^3$ and $4.2 \times 10^3$. Although the two $\epsilon$ values for the 246.5 nm peak were comparable, the $\epsilon$'s for the 305 nm peak suggested a maximum purity of approximately

68 percent. Since the same solvent (methanol) was utilized in obtaining spectra of the reference and test compound, and linearity of the Beer Lambert Law would be expected at the concentrations tested, the molar extinction coefficients should give a reasonable estimate of purity of this compound. The wide melting point range, the extraneous spots revealed by TLC, and the extraneous peaks in the ultraviolet spectrum and the nuclear magnetic resonance spectrum, all indicated the presence of impurities.

Throughout this report the term 1-amino-2-methylanthraquinone is used to represent this technical-grade 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-Amino-2-methylanthraquinone was administered to the dosed animals as a component of the diet. The chemical was mixed in the feed in a 6 kg capacity Patterson-Kelley standard model stainless steel twin-shell V-blender. After 20 minutes of blending, the mixtures were placed in double plastic bags and stored in the dark at 4°C. Mixtures were prepared weekly and stored for not longer than 2 weeks.

C. Animals

Two animal species, rats and mice, were used in the chronic carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. All the rats and the mice assigned to

the dosed groups in the chronic bioassay were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The mice assigned to the control groups in the chronic bioassay were supplied by ARS/Sprague-Dawley, Madison, Wisconsin.

Upon arrival, a sample of animals was examined for parasites and other signs of disease. The remaining animals were quarantined by species for 2 weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given sex and species.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. For the first 7 months of the bioassay containment was in stainless- and galvanized-steel wire-mesh cages suspended above newspapers. During this period newspapers were replaced daily and cages and racks were washed weekly. For the remainder of the bioassay, suspended polycarbonate cages equipped with disposable nonwoven fiber filter sheets were used for rats. Fresh corncob bedding (SAN-I-CEL®, Paxton Processing Company,

Paxton, Illinois) and clean cages were provided twice weekly during this period. Once every 2 weeks the disposable filters were replaced and the stainless steel cage racks (Fenco Cage Products, Boston, Massachusetts) were cleaned.

Mice were housed by sex, ten per cage for the first 11 months of the bioassay and five per cage thereafter. Containment was in polycarbonate cages fitted during periods of compound administration with perforated stainless steel lids, and with stainless steel wire bar lids during the final observation period. Both types of lids were supplied by Lab Products, Inc., and nonwoven fiber filter bonnets were secured over all. Clean cages, lids, filters, and bedding were provided three times weekly when cage populations were ten and twice weekly when the cage populations were reduced to five. Reusable filter bonnets and pipe racks were sanitized once every 2 weeks throughout the study. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was provided for the first 6 months of the bioassay, corncob bedding (SAN-I-CEL®) for the next 12 months, and another corncob bedding (Bed-o-Cobs®, The Andersons Cob Division, Maumee, Ohio) was used for the remainder of the study.

Water was available ad libitum for both species from 250 ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. Glass water bottles were used for the first 7 months and polycarbonate bottles were used thereafter. Bottles were replaced

twice weekly and, in the case of rats because of their greater water consumption, refilled as needed between changes. Wayne Lab-Blox® meal was used throughout the period of chemical administration. The treated or untreated food, replenished daily, was available ad libitum to the appropriate groups of both rats and mice. Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) equipped with stainless steel baffles were used to dispense food and were replaced weekly. During the final observation period, rats were provided food pellets on the cage floor while mice obtained food pellets from a food hopper incorporated into the cage lid.

Dosed rats were housed in a room with other rats receiving diets containing* 3-amino-4-ethoxyacetanilide (17026-81-2); 4-nitroanthranilic acid (619-17-0); 5-nitroacenaphthene (602-87-9); and 5-nitro-o-toluidine (99-55-8). Control rats were housed in a room with other rats receiving diets containing 3-nitro-p-acetophenetide (1777-84-0); 2-methyl-1-nitroanthraquinone (129-15-7); and amitrole (61-82-5).

Dosed mice were housed in a room with other mice receiving diets containing 3-amino-4-ethoxyacetanilide (17026-81-2); 4-nitroanthranilic acid (619-17-0); 5-nitro-o-anisidine (99-59-2); 2,4-dinitrotoluene (121-14-2); N,N-dimethyl-p-nitrosoaniline (138-89-6); 2,5-toluenediamine sulfate (6369-59-1); 2,4-diaminoanisole sulfate (615-05-4); 2-aminoanthraquinone (117-79-3); 3-nitro-p-acetophenetide

*CAS registry numbers are given in parentheses.

(1777-84-0); 1-nitronaphthalene (86-57-7); 5-nitroacenaphthene (602-87-9); APC (8003-03-0); and amitrole (61-82-5). Control mice shared a room with other mice receiving diets containing p-cresidine (120-71-8); fenaminosulf (140-56-7); 4-chloro-m-phenylenediamine (5131-60-2); and cinnamyl anthranilate (87-29-6).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 1-amino-2-methylanthraquinone for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among ten groups, each consisting of five males and five females. The chemical was incorporated into the basal laboratory diet and supplied ad libitum to nine of the ten groups of each species in concentrations of 0.03, 0.06, 0.12, 0.24, 0.50, 1.50, 2.50, 3.50, and 4.50 percent. The tenth group of each species served as a control group, 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 diet.

The highest dosage causing no deaths, no compound-related gross abnormalities, and no mean body weight depression in excess of 20 percent relative to controls was selected as the high concentration utilized for the rat and mouse chronic bioassays.

Compound-related mean body weight depression, mortality, and gross lesions were observed in both species during the subchronic

test. Mean body weight gain, expressed as a percentage of the weight gained by the controls, was calculated and recorded at the end of the observation period.

All rats receiving doses of 1.50 percent or higher, all male mice receiving doses of 0.24 percent or higher, and all female mice receiving doses of 0.50 percent or higher died during the 8-week subchronic study. Two male rats receiving 0.5 percent, two male mice receiving 0.12 percent, and four female mice receiving 0.24 percent 1-amino-2-methylanthraquinone in their diet died. Compound-related gross lesions encountered at dosages above 0.24 percent in rats and 0.06 percent in mice included pitted, enlarged, discolored kidneys; enlarged lymph nodes; and reddened adrenals.

In rats receiving 0.24 percent 1-amino-2-methylanthraquinone, the mean male weight gain was 94 percent and the mean female weight gain was 78 percent of the weight gained by the respective controls. Body weight gain was 100 and 80 percent in the males and 84 and 75 percent in the females receiving 0.06 and 0.12 percent, respectively, as compared to their respective controls.

The high concentration selected for administration in the chronic study was 0.06 percent for both species.

F. Experimental Design

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

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
1-AMINO-2-METHYLANTHRAQUINONE FEEDING EXPERIMENT

| | INITIAL GROUP SIZE | 1-AMINO-2-METHYLANTHRAQUINONE CONCENTRATION[a] | OBSERVATION PERIOD TREATED (WEEKS) | OBSERVATION PERIOD UNTREATED (WEEKS) | TIME-WEIGHTED AVERAGE CONCENTRATION[b] |
|---|---|---|---|---|---|
| MALE | | | | | |
| CONTROL | 50 | 0 | 0 | 108 | 0 |
| LOW DOSE | 50 | 0.03<br>0.12<br>0 | 16<br>62 | 26 | 0.10 |
| HIGH DOSE | 50 | 0.06<br>0.24<br>0 | 16<br>62 | 28 | 0.20 |
| FEMALE | | | | | |
| CONTROL | 50 | 0 | 0 | 108 | 0 |
| LOW DOSE | 45 | 0.03<br>0.12<br>0 | 16<br>62 | 27 | 0.10 |
| HIGH DOSE | 48 | 0.06<br>0.24<br>0 | 16<br>62 | 28 | 0.20 |

[a] Concentrations are percentages in feed.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1-AMINO-2-METHYLANTHRAQUINONE FEEDING EXPERIMENT

| | INITIAL GROUP SIZE | 1-AMINO-2-METHYLANTHRAQUINONE CONCENTRATION[a] | OBSERVATION PERIOD | | TIME-WEIGHTED AVERAGE CONCENTRATION[b] |
|---|---|---|---|---|---|
| | | | TREATED (WEEKS) | UNTREATED (WEEKS) | |
| MALE | | | | | |
| CONTROL | 50 | 0 | 0 | 98 | 0 |
| DOSE A | 50 | 0.03 | 16 | | 0.06 |
| | | 0.12 | 26 | | |
| | | 0.03 | 31 | | |
| | | 0 | | 24 | |
| DOSE B | 50 | 0.06 | 73 | | 0.06 |
| | | 0 | | 24 | |
| FEMALE | | | | | |
| CONTROL | 50 | 0 | 0 | 98 | 0 |
| DOSE A | 50 | 0.03 | 16 | | 0.06 |
| | | 0.12 | 26 | | |
| | | 0.03 | 31 | | |
| | | 0 | | 24 | |
| DOSE B | 49 | 0.06 | 73 | | 0.06 |
| | | 0 | | 25 | |

[a] Concentrations are percentages in feed.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

At initiation of the study all rats were approximately 6 weeks old. Dosed rats received initial dietary concentrations of 0.06 and 0.03 percent. Throughout this report those rats initially receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. In week 17 high and low concentrations were increased to 0.24 and 0.12 percent, respectively, for the remaining 62 weeks since no compound-related mean weight depression had been observed. After the 78-week dosing period the animals were observed for up to 28 additional weeks.

At initiation of the study all mice were approximately 6 weeks old. The group of mice initially receiving 0.03 percent of the test compound in the diet is referred to as the dose A group throughout this report due to the fact that for 26 weeks these mice were receiving 1-amino-2-methylanthraquinone at twice the concentration being fed to the mice started on test at a concentration of 0.06 percent, referred to as the dose B group throughout this report. Dose B mice received a dietary concentration of 0.06 percent for the entire period of compound administration. Dose A mice received an initial concentration of 0.03 percent. In week 17, the concentration for dose A mice was increased to 0.12 percent, as no compound-related mean weight depression had been observed. After 42 weeks on test, the low concentration was decreased because of animal deaths from toxicity to the original level of 0.03 percent, and this level was

maintained for the remaining 31 weeks of the dosing period. As the result of variations in dietary concentrations fed to dose A mice during this bioassay, the time-weighted average concentration of 1-amino-2-methylanthraquinone fed to all dosed groups of mice was 0.06 percent of the diet. After the 73-week dosing period the mice were observed for up to 25 additional weeks.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. From the first day, all animals were inspected twice daily for mortality. Food consumption, for two cages from each group, was monitored for seven consecutive days once a month for the first nine months of the bioassay and for three consecutive days each month thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide inhalation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

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, ear, mammary gland, uterus, 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 placed on experiment in each group.

H. Data Recording and Statistical Analyses

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

as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the 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

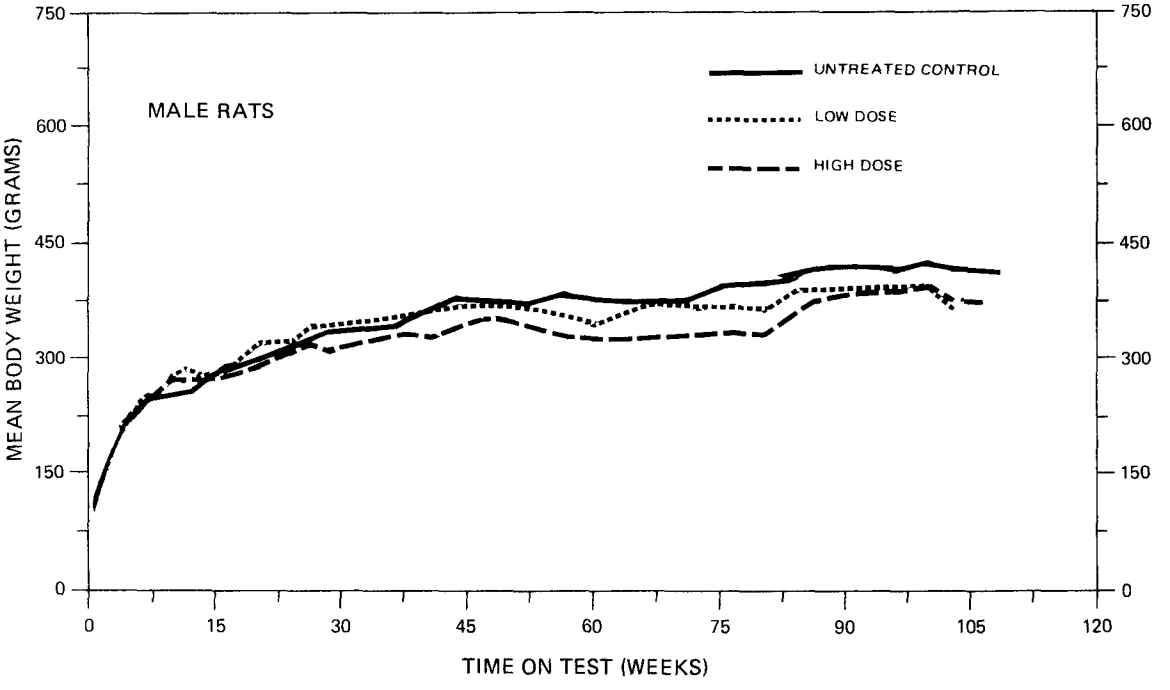
Relatively consistent dose-related mean body weight depression was observed in both male and female rats (Figure 2) and was readily apparent after week 16 in males and week 22 in females.

During the course of the bioassay, palpable subcutaneous masses were the clinical sign most commonly reported. They occurred in six female controls, four male controls, two low dose females, one low dose male, one high dose female, and one high dose male. Three high dose males and three control females were observed to have white discoloration of the eyes. Isolated clinical observations included one high dose male blinded in one eye, one high dose male suffering from severe posterior ataxia, and emaciation of one low dose male.

### B. Survival

The estimated probabilities of survival for male and female rats in the control and 1-amino-2-methylanthraquinone-dose groups are shown in Figure 3. For both males and females there was no statistically significant association between dosage and mortality.

A sufficient number of males were at risk from late-developing tumors as 62 percent (31/50) of the high dose, 90 percent (45/50) of the low dose, and 68 percent (34/50) of the control rats survived on test until the end of the study. Five high dose males were sacrificed in week 79; five control males were sacrificed in week 80.



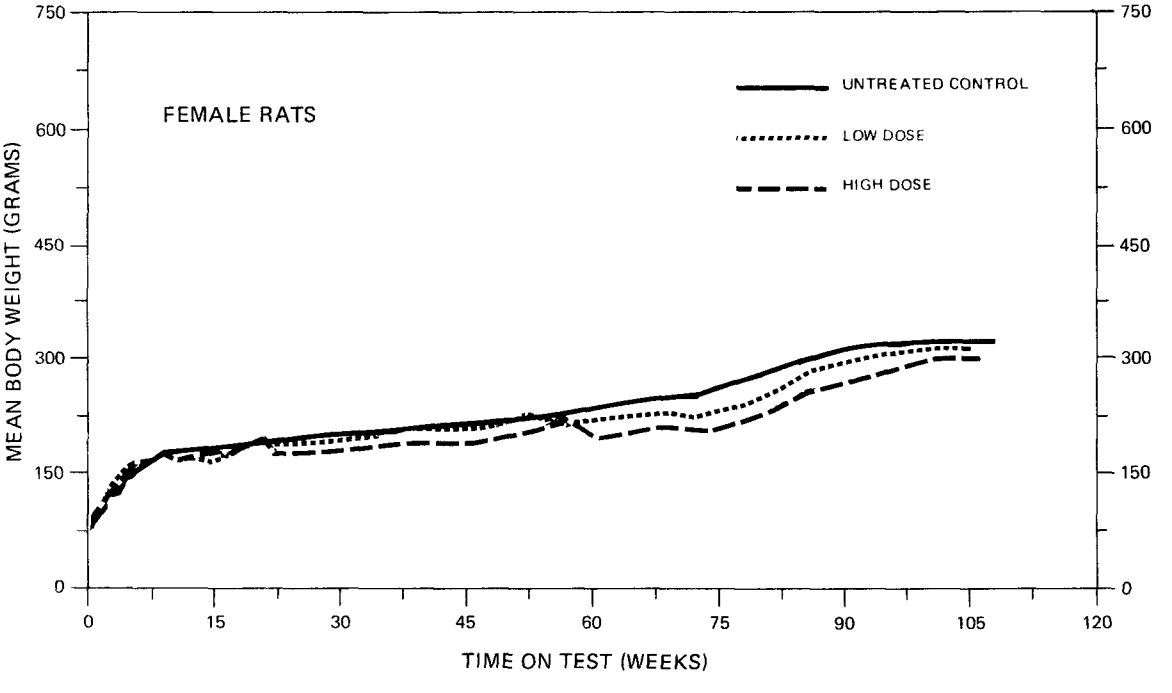
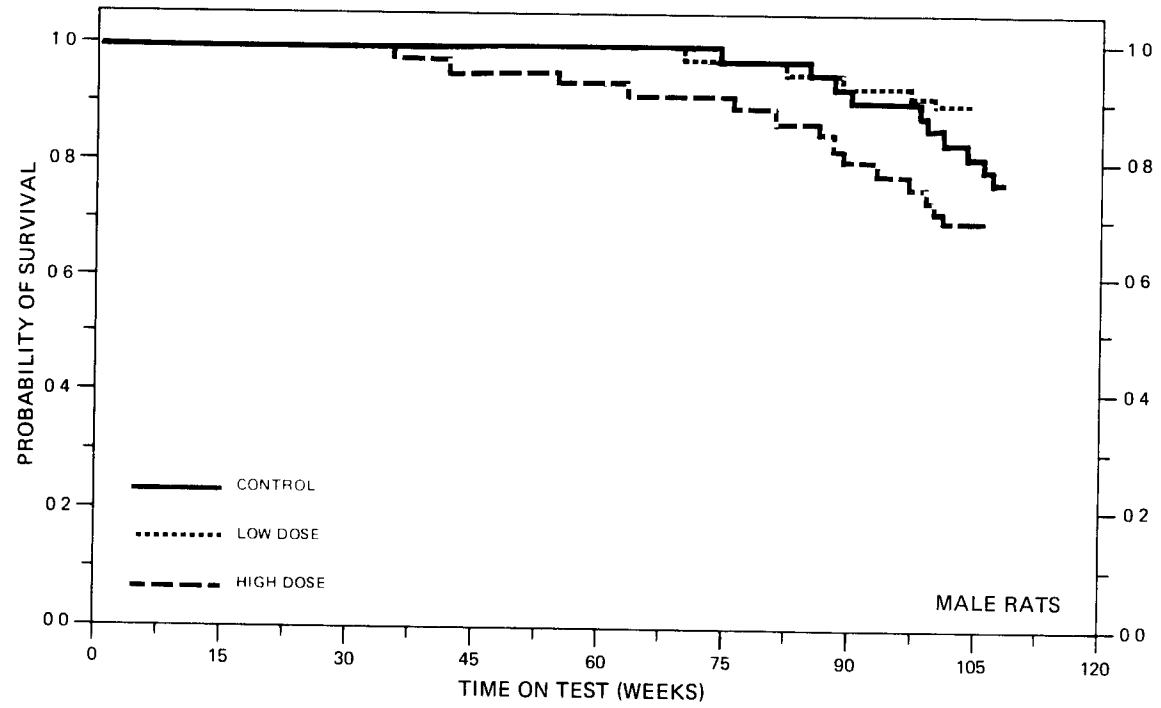




**FIGURE 2**
**GROWTH CURVES FOR 1-AMINO-2-METHYLANTHRAQUINONE CHRONIC STUDY RATS**



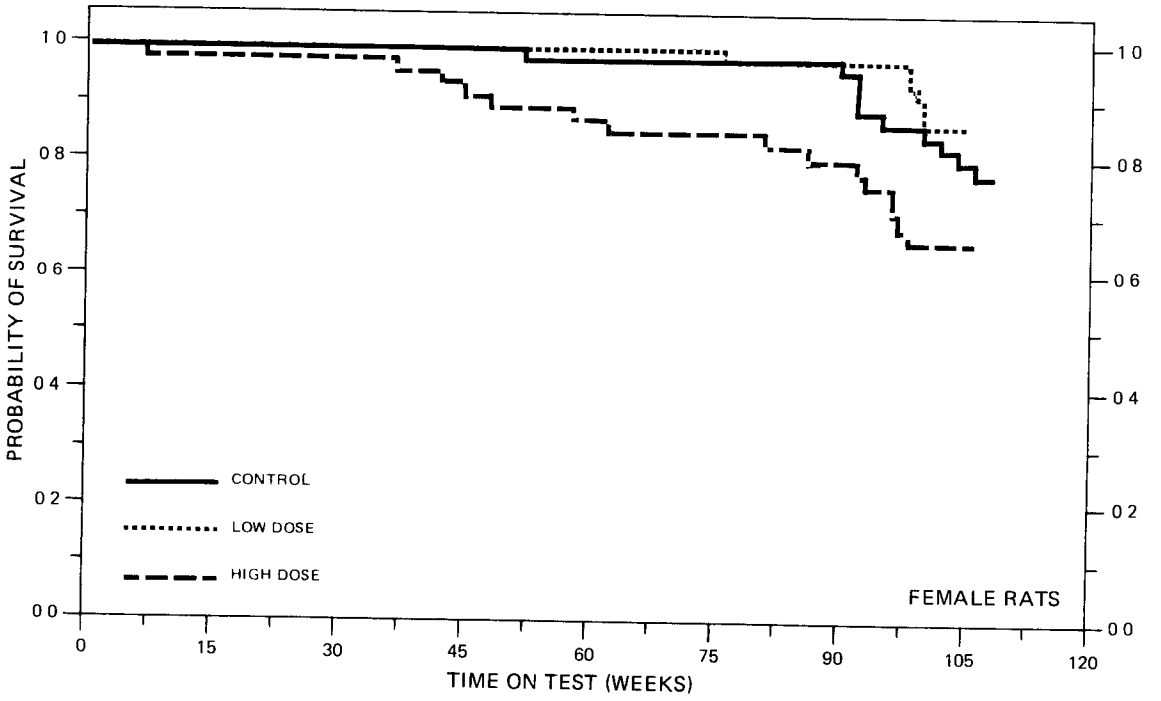




FIGURE 3
SURVIVAL COMPARISONS OF 1-AMINO-2-METHYLANTHRAQUINONE CHRONIC STUDY RATS

For females the survival was also adequate as 56 percent (28/50) of the high dose, 78 percent (39/50) of the low dose, and 70 percent (35/50) of the control rats survived on test until the end of the study. Five high dose females were sacrificed in week 79; five control females were sacrificed in week 80.

C. Pathology

Histopathologic findings on neoplasms in rats are tabulated in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are tabulated in Appendix C (Tables C1 and C2).

Hepatocellular carcinomas occurred in 2/48 (4 percent), 7/50 (14 percent), and 10/48 (21 percent) control, low dose, and high dose male rats, respectively, and in 1/49 (2 percent), 3/45 (7 percent), and 10/44 (23 percent) control, low dose, and high dose female rats, respectively. In addition, neoplastic nodules of the liver were found in 1/48 (2 percent), 18/50 (36 percent), and 14/48 (29 percent) control, low dose, and high dose male rats, respectively, and 2/49 (4 percent), 8/45 (18 percent), and 1/44 (2 percent) control, low dose, and high dose female rats, respectively. Morphology of the neoplastic nodules and hepatocellular carcinomas was similar to that described by Squire and Levitt (1975). Neoplastic nodules were small and compressed the adjacent parenchyma in areas. Cells were large and cytoplasm was acidophilic. Nuclei were hyperchromatic and a few mitotic figures were present. Hepatocellular carcinoma involved a part or an entire lobe of the liver. Lobular architecture was

distorted and liver plates were several cells thick. Pleomorphism in size of neoplastic hepatocytes was noted. Cytoplasm of the cells was acidophilic or vacuolated. Nuclei were large and nucleoli were prominent. Mitotic figures were not numerous.

Neither renal tubular-cell neoplasms nor renal tubular-cell hyperplasia was seen in the control rats of either sex. A dose-related spectrum of changes ranging from hyperplasia to adenoma to adenocarcinoma observed in the kidneys of dosed rats is summarized in the following table:

| | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | Control | Low Dose | High Dose | Control | Low Dose | High Dose |
| Number of Animals with Kidneys Examined Histopathologically | (48) | (50) | (48) | (49) | (45) | (43) |
| Renal Tubular-Cell Hyperplasia | 0 | 11 | 13 | 0 | 3 | 1 |
| Renal Tubular-Cell Adenoma | 0 | 5 | 6 | 0 | 0 | 1 |
| Renal Tubular-Cell Adenocarcinoma | 0 | 0 | 4 | 0 | 0 | 0 |
| Adenocarcinoma NOS | 0 | 1 | 0 | 0 | 0 | 0 |
| Carcinoma NOS | 0 | 0 | 0 | 1 | 0 | 0 |
| Renal Pelvis Transitional-Cell Carcinoma | 0 | 1 | 1 | 0 | 1 | 0 |

A focal increase of tubular cells with a basophilic cytoplasm and large vesicular nuclei was considered renal tubular-cell hyperplasia. Renal tubular-cell adenomas were nodular and were demarcated

from the rest of the renal parenchyma. Cells were arranged in a tubular pattern or occurred as a solid mass. Cytoplasm of cells was basophilic and nuclei were vesicular. There were a few mitotic figures. Two rats had multiple tumors of this nature.

Renal tubular-cell adenocarcinomas were large and circumscribed. They had replaced much of the normal renal tissue. In areas, the neoplasms had compressed adjacent tubules or glomeruli. Cells were arranged in a trabecular pattern. Thin strands of fibrovascular tissue dissected the tumor parenchyma into nodules of varying sizes and shapes. In areas, tumor cells attempted to form tubules. Cytoplasm of cells was either vacuolated or acidophilic. Nuclear pleomorphism was not evident and mitotic figures were not numerous. Clusters of lymphocytes, varying degrees of hemorrhage, and areas of necrosis were present in the tumor mass.

A transitional-cell carcinoma of the kidney was diagnosed in 1/45 low dose female rats. Transitional-cell carcinomas of the renal pelvis occurred in 1/50 low dose male rats and 1/48 high dose male rats. In the low dose male rat, the carcinoma metastasized to the lung. Because of the small number of rats with this type of neoplasm, no clear-cut effect of 1-amino-2-methylanthraquinone on the transitional-cell epithelium could be demonstrated.

This histopathologic examination provided evidence for the carcinogenicity of 1-amino-2-methylanthraquinone in Fischer 344 rats for the following reasons:

(1) there was an increase in the incidence of neoplastic nodules of the liver and hepatocellular carcinomas in dosed rats; and

(2) hyperplastic and neoplastic lesions of renal tubules occurred in dosed rats in a dose-related fashion, predominantly in males.

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 any of the control or 1-amino-2-methylanthraquinone-dosed groups and where such tumors were observed in at least 5 percent of the group.

High numbers of liver tumors were observed in both male and female rats. In males the Cochran-Armitage test showed a significant ($P = 0.012$) positive association between dosage and the incidence of hepatocellular carcinomas. The Fisher exact test results supported these findings by a significant ($P = 0.014$) comparison of high dose to control. In females again the Cochran-Armitage test showed a significant ($P = 0.001$) positive association between dose and the incidence of hepatocellular carcinomas. The Fisher exact test comparing high dose to control was also significant ($P = 0.002$). When incidences were combined so that the numerator represented a rat with either a hepatocellular carcinoma or a neoplastic nodule, for both sexes the Cochran-Armitage test ($P \leq 0.005$) and both the high dose and the low dose Fisher exact test comparisons ($P \leq 0.004$) were

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE[a]

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma[b] | 2/48(0.04) | 7/50(0.14) | 10/48(0.21) |
| P Values[c] | P = 0.012 | N.S. | P = 0.014 |
| Relative Risk (Control)[d] | --- | 3.360 | 5.000 |
| Lower Limit | --- | 0.681 | 1.143 |
| Upper Limit | --- | 31.860 | 44.920 |
| Weeks to First Observed Tumor | 106 | 104 | 100 |
| Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b] | 3/48(0.06) | 25/50(0.50) | 24/48(0.50) |
| P Values[c] | P < 0.001 | P < 0.001 | P < 0.001 |
| Departure from Linear Trend[e] | P = 0.009 | --- | --- |
| Relative Risk (Control)[d] | --- | 8.000 | 8.000 |
| Lower Limit | --- | 2.694 | 2.686 |
| Upper Limit | --- | 38.152 | 38.147 |
| Weeks to First Observed Tumor | 99 | 104 | 76 |
| Hematopoietic System: Leukemia or Malignant Lymphoma[b] | 6/48(0.13) | 1/49(0.02) | 2/49(0.04) |
| P Values[c] | N.S. | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.163 | 0.327 |
| Lower Limit | --- | 0.004 | 0.034 |
| Upper Limit | --- | 1.274 | 1.720 |
| Weeks to First Observed Tumor | 98 | 104 | 99 |

TABLE 3 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b] | 0/48(0.00) | 3/49(0.06) | 2/48(0.04) |
| P Values[c] | N.S. | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | Infinite | Infinite |
| Lower Limit | --- | 0.590 | 0.296 |
| Upper Limit | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | 104 | 105 |
| Kidney: Tubular-Cell Adenoma[b] | 0/48(0.00) | 5/50(0.10) | 6/48(0.13) |
| P Values[c] | P = 0.017 | P = 0.031 | P = 0.013 |
| Relative Risk (Control)[d] | --- | Infinite | Infinite |
| Lower Limit | --- | 1.212 | 1.602 |
| Upper Limit | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | 97 | 97 |
| Kidney: Tubular-Cell Adenocarcinoma or Adenocarcinoma NOS[b] | 0/48(0.00) | 1/50(0.02) | 4/48(0.08) |
| P Values[c] | P = 0.025 | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | Infinite | Infinite |
| Lower Limit | --- | 0.052 | 0.928 |
| Upper Limit | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | 104 | 89 |

TABLE 3 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Kidney: Tubular-Cell Adenoma, Tubular-Cell Adenocarcinoma or Adenocarcinoma NOS[b] | 0/48(0.00) | 6/50(0.12) | 10/48(0.21) |
| P Values[c] | P = 0.001 | P = 0.015 | P = 0.001 |
| Relative Risk (Control)[d] | --- | Infinite | Infinite |
| Lower Limit | --- | 1.537 | 2.980 |
| Upper Limit | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | 97 | 89 |
| Pituitary: Adenoma NOS or Chromophobe Adenoma[b] | 1/41(0.02) | 10/46(0.22) | 8/39(0.21) |
| P Values[c] | P = 0.017 | P = 0.006 | P = 0.012 |
| Relative Risk (Control)[d] | --- | 8.913 | 8.410 |
| Lower Limit | --- | 1.361 | 1.211 |
| Upper Limit | --- | 376.318 | 361.434 |
| Weeks to First Observed Tumor | 108 | 70 | 79 |
| Adrenal: Pheochromocytoma[b] | 10/47(0.21) | 10/49(0.20) | 6/48(0.13) |
| P Values[c] | N.S. | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.959 | 0.587 |
| Lower Limit | --- | 0.396 | 0.191 |
| Upper Limit | --- | 2.330 | 1.634 |
| Weeks to First Observed Tumor | 99 | 70 | 105 |

TABLE 3 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b] | 0/39(0.00) | 3/47(0.06) | 5/46(0.11) |
| P Values[c] | P = 0.032 | N.S. | P = 0.042 |
| Relative Risk (Control)[d] | --- | Infinite | Infinite |
| Lower Limit | --- | 0.503 | 1.078 |
| Upper Limit | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | 104 | 79 |
| Testis: Interstitial-Cell Tumor[b] | 45/47(0.96) | 48/50(0.96) | 43/48(0.90) |
| P Values[c] | N.S. | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 1.003 | 0.936 |
| Lower Limit | --- | 0.931 | 0.865 |
| Upper Limit | --- | 1.080 | 1.067 |
| Weeks to First Observed Tumor | 80 | 70 | 76 |
| Body cavities: Mesothelioma NOS[b] | 0/48(0.00) | 1/49(0.02) | 4/49(0.08) |
| P Values[c] | P = 0.027 | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | Infinite | Infinite |
| Lower Limit | --- | 0.053 | 0.909 |
| Upper Limit | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | 104 | 79 |

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 0.10 or 0.20 percent 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 indication (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-AMINO-2-METHYLANTHRAQUINONE[a]

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma[b] | 1/49(0.02) | 3/45(0.07) | 10/44(0.23) |
| P Values[c] | P = 0.001 | N.S. | P = 0.002 |
| Relative Risk (Control)[d] | --- | 3.267 | 11.140 |
| Lower Limit | --- | 0.274 | 1.690 |
| Upper Limit | --- | 167.567 | 469.425 |
| Weeks to First Observed Tumor | 108 | 105 | 105 |
| Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b] | 2/49(0.04) | 11/45(0.24) | 11/44(0.25) |
| P Values[c] | P = 0.005 | P = 0.004 | P = 0.004 |
| Relative Risk (Control)[d] | --- | 5.989 | 6.125 |
| Lower Limit | --- | 1.402 | 1.444 |
| Upper Limit | --- | 52.986 | 54.128 |
| Weeks to First Observed Tumor | 92 | 104 | 105 |
| Hematopoietic System: Leukemia or Malignant Lymphoma[b] | 7/49(0.14) | 2/45(0.04) | 1/44(0.02) |
| P Values[c] | P = 0.020(N) | N.S. | P = 0.042(N) |
| Relative Risk (Control)[d] | --- | 0.311 | 0.159 |
| Lower Limit | --- | 0.033 | 0.004 |
| Upper Limit | --- | 1.529 | 1.165 |
| Weeks to First Observed Tumor | 106 | 104 | 98 |

TABLE 4 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Pituitary: Adenoma NOS or Chromophobe Adenoma[b] | 18/44(0.41) | 14/40(0.35) | 20/39(0.51) |
| P Values[c] | N.S. | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.856 | 1.254 |
| Lower Limit | --- | 0.458 | 0.745 |
| Upper Limit | --- | 1.562 | 2.090 |
| Weeks to First Observed Tumor | 90 | 76 | 58 |
| Mammary Gland: Adenoma, Fibroadenoma or Adenocarcinoma[b] | 18/49(0.37) | 6/45(0.13) | 3/44(0.07) |
| P Values[c] | P < 0.001(N) | P = 0.009(N) | P < 0.001(N) |
| Relative Risk (Control)[d] | --- | 0.363 | 0.186 |
| Lower Limit | --- | 0.130 | 0.038 |
| Upper Limit | --- | 0.858 | 0.579 |
| Weeks to First Observed Tumor | 80 | 76 | 106 |
| Uterus: Endometrial Stromal Polyp[b] | 12/49(0.24) | 10/44(0.23) | 2/42(0.05) |
| P Values[c] | P = 0.012(N) | N.S. | P = 0.009(N) |
| Relative Risk (Control)[d] | --- | 0.928 | 0.194 |
| Lower Limit | --- | 0.399 | 0.022 |
| Upper Limit | --- | 2.099 | 0.807 |
| Weeks to First Observed Tumor | 80 | 98 | 106 |

TABLE 4 (CONCLUDED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b] | 3/40(0.07) | 2/43(0.05) | 1/38(0.03) |
| P Values[c] | N.S. | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.620 | 0.351 |
| Lower Limit | --- | 0.054 | 0.007 |
| Upper Limit | --- | 5.138 | 4.140 |
| Weeks to First Observed Tumor | 108 | 104 | 105 |

[a]Treated groups received time-weighted average doses of 0.10 or 0.20 percent 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.

significant. Based upon these results the administration of 1-amino-2-methylanthraquinone was associated with an increased incidence of hepatocellular carcinomas in both male and female rats.

In male rats significant numbers of kidney neoplasms were also noted. When incidences were combined so that the numerator represented male rats with either a tubular-cell adenoma, a tubular-cell adenocarcinoma, or an adenocarcinoma NOS, then the Cochran-Armitage test ($P = 0.001$) and the Fisher exact tests comparing both high dose to control ($P = 0.001$) and low dose to control ($P = 0.015$) were significant. Based upon these results, administration of 1-amino-2-methylanthraquinone was associated with an increased incidence of tubular-cell neoplasms of the kidney in male rats.

For male rats the Cochran-Armitage test also indicated a significant ($P = 0.017$) positive association between dose and the combined incidence of adenomas NOS or chromophobe adenomas of the pituitary. The Fisher exact tests confirmed this finding for the comparison of both low dose ($P = 0.006$) and high dose ($P = 0.012$) to control. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, however, 37/334 (11 percent) of the untreated males had a pituitary adenoma, compared to the 1/41 (2 percent) observed in the control group for this bioassay. Additionally, the incidences in several historical control groups were above those incidence rates observed in these dosed groups.

For males the Cochran-Armitage test indicated significant associations between dose and both the incidence of mesotheliomas of the tunica vaginalis and the incidence of C-cell thyroid neoplasms. In both cases, however, the Fisher exact tests were not significant under the Bonferroni criterion.

For females the possibility of significant negative associations between dose and incidence were observed for mammary tumors and for endometrial stromal polyps. For the mammary tumors, however, historical control data showed 125/589 (21 percent) of the untreated Fischer 344 female rats with either an adenoma, a fibroadenoma, or an adenocarcinoma of the mammary gland--compared to the 18/49 (37 percent), 6/45 (13 percent), and 3/44 (7 percent) observed in the control, low dose, and high dose groups, respectively, in this bioassay. The Cochran-Armitage test showed a significant negative association for leukemia or malignant lymphoma, but the Fisher exact tests were not significant under the Bonferroni criterion.

Summarizing these results, the statistical conclusions were that the incidences of hepatocellular carcinomas in both male and female rats and of kidney tumors in male rats were associated with the administration of 1-amino-2-methylanthraquinone.

## IV. CHRONIC TESTING RESULTS: MICE

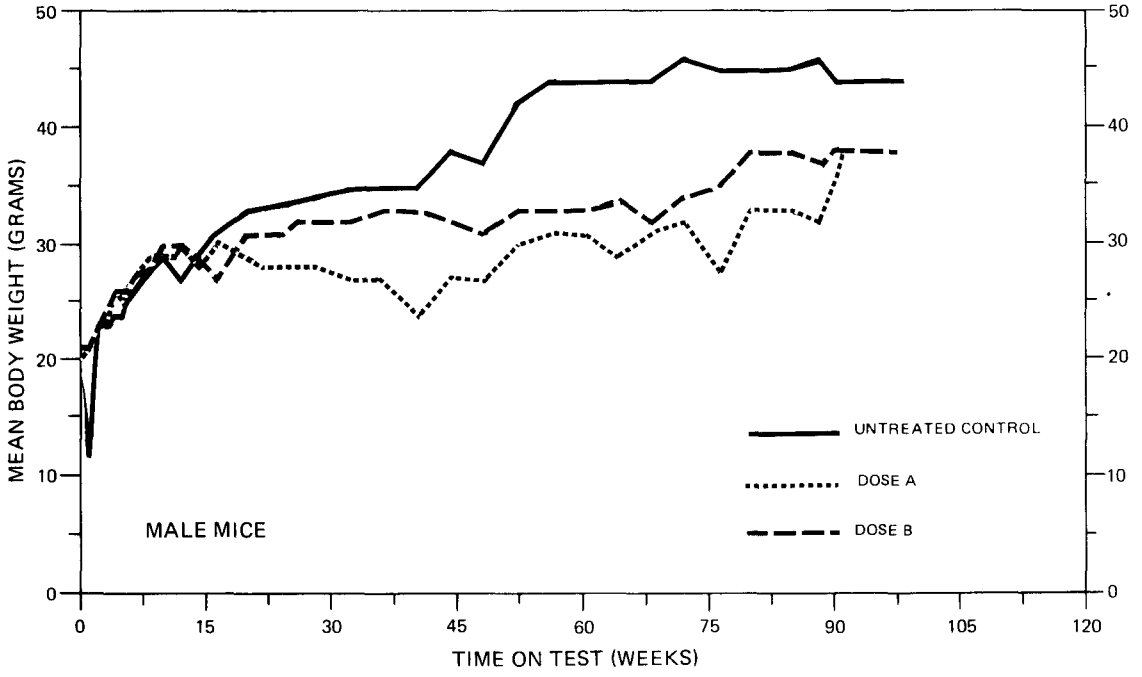
### A. Body Weights and Clinical Observations

Relatively consistent and severe dose-related mean body weight depression was observed in the female mice and, to a lesser extent, in the male mice (Figure 4). The inconsistency observed in the weight pattern of the dose A males after week 48 and until week 76 may have been indirectly due to a reduction of the concentration of the chemical in the food beginning in week 43. This reduction was initiated because of the numerous deaths experienced by the dose A group. The net result may have been increased food consumption and subsequent weight gain by the remaining, perhaps most healthy, animals.

No clinical abnormalities were recorded for mice of either sex.

### B. Survival

The estimated probabilities of survival for male and female mice in the control and 1-amino-2-methylanthraquinone-dosed groups are shown in Figure 5. For both males and females the Cox tests indicated the survival of the dose A groups was significantly ($P < 0.001$) lower than that of the dose B groups or the control groups. This appears to have been associated with an increase in dosage for the dose A groups in week 17 from 0.03 to 0.12 percent 1-amino-2-methylanthraquinone in their feed. In week 43 the dosage for the dose A groups was changed back to 0.03 percent. Dose B groups received the chemical at a dietary concentration of 0.06 percent. As a result of these dosage



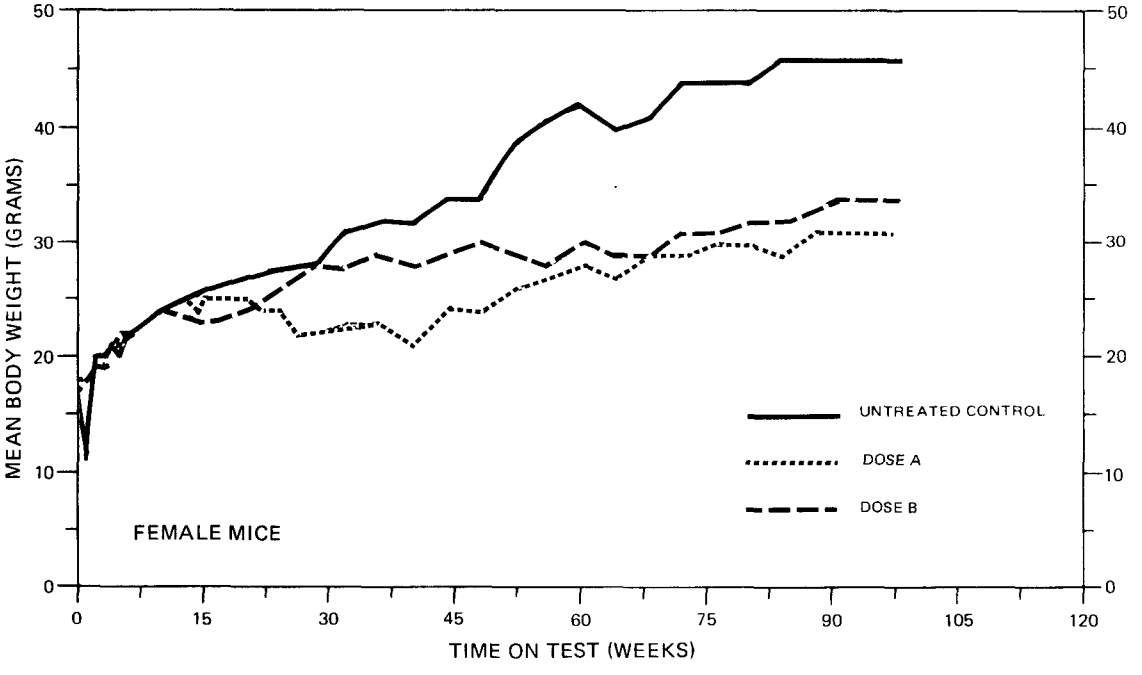




**FIGURE 4**
**GROWTH CURVES FOR 1-AMINO-2-METHYLANTHRAQUINONE CHRONIC STUDY MICE**

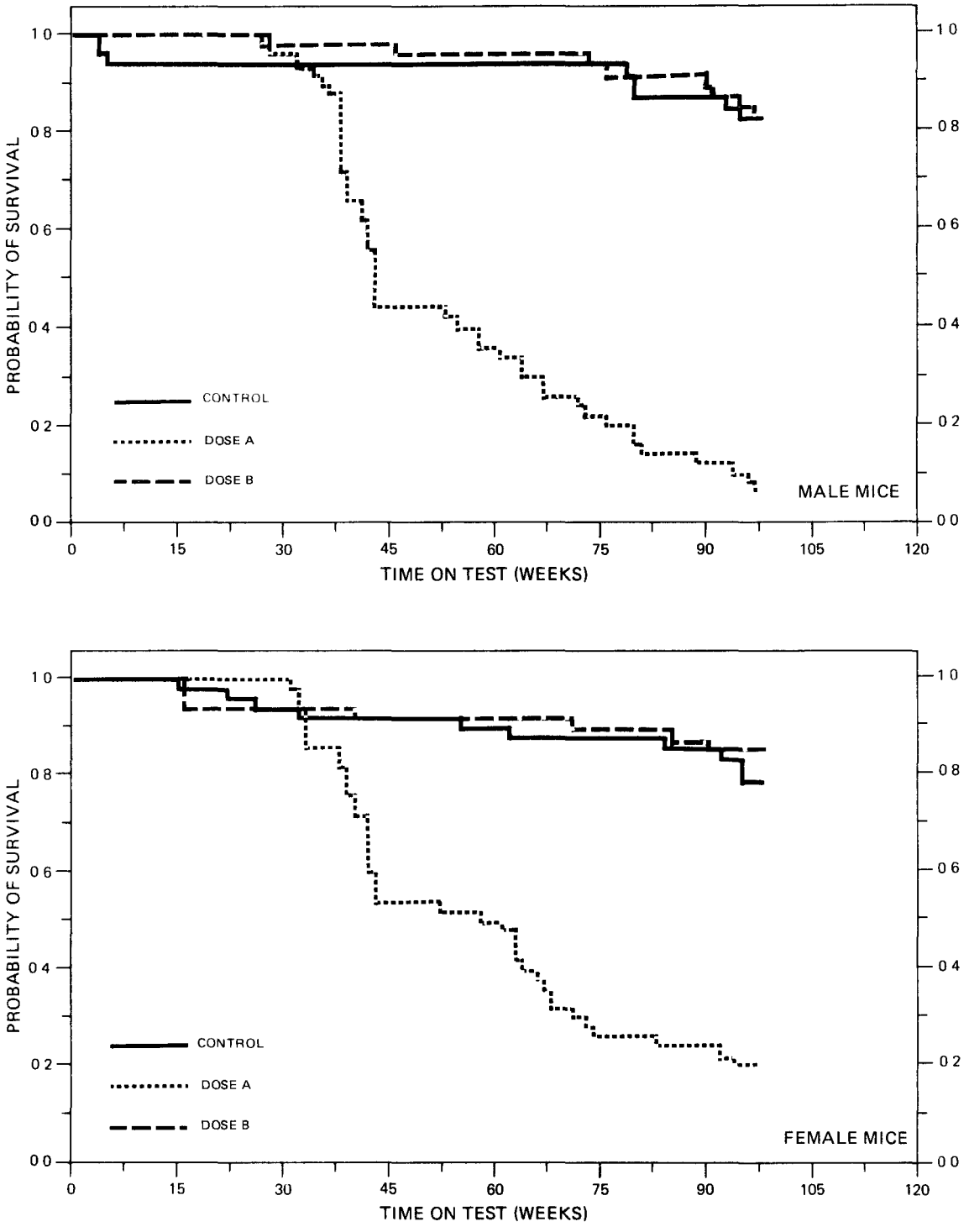



**FIGURE 5**
**SURVIVAL COMPARISONS OF 1-AMINO-2-METHYLANTHRAQUINONE CHRONIC STUDY MICE**

changes, the time-weighted average concentrations of 1-amino-2-methylanthraquinone received by the dose A groups and the dose B groups were approximately the same (0.062 and 0.06 percent, respectively).

By the end of week 43, 56 percent (28/50) of the dose A group males and 46 percent (23/50) of the dose A group females had died. As such, there were not adequate numbers of dose A group mice at risk from late-developing tumors.

For males, however, there were adequate numbers of dose B group and control group mice at risk from late-developing tumors, as 74 percent (37/50) of both the dose B group and the control group survived on test until the end of the study. Five dose B group males were sacrificed in week 79; five control males were sacrificed in week 78.

The survival of female dose B and control mice was also adequate as 74 percent (37/50) of the dose B group and 70 percent (35/50) of the control group survived on test until the end of the study. Five control mice were sacrificed in week 78; five dose B group mice were sacrificed in weeks 79 and 80.

C. Pathology

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

Hepatocellular carcinomas occurred in both control and dosed mice and did not appear to be compound-related. In male mice, this tumor was found in 10/45 (22 percent) control, 1/36 (3 percent)

dose A, and 8/45 (18 percent) dose B mice. In female mice, hepatic tumors were seen in 4/45 (9 percent) control, 2/34 (6 percent) dose A, and in 12/44 (27 percent) dose B mice.

Adenocarcinoma of the kidney, morphologically similar to that in rats, was found in two dose B male mice. The occurrence of these tumors is of interest in view of the occurrence of renal tumors in the rats.

Compound-related nonneoplastic lesions involved only the kidney. The incidence of glomerulonephritis (glomerulosclerosis) and interstitial (diffuse) fibrosis in these mice is shown in the following table:

| | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | Control | Dose A | Dose B | Control | Dose A | Dose B |
| Number of Animals with Kidneys Examined Histopathologically | (45) | (37) | (45) | (43) | (37) | (42) |
| Glomerulonephritis NOS | 0 | 24 | 42 | 0 | 23 | 31 |
| Interstitial Fibrosis | 0 | 9 | 32 | 0 | 12 | 13 |

Degenerative changes in renal tubules ranged from loss of cytoplasmic basophilia to necrosis. Large tubular cells with basophilic cytoplasm and vesicular nuclei suggested regeneration. Clusters of inflammatory cells were present in the cortex.

In areas, some of the renal tubules were cystic, the glomeruli were atrophic, and the Bowman's space distended. Both the basement

membrane and mesangium were thickened in a few glomeruli. Interstitial fibrosis was present in many mice.

The results of this histopathologic examination provided evidence for the carcinogenicity of 1-amino-2-methylanthraquinone in B6C3F1 mice, as administration of the compound was associated with increased numbers of liver tumors in female mice. 1-Amino-2-methylanthraquinone was also nephrotoxic at the doses used to both sexes of B6C3F1 mice as shown by the occurrence of glomerulonephritis and interstitial fibrosis.

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 any of the control or 1-amino-2-methylanthraquinone-dosed groups and where such tumors were observed in at least 5 percent of the group. Because the time-weighted average dose received by the dose A group was approximately the same as that received by the dose B group, it was inappropriate to use the Cochran-Armitage test with these data. Because the manner in which the dosages were changed resulted in poor survival in the dose A group, the following analyses are based solely upon those mice surviving at least 52 weeks.

In female mice a number of liver neoplasms were observed. When incidences were combined so that the numerator represented female mice with either hepatocellular carcinomas or neoplastic nodules,

TABLE 5

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE [a,e]

| TOPOGRAPHY:MORPHOLOGY | CONTROL | DOSE A | DOSE B |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma[b] | 4/45(0.09) | 0/10(0.00) | 1/43(0.02) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.000 | 0.262 |
| Lower Limit | --- | 0.000 | 0.005 |
| Upper Limit | --- | 4.357 | 2.505 |
| Weeks to First Observed Tumor | 97 | --- | 79 |
| Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b] | 11/45(0.24) | 0/10(0.00) | 5/43(0.12) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.000 | 0.476 |
| Lower Limit | --- | 0.000 | 0.141 |
| Upper Limit | --- | 1.212 | 1.350 |
| Weeks to First Observed Tumor | 78 | --- | 79 |
| Circulatory System: Hemangiosarcoma[b] | 0/46(0.00) | 0/12(0.00) | 3/45(0.07) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | --- | Infinite |
| Lower Limit | --- | --- | 0.617 |
| Upper Limit | --- | --- | Infinite |
| Weeks to First Observed Tumor | --- | --- | 97 |

TABLE 5 (CONCLUDED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | DOSE A | DOSE B |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma[b] | 10/45(0.22) | 1/11(0.09) | 8/44(0.18) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.409 | 0.818 |
| Lower Limit | --- | 0.010 | 0.310 |
| Upper Limit | --- | 2.336 | 2.081 |
| Weeks to First Observed Tumor | 93 | 76 | 79 |

[a]Treated groups received time-weighted average doses of approximately 0.06 percent in feed.

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

[c]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 that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. A negative designation (N) indicates a lower incidence in the treated group than in the control group.

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

[e]These analyses were based solely upon animals surviving at least 52 weeks.

TABLE 6

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE[a,e]

| TOPOGRAPHY:MORPHOLOGY | CONTROL | DOSE A | DOSE B |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma[b] | 4/44(0.09) | 2/16(0.13) | 9/43(0.21) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 1.375 | 2.302 |
| Lower Limit | --- | 0.132 | 0.700 |
| Upper Limit | --- | 8.336 | 9.502 |
| Weeks to First Observed Tumor | 78 | 97 | 97 |
| Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b] | 4/44(0.09) | 2/16(0.13) | 12/43(0.28) |
| P Values[c] | --- | N.S. | P = 0.022 |
| Relative Risk (Control)[d] | --- | 1.375 | 3.070 |
| Lower Limit | --- | 0.132 | 1.021 |
| Upper Limit | --- | 8.336 | 12.053 |
| Weeks to First Observed Tumor | 78 | 97 | 97 |
| Hematopoietic System: Leukemia or Malignant Lymphoma[b] | 12/45(0.27) | 1/18(0.06) | 5/43(0.12) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.208 | 0.436 |
| Lower Limit | --- | 0.005 | 0.141 |
| Upper Limit | --- | 1.366 | 1.350 |
| Weeks to First Observed Tumor | 95 | 97 | 90 |

TABLE 6 (CONCLUDED)

| TOPOGRAPHY:MORPHOLOGY | CONTROL | DOSE A | DOSE B |
|---|---|---|---|
| Pituitary: Adenoma NOS[b] | 6/37(0.16) | 0/11(0.00) | 3/34(0.09) |
| P Values[c] | --- | N.S. | N.S. |
| Relative Risk (Control)[d] | --- | 0.000 | 0.544 |
| Lower Limit | --- | 0.000 | 0.095 |
| Upper Limit | --- | 1.903 | 2.328 |
| Weeks to First Observed Tumor | 98 | --- | 97 |

[a]Treated groups received time-weighted average doses of approximately 0.06 percent in feed.

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

[c]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 that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. A negative designation (N) indicates a lower incidence in the treated group than in the control group.

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

[e]These analyses were based solely upon animals surviving at least 52 weeks.

the Fisher exact text indicated that the incidence of liver tumors was significantly (P = 0.022) greater in the dose B group than in the control. In historical data collected by this laboratory for the NCI Carcinogenesis Testing Program, 13/350 (4 percent) untreated female B6C3F1 mice had one of these tumors, compared to the 4/44 (9 percent), 2/16 (13 percent), and 12/43 (28 percent) observed in the control, dose A, and dose B groups, respectively, in this bioassay. Based upon these results, the administration of 1-amino-2-methylanthraquinone was associated with an increased incidence of liver neoplasms in female mice.

No other test at any other site in either sex was statistically 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-amino-2-methylanthraquinone that could not be established under the conditions of this test.

# V. DISCUSSION

Under the conditions of this bioassay adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors in all except the male and female dose A mouse groups. The poor survival may be attributable to the concentration of 1-amino-2-methylanthraquinone administered to these groups from weeks 17 through 42 (0.12 percent). Although dose A mouse groups were started as the low dose groups, the concentration given of the test chemical in feed from weeks 17 through 42 was twice the highest concentration received by the dose B groups.

Hepatocellular carcinomas were observed, respectively, in 2/48 (4 percent), 7/50 (14 percent), and 10/48 (21 percent) of the control, low dose, and high dose male rats and in 1/49 (2 percent), 3/45 (7 percent), and 10/44 (23 percent) of the control, low dose, and high dose female rats. The Cochran-Armitage tests indicated a significant positive association between dosage and the incidences of these neoplasms in both sexes and the Fisher exact comparison of the high dose to the control group for each sex supported these findings. Neoplastic liver nodules were detected in 1/48 (2 percent), 18/50 (36 percent), and 14/48 (29 percent) of the control, low dose, and high dose male rats and in 2/49 (4 percent), 8/45 (18 percent), and 1/44 (2 percent) of the control, low dose, and high dose female rats, respectively. For each sex the Cochran-Armitage test revealed a significant positive association between compound administration and the incidence of these

nodules. In the males, the high dose to control Fisher exact comparison supported this finding but in females only the low dose to control Fisher exact comparison supported the association. When all the female rats in each group having either hepatocellular carcinomas or neoplastic liver nodules were combined and the resulting incidences of females with these tumors were statistically analyzed, both the high dose to control and the low dose to control Fisher exact tests indicated significant positive associations between compound administration and the occurrence of these neoplasms.

A spectrum of compound-related renal changes was noted, ranging from hyperplasias to adenomas and adenocarcinomas, particularly among the male rats. Statistical analyses of these kidney tumors, using the Cochran-Armitage test, revealed significant associations between dosage and the incidence of tubular-cell adenomas and the combined incidence of tubular-cell adenomas, tubular-cell adenocarcinomas, and adenocarcinomas NOS. The Fisher exact comparisons of high dose to control supported both of these associations in male rats.

The only other statistically significant positive association between chemical administration and increased tumor incidence in rats was demonstrated for males with pituitary adenomas. The Cochran-Armitage test indicated the positive association and it was supported by both the high and low dose Fisher exact comparisons. The incidence of pituitary adenomas in male rat controls (1/41 or 2 percent) was unusually low compared to historical controls (37/334 or 11 percent).

In addition, the incidences of these neoplasms in some of the historical control groups from this laboratory have closely approximated the incidences observed in the dosed male rats in this bioassay. For this reason, the statistical results based on observed tumor incidences are not considered sufficient proof that the compound induced pituitary adenomas in male rats.

When those female mice having hepatocellular carcinomas were combined with those having neoplastic liver nodules and the resulting incidence of dose B females having these tumors was compared to the incidence in control females, a significant positive association between compound administration and tumor incidence was demonstrated. No other neoplasms occurred in statistically significant positive incidences in male or female mice.

The detection of adenocarcinomas of the kidney in two dose B male mice was of interest, considering the renal abnormalities reported in rats. The only compound-related nonneoplastic lesions in the mice were glomerulonephritis and interstitial (diffuse) fibrosis, both of which occurred only in dosed animals. As a result, the compound was determined to be nephrotoxic in mice at the concentrations administered in the feed.

Under the conditions of this bioassay, 1-amino-2-methylanthraquinone was carcinogenic in male and female Fischer 344 rats, inducing hepatocellular carcinomas in rats of both sexes. It also induced renal neoplasms in male rats. The compound was carcinogenic in

female B6C3F1 mice, producing an increased incidence of liver tumors (i.e., the combined incidence of neoplastic nodules and hepatocellular carcinomas).

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Review of the Bioassay of 1-Amino-2-Methylanthraquinone*
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-Amino-2-Methylanthraquinone for carcinogenicity.

The reviewer said that the compound induced liver tumors in both sexes of treated rats and in female mice. It also induced kidney tumors in male rats and was nephrotoxic in mice. The reviewer opined that the hepatic effect in male mice may have been masked by the high spontaneous incidence of liver tumors in this sex. He noted the negative trend for mammary tumors in treated female rats. The reviewer considered the experimental design acceptable

and he moved that the report on the bioassay of 1-Amino-2-Methylanthraquinone 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.

☆U.S. GOVERNMENT PRINTING OFFICE: 1978-260-899/3195

# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS MISSING | 1 | | |
| ANIMALS NECROPSIED | 48 | 49 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 48 | 48 | 48 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (48) | (49) | (49) |
| SQUAMOUS CELL PAPILLOMA | 1 (2%) | 1 (2%) | |
| SQUAMOUS CELL CARCINOMA | 1 (2%) | | |
| BASAL-CELL CARCINOMA | 1 (2%) | | |
| *SUBCUT TISSUE | (48) | (49) | (49) |
| FIBROMA | 2 (4%) | | 2 (4%) |
| FIBROSARCOMA | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (48) | (49) | (48) |
| CARCINOMA, NOS, METASTATIC | 1 (2%) | | |
| TRANSITIONAL-CELL CARCINOMA, MET | | 1 (2%) | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | 2 (4%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 3 (6%) | |
| OSTEOSARCOMA, METASTATIC | 1 (2%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (48) | (49) | (49) |
| MALIGNANT LYMPHOMA, NOS | | | 1 (2%) |
| LEUKEMIA,NOS | 1 (2%) | | |
| MYELOMONOCYTIC LEUKEMIA | 5 (10%) | | 1 (2%) |
| #SPLEEN | (48) | (49) | (48) |
| OSTEOSARCOMA, METASTATIC | 1 (2%) | | |
| MYELOMONOCYTIC LEUKEMIA | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |

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

TABLE A1 (CONTINUED)

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (48) | (50) | (48) |
| NEOPLASTIC NODULE | 1 (2%) | 18 (36%) | 14 (29%) |
| HEPATOCELLULAR CARCINOMA | 2 (4%) | 7 (14%) | 10 (21%) |
| #PANCREAS | (45) | (48) | (47) |
| ACINAR-CELL ADENOMA | | | 1 (2%) |
| #STOMACH | (48) | (47) | (47) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (48) | (50) | (48) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| TUBULAR-CELL ADENOMA | | 5 (10%) | 6 (13%) |
| TUBULAR-CELL ADENOCARCINOMA | | | 4 (8%) |
| #KIDNEY/PELVIS | (48) | (50) | (48) |
| TRANSITIONAL-CELL CARCINOMA | | 1 (2%) | 1 (2%) |
| #URINARY BLADDER | (46) | (48) | (45) |
| TRANSITIONAL-CELL PAPILLOMA | 1 (2%) | | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (41) | (46) | (39) |
| ADENOMA, NOS | 1 (2%) | 2 (4%) | 1 (3%) |
| CHROMOPHOBE ADENOMA | | 8 (17%) | 7 (18%) |
| #ADRENAL | (47) | (49) | (48) |
| CORTICAL ADENOMA | 1 (2%) | | |
| PHEOCHROMOCYTOMA | 10 (21%) | 10 (20%) | 6 (13%) |
| GANGLIONEUROMA | 1 (2%) | | |
| #THYROID | (39) | (47) | (46) |
| FOLLICULAR-CELL CARCINOMA | | 1 (2%) | |
| C-CELL ADENOMA | | 2 (4%) | 3 (7%) |
| C-CELL CARCINOMA | | 1 (2%) | 2 (4%) |
| #PANCREATIC ISLETS | (45) | (48) | (47) |
| ISLET-CELL ADENOMA | 3 (7%) | 1 (2%) | 1 (2%) |

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

TABLE A1 (CONTINUED)

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (48) | (49) | (49) |
| PAPILLARY ADENOCARCINOMA | 1 (2%) | | |
| FIBROADENOMA | 1 (2%) | | |
| *PREPUTIAL GLAND | (48) | (49) | (49) |
| CARCINOMA,NOS | 2 (4%) | | |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| ADENOMA, NOS | | 1 (2%) | |
| *TESTIS | (47) | (50) | (48) |
| INTERSTITIAL-CELL TUMOR | 45 (96%) | 48 (96%) | 43 (90%) |
| **NERVOUS SYSTEM** | | | |
| NONE | | | |
| **SPECIAL SENSE ORGANS** | | | |
| NONE | | | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| NONE | | | |
| **BODY CAVITIES** | | | |
| *BODY CAVITIES | (48) | (49) | (49) |
| MESOTHELIOMA, NOS | | 1 (2%) | 4 (8%) |
| *PERITONEUM | (48) | (49) | (49) |
| MESOTHELIOMA, NOS | 1 (2%) | | |
| **ALL OTHER SYSTEMS** | | | |
| NONE | | | |

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

TABLE A1 (CONCLUDED)

| | CONTROL(UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 5 | 3 | 10 |
| MORIBUND SACRIFICE | 5 | 2 | 4 |
| SCHEDULED SACRIFICE | 5 | | 5 |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 34 | 45 | 31 |
| ANIMAL MISSING | 1 | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 45 | 48 | 45 |
| TOTAL PRIMARY TUMORS | 81 | 115 | 111 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 45 | 48 | 45 |
| TOTAL BENIGN TUMORS | 66 | 79 | 73 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 10 | 17 | 17 |
| TOTAL MALIGNANT TUMORS | 13 | 17 | 20 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 2 | 1 | |
| TOTAL SECONDARY TUMORS | 3 | 1 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT | 2 | 19 | 17 |
| TOTAL UNCERTAIN TUMORS | 2 | 19 | 18 |
| 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-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 45@ | 48@ |
| ANIMALS NECROPSIED | 49 | 45 | 44 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 49 | 45 | 42 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (49) | (45) | (44) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| *SUBCUT TISSUE | (49) | (45) | (44) |
| FIBROMA | | 1 (2%) | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (49) | (44) | (43) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 2 (5%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (49) | (45) | (44) |
| MALIGNANT LYMPHOMA, NOS | 2 (4%) | | |
| MYELOMONOCYTIC LEUKEMIA | 4 (8%) | 1 (2%) | |
| LYMPHOCYTIC LEUKEMIA | | | 1 (2%) |
| *UPPER TRUNK | (49) | (45) | (44) |
| MYELOMONOCYTIC LEUKEMIA | 1 (2%) | | |
| #LYMPH NODE | (42) | (44) | (40) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (49) | (45) | (44) |
| NEOPLASTIC NODULE | 2 (4%) | 8 (18%) | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT 5 IN THE LOW-DOSE GROUP AND 2 IN THE HIGH-DOSE GROUP WERE FOUND TO BE MALE ANIMALS IN FEMALE GROUPS.

TABLE A2 (CONTINUED)

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| HEPATOCELLULAR CARCINOMA | 1 (2%) | 3 (7%) | 10 (23%) |
| #PANCREAS | (47) | (45) | (41) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | |
| #STOMACH | (49) | (45) | (42) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (49) | (45) | (43) |
| CARCINOMA,NOS | 1 (2%) | | |
| TRANSITIONAL-CELL CARCINOMA | | 1 (2%) | |
| TUBULAR-CELL ADENOMA | | | 1 (2%) |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (44) | (40) | (39) |
| ADENOMA, NOS | 18 (41%) | 5 (13%) | 13 (33%) |
| CHROMOPHOBE ADENOMA | | 9 (23%) | 7 (18%) |
| #ADRENAL | (49) | (45) | (41) |
| CORTICAL ADENOMA | | 1 (2%) | |
| CORTICAL CARCINOMA | 1 (2%) | | |
| PHEOCHROMOCYTOMA | 2 (4%) | 1 (2%) | |
| #THYROID | (40) | (43) | (38) |
| ADENOMA, NOS | | | 1 (3%) |
| FOLLICULAR-CELL CARCINOMA | 1 (3%) | | |
| C-CELL ADENOMA | 2 (5%) | 2 (5%) | 1 (3%) |
| C-CELL CARCINOMA | 1 (3%) | | |
| PAPILLARY CYSTADENOMA, NOS | | | 1 (3%) |
| #PANCREATIC ISLETS | (47) | (45) | (41) |
| ISLET-CELL ADENOMA | 1 (2%) | | |
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (49) | (45) | (44) |
| ADENOMA, NOS | 2 (4%) | 1 (2%) | |
| ADENOCARCINOMA, NOS | | 2 (4%) | |
| FIBROADENOMA | 16 (33%) | 4 (9%) | 3 (7%) |
| *CLITORAL GLAND | (49) | (45) | (44) |
| ADENOMA, NOS | 1 (2%) | | |

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

TABEL A2 (CONTINUED)

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| #UTERUS | (49) | (44) | (42) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| LEIOMYOSARCOMA | 1 (2%) | | |
| ENDOMETRIAL STROMAL POLYP | 12 (24%) | 10 (23%) | 2 (5%) |
| ENDOMETRIAL STROMAL SARCOMA | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (49) | (44) | (42) |
| ADENOCARCINOMA, NOS | 2 (4%) | | |
| #OVARY | (47) | (44) | (42) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| #BRAIN | (49) | (45) | (42) |
| SQUAMOUS CELL CARCINOMA, INVASIV | | 1 (2%) | |
| OLIGODENDROGLIOMA | 1 (2%) | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *PERITONEUM | (49) | (45) | (44) |
| MESOTHELIOMA, NOS | 1 (2%) | | |
| ALL OTHER SYSTEMS | | | |
| SITE UNKNOWN | | | |
| SQUAMOUS CELL CARCINOMA | | 1 | |
| OMENTUM | | | |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 | |

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

TABLE A2 (CONCLUDED)

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 45 | 48 |
| NATURAL DEATH@ | 3 | 1 | 13 |
| MORIBUND SACRIFICE | 7 | 5 | 2 |
| SCHEDULED SACRIFICE | 5 | | 5 |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 35 | 39 | 28 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 45 | 31 | 28 |
| TOTAL PRIMARY TUMORS | 73 | 55 | 43 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 37 | 23 | 23 |
| TOTAL BENIGN TUMORS | 54 | 34 | 30 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 13 | 11 | 11 |
| TOTAL MALIGNANT TUMORS | 16 | 13 | 12 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | 2 | |
| TOTAL SECONDARY TUMORS | | 5 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT | 3 | 8 | 1 |
| TOTAL UNCERTAIN TUMORS | 3 | 8 | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| * PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS | | | |
| # SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN | | | |

# APPENDIX B

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE
TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 46 | 35 | 46 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 45 | 34 | 45 |
| INTEGUMENTARY SYSTEM | | | |
| NONE | | | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (45) | (21) | (43) |
| HEPATOCELLULAR CARCINOMA, METAST | 1 (2%) | | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 7 (16%) | | 4 (9%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 4 (9%) | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (46) | (35) | (46) |
| MALIGNANT LYMPHOMA, NOS | | | 1 (2%) |
| #SPLEEN | (45) | (22) | (43) |
| HEMANGIOSARCOMA | | | 2 (5%) |
| MALIGNANT LYMPHOMA, NOS | | | 1 (2%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | | |
| #MANDIBULAR L. NODE | (35) | (13) | (36) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (3%) | | |
| CIRCULATORY SYSTEM | | | |
| #HEART | (44) | (21) | (42) |
| HEMANGIOSARCOMA | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #SALIVARY GLAND | (43) | (21) | (40) |
| HEMANGIOSARCOMA | | | 1 (3%) |

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

TABLE B1 (CONTINUED)

| | CONTROL(UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| #LIVER | (45) | (36) | (45) |
| HEPATOCELLULAR CARCINOMA | 10 (22%) | 1 (3%) | 8 (18%) |
| #STOMACH | (42) | (22) | (43) |
| SQUAMOUS CELL PAPILLOMA | 1 (2%) | | |
| URINARY SYSTEM | | | |
| #KIDNEY | (45) | (37) | (45) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| TUBULAR-CELL ADENOCARCINOMA | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| NONE | | | |
| REPRODUCTIVE SYSTEM | | | |
| NONE | | | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EAR CANAL | (46) | (35) | (46) |
| SQUAMOUS CELL CARCINOMA | 1 (2%) | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

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

TABLE B1 (CONCLUDED)

| | CONTROL (UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 7 | 36 | 7 |
| MORIBUND SACRIFICE | 1 | 11 | 1 |
| SCHEDULED SACRIFICE | 5 | | 5 |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 37 | 3 | 37 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 21 | 1 | 18 |
| TOTAL PRIMARY TUMORS | 25 | 1 | 21 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 8 | | 4 |
| TOTAL BENIGN TUMORS | 8 | | 4 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 15 | 1 | 16 |
| TOTAL MALIGNANT TUMORS | 17 | 1 | 17 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | | |
| TOTAL SECONDARY TUMORS | 1 | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE
TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 49@ |
| ANIMALS NECROPSIED | 46 | 38 | 45 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 45 | 34 | 44 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (46) | (38) | (45) |
| FIBROSARCOMA | 2 (4%) | | |
| *SUBCUT TISSUE | (46) | (38) | (45) |
| LEIOMYOSARCOMA | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (45) | (27) | (43) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (2%) | | |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 1 (4%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (46) | (38) | (45) |
| MALIGNANT LYMPHOMA, NOS | 3 (7%) | | 1 (2%) |
| MALIG.LYMPHOMA, UNDIFFER-TYPE | 1 (2%) | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 6 (13%) | 1 (3%) | 4 (9%) |
| LYMPHOCYTIC LEUKEMIA | 1 (2%) | | |
| #PEYERS PATCH | (43) | (23) | (44) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | | |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (45) | (34) | (44) |
| NEOPLASTIC NODULE | | | 3 (7%) |

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

TABLE B2 (CONTINUED)

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| HEPATOCELLULAR CARCINOMA | 4 (9%) | 2 (6%) | 9 (20%) |
| #STOMACH | (42) | (24) | (43) |
| SQUAMOUS CELL PAPILLOMA | 3 (7%) | | |
| URINARY SYSTEM | | | |
| NONE | | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (37) | (19) | (35) |
| ADENOMA, NOS | 6 (16%) | | 3 (9%) |
| #ADRENAL | (43) | (27) | (42) |
| CORTICAL ADENOMA | 1 (2%) | | |
| #PANCREATIC ISLETS | (41) | (27) | (42) |
| ISLET-CELL ADENOMA | 1 (2%) | | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (46) | (38) | (45) |
| ADENOCARCINOMA, NOS | 1 (2%) | | |
| #UTERUS | (43) | (22) | (41) |
| ENDOMETRIAL STROMAL POLYP | | | 1 (2%) |
| #OVARY | (41) | (22) | (41) |
| LUTEOMA | 1 (2%) | | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |

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

TABLE B2 (CONCLUDED)

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 49 |
| NATURAL DEATH@ | 8 | 32 | 6 |
| MORIBUND SACRIFICE | 2 | 8 | 1 |
| SCHEDULED SACRIFICE | 5 | | 5 |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 35 | 10 | 37 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 22 | 4 | 16 |
| TOTAL PRIMARY TUMORS | 32 | 4 | 22 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 12 | | 4 |
| TOTAL BENIGN TUMORS | 13 | | 4 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 18 | 4 | 12 |
| TOTAL MALIGNANT TUMORS | 19 | 4 | 15 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | |
| TOTAL SECONDARY TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | 3 |
| TOTAL UNCERTAIN TUMORS | | | 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

# APPENDIX C

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MALE RATS TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS MISSING | 1 | | |
| ANIMALS NECROPSIED | 48 | 49 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 48 | 48 | 48 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (48) | (49) | (49) |
| NUCLEAR-SHAPE ALTERATION | | | 1 (2%) |
| HYPERKERATOSIS | | 1 (2%) | |
| *SUBCUT TISSUE | (48) | (49) | (49) |
| FIBROSIS | | 1 (2%) | |
| NECROSIS, NOS | | 1 (2%) | |
| NECROSIS, FAT | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #TRACHEA | (45) | (47) | (47) |
| INFLAMMATION, NOS | | 8 (17%) | 4 (9%) |
| INFLAMMATION, ACUTE/CHRONIC | 18 (40%) | | |
| #LUNG/BRONCHUS | (48) | (49) | (48) |
| BRONCHIECTASIS | 3 (6%) | 1 (2%) | 4 (8%) |
| INFLAMMATION, NOS | | 3 (6%) | 3 (6%) |
| INFLAMMATION, FOCAL | | 4 (8%) | 5 (10%) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| #LUNG/BRONCHIOLE | (48) | (49) | (48) |
| INFLAMMATION, NOS | | | 1 (2%) |
| #LUNG | (48) | (49) | (48) |
| MINERALIZATION | | | 1 (2%) |
| CONGESTION, NOS | 1 (2%) | | |
| LOBAR PNEUMONIA, NOS | | | 1 (2%) |
| INFLAMMATION, FOCAL | 2 (4%) | 1 (2%) | |
| INFLAMMATION, INTERSTITIAL | | 22 (45%) | 22 (46%) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| ABSCESS, NOS | 1 (2%) | | |
| PNEUMONIA, CHRONIC MURINE | | 1 (2%) | |

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

TABLE C1 (CONTINUED)

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| GRANULOMA, NOS | 1 (2%) | | |
| HEMOSIDEROSIS | | | 1 (2%) |
| HYPERPLASIA, NOS | | 2 (4%) | |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | 5 (10%) |
| HYPERPLASIA, FOCAL | 1 (2%) | | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 1 (2%) | | |
| **HEMATOPOIETIC SYSTEM** | | | |
| #BONE MARROW | (48) | (50) | (47) |
| MYELOFIBROSIS | 1 (2%) | | |
| MEGAKARYOCYTOSIS | | 1 (2%) | |
| HYPERPLASIA, HEMATOPOIETIC | 1 (2%) | | |
| HYPERPLASIA, GRANULOCYTIC | 1 (2%) | | |
| HYPERPLASIA, MEGAKARYOCYTIC | 1 (2%) | | |
| #SPLEEN | (48) | (49) | (48) |
| CONGESTION, NOS | | 2 (4%) | |
| FIBROSIS, FOCAL | | 1 (2%) | |
| HEMOSIDEROSIS | | 12 (24%) | 7 (15%) |
| HYPERPLASIA, HEMATOPOIETIC | | 15 (31%) | 4 (8%) |
| HYPERPLASIA, ERYTHROID | | 29 (59%) | 23 (48%) |
| HYPERPLASIA, RETICULUM CELL | | | 1 (2%) |
| ERYTHROPOIESIS | 1 (2%) | | |
| #LYMPH NODE | (42) | (47) | (46) |
| INFLAMMATION, NOS | | 1 (2%) | |
| HYPERPLASIA, NOS | | | 8 (17%) |
| RETICULOCYTOSIS | | | 1 (2%) |
| LYMPHOCYTOSIS | | 1 (2%) | 1 (2%) |
| PLASMACYTOSIS | | | 2 (4%) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | 2 (4%) |
| #MANDIBULAR L. NODE | (42) | (47) | (46) |
| DILATATION, NOS | 1 (2%) | | |
| HYPERPLASIA, NOS | 1 (2%) | | |
| **CIRCULATORY SYSTEM** | | | |
| #HEART | (48) | (50) | (48) |
| FIBROSIS, FOCAL | 11 (23%) | | |
| FIBROSIS, DIFFUSE | 1 (2%) | | |
| #MYOCARDIUM | (48) | (50) | (48) |
| INFLAMMATION, INTERSTITIAL | 2 (4%) | 41 (82%) | 31 (65%) |

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

TABLE C1 (CONTINUED)

| | CONTROL (UNIR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| INFLAMMATION, ACUTE/CHRONIC | 3 (6%) | | |
| FIBROSIS | | 15 (30%) | 3 (6%) |
| FIBROSIS, FOCAL | 2 (4%) | | |
| DEGENERATION, NOS | 1 (2%) | | 1 (2%) |
| #ENDOCARDIUM | (48) | (50) | (48) |
| INFLAMMATION, FOCAL | | | 1 (2%) |
| #CARDIAC VALVE | (48) | (50) | (48) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| *CORONARY ARTERY | (48) | (49) | (49) |
| MINERALIZATION | | 1 (2%) | 4 (8%) |
| PERIVASCULITIS | 1 (2%) | | |
| *PULMONARY ARTERY | (48) | (49) | (49) |
| MINERALIZATION | 11 (23%) | 4 (8%) | 9 (18%) |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (48) | (50) | (48) |
| INFLAMMATION, NECROTIZING | 1 (2%) | | |
| ABSCESS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | 8 (17%) | | |
| NECROSIS, COAGULATIVE | | | 2 (4%) |
| NECROSIS, HEMORRHAGIC | | | 1 (2%) |
| METAMORPHOSIS FATTY | 4 (8%) | 14 (28%) | 8 (17%) |
| CHOLESTEROL DEPOSIT | | | 3 (6%) |
| CYTOPLASMIC VACUOLIZATION | | | 3 (6%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | 8 (17%) | 13 (26%) | 13 (27%) |
| ANGIECTASIS | 2 (4%) | 2 (4%) | 1 (2%) |
| ERYTHROPOIESIS | 1 (2%) | | |
| #LIVER/CENTRILOBULAR | (48) | (50) | (48) |
| DEGENERATION, EOSINOPHILIC | 2 (4%) | | |
| *BILE DUCT | (48) | (49) | (49) |
| CALCULUS, NOS | | 1 (2%) | |
| INFLAMMATION, NOS | | 7 (14%) | 4 (8%) |
| HYPERPLASIA, NOS | 6 (13%) | 43 (88%) | 47 (96%) |
| *PANCREAS | (45) | (48) | (47) |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, NOS | | 17 (35%) | 18 (38%) |

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

TABLE C1 (CONTINUED)

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| INFLAMMATION, ACUTE/CHRONIC | 6 (13%) | | |
| PERIARTERITIS | 1 (2%) | | |
| ATROPHY, FOCAL | 1 (2%) | | |
| #PANCREATIC DUCT | (45) | (48) | (47) |
| HYPERPLASIA, NOS | | | 3 (6%) |
| #PANCREATIC ACINUS | (45) | (48) | (47) |
| INFLAMMATION, NOS | | | 1 (2%) |
| ATROPHY, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 3 (6%) |
| #STOMACH | (48) | (47) | (47) |
| EPIDERMAL INCLUSION CYST | 1 (2%) | | |
| INFLAMMATION, NOS | | 1 (2%) | 2 (4%) |
| ULCER, NOS | | 5 (11%) | 1 (2%) |
| INFLAMMATION, ACUTE/CHRONIC | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERKERATOSIS | | 6 (13%) | 7 (15%) |
| ACANTHOSIS | | 11 (23%) | 8 (17%) |
| #GASTRIC MUCOSA | (48) | (47) | (47) |
| DEGENERATION, NOS | | | 1 (2%) |
| #PEYERS PATCH | (45) | (48) | (47) |
| HYPERPLASIA, NOS | | 1 (2%) | 9 (19%) |
| HYPERPLASIA, RETICULUM CELL | 1 (2%) | | |
| #ILEUM | (45) | (48) | (47) |
| HYPERPLASIA, LYMPHOID | 1 (2%) | | |
| #COLON | (44) | (46) | (41) |
| NEMATODIASIS | 4 (9%) | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (48) | (50) | (48) |
| GLOMERULONEPHRITIS, NOS | 3 (6%) | 46 (92%) | 45 (94%) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| FIBROSIS | | | 1 (2%) |
| FIBROSIS, FOCAL | | | 1 (2%) |
| NEPHROSIS, NOS | 41 (85%) | | |
| GLOMERULOSCLEROSIS, NOS | | | 1 (2%) |
| HYPERPLASIA, TUBULAR CELL | | 11 (22%) | 13 (27%) |
| HYPERPLASIA, EPITHELIAL | | 2 (4%) | |

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

TABLE C1 (CONTINUED)

| | CONTROL(UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| #KIDNEY/TUBULE | (48) | (50) | (48) |
| MINERALIZATION | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | 1 (2%) | 1 (2%) |
| #KIDNEY/PELVIS | (48) | (50) | (48) |
| MINERALIZATION | 1 (2%) | 3 (6%) | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | | | 2 (4%) |
| #URINARY BLADDER | (46) | (48) | (45) |
| HYPERPLASIA, EPITHELIAL | | | 1 (2%) |
| METAPLASIA, SQUAMOUS | 1 (2%) | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (41) | (46) | (39) |
| HYPERPLASIA, NOS | | 1 (2%) | 1 (3%) |
| HYPERPLASIA, FOCAL | 3 (7%) | 1 (2%) | 3 (8%) |
| #ADRENAL | (47) | (49) | (48) |
| METAMORPHOSIS FATTY | 1 (2%) | | |
| ANGIECTASIS | 3 (6%) | | |
| #ADRENAL CORTEX | (47) | (49) | (48) |
| NODULE | | 1 (2%) | |
| HYPERPLASIA, FOCAL | 1 (2%) | | 1 (2%) |
| #ADRENAL MEDULLA | (47) | (49) | (48) |
| NECROSIS, COAGULATIVE | | 1 (2%) | |
| HYPERPLASIA, NODULAR | | 4 (8%) | 9 (19%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #THYROID | (39) | (47) | (46) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| HYPERPLASIA, C-CELL | 1 (3%) | | 3 (7%) |
| #PANCREATIC ISLETS | (45) | (48) | (47) |
| HYPERPLASIA, NOS | | 1 (2%) | 2 (4%) |
| HYPERPLASIA, FOCAL | 1 (2%) | | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (48) | (49) | (49) |
| GALACTOCELE | 1 (2%) | 2 (4%) | 1 (2%) |

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

TABLE C1 (CONTINUED)

| | CONTROL (UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| HYPERPLASIA, NOS | 3 (6%) | 20 (41%) | 13 (27%) |
| #PROSTATE | (43) | (48) | (46) |
| INFLAMMATION, NOS | | 22 (46%) | 25 (54%) |
| INFLAMMATION, FOCAL | 1 (2%) | | |
| INFLAMMATION, ACUTE | 6 (14%) | | |
| INFLAMMATION, ACUTE FOCAL | 8 (19%) | | |
| INFLAMMATION, ACUTE/CHRONIC | 2 (5%) | | |
| HYPERPLASIA, NOS | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| METAPLASIA, SQUAMOUS | | 3 (6%) | |
| *SEMINAL VESICLE | (48) | (49) | (49) |
| ATROPHY, NOS | 2 (4%) | | 1 (2%) |
| #TESTIS | (47) | (50) | (48) |
| MINERALIZATION | | 2 (4%) | 2 (4%) |
| DEGENERATION, NOS | 39 (83%) | | |
| ATROPHY, NOS | | 5 (10%) | 8 (17%) |
| HYPERPLASIA, NOS | | | 3 (6%) |
| HYPERPLASIA, INTERSTITIAL CELL | 1 (2%) | 1 (2%) | 5 (10%) |
| #TESTIS/TUBULE | (47) | (50) | (48) |
| MINERALIZATION | | | 5 (10%) |
| DEGENERATION, NOS | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| #BRAIN | (47) | (50) | (47) |
| INFLAMMATION, FOCAL GRANULOMATOU | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (48) | (49) | (49) |
| CATARACT | | 2 (4%) | 3 (6%) |
| *EYE/CORNEA | (48) | (49) | (49) |
| INFLAMMATION, NOS | | 1 (2%) | |
| *EYE/RETINA | (48) | (49) | (49) |
| ATROPHY, NOS | | 1 (2%) | 2 (4%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *BONE | (48) | (49) | (49) |
| INFLAMMATION, NOS | | 1 (2%) | |

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

TABLE C1 (CONCLUDED)

| | CONTROL(UNTR) 01-0070 | LOW DOSE 01-0066 | HIGH DOSE 01-0067 |
|---|---|---|---|
| FIBROSIS | | | 1 (2%) |
| RESORPTION | | 1 (2%) | 1 (2%) |
| **BODY CAVITIES** | | | |
| NONE | | | |
| **ALL OTHER SYSTEMS** | | | |
| ADIPOSE TISSUE | | | |
| INFLAMMATION, ACUTE/CHRONIC | 2 | | |
| OMENTUM | | | |
| NECROSIS, NOS | | 1 | 1 |
| **SPECIAL MORPHOLOGY SUMMARY** | | | |
| ANIMAL MISSING/NO NECROPSY | 1 | | |
| AUTO/NECROPSY/HISTO PERF | 1 | | |
| AUTO/NECROPSY/NO HISTO | | 1 | 1 |
| AUTOLYSIS/NO NECROPSY | 1 | 1 | 1 |

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN FEMALE RATS TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 45@ | 48@ |
| ANIMALS NECROPSIED | 49 | 45 | 44 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 49 | 45 | 42 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (49) | (45) | (44) |
| EPIDERMAL INCLUSION CYST | 1 (2%) | | |
| *SUBCUT TISSUE | (49) | (45) | (44) |
| ABSCESS, NOS | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #TRACHEA | (49) | (43) | (42) |
| INFLAMMATION, NOS | | 3 (7%) | |
| INFLAMMATION, ACUTE/CHRONIC | 15 (31%) | | |
| #LUNG/BRONCHUS | (49) | (44) | (43) |
| BRONCHIECTASIS | | 1 (2%) | |
| INFLAMMATION, FOCAL | | 2 (5%) | 3 (7%) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| #LUNG | (49) | (44) | (43) |
| INFLAMMATION, FOCAL | 2 (4%) | | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 2 (4%) | 25 (57%) | 16 (37%) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | | 3 (7%) | 2 (5%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 1 (2%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (46) | (45) | (43) |
| OSTEOSCLEROSIS | 1 (2%) | | |
| #SPLEEN | (48) | (45) | (43) |
| HEMOSIDEROSIS | | 22 (49%) | 17 (40%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT 5 IN THE LOW-DOSE GROUP AND 2 IN THE HIGH-DOSE GROUP WERE FOUND TO BE MALE ANIMALS IN FEMALE GROUPS.

TABLE C2 (CONTINUED)

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| HYPERPLASIA, HEMATOPOIETIC | 1 (2%) | 29 (64%) | 22 (51%) |
| HYPERPLASIA, ERYTHROID | | 39 (87%) | 27 (63%) |
| HYPERPLASIA, RETICULUM CELL | 1 (2%) | | |
| #LYMPH NODE | (42) | (44) | (40) |
| INFLAMMATION, NOS | | 1 (2%) | 2 (5%) |
| HYPERPLASIA, NOS | | | 5 (13%) |
| RETICULOCYTOSIS | | 2 (5%) | 1 (3%) |
| LYMPHOCYTOSIS | | 1 (2%) | 1 (3%) |
| PLASMACYTOSIS | | | 4 (10%) |
| HYPERPLASIA, RETICULUM CELL | | 2 (5%) | |
| HYPERPLASIA, LYMPHOID | | 2 (5%) | 1 (3%) |
| #MEDIASTINAL L.NODE | (42) | (44) | (40) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| PLASMACYTOSIS | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | |
| #HEART | (49) | (45) | (43) |
| FIBROSIS, FOCAL | 1 (2%) | | |
| FIBROSIS, DIFFUSE | 1 (2%) | | |
| PERIARTERITIS | | 1 (2%) | |
| #MYOCARDIUM | (49) | (45) | (43) |
| INFLAMMATION, NOS | | 1 (2%) | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 2 (4%) | 31 (69%) | 25 (58%) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| FIBROSIS | | 3 (7%) | 8 (19%) |
| FIBROSIS, FOCAL | 2 (4%) | | |
| FIBROSIS, DIFFUSE | | 1 (2%) | |
| #CARDIAC VALVE | (49) | (45) | (43) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| *PULMONARY ARTERY | (49) | (45) | (44) |
| MINERALIZATION | 9 (18%) | 2 (4%) | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (49) | (45) | (44) |
| DEGENERATION, EOSINOPHILIC | 2 (4%) | | |
| NECROSIS, FOCAL | 3 (6%) | 7 (16%) | 4 (9%) |
| NECROSIS, COAGULATIVE | | 1 (2%) | |

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

TABLE C2 (CONTINUED)

| | CONTROL(UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| METAMORPHOSIS FATTY | 4 (8%) | 4 (9%) | 3 (7%) |
| CYTOPLASMIC VACUOLIZATION | | 1 (2%) | 2 (5%) |
| HYPERPLASIA, FOCAL | 29 (59%) | 25 (56%) | 26 (59%) |
| HYPERPLASIA, DIFFUSE | | 1 (2%) | |
| ANGIECTASIS | 1 (2%) | 1 (2%) | |
| *BILE DUCT | (49) | (45) | (44) |
| INFLAMMATION, NOS | | 4 (9%) | 4 (9%) |
| HYPERPLASIA, NOS | 5 (10%) | 33 (73%) | 38 (86%) |
| HYPERPLASIA, FOCAL | 1 (2%) | | |
| #PANCREAS | (47) | (45) | (41) |
| INFLAMMATION, NOS | | 17 (38%) | 19 (46%) |
| INFLAMMATION, ACUTE/CHRONIC | 4 (9%) | | |
| ATROPHY, NOS | 1 (2%) | | |
| #PANCREATIC ACINUS | (47) | (45) | (41) |
| HYPERPLASIA, NOS | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #STOMACH | (49) | (45) | (42) |
| INFLAMMATION, NOS | | | 1 (2%) |
| ULCER, NOS | | 1 (2%) | |
| INFLAMMATION, FOCAL | | | 1 (2%) |
| ULCER, FOCAL | 1 (2%) | | |
| HYPERPLASIA, NOS | | | 2 (5%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| HYPERKERATOSIS | | 4 (9%) | 7 (17%) |
| ACANTHOSIS | | 5 (11%) | 10 (24%) |
| #PEYERS PATCH | (49) | (45) | (41) |
| HYPERPLASIA, NOS | | 8 (18%) | 10 (24%) |
| #COLON | (44) | (41) | (37) |
| NEMATODIASIS | 2 (5%) | 1 (2%) | 5 (14%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (49) | (45) | (43) |
| MINERALIZATION | 1 (2%) | | 1 (2%) |
| POLYCYSTIC KIDNEY | | | 1 (2%) |
| GLOMERULONEPHRITIS, NOS | | 43 (96%) | 41 (95%) |
| NEPHROSIS, NOS | 34 (69%) | | |
| HYPERPLASIA, TUBULAR CELL | | 3 (7%) | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | 4 (9%) |

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

TABLE C2 (CONTINUED)

| | CONTROL(UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| #KIDNEY/TUBULE | (49) | (45) | (43) |
| MINERALIZATION | | | 1 (2%) |
| #KIDNEY/PELVIS | (49) | (45) | (43) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #URINARY BLADDER | (49) | (44) | (41) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (44) | (40) | (39) |
| HYPERPLASIA, NOS | 1 (2%) | | |
| HYPERPLASIA, FOCAL | 2 (5%) | | 1 (3%) |
| #ADRENAL | (49) | (45) | (41) |
| METAMORPHOSIS FATTY | 3 (6%) | | |
| #ADRENAL CORTEX | (49) | (45) | (41) |
| NODULE | | 1 (2%) | 1 (2%) |
| METAMORPHOSIS FATTY | 3 (6%) | | |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | 1 (2%) | 1 (2%) | 2 (5%) |
| #ADRENAL MEDULLA | (49) | (45) | (41) |
| HYPERPLASIA, NODULAR | | 1 (2%) | 2 (5%) |
| HYPERPLASIA, NOS | 1 (2%) | | |
| HYPERPLASIA, FOCAL | 1 (2%) | | |
| #THYROID | (40) | (43) | (38) |
| HYPERPLASIA, C-CELL | | 4 (9%) | 1 (3%) |
| #THYROID FOLLICLE | (40) | (43) | (38) |
| NECROSIS, FOCAL | | 1 (2%) | |
| #PANCREATIC ISLETS | (47) | (45) | (41) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (49) | (45) | (44) |
| GALACTOCELE | 9 (18%) | 8 (18%) | 7 (16%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |

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

TABLE C2 (CONTINUED)

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| HYPERPLASIA, NOS | 23 (47%) | 22 (49%) | 18 (41%) |
| HYPERPLASIA, FOCAL | 2 (4%) | | |
| *VAGINA | (49) | (45) | (44) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| #UTERUS | (49) | (44) | (42) |
| HYDROMETRA | 6 (12%) | | |
| ABSCESS, NOS | | 1 (2%) | |
| HYPERPLASIA, ADENOMATOUS | | 6 (14%) | 1 (2%) |
| #CERVIX UTERI | (49) | (44) | (42) |
| INFLAMMATION, ACUTE/CHRONIC | 2 (4%) | | |
| HYPERPLASIA, BASAL CELL | 1 (2%) | | |
| ACANTHOSIS | 1 (2%) | | |
| #UTERUS/ENDOMETRIUM | (49) | (44) | (42) |
| INFLAMMATION, NOS | | 20 (45%) | 8 (19%) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| INFLAMMATION, ACUTE | 23 (47%) | | |
| HYPERPLASIA, NOS | 5 (10%) | 6 (14%) | 2 (5%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| HYPERPLASIA, CYSTIC | 5 (10%) | | 1 (2%) |
| HYPERPLASIA, STROMAL | | 1 (2%) | |
| #OVARY/OVIDUCT | (49) | (44) | (42) |
| INFLAMMATION, NOS | | 2 (5%) | 2 (5%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| #OVARY | (47) | (44) | (42) |
| CYST, NOS | 2 (4%) | 6 (14%) | 5 (12%) |
| INFLAMMATION, NOS | | 2 (5%) | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (49) | (45) | (44) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| SYNECHIA, NOS | 1 (2%) | | |
| CATARACT | 1 (2%) | 1 (2%) | |
| *EYE/CORNEA | (49) | (45) | (44) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |

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

TABLE C2 (CONCLUDED)

| | CONTROL (UNTR) 02-0070 | LOW DOSE 02-0066 | HIGH DOSE 02-0067 |
|---|---|---|---|
| *EYE/RETINA | (49) | (45) | (44) |
| DEGENERATION, NOS | 1 (2%) | | |
| CATARACT | | 1 (2%) | |
| ATROPHY, NOS | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| *STERNUM | (49) | (45) | (44) |
| OSTEOPETROSIS | 1 (2%) | | |
| BODY CAVITIES | | | |
| *MEDIASTINUM | (49) | (45) | (44) |
| PERIARTERITIS | 1 (2%) | | |
| ALL OTHER SYSTEMS | | | |
| ADIPOSE TISSUE | | | |
| INFLAMMATION, ACUTE/CHRONIC | 3 | | |
| INFLAMMATION, CHRONIC | 2 | | |
| OMENTUM | | | |
| MINERALIZATION | 1 | | |
| NECROSIS, NOS | | 1 | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| AUTO/NECROPSY/NO HISTO | | | 2 |
| AUTOLYSIS/NO NECROPSY | 1 | | 4 |

# 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-AMINO-2-METHYLANTHRAQUINONE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MALE MICE TREATED WITH 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 46 | 35 | 46 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 45 | 34 | 45 |
| INTEGUMENTARY SYSTEM | | | |
| NONE | | | |
| RESPIRATORY SYSTEM | | | |
| #TRACHEA | (44) | (18) | (42) |
| INFLAMMATION, NOS | | 1 (6%) | |
| #LUNG | (45) | (21) | (43) |
| INFLAMMATION, FOCAL | | 1 (5%) | |
| INFLAMMATION, INTERSTITIAL | | 5 (24%) | 1 (2%) |
| PERIVASCULITIS | | 1 (5%) | 3 (7%) |
| ARTERIOSCLEROSIS, NOS | 1 (2%) | | |
| HYPERPLASIA, ADENOMATOUS | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (45) | (19) | (43) |
| MYELOFIBROSIS | | | 1 (2%) |
| #SPLEEN | (45) | (22) | (43) |
| FIBROSIS | 1 (2%) | | |
| HEMOSIDEROSIS | | 1 (5%) | |
| HYPERPLASIA, NOS | | 2 (9%) | 4 (9%) |
| HYPERPLASIA, HEMATOPOIETIC | | | 3 (7%) |
| HYPERPLASIA, ERYTHROID | | | 1 (2%) |
| HYPERPLASIA, RETICULUM CELL | 3 (7%) | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | | 8 (19%) |
| HEMATOPOIESIS | 1 (2%) | | |
| #LYMPH NODE | (35) | (13) | (36) |
| HEMORRHAGE | | | 1 (3%) |
| INFLAMMATION, NOS | | 1 (8%) | 7 (19%) |

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

TABLE D1 (CONTINUED)

| | CONTROL(UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| HYPERPLASIA, NOS | | 1 (8%) | 2 (6%) |
| RETICULOCYTOSIS | | | 1 (3%) |
| HYPERPLASIA, HEMATOPOIETIC | | | 1 (3%) |
| HYPERPLASIA, LYMPHOID | | | 1 (3%) |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (45) | (36) | (45) |
| DEGENERATION, NOS | 1 (2%) | | |
| NECROSIS, FOCAL | | 1 (3%) | 1 (2%) |
| METAMORPHOSIS FATTY | 3 (7%) | | |
| HYPERPLASTIC NODULE | | 1 (3%) | 2 (4%) |
| HYPERPLASIA, FOCAL | | | 2 (4%) |
| #LIVER/PERIPORTAL | (45) | (36) | (45) |
| INFLAMMATION, NOS | 1 (2%) | | |
| #LIVER/KUPFFER CELL | (45) | (36) | (45) |
| HYPERPLASIA, NOS | 2 (4%) | | |
| #LIVER/HEPATOCYTES | (45) | (36) | (45) |
| HYPERTROPHY, NOS | | | 1 (2%) |
| #BILE DUCT | (46) | (35) | (46) |
| INFLAMMATION, NOS | 1 (2%) | | |
| #PANCREAS | (44) | (23) | (42) |
| INFLAMMATION, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | | 1 (2%) |
| METAMORPHOSIS FATTY | | 1 (4%) | |
| #PANCREATIC ACINUS | (44) | (23) | (42) |
| HYPERTROPHY, FOCAL | | | 1 (2%) |
| #STOMACH | (42) | (22) | (43) |
| HYPERPLASIA, FOCAL | 1 (2%) | | 1 (2%) |
| HYPERKERATOSIS | | 1 (5%) | 1 (2%) |
| ACANTHOSIS | | 1 (5%) | 1 (2%) |
| #PEYERS PATCH | (43) | (20) | (44) |
| HYPERPLASIA, NOS | | | 3 (7%) |

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

TABLE D1 (CONTINUED)

| | CONTROL (UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| #COLON | (38) | (17) | (43) |
| PARASITISM | | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (45) | (37) | (45) |
| CALCULUS, NOS | 20 (44%) | | |
| MINERALIZATION | | | 1 (2%) |
| GLOMERULONEPHRITIS, NOS | | 24 (65%) | 42 (93%) |
| PYELONEPHRITIS, NOS | | 5 (14%) | |
| INFLAMMATION, NOS | | 1 (3%) | |
| INFLAMMATION, FOCAL | | | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | 5 (11%) | 2 (5%) | |
| INFLAMMATION, CHRONIC | 1 (2%) | 2 (5%) | |
| GLOMERULONEPHRITIS, CHRONIC | | 1 (3%) | |
| INFLAMMATION WITH FIBROSIS | | | 2 (4%) |
| FIBROSIS, DIFFUSE | | 9 (24%) | 32 (71%) |
| PERIVASCULITIS | 2 (4%) | | |
| DEGENERATION, CYSTIC | | | 16 (36%) |
| ARTERIOSCLEROSIS, NOS | 1 (2%) | | |
| NEPHROSIS, NOS | 1 (2%) | | |
| GLOMERULOSCLEROSIS, NOS | | 7 (19%) | |
| HYPERPLASIA, TUBULAR CELL | 2 (4%) | | |
| #KIDNEY/TUBULE | (45) | (37) | (45) |
| MINERALIZATION | | | 1 (2%) |
| INFLAMMATION, NOS | | 2 (5%) | |
| DEGENERATION, NOS | 1 (2%) | | |
| DEGENERATION, CYSTIC | | | 4 (9%) |
| METAMORPHOSIS FATTY | 9 (20%) | | |
| #URINARY BLADDER | (44) | (20) | (43) |
| HYPERPLASIA, EPITHELIAL | | 3 (15%) | 1 (2%) |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #ADRENAL CORTEX | (43) | (24) | (38) |
| HYPERPLASIA, NOS | | | 4 (11%) |
| #THYROID | (40) | (18) | (37) |
| PERIVASCULITIS | | 1 (6%) | |
| #PANCREATIC ISLETS | (44) | (23) | (42) |
| HYPERPLASIA, NOS | | | 1 (2%) |

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

TABLE D1 (CONCLUDED)

| | CONTROL (UNTR) 05-0077 | DOSE A 05-0066 | DOSE B 05-0067 |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| #TESTIS | (45) | (22) | (44) |
| HYPERPLASIA, INTERSTITIAL CELL | | | 1 (2%) |
| #TESTIS/TUBULE | (45) | (22) | (44) |
| MINERALIZATION | | 1 (5%) | |
| DEGENERATION, NOS | 2 (4%) | | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (46) | (35) | (46) |
| STEATITIS | 1 (2%) | | |
| *PERICARDIUM | (46) | (35) | (46) |
| INFLAMMATION, FOCAL | | | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (46) | (35) | (46) |
| PERIVASCULITIS | | | 1 (2%) |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | 8 | | |
| AUTO/NECROPSY/NO HISTO | 1 | 1 | 1 |
| AUTOLYSIS/NO NECROPSY | 4 | 15 | 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 1-AMINO-2-METHYLANTHRAQUINONE

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 49@ |
| ANIMALS NECROPSIED | 46 | 38 | 45 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 45 | 34 | 44 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (46) | (38) | (45) |
| FIBROSIS | 1 (2%) | | |
| FIBROSIS, FOCAL | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (45) | (27) | (43) |
| MINERALIZATION | | 1 (4%) | |
| INFLAMMATION, FOCAL | | 1 (4%) | |
| INFLAMMATION, INTERSTITIAL | 2 (4%) | | 1 (2%) |
| PERIARTERITIS | 1 (2%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (44) | (25) | (43) |
| MYELOFIBROSIS | | 4 (16%) | 6 (14%) |
| #SPLEEN | (43) | (26) | (44) |
| HYPERPLASIA, NOS | | | 4 (9%) |
| HYPERPLASIA, HEMATOPOIETIC | | | 4 (9%) |
| HYPERPLASIA, ERYTHROID | | | 2 (5%) |
| HYPERPLASIA, RETICULUM CELL | 2 (5%) | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 4 (9%) | | 5 (11%) |
| HEMATOPOIESIS | 1 (2%) | | |
| #LYMPH NODE | (41) | (15) | (39) |
| INFLAMMATION, NOS | | 1 (7%) | 2 (5%) |
| HYPERPLASIA, LYMPHOID | | 1 (7%) | 1 (3%) |
| #MESENTERIC L. NODE | (41) | (15) | (39) |
| HYPERPLASIA, RETICULUM CELL | | | 1 (3%) |

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

TABLE D2 (CONTINUED)

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| CIRCULATORY SYSTEM | | | |
| #MYOCARDIUM | (45) | (27) | (43) |
| CALCIFICATION, FOCAL | 1 (2%) | | |
| *PULMONARY ARTERY | (46) | (38) | (45) |
| HYPERPLASIA, NOS | 1 (2%) | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (45) | (34) | (44) |
| NECROSIS, FOCAL | | | 2 (5%) |
| HYPERTROPHY, FOCAL | | | 1 (2%) |
| HYPERPLASIA, NODULAR | | | 1 (2%) |
| HYPERPLASTIC NODULE | | 3 (9%) | 1 (2%) |
| HYPERPLASIA, FOCAL | 1 (2%) | | 5 (11%) |
| HYPERPLASIA, DIFFUSE | 1 (2%) | | |
| HEMATOPOIESIS | | | 1 (2%) |
| #LIVER/PERIPORTAL | (45) | (34) | (44) |
| INFLAMMATION, NOS | 1 (2%) | | |
| #LIVER/KUPFFER CELL | (45) | (34) | (44) |
| HYPERPLASIA, NOS | 1 (2%) | | |
| *BILE DUCT | (46) | (38) | (45) |
| INFLAMMATION, NOS | 1 (2%) | | |
| #PANCREAS | (41) | (27) | (42) |
| INFLAMMATION, NOS | | | 1 (2%) |
| #STOMACH | (42) | (24) | (43) |
| ULCER, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| HYPERKERATOSIS | | | 2 (5%) |
| ACANTHOSIS | | | 2 (5%) |
| #PEYERS PATCH | (43) | (23) | (44) |
| HYPERPLASIA, NOS | | | 2 (5%) |
| #COLON | (41) | (22) | (37) |
| PARASITISM | | 1 (5%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (43) | (37) | (42) |
| MINERALIZATION | | 2 (5%) | |

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

TABLE D2 (CONTINUED)

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| GLOMERULONEPHRITIS, NOS | | 23 (62%) | 31 (74%) |
| PYELONEPHRITIS, NOS | | 1 (3%) | |
| INFLAMMATION, NOS | | 2 (5%) | 1 (2%) |
| INFLAMMATION, FOCAL | | | 2 (5%) |
| INFLAMMATION, INTERSTITIAL | 3 (7%) | 3 (8%) | |
| INFLAMMATION, CHRONIC | | 3 (8%) | |
| FIBROSIS, DIFFUSE | | 12 (32%) | 13 (31%) |
| PERIVASCULITIS | 4 (9%) | | |
| DEGENERATION, CYSTIC | | | 5 (12%) |
| GLOMERULOSCLEROSIS, NOS | | 3 (8%) | 1 (2%) |
| #KIDNEY/GLOMERULUS | (43) | (37) | (42) |
| DEGENERATION, CYSTIC | | | 4 (10%) |
| AMYLOIDOSIS | 1 (2%) | | |
| #KIDNEY/TUBULE | (43) | (37) | (42) |
| DEGENERATION, CYSTIC | | | 3 (7%) |
| #KIDNEY/PELVIS | (43) | (37) | (42) |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%) | | |
| #URINARY BLADDER | (41) | (23) | (42) |
| INFLAMMATION, NOS | | | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | | 1 (4%) | 4 (10%) |
| **ENDOCRINE SYSTEM** | | | |
| #ADRENAL CORTEX | (43) | (27) | (42) |
| HYPERPLASIA, NOS | | 1 (4%) | 5 (12%) |
| HYPERPLASIA, INTRADUCTAL | | | 1 (2%) |
| #THYROID | (30) | (18) | (35) |
| HYPERPLASIA, PAPILLARY | | | 1 (3%) |
| #PANCREATIC ISLETS | (41) | (27) | (42) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (46) | (38) | (45) |
| HYPERPLASIA, NOS | | | 2 (4%) |
| #UTERUS | (43) | (22) | (41) |
| HYDROMETRA | 4 (9%) | 4 (18%) | 6 (15%) |

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

TABLE D2 (CONTINUED)

| | CONTROL (UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| HYPERPLASIA, ADENOMATOUS | | | 1 (2%) |
| HYPERPLASIA, STROMAL | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (43) | (22) | (41) |
| CYST, NOS | 2 (5%) | | |
| INFLAMMATION, NOS | | 1 (5%) | 4 (10%) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| HYPERPLASIA, NOS | 1 (2%) | 1 (5%) | 4 (10%) |
| HYPERPLASIA, CYSTIC | 35 (81%) | 1 (5%) | 9 (22%) |
| #OVARY/OVIDUCT | (43) | (22) | (41) |
| INFLAMMATION, NOS | | | 2 (5%) |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| #OVARY | (41) | (22) | (41) |
| CYST, NOS | 1 (2%) | 1 (5%) | 7 (17%) |
| HEMORRHAGE | | 1 (5%) | |
| INFLAMMATION, NOS | | | 3 (7%) |
| #OVARY/FOLLICLE | (41) | (22) | (41) |
| HEMORRHAGE | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *BONE | (46) | (38) | (45) |
| FIBROSIS | | 1 (3%) | 1 (2%) |
| RESORPTION | | 1 (3%) | 1 (2%) |
| *VERTEBRA | (46) | (38) | (45) |
| OSTEOSCLEROSIS | 1 (2%) | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

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

TABLE D2 (CONCLUDED)

| | CONTROL(UNTR) 06-0077 | DOSE A 06-0066 | DOSE B 06-0067 |
|---|---|---|---|
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | 1 | | 1 |
| NECROPSY PERF/NO HISTO PERFORMED | | | 1 |
| AUTO/NECROPSY/HISTO PERF | 1 | | |
| AUTO/NECROPSY/NO HISTO | 1 | 4 | |
| AUTOLYSIS/NO NECROPSY | 4 | 12 | 4 |

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

DHEW Publication No. (NIH) 78-1366