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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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2-AMINOANTHRAQUINONE

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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REPORT ON THE BIOASSAY OF 2-AMINOANTHRAQUINONE
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 2-aminoanthraquinone 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 2-aminoanthraquinone 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 analyses were performed by Mason Research Institute (3) and 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), Dr. A. S. Krishna Murthy (3), and Dr. Yoon (3) at the Mason Research Institute, the pathology narratives were written by Dr. A. S. Krishna Murthy (3), 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) and Mr. R. M. Helfand (5), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (5) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (5), task leader Dr. M. R. Kornreich (5,10), senior biologist Ms. P. Walker (5), biochemist Dr. B. Fuller (5), and technical editor Ms. P. A. Miller (5). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,10), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,11), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of 2-aminoanthraquinone for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 2-Aminoanthraquinone was administered in the feed, at either of two concentrations (except for female rats), to groups of 50 male and 50 female animals of each species. The time-weighted average dietary concentrations used in the chronic bioassay were 0.69 and 0.35 percent for high and low dose male rats, respectively, 0.2 percent for the treated female rats, and 1.0 and 0.5 percent, respectively, for high and low dose mice of both sexes. After a 78-week period of chemical administration (80 weeks for high dose mice), observation of the rats continued for up to an additional 32 weeks and observation of the mice continued for up to an additional 16 weeks.

In both species adequate numbers of animals in all groups, except the treated female rats, survived sufficiently long to be at risk from late-developing tumors. The survival among treated female rats was poor and, as a result, no conclusions could be made regarding the carcinogenicity of the compound in these animals.

When male rats having either hepatocellular carcinomas or neoplastic nodules of the liver were combined and the resulting tumor incidences were analyzed statistically, there was a significant positive association between dosage and the incidences of these combined neoplasms. Hepatocellular carcinomas were observed at significantly higher incidences when dosed mice were compared to controls. There was a significantly higher incidence of malignant hematopoietic lymphomas in high dose female mice when compared to controls.

Under the conditions of this bioassay, dietary administration of 2-aminoanthraquinone was carcinogenic in male Fischer 344 rats, causing a combination of hepatocellular carcinomas and neoplastic nodules of the liver. The compound was also carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes and malignant hematopoietic lymphomas in females.

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I. INTRODUCTION

2-Aminoanthraquinone (Figure 1) (NCI No. C01876), an intermediate in the synthesis of anthraquinone dyes, was selected for bioassay by the National Cancer Institute in an attempt to determine which chemicals 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 structural relationship of 2-aminoanthraquinone to two documented carcinogens, 2-naphthylamine (Occupational Safety and Health Administration, 1973) and 2-anthramine (Griswald et al., 1968), was also a factor in its selection.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 2-amino-9,10-anthracenedione.* It is also commonly referred to as AAQ.

Although the unsubstituted aminoanthraquinones have no importance as dyes in and of themselves, introduction of the amino group into the anthraquinone nucleus provides the basis for innumerable anthraquinone dye intermediates (Cofrancesco, 1963). 2-Aminoanthraquinone per se is a direct precursor of five dyes and one pigment that are produced commercially in the United States. These include Colour Index Vat Blues

*The CAS registry number is 117-79-3.

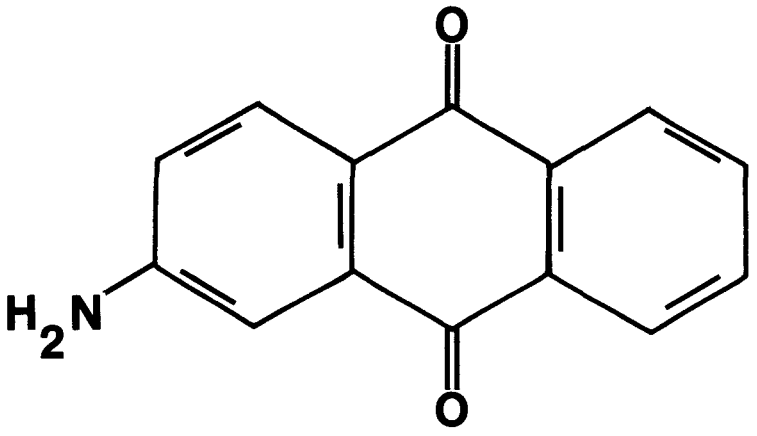


FIGURE 1
CHEMICAL STRUCTURE OF 2-AMINOANTHRAQUINONE

4, 6, 12 and 24; Vat Yellow 1; and Pigment Blue 22 (Society of Dyers and Colourists, 1971; as cited in Urso, 1977).

Recent production statistics for 2-aminoanthraquinone are considered proprietary and are therefore not available. However, 2.01 x 10^5 pounds of the compound and its salts were produced in 1971, the latest year for which such data were reported (U.S. Tariff Commission, 1973; as cited in Urso, 1977). Imports of 2-aminoanthraquinone through principal U.S. customs districts are quite substantial and amounted to 3.57 x 10^5 pounds in 1974 (U.S. International Trade Commission, 1976; as cited in Urso, 1977).

Since 2-aminoanthraquinone appears to be used on a commercial scale exclusively by the dye industry, the potential for exposure to the compound is greatest for workers at dye manufacturing facilities.

II. MATERIALS AND METHODS

A. Chemicals

One batch of 2-aminoanthraquinone was purchased from J. T. Baker Chemical Company (Lot #1-8041) and a second batch was purchased from American Cyanamid. The second batch did not bear a lot number when it was received at Mason Research Institute. The batch received from Baker was used only for the first 8 weeks of the chronic bioassay of male rats (female rats and mice of both sexes were not yet on test). After week 8 of the male rat bioassay, only the American Cyanamid batch was used for dosed feed preparation. Dosed female rats and all dosed mice received only the American Cyanamid chemical.

The initial chemical analyses of both batches were performed at Mason Research Institute. Five years later a sample of the American Cyanamid batch was analyzed by Midwest Research Institute. The melting points determined at Mason Research Institute were 215° to 235°C for the American Cyanamid batch. The chemical decomposed at 235°C. When the American Cyanamid batch was tested at Midwest Research Institute, a melting point range of 255° to 292°C was observed, with decomposition noted at 292°C. The deviation of these observed melting point ranges from the melting point range of 303° to 306°C reported in the literature (Pollock and Stevens, 1965), suggests that either the chemicals tested were of very low purity or that attempts to determine the melting point were unsuccessful because decomposition occurred before the melting point was reached. The ultraviolet

spectra for the compound purchased from American Cyanamid and the literature reference spectra (Sadtler Standard Spectra,a) are shown below:

	American Cyanamid (Analyzed by Midwest)	Reference
Solvent:	Methanol	Methanol
	445	445
	297	297
	279	
	240	240

The ultraviolet spectra of the American Cyanamid sample in methanol determined at Midwest Research Institute included all three of the peaks found in the reference spectrum, confirming identity of the compound, and also had a peak at 279 nm. The extra peak indicated the presence of an impurity. The ultraviolet spectra of both batches determined in chloroform at Mason Research Institute do not agree with the reference spectra.

The infrared spectrum, determined at Midwest Research Institute for the American Cyanamid batch, was consistent with the literature spectrum (Sadtler Standard Spectra,b).

Throughout this report the term 2-aminoanthraquinone is used to represent these materials.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinos).

2-Aminoanthraquinone 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 1 week.

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 rats and their controls were supplied by Laboratory Supply Company, Inc., Indianapolis, Indiana. The high dose and high dose control mice and some of the low dose mice (male and female) were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The remaining low dose mice and all the low dose control mice were supplied by ARS/Sprague-Dawley, Madison, Wisconsin. Each group of animals to be dosed was received in a shipment separate from their controls.

Upon arrival, a sample of animals was examined for parasites and other signs of disease. The remaining animals were quarantined for two weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that 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. During quarantine and for the first 13 months of study, rats were housed in galvanized- or stainless-steel wire-mesh cages suspended above newspapers. Newspapers under cages were replaced daily and cages and racks washed weekly. For the remainder of the study, rats were housed in suspended polycarbonate cages equipped with disposable nonwoven fiber filter sheets. Clean bedding and cages were provided twice weekly. Stainless steel cage racks were cleaned once every two weeks, and disposable filters were replaced at that time.

Mice were housed by sex in shoe box type polycarbonate cages fitted with perforated stainless steel lids and nonwoven fiber filters. All mice were housed either five or ten per cage. Cages, lids, and bedding were provided two to three times per week. Reusable filter bonnets and pipe racks were sanitized every two weeks throughout the study.

Water was available ad libitum for both species from 250 ml water bottles equipped with rubber stoppers and stainless steel

sipper tubes. Bottles were replaced twice weekly and, for rats only, refilled as needed between changes.

Wayne Lab-Blox® was supplied ad libitum throughout the entire test. Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) containing stainless steel baffles or stainless steel gangstyle hoppers were used to distribute powdered feed. Pelleted Wayne Lab-Blox® was supplied during the quarantine period and final observation period. Mice were fed pellets from a wire bar hopper incorporated into the cage lid, while rats received pellets on the cage floor.

All rats were housed in a room in which other rats were receiving diets containing* 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 3-amino-9-ethylcarbazole hydrochloride; 6-nitrobenzimidazole (94-52-0); 1-nitronaphthalene (86-57-7); and APC (8003-03-0).

All dosed mice in this study were housed with their respective diet controls.

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 2-aminoanthraquinone 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 four groups, each consisting of five males and five females. 2-Aminoanthraquinone was incorporated into the basal laboratory diet and

*CAS registry numbers are given in parentheses.

supplied ad libitum to three of the four groups of each species in concentrations of 1.0, 3.0, and 5.0 percent. The fourth 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 4 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet.

The highest concentration causing no deaths, no compound-related gross abnormalities, and no mean group 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.

No deaths were recorded for any dosed rat group. Mean body weight depression was approximately 6 and 10 percent for males receiving chemical concentrations of 1.0 and 3.0 percent, respectively, and 18 and 19 percent for females receiving the same respective concentrations. The high concentration selected for use in the rat chronic bioassay was 2.0 percent for both males and females.

The only death recorded among dosed mice was one male receiving 5.0 percent 2-aminoanthraquinone. Mean body weight depression was approximately 8 percent for males receiving concentrations of 1.0 and 3.0 percent, respectively, and 14 and 18 percent for females receiving the same respective concentrations. The high concentration ultimately selected for use in the mouse chronic bioassay was 1.0 percent for both males and females.

F. Experimental Design

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

There were 10 rat groups (male and female) originally included in this research. As five of these groups consisted of too few animals for meaningful statistical analysis for bioassay purposes and/or included gonadectomized and ovariectomized rats, only the 5 remaining rat groups were considered when evaluating this bioassay.

Dosed male rats were approximately 6 weeks old when chemical administration was initiated and they shared the same median date of birth. Control males were approximately 3 weeks older than the dosed males. The initial concentrations of 2-aminoanthraquinone administered to male rats were 2.0 and 1.0 percent, respectively. Throughout this report those males initially receiving 2.0 percent are referred to as the high dose group and those initially receiving 1.0 percent are referred to as the low dose group. After having received 2-aminoanthraquinone at the indicated concentrations for 10 weeks, the dosages were reduced to 0.5 and 0.25 percent for the high and low dose groups, respectively. These concentrations were maintained for the remainder of the chemical administration period. The dosed group of female rats was approximately 6 weeks old when they

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
2-AMINOANTHRAQUINONE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	2-AMINOANTHRAQUINONE CONCENTRATION[a]	OBSERVATION PERIOD		TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
			TREATED (WEEKS)	UNTREATED (WEEKS)	
MALE					
CONTROL	50	0	0	107	0
LOW DOSE	50	1.0 0.25 0	10 68	 28	0.35
HIGH DOSE	50	2.0 0.5 0	10 68	 28	0.69
FEMALE					
CONTROL	25	0	0	109	0
DOSED	50	0.2 0	78	 32	0.2

[a] Concentrations in percentages in feed.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
2-AMINOANTHRAQUINONE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	2-AMINOANTHRAQUINONE CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	93
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	49	0.5	78	
		0		16
HIGH DOSE	50	1.0	80	
		0		15
FEMALE				
LOW DOSE CONTROL	50	0	0	94
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.5	78	
		0		16
HIGH DOSE	50	1.0	80	
		0		16

[a]Concentrations in percentages in feed.

were included in the bioassay. The control females were also approximately 6 weeks old when they were included in the bioassay, 11 weeks after compound administration had been initiated for the dosed females. The dosed females received 0.2 percent 2-aminoanthraquinone for the 78-week period of compound administration. Dosed male rats were observed for an additional 28 weeks after compound administration ceased and dosed female rats were observed for an additional 32 weeks.

The concentrations utilized for both male and female mice were 1.0 and 0.5 percent. Throughout this report those mice receiving a dietary 2-aminoanthraquinone concentration of 1.0 percent are referred to as the high dose groups while those receiving 0.5 percent are referred to as the low dose groups. The low dose mice were approximately 6 weeks old when they were first administered the compound. At that time the low dose control mice were approximately 3 weeks older. The high dose mice were also approximately 6 weeks old when they first received the compound, which was approximately 8 months after the low dose mice had been started on test. The high dose control mice were approximately 3 weeks younger than the high dose mice. The high dose mice were dosed for 80 weeks while the low dose mice received the chemical for 78 weeks. An observation period of up to 16 weeks followed the period of compound administration.

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, brain, ear, testis, prostate, Zymbal's gland, 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

Slight mean body weight depression was observed when dosed males were compared with control males. There was a more distinct difference between the mean body weights of the dosed and control females (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

One low dose male rat developed a palpable mass on the ventral surface and one control male had a crusted lesion on the dorsolateral surface. No other clinical abnormalities were observed in dosed or control rats of either sex.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 2-aminoanthraquinone-dosed groups are shown in Figure 3. For male rats, there was no significant association between dose and mortality. For female rats a significant positive association between chemical administration and mortality was observed.

For males ten rats were sacrificed from the control group in week 29 and five rats were sacrificed from each dosed and control group in week 78. Adequate number of males were at risk from late-developing tumors with 70 percent (35/50) of the high dose, 64 percent (32/50) of the low dose, and 54 percent (27/50) of the controls surviving on test until the termination of the study.

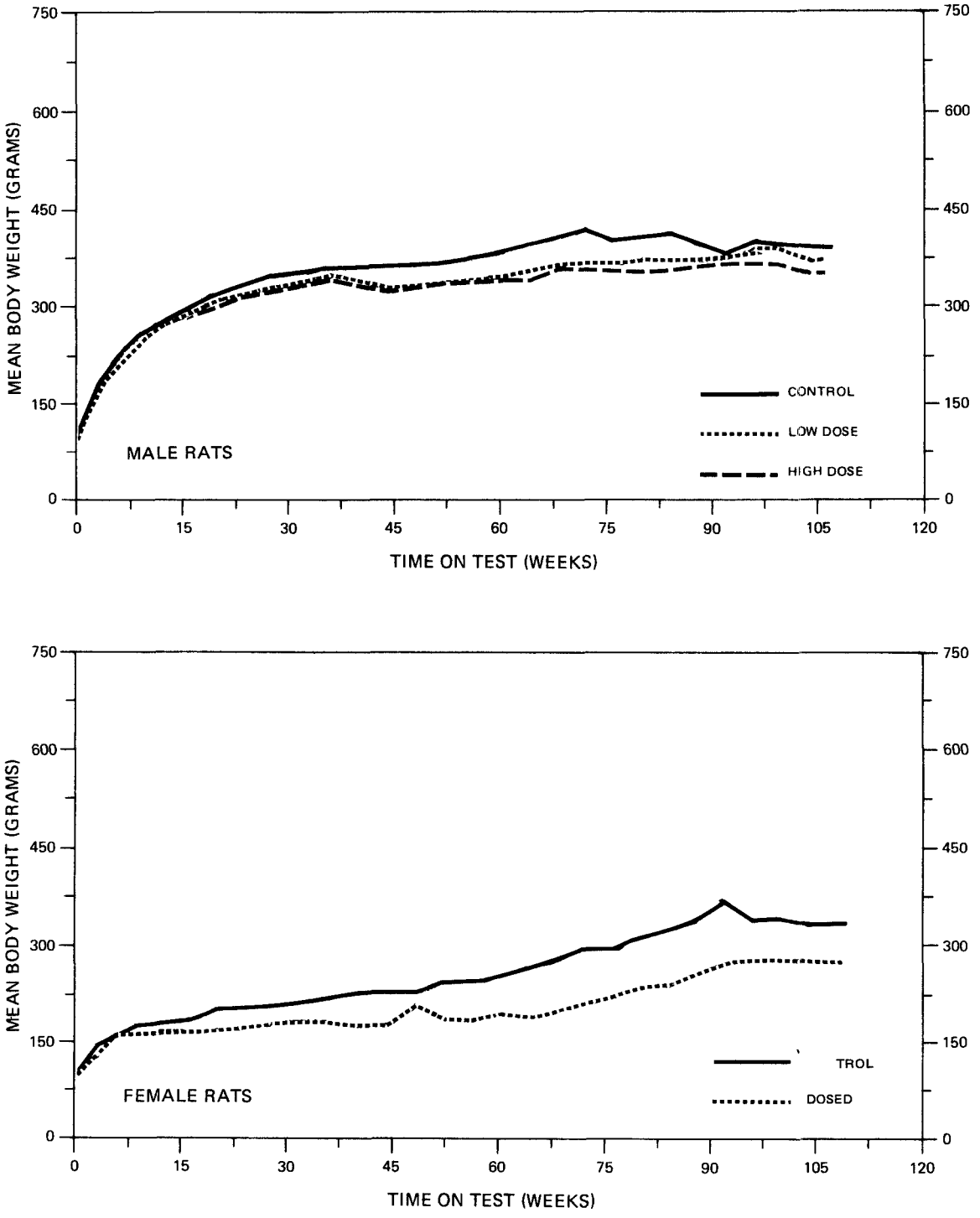
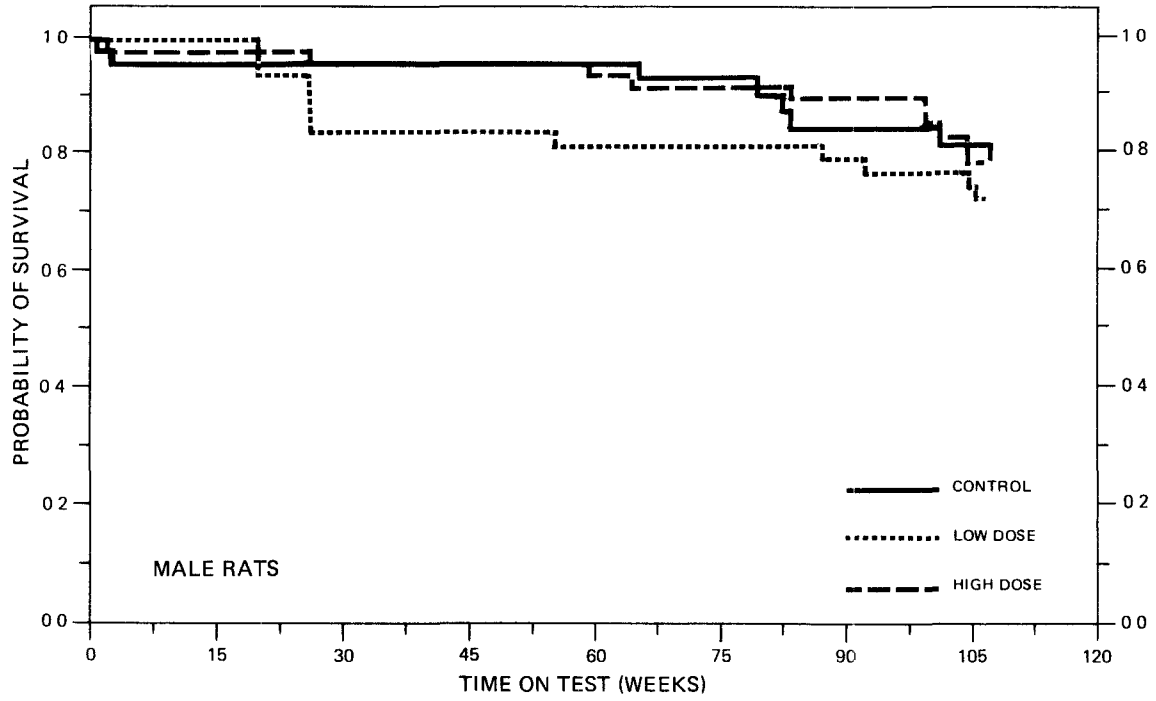


FIGURE 2
GROWTH CURVES FOR 2-AMINOANTHRAQUINONE CHRONIC STUDY RATS



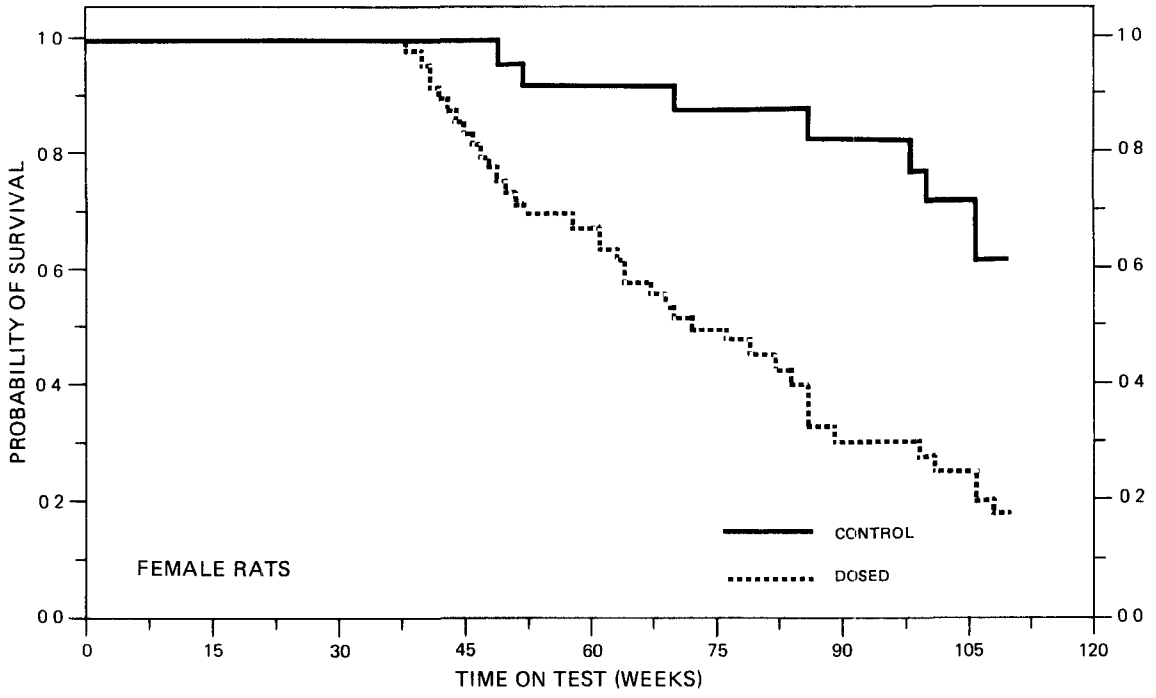


FIGURE 3
SURVIVAL COMPARISONS OF 2-AMINOANTHRAQUINONE CHRONIC STUDY RATS

For females five rats were sacrificed from the dosed group and five from the control group in week 78. Survival in the dosed group declined steadily from week 40 on. After one year, 70 percent (35/50) of the dosed rats and 92 percent (23/25) of the control rats were alive on test. By the termination of the study, however, only 14 percent (7/50) of the dosed rats and 48 percent (12/25) of the control rats remained alive. Survival of female rats was not adequate to permit analysis of late-developing tumors.

C. Pathology

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

The incidence of hepatic neoplasms in male rats fed the two concentrations of 2-aminoanthraquinone appeared to be compound-related. Hepatocellular carcinomas occurred in 8/49 (16 percent) low dose, 5/46 (11 percent) high dose and 0/46 control male rats. Hepatocellular carcinoma was found in 1/42 (2 percent) dosed females but in none of the controls. Neoplastic nodules were also commonly observed in dosed male rats.

Morphology of the hepatocellular carcinoma and neoplastic nodules was similar to that described by Squire and Levitt (1975). Hepatocellular carcinoma involved one or many lobes of the liver. The tumor appeared well-differentiated, but the normal lobular architecture was distorted. Liver plates were two cells in thickness. There was a

pleomorphism in the size of transformed hepatocytes. Cytoplasm of the cells was either acidophilic or basophilic. In some tumors, cytoplasm of the cells was vacuolated and suggested fatty infiltration. Nuclei were hyperchromatic and nucleoli prominent. Mitotic figures were numerous. Areas of necrosis and clusters of inflammatory cells were found in a few tumors. The tumor had metastasized to the lung in one control female rat, but in none of the dosed rats.

Neoplastic nodules were smaller, demarcated, and compressed the normal liver in areas. Cells in these nodules were large. Cytoplasm of the cells was basophilic and the nuclei were large. A few mitotic figures were present.

2-Aminoanthraquinone is considered to be a hepatocarcinogen since there was an increase in the incidence of hepatocellular carcinomas and neoplastic nodules of the liver in male Fischer 344 rats fed the two concentrations of the chemical.

One low dose male rat and 16/42 (38 percent) of the female rats originally included in the bioassay had foreign body granulomatous nephritis (FBGN) of the kidney and died in less than 25 weeks. This lesion differed from the renal changes normally seen in aging Fischer 344 rats, in that the lumen of cortical tubules were plugged with crystals, and there was a granulomatous reaction and fibrosis. The lesions resembled those described by Baker et al. (1975) as foreign body granulomatous nephritis (FBGN). In those female rats fed 0.2 percent 2-aminoanthraquinone which survived as long as the respective controls, the incidence of neoplasms was low.

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 malignant tumor in either sex where at least two such tumors were observed in at least one of the control or 2-aminoanthraquinone-dosed groups and where such tumors were observed in at least 5 percent of the group. Because of the sacrifice of 10 male control rats in week 29, the analyses for males were based solely on those rats surviving at least 30 weeks.

For males the Cochran-Armitage test showed a significant ($P < 0.001$) positive association between dose and the combined incidence of hepatocellular carcinomas or neoplastic nodules of the liver. The departure from linear trend was also significant ($P = 0.006$) due to the comparable incidence rates in both dosed groups. These positive results were supported by significant ($P < 0.001$) Fisher exact tests when either dosed group was compared to the control. When hepatocellular carcinomas alone were considered, the Fisher exact test showed a significantly ($P = 0.005$) higher incidence in the low dose than in the control. The high dose comparison had a probability level of $P = 0.048$, a marginal result which was not significant under the Bonferroni criterion. Based on these statistical findings the administration of 2-aminoanthraquinone was associated with the increased incidence of hepatocellular neoplasms in male rats.

TABLE 3

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH 2-AMINOANTHRAQUINONE[a,f]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	0/36(0.00)	8/41(0.20)	5/45(0.11)
P Values[c]	N.S.	P = 0.005	P = 0.048
Departure from Linear Trend[e]	P = 0.018	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	2.032	1.020
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	78	78
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	0/36(0.00)	18/41(0.44)	18/45(0.40)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P = 0.006	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	5.134	4.667
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	78	78
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	12/32(0.38)	4/38(0.11)	3/42(0.07)
P Values[c]	P = 0.001(N)	P = 0.008(N)	P = 0.002(N)
Relative Risk (Control)[d]	---	0.281	0.190
Lower Limit	---	0.074	0.038
Upper Limit	---	0.824	0.635
Weeks to First Observed Tumor	101	106	106

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	6/35(0.17)	2/40(0.05)	5/44(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.292	0.663
Lower Limit	---	0.030	0.175
Upper Limit	---	1.511	2.398
Weeks to First Observed Tumor	107	106	104
Thyroid: C-Cell Adenoma[b]	1/35(0.03)	0/39(0.00)	5/39(0.13)
P Values[c]	P = 0.044	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	4.487
Lower Limit	---	0.000	0.539
Upper Limit	---	16.661	206.175
Weeks to First Observed Tumor	107	---	104
Pancreatic Islets: Islet-Cell Adenoma[b]	2/32(0.06)	1/39(0.03)	1/44(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.410	0.364
Lower Limit	---	0.007	0.006
Upper Limit	---	7.536	6.707
Weeks to First Observed Tumor	107	106	106

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	33/35(0.94)	36/39(0.92)	38/45(0.84)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.979	0.896
Lower Limit	---	0.886	0.812
Upper Limit	---	1.115	1.077
Weeks to First Observed Tumor	78	78	78

[a]Treated groups received time-weighted average doses of 34.6 or 69.2 ppm in feed.

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

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

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

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

[f]These analyses were based solely upon animals surviving at least 30 weeks.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH 2-AMINOANTHRAQUINONE[a]

TOPOGRAPHY: MORPHOLOGY	CONTROL	DOSED
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/23(0.09)	2/43(0.05)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.535
Lower Limit	---	0.042
Upper Limit	---	7.038
Weeks to First Observed Tumor	106	106
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	2/23(0.09)	1/42(0.02)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.274
Lower Limit	---	0.005
Upper Limit	---	5.023
Weeks to First Observed Tumor	106	106
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	8/21(0.38)	6/30(0.20)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.525
Lower Limit	---	0.182
Upper Limit	---	1.477
Weeks to First Observed Tumor	78	78

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	DOSED
Adrenal: Cortical Adenoma[b]	0/23(0.00)	2/39(0.05)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	Infinite
Lower Limit	---	0.180
Upper Limit	---	Infinite
Weeks to First Observed Tumor	---	67
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	3/23(0.13)	3/39(0.08)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.590
Lower Limit	---	0.087
Upper Limit	---	4.106
Weeks to First Observed Tumor	109	76
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	3/21(0.14)	2/29(0.07)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.483
Lower Limit	---	0.044
Upper Limit	---	3.871
Weeks to First Observed Tumor	109	50

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	DOSED
Mammary Gland: Adenocarcinoma NOS or Papillary Cystadenoma NOS[b]	2/23(0.09)	0/43(0.00)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.000
Lower Limit	---	0.107
Upper Limit	---	1.794
Weeks to First Observed Tumor	98	---
Mammary Gland: Fibroadenoma[b]	4/23(0.17)	3/43(0.07)
P Values[c]	---	N.S.
Relative Risk (Control)[d]	---	0.401
Lower Limit	---	0.065
Upper Limit	---	2.194
Weeks to First Observed Tumor	109	64

[a]Treated groups received concentrations of 0.2 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 the 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. 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.

Also in male rats the Cochran-Armitage test indicated a significant (P = 0.044) positive association between dose and the incidence of thyroid C-cell adenomas. The Fisher exact tests, however, were not significant.

For male rats the possibility of a negative association between chemical administration and tumor incidence was observed for the combined incidence of pituitary adenomas NOS and chromophobe adenomas. This may have been due, however, to the greater than expected incidence of these tumors in the control group (12/41 or 29 percent) when compared to the historical control incidence for these tumors 35/334 (11 percent) in data on untreated male Fischer 344 rats collected by this laboratory for the NCI Carcinogenesis Testing Program.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Slight mean body weight depression was observed when low dose males were compared with low dose control males. There was a more distinct difference between the mean body weights of the low dose female and low dose control females. Distinct differences in mean body weights were not apparent when high dose mice of either sex were compared to their high dose controls (Figure 4). It may be noted that for both sexes the mean body weights of the two control groups which came from different suppliers were appreciably different.

No clinical abnormalities were observed in dosed or control mice of either sex.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 2-aminoanthraquinone-dosed groups are shown in Figure 5. The Tarone test for positive association between dosage and mortality was not significant for either male or female mice.

Five male mice were sacrificed from the high dose control in week 49 and five more in week 78. Additionally, five males were sacrificed from the high dose group in week 78, plus five from the low dose control in week 80. At the termination of the study, 86 percent (43/50) of the high dose, 94 percent (46/49) of the low dose, 78 percent (39/50) of the high dose control and 82 percent (41/50) of

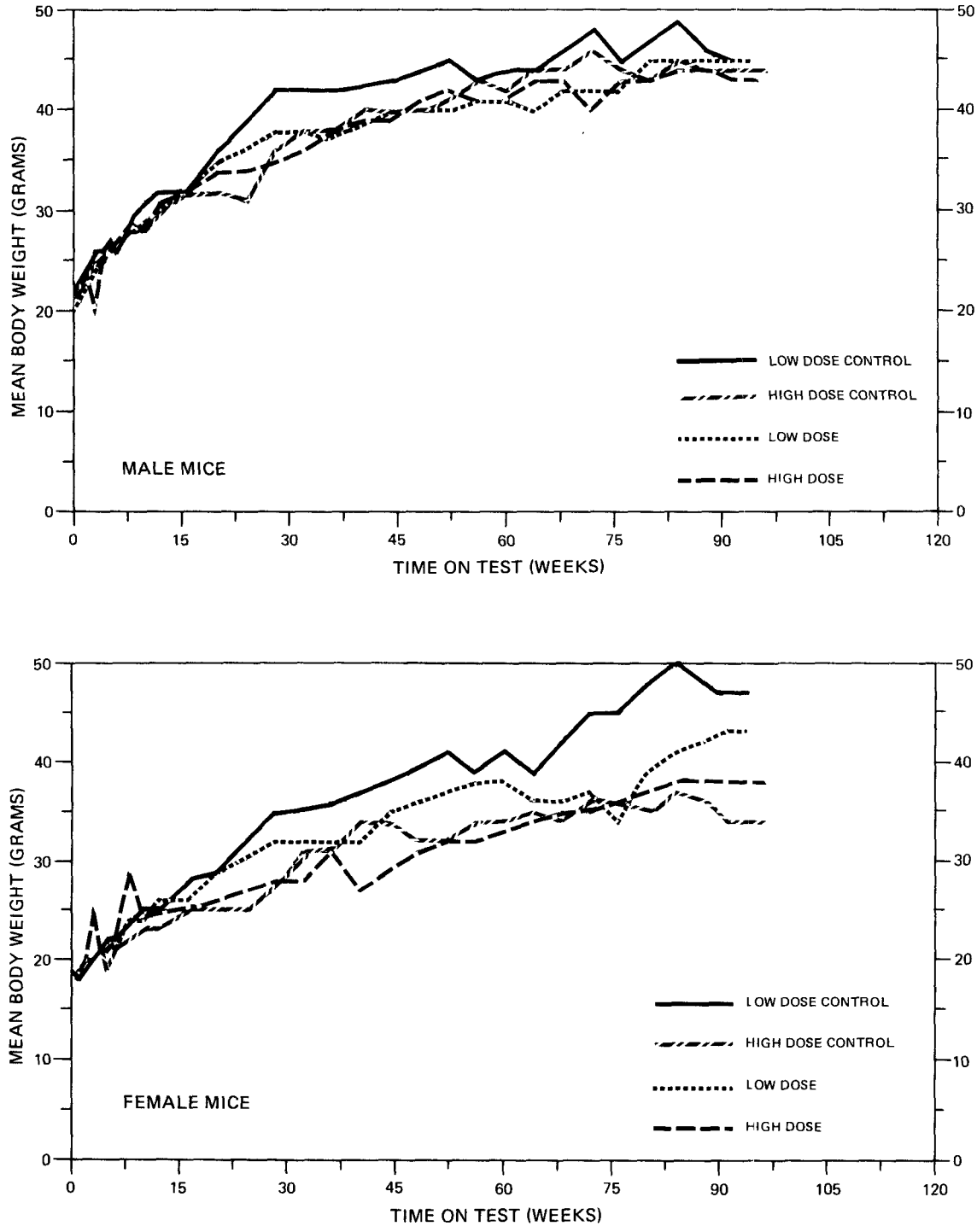
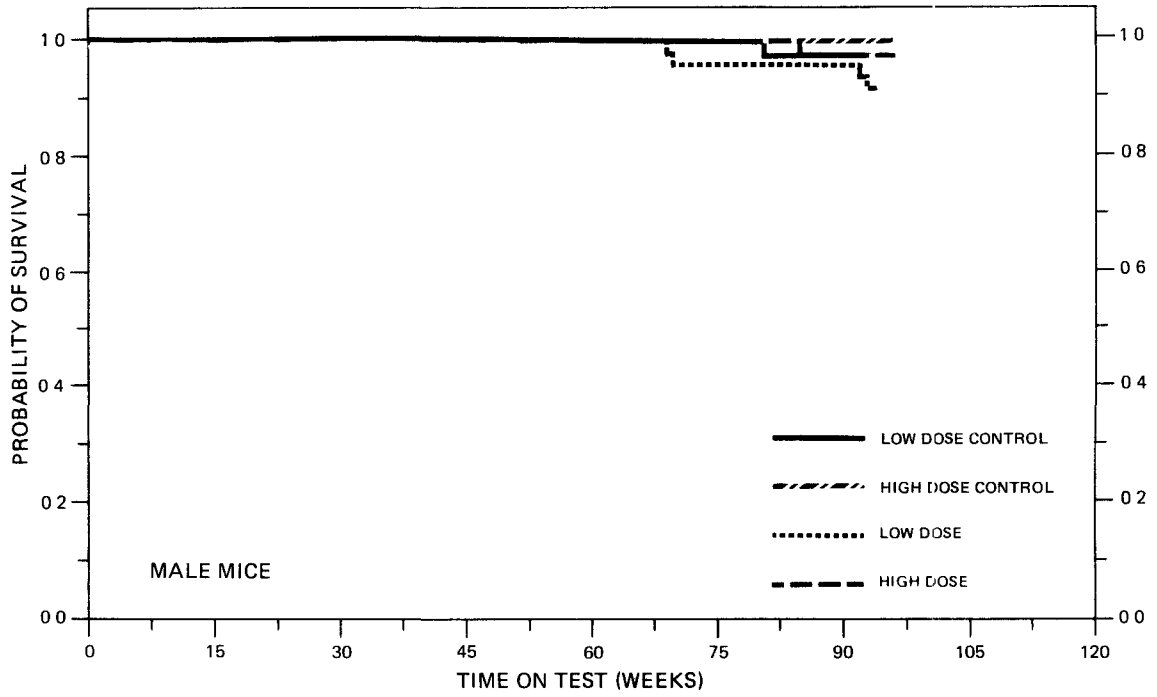


FIGURE 4
GROWTH CURVES FOR 2-AMINOANTHRAQUINONE CHRONIC STUDY MICE



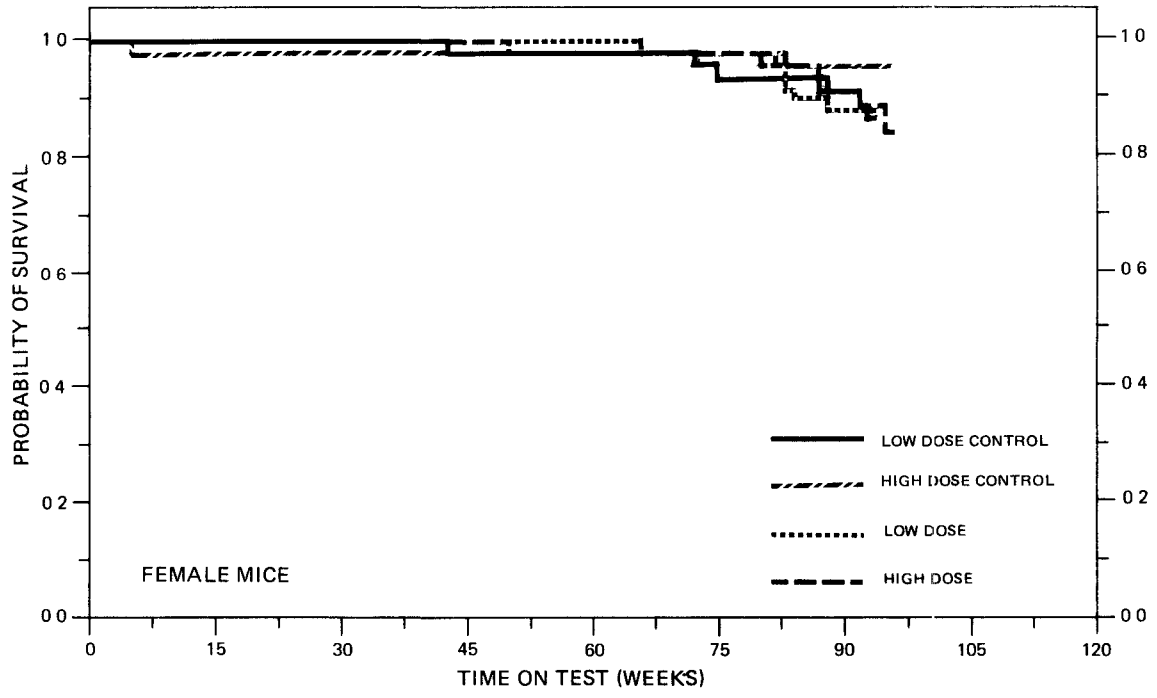


FIGURE 5
SURVIVAL COMPARISONS OF 2-AMINOANTHRAQUINONE CHRONIC STUDY MICE

the low dose control mice were alive on test. Adequate numbers of males were at risk from late-developing tumors.

Five female mice from the high dose control were sacrificed in week 49 with five more sacrificed in week 78. Additionally, five females were sacrificed from the high dose group in week 78 and five from the low dose control in week 80. With 76 percent (38/50) of the high dose, 88 percent (44/50) of the low dose, 76 percent (38/50) of the high dose control, and 78 percent (39/50) of the low dose control mice surviving on test until the termination of the study, adequate numbers of females survived sufficiently long to be at risk from late-developing tumors.

C. Pathology

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

A dose-related increase in the incidence of hepatocellular carcinomas was found in both sexes of mice receiving 2-aminoanthraquinone. In male mice, this tumor occurred in 20/47 (43 percent) of the low dose group, 36/49 (73 percent) of the high dose group, and in 18/94 (19 percent) of the controls. In female mice, this tumor was present in 5/47 (11 percent) of the low dose group, 12/47 (26 percent) of the high dose group, and 5/96 (5 percent) of the controls.

Morphology of the hepatocellular carcinoma in these mice was similar to that described in Butler and Newberne (1975). The tumor

had replaced a part or a whole lobe of the liver. The normal architecture was distorted with the tumor cells arranged in abnormal trabecular patterns. Cytoplasm of the cells was eosinophilic and vacuolated in areas. A pleomorphism in nuclear size was evident. Nuclei were vesicular, and mitotic figures were present. Inclusions were seen in some of the nuclei. Metastases to other organs were not found.

An increased incidence of malignant lymphomas was observed in high dose female mice when compared to controls. These lesions were found in 12/49 (24 percent) of the high dose females and 7/97 (7 percent) of the controls. The incidences of these lesions in the low dose and control groups were similar.

The dosed mice had the usual spectrum of nonneoplastic lesions, and none appeared to be compound-related.

2-Aminoanthraquinone is considered to be a hepatocarcinogen, as there was a dose-related increase in the incidence of hepatocellular carcinomas in B6C3F1 mice receiving this chemical. Administration of the chemical was also associated with an increased incidence of malignant lymphomas in high dose female B6C3F1 mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 2-AMINOANTHRAQUINONE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	2/46(0.04)	5/49(0.10)	4/45(0.09)	5/50(0.10)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.044	0.980
Lower Limit	---	---	0.310	0.240
Upper Limit	---	---	21.695	3.999
Weeks to First Observed Tumor	93	96	94	85
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	7/46(0.15)	10/49(0.20)	8/45(0.18)	11/50(0.22)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.168	1.078
Lower Limit	---	---	0.404	0.459
Upper Limit	---	---	3.468	2.570
Weeks to First Observed Tumor	80	96	94	85
Hematopoietic System: Malignant Lymphoma[b]	2/46(0.04)	5/49(0.10)	0/48(0.00)	2/50(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.392
Lower Limit	---	---	0.000	0.039
Upper Limit	---	---	3.236	2.266
Weeks to First Observed Tumor	93	96	---	78

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	12/46(0.26)	6/48(0.13)	20/47(0.43)	36/49(0.73)
P Values[c]	---	---	N.S.	P < 0.001
Relative Risk (Control)[d]	---	---	1.631	5.878
Lower Limit	---	---	0.867	2.843
Upper Limit	---	---	3.192	14.070
Weeks to First Observed Tumor	93	78	94	78
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	12/46(0.26)	8/48(0.17)	20/47(0.43)	36/49(0.73)
P Values[c]	---	---	N.S.	P < 0.001
Relative Risk (Control)[d]	---	---	1.631	4.408
Lower Limit	---	---	0.867	2.353
Upper Limit	---	---	3.192	8.925
Weeks to First Observed Tumor	93	78	94	78

[a]Treated groups received doses of 0.5 or 1.0 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 the 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.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 2-AMINOANTHRAQUINONE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/46(0.02)	3/50(0.06)	2/48(0.04)	3/48(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.917	1.042
Lower Limit	---	---	0.103	0.146
Upper Limit	---	---	110.703	7.419
Weeks to First Observed Tumor	94	78	94	95
Hematopoietic System: Malignant Lymphoma[b]	5/47(0.11)	2/50(0.04)	6/48(0.13)	12/49(0.24)
P Values[c]	---	---	N.S.	P = 0.003
Relative Risk (Control)[d]	---	---	1.175	6.122
Lower Limit	---	---	0.321	1.464
Upper Limit	---	---	4.548	53.856
Weeks to First Observed Tumor	80	96	83	82
Liver: Hepatocellular Carcinoma[b]	4/46(0.09)	1/50(0.02)	5/47(0.11)	12/47(0.26)
P Values[c]	---	---	N.S.	P = 0.001
Relative Risk (Control)[d]	---	---	1.223	12.766
Lower Limit	---	---	0.281	2.015
Upper Limit	---	---	5.803	530.576
Weeks to First Observed Tumor	94	96	94	78

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	4/37(0.11)	3/42(0.07)	4/42(0.10)	3/36(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.881	1.167
Lower Limit	---	---	0.176	0.165
Upper Limit	---	---	4.417	8.184
Weeks to First Observed Tumor	80	96	94	96

[a]Treated groups received doses of 0.5 or 1.0 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 the 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.

tumors were observed in at least one of the control or 2-aminoanthraquinone-dosed groups and where such tumors were observed in at least 5 percent of the group. Cochran-Armitage tests were not used in these analyses since the high dose and the high dose control groups came from a different supplier and were started at a different time from the low dose and the low dose control groups.

Hepatocellular carcinomas were observed in a large number of male and female mice. In male mice a significant ($P < 0.001$) Fisher exact test result was obtained for the comparison of the high dose group to the high dose control. Similarly, in female mice the Fisher exact test was significant ($P = 0.001$) for the comparison of high dose to the high dose controls. Based on these statistical findings the administration of 2-aminoanthraquinone was associated with the increased incidence of hepatocellular carcinomas in both male and female mice.

For female mice, the incidence of malignant lymphoma was increased in the high dose group relative to that in the high dose control group, with a significant ($P = 0.003$) comparison using the Fisher exact test. Incidences of 24 percent (12/49) and 4 percent (2/50) were observed in the high dose and high dose control groups, respectively, compared to the historical incidence of a maximum of 12 percent (43/350) in untreated female B6C3F1 mice observed at Mason Research Institute for the NCI Carcinogenesis Testing Program. Based on these findings, there was a possibility that the administration of

2-aminoanthraquinone was associated with the development of malignant lymphomas in female mice.

V. DISCUSSION

There were no significant positive associations between the dietary concentrations of 2-aminoanthraquinone and mortality in male rats or in mice of either sex; there was a significant positive association, however, between dose and mortality in female rats. Adequate numbers of animals in all groups, except the dosed female rats, survived sufficiently long to be at risk from late-developing tumors.

When male rats having either hepatocellular carcinomas or neoplastic nodules of the liver were combined and the resulting incidences (i.e., 0/46, 18/49 [37 percent], and 18/46 [39 percent] in the control, low dose, and high dose, respectively) were analyzed statistically, there was a significant positive association between dosage and the incidences of these combined neoplasms. Both the high dose to control and the low dose to control Fisher exact comparisons supported this finding. When those males having hepatocellular carcinomas alone were evaluated, the low dose to control Fisher exact comparison was significant; however, the high dose to control comparison was not. Dietary exposure to the compound resulted in nephrotoxicity in female rats, as the majority of the females examined had foreign body granulomatous nephritis.

Hepatocellular carcinomas were observed at higher incidences in dosed mice when compared to controls (i.e., 12/46 [26 percent], 6/48 [13 percent], 20/47 [43 percent], and 36/49 [73 percent] in the low

dose control, high dose control, low dose, and high dose males, respectively, and 4/46 [9 percent], 1/50 [2 percent], 5/47 [11 percent] and 12/47 [26 percent] in the low dose control, high dose control, low dose, and high dose females). For both sexes the high dose to control Fisher exact comparisons were significant. For female mice there was a significantly higher incidence of malignant hematopoietic lymphomas in the high dose group when compared to the high dose control. In addition, the incidence observed in the high dose females in this bioassay (i.e., 12/49 or 24 percent) is twice the historical incidence observed in control female mice maintained at Mason Research Institute during the NCI Carcinogenesis Testing Program.

In a previous report, no evidence was provided for the carcinogenicity of 2-aminoanthraquinone in female Sprague-Dawley rats following administration of a total of 1000 mg of the compound. The animals were intubated with 10 equal doses over a period of 30 days, the first dose administered when they were 40 days old. Final observations in this study were completed approximately 9 months after the first dose was given (Griswald et al., 1968).

Under the conditions of this bioassay, dietary administration of 2-aminoanthraquinone was carcinogenic in male Fischer 344 rats, causing a combination of hepatocellular carcinomas and neoplastic nodules of the liver. The compound was also carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes, and it was associated with malignant lymphomas in females. No evidence was provided for the carcinogenicity of 2-aminoanthraquinone in female rats.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 2-AMINOANTHRAQUINONE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 2-AMINOANTHRAQUINONE

	CONTROL(UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	46	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	46	49	46
INTEGUMENTARY SYSTEM			
*SKIN	(46)	(49)	(47)
FIBROSARCOMA			1 (2%)
*SUBCUT TISSUE	(46)	(49)	(47)
FIBROMA		1 (2%)	
LEIOMYCSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(45)	(49)	(45)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
#LUNG	(46)	(49)	(46)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(46)	(49)	(47)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
MONOCYTIC LEUKEMIA	1 (2%)		
#LYMPH NODE	(38)	(43)	(40)
ADENOCARCINOMA, NOS, METASTATIC	1 (3%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
DIGESTIVE SYSTEM			
#LIVER	(46)	(49)	(46)
NEOPLASTIC NODULE		10 (20%)	13 (28%)
HEPATOCELLULAR CARCINOMA		8 (16%)	5 (11%)
#STOMACH	(45)	(47)	(46)
PAPILLOMA, NOS			1 (2%)
#SMALL INTESTINE	(43)	(47)	(45)
LEIOMYOMA			1 (2%)
#DUODENUM	(43)	(47)	(45)
LEIOMYOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(46)	(43)
ADENOMA, NOS	2 (5%)	1 (2%)	3 (7%)
CHROMOPHOBE ADENOMA	10 (24%)	3 (7%)	
#ADRENAL	(43)	(48)	(45)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
PHEOCHROMOCYTOMA	6 (14%)	2 (4%)	3 (7%)
PHEOCHROMOCYTOMA, MALIGNANT			2 (4%)
#THYROID	(45)	(46)	(40)
ADENOMA, NOS	1 (2%)	1 (2%)	
ADENOCARCINOMA, NOS	2 (4%)		1 (3%)
C-CELL ADENOMA	1 (2%)		5 (13%)
C-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(42)	(47)	(45)
ISLET-CELL ADENOMA	2 (5%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(46)	(49)	(47)
ADENOCARCINOMA, NOS			1 (2%)

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
FIBROADENOMA			1 (2%)
#PROSTATE	(45)	(47)	(44)
PARAGANGLIOMA, NOS	1 (2%)		
#TESTIS	(45)	(47)	(46)
INTERSTITIAL-CELL TUMOR	33 (73%)	36 (77%)	38 (83%)
NERVOUS SYSTEM			
#BRAIN	(44)	(48)	(46)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*BODY CAVITIES	(46)	(49)	(47)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	3	6
MORIBUND SACRIFICE	2	10	4
SCHEDULED SACRIFICE	15	5	5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	27	32	35
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL(UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	39	42
TOTAL PRIMARY TUMORS	61	68	79
TOTAL ANIMALS WITH BENIGN TUMORS	33	37	39
TOTAL BENIGN TUMORS	55	46	54
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	11	10
TOTAL MALIGNANT TUMORS	5	11	12
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	2
TOTAL SECONDARY TUMORS	4	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	11	13
TOTAL UNCERTAIN TUMORS	1	11	13
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 2-AMINOANTHRAQUINONE

	CONTROL (UNTR) 02-0084	DOSED 02-0078
ANIMALS INITIALLY IN STUDY	25	50
ANIMALS NECROPSIED	23	43
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	23	43
INTEGUMENTARY SYSTEM		
*SKIN	(23)	(43)
SQUAMOUS CELL CARCINOMA		1 (2%)
SEBACEOUS ADENOCARCINOMA	1 (4%)	
RESPIRATORY SYSTEM		
#LUNG	(23)	(42)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(23)	(43)
UNDIFFERENTIATED LEUKEMIA	2 (9%)	
MYELOMONOCYTIC LEUKEMIA		2 (5%)
#SPLEEN	(23)	(39)
SARCOMA, NOS		1 (3%)
CIRCULATORY SYSTEM		
NONE		
DIGESTIVE SYSTEM		
#LIVER	(23)	(42)
NEOPLASTIC NODULE	2 (9%)	
HEPATOCELLULAR CARCINOMA		1 (2%)
URINARY SYSTEM		
NONE		

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

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 02-0084	DOSED 02-0078
ENDOCRINE SYSTEM		
#PITUITARY	(21)	(30)
ADENOMA, NOS	1 (5%)	4 (13%)
CHROMOPHOBE ADENOMA	7 (33%)	2 (7%)
#ADRENAL	(23)	(39)
CORTICAL ADENOMA		2 (5%)
PHEOCHROMOCYTOMA	2 (9%)	3 (8%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (4%)	
#THYROID	(21)	(29)
C-CELL ADENOMA	2 (10%)	1 (3%)
C-CELL CARCINOMA	1 (5%)	1 (3%)
#THYROID FOLLICLE	(21)	(29)
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (5%)	
#PARATHYROID	(9)	(14)
ADENOMA, NOS		1 (7%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(23)	(43)
ADENOCARCINOMA, NOS	2 (9%)	
INFILTRATING DUCT CARCINOMA	1 (4%)	
FIBROADENOMA	4 (17%)	3 (7%)
#UTERUS	(23)	(33)
ENDOMETRIAL STROMAL POLYP	6 (26%)	1 (3%)
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
*ZYMBAL'S GLAND	(23)	(43)
SQUAMOUS CELL CARCINOMA		1 (2%)
MUSCULOSKELETAL SYSTEM		
NONE		

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

TABLE A2 (CONCLUDED)

	CONTROL(UNTR) 02-0084	DOSED 02-0078
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	25	50
NATURAL DEATH@	3	20
MORIBUND SACRIFICE	5	18
SCHEDULED SACRIFICE	5	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	12	7
ANIMAL MISSING		
@ INCLUDES AUTOLYZED ANIMALS		
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	17
TOTAL PRIMARY TUMORS	34	25
TOTAL ANIMALS WITH BENIGN TUMORS	18	14
TOTAL BENIGN TUMORS	23	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	6
TOTAL MALIGNANT TUMORS	9	8
TOTAL ANIMALS WITH SECONDARY TUMORS#		
TOTAL SECONDARY TUMORS		
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	2	
TOTAL UNCERTAIN TUMORS	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC		
TOTAL UNCERTAIN TUMORS		
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS		
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN		

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 2-AMINOANTHRAQUINONE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 2-AMINOANTHRAQUINONE

	HIGH DOSE CONTROL(UNTR) 05-0118	LOW DOSE CONTROL(UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
ANIMALS INITIALLY IN STUDY	50	50	49	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	46	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	46	47	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(49)	(46)	(48)	(50)
LEUCMYCSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(49)	(46)	(45)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	5 (11%)	4 (9%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	2 (4%)	4 (9%)	5 (10%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(46)	(48)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	1 (2%)		
#SPLEEN	(49)	(46)	(46)	(49)
HEMANGIOSARCOMA	1 (2%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			1 (2%)
#LYMPH NODE	(42)	(34)	(36)	(42)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#PEYERS PATCH	(49)	(46)	(47)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
CIRCULATORY SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(37)	(47)	(50)
CARCINOSARCOMA			1 (2%)	
#LIVER	(48)	(46)	(47)	(49)
HEPATOCELLULAR ADENOMA	2 (4%)			
HEPATOCELLULAR CARCINOMA	6 (13%)	12 (26%)	20 (43%)	36 (73%)
HEMANGIOSARCOMA, UNC PRIM OR MET	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(49)	(46)	(47)	(50)
TUBULAR-CELL ADENOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(39)	(42)	(42)
ADENOMA, NOS		1 (3%)	1 (2%)	
#ADRENAL	(44)	(44)	(46)	(38)
PHEOCHROMOCYTOMA	1 (2%)			1 (3%)
#THYROID	(45)	(44)	(44)	(46)
ADENOCARCINOMA, NOS		2 (5%)		
REPRODUCTIVE SYSTEM				
#TESTIS	(48)	(46)	(46)	(49)
INTERSTITIAL-CELL TUMOR				2 (4%)
SEMINOMA/DYSGERMINOMA		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(49)	(46)	(48)	(50)
ADENOCARCINOMA, NOS			1 (2%)	

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

TABLE B1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
PAPILLARY ADENOMA				1 (2%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@		1	3	1
MORIBUND SACRIFICE			1	1
SCHEDULED SACRIFICE	10	5		5
ACCIDENTALLY KILLED		3		
TERMINAL SACRIFICE	39	41	46	43
ANIMAL MISSING	1			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	19	28	42
TOTAL PRIMARY TUMORS	26	26	32	54
TOTAL ANIMALS WITH BENIGN TUMORS	8	6	6	10
TOTAL BENIGN TUMORS	8	7	6	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	16	22	38
TOTAL MALIGNANT TUMORS	17	19	26	44
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1	
TOTAL SECONDARY TUMORS	1	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC	1			
TOTAL UNCERTAIN TUMORS	1			

* 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 2 AMINOANTHRAQUINONE

	HIGH DOSE CONTROL(UNTR) 06-0118	LOW DOSE CONTROL(UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	47	48	49
ANIMAIS EXAMINED HISTOPATHOLOGICALLY **	50	47	48	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(47)	(48)	(49)
FIBROSARCOMA			2 (4%)	
RESPIRATORY SYSTEM				
#IUNG	(50)	(46)	(48)	(48)
CARCINOMA, NOS, METASTATIC		1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(47)	(48)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	1 (2%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	4 (8%)	8 (16%)
#SPLEEN	(49)	(45)	(48)	(46)
HEMANGIOSARCOMA		1 (2%)		
#LYMPH NODE	(44)	(27)	(39)	(36)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (3%)
#LIVER	(50)	(46)	(47)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#PEYERS PATCH	(48)	(45)	(48)	(39)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	1 (3%)
CIRCULATORY SYSTEM				
NONE				

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
DIGESTIVE SYSTEM				
#LIVER	(50)	(46)	(47)	(47)
CARCINOMA, NOS, METASTATIC		1 (2%)		
HEPATOCELLULAR CARCINOMA	1 (2%)	4 (9%)	5 (11%)	12 (26%)
#STOMACH	(49)	(45)	(48)	(46)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(37)	(42)	(36)
ADENOMA, NOS	1 (2%)	3 (8%)	3 (7%)	3 (8%)
CHROMOPHOBE ADENOMA	2 (5%)	1 (3%)	1 (2%)	
#THYROID	(44)	(44)	(42)	(42)
FOLLICULAR-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(47)	(48)	(49)
FIBROADENOMA		1 (2%)		
#UTERUS	(47)	(43)	(48)	(46)
ADENOMA, NOS			1 (2%)	
ADENOCARCINOMA, NOS				1 (2%)
LEIOMYOSARCOMA				1 (2%)
ENDOMETRIAL STROMAL POLYP		1 (2%)		
#UTERUS/ENDOMETRIUM	(47)	(43)	(48)	(46)
CARCINOMA, NOS		1 (2%)		
#OVARY/OVIDUCT	(47)	(43)	(48)	(46)
PAPILLARY ADENOMA	1 (2%)	1 (2%)		
INTRADUCTAL PAPILLOMA		1 (2%)		
NERVOUS SYSTEM				
NONE				

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(47)	(48)	(49)
PAPILLARY ADENOMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(47)	(48)	(49)
HEMANGIOSARCOMA		1 (2%)		
ALL OTHER SYSTEMS				
SITE UNKNOWN				
SARCOMA, NOS			1	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	2	5	2	7
MORIBUND SACRIFICE		1	4	
SCHEDULED SACRIFICE	10	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	38	39	44	38
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	17	16	29
TOTAL PRIMARY TUMORS	11	21	22	33
TOTAL ANIMALS WITH BENIGN TUMORS	7	7	7	6
TOTAL BENIGN TUMORS	7	8	8	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	11	12	25
TOTAL MALIGNANT TUMORS	4	13	14	27
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		
TOTAL SECONDARY TUMORS		2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 2-AMINOANTHRAQUINONE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 2-AMINOANTHRAQUINONE

	CONTROL (UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	46	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	46	49	46
INTEGUMENTARY SYSTEM			
*SKIN	(46)	(49)	(47)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	
FIBROSIS		1 (2%)	
*SUBCUT TISSUE	(46)	(49)	(47)
FIBROSIS		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(45)	(49)	(45)
INFLAMMATION, NOS	9 (20%)	7 (14%)	2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			21 (47%)
INFLAMMATION, CHRONIC	10 (22%)	8 (16%)	1 (2%)
#LUNG/BRONCHUS	(46)	(49)	(46)
BRONCHIECTASIS			2 (4%)
INFLAMMATION, NOS		2 (4%)	
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, CHRONIC	8 (17%)	6 (12%)	1 (2%)
#BRONCHIAL MUCOUS GLA	(46)	(49)	(46)
ABSCESS, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#LUNG/BRONCHICLE	(46)	(49)	(46)
INFLAMMATION, NOS	1 (2%)		1 (2%)
INFLAMMATION, FOCAL	1 (2%)		
#LUNG	(46)	(49)	(46)
MINERALIZATION		2 (4%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
ATELECTASIS	1 (2%)	1 (2%)	
CONGESTION, NOS	1 (2%)	1 (2%)	
EDEMA, NOS	1 (2%)		
INFLAMMATION, NOS	1 (2%)	1 (2%)	
INFLAMMATION, FOCAL	3 (7%)	7 (14%)	
INFLAMMATION, INTERSTITIAL	1 (2%)	5 (10%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
PNEUMONIA, CHRONIC MURINE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
PERIVASCULITIS	5 (11%)	4 (8%)	1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#LUNG/ALVEOLI	(46)	(49)	(46)
INFLAMMATION, NOS		2 (4%)	
INFLAMMATION, FOCAL		1 (2%)	
FIBROSIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(46)	(48)	(46)
THROMBOSIS, NOS	1 (2%)		
FIBROSIS	1 (2%)		
INFARCT, HEALED	1 (2%)		
RETICULOCYTOSIS	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HYPERPLASIA, ERYTHROID	12 (26%)	10 (21%)	1 (2%)
HYPERPLASIA, RETICULUM CELL	8 (17%)		
HEMATOPOIESIS		3 (6%)	
ERYTHROPOIESIS		8 (17%)	1 (2%)
MYELOPOIESIS		6 (13%)	1 (2%)
#LYMPH NODE	(38)	(43)	(40)
INFLAMMATION, NOS	1 (3%)		
HYPERPLASIA, NOS	1 (3%)		1 (3%)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, RETICULUM CELL	3 (8%)		
#SUBMANDIBULAR L.NODE	(38)	(43)	(40)
HEMORRHAGE		1 (2%)	
#MEDIASTINAL L.NODE	(38)	(43)	(40)
PLASMACYTOSIS	1 (3%)		
#RENAL LYMPH NODE	(38)	(43)	(40)
CONGESTION, NOS		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
CIRCULATORY SYSTEM			
*LYMPHATIC VESSELS	(46)	(49)	(47)
INFLAMMATION, NOS	1 (2%)		
#HEART	(46)	(49)	(46)
FIBROSIS, FOCAL			2 (4%)
FIBROSIS, DIFFUSE			1 (2%)
PERIARTERITIS			1 (2%)
#MYOCARDIUM	(46)	(49)	(46)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL	22 (48%)	33 (67%)	4 (9%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	3 (7%)	3 (6%)	
FIBROSIS	7 (15%)	18 (37%)	2 (4%)
FIBROSIS, FOCAL			4 (9%)
*AORTA	(46)	(49)	(47)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
PERIARTERITIS		1 (2%)	
*CORONARY ARTERY	(46)	(49)	(47)
HEMORRHAGE			1 (2%)
*PULMONARY ARTERY	(46)	(49)	(47)
HYPERTROPHY, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(38)	(44)	(46)
HEMORRHAGE		1 (2%)	
#PAROTID GLAND	(38)	(44)	(46)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#LIVER	(46)	(49)	(46)
FIBROSIS		1 (2%)	
DEGENERATION, NOS			5 (11%)
NECROSIS, FOCAL	3 (7%)	6 (12%)	1 (2%)
NECROSIS, COAGULATIVE	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)	31 (63%)	26 (57%)
HYPERPLASIA, NODULAR		3 (6%)	6 (13%)

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
HYPERPLASIA, FOCAL	23 (50%)	25 (51%)	27 (59%)
HYPERPLASIA, DIFFUSE		1 (2%)	
ANGIECTASIS			1 (2%)
#LIVER/PERIPORTAL	(46)	(49)	(46)
FIBROSIS	1 (2%)		
*BILE DUCT	(46)	(49)	(47)
INFLAMMATION, NOS	6 (13%)	2 (4%)	
HYPERPLASIA, NOS	32 (70%)	13 (27%)	6 (13%)
HYPERPLASIA, FOCAL	1 (2%)		7 (15%)
#PANCREAS	(42)	(47)	(45)
INFLAMMATION, NOS	10 (24%)	20 (43%)	2 (4%)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			7 (16%)
HYPERPLASIA, INTRADUCTAL	1 (2%)	1 (2%)	
#PANCREATIC DUCT	(42)	(47)	(45)
HYPERPLASIA, NOS		2 (4%)	
#PANCREATIC ACINUS	(42)	(47)	(45)
ATROPHY, NOS	4 (10%)	1 (2%)	2 (4%)
#STOMACH	(45)	(47)	(46)
EPIDERMAL INCLUSION CYST	1 (2%)		
ULCER, NOS	2 (4%)		
INFLAMMATION, FOCAL		2 (4%)	1 (2%)
HYPERPLASIA, NOS	6 (13%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
HYPERPLASIA, FOCAL		3 (6%)	1 (2%)
HYPERKERATOSIS	1 (2%)		
ACANTHOSIS	1 (2%)		
#PEYERS PATCH	(43)	(47)	(45)
INFLAMMATION PROLIFERATIVE		1 (2%)	
HYPERPLASIA, NOS	7 (16%)	4 (9%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#COLON	(43)	(46)	(44)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
NEMATODIASIS	3 (7%)	4 (9%)	7 (16%)
PARASITISM		2 (4%)	

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
URINARY SYSTEM			
#KIDNEY	(46)	(49)	(46)
CONGESTION, NOS		1 (2%)	
GLOMERULONEPHRITIS, NOS	33 (72%)	38 (78%)	37 (80%)
GLOMERULONEPHRITIS, FOCAL			3 (7%)
INFLAMMATION, INTERSTITIAL	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
GRANULOMA, FOREIGN BODY		1 (2%)	
FIBROSIS			1 (2%)
NEPHROSIS, NOS		7 (14%)	1 (2%)
#URINARY BLADDER	(42)	(47)	(46)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL	3 (7%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(46)	(43)
HYPERPLASIA, NOS	3 (7%)		
HYPERPLASIA, FOCAL			6 (14%)
HYPERPLASIA, CHROMOPHOBE-CELL	2 (5%)		
#ADRENAL	(43)	(48)	(45)
METAMORPHOSIS FATTY		3 (6%)	2 (4%)
HYPERPLASIA, NODULAR			1 (2%)
#ADRENAL CORTEX	(43)	(48)	(45)
NODULE		2 (4%)	
NECROSIS, FOCAL		1 (2%)	
HYPERTROPHY, FOCAL	1 (2%)		
HYPERPLASIA, NODULAR		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA	(43)	(48)	(45)
NECROSIS, NOS	1 (2%)		
CALCIFICATION, NOS	1 (2%)		
HYPERPLASIA, NODULAR	1 (2%)		
HYPERPLASIA, NOS	6 (14%)	3 (6%)	
HYPERPLASIA, FOCAL			3 (7%)
#THYROID	(45)	(46)	(40)
INFLAMMATION, FOCAL		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
HYPERPLASIA, ADENOMATOUS	1 (2%)		1 (3%)
HYPERPLASIA, C-CELL	1 (2%)	2 (4%)	
#PARATHYROID	(32)	(28)	(32)
HYPERPLASIA, NOS		1 (4%)	
#PANCREATIC ISLETS	(42)	(47)	(45)
HYPERPLASIA, NOS	2 (5%)	3 (6%)	
HYPERPLASIA, FOCAL			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(46)	(49)	(47)
GALACTOCELE			2 (4%)
HYPERPLASIA, NOS	5 (11%)	3 (6%)	1 (2%)
*PREPUTIAL GLAND	(46)	(49)	(47)
ABSCESS, NOS	1 (2%)		1 (2%)
HYPERPLASIA, NOS	1 (2%)		
#PROSTATE	(45)	(47)	(44)
INFLAMMATION, NOS	21 (47%)	21 (45%)	5 (11%)
INFLAMMATION, FOCAL	3 (7%)	1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, ACUTE			3 (7%)
INFLAMMATION, ACUTE FOCAL			3 (7%)
INFLAMMATION, ACUTE/CHRONIC			4 (9%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	5 (11%)	3 (6%)	
HYPERPLASIA, PAPILLARY	2 (4%)		
METAPLASIA, SQUAMOUS	5 (11%)	4 (9%)	2 (5%)
#TESTIS	(45)	(47)	(46)
MINERALIZATION		18 (38%)	2 (4%)
DEGENERATION, NOS			32 (70%)
ATROPHY, NOS	2 (4%)	29 (62%)	3 (7%)
ASPERMATOGENESIS	1 (2%)		
HYPERPLASIA, INTERSTITIAL CELL	19 (42%)	30 (64%)	10 (22%)
#TESTIS/TUBULE	(45)	(47)	(46)
DEGENERATION, NOS	6 (13%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
#CEREBRUM	(44)	(48)	(46)
ABSCESS, NOS			1 (2%)

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-0037	LOW DOSE 01-0031	HIGH DOSE 01-0032
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*CARTILAGE,NOS	(46)	(49)	(47)
CYST, NOS	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF	1	1	
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY	4	1	3

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 2-AMINOANTHRAQUINONE

	CONTROL(UNTR) 02-0084	DOSED 02-0078
ANIMALS INITIALLY IN STUDY	25	50
ANIMALS NECROPSIED	23	43
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	23	43
INTEGUMENTARY SYSTEM		
NONE		
RESPIRATORY SYSTEM		
*LARYNX	(23)	(43)
INFLAMMATION ACUTE AND CHRONIC	1 (4%)	
INFLAMMATION, CHRONIC	3 (13%)	
#TRACHEA	(5)	(36)
INFLAMMATION, NOS		1 (3%)
#LUNG/BRONCHUS	(23)	(42)
INFLAMMATION, NOS		1 (2%)
#LUNG	(23)	(42)
MINERALIZATION		1 (2%)
INFLAMMATION, INTERSTITIAL	3 (13%)	12 (29%)
INFLAMMATION, NECROTIZING		1 (2%)
PNEUMONIA, CHRONIC MURINE	8 (35%)	
GRANULOMA, FOREIGN BODY	1 (4%)	
CALCIFICATION, FOCAL	1 (4%)	
HYPERPLASIA, EPITHELIAL	1 (4%)	4 (10%)
#LUNG/ALVEOLI	(23)	(42)
MINERALIZATION		1 (2%)
FIBROSIS, FOCAL		1 (2%)
HEMATOPOIETIC SYSTEM		
#BONE MARROW	(22)	(35)
HYPERPLASIA, HEMATOPOIETIC	1 (5%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0084	DOSED 02-0078
#SPLEEN	(23)	(39)
HEMATOMA, NOS	1 (4%)	
HEMOSIDEROSIS	2 (9%)	18 (46%)
HYPERPLASIA, HEMATOPOIETIC	3 (13%)	7 (18%)
HYPERPLASIA, ERYTHROID	4 (17%)	7 (18%)
HEMATOPOIESIS	3 (13%)	
#LYMPH NODE	(21)	(29)
INFLAMMATION, NOS		1 (3%)
RETICULOCYTOSIS		2 (7%)
LYMPHOCYTOSIS		2 (7%)
PLASMACYTOSIS		1 (3%)
CIRCULATORY SYSTEM		
#MYOCARDIUM	(23)	(41)
MINERALIZATION		1 (2%)
INFLAMMATION, INTERSTITIAL	1 (4%)	9 (22%)
FIBROSIS		9 (22%)
DEGENERATION, NOS	4 (17%)	
*AORTA	(23)	(43)
MINERALIZATION		1 (2%)
DIGESTIVE SYSTEM		
#LIVER	(23)	(42)
CONGESTION, CHRONIC PASSIVE	1 (4%)	
FIBROSIS, FOCAL		1 (2%)
CHOLANGIOFIBROSIS	1 (4%)	
FIBROSIS SEPTAL LIVER		1 (2%)
METAMORPHOSIS FATTY	2 (9%)	1 (2%)
BASOPHILIC CYTO CHANGE	4 (17%)	
HYPERPLASIA, FOCAL	3 (13%)	8 (19%)
*BILE DUCT	(23)	(43)
INFLAMMATION, NOS		1 (2%)
HYPERPLASIA, NOS	2 (9%)	9 (21%)
#PANCREAS	(22)	(34)
INFLAMMATION, NOS		2 (6%)
#STOMACH	(23)	(34)
MINERALIZATION		5 (15%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0084	DOSED 02-0078
INFLAMMATION, NOS		1 (3%)
NECROSIS, NOS		2 (6%)
HYPERPLASIA, BASAL CELL		4 (12%)
HYPERKERATOSIS		1 (3%)
ACANTHOSIS		3 (9%)
#GASTRIC MUCOSA	(23)	(34)
MINERALIZATION		6 (18%)
#GASTRIC MUSCULARIS	(23)	(34)
MINERALIZATION		4 (12%)
#PEYERS PATCH	(23)	(33)
HYPERPLASIA, NOS	4 (17%)	2 (6%)
#COLON	(22)	(30)
PARASITISM	2 (9%)	
*RECTUM	(23)	(43)
HYPERKERATOSIS		1 (2%)
URINARY SYSTEM		
#KIDNEY	(23)	(43)
MINERALIZATION		3 (7%)
GLOMERULONEPHRITIS, NOS	4 (17%)	24 (56%)
PYELONEPHRITIS, ACUTE	1 (4%)	
PYELONEPHRITIS, CHRONIC	1 (4%)	
GRANULOMA, FOREIGN BODY		16 (37%)
FIBROSIS, DIFFUSE		19 (44%)
NEPHROSIS, NOS	10 (43%)	
GLOMERULOSCLEROSIS, NOS		2 (5%)
CALCIFICATION, FOCAL	1 (4%)	
PIGMENTATION, NOS		4 (9%)
METAPLASIA, NOS		4 (9%)
REGENERATION, NOS		1 (2%)
#KIDNEY/TUBULE	(23)	(43)
MINERALIZATION		1 (2%)
CYST, NOS		1 (2%)
INFLAMMATION, NOS		1 (2%)
NEPHROSIS, NOS		2 (5%)
NECROSIS, NOS	1 (4%)	
NECROSIS, FOCAL		1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0084	DOSED 02-0078
#URINARY BLADDER	(22)	(34)
HYPERPLASIA, EPITHELIAL		1 (3%)
ENDOCRINE SYSTEM		
#PITUITARY	(21)	(30)
HEMORRHAGIC CYST	1 (5%)	
HYPERPLASIA, FOCAL	1 (5%)	
#ADRENAL MEDULLA	(23)	(39)
HYPERPLASIA, NODULAR		1 (3%)
HYPERPLASIA, FOCAL		1 (3%)
#THYROID	(21)	(29)
HYPERPLASIA, C-CELL	3 (14%)	1 (3%)
#PARATHYROID	(9)	(14)
HYPERPLASIA, NOS		2 (14%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(23)	(43)
GALACTOCELE	1 (4%)	1 (2%)
HYPERPLASIA, NOS	1 (4%)	9 (21%)
LACTATION	9 (39%)	
*VAGINA	(23)	(43)
INFLAMMATION, NOS		1 (2%)
#UTERUS	(23)	(33)
PYOMETRA	3 (13%)	
HYPERPLASIA, ADENOMATOUS		1 (3%)
#UTERUS/ENDOMETRIUM	(23)	(33)
INFLAMMATION, NOS	1 (4%)	4 (12%)
INFLAMMATION, SUPPURATIVE		1 (3%)
INFLAMMATION, NECROTIZING		1 (3%)
INFLAMMATION, CHRONIC	1 (4%)	
HYPERPLASIA, NOS	1 (4%)	1 (3%)
HYPERPLASIA, CYSTIC	1 (4%)	
#OVARY/OVIDUCT	(23)	(33)
INFLAMMATION, NOS		2 (6%)

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 02-0084	DOSED 02-0078
INFLAMMATION, SUPPURATIVE		1 (3%)
INFLAMMATION, ACUTE	1 (4%)	
ABSCESS, NOS	1 (4%)	
#OVARY	(22)	(34)
MINERALIZATION		1 (3%)
CYST, NOS	3 (14%)	1 (3%)
INFLAMMATION, NOS		1 (3%)
NERVOUS SYSTEM		
#BRAIN	(23)	(36)
HYDROCEPHALUS, NOS	1 (4%)	
HEMORRHAGE	1 (4%)	
CALCIFICATION, FOCAL	1 (4%)	
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
*PLEURA	(23)	(43)
NECROSIS, NOS		1 (2%)
ALL OTHER SYSTEMS		
NONE		
SPECIAL MORPHOLOGY SUMMARY		
AUTO/NECROPSY/HISTO PERF		1
AUTOLYSIS/NO NECROPSY	2	7

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 2-AMINOANTHRAQUINONE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 2-AMINOANTHRAQUINONE

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
ANIMALS INITIALLY IN STUDY	50	50	49	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	46	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	46	47	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(46)	(48)	(50)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	3 (6%)		1 (2%)	
INFLAMMATION, NECROTIZING	1 (2%)			
GRANULOMA, PYOGENIC		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(46)	(45)	(49)
INFLAMMATION, NOS				1 (2%)
#LUNG/BRONCHUS	(49)	(46)	(45)	(50)
INFLAMMATION, FOCAL	1 (2%)	1 (2%)	2 (4%)	
#LUNG/BRONCHIOLE	(49)	(46)	(45)	(50)
INFLAMMATION, FOCAL	1 (2%)			
#LUNG	(49)	(46)	(45)	(50)
EMPHYSEMA, NOS		1 (2%)		
HEMORRHAGE		1 (2%)	2 (4%)	
INFLAMMATION, FOCAL			1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL	10 (20%)	7 (15%)	12 (27%)	7 (14%)
HYPERPLASIA, EPITHELIAL			1 (2%)	2 (4%)
#LUNG/ALVEOLI	(49)	(46)	(45)	(50)
INFLAMMATION, NOS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#SPLEEN	(49)	(46)	(46)	(49)
INFLAMMATION, NOS			1 (2%)	

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
FIBROSIS				1 (2%)
HYPERPLASIA, NOS	6 (12%)		21 (46%)	10 (20%)
RETICULOCYTOSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC	5 (10%)		6 (13%)	6 (12%)
HYPERPLASIA, ERYTHROID		1 (2%)	3 (7%)	2 (4%)
HYPERPLASIA, RETICULUM CELL				1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)		2 (4%)	2 (4%)
HEMATOPOIESIS		1 (2%)		
#LYMPH NODE	(42)	(34)	(36)	(42)
HEMORRHAGE		1 (3%)	1 (3%)	1 (2%)
INFLAMMATION, NOS	10 (24%)		19 (53%)	14 (33%)
HYPERPLASIA, NOS	1 (2%)	1 (3%)		
RETICULOCYTOSIS	2 (5%)		5 (14%)	4 (10%)
LYMPHOCYTOSIS			5 (14%)	4 (10%)
PLASMACYTOSIS				1 (2%)
MEGAKARYOCYTOSIS			1 (3%)	
HYPERPLASIA, HEMATOPOIETIC				1 (2%)
HYPERPLASIA, RETICULUM CELL			2 (6%)	
HYPERPLASIA, LYMPHOID	3 (7%)		5 (14%)	3 (7%)
#MANDIBULAR L. NODE	(42)	(34)	(36)	(42)
HYPERPLASIA, RETICULUM CELL		1 (3%)		
#MESENTERIC L. NODE	(42)	(34)	(36)	(42)
THROMBOSIS, NOS		1 (3%)		
HEMORRHAGE		1 (3%)		
CIRCULATORY SYSTEM				
*CARDIOVASCULAR SYSTE	(49)	(46)	(48)	(50)
PERIVASCULITIS				1 (2%)
#HEART	(49)	(46)	(46)	(49)
MINERALIZATION	1 (2%)			
#MYOCARDIUM	(49)	(46)	(46)	(49)
INFLAMMATION, NOS			1 (2%)	1 (2%)
FIBROSIS				1 (2%)
#ENDOCARDIUM	(49)	(46)	(46)	(49)
INFLAMMATION PROLIFERATIVE		1 (2%)		
*AORTA	(49)	(46)	(48)	(50)
INFLAMMATION, NOS			1 (2%)	1 (2%)

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(37)	(47)	(50)
PERIVASCULAR CUFFING		5 (14%)		
#LIVER	(48)	(46)	(47)	(49)
MINERALIZATION			1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)		
FIBROSIS, FOCAL			1 (2%)	
NECROSIS, FOCAL	9 (19%)	2 (4%)	16 (34%)	5 (10%)
NECROSIS, COAGULATIVE				1 (2%)
NECROSIS, HEMORRHAGIC		1 (2%)		
METAMORPHOSIS FATTY		8 (17%)	3 (6%)	
CYTOPLASMIC VACUOLIZATION			2 (4%)	
HYPERPLASTIC NODULE	1 (2%)		10 (21%)	6 (12%)
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)		
*GALLBLADDER	(49)	(46)	(48)	(50)
INFLAMMATION, NOS			1 (2%)	
*BILE DUCT	(49)	(46)	(48)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
HYPERPLASIA, NOS			1 (2%)	
#PANCREAS	(47)	(44)	(45)	(45)
INFLAMMATION, NOS	1 (2%)		3 (7%)	
INFLAMMATION, FOCAL		2 (5%)		
INFLAMMATION, INTERSTITIAL		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
DEGENERATION, CYSTIC			1 (2%)	
HYPERPLASIA, FOCAL		2 (5%)		
#PANCREATIC DUCT	(47)	(44)	(45)	(45)
HYPERPLASIA, NOS			1 (2%)	
#PANCREATIC ACINUS	(47)	(44)	(45)	(45)
NECROSIS, NOS			1 (2%)	
ATROPHY, FOCAL		1 (2%)		
#STOMACH	(48)	(45)	(46)	(47)
INFLAMMATION, NOS		2 (4%)	7 (15%)	2 (4%)
INFLAMMATION, FOCAL	2 (4%)		3 (7%)	5 (11%)
INFLAMMATION, NECROTIZING	1 (2%)			

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
INFLAMMATION, ACUTE		1 (2%)		
HYPERPLASIA, EPITHELIAL		2 (4%)		
HYPERPLASIA, FOCAL	1 (2%)		2 (4%)	
HYPERPLASIA, ADENOMATOUS		2 (4%)		
HYPERKERATOSIS	1 (2%)		1 (2%)	2 (4%)
ACANTHOSIS	1 (2%)		1 (2%)	5 (11%)
#GASTRIC MUCOSA	(48)	(45)	(46)	(47)
HYPERPLASIA, FOCAL			5 (11%)	
#PEYERS PATCH	(49)	(46)	(47)	(47)
HYPERPLASIA, NOS	7 (14%)		3 (6%)	9 (19%)
#COLON	(43)	(41)	(45)	(43)
NEMATODIASIS				4 (9%)
PARASITISM	3 (7%)			
URINARY SYSTEM				
#KIDNEY	(49)	(46)	(47)	(50)
GLOMERULONEPHRITIS, NOS	2 (4%)	2 (4%)		12 (24%)
GLOMERULONEPHRITIS, FOCAL		1 (2%)		
INFLAMMATION, INTERSTITIAL	16 (33%)	7 (15%)	31 (66%)	16 (32%)
HYPERPLASIA, TUBULAR CELL				1 (2%)
METAPLASIA, OSSEOUS		1 (2%)		
#KIDNEY/TUBULE	(49)	(46)	(47)	(50)
MINERALIZATION			1 (2%)	
#KIDNEY/PELVIS	(49)	(46)	(47)	(50)
INFLAMMATION, ACUTE/CHRONIC		3 (7%)		
#URINARY BLADDER	(48)	(46)	(47)	(48)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL	4 (8%)	2 (4%)	7 (15%)	7 (15%)
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(39)	(42)	(42)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL		1 (3%)		2 (5%)
#ADRENAL	(44)	(44)	(46)	(38)
NECROSIS, FOCAL		1 (2%)		

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
HYPERPLASIA, NOS	3 (7%)			
#ADRENAL/CAPSULE	(44)	(44)	(46)	(38)
NODULE				1 (3%)
HYPERPLASIA, NOS	3 (7%)		5 (11%)	1 (3%)
#ADRENAL CORTEX	(44)	(44)	(46)	(38)
NODULE			1 (2%)	
NECROSIS, FOCAL			1 (2%)	
HYPERPLASIA, NOS		2 (5%)		
HYPERPLASIA, FOCAL		14 (32%)		
#THYROID	(45)	(44)	(44)	(46)
HYPERPLASIA, FOCAL				1 (2%)
HYPERPLASIA, PAPILLARY			1 (2%)	1 (2%)
#PARATHYROID	(24)	(17)	(17)	(22)
CYST, NOS		1 (6%)		
#PANCREATIC ISLETS	(47)	(44)	(45)	(45)
HYPERPLASIA, NOS				2 (4%)
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(49)	(46)	(48)	(50)
ABSCESS, NOS	1 (2%)			
#PROSTATE	(49)	(46)	(46)	(43)
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, FOCAL			2 (4%)	1 (2%)
#TESTIS	(48)	(46)	(46)	(49)
ATROPHY, NOS				2 (4%)
ATROPHY, FOCAL			1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL			10 (22%)	8 (16%)
#TESTIS/TUBULE	(48)	(46)	(46)	(49)
DEGENERATION, NOS		3 (7%)		1 (2%)
*EPIDIDYMIS	(49)	(46)	(48)	(50)
INFLAMMATION, NOS	1 (2%)			
NERVOUS SYSTEM				
#BRAIN	(49)	(46)	(46)	(49)
PERIVASCULITIS				1 (2%)

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

TABLE D1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0032	HIGH DOSE 05-0112
NECROSIS, NOS				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(49)	(46)	(48)	(50)
NECROSIS, FAT		1 (2%)		
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, ACUTE	1			
OMENTUM				
NECROSIS, FAT	1			1
CALCIFICATION, NOS				1
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	2		
ANIMAL MISSING/NO NECROPSY	1			
ACCIDENTAL DEATH		3		
AUTO/NECROPSY/NO HISTO			1	
AUTOLYSIS/NO NECROPSY		1	2	

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 2-AMINOANTHRAQUINONE

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	47	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	48	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(47)	(48)	(49)
ABSCESS, NOS	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(50)	(46)	(48)	(48)
INFLAMMATION, FOCAL	1 (2%)			
#LUNG/BRONCHIOLE	(50)	(46)	(48)	(48)
HYPERPLASIA, NOS	1 (2%)			
#LUNG	(50)	(46)	(48)	(48)
INFLAMMATION, INTERSTITIAL	14 (28%)	2 (4%)	5 (10%)	7 (15%)
HYPERPLASIA, EPITHELIAL			1 (2%)	1 (2%)
#LUNG/ALVEOLI	(50)	(46)	(48)	(48)
EMPHYSEMA, NOS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(45)	(46)	(42)
HYPOPLASIA, NOS		1 (2%)		
MYELOFIBROSIS		1 (2%)		2 (5%)
MEGAKARYOCYTOSIS				1 (2%)
#SPLEEN	(49)	(45)	(48)	(46)
HYPERPLASIA, NOS	9 (18%)		18 (38%)	9 (20%)
LYMPHOCYTOSIS		2 (4%)		
HYPERPLASIA, HEMATOPOIETIC	6 (12%)		11 (23%)	7 (15%)
HYPERPLASIA, ERYTHROID				7 (15%)
HYPERPLASIA, LYMPHOID	2 (4%)	3 (7%)		1 (2%)

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
HEMATOPOIESIS		2 (4%)		
#HEMOLYMPH NODES	(49)	(45)	(48)	(46)
INFLAMMATION, NOS	2 (4%)			
HYPERPLASIA, NOS	1 (2%)			
#LYMPH NODE	(44)	(27)	(39)	(36)
HEMORRHAGE			1 (3%)	
INFLAMMATION, NOS	9 (20%)		18 (46%)	7 (19%)
NECROSIS, NOS			1 (3%)	
HYPERPLASIA, NOS	3 (7%)			
RETICULOCYTOSIS	1 (2%)			
PLASMACYTOSIS				2 (6%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		1 (3%)	
HYPERPLASIA, LYMPHOID	4 (9%)			
#PANCREATIC L.NODE	(44)	(27)	(39)	(36)
HYPERPLASIA, RETICULUM CELL		1 (4%)		
CIRCULATORY SYSTEM				
*CARDIOVASCULAR SYSTEM	(50)	(47)	(48)	(49)
PERIVASCULITIS				1 (2%)
#HEART/ATRIUM	(50)	(46)	(47)	(49)
CALCIFICATION, FOCAL		1 (2%)		
#MYOCARDIUM	(50)	(46)	(47)	(49)
INFLAMMATION, FOCAL	1 (2%)			
FIBROSIS, FOCAL			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(29)	(48)	(44)
PERIVASCULAR CUFFING	3 (6%)	1 (3%)		
#LIVER	(50)	(46)	(47)	(47)
NECROSIS, FOCAL	7 (14%)	1 (2%)	11 (23%)	5 (11%)
NECROSIS, COAGULATIVE		1 (2%)		
METAMORPHOSIS FATTY			2 (4%)	
HYPERPLASIA, NODULAR		2 (4%)		
HYPERPLASTIC NODULE			1 (2%)	5 (11%)
HYPERPLASIA, FOCAL			1 (2%)	

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
ANGIECTASIS		1 (2%)		
HEMATOPOIESIS				2 (4%)
#LIVER/PERIPORTAL	(50)	(46)	(47)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)		
*GALLBLADDER	(50)	(47)	(48)	(49)
INFLAMMATION, NOS			1 (2%)	
#PANCREAS	(48)	(39)	(47)	(40)
INFLAMMATION, NOS	2 (4%)		1 (2%)	1 (3%)
#PANCREATIC DUCT	(48)	(39)	(47)	(40)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (3%)		
#STOMACH	(49)	(45)	(48)	(46)
INFLAMMATION, NOS	1 (2%)	3 (7%)	7 (15%)	2 (4%)
INFLAMMATION, FOCAL	1 (2%)		5 (10%)	
HYPERKERATOSIS			5 (10%)	
ACANTHOSIS	2 (4%)		5 (10%)	2 (4%)
#GASTRIC MUCOSA	(49)	(45)	(48)	(46)
HYPERPLASIA, FOCAL			4 (8%)	
#PEYERS PATCH	(48)	(45)	(48)	(39)
HYPERPLASIA, NOS	7 (15%)	1 (2%)	2 (4%)	4 (10%)
#DUODENUM	(48)	(45)	(48)	(39)
ECTOPIA		1 (2%)		
#COLON	(38)	(43)	(46)	(33)
PARASITISM				2 (6%)
URINARY SYSTEM				
#KIDNEY	(50)	(45)	(47)	(46)
GLOMERULONEPHRITIS, NOS	4 (8%)	2 (4%)		7 (15%)
INFLAMMATION, NOS				1 (2%)
GLOMERULONEPHRITIS, FOCAL	1 (2%)	1 (2%)		
INFLAMMATION, INTERSTITIAL	12 (24%)	9 (20%)	9 (19%)	8 (17%)
#KIDNEY/TUBULE	(50)	(45)	(47)	(46)
MINERALIZATION	1 (2%)			
DEGENERATION, CYSTIC				1 (2%)

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
#KIDNEY/PELVIS	(50)	(45)	(47)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
#URINARY BLADDER	(48)	(42)	(47)	(44)
INFLAMMATION, NOS			2 (4%)	
HYPERPLASIA, EPITHELIAL	1 (2%)		7 (15%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(37)	(42)	(36)
HYPERPLASIA, FOCAL				2 (6%)
#ADRENAL/CAPSULE	(48)	(44)	(46)	(44)
HYPERPLASIA, NOS	5 (10%)		8 (17%)	3 (7%)
#ADRENAL CORTEX	(48)	(44)	(46)	(44)
NODULE	1 (2%)	1 (2%)		
HYPERPLASIA, NOS	1 (2%)	2 (5%)		
#THYROID	(44)	(44)	(42)	(42)
INFLAMMATION, FOCAL	1 (2%)			
NECROSIS, FOCAL				1 (2%)
HYPERPLASIA, PAPILLARY	2 (5%)			2 (5%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(47)	(48)	(49)
HYPERPLASIA, NOS	1 (2%)			3 (6%)
#UTERUS	(47)	(43)	(48)	(46)
HYDROMETRA	13 (28%)	4 (9%)	8 (17%)	13 (28%)
ABSCESS, NOS				1 (2%)
HYPERPLASIA, ADENOMATOUS			2 (4%)	
METAPLASIA, SQUAMOUS		1 (2%)		
#UTERUS/ENDOMETRIUM	(47)	(43)	(48)	(46)
INFLAMMATION, NOS	8 (17%)	1 (2%)	4 (8%)	4 (9%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
HYPERPLASIA, NOS	8 (17%)		8 (17%)	9 (20%)
HYPERPLASIA, CYSTIC	6 (13%)	33 (77%)	28 (58%)	6 (13%)
METAPLASIA, SQUAMOUS			1 (2%)	

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
#OVARY/OVIDUCT	(47)	(43)	(48)	(46)
INFLAMMATION, NOS	4 (9%)			1 (2%)
ABSCESS, NOS	1 (2%)			
DEGENERATION, NOS			1 (2%)	
#OVARY	(48)	(44)	(48)	(45)
CYST, NOS	10 (21%)	5 (11%)	7 (15%)	2 (4%)
INFLAMMATION, NOS	4 (8%)			2 (4%)
INFLAMMATION, NECROTIZING				1 (2%)
ABSCESS, NOS				1 (2%)
PERIARTERITIS	1 (2%)			
DEGENERATION, CYSTIC	3 (6%)			4 (9%)
HYPERPLASIA, NOS			1 (2%)	
#OVARY/FOLLICLE	(48)	(44)	(48)	(45)
HEMORRHAGE			2 (4%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PLEURA	(50)	(47)	(48)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)		
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT				1

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

TABLE D2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0032	HIGH DOSE 06-0112
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	3	1		1
AUTO/NECROPSY/HISTO PERF	1	1		2
AUTOLYSIS/NO NECROPSY		3	2	1

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

Review of the Bioassay of 2-Aminoanthraquinone* 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 2-Aminoanthraquinone for carcinogenicity.

The reviewer said that the compound induced hepatocellular carcinomas in male rats and in both sexes of mice but that the treated female rats died of nephrotoxicity. After a brief description of the experimental design, a discussion ensued on the nature of the "foreign body granulomatous nephritis" found in the treated female rats. In view of the findings, the reviewer said that the compound must be considered to pose a potential carcinogenic risk to humans. He added that nephrotoxicity also may pose a human hazard. The reviewer moved that the report on the bioassay of 2-Aminoanthraquinone 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

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

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