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BIOASSAY OF 4-NITROANTHRANILIC ACID FOR POSSIBLE CARCINOGENICITY

CAS No. 619-17-0

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

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REPORT ON BIOASSAY OF 4-NITROANTHRANILIC ACID FOR POSSIBLE CARCINOGENICITY

Availability

4-Nitroanthranilic acid (CAS 619-17-0) has been tested for cancer-causing activity with rats and mice in the Bioassay Program, Division of Cancer Cause and Prevention, National Cancer Institute. A report is available to the public.

Summary: A bioassay of 4-nitroanthranilic acid for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. Applications of the chemical include use in the past as an intermediate in the manufacture of dyes. 4-Nitroanthranilic acid was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Under the conditions of this bioassay evidence was not provided for the carcinogenicity of 4-nitroanthranilic acid in Fischer 344 rats or B6C3F1 mice.

Single copies of the report are available from the Office of Cancer Communications, National Cancer Institute, Building 31, Room 10A21, National Institutes of Health, Bethesda, Maryland 20014.

Dated:
October 20, 1978

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Director
National Institutes of Health

(Catalogue of Federal Domestic Assistance Program Number 13.393, Cancer Cause and Prevention Research)

REPORT ON THE BIOASSAY OF 4-NITROANTHRANILIC ACID
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 4-nitroanthranilic acid 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 4-nitroanthranilic acid was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. R. W. Fleischman (3), Dr. D. W. Hayden (3), Dr. A. S. Krishna Murthy (3), Dr. A. Russfield (3), and Dr. Yoon (3) at the Mason Research Institute, the pathology narratives were written by Dr. A. Russfield (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), using

methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (8).

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), 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), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,9), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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

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

3. Mason Research Institute, 57 Union Street, Worcester, Massachusetts.

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

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

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

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

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

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

SUMMARY

A bioassay of 4-nitroanthranilic acid for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 4-Nitroanthranilic acid was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low time-weighted average concentrations used for the chronic study were, respectively, 1.5 and 0.46 percent for rats and 1.0 and 0.46 percent for mice. After a 78-week period of chemical administration, the rats were observed for an additional period of up to 32 weeks and the mice for an additional period of up to 17 weeks. For rats 50 animals of each sex were placed on test as low dose controls and 25 animals of each sex were placed on test as high dose controls. For mice 50 animals of each sex were placed on test as controls for each dosed group.

No statistically significant increases in tumor incidence were observed among rats or mice receiving diets containing 4-nitroanthranilic acid.

Under the conditions of this bioassay evidence was not provided for the carcinogenicity of 4-nitroanthranilic acid in Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

4-Nitroanthranilic acid (NCI No. C01945), a nitrobenzene derivative formerly used as a dye intermediate, was selected for bioassay by the National Cancer Institute along with other dye intermediates in an attempt to identify those chemicals which may be responsible for the increased incidence of bladder cancer observed among workers in the dye manufacturing industry (Wynder et al., 1963; Anthony and Thomas, 1970). Aromatic nitro and amino compounds are thought to contribute to the increased cancer risk in this industry (Wynder et al., 1963).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 2-amino-4-nitro-benzoic acid.*

4-Nitroanthranilic acid does not appear to be in current use commercially in the United States for any application and has not been produced in this country in commercial quantities (greater than 1000 pounds or $1000 in value annually) since 1968 (Urso, 1977).

Although exposure to 4-nitroanthranilic acid is presently restricted to those engaged in laboratory research, workers at dye manufacturing facilities may have experienced significant contact with the chemical in the past. Little is known concerning the toxicity of 4-nitroanthranilic acid in humans.

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*The CAS registry number is 619-17-0.

II. MATERIALS AND METHODS

A. Chemicals

4-Nitroanthranilic acid (Figure 1) was purchased from J. T. Baker Chemical Company, Phillipsburg, New Jersey. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The experimentally determined melting point (264° to 267°C) suggested a compound of high purity due to its narrow range and proximity to the value (264°C) reported in the literature (Rupe and Kerstend, 1926). Analysis by thin-layer chromatography utilized two solvent systems (chloroform: 1,4-dioxane:acetic acid and butanol:diethylamine:water). Each plate was visualized by ultraviolet light and by furfural. The presence of three impurities of lower motility than the major compound was indicated by these analyses. Elemental analysis was consistent with $C_7H_6N_2O_4$, the molecular formula for 4-nitroanthranilic acid. Titration of the carboxyl group with sodium hydroxide gave a result that was 98 percent of the theoretical. This cannot be construed as a purity minimum, since possible contaminating compounds might also contain a carboxyl group. High pressure liquid chromatography showed the presence of two peaks. Nuclear magnetic resonance and infrared analyses were consistent with the structure of the compound. The results suggested a compound of high purity with the presence of some minor impurities.

Throughout this report the term 4-nitroanthranilic acid is used to represent this material.

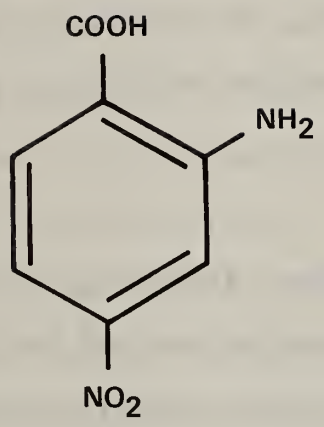

FIGURE 1
CHEMICAL STRUCTURE OF 4-NITROANTHRANILIC ACID

B. Dietary Preparation

The basal laboratory diet for both treated and control animals was Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 4-Nitroanthranilic acid was administered to the treated animals as a component of the diet. The chemical was ground into a powder and mixed with an aliquot of ground feed. Once visual homogeneity was attained, the mixture was placed into a 6 kg capacity Patterson-Kelley twin-shell stainless steel V-blender with the remainder of the meal. After 20 minutes of blending, the mixtures were placed in double plastic bags and stored in the dark at 4°C. The mixtures were used for only one week.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. High dose* treated and high dose control rats and low dose* treated, high dose treated, and high dose control mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Low dose treated and low dose control rats and low dose control mice were supplied by ARS/Sprague-Dawley, Madison, Wisconsin. All treated rat and mouse groups were received in separate shipments from their respective controls.

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*As defined on pages 9 and 12.

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

D. Animal Maintenance

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

Rats were housed five per cage by sex. During quarantine and for the first 13 months of study, low dose treated rats and their controls were housed in galvanized- or stainless-steel wire-mesh cages suspended above newspapers. High dose treated rats and their controls were housed in galvanized wire-mesh cages during quarantine and for the first 11 months of study. 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. Low dose treated rats and their controls were provided with Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products

Company, Norway, Maine) for 9 months after being placed in polycarbonate cages. Corncob bedding (SAN-I-CEL®, Paxton Processing Company, Paxton, Illinois) was used for these animals and for high dose treated rats and their controls for the next 12 months. For the remainder of the study, Bed-o-Cobs® (The Andersons Cob Division, Maumee, Ohio) was provided in rat cages. Stainless steel cage racks were cleaned once every 2 weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate cages. During quarantine and periods of chemical administration, cages were fitted with perforated stainless steel lids. During the observation period, stainless steel wire bar lids were used. Both types of lids were from Lab Products, Inc., Garfield, New Jersey. All mice were housed ten per cage for the first part of the study. High dose treated and control mice and low dose treated and control mice were reduced to five per cage after 13, 14, 19 and 19 months, respectively. Cages, lids, filters, and bedding were provided three times per week when cage populations were ten and twice per week when cage populations were five. Ab-sorb-dri® bedding was used for 2 months (high dose treated mice), 4 months (high dose control mice) or 9 months (low dose treated and control mice). Subsequently, SAN-I-CEL® was used for 12 months, then Bed-o-Cobs® was used for the remainder of the study. Reusable filter bonnets and pipe racks were sanitized every 2 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. Pelleted Wayne Lab-Blox® was supplied during the quarantine and final observation periods. Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) containing stainless steel baffles were used to distribute powdered feed to all mice and to low dose treated and control rats during the entire period of compound administration and to high dose treated and control rats for the first 13 months. High dose treated and control rats were fed from stainless steel gangstyle feed hoppers (Scientific Cages, Inc., Bryan, Texas) during the last 5 months of the study. Food hoppers were changed on the same schedule as were cages. Food was replenished daily in Alpine® feed cups. During the final observation period, mice were fed pellets from a wire bar hopper incorporated into the cage lid, and rats were fed pellets on the cage floor.

Low dose treated rats and their controls were housed in a room with other rats receiving diets containing* acetylaminofluorene (53-93-3); dulcin (150-69-6) and L-arginine glutamate (4320-30-3); sodium nitrite (7632-00-0); L-arginine glutamate (4320-30-3); N-butylurea

*CAS registry numbers are given in parentheses.

(592-31-4); N,N-dimethyl-p-nitrosoaniline (138-89-6); 2,5-toluenediamine sulfate (6369-59-1); 2,4-dinitrotoluene (121-14-2); 1,5-naphthalenediamine (2243-62-1); N-(1-naphthyl)ethylenediamine dihydrochloride (1465-25-4); 2-chloro-p-phenylenediamine sulfate (61702-44-1); aniline hydrochloride (142-04-1); and p-anisidine hydrochloride (20265-97-8). High dose control rats were housed with other rats receiving diets containing 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 2-aminoanthraquinone (117-79-3); 3-amino-9-ethylcarbazole hydrochloride; 6-nitrobenzimidazole (94-52-0); 1-nitronaphthalene (86-57-7); 2,4-diaminoanisole sulfate (615-05-4); and APC (8003-03-0). High dose treated rats were housed with other rats receiving diets containing 3-amino-4-ethoxyacetanilide (17026-81-2); 1-amino-2-methylanthraquinone (82-28-0); 5-nitro-o-anisidine (99-59-2); and 5-nitroacenaphthene (602-87-9).

High dose, low dose, and high dose control mice were housed in a room with other mice receiving diets containing 2,5-toluenediamine sulfate (6369-59-1); 2-aminoanthraquinone (117-79-3); N,N-dimethyl-p-nitrosoaniline (138-89-6); 3-amino-4-ethoxyacetanilide (17026-81-2); 3-amino-9-ethylcarbazole hydrochloride; 1-amino-2-methylanthraquinone (82-28-0); 5-nitro-o-anisidine (99-59-2); 2,4-dinitrotoluene (121-14-2); 1-nitronaphthalene (86-57-7); 5-nitroacenaphthene (602-87-9); 3-nitro-p-acetophenetide (1777-84-0); and 2,4-diaminoanisole sulfate (615-05-4). Low dose control mice were housed in a room with other

mice receiving diets containing 2-methyl-1-nitroanthraquinone (129-15-7); p-cresidine (120-71-8); fenaminosulf (140-56-7); 4-chloro-m-phenylenediamine (5131-60-2); and cinnamyl anthranilate (87-29-6).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 4-nitroanthranilic acid for administration to treated 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. 4-Nitroanthranilic acid was incorporated into the basal laboratory diet and supplied ad libitum to three of the four rat groups and three of the four mouse groups in concentrations of 0.45, 0.90, and 1.35 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 untreated basal diet.

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

Four of the five female rats treated with 0.90 percent 4-nitroanthranilic acid died. No other deaths were recorded for any treated rat group. Mean weight depression was approximately 20 percent for males receiving a chemical concentration of 1.35 percent, and 2

percent for females receiving the same concentration. The high concentration selected for use in the rat chronic bioassay was 1.50 percent for both males and females.

The only deaths recorded among treated mice were three males receiving 1.35 percent 4-nitroanthranilic acid. Mean weight depression was approximately 6 and 14 percent for males treated with concentrations of 0.90 and 1.35 percent, respectively, and 19 and 4 percent for females receiving the same respective concentrations. The high concentration selected for use in the mouse chronic bioassay was 1.00 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 average concentrations) are summarized in Tables 1 and 2.

Low dose and high dose rats were each started on test 2 weeks after their respective control groups. All rats were approximately 6 weeks old at the time they were placed on test. Rats received initial dietary concentrations of 1.50 and 0.45 percent. Throughout this report those rats receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. The low concentration was increased to 0.46 percent in week 17 in order to facilitate dosage formulation. Dosed rats received 4-nitroanthranilic acid in

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
4-NITROANTHRANILIC ACID FEEDING EXPERIMENT

	INITIAL GROUP SIZE	4-NITROANTHRANILIC ACID CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[a,b]
MALE					
LOW DOSE CONTROL	50	0	0	107	0
HIGH DOSE CONTROL	25	0	0	109	0
LOW DOSE	50	0.45 0.46 0	16 62	 28	0.46
HIGH DOSE	50	1.50 0	78	 32	1.50
FEMALE					
LOW DOSE CONTROL	50	0	0	107	0
HIGH DOSE CONTROL	25	0	0	109	0
LOW DOSE	50	0.45 0.46 0	16 62	 28	0.46
HIGH DOSE	50	1.50 0	78	 32	1.50

[a] Concentrations given in percentages of feed.

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
4-NITROANTHRANILIC ACID FEEDING EXPERIMENT

	INITIAL GROUP SIZE	4-NITROANTHRANILIC ACID CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	93
HIGH DOSE CONTROL	50	0	0	98
LOW DOSE	50	0.46 0	78	16
HIGH DOSE	50	1.00 0	78	17
FEMALE				
LOW DOSE CONTROL	50	0	0	94
HIGH DOSE CONTROL	50	0	0	98
LOW DOSE	50	0.46 0	78	18
HIGH DOSE	50	1.00 0	78	18

[a]Concentrations in percentages of feed.

the feed for 78 weeks. High and low dose control animals received untreated feed during the same period. Rats were observed for an additional 28 to 32 weeks after the period of chemical administration.

Low dose mice were placed on test 2 weeks after their controls. High dose mice were placed on test 8 weeks after their controls. All mice were approximately 6 weeks old when they were placed on test. Mice received concentrations of 1.00 and 0.46 percent of the chemical in their feed. Throughout this report those mice receiving the former concentration are referred to as the high dose groups, while those receiving the latter concentration are referred to as the low dose groups. Dosed mice received 4-nitroanthranilic acid in the feed for 78 weeks. High and low dose control animals received untreated feed. Mice were observed for an additional 16 to 18 weeks after the period of chemical administration.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice daily for mortality. Food consumption, 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. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

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

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

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

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined

microscopically varies and does not necessarily represent the number of animals that were 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

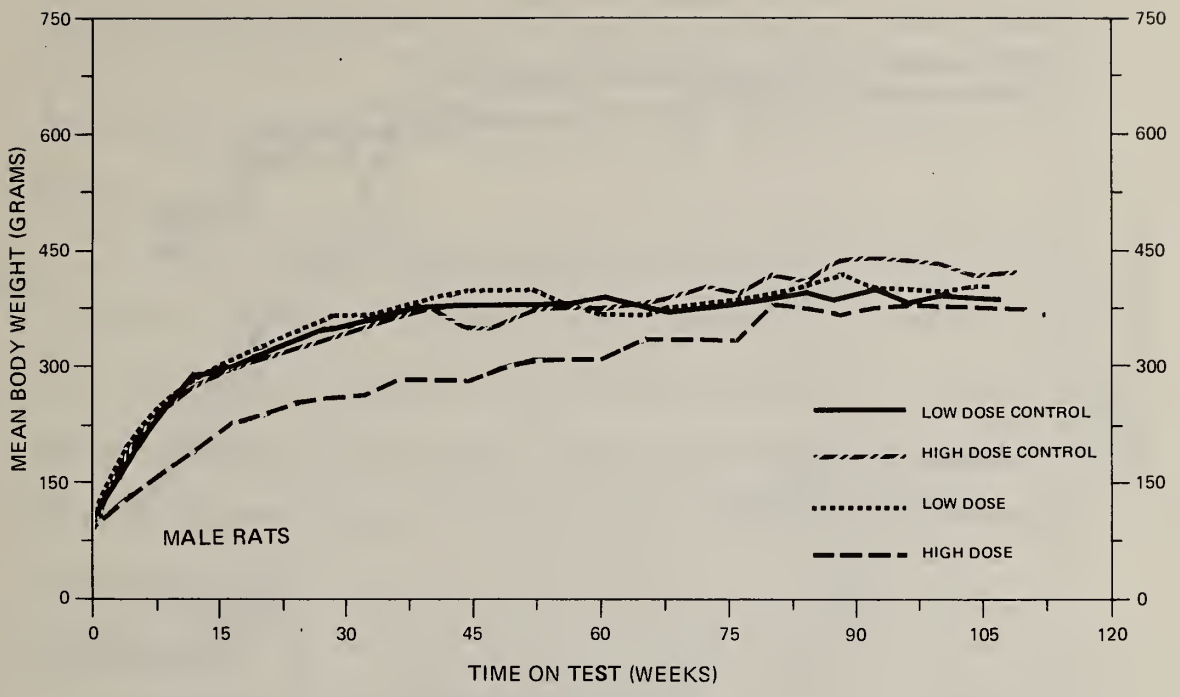
Compound-related mean body weight depression was apparent among high dose rats of both sexes but not among low dose rats (Figure 2).

White discoloration of the lens was observed in the eyes of one high dose male and six high dose females. Shortly after this observation was made only one of the seven afflicted animals was alive (a high dose female). Palpable subcutaneous masses were found in four low dose females, one low dose control female, one low dose male, and one high dose male. One low dose male and one high dose female had lesions on or near the tail and one low dose male developed a firm nodule on the tail. Clinical observations peculiar to the control groups were ulcerative inguinal lesions in one low dose control female and one low dose control male.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 4-nitroanthranilic acid-dosed groups are shown in Figure 3. For both male and female rats the Cox test indicated a significant difference in survival between the high dose and the high dose control.

Five males from each group were sacrificed in week 77 or 78. Survival was good in all groups until about week 80, after which the high dose group showed increased mortality. In week 90, 56 percent (28/50) of the high dose, 74 percent (37/50) of the low dose, 64



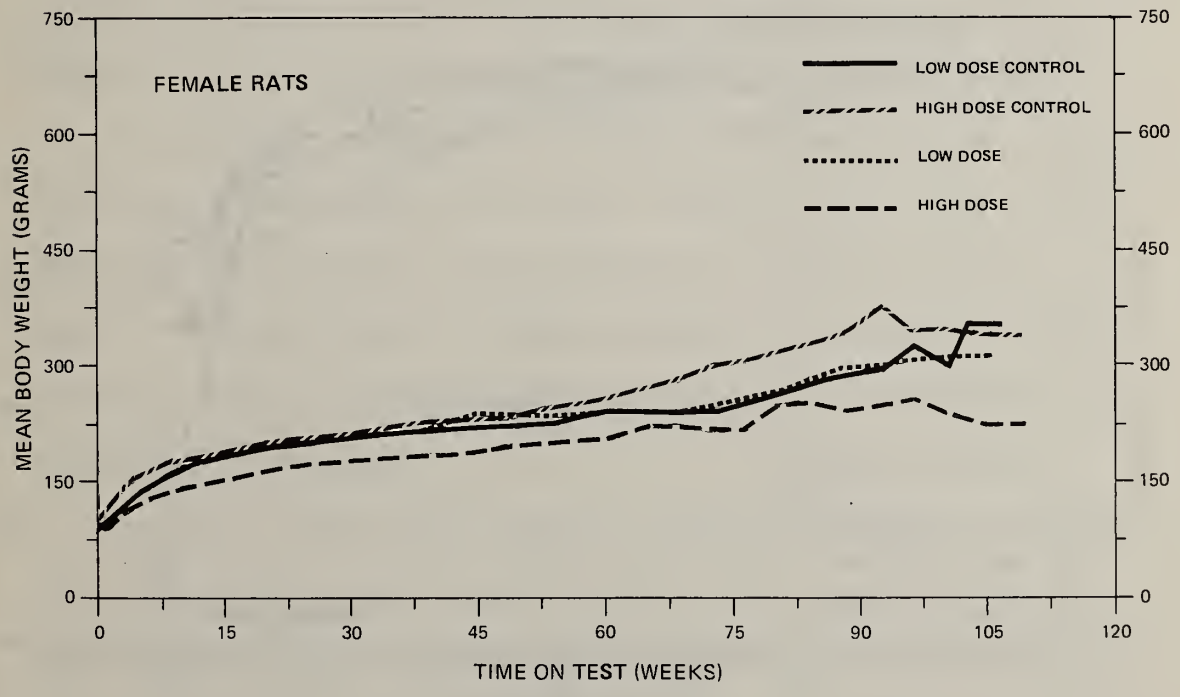
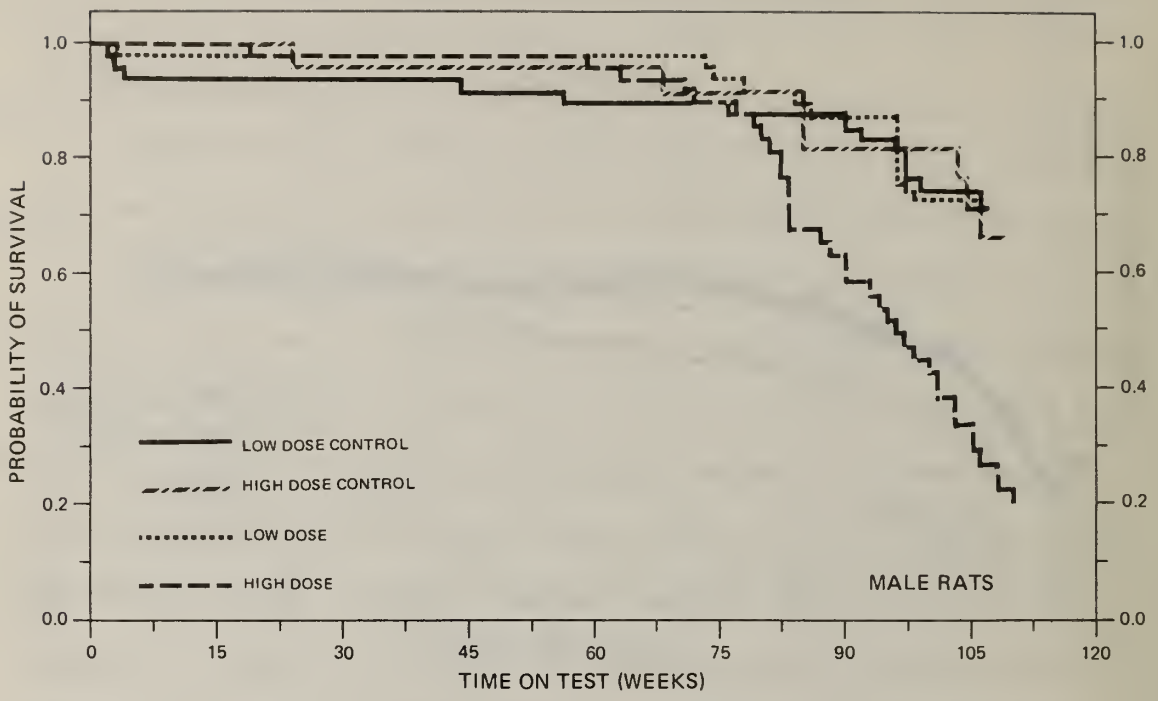


FIGURE 2
GROWTH CURVES FOR 4-NITROANTHRANILIC ACID CHRONIC STUDY RATS



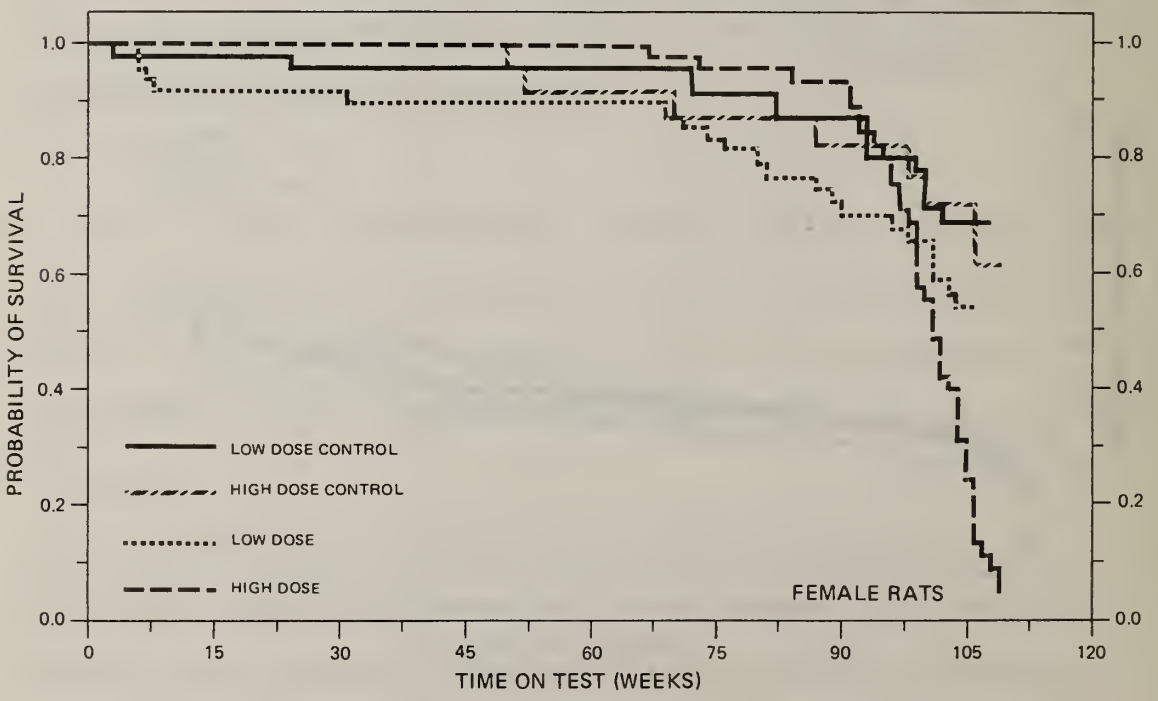


FIGURE 3
SURVIVAL COMPARISONS OF 4-NITROANTHRANILIC ACID CHRONIC STUDY RATS

percent (16/25) of the high dose control and 78 percent (39/50) of the low dose control rats were still alive on test. Thus, there were adequate numbers of male rats at risk from late-developing tumors.

Five females from each group were sacrificed in week 77 or 78. In week 90, 84 percent (42/50) of the high dose, 64 percent (32/50) of the low dose, 64 percent (16/25) of the high dose control and 78 percent (39/50) of the low dose control rats were still alive on test. Thus, there were adequate numbers of female rats at risk from late-developing tumors.

C. Pathology

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

The sites at which tumors were most often found were the pituitary gland in both sexes, the testes in males, and the uterus and mammary gland in females. The incidences of interstitial-cell tumors of the testes and of leukemia appeared to be reduced in high dose male rats by 4-nitroanthranilic acid feeding, possibly due to shortened lifespans.

There was a marginally increased number of neoplasms of the skin and subcutaneous tissue in low dose males, but this effect was not dose-related. The few transitional-cell tumors that were found all

occurred in treated rats (papillomas of the kidney/pelvis and bladder in two high dose males and a papilloma of the bladder in one high dose female). An oligodendroglioma was an unusual tumor found in the brain of one low dose female.

Rats of all groups exhibited the usual spectrum of nonneoplastic inflammatory and degenerative lesions. In addition, high dose rats showed extensive metastatic calcification in various tissues and parathyroid hyperplasia. These animals also had severe renal disease.

The results of this histopathologic evaluation provided no evidence for the carcinogenicity of 4-nitroanthranilic acid when administered in the diet to Fischer 344 rats under the conditions of this experiment.

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 4-nitroanthranilic acid-dosed groups and where such tumors were observed in at least 5 percent of the group. The Cochran-Armitage test was not used in these analyses since the low dose group and its control were started at a different time from the high dose group and its control.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between the administration of 4-nitroanthranilic acid and tumor incidence. Thus, at the

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 4-NITROANTHRANILIC ACID[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Skin: Squamous-Cell Carcinoma or Basal-Cell Carcinoma[b]	1/46(0.02)	0/25(0.00)	3/46(0.07)	0/48(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	3.000	---
Lower Limit	---	---	0.252	---
Upper Limit	---	---	153.954	---
Weeks to First Observed Tumor	107	---	74	---
Subcutaneous Tissue: Lipoma[b]	0/46(0.00)	0/25(0.00)	3/46(0.07)	0/48(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.602	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	96	---
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/45(0.00)	1/25(0.04)	3/44(0.07)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	1.064
Lower Limit	---	---	0.616	0.059
Upper Limit	---	---	Infinite	61.436
Weeks to First Observed Tumor	---	109	97	77

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	1/45(0.02)	3/25(0.12)	4/44(0.09)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	4.091	0.355
Lower Limit	---	---	0.426	0.032
Upper Limit	---	---	196.572	2.923
Weeks to First Observed Tumor	105	78	96	77
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/46(0.09)	4/25(0.16)	4/46(0.09)	0/48(0.00)
P Values[c]	---	---	N.S.	P = 0.012(N)
Relative Risk (Control)[d]	---	---	1.000	0.000
Lower Limit	---	---	0.198	0.000
Upper Limit	---	---	5.058	0.557
Weeks to First Observed Tumor	99	85	73	---
Pituitary: Adenoma NOS, Chromophobe Adenoma, or Basophil Adenoma[b]	9/44(0.20)	3/21(0.14)	4/38(0.11)	1/33(0.03)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.515	0.212
Lower Limit	---	---	0.125	0.004
Upper Limit	---	---	1.678	2.457
Weeks to First Observed Tumor	105	78	105	79

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma NOS or Malignant Pheochromocytoma[b]	6/45(0.13)	4/25(0.16)	3/43(0.07)	5/47(0.11)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.523	0.665
Lower Limit	---	---	0.089	0.160
Upper Limit	---	---	2.281	3.106
Weeks to First Observed Tumor	97	68	84	79
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	3/42(0.07)	0/23(0.00)	2/41(0.05)	3/40(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.683	Infinite
Lower Limit	---	---	0.060	0.357
Upper Limit	---	---	5.651	Infinite
Weeks to First Observed Tumor	106	---	105	98
Testis: Interstitial-Cell Tumor[b]	44/45(0.98)	19/24(0.79)	37/43(0.86)	1/45(0.02)
P Values[c]	---	---	N.S.	P < 0.001(N)
Relative Risk (Control)[d]	---	---	0.880	0.028
Lower Limit	---	---	0.838	0.001
Upper Limit	---	---	1.018	0.151
Weeks to First Observed Tumor	77	78	74	110

TABLE 3 (Concluded)

[a]Treated groups received time-weighted average doses of 0.46 or 1.5 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 its 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 of the relative risk of the treated group to the control group.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH 4-NITROANTHRANILIC ACID[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/48(0.06)	2/23(0.09)	2/46(0.04)	1/46(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.696	0.250
Lower Limit	---	---	0.060	0.004
Upper Limit	---	---	5.792	4.600
Weeks to First Observed Tumor	105	106	106	99
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	1/47(0.02)	2/23(0.09)	0/45(0.00)	2/43(0.05)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.535
Lower Limit	---	---	0.000	0.042
Upper Limit	---	---	19.447	7.038
Weeks to First Observed Tumor	107	106	---	77
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	19/46(0.41)	8/21(0.38)	19/44(0.43)	9/31(0.29)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.045	0.762
Lower Limit	---	---	0.613	0.322
Upper Limit	---	---	1.779	1.919
Weeks to First Observed Tumor	72	78	74	73

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma NOS or Malignant Pheochromocytoma[b]	2/47(0.04)	3/23(0.13)	0/44(0.00)	7/45(0.16)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	1.193
Lower Limit	---	---	0.000	0.308
Upper Limit	---	---	3.599	6.659
Weeks to First Observed Tumor	105	109	---	84
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	2/45(0.04)	3/21(0.14)	3/41(0.07)	3/38(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.646	0.553
Lower Limit	---	---	0.199	0.083
Upper Limit	---	---	18.875	3.833
Weeks to First Observed Tumor	105	109	78	73
Mammary Gland: Fibroadenoma[b]	9/48(0.19)	4/23(0.17)	8/46(0.17)	3/46(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.928	0.375
Lower Limit	---	---	0.341	0.061
Upper Limit	---	---	2.469	2.059
Weeks to First Observed Tumor	93	109	89	77

TABLE 4 (Concluded)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	15/46(0.33)	6/23(0.26)	10/43(0.23)	3/38(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.713	0.303
Lower Limit	---	---	0.322	0.055
Upper Limit	---	---	1.502	1.280
Weeks to First Observed Tumor	78	87	78	97

[a]Treated groups received time-weighted average doses of 0.46 or 1.5 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 its 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 of the relative risk of the treated group to the control group.

dose levels used in this experiment there was no convincing evidence that 4-nitroanthranilic acid was a carcinogen in Fischer 344 rats.

For male rats, the Fisher exact test comparing the incidence of interstitial-cell tumors of the testis in the high dose treated group with that in the high dose control yielded a negative result ($P < 0.001$). The historical data on this tumor in untreated male Fischer 344 rats collected by Mason Research Institute for the NCI Carcinogenesis Testing Program was 251/334 (75 percent), which compared favorably with the incidence levels in the two controls and the low dose treated group. However, the observed incidence of interstitial-cell tumors of the testis in the high dose group was far below this. Some--but not all--of this effect may be attributable to the elevated mortality in the high dose group.

In male rats a possibly negative association between dose and incidence was indicated for the comparison of the incidence of leukemia or malignant lymphoma in the high dose treated group with the incidence in the high dose control. This effect, however, is probably attributable to the elevated mortality in the high dose group.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that

many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by 4-nitroanthranilic acid that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Mean body weight depression became apparent in all treated groups of mice after approximately 5 months of compound administration (Figure 4).

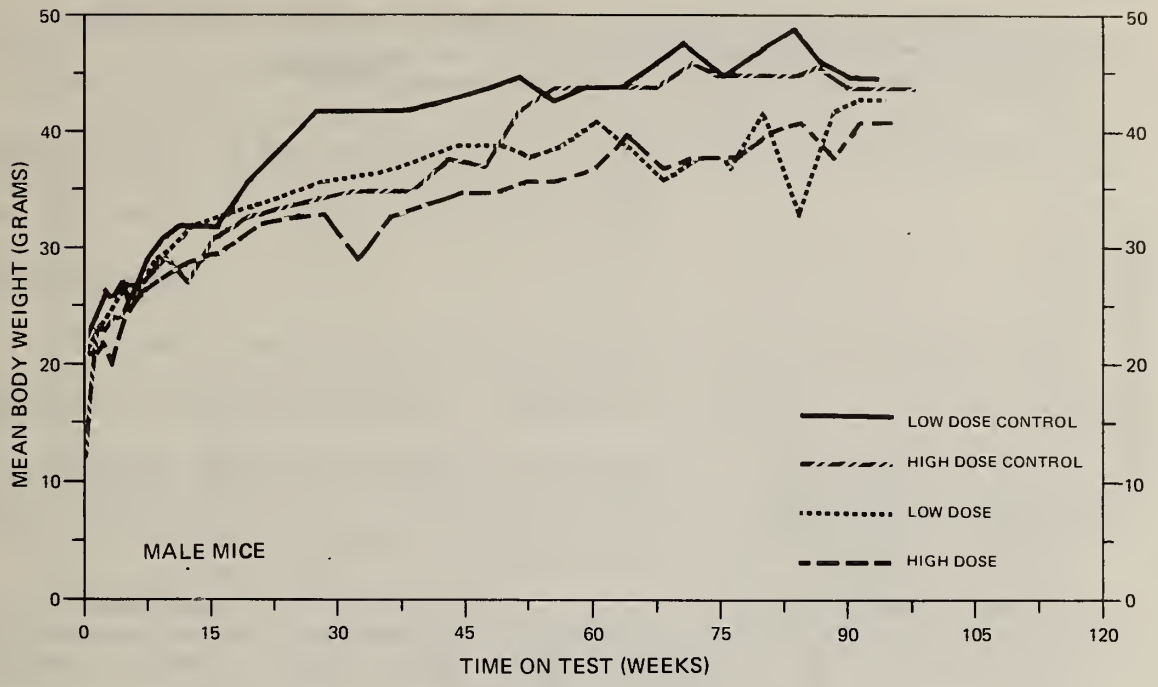
No clinical abnormalities were observed in treated or untreated mice of either sex.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 4-nitroanthranilic acid-dosed groups are shown in Figure 5. For both male and female mice the Cox tests indicated no significant positive associations between increased dosage and accelerated mortality.

Five males were sacrificed from the high dose and high dose control groups in week 78, and from the low dose control group in week 80. Survival was good with 90 percent (45/50) of the high dose, 98 percent (49/50) of the low dose, 74 percent (37/50) of the high dose control and 82 percent (41/50) of the low dose control surviving on test until the termination of the experiment. Thus, there were adequate numbers of male mice at risk from late-developing tumors.

Five females from the high dose and high dose control groups were sacrificed in week 78 and five from the low dose control group in week 80. There were adequate numbers of female mice at risk from



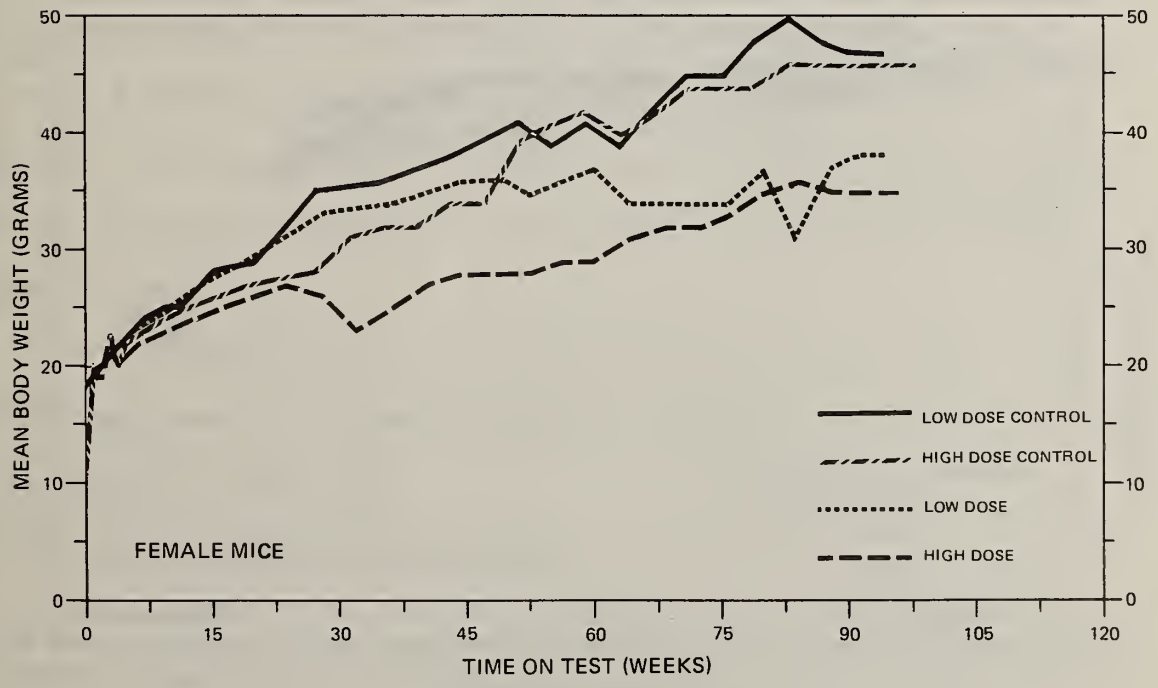
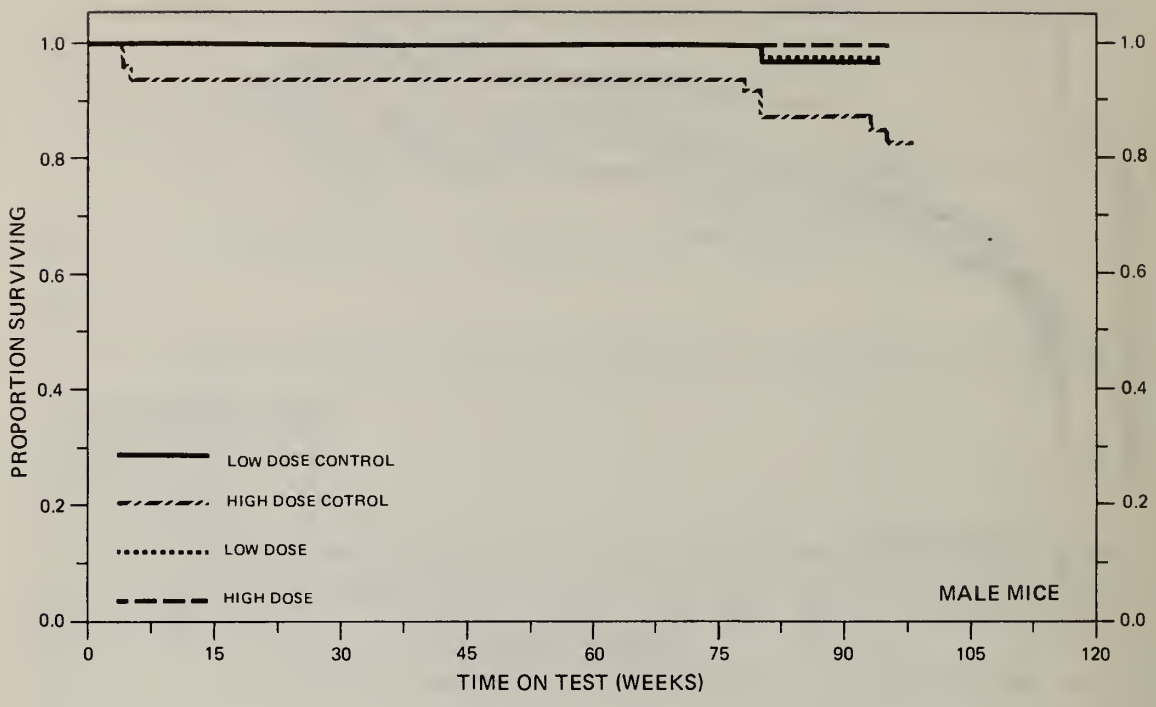


FIGURE 4
GROWTH CURVES FOR 4-NITROANTHRANILIC ACID CHRONIC STUDY MICE



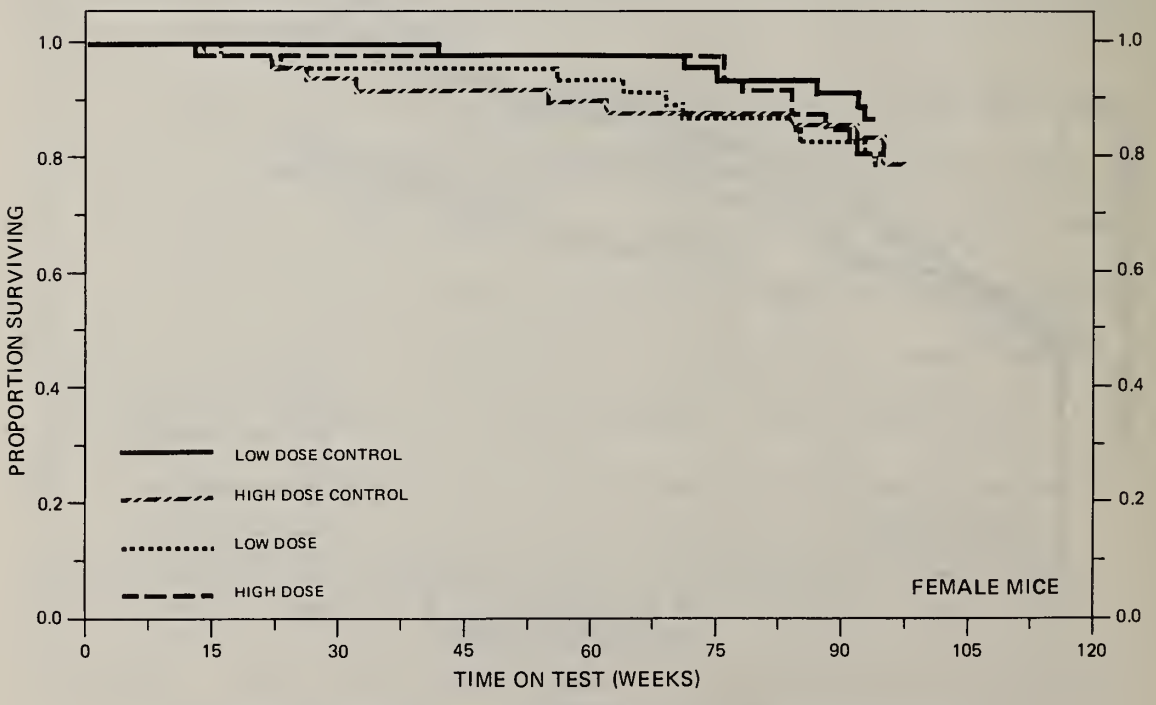


FIGURE 5
SURVIVAL COMPARISONS OF 4-NITROANTHRANILIC ACID CHRONIC STUDY MICE

late-developing tumors as 72 percent (36/50) of the high dose, 74 percent (37/50) of the low dose, 70 percent (35/50) of the high dose controls, and 78 percent (39/50) of the low dose controls survived on test until the termination of the study.

C. Pathology

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

No increases in tumor incidence were considered to be related to the feeding of 4-nitroanthranilic acid. The tumors most frequently observed in all groups involved the lung, the liver, and the hematopoietic system. Two rare tumors were observed: a testicular seminoma in one low dose control male and a hemangiosarcoma of the urinary bladder in one high dose female. No nonneoplastic toxic lesions could be attributed to compound administration, although the usual spectrum of degenerative and inflammatory lesions was observed in all groups.

This histopathologic evaluation provided no evidence that 4-nitroanthranilic acid was carcinogenic to B6C3F1 mice under the conditions of this study.

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 4-NITROANTHRANILIC ACID[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	4/45(0.09)	3/50(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.675	0.225
Lower Limit	---	0.104	0.005
Upper Limit	---	3.779	2.167
Weeks to First Observed Tumor	97	94	95
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	11/45(0.24)	10/50(0.20)	4/50(0.08)
P Values[c]	N.S.	N.S.	P = 0.027(N)
Relative Risk (Control)[d]	---	0.818	0.327
Lower Limit	---	0.346	0.082
Upper Limit	---	1.919	1.017
Weeks to First Observed Tumor	78	94	95
Hematopoietic System: Malignant Lymphoma[b]	2/46(0.04)	3/50(0.06)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.380	1.380
Lower Limit	---	0.166	0.166
Upper Limit	---	15.934	15.934
Weeks to First Observed Tumor	97	94	78

TABLE 5 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangioma or Hemangiosarcoma[b]	0/45(0.00)	0/50(0.00)	3/50(0.06)
P Values[c]	P = 0.035	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.543
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	78
Liver: Hepatocellular Carcinoma[b]	10/45(0.22)	10/50(0.20)	9/50(0.18)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.900	0.810
Lower Limit	---	0.372	0.321
Upper Limit	---	2.186	2.018
Weeks to First Observed Tumor	93	94	95
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	10/45(0.22)	16/50(0.32)	9/50(0.18)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.440	0.810
Lower Limit	---	0.690	0.321
Upper Limit	---	3.174	2.018
Weeks to First Observed Tumor	93	94	95

TABLE 5 (Concluded)

[a]Treated groups received doses of 0.46 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 with $P < 0.05$; 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 of 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 4-NITROANTHRANILIC ACID[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/45(0.02)	5/41(0.12)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	5.488	0.938
Lower Limit	---	0.651	0.012
Upper Limit	---	252.552	72.085
Weeks to First Observed Tumor	98	94	78
Hematopoietic System: Malignant Lymphoma or Leukemia[b]	12/46(0.26)	5/42(0.12)	8/49(0.16)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.456	0.626
Lower Limit	---	0.137	0.245
Upper Limit	---	1.261	1.509
Weeks to First Observed Tumor	94	94	76
Circulatory System: Hemangioma or Hemangiosarcoma[b]	0/46(0.00)	1/42(0.02)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.059	0.566
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	94	76

TABLE 6 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	4/45(0.09)	0/41(0.00)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.239
Lower Limit	---	0.000	0.005
Upper Limit	---	1.176	2.300
Weeks to First Observed Tumor	78	---	95
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	4/45(0.09)	1/41(0.02)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.274	0.239
Lower Limit	---	0.006	0.005
Upper Limit	---	2.623	2.300
Weeks to First Observed Tumor	78	94	95
Stomach: Squamous-Cell Papilloma[b]	3/42(0.07)	3/40(0.08)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.050	0.000
Lower Limit	---	0.149	0.000
Upper Limit	---	7.404	1.482
Weeks to First Observed Tumor	98	94	---

TABLE 6 (Concluded)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS, Chromophobe Adenoma, or Basophil Adenoma[b]	6/37(0.16)	4/36(0.11)	0/40(0.00)
P Values[c]	P = 0.010(N)	N.S.	P = 0.010(N)
Relative Risk (Control)[d]	---	0.685	0.000
Lower Limit	---	0.154	0.000
Upper Limit	---	2.638	0.573
Weeks to First Observed Tumor	98	94	---

[a]Treated groups received doses of 0.46 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 4-nitroanthranilic acid-dosed groups and where such tumors were observed in at least 5 percent of the group. Since the low dose control mice came from a different supplier, the high dose control mice were used as the control for both dosed groups.

For males the Cochran-Armitage test indicated a significant (P = 0.035) positive association between dose and the combined incidence of hemangiosarcomas or hemangiomas. The Fisher exact tests, however, were not significant.

No other statistical tests for any site in mice of either sex indicated a significant positive association between the administration of 4-nitroanthranilic acid and tumor incidence under the Bonferroni criterion. Thus, at the dose levels used in this experiment there was no convincing evidence that 4-nitroanthranilic acid was a carcinogen in B6C3F1 mice.

In female mice the Fisher exact test comparing the combined incidence of pituitary adenomas NOS, chromophobe adenomas, or basophil adenomas in the high dose treated group to that in the high dose control group indicated a significant (P = 0.010) negative association. The Cochran-Armitage test was also significant (P = 0.010). The historical incidence of this type of tumor in B6C3F1 untreated female mice raised at Mason Research Institute for the NCI Carcinogenesis Testing Program was 22/350 (6 percent), compared to the 6/37 (16

percent) observed in the control group and the 0/40 observed in the high dose group.

In male mice the Fisher exact test comparing the combined incidence of alveolar/bronchiolar adenomas or alveolar/bronchiolar carcinomas in the high dose treated group to that in the high dose control group yielded a significant negative association ($P = 0.027$). This result, however, was not significant under the Bonferroni criterion.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by 4-nitroanthranilic acid that could not be established under the conditions of this test.

V. DISCUSSION

In both species, adequate numbers of animals in all groups survived long enough to be at risk from late-developing tumors. Depression of mean group body weight, relative to controls, was observed for high dose rat groups and all dosed mouse groups. This observed growth retardation indicates that concentrations of 4-nitroanthranilic acid fed to these animals approximated maximum tolerated dosages.

In rats none of the statistical tests applied indicated a significant positive association between the dietary administration of 4-nitroanthranilic acid and tumor incidence. Isolated occurrences of rare transitional-cell papillomas of the kidney/pelvis, and bladder and a single oligodendroglioma of the brain were noted in treated rats. These neoplasms were not considered evidence of carcinogenicity of 4-nitroanthranilic acid.

For some sites, tumor incidences in the high dose rat groups were lower than in corresponding control groups. The most likely cause of these reduced tumor incidences in high dose groups is the elevated mortality observed among high dose groups during the observation period following compound administration. Of the 50 high dose rats of each sex placed on test, only 6 males and 2 females died natural deaths during the dosing period, but 30 males and 41 females died during the untreated observation period. The high dose rats in this study received triple the dosage administered to the low dose rats.

In mice, none of the statistical tests indicated significantly increased tumor incidences associated with 4-nitroanthranilic acid administration.

Under the conditions of this bioassay, evidence was not provided for the carcinogenicity of 4-nitroanthranilic acid in Fischer 344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 4-NITROANTHRANILIC ACID

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS MISSING			2	
ANIMALS NECROPSIED	46	25	46	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	45	25	44	48
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(25)	(46)	(48)
SQUAMOUS CELL PAPILLOMA			2 (4%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)	
BASAL-CELL CARCINOMA			2 (4%)	
TRICHOEPITHELIOMA				1 (2%)
*SUBCUT TISSUE	(46)	(25)	(46)	(48)
FIBROMA			1 (2%)	
LIPOMA			3 (7%)	
HEMANGIOMA				1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(45)	(11)	(42)	(8)
SQUAMOUS CELL CARCINOMA	1 (2%)			
*LUNG	(45)	(25)	(44)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (8%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (4%)	3 (7%)	2 (4%)
PHEOCHROMOCYTOMA, METASTATIC		1 (4%)		
FIBROSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(25)	(46)	(48)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
UNDIFFERENTIATED LEUKEMIA		2 (8%)		
MYELOMONOCYTIC LEUKEMIA	1 (2%)		4 (9%)	
LYMPHOCYTIC LEUKEMIA	2 (4%)	2 (8%)		
*BONE MARROW	(45)	(25)	(42)	(45)
SEBACEOUS ADENOCARCINOMA, METAST				1 (2%)

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
*CERVICAL LYMPH NODE	(41)	(24)	(38)	(29)
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (3%)
*MEDIASTINAL L.NODE	(41)	(24)	(38)	(29)
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (3%)
C-CELL CARCINOMA, METASTATIC				1 (3%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*SALIVARY GLAND	(43)	(24)	(40)	(40)
CARCINOMA,NOS			1 (3%)	
*LIVER	(45)	(25)	(44)	(46)
NEOPLASTIC NODULE				1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)	
*STOMACH	(45)	(24)	(43)	(46)
SQUAMOUS CELL PAPILLOMA		1 (4%)		
BASAL-CELL CARCINOMA		1 (4%)		1 (2%)
URINARY SYSTEM				
*KIDNEY/PELVIS	(45)	(24)	(44)	(47)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
*URINARY BLADDER	(44)	(23)	(43)	(43)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
ENDOCRINE SYSTEM				
*PITUITARY	(44)	(21)	(38)	(33)
ADENOMA, NOS	9 (20%)	1 (5%)	2 (5%)	
CHROMOPHOBE ADENOMA			2 (5%)	1 (3%)
BASOPHIL ADENOMA		2 (10%)		
*ADRENAL	(45)	(25)	(43)	(47)
CORTICAL ADENOMA	1 (2%)			

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
PHEOCHROMOCYTOMA	6 (13%)	2 (8%)	3 (7%)	4 (9%)
PHEOCHROMOCYTOMA, MALIGNANT		2 (8%)		1 (2%)
GANGLIONEUROMA			1 (2%)	
#THYROID	(42)	(23)	(41)	(40)
C-CELL ADENOMA	2 (5%)		2 (5%)	2 (5%)
C-CELL CARCINOMA	1 (2%)			1 (3%)
#PANCREATIC ISLETS	(45)	(25)	(43)	(43)
ISLET-CELL ADENOMA	1 (2%)	2 (8%)	2 (5%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(25)	(46)	(48)
FIBROSARCOMA			1 (2%)	
FIBROADENOMA		1 (4%)		
*PREPUTIAL GLAND	(46)	(25)	(46)	(48)
CARCINOMA,NOS		1 (4%)		1 (2%)
ADENOMA, NOS	1 (2%)	1 (4%)		
SEBACEOUS ADENOMA				1 (2%)
SEBACEOUS ADENOCARCINOMA				1 (2%)
#TESTIS	(45)	(24)	(43)	(45)
INTERSTITIAL-CELL TUMOR	44 (98%)	19 (79%)	37 (86%)	1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR CANAL	(46)	(25)	(46)	(48)
SQUAMOUS CELL CARCINOMA		1 (4%)		
*ZYMBAL'S GLAND	(46)	(25)	(46)	(48)
SEBACEOUS ADENOCARCINOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
BODY CAVITIES				
*BODY CAVITIES	(46)	(25)	(46)	(48)
MESOTHELIOMA, NOS	3 (7%)		2 (4%)	
*MEDIASTINUM	(46)	(25)	(46)	(48)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (4%)		
*PLEURA	(46)	(25)	(46)	(48)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (4%)		
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	7	3	7	22
MORIBUND SACRIFICE	6	4	6	14
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	22	13	30	9
ANIMAL MISSING			2	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	44	22	43	16
TOTAL PRIMARY TUMORS	75	41	71	22
TOTAL ANIMALS WITH BENIGN TUMORS	44	20	40	9
TOTAL BENIGN TUMORS	65	31	56	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	9	12	7
TOTAL MALIGNANT TUMORS	7	10	13	8
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1	4
TOTAL SECONDARY TUMORS		3	1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3		2	1
TOTAL UNCERTAIN TUMORS	3		2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	48	23	46	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	23	45	45
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(23)	(46)	(46)
ADENOMA, NOS			1 (2%)	
SEBACEOUS ADENOCARCINOMA		1 (4%)		
FIBROMA	1 (2%)			
FIBROSARCOMA	1 (2%)			
FIBROADENOMA	1 (2%)			
*SUBCUT TISSUE	(48)	(23)	(46)	(46)
FIBROMA			2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(47)	(23)	(45)	(43)
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)			
FIBROSARCOMA			1 (2%)	
LEIOMYOSARCOMA			1 (2%)	
LEIOMYOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(23)	(46)	(46)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
UNDIFFERENTIATED LEUKEMIA		2 (9%)		
MYELOMONOCYTIC LEUKEMIA	1 (2%)		1 (2%)	
#BONE MARROW	(47)	(22)	(43)	(42)
UNDIFFERENTIATED LEUKEMIA			1 (2%)	
#SPLEEN	(47)	(23)	(45)	(43)
HEMANGIOMA				1 (2%)

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
MYELOMONOCYTIC LEUKEMIA	1 (2%)			
#TRACHEAL LYMPH NODE	(42)	(21)	(39)	(28)
FIBROSARCOMA, METASTATIC			1 (3%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(47)	(23)	(45)	(43)
NEOPLASTIC NODULE		2 (9%)		1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)			1 (2%)
#STOMACH	(46)	(23)	(44)	(43)
SQUAMOUS CELL PAPILLOMA				2 (5%)
BASAL-CELL CARCINOMA				1 (2%)
URINARY SYSTEM				
#URINARY BLADDER	(46)	(22)	(41)	(37)
TRANSITIONAL-CELL PAPILLOMA				1 (3%)
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(21)	(44)	(31)
CARCINOMA, NOS	1 (2%)			
ADENOMA, NOS	19 (41%)	1 (5%)	11 (25%)	1 (3%)
CHROMOPHOBE ADENOMA		7 (33%)	8 (18%)	8 (26%)
#ADRENAL	(47)	(23)	(44)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
CORTICAL ADENOMA	1 (2%)			
PHEOCHROMOCYTOMA	2 (4%)	2 (9%)		6 (13%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (4%)		1 (2%)
#THYROID	(45)	(21)	(41)	(38)
C-CELL ADENOMA	2 (4%)	2 (10%)	2 (5%)	2 (5%)
C-CELL CARCINOMA		1 (5%)	1 (2%)	1 (3%)
#THYROID FOLLICLE	(45)	(21)	(41)	(38)
PAPILLARY CYSTADENOCARCINOMA, NOS		1 (5%)		

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
*PANCREATIC ISLETS	(46)	(22)	(44)	(39)
ISLET-CELL ADENOMA	2 (4%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(23)	(46)	(46)
ADENOCARCINOMA, NOS		2 (9%)	1 (2%)	
PAPILLARY CYSTADENOMA, NOS	2 (4%)			
INFILTRATING DUCT CARCINOMA		1 (4%)		
FIBROADENOMA	9 (19%)	4 (17%)	8 (17%)	3 (7%)
*CLITORAL GLAND	(48)	(23)	(46)	(46)
CARCINOMA,NOS			1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)	
ADENOMA, NOS			2 (4%)	
*VAGINA	(48)	(23)	(46)	(46)
FIBROSARCOMA	1 (2%)			
LYMPHANGIOSARCOMA	1 (2%)			
#UTERUS	(46)	(23)	(43)	(38)
ADENOCARCINOMA, NOS			2 (5%)	
LEIOMYOSARCOMA			1 (2%)	
ENDOMETRIAL STROMAL POLYP	15 (33%)	6 (26%)	10 (23%)	3 (8%)
#UTERUS/ENDOMETRIUM	(46)	(23)	(43)	(38)
CARCINOMA,NOS	1 (2%)			
NERVOUS SYSTEM				
*BRAIN	(47)	(23)	(43)	(42)
OLIGODENDROGLIOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*EAR CANAL	(48)	(23)	(46)	(46)
FIBROSARCOMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE A2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
BODY CAVITIES				
*BODY CAVITIES	(48)	(23)	(46)	(46)
MESOTHELIOMA, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	6	3	11	31
MORIBUND SACRIFICE	8	5	10	12
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	21	12	24	2
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	38	19	35	22
TOTAL PRIMARY TUMORS	66	34	59	34
TOTAL ANIMALS WITH BENIGN TUMORS	36	18	33	19
TOTAL BENIGN TUMORS	54	23	46	27
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	8	12	4
TOTAL MALIGNANT TUMORS	12	9	13	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			3	
TOTAL SECONDARY TUMORS			3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2		2
TOTAL UNCERTAIN TUMORS		2		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 4-NITROANTHRANILIC ACID

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	46	46	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	45	50	50
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(46)	(45)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (11%)	7 (16%)	8 (16%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	4 (9%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(46)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)	
*SUBCUT TISSUE	(46)	(46)	(50)	(50)
PLASMA-CELL TUMOR			1 (2%)	
#BONE MARROW	(46)	(45)	(50)	(50)
HEMANGIOMA				1 (2%)
#SPLEEN	(46)	(45)	(50)	(49)
HEMANGIOMA				1 (2%)
HEMANGIOSARCOMA				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#MANDIBULAR L. NODE	(34)	(35)	(45)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)		
#SMALL INTESTINE	(46)	(43)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				2 (4%)

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

TABLE B1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(46)	(45)	(50)	(50)
HEPATOCELLULAR ADENOMA			6 (12%)	
HEPATOCELLULAR CARCINOMA	12 (26%)	10 (22%)	10 (20%)	9 (18%)
*STOMACH	(45)	(42)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	2 (4%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(39)	(36)	(44)	(39)
ADENOMA, NOS	1 (3%)			
#ADRENAL	(44)	(43)	(50)	(50)
PHEOCHROMOCYTOMA			1 (2%)	
#ADRENAL/CAPSULE	(44)	(43)	(50)	(50)
ADENOMA, NOS			1 (2%)	
#THYROID	(44)	(40)	(49)	(45)
ADENOCARCINOMA, NOS	2 (5%)			
REPRODUCTIVE SYSTEM				
#PREPUTIAL GLAND	(46)	(46)	(50)	(50)
CARCINOMA,NOS			1 (2%)	
#TESTIS	(46)	(45)	(50)	(50)
SEMINOMA/DYSGERMINOMA	1 (2%)			
NERVOUS SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(46)	(46)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		1 (2%)	
*EAR CANAL	(46)	(46)	(50)	(50)
SQUAMOUS CELL CARCINOMA		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	7		
MORIBUND SACRIFICE		1	1	
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED	3			
TERMINAL SACRIFICE	41	37	49	45
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	21	30	15
TOTAL PRIMARY TUMORS	26	25	37	19
TOTAL ANIMALS WITH BENIGN TUMORS	6	8	17	4
TOTAL BENIGN TUMORS	7	8	19	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	15	16	12
TOTAL MALIGNANT TUMORS	19	17	17	14
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1	
TOTAL SECONDARY TUMORS	1	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	
TOTAL UNCERTAIN TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			3	
ANIMALS NECROPSIED	47	46	42	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	46	41	48
INTEGUMENTARY SYSTEM				
*SKIN	(47)	(46)	(42)	(49)
SQUAMOUS CELL PAPILLOMA				1 (2%)
FIBROSARCOMA		2 (4%)		
*SUBCUT TISSUE	(47)	(46)	(42)	(49)
HEMANGIOSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
*LUNG	(46)	(45)	(41)	(48)
CARCINOMA, NOS, METASTATIC	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	5 (12%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(47)	(46)	(42)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)	3 (7%)		
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	6 (13%)		5 (10%)
MALIGNANT LYMPHOMA, MIXED TYPE			3 (7%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)		
*SPLEEN	(45)	(43)	(39)	(48)
HEMANGIOSARCOMA	1 (2%)		1 (3%)	
*MESENTERIC L. NODE	(27)	(41)	(38)	(42)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (3%)	
*LIVER	(46)	(45)	(41)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			

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

TABLE B2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
*PEYERS PATCH	(45)	(43)	(40)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
*KIDNEY	(45)	(43)	(41)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
*THYMUS	(21)	(27)	(37)	(37)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (3%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*LIVER	(46)	(45)	(41)	(47)
CARCINOMA, NOS, METASTATIC	1 (2%)			
HEPATOCELLULAR ADENOMA			1 (2%)	
HEPATOCELLULAR CARCINOMA	4 (9%)	4 (9%)		1 (2%)
HEMANGIOSARCOMA			1 (2%)	
*STOMACH	(45)	(42)	(40)	(47)
SQUAMOUS CELL PAPILLOMA		3 (7%)	3 (8%)	
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
*URINARY BLADDER	(42)	(41)	(39)	(43)
HEMANGIOSARCOMA				1 (2%)
ENDOCRINE SYSTEM				
*PITUITARY	(37)	(37)	(36)	(40)
ADENOMA, NOS	3 (8%)	6 (16%)	3 (8%)	
CHROMOPHOBE ADENOMA	1 (3%)			
BASOPHIL ADENOMA			1 (3%)	
*ADRENAL	(44)	(43)	(40)	(47)
CORTICAL ADENOMA		1 (2%)	2 (5%)	
*THYROID	(44)	(30)	(37)	(42)
PAPILLARY CYSTADENOMA, NOS			1 (3%)	1 (2%)

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

TABLE B2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
*PANCREATIC ISLETS	(39)	(41)	(41)	(43)
ISLET-CELL ADENOMA		1 (2%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(47)	(46)	(42)	(49)
ADENOCARCINOMA, NOS		1 (2%)		
FIBROADENOMA	1 (2%)			
*UTERUS	(43)	(43)	(40)	(46)
ENDOMETRIAL STROMAL POLYP	1 (2%)		1 (3%)	2 (4%)
*UTERUS/ENDOMETRIUM	(43)	(43)	(40)	(46)
CARCINOMA, NOS	1 (2%)			
*OVARY/OVIDUCT	(43)	(43)	(40)	(46)
PAPILLARY ADENOMA	1 (2%)			
INTRADUCTAL PAPILLOMA	1 (2%)			
*OVARY	(44)	(41)	(39)	(44)
LUTEOMA		1 (2%)		
TUBULAR ADENOMA			1 (3%)	1 (2%)
HEMANGIOMA				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR CANAL	(47)	(46)	(42)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(47)	(46)	(42)	(49)
HEMANGIOSARCOMA	1 (2%)			

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

TABLE B2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	5	8	10	9
MORIBUND SACRIFICE	1	2		
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	39	35	37	36
ANIMAL MISSING			3	
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	22	18	18
TOTAL PRIMARY TUMORS	21	32	25	20
TOTAL ANIMALS WITH BENIGN TUMORS	7	12	12	7
TOTAL BENIGN TUMORS	8	13	18	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	18	7	12
TOTAL MALIGNANT TUMORS	13	19	7	13
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 4-NITROANTHRANILIC ACID

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS MISSING			2	
ANIMALS NECROPSIED	46	25	46	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	45	25	44	48
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(25)	(46)	(48)
ABSCESS, NOS				2 (4%)
FIBROSIS			1 (2%)	2 (4%)
NECROSIS, NOS		1 (4%)		
*SUBCUT TISSUE	(46)	(25)	(46)	(48)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)	
KELOID	1 (2%)			
FIBROUS DYSPLASIA	1 (2%)			
RESPIRATORY SYSTEM				
*LARYNX	(46)	(25)	(46)	(48)
INFLAMMATION ACUTE AND CHRONIC		1 (4%)		
INFLAMMATION, CHRONIC		7 (28%)		5 (10%)
#TRACHEA	(45)	(11)	(42)	(8)
INFLAMMATION, NOS		1 (9%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)			
INFLAMMATION, ACUTE/CHRONIC	24 (53%)		30 (71%)	
METAPLASIA, SQUAMOUS			1 (2%)	
#LUNG/BRONCHUS	(45)	(25)	(44)	(47)
BRONCHIECTASIS		2 (8%)		1 (2%)
INFLAMMATION, FOCAL		1 (4%)		
INFLAMMATION, ACUTE			1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)			
#LUNG/BRONCHIOLE	(45)	(25)	(44)	(47)
BRONCHIOLECTASIS	1 (2%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (11%)			
INFLAMMATION, ACUTE/CHRONIC	3 (7%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
HYPERPLASIA, LYMPHOID	6 (13%)		1 (2%)	
#LUNG	(45)	(25)	(44)	(47)
EMPHYSEMA, NOS	1 (2%)			
ATELECTASIS	1 (2%)			
EDEMA, NOS			1 (2%)	
BRONCHOPNEUMONIA, NOS				1 (2%)
INFLAMMATION, FOCAL			1 (2%)	
INFLAMMATION, INTERSTITIAL	4 (9%)	2 (8%)		
BRONCHOPNEUMONIA, ACUTE		1 (4%)		1 (2%)
ABSCESS, NOS	2 (4%)	1 (4%)		1 (2%)
PNEUMONIA, CHRONIC MURINE		11 (44%)		13 (28%)
GRANULOMA, NOS		1 (4%)		
PERIVASCULITIS	5 (11%)			
INFARCT, FOCAL				1 (2%)
CALCIFICATION, FOCAL				2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)			
METAPLASIA, SQUAMOUS				1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(45)	(25)	(42)	(45)
HEMORRHAGE	1 (2%)			
FIBROSIS, FOCAL				1 (2%)
KARYORRHEXIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC	4 (9%)	2 (8%)		
ERYTHROPOIESIS	1 (2%)			
MYELOPOIESIS	1 (2%)			
#SPLEEN	(45)	(25)	(44)	(47)
CONGESTION, NOS	1 (2%)			
PERIARTERITIS				1 (2%)
HEMOSIDEROSIS		1 (4%)		
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	1 (4%)		
HYPERPLASIA, ERYTHROID		1 (4%)		
HYPERPLASIA, LYMPHOID	1 (2%)			
HEMATOPOIESIS	1 (2%)			
MYELOPOIESIS	1 (2%)			
#SPLENIC CAPSULE	(45)	(25)	(44)	(47)
HEMORRHAGE	1 (2%)			
#LYMPH NODE	(41)	(24)	(38)	(29)
PLASMACYTOSIS		1 (4%)		

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
#SUBMANDIBULAR L.NODE	(41)	(24)	(38)	(29)
HYPERPLASIA, NOS				1 (3%)
#MANDIBULAR L. NODE	(41)	(24)	(38)	(29)
HYPERPLASIA, NOS				1 (3%)
#LUMBAR LYMPH NODE	(41)	(24)	(38)	(29)
INFLAMMATION ACUTE AND CHRONIC				1 (3%)
#MESENTERIC L. NODE	(41)	(24)	(38)	(29)
HYPERPLASIA, NOS				1 (3%)
#THYMUS	(35)	(22)	(27)	(33)
HYPERPLASIA, EPITHELIAL	1 (3%)			
CIRCULATORY SYSTEM				
#HEART	(45)	(25)	(44)	(47)
THROMBUS, MURAL				2 (4%)
PERIARTERITIS		1 (4%)	2 (5%)	
PERIVASCULITIS	2 (4%)			
CALCIFICATION, FOCAL				10 (21%)
#MYOCARDIUM	(45)	(25)	(44)	(47)
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, INTERSTITIAL			5 (11%)	
INFLAMMATION, ACUTE/CHRONIC	3 (7%)		5 (11%)	
FIBROSIS	1 (2%)		2 (5%)	
FIBROSIS, FOCAL		1 (4%)	6 (14%)	
FIBROSIS, DIFFUSE			4 (9%)	
DEGENERATION, NOS	13 (29%)	10 (40%)		15 (32%)
#ENDOCARDIUM	(45)	(25)	(44)	(47)
CALCIFICATION, NOS				3 (6%)
*AORTA	(46)	(25)	(46)	(48)
MEDIAL CALCIFICATION				7 (15%)
CALCIFICATION, NOS				5 (10%)
CALCIFICATION, FOCAL		1 (4%)		
*CORONARY ARTERY	(46)	(25)	(46)	(48)
MEDIAL CALCIFICATION				1 (2%)
CALCIFICATION, NOS				2 (4%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
*MESENTERIC ARTERY	(46)	(25)	(46)	(48)
THROMBOSIS, NOS				3 (6%)
MEDIAL CALCIFICATION				2 (4%)
CALCIFICATION, NOS				4 (8%)
DIGESTIVE SYSTEM				
*ALVEOLUS DENTALIS	(46)	(25)	(46)	(48)
INFLAMMATION, ACUTE				1 (2%)
*PAROTID GLAND	(43)	(24)	(40)	(40)
INFLAMMATION, INTERSTITIAL	1 (2%)			
*SUBMAXILLARY GLAND	(43)	(24)	(40)	(40)
HYPERPLASIA, FOCAL	1 (2%)			
*LIVER	(45)	(25)	(44)	(46)
CONGESTION, NOS	1 (2%)			
CONGESTION, CHRONIC PASSIVE		1 (4%)		
INFLAMMATION, ACUTE FOCAL	2 (4%)			
CHOLANGIOFIBROSIS		1 (4%)		
PERIARTERITIS				1 (2%)
DEGENERATION, NOS	2 (4%)			
DEGENERATION, HYALINE			1 (2%)	
DEGENERATION, EOSINOPHILIC			5 (11%)	
NECROSIS, FOCAL	1 (2%)	1 (4%)	2 (5%)	2 (4%)
METAMORPHOSIS FATTY	3 (7%)	4 (16%)	6 (14%)	
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL	8 (18%)		28 (64%)	
*LIVER/CENTRILOBULAR	(45)	(25)	(44)	(46)
DEGENERATION, NOS			3 (7%)	
INFARCT, NOS				1 (2%)
METAMORPHOSIS FATTY	1 (2%)			
*LIVER/HEPATOCYTES	(45)	(25)	(44)	(46)
HYPERPLASIA, FOCAL	6 (13%)			
*BILE DUCT	(46)	(25)	(46)	(48)
INFLAMMATION, NOS	5 (11%)			
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
HYPERPLASIA, NOS	11 (24%)	6 (24%)	28 (61%)	

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
HYPERPLASIA, FOCAL			7 (15%)	
#PANCREAS	(45)	(25)	(43)	(43)
HEMORRHAGIC CYST				1 (2%)
INFLAMMATION, NOS	1 (2%)	1 (4%)		
INFLAMMATION, INTERSTITIAL	1 (2%)			
INFLAMMATION, NECROTIZING				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)		6 (14%)	
PERIARTERITIS				5 (12%)
ATROPHY, FOCAL			1 (2%)	
#PANCREATIC DUCT	(45)	(25)	(43)	(43)
HYPERPLASIA, NOS		1 (4%)		
#PANCREATIC ACINUS	(45)	(25)	(43)	(43)
ATROPHY, NOS	13 (29%)			
ATROPHY, FOCAL	2 (4%)		2 (5%)	
#ESOPHAGUS	(44)	(25)	(43)	(36)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
#STOMACH	(45)	(24)	(43)	(46)
EPIDERMAL INCLUSION CYST		1 (4%)		
PERIARTERITIS				1 (2%)
CALCIFICATION, NOS				3 (7%)
CALCIFICATION, FOCAL				18 (39%)
HYPERKERATOSIS	1 (2%)			
#GASTRIC MUCOSA	(45)	(24)	(43)	(46)
CALCIFICATION, NOS				1 (2%)
#PEYERS PATCH	(45)	(24)	(43)	(45)
HYPERPLASIA, NOS		2 (8%)		
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)	
#JEJUNUM	(45)	(24)	(43)	(45)
HEMORRHAGE				1 (2%)
INFARCT, NOS				1 (2%)
#ILEUM	(45)	(24)	(43)	(45)
PERIARTERITIS				1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)	1 (2%)
#COLON	(44)	(24)	(38)	(38)
PARASITISM			5 (13%)	1 (3%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
URINARY SYSTEM				
*KIDNEY	(45)	(24)	(44)	(47)
CONGESTION, NOS	1 (2%)			
GLOMERULONEPHRITIS, NOS	34 (76%)	5 (21%)	31 (70%)	
GLOMERULONEPHRITIS, FOCAL			3 (7%)	
INFLAMMATION, INTERSTITIAL	5 (11%)		2 (5%)	
PERIARTERITIS				1 (2%)
NEPHROPATHY		1 (4%)		
NEPHROSIS, NOS		16 (67%)		41 (87%)
CALCIFICATION, FOCAL				19 (40%)
*KIDNEY/MEDULLA	(45)	(24)	(44)	(47)
MULTIPLE CYSTS	1 (2%)			
*KIDNEY/GLOMERULUS	(45)	(24)	(44)	(47)
INFLAMMATION, MEMBRANOUS	9 (20%)			
*URINARY BLADDER	(44)	(23)	(43)	(43)
CALCULUS, NOS		3 (13%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INCLUSION, CYTOPLASMIC			1 (2%)	
ENDOCRINE SYSTEM				
*PITUITARY	(44)	(21)	(38)	(33)
CONGESTION, NOS	1 (2%)			
HYPERPLASIA, NODULAR				1 (3%)
HYPERPLASIA, FOCAL	6 (14%)		3 (8%)	
HYPERPLASIA, CHROMOPHOBE-CELL			1 (3%)	1 (3%)
*PITUITARY/BASOPHIL	(44)	(21)	(38)	(33)
NODULE		1 (5%)		
*ADRENAL	(45)	(25)	(43)	(47)
HYPERPLASIA, NODULAR			3 (7%)	
*ADRENAL CORTEX	(45)	(25)	(43)	(47)
NODULE	1 (2%)			1 (2%)
HYPERTROPHY, FOCAL		1 (4%)		
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASIA, FOCAL	7 (16%)		3 (7%)	
*ADRENAL MEDULLA	(45)	(25)	(43)	(47)
HYPERPLASIA, NOS	2 (4%)		1 (2%)	1 (2%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
HYPERPLASIA, FOCAL	4 (9%)		1 (2%)	
#THYROID	(42)	(23)	(41)	(40)
ULTIMOBRANCHIAL CYST				1 (3%)
HYPERPLASIA, FOCAL	2 (5%)			
HYPERPLASIA, C-CELL	1 (2%)		1 (2%)	2 (5%)
#PARATHYROID	(32)	(15)	(26)	(29)
HYPERPLASIA, NOS				8 (28%)
#PANCREATIC ISLETS	(45)	(25)	(43)	(43)
HYPERPLASIA, NOS	2 (4%)		1 (2%)	
HYPERPLASIA, FOCAL			2 (5%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(25)	(46)	(48)
GALACTOCELE			1 (2%)	
HYPERPLASIA, NOS	3 (7%)	3 (12%)		
LACTATION		7 (28%)		1 (2%)
*PREPUTIAL GLAND	(46)	(25)	(46)	(48)
ABSCESS, NOS	2 (4%)			
#PROSTATE	(45)	(23)	(43)	(46)
INFLAMMATION, NOS		1 (4%)	1 (2%)	
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, ACUTE	10 (22%)		6 (14%)	3 (7%)
INFLAMMATION, ACUTE FOCAL	4 (9%)		4 (9%)	
INFLAMMATION, ACUTE/CHRONIC			3 (7%)	
DEGENERATION, NOS	13 (29%)			
ATROPHY, NOS	2 (4%)	4 (17%)		1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, PAPILLARY	2 (4%)			
HYPERPLASIA, ADENOMATOUS	1 (2%)			
*SEMINAL VESICLE	(46)	(25)	(46)	(48)
ATROPHY, NOS	26 (57%)	1 (4%)		1 (2%)
HYPERPLASIA, PAPILLARY	1 (2%)			
*COAGULATING GLAND	(46)	(25)	(46)	(48)
ATROPHY, NOS	3 (7%)			
#TESTIS	(45)	(24)	(43)	(45)
PERIARTERITIS				23 (51%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
DEGENERATION, NOS			37 (86%)	1 (2%)
CALCIFICATION, FOCAL		4 (17%)		1 (2%)
ATROPHY, NOS	1 (2%)	12 (50%)		39 (87%)
HYPOSPERMATOGENESIS				5 (11%)
HYPERPLASIA, INTERSTITIAL CELL		2 (8%)	8 (19%)	
#TESTIS/TUBULE	(45)	(24)	(43)	(45)
DEGENERATION, NOS	10 (22%)			
*EPIDIDYMIS	(46)	(25)	(46)	(48)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(45)	(25)	(43)	(46)
HEMORRHAGE		2 (8%)		
CALCIFICATION, FOCAL		1 (4%)		
#CEREBRAL CORTEX	(45)	(25)	(43)	(46)
HEMORRHAGE	1 (2%)			
MALACIA	1 (2%)			
#CEREBELLUM	(45)	(25)	(43)	(46)
INFARCT HEMORRHAGIC			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE	(46)	(25)	(46)	(48)
SYNECHIA, POSTERIOR	1 (2%)			1 (2%)
CATARACT	1 (2%)		1 (2%)	
*EYE/RETINA	(46)	(25)	(46)	(48)
DEGENERATION, NOS			1 (2%)	3 (6%)
*EAR	(46)	(25)	(46)	(48)
METAPLASIA, SQUAMOUS				1 (2%)
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(46)	(25)	(46)	(48)
CALCIFICATION, FOCAL		1 (4%)		

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

TABLE C1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0030	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0034	HIGH DOSE 01-0104
BODY CAVITIES				
*MESENTERY	(46)	(25)	(46)	(48)
PERIARTERITIS				3 (6%)
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
NECROSIS, NOS				2
OMENTUM				
INFLAMMATION, ACUTE/CHRONIC			1	
NECROSIS, FOCAL			2	
SPECIAL MORPHOLOGY SUMMARY				
ANIMAL MISSING/NO NECROPSY			2	
AUTO/NECROPSY/HISTO PERF				1
AUTO/NECROPSY/NO HISTO	1		2	
AUTOLYSIS/NO NECROPSY	4		2	2

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 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	48	23	46	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	23	45	45
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(23)	(46)	(46)
FIBROSIS			1 (2%)	
RESPIRATORY SYSTEM				
*LARYNX	(48)	(23)	(46)	(46)
INFLAMMATION ACUTE AND CHRONIC		1 (4%)		
INFLAMMATION, CHRONIC		3 (13%)		3 (7%)
#TRACHEA	(47)	(5)	(45)	(5)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (9%)			
INFLAMMATION, ACUTE/CHRONIC	18 (38%)		24 (53%)	
INFLAMMATION, CHRONIC			2 (4%)	
POLYP, INFLAMMATORY	1 (2%)			
#LUNG/BRONCHUS	(47)	(23)	(45)	(43)
BRONCHIECTASIS	2 (4%)		3 (7%)	
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS	1 (2%)			
#LUNG/BRONCHIOLE	(47)	(23)	(45)	(43)
INFLAMMATION, NOS	4 (9%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	7 (15%)			
INFLAMMATION, ACUTE/CHRONIC	5 (11%)			
HYPERPLASIA, LYMPHOID	2 (4%)			
#LUNG	(47)	(23)	(45)	(43)
EDEMA, NOS			2 (4%)	
INFLAMMATION, FOCAL			4 (9%)	
INFLAMMATION, INTERSTITIAL	4 (9%)	3 (13%)		

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
PNEUMONIA, CHRONIC MURINE		8 (35%)		20 (47%)
GRANULOMA, NOS				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)	
GRANULOMA, FOREIGN BODY		1 (4%)		
FIBROSIS, DIFFUSE			1 (2%)	
PERIVASCULITIS	15 (32%)		1 (2%)	
INFARCT, FOCAL				1 (2%)
CALCIFICATION, FOCAL		1 (4%)		20 (47%)
HYPERPLASIA, EPITHELIAL		1 (4%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)	
#LUNG/ALVEOLI	(47)	(23)	(45)	(43)
EPITHELIALIZATION	1 (2%)			
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(47)	(22)	(43)	(42)
HYPOPLASIA, NOS	1 (2%)			
OSTEOSCLEROSIS				16 (38%)
MYELOFIBROSIS			1 (2%)	6 (14%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	1 (5%)	2 (5%)	
#SPLEEN	(47)	(23)	(45)	(43)
CONGESTION, NOS	1 (2%)			
HEMATOMA, NOS		1 (4%)		
INFLAMMATION, ACUTE			1 (2%)	
CALCIFICATION, NOS				6 (14%)
HEMOSIDEROSIS		2 (9%)	2 (4%)	
HYPERPLASIA, HEMATOPOIETIC		3 (13%)	3 (7%)	
HYPERPLASIA, ERYTHROID		4 (17%)	3 (7%)	
HEMATOPOIESIS	2 (4%)	3 (13%)		
#LUMBAR LYMPH NODE	(42)	(21)	(39)	(28)
LYMPHANGIECTASIS			1 (3%)	
#MESENTERIC L. NODE	(42)	(21)	(39)	(28)
HEMORRHAGE			1 (3%)	
#THYMUS	(36)	(20)	(31)	(35)
ATROPHY, NOS				3 (9%)
CIRCULATORY SYSTEM				
#HEART	(47)	(23)	(45)	(43)
THROMBUS, MURAL				3 (7%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
PERIARTERITIS	2 (4%)			
PERIVASCULITIS	1 (2%)			
CALCIFICATION, FOCAL				24 (56%)
HYPERTROPHY, NOS	1 (2%)			
*MYOCARDIUM	(47)	(23)	(45)	(43)
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, INTERSTITIAL		1 (4%)		
INFLAMMATION, ACUTE/CHRONIC	2 (4%)		6 (13%)	
INFLAMMATION, CHRONIC FOCAL			2 (4%)	
FIBROSIS, FOCAL			1 (2%)	
FIBROSIS, DIFFUSE			1 (2%)	
DEGENERATION, NOS	2 (4%)	4 (17%)		27 (63%)
CALCIFICATION, FOCAL				1 (2%)
*ENDOCARDIUM	(47)	(23)	(45)	(43)
INFLAMMATION, ACUTE/CHRONIC	3 (6%)			
*AORTA	(48)	(23)	(46)	(46)
MEDIAL CALCIFICATION				22 (48%)
CALCIFICATION, NOS				1 (2%)
*CORONARY ARTERY	(48)	(23)	(46)	(46)
CALCIFICATION, NOS				18 (39%)
*PULMONARY ARTERY	(48)	(23)	(46)	(46)
CALCIFICATION, NOS				1 (2%)
CALCIFICATION, FOCAL				1 (2%)
*MESENTERIC ARTERY	(48)	(23)	(46)	(46)
MEDIAL CALCIFICATION				1 (2%)
CALCIFICATION, NOS				4 (9%)
DIGESTIVE SYSTEM				
*SALIVARY GLAND	(46)	(22)	(43)	(38)
CALCIFICATION, NOS				5 (13%)
CALCIFICATION, FOCAL				1 (3%)
*LIVER	(47)	(23)	(45)	(43)
CONGESTION, CHRONIC PASSIVE		1 (4%)		7 (16%)
HEMORRHAGE	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, ACUTE FOCAL				1 (2%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
SCLEROSIS	1 (2%)			
CHOLANGIOFIBROSIS		1 (4%)		
PERIVASCULITIS	1 (2%)			
NECROSIS, FOCAL	1 (2%)		1 (2%)	5 (12%)
NECROSIS, COAGULATIVE	1 (2%)			
METAMORPHOSIS FATTY	4 (9%)	2 (9%)	4 (9%)	2 (5%)
BASOPHILIC CYTO CHANGE		4 (17%)		
HYPERTROPHY, NOS	1 (2%)			
HYPERPLASIA, NOS	1 (2%)		1 (2%)	
HYPERPLASIA, FOCAL	21 (45%)	3 (13%)	26 (58%)	
HYPERPLASIA, DIFFUSE	1 (2%)			
#LIVER/CENTRILOBULAR	(47)	(23)	(45)	(43)
NECROSIS, NOS			2 (4%)	
METAMORPHOSIS FATTY			1 (2%)	
#LIVER/HEPATOCYTES	(47)	(23)	(45)	(43)
HYPERPLASIA, FOCAL	2 (4%)			
*BILE DUCT	(48)	(23)	(46)	(46)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION WITH FIBROSIS	1 (2%)			
HYPERPLASIA, NOS	4 (8%)	2 (9%)	2 (4%)	
HYPERPLASIA, FOCAL			2 (4%)	
*PANCREAS	(46)	(22)	(44)	(39)
INFLAMMATION, INTERSTITIAL	2 (4%)			
INFLAMMATION, ACUTE/CHRONIC			7 (16%)	
CALCIFICATION, NOS				3 (8%)
ATROPHY, NOS	1 (2%)			
ATROPHY, FOCAL			1 (2%)	
*PANCREATIC ACINUS	(46)	(22)	(44)	(39)
DEGENERATION, GRANULAR	1 (2%)			
ATROPHY, NOS	4 (9%)		1 (2%)	
ATROPHY, FOCAL	1 (2%)		5 (11%)	
*STOMACH	(46)	(23)	(44)	(43)
ULCER, NOS				3 (7%)
INFLAMMATION, ACUTE				1 (2%)
REACTION, FOREIGN BODY				1 (2%)
CALCIFICATION, FOCAL				22 (51%)
*GASTRIC MUCOSA	(46)	(23)	(44)	(43)
CALCIFICATION, NOS				6 (14%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
*SMALL INTESTINE	(47)	(23)	(42)	(39)
GRANULOMA, NOS				1 (3%)
HYPERPLASIA, LYMPHOID	1 (2%)			1 (3%)
#PEYERS PATCH	(47)	(23)	(42)	(39)
HYPERPLASIA, NOS		4 (17%)		
HYPERPLASIA, LYMPHOID			1 (2%)	
*ILEUM	(47)	(23)	(42)	(39)
HYPERPLASIA, LYMPHOID			1 (2%)	
*COLON	(46)	(22)	(41)	(32)
ULCER, FOCAL	1 (2%)			
NEMATODIASIS				1 (3%)
PARASITISM		2 (9%)	7 (17%)	
CALCIFICATION, FOCAL				1 (3%)
URINARY SYSTEM				
*KIDNEY	(47)	(23)	(45)	(45)
FOREIGN BODY, NOS				1 (2%)
GLOMERULONEPHRITIS, NOS	32 (68%)	4 (17%)	12 (27%)	
GLOMERULONEPHRITIS, FOCAL			1 (2%)	
INFLAMMATION, INTERSTITIAL	2 (4%)		3 (7%)	
PYELONEPHRITIS, ACUTE		1 (4%)		
PNEUMONIA, CHRONIC MURINE				1 (2%)
GLOMERULONEPHRITIS, CHRONIC				1 (2%)
PYELONEPHRITIS, CHRONIC		1 (4%)		
NEPHROSIS, NOS		10 (43%)		40 (89%)
CALCIFICATION, FOCAL		1 (4%)		26 (58%)
*KIDNEY/CORTEX	(47)	(23)	(45)	(45)
CYST, NOS	1 (2%)			
*KIDNEY/GLOMERULUS	(47)	(23)	(45)	(45)
INFLAMMATION, MEMBRANOUS	7 (15%)			
*KIDNEY/TUBULE	(47)	(23)	(45)	(45)
NECROSIS, NOS		1 (4%)		
*KIDNEY/PELVIS	(47)	(23)	(45)	(45)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(21)	(44)	(31)
MINERALIZATION			1 (2%)	
CYST, NOS			1 (2%)	
HEMORRHAGIC CYST		1 (5%)		
NECROSIS, FOCAL	1 (2%)			
HYPERTROPHY, FOCAL	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	6 (13%)	1 (5%)		
#ADRENAL	(47)	(23)	(44)	(45)
METAMORPHOSIS FATTY	1 (2%)		5 (11%)	
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)	
HEMATOPOIESIS			1 (2%)	
#ADRENAL CORTEX	(47)	(23)	(44)	(45)
HEMORRHAGE	2 (4%)			
NODULE	4 (9%)			
DEGENERATION, NOS	2 (4%)			
NECROSIS, FOCAL	1 (2%)			
METAMORPHOSIS FATTY	1 (2%)			
PIGMENTATION, NOS	1 (2%)			
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASIA, FOCAL	9 (19%)		2 (5%)	
#ADRENAL MEDULLA	(47)	(23)	(44)	(45)
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASIA, NOS				3 (7%)
HYPERPLASIA, FOCAL	2 (4%)			
#THYROID	(45)	(21)	(41)	(38)
ULTIMOBRANCHIAL CYST				2 (5%)
HYPERPLASIA, FOCAL	3 (7%)			
HYPERPLASIA, C-CELL	1 (2%)	3 (14%)	2 (5%)	3 (8%)
#PARATHYROID	(28)	(9)	(28)	(31)
HYPERPLASIA, NOS				21 (68%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(23)	(46)	(46)
DILATATION/DUCTS			4 (9%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
GALACTOCELE	6 (13%)	1 (4%)	4 (9%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)	
CALCIFICATION, FOCAL				1 (2%)
HYPERPLASIA, NOS	1 (2%)	1 (4%)	13 (28%)	
HYPERPLASIA, CYSTIC	1 (2%)			
LACTATION		9 (39%)		16 (35%)
*MAMMARY DUCT	(48)	(23)	(46)	(46)
FIBROSIS			1 (2%)	
*CLITORAL GLAND	(48)	(23)	(46)	(46)
ABSCESS, NOS	1 (2%)		1 (2%)	
*VAGINA	(48)	(23)	(46)	(46)
POLYP	1 (2%)		1 (2%)	
*UTERUS	(46)	(23)	(43)	(38)
HYDROMETRA	2 (4%)		6 (14%)	
PYOMETRA		3 (13%)		4 (11%)
*UTERUS/ENDOMETRIUM	(46)	(23)	(43)	(38)
INFLAMMATION, NOS		1 (4%)		
INFLAMMATION, ACUTE	6 (13%)		18 (42%)	
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
INFLAMMATION, ACUTE VESICULAR			1 (2%)	
INFLAMMATION ACUTE AND CHRONIC				2 (5%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC		1 (4%)		
ATROPHY, NOS				1 (3%)
HYPERTROPHY, NOS	1 (2%)			
HYPERPLASIA, NOS	1 (2%)	1 (4%)	1 (2%)	
HYPERPLASIA, CYSTIC	7 (15%)	1 (4%)	6 (14%)	
*UTERUS/MYOMETRIUM	(46)	(23)	(43)	(38)
ABSCESS, NOS				1 (3%)
*OVARY/OVIDUCT	(46)	(23)	(43)	(38)
RETENTION FLUID	1 (2%)			
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, ACUTE	1 (2%)	1 (4%)		1 (3%)
ABSCESS, NOS		1 (4%)		1 (3%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
*OVARY	(47)	(22)	(43)	(36)
CYST, NOS	4 (9%)	3 (14%)	6 (14%)	3 (8%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
INFLAMMATION, ACUTE				2 (6%)
ABSCESS, NOS				1 (3%)
HYPERPLASIA, NOS	1 (2%)			
NERVOUS SYSTEM				
*BRAIN/MENINGES	(47)	(23)	(43)	(42)
INFLAMMATION, ACUTE				2 (5%)
*BRAIN	(47)	(23)	(43)	(42)
HYDROCEPHALUS, NOS		1 (4%)		
HEMORRHAGE		1 (4%)		
INFLAMMATION, SUPPURATIVE			1 (2%)	
GLIOSIS			1 (2%)	
MALACIA			1 (2%)	
CALCIFICATION, FOCAL		1 (4%)		
SPECIAL SENSE ORGANS				
*EYE	(48)	(23)	(46)	(46)
CATARACT	1 (2%)			
*EYE/CORNEA	(48)	(23)	(46)	(46)
INFLAMMATION, NOS				1 (2%)
*EYE/RETINA	(48)	(23)	(46)	(46)
DEGENERATION, NOS	1 (2%)			
*MIDDLE EAR	(48)	(23)	(46)	(46)
INFLAMMATION, SUPPURATIVE			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*BURSA	(48)	(23)	(46)	(46)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
BODY CAVITIES				
*MESENTERY	(48)	(23)	(46)	(46)
CALCIFICATION, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				

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

TABLE C2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0030	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0034	HIGH DOSE 02-0104
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/NO HISTO	1		1	1
AUTOLYSIS/NO NECROPSY	2	2	4	4

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 4-NITROANTHRANILIC ACID

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	46	46	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	45	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(46)	(50)	(50)
ULCER, NOS			1 (2%)	
INFLAMMATION, GRANULOMATOUS				1 (2%)
GRANULOMA, PYOGENIC	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(46)	(45)	(50)	(50)
INFLAMMATION, FOCAL	1 (2%)			
#LUNG/BRONCHIOLE	(46)	(45)	(50)	(50)
METAPLASIA, NOS				1 (2%)
#LUNG	(46)	(45)	(50)	(50)
EMPHYSEMA, NOS	1 (2%)			
HEMORRHAGE	1 (2%)			
INFLAMMATION, INTERSTITIAL	7 (15%)			
ABSCESS, NOS			1 (2%)	
PNEUMONIA, CHRONIC MURINE			4 (8%)	6 (12%)
ARTERIOSCLEROSIS, NOS		1 (2%)		
#LUNG/ALVEOLI	(46)	(45)	(50)	(50)
INFLAMMATION, NOS	1 (2%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(46)	(45)	(50)	(49)
CONGESTION, NOS			2 (4%)	
FIBROSIS		1 (2%)		
HYPERPLASIA, ERYTHROID	1 (2%)			

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
HYPERPLASIA, RETICULUM CELL		3 (7%)		
HYPERPLASIA, LYMPHOID			1 (2%)	
HEMATOPOIESIS	1 (2%)	1 (2%)		1 (2%)
*LYMPH NODE	(34)	(35)	(45)	(50)
HEMORRHAGE	1 (3%)			
HYPERPLASIA, NOS	1 (3%)			
*MANDIBULAR L. NODE	(34)	(35)	(45)	(50)
HYPERPLASIA, RETICULUM CELL	1 (3%)			
*MESENTERIC L. NODE	(34)	(35)	(45)	(50)
THROMBOSIS, NOS	1 (3%)			
HEMORRHAGE	1 (3%)			
CIRCULATORY SYSTEM				
*ENDOCARDIUM	(46)	(44)	(50)	(50)
INFLAMMATION PROLIFERATIVE	1 (2%)			
DIGESTIVE SYSTEM				
*SALIVARY GLAND	(37)	(43)	(49)	(50)
CALCULUS, NOS			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
PERIVASCULAR CUFFING	5 (14%)			
*LIVER	(46)	(45)	(50)	(50)
INFLAMMATION, FOCAL		2 (4%)		
INFLAMMATION, NECROTIZING	1 (2%)			
INFLAMMATION, CHRONIC FOCAL				1 (2%)
DEGENERATION, NOS		1 (2%)		
NECROSIS, FOCAL	2 (4%)			
NECROSIS, HEMORRHAGIC	1 (2%)			
METAMORPHOSIS FATTY	8 (17%)	3 (7%)	1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL	1 (2%)			
HEMATOPOIESIS			1 (2%)	
*LIVER/PERIPORTAL	(46)	(45)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
*BILE DUCT	(46)	(46)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
*PANCREAS	(44)	(44)	(50)	(48)
CYST, NOS			1 (2%)	
INFLAMMATION, FOCAL	2 (5%)			
INFLAMMATION, INTERSTITIAL	1 (2%)			
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
HYPERPLASIA, FOCAL	2 (5%)			
*PANCREATIC ACINUS	(44)	(44)	(50)	(48)
ATROPHY, FOCAL	1 (2%)			
*STOMACH	(45)	(42)	(50)	(50)
VEGETABLE FOREIGN BODY				1 (2%)
INFLAMMATION, NOS	2 (4%)			
INFLAMMATION, ACUTE	1 (2%)			
INFLAMMATION, GRANULOMATOUS				1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)		
HYPERPLASIA, ADENOMATOUS	2 (4%)			
*SMALL INTESTINE	(46)	(43)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)	1 (2%)
*ILEUM	(46)	(43)	(50)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
*COLON	(41)	(38)	(49)	(47)
PARASITISM				3 (6%)
URINARY SYSTEM				
*KIDNEY	(46)	(45)	(50)	(50)
CALCULUS, NOS		20 (44%)		
GLOMERULONEPHRITIS, NOS	2 (4%)			
GLOMERULONEPHRITIS, FOCAL	1 (2%)			
INFLAMMATION, INTERSTITIAL	7 (15%)	5 (11%)		
INFLAMMATION, CHRONIC		1 (2%)		
PYELONEPHRITIS, CHRONIC			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
PERIVASCULITIS		2 (4%)		
NEPHROPATHY				1 (2%)
ARTERIOSCLEROSIS, NOS		1 (2%)		

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
NEPHROSIS, NOS		1 (2%)		
AMYLOIDOSIS				2 (4%)
HYPERPLASIA, TUBULAR CELL		2 (4%)		
METAPLASIA, OSSEOUS	1 (2%)			
#KIDNEY/TUBULE	(46)	(45)	(50)	(50)
DEGENERATION, NOS		1 (2%)		
METAMORPHOSIS FATTY		9 (20%)		
ATYPIA, NOS				1 (2%)
#KIDNEY/PELVIS	(46)	(45)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	3 (7%)			
#URINARY BLADDER	(46)	(44)	(50)	(50)
HYPERPLASIA, EPITHELIAL	2 (4%)			
*URETHRA	(46)	(46)	(50)	(50)
CALCULUS, NOS			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(39)	(36)	(44)	(39)
HYPERPLASIA, FOCAL	1 (3%)			
#ADRENAL	(44)	(43)	(50)	(50)
ACCESSORY STRUCTURE				1 (2%)
NECROSIS, FOCAL	1 (2%)			
#ADRENAL/CAPSULE	(44)	(43)	(50)	(50)
HYPERPLASIA, NOS			29 (58%)	29 (58%)
#ADRENAL CORTEX	(44)	(43)	(50)	(50)
HYPERPLASIA, NOS	2 (5%)			
HYPERPLASIA, FOCAL	14 (32%)			
#PARATHYROID	(17)	(18)	(25)	(19)
CYST, NOS	1 (6%)			
REPRODUCTIVE SYSTEM				
#PROSTATE	(46)	(44)	(49)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)			
#TESTIS/TUBULE	(46)	(45)	(50)	(50)
DEGENERATION, NOS	3 (7%)	2 (4%)		

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

TABLE D1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 05-0030	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE 05-0034	HIGH DOSE 05-0103
NERVOUS SYSTEM				
#BRAIN	(46)	(45)	(50)	(50)
CALCIFICATION, FOCAL			9 (18%)	7 (14%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(46)	(46)	(50)	(50)
STEATITIS		1 (2%)		
NECROSIS, FAT	1 (2%)			
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
NECROSIS, FAT				1
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	8	4	10
ACCIDENTAL DEATH	3			
AUTO/NECROPSY/NO HISTO		1		
AUTOLYSIS/NO NECROPSY	1	4		

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 4-NITROANTHRANILIC ACID

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			3	
ANIMALS NECROPSIED	47	46	42	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	46	41	48
INTEGUMENTARY SYSTEM				
*SKIN	(47)	(46)	(42)	(49)
INFLAMMATION, ACUTE			1 (2%)	
FIBROSIS		1 (2%)		
FIBROSIS, FOCAL		1 (2%)		
RESPIRATORY SYSTEM				
*LARYNX	(47)	(46)	(42)	(49)
INFLAMMATION, CHRONIC			1 (2%)	
*LUNG	(46)	(45)	(41)	(48)
INFLAMMATION, INTERSTITIAL	2 (4%)	2 (4%)		
PNEUMONIA, CHRONIC MURINE			6 (15%)	2 (4%)
PERIARTERITIS		1 (2%)		1 (2%)
*LUNG/ALVEOLI	(46)	(45)	(41)	(48)
EMPHYSEMA, NOS	1 (2%)			
HEMATOPOIETIC SYSTEM				
*BONE MARROW	(45)	(44)	(40)	(48)
HYPOPLASIA, NOS	1 (2%)			
MYELOFIBROSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC			3 (8%)	
*SPLEEN	(45)	(43)	(39)	(48)
AMYLOIDOSIS				1 (2%)
LYMPHOCYTOSIS	2 (4%)			
HYPERPLASIA, RETICULUM CELL		2 (5%)		
HYPERPLASIA, LYMPHOID	3 (7%)	4 (9%)	1 (3%)	
HEMATOPOIESIS	2 (4%)	1 (2%)	3 (8%)	3 (6%)

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
#ABDOMINAL LYMPH NODE	(27)	(41)	(38)	(42)
INFLAMMATION ACUTE AND CHRONIC				1 (2%)
HYPERPLASIA, NOS			2 (5%)	
#PANCREATIC L.NODE	(27)	(41)	(38)	(42)
HYPERPLASIA, NOS			1 (3%)	
HYPERPLASIA, RETICULUM CELL	1 (4%)			
CIRCULATORY SYSTEM				
#HEART	(46)	(45)	(41)	(48)
PERIARTERITIS				1 (2%)
#HEART/ATRIUM	(46)	(45)	(41)	(48)
CALCIFICATION, FOCAL	1 (2%)			
#MYOCARDIUM	(46)	(45)	(41)	(48)
CALCIFICATION, FOCAL		1 (2%)		
*PULMONARY ARTERY	(47)	(46)	(42)	(49)
HYPERPLASIA, NOS		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(29)	(43)	(40)	(46)
INFLAMMATION, CHRONIC			1 (3%)	
PERIVASCULAR CUFFING	1 (3%)			
#LIVER	(46)	(45)	(41)	(47)
INFLAMMATION, FOCAL		1 (2%)		
NECROSIS, FOCAL	1 (2%)			
NECROSIS, COAGULATIVE	1 (2%)			
CYTOPLASMIC CHANGE, NOS		1 (2%)		
HYPERPLASIA, NODULAR	2 (4%)			
HYPERPLASIA, DIFFUSE		1 (2%)		
ANGIECTASIS	1 (2%)			
#LIVER/CENTRILOBULAR	(46)	(45)	(41)	(47)
NECROSIS, NOS				1 (2%)
#LIVER/PERIPORTAL	(46)	(45)	(41)	(47)
INFLAMMATION, NOS		1 (2%)		

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
HYPERPLASIA, LYMPHOID	1 (2%)			
*BILE DUCT	(47)	(46)	(42)	(49)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	1 (2%)
#PANCREAS	(39)	(41)	(41)	(43)
DILATATION/DUCTS				1 (2%)
INFLAMMATION, CHRONIC FOCAL			2 (5%)	1 (2%)
ATROPHY, FOCAL			1 (2%)	
#PANCREATIC DUCT	(39)	(41)	(41)	(43)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (3%)			
#STOMACH	(45)	(42)	(40)	(47)
INFLAMMATION, NOS	3 (7%)			
ULCER, NOS			1 (3%)	1 (2%)
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (3%)	
#PEYERS PATCH	(45)	(43)	(40)	(45)
HYPERPLASIA, NOS	1 (2%)			
#DUODENUM	(45)	(43)	(40)	(45)
ECTOPIA	1 (2%)			
#COLON	(43)	(41)	(38)	(42)
PERIARTERITIS				1 (2%)
PARASITISM				1 (2%)
URINARY SYSTEM				
*KIDNEY	(45)	(43)	(41)	(47)
GLOMERULONEPHRITIS, NOS	2 (4%)			
GLOMERULONEPHRITIS, FOCAL	1 (2%)			
INFLAMMATION, INTERSTITIAL	9 (20%)	3 (7%)		
GLOMERULONEPHRITIS, CHRONIC			1 (2%)	
PERIVASCULITIS		4 (9%)		
NEPHROPATHY				3 (6%)
AMYLOIDOSIS				1 (2%)
CALCIFICATION, FOCAL			1 (2%)	
*KIDNEY/GLOMERULUS	(45)	(43)	(41)	(47)
AMYLOIDOSIS		1 (2%)		

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
#KIDNEY/PELVIS	(45)	(43)	(41)	(47)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)		
#URINARY BLADDER	(42)	(41)	(39)	(43)
INFLAMMATION, CHRONIC			1 (3%)	
PERIVASCULITIS			1 (3%)	
ENDOCRINE SYSTEM				
#PITUITARY	(37)	(37)	(36)	(40)
HYPERPLASIA, FOCAL				1 (3%)
#ADRENAL	(44)	(43)	(40)	(47)
AMYLOIDOSIS				1 (2%)
#ADRENAL/CAPSULE	(44)	(43)	(40)	(47)
HYPERPLASIA, NOS			38 (95%)	41 (87%)
#ADRENAL CORTEX	(44)	(43)	(40)	(47)
NODULE	1 (2%)		1 (3%)	
HYPERPLASIA, NOS	2 (5%)			
#THYROID	(44)	(30)	(37)	(42)
HYPERPLASIA, FOLLICULAR-CELL			1 (3%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(47)	(46)	(42)	(49)
LACTATION			1 (2%)	
*UTERUS	(43)	(43)	(40)	(46)
HYDROMETRA	4 (9%)	4 (9%)	5 (13%)	9 (20%)
PYOMETRA			8 (20%)	6 (13%)
ATROPHY, NOS			1 (3%)	1 (2%)
METAPLASIA, SQUAMOUS	1 (2%)			
*UTERUS/ENDOMETRIUM	(43)	(43)	(40)	(46)
CYST, NOS		2 (5%)		
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE				3 (7%)
INFLAMMATION ACUTE AND CHRONIC			1 (3%)	
INFLAMMATION, CHRONIC			1 (3%)	

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
HYPERPLASIA, NOS		1 (2%)	1 (3%)	
HYPERPLASIA, CYSTIC	33 (77%)	35 (81%)	17 (43%)	7 (15%)
METAPLASIA, SQUAMOUS			1 (3%)	
*OVARY/OVIDUCT	(43)	(43)	(40)	(46)
ABSCESS, NOS			10 (25%)	6 (13%)
*OVARY	(44)	(41)	(39)	(44)
CYST, NOS	5 (11%)	1 (2%)	9 (23%)	7 (16%)
THROMBOSIS, NOS				1 (2%)
INFLAMMATION ACUTE AND CHRONIC				1 (2%)
INFLAMMATION, CHRONIC			1 (3%)	1 (2%)
AMYLOIDOSIS				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(45)	(43)	(39)	(46)
CALCIFICATION, FOCAL			5 (13%)	1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*VERTEBRA	(47)	(46)	(42)	(49)
OSTEOSCLEROSIS		1 (2%)		
BODY CAVITIES				
*ABDOMINAL CAVITY	(47)	(46)	(42)	(49)
NECROSIS, FAT				1 (2%)
*PERITONEUM	(47)	(46)	(42)	(49)
INFLAMMATION WITH FIBROSIS			1 (2%)	
*PLEURA	(47)	(46)	(42)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)			
ALL OTHER SYSTEMS				
NONE				

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

TABLE D2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 06-0030	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE 06-0034	HIGH DOSE 06-0103
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1	1	1
ANIMAL MISSING/NO NECROPSY			3	
AUTO/NECROPSY/HISTO PERF	1	2	1	3
AUTO/NECROPSY/NO HISTO			1	1
AUTOLYSIS/NO NECROPSY	3	4	5	1

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

Review of the Bioassay of 4-Nitroanthranilic Acid*
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 4-Nitroanthranilic Acid for carcinogenicity.

The reviewer agreed with the conclusion that the compound was not carcinogenic in rats or mice, under the conditions of test. He considered both the experimental design and the animal survival rate to be adequate. He noted a negative trend in several tumor types among treated animals. The reviewer moved that the report on the bioassay of 4-Nitroanthranilic Acid be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

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

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

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