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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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BIOASSAY OF

5-NITRO-o-ANISIDINE

FOR POSSIBLE CARCINOGENICITY

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

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REPORT ON THE BIOASSAY OF 5-NITRO-o-ANISIDINE
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 5-nitro-o-anisidine 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 5-nitro-o-anisidine 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).

Histopathologic examinations were performed by Dr. D. W. Hayden (3), and Dr. Yoon (3) at the Mason Research Institute, the pathology narratives were written by Dr. R. L. Schueler (4), and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (4).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (5); the statistical analysis was performed by Mr. W. W. Belew (6,7) 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 (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6,9), senior biologist Ms. P. Walker (6), biochemist Dr. B. Fuller (6), chemist Dr. N. Zimmerman (6), and technical editor Ms. P. A. Miller (6). 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 (1,9), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of 5-nitro-o-anisidine for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 5-Nitro-o-anisidine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The dietary concentrations used in the chronic bioassay for low and high dose rats were 0.4 and 0.8 percent, respectively. Dose A and B mice were fed dietary concentrations of 0.8 and 1.6 percent when initially placed on test, but after week 15 the concentration fed to dose B mice was reduced to 0.4 percent. After a 78-week period of chemical administration, observation of rats continued for up to an additional 28 weeks and observation of mice continued for up to an additional 19 weeks. For each species, 50 animals of each sex were placed on test as controls for the group receiving the higher concentration and 49 to 50 animals of each sex were placed on test as controls for the group receiving the lower concentration.

In both species, adequate numbers of animals in all groups survived long enough to be at risk from late-developing tumors.

Feeding of 5-nitro-o-anisidine to rats was associated with increased incidences of tumors of the integumentary system. Basal-cell carcinomas, trichoepitheliomas, squamous-cell carcinomas and sebaceous adenocarcinomas each occurred in the skin of high dose male rats at statistically significant incidences. For both male and female rats, carcinomas (the combined incidence of sebaceous adenocarcinomas, ceruminous carcinomas and squamous-cell carcinomas) of the Zymbal's gland or the skin of the ear were significant in the high dose groups. In the clitoral gland of dosed female rats, the incidence of carcinomas and the incidence of adenomas were each significant.

Among mice, the incidence of hepatocellular carcinoma was statistically significant for dose B females when compared to their appropriate controls.

Under the conditions of this bioassay, dietary administration of 5-nitro-o-anisidine was carcinogenic in Fischer 344 rats, causing tumors of the integumentary system in males and females and of the clitoral gland in females. The compound was also carcinogenic to female B6C3F1 mice, causing hepatocellular carcinomas.

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I. INTRODUCTION

5-Nitro-o-anisidine (Figure 1) (NCI No. C01934), a tri-substituted benzene derivative used as an intermediate in the synthesis of dyes, was selected for bioassay by the National Cancer Institute along with other dye intermediates in an attempt to determine which chemicals may be responsible for the increased incidence of bladder cancer observed among workers in the dye manufacturing industry (Wynder et al., 1963; Anthony and Thomas, 1970). Aromatic 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-methoxy-5-nitro-benzenamine.* It is also known as 3-amino-4-methoxy-nitrobenzene; 2-methoxy-5-nitroaniline; 2-amino-4-nitroanisole; Fast Scarlet R; and C.I. (Colour Index) Azoic Diazo Component 13 (C.I. No. 37130).

5-Nitro-o-anisidine is a chemical intermediate in the production of C.I. Pigment Red 23 which is used as a colorant in a wide variety of commodities including printing inks, interior latex paints, lacquers, rubber, plastics, floor coverings, paper coatings, and textiles (Schlapfer, 1973; Society of Dyers and Colourists, 1971b; Society of Dyers and Colourists, 1971c as cited in Urso, 1977). 5-Nitro-o-anisidine can also be used, along with certain C.I. coupling components, to

*The CAS registry number is 99-59-2.

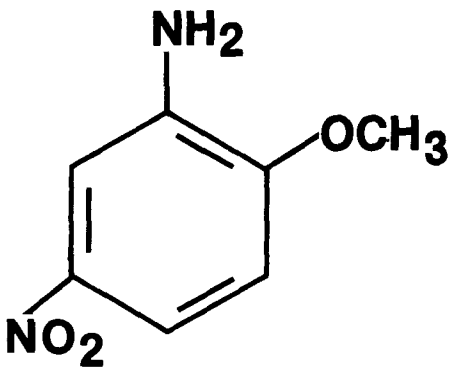


FIGURE 1
CHEMICAL STRUCTURE OF 5-NITRO-o-ANISIDINE

produce various red, brown, yellow, and violet hues on cotton, silk, acetate, and nylon (Society of Dyers and Colourists, 1971a as cited in Urso, 1977).

Production statistics for dye intermediates bearing Colour Index classifications are reported independently from those for identical compounds bearing chemical names. In 1975, five U.S. companies reported production of 191 thousand pounds of C.I. Azoic Diazo Component 13, salt, the stabilized diazonium salt of 5-nitro-o-anisidine. In that same year, C.I. Azoic Diazo Component 13, base, was produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by only one of these companies; production statistics for the base are therefore considered proprietary and are not available (U.S. International Trade Commission, 1977a). Domestic production of Azoic Diazo Components as a class appears to be declining, with decreases of 25.7 and 19.6 percent noted from 1974 to 1975 for bases and salts, respectively (U.S. International Trade Commission, 1977a). 5-Nitro-o-anisidine itself was not listed in Synthetic Organic Chemicals, U.S. Production and Sales, 1975 (U.S. International Trade Commission, 1977a), implying that it was not produced commercially in that year. The compound was, however, included in the 1977 Directory of Chemical Producers, U.S.A. (Stanford Research Institute, 1977) and is presently manufactured on a commercial scale by two companies, one of which also produces C.I. Azoic Diazo Component 13.

Imports of 5-nitro-o-anisidine through principal U.S. customs districts amounted to 75 thousand pounds in 1975 and included 45 thousand pounds of C.I. Azoic Diazo Component 13, base (U.S. International Trade Commission, 1977b as cited in Urso, 1977). This quantity represents a 45 percent decrease over the 1974 figure of 136 thousand pounds (U.S. International Trade Commission, 1976 as cited in Urso, 1977).

II. MATERIALS AND METHODS

A. Chemicals

5-Nitro-o-anisidine was purchased from Carroll Products, Wood River Junction, Rhode Island. Chemical analysis was performed by Mason Research Institute, Worcester, Massachusetts. The experimentally determined melting point of 118°C was identical with that reported in the literature (Weast, 1977). Infrared analysis was consistent with the structure of the compound. Thin-layer chromatography did not show the presence of impurities. The evidence suggests that the purchased compound was of high purity.

Throughout this report the term 5-nitro-o-anisidine is used to represent this compound.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 5-Nitro-o-anisidine was administered to the dosed animals as a component of the diet. Proper amounts of the chemical were removed from the stock bottle under an exhaust hood. The compound was blended in an aluminum bowl with an aliquot of the ground feed. Once visual homogeneity was attained, the mixture was placed into a 6 kg capacity Patterson-Kelley twin shell V-blender along with the remainder of the meal. The blender was sealed and operated for 20 minutes. The mixtures were placed into plastic bags and stored in the dark at 4°C. The dietary preparations were used for only 1 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 rats, mice assigned to the dose B group (see p. 14), and all control animals were obtained from Charles River Breeding Laboratories, Wilmington, Massachusetts. Low dose rats and dose A mice were obtained from ARS/Sprague-Dawley, Madison, Wisconsin. Dosed and control animals for both species were received in separate shipments.

Upon arrival, a sample of animals was examined for parasites and other signs of disease. The remaining animals were quarantined by species for 2 weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that 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, high dose rats and their controls were housed in galvanized- or stainless-steel wire-mesh cages (Fenco Cage Products, Boston, Massachusetts) suspended above newspapers.

Low dose rats and their controls were held in galvanized- or stainless-steel wire-mesh cages during quarantine and for the first 7 months of study. Newspapers under cages were replaced daily and cages and racks washed weekly. For the remainder of the study, all rats were held in suspended polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) equipped with disposable nonwoven fiber filter sheets. Clean cages and bedding were provided twice weekly. Low dose rats and their controls were provided with SAN-I-CEL® corncob bedding (Paxton Processing Company, Paxton, Illinois) while in polycarbonate cages. High dose rats were provided with SAN-I-CEL® for 7 months, after which Aspen hardwood chip bedding (American Excelsior Company, Baltimore, Maryland) was used for these animals for the remainder of the study. Stainless steel cage racks were cleaned once every 2 weeks, and new disposable filters were installed at that time.

Mice were housed by sex in polycarbonate cages. During quarantine and dosing periods, cages were fitted with perforated stainless steel lids. During the final observation period, stainless steel wire bar lids were used. Both types of lids were from Lab Products, Inc. Nonwoven fiber filter bonnets were used over cage lids. Dose B mice and their controls were housed ten per cage for the first 11 months and five per cage thereafter. Dose A mice and their controls were reduced to five per cage after 18 months. Clean cages, lids, filters, and bedding were provided three times per week when cage populations were ten and twice per week when cage populations were

reduced to five. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used for 1 month (for dose B mice and their controls) and 7 months (for dose A mice and their controls). SAN-I-CEL® was used for the next 12 months. Bed-o-Cobs® corncob bedding (The Andersons Cob Division, Maumee, Ohio) was used for the next 8 months, and Aspen bedding 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 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, water was supplied as needed between changes. Food and water were supplied ad libitum.

Pelleted Wayne Lab-Blox® was supplied to low dose rats and their controls during the quarantine period and to all rats and mice during the final observation period. During the 78-week dosing period, all animals were supplied with Wayne Lab-Blox® meal containing the appropriate concentration of 5-nitro-o-anisidine. Control animals had untreated meal available. Throughout the study, meal was supplied to all mice and to low dose rats and their controls in Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) equipped with stainless steel baffles. High dose rats and their controls were supplied food from Alpine® feed cups for the first 11

months of study and thereafter from stainless steel gangstyle feed hoppers (Scientific Cages, Inc., Bryan, Texas). 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.

All dosed rats were housed in a room with other rats receiving diets containing* 3-amino-4-ethoxyacetanilide (17026-81-2); 1-amino-2-methylanthraquinone (82-28-0); 4-nitroanthranilic acid (619-17-0); and 5-nitroacenaphthene (602-87-9). All control rats were in a room with other rats receiving diets containing 3-nitro-p-acetophenetide (1777-84-0); amitrole (61-82-5); and 2-methyl-1-nitroanthraquinone (129-15-7).

Dose B mice were housed in a room with other mice receiving diets containing 2,5-toluenediamine sulfate (6369-59-1); 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 1-nitronaphthalene (86-57-7); 3-amino-9-ethylcarbazole hydrochloride; 6-nitrobenzimidazole (94-52-0); and 2,4-diaminoanisole sulfate (615-05-4). Dose A mice and all control mice were housed in a room with other mice receiving diets containing 1-amino-2-methylanthraquinone (82-28-0); N,N-dimethyl-p-nitrosoaniline (138-89-6); 2,5-toluenediamine sulfate (6369-59-1); 2,4-dinitrotoluene (121-14-2); 1-nitronaphthalene (86-57-7); 3-amino-9-ethylcarbazole hydrochloride; 2-aminoanthraquinone

*CAS registry numbers are given in parentheses.

(117-79-3); 3-amino-4-ethoxyacetanilide (17026-81-2); 5-nitroacenaphthene (602-87-9); 2,4-diaminoanisole sulfate (615-05-4); amitrole (61-82-5); 3-nitro-p-acetophenetide (1777-84-0); 4-nitroanthranilic acid (619-17-0); and APC (8003-03-0).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentration of 5-nitro-o-anisidine for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among five groups, each consisting of five males and five females. 5-Nitro-o-anisidine was incorporated into the laboratory diet and supplied ad libitum to four of the five groups of each species in concentrations of 0.05, 0.1, 0.2, and 0.4 percent. The fifth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for 7 weeks, followed by a 1-week observation period during which all animals were fed the basal laboratory diet. All survivors were sacrificed at the end of the observation period and gross necropsies were performed.

The highest concentration causing no deaths, no compound-related gross abnormalities, and no mean body weight depression in excess of 10 percent relative to controls during the 8-week subchronic test was selected as the high concentration utilized for the chronic bioassay.

In rats no deaths occurred at any doses tested. The single gross abnormality observed, a darkened spleen, was encountered in two

female rats receiving 0.4 percent 5-nitro-o-anisidine. A dietary concentration of 0.2 percent produced no mean body weight depression in male or female rats. A dietary concentration of 0.4 percent produced mean body weight depressions of 0.7 and 10.0 percent in male and female rats, respectively. The high concentration selected for administration to rats in the chronic bioassay was 0.4 percent.

No deaths occurred in mice at any doses tested. A dietary concentration of 0.4 percent produced 7.9 percent mean body weight depression in male mice and no mean body weight depression in female mice. The high concentration selected for administration to mice in the chronic bioassay was 0.8 percent.

F. Experimental Design

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

All rats were approximately 6 weeks old at the time the test was initiated. The initial concentrations of 5-nitro-o-anisidine in diets were 0.4 and 0.2 percent. The rat group receiving a concentration of 0.2 percent was sacrificed after 16 weeks and no histopathologic examinations were performed because the dose level was considered, on the basis of mean body weight depression, to be too low. A new rat group, receiving a dietary concentration of 0.8 percent, was started approximately 7 months after the initiation of the chronic study. Throughout

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
5-NITRO-o-ANISIDINE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	5-NITRO-o-ANISIDINE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	108
HIGH DOSE CONTROL	49	0	0	109
LOW DOSE	50	0.4 0	78	 28
HIGH DOSE	50	0.8 0	78	 24
FEMALE				
LOW DOSE CONTROL	50	0	0	108
HIGH DOSE CONTROL	50	0	0	109
LOW DOSE	50	0.4 0	78	 28
HIGH DOSE	50	0.8 0	78	 28

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
5-NITRO-o-ANISIDINE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	5-NITRO-o-ANISIDINE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[a]
MALE					
DOSE A CONTROL	50	0	0	95	0
DOSE B CONTROL	50	0	0	96	0
DOSE A	50	0.8 0	78	 18	0.8
DOSE B	50	1.6 0.4 0	15 63	 18	0.6
FEMALE					
DOSE A CONTROL	50	0	0	96	0
DOSE B CONTROL	50	0	0	96	0
DOSE A	50	0.8 0	78	 19	0.8
DOSE B	50	1.6 0.4 0	15 63	 18	0.6

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

this report those rats receiving the 0.8 percent concentration are referred to as the high dose groups and those receiving the 0.4 percent concentration are referred to as the low dose groups. A high dose control group was started approximately a week before the high dose group was initiated. The dosed rats were supplied with feed containing 5-nitro-o-anisidine for a total of 78 weeks, followed by an observation period of up to 28 weeks.

All mice were approximately 6 weeks old at the time they were placed on test. The initial concentrations of 5-nitro-o-anisidine in diets were 0.8 and 0.4 percent. The mouse group receiving 0.4 percent was sacrificed after 16 weeks and no histopathologic examinations were performed because, based on the absence of weight depression, the dose level was considered to be too low. A new group, receiving 1.6 percent, and a control group were started approximately 7 months after the initiation of the chronic study. The dietary concentration administered to this group was lowered to 0.4 percent after 15 weeks of chemical administration. Throughout this report those mice initially receiving a concentration of 1.6 percent are referred to as the dose B groups and those receiving a concentration of 0.8 percent are referred to as the dose A groups. The terms dose A and dose B groups are used instead of the more common terms, high and low dose groups, because the groups that initially received a higher dietary concentration of the compound ultimately received a lower time-weighted average concentration, due

to dose changes. The dosed mice were supplied with feed containing 5-nitro-o-anisidine for a total of 78 weeks, followed by an observation period of up to 19 weeks.

G. Clinical and Histopathologic Examinations

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

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

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

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, muscle, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, 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 (Armitage, 1971, pp. 362-365) was not used.

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 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

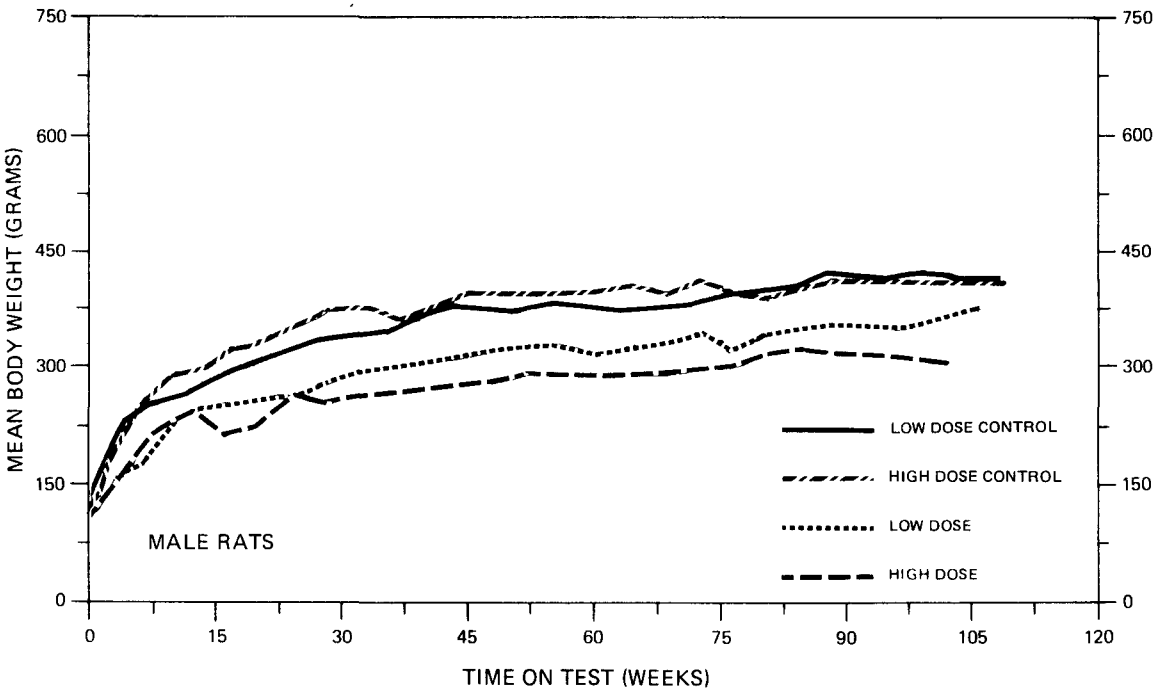
percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically 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

Mean body weight depression was observed in all dosed groups when compared to their control groups. The mean body weight difference between high dose groups and their control groups was greater than that between low dose groups and their controls (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Twelve high dose males and two high dose females had subcutaneous and/or cutaneous growths. Similar subcutaneous and/or cutaneous growths were observed in two low dose males and three low dose females. Two high dose control male rats developed subcutaneous and/or cutaneous growths, as did 10 high dose female rats. Similar growths were recorded in four low dose control male rats and six low dose control female rats. A crusted lesion was observed on the dorsal surface of one high dose male, and one high dose male displayed bleeding from the ear canal. White discoloration of the eyes was recorded in the two high dose females, one high dose control female, and three low dose control females. Exopthalmia was observed in one high dose control female and alopecia was present in one female of the same group. No other clinical abnormalities were observed.



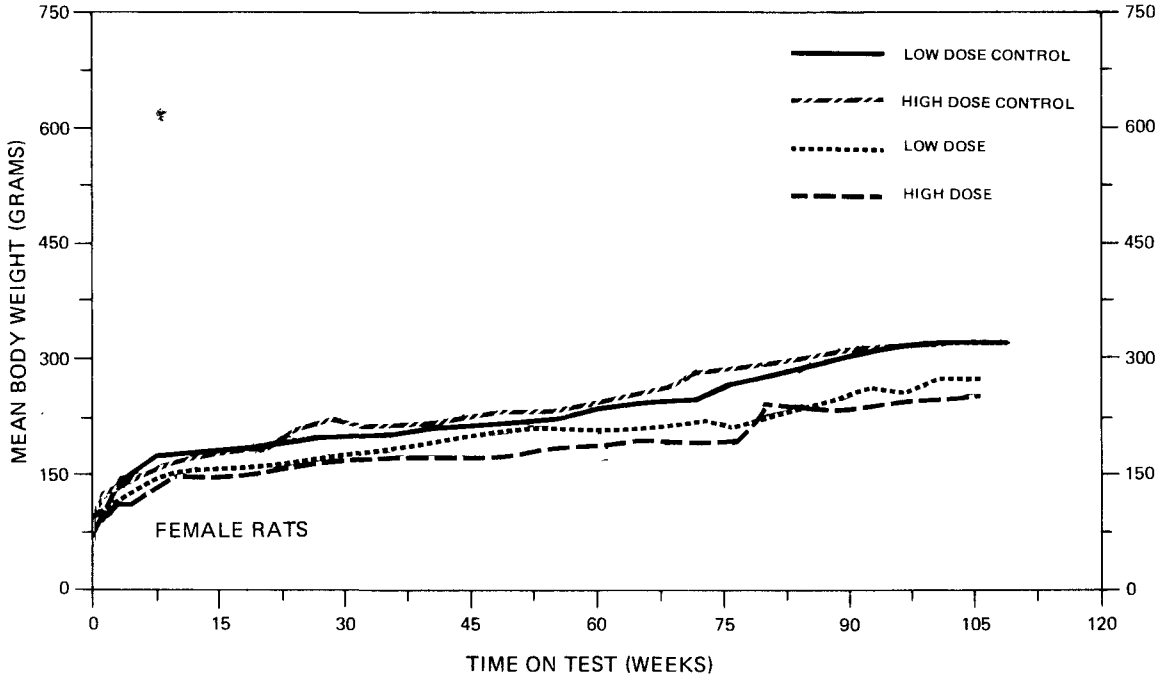


FIGURE 2
GROWTH CURVES FOR 5-NITRO-o-ANISIDINE CHRONIC STUDY RATS

B. Survival

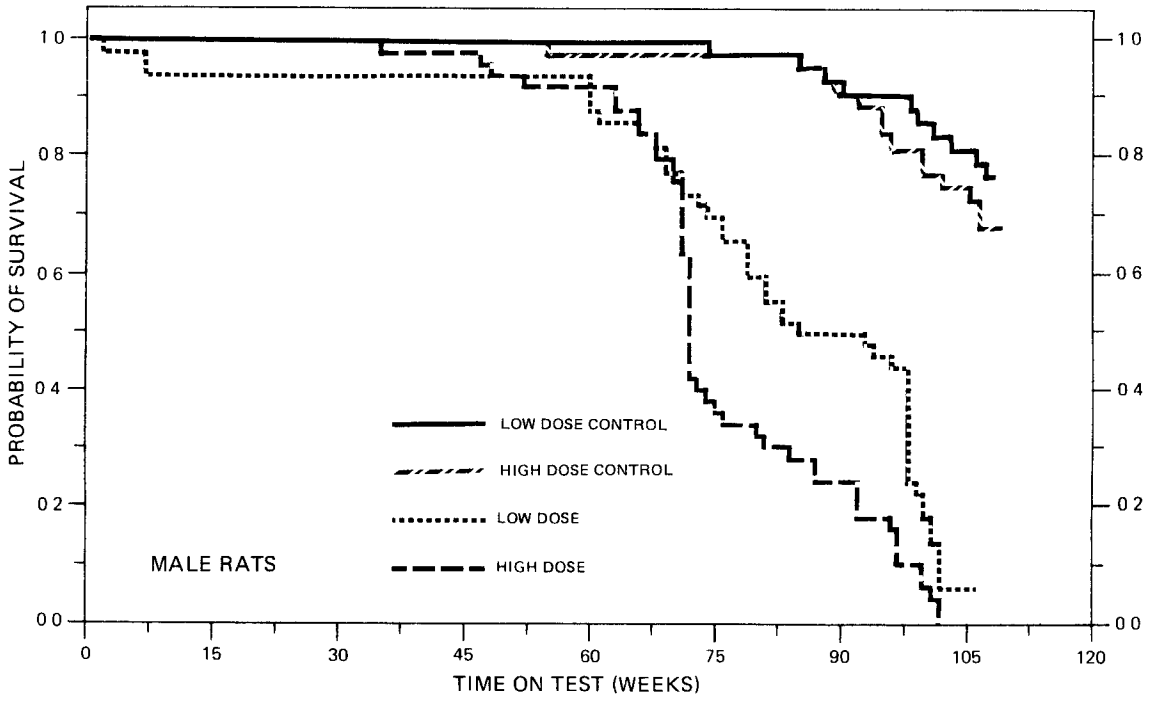
The estimated probabilities of survival for male and female rats in the control and 5-nitro-o-anisidine-dosed groups are shown in Figure 3. For both males and females the Cox tests indicated that both the high dose and the low dose group had significantly greater mortality than their respective controls.

For males the survival of both dosed groups was good for at least 65 weeks, followed by sharp increases in mortality with 17 high dose rats dying in weeks 71 and 72. Five high dose controls were sacrificed in week 78 and five low dose controls in week 80. Adequate numbers of males were at risk from late-developing tumors as at least 39 males from each of the groups survived on test at least 70 weeks.

For females five high dose controls were sacrificed in week 78 and five low dose controls in week 80. Adequate numbers of females were at risk from late-developing tumors with 58 percent (29/50) of the high dose, 74 percent (37/50) of the low dose, 86 percent (43/50) of the high dose control, and 88 percent (44/50) of the low dose control surviving on test at least 85 weeks.

C. Pathology

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



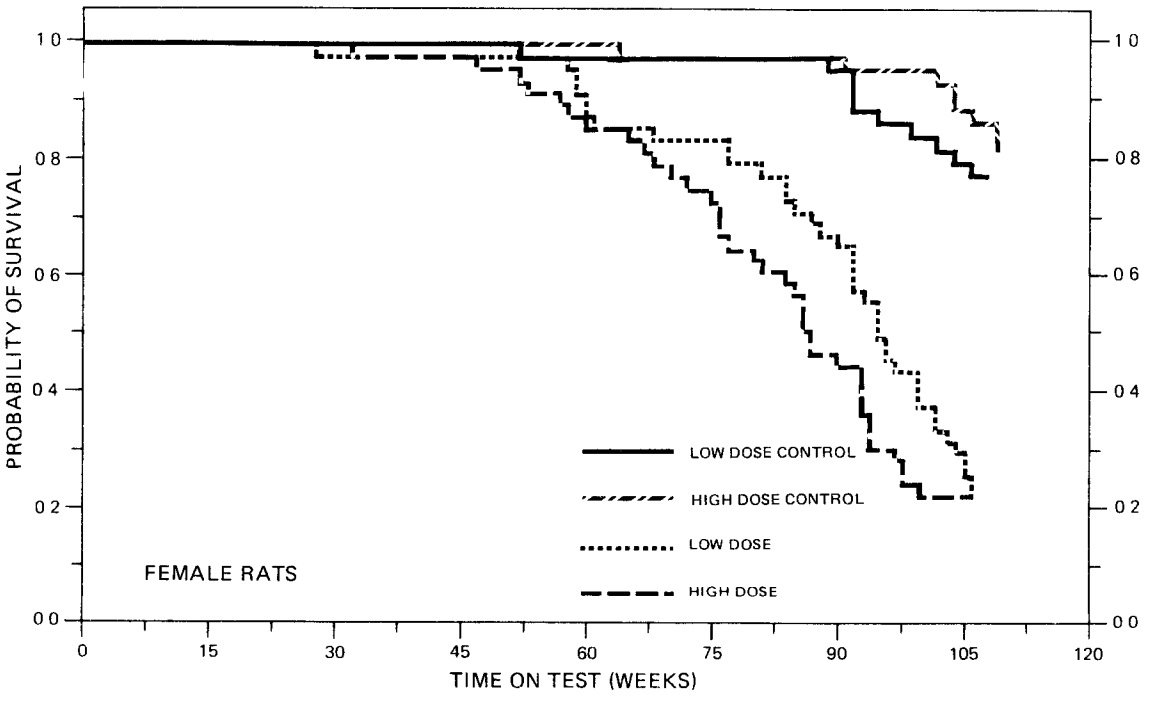


FIGURE 3
SURVIVAL COMPARISONS OF 5-NITRO-o-ANISIDINE CHRONIC STUDY RATS

Neoplasms attributed to the administration of 5-nitro-o-anisidine were found in the integument and associated glands. Some dosed rats had tumors at more than one body site.

Basal-cell carcinoma of the skin occurred in 1/48 (2 percent) low dose control, 7/50 (14 percent) low dose, and 30/48 (63 percent) high dose males, and in 1/50 (2 percent) high dose control and 1/46 (2 percent) high dose female rats. This tumor was defined as a tumor of undifferentiated cells of the basal layer of the epidermis growing down into the dermis, sometimes in a polarized arrangement or forming a lacey pattern. Tumor cells were small with oval, deep-staining nuclei and scanty indistinct cytoplasm (Zackheim, 1973).

Sebaceous adenocarcinoma occurred in 5/50 (10 percent) low dose and 21/48 (44 percent) high dose male and in 1/49 (2 percent) low dose and 2/46 (4 percent) high dose female rats while none occurred in the control animals. This tumor arose either in the skin or in the ear canal (Zymbal's gland). It consisted of a variable mixture of basal cells proliferating from the wall of a sebaceous gland, of fully differentiated sebaceous cells with abundant foamy cytoplasm, and of intermediate cells having a small amount of foamy cytoplasm. Tumors arising in the ear canal usually exhibited superficial squamous differentiation (Pliss, 1973).

Trichoepitheliomas occurred in 20/50 (40 percent) low dose and 9/48 (19 percent) high dose male rats, while none occurred in the control groups. This tumor also arose from basal cells of the epidermis

and contained cystic structures composed of whorled squamous cells surrounded by undifferentiated basal cells and exhibiting no zone of transition (Zackheim, 1973). In some instances the contents of the cyst resembled those of a normal hair follicle.

Squamous-cell carcinoma occurred in 1/48 low dose control males, 3/50 low dose and 12/48 high dose males, and in 2/49 low dose and 3/46 high dose females. The tumor was characterized by invasion of adjacent tissue by whorls and strands of neoplastic cells, some of which exhibited keratinization and some of which might be small and poorly differentiated (Zackheim, 1973). Mitoses were often abundant.

Mammary adenocarcinoma was observed in 0/99 control, 11/49 low dose and 5/46 high dose female rats. This was defined as a tumor arising from glandular epithelium of the mammary gland and having a more or less well-marked acinar pattern. Nuclei were round with prominent nucleoli. Cytoplasm was usually acidophilic and occasionally contained large secretion vacuoles. Secretion was often found in the lumens of acini.

The incidences of adenoma NOS, carcinoma NOS, squamous-cell carcinoma, or cystadenoma NOS of the preputial gland (2/96 [2 percent] controls, 3/50 [6 percent] low dose, 6/48 [13 percent] high dose) in male rats and of adenoma NOS, carcinoma NOS, squamous-cell papilloma, squamous-cell carcinoma, adenocarcinoma NOS, or papillary adenoma of the clitoral gland (4/99 [4 percent] controls, 13/49 [27 percent] low dose, 14/46 [30 percent] high dose) in female rats was elevated.

The morphology of these tumors was similar in both sexes. The characteristic feature of these tumors was the presence of at least a few large cells having abundant cytoplasm packed with coarse, brightly acidophilic granules. Some of these tumors exhibited enough superficial squamous differentiation to be classified as squamous-cell neoplasms. Other tumors with minimal squamous change were classified as adenomas if they consisted of masses of large, often granulated cells with large, rounded vesicular nuclei surrounding a central cavity and having a well-defined intact outer border. If the outer border of the tumor was irregular and consistent with invasion of surrounding tissue, the tumors were classified as adenocarcinomas or carcinomas. The boundary lines between the varieties of these tumors were not distinct so that there was a continuous spectrum from adenoma to carcinoma.

Nonneoplastic cutaneous lesions were observed among male rats in both dosed groups and included cystic and hyperplastic lesions.

Based upon this histopathologic evaluation, 5-nitro-o-anisidine was carcinogenic to Fischer 344 rats. Benign and malignant neoplasms of the skin and its glands were induced by oral administration of the compound.

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

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 5-NITRO-o-ANISIDINE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Skin: Basal-Cell Carcinoma[b]	1/48(0.02)	0/48(0.00)	7/50(0.14)	30/48(0.63)
P Values[c]	---	---	P = 0.034	P < 0.001
Relative Risk (Control)[d]	---	---	6.720	Infinite
Lower Limit	---	---	0.914	10.044
Upper Limit	---	---	296.013	Infinite
Weeks to First Observed Tumor	107	---	74	48
Skin: Trichoepithelioma[b]	0/48(0.00)	0/48(0.00)	20/50(0.40)	9/48(0.19)
P Values[c]	---	---	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	6.208	2.633
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	76	68
Skin: Papilloma NOS or Squamous-Cell Papilloma[b]	1/48(0.02)	0/48(0.00)	2/50(0.04)	4/48(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.920	Infinite
Lower Limit	---	---	0.103	0.928
Upper Limit	---	---	110.993	Infinite
Weeks to First Observed Tumor	108	---	81	71

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Skin: (Excluding skin of ear): Squamous-Cell Carcinoma[b]	0/48(0.00)	0/48(0.00)	3/50(0.06)	11/48(0.23)
P Values[c]	---	---	N.S.	P < 0.001
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.578	3.325
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	60	66
Skin: (Excluding skin of ear): Sebaceous Adenocarcinoma[b]	0/48(0.00)	0/48(0.00)	5/50(0.10)	18/48(0.38)
P Values[c]	---	---	P = 0.031	P < 0.001
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	1.212	5.770
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	66	47
Skin: (Excluding skin of ear): Sebaceous Adenoma or Sebaceous Adenocarcinoma[b]	0/48(0.00)	0/48(0.00)	14/50(0.28)	23/48(0.48)
P Values[c]	---	---	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	4.192	7.533
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	60	47

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Skin or Adnexa (Excluding skin of ear): Squamous-Cell Carcinoma, Basal-Cell Carcinoma, Trichoepithelioma, Sebaceous Adenocarcinoma, or Sweat-Gland Carcinoma[b]	1/48(0.02)	0/48(0.00)	30/50(0.60)	40/48(0.83)
P Values[c]	---	---	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	---	28.800	Infinite
Lower Limit	---	---	5.228	13.896
Upper Limit	---	---	999.999	Infinite
Weeks to First Observed Tumor	107	---	60	47
Skin and Subcutaneous Tissue: Fibroma[b]	2/48(0.04)	3/48(0.06)	3/50(0.06)	1/48(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.440	0.333
Lower Limit	---	---	0.173	0.006
Upper Limit	---	---	16.632	3.976
Weeks to First Observed Tumor	99	95	79	101
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/48(0.00)	1/48(0.02)	4/49(0.08)	1/48(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	1.000
Lower Limit	---	---	0.909	0.013
Upper Limit	---	---	Infinite	76.887
Weeks to First Observed Tumor	---	109	98	100

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	6/48(0.13)	6/48(0.13)	0/50(0.00)	0/48(0.00)
P Values[c]	---	---	P = 0.012(N)	P = 0.013(N)
Relative Risk (Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	0.600	0.624
Weeks to First Observed Tumor	98	92	---	---
Liver: Neoplastic Nodule[b]	1/48(0.02)	0/48(0.00)	3/48(0.06)	1/48(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	3.000	Infinite
Lower Limit	---	---	0.252	0.054
Upper Limit	---	---	154.112	Infinite
Weeks to First Observed Tumor	99	---	96	75
Pituitary: Adenoma NOS[b]	1/41(0.02)	9/38(0.24)	8/44(0.18)	5/39(0.13)
P Values[c]	---	---	P = 0.019	N.S.
Relative Risk (Control)[d]	---	---	7.455	0.541
Lower Limit	---	---	1.070	0.157
Upper Limit	---	---	321.866	1.624
Weeks to First Observed Tumor	108	85	66	72

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Cortical Adenoma or Cortical Carcinoma[b]	1/47(0.02)	0/47(0.00)	1/48(0.02)	5/48(0.10)
P Values[c]	---	---	N.S.	P = 0.030
Relative Risk (Control)[d]	---	---	0.979	Infinite
Lower Limit	---	---	0.013	1.237
Upper Limit	---	---	75.277	Infinite
Weeks to First Observed Tumor	106	---	98	70
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	10/47(0.21)	8/47(0.17)	6/48(0.13)	14/48(0.29)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.588	1.714
Lower Limit	---	---	0.191	0.745
Upper Limit	---	---	1.634	4.262
Weeks to First Observed Tumor	99	106	83	71
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	0/39(0.00)	1/48(0.02)	4/47(0.09)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	2.043
Lower Limit	---	---	0.775	0.110
Upper Limit	---	---	Infinite	117.920
Weeks to First Observed Tumor	---	109	100	72

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	3/45(0.07)	0/46(0.00)	4/44(0.09)	0/46(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.364	---
Lower Limit	---	---	0.245	---
Upper Limit	---	---	8.822	---
Weeks to First Observed Tumor	85	---	98	---
Preputial Gland: Adenoma NOS or Carcinoma NOS[b]	2/48(0.04)	0/48(0.00)	2/50(0.04)	5/48(0.10)
P Values[c]	---	---	N.S.	P = 0.028
Relative Risk (Control)[d]	---	---	0.960	Infinite
Lower Limit	---	---	0.072	1.263
Upper Limit	---	---	12.789	Infinite
Weeks to First Observed Tumor	103	---	96	70
Testis: Interstitial-Cell Tumor[b]	45/47(0.96)	42/47(0.89)	37/47(0.79)	16/48(0.33)
P Values[c]	---	---	P = 0.014(N)	P < 0.001(N)
Relative Risk (Control)[d]	---	---	0.822	0.373
Lower Limit	---	---	0.754	0.281
Upper Limit	---	---	0.980	0.542
Weeks to First Observed Tumor	80	78	61	72

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Zymbal's Gland or Skin of Ear: Sebaceous Adenocarcinoma, Ceruminous Carcinoma, or Squamous-Cell Carcinoma[b]	1/48(0.02)	0/48(0.00)	2/50(0.04)	10/48(0.21)
P Values[c]	---	---	N.S.	P = 0.001
Relative Risk (Control)[d]	---	---	1.920	Infinite
Lower Limit	---	---	0.103	2.979
Upper Limit	---	---	110.993	Infinite
Weeks to First Observed Tumor	99	---	79	63
Body Cavities: Mesothelioma NOS or Mesothelioma, Malignant[b]	1/48(0.02)	2/48(0.04)	5/50(0.10)	2/48(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	4.800	1.000
Lower Limit	---	---	0.566	0.075
Upper Limit	---	---	222.171	13.306
Weeks to First Observed Tumor	108	106	71	72

[a]Treated groups received doses of 0.4 or 0.8 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 on 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 5-NITRO-o-ANISIDINE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Skin (Excluding skin of ear): Squamous-Cell Carcinoma, Basal-Cell Carcinoma, or Sebaceous Adenocarcinoma[b]	0/49(0.00)	1/50(0.02)	2/49(0.04)	5/46(0.11)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	5.435
Lower Limit	---	---	0.296	0.640
Upper Limit	---	---	Infinite	250.926
Weeks to First Observed Tumor	---	109	59	75
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/49(0.00)	1/50(0.02)	5/49(0.10)	1/43(0.02)
P Values[c]	---	---	P = 0.028	N.S.
Relative Risk (Control)[d]	---	---	Infinite	1.163
Lower Limit	---	---	1.262	0.015
Upper Limit	---	---	Infinite	89.179
Weeks to First Observed Tumor	---	109	92	87
Pituitary: Adenoma NOS[b]	18/44(0.41)	17/40(0.43)	10/46(0.22)	5/41(0.12)
P Values[c]	---	---	P = 0.041(N)	P = 0.002(N)
Relative Risk (Control)[d]	---	---	0.531	0.287
Lower Limit	---	---	0.250	0.093
Upper Limit	---	---	1.071	0.720
Weeks to First Observed Tumor	89	78	84	84

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Cortical Adenoma or Cortical Carcinoma[b]	1/49(0.02)	1/49(0.02)	2/49(0.04)	3/44(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.000	3.341
Lower Limit	---	---	0.108	0.280
Upper Limit	---	---	115.581	171.218
Weeks to First Observed Tumor	104	109	102	86
Adrenal: Pheochromocytoma[b]	2/49(0.04)	3/49(0.06)	3/49(0.06)	6/44(0.14)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.500	2.227
Lower Limit	---	---	0.180	0.508
Upper Limit	---	---	17.316	13.017
Weeks to First Observed Tumor	108	109	84	86
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	3/40(0.08)	2/45(0.04)	3/49(0.06)	1/42(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.816	0.536
Lower Limit	---	---	0.116	0.009
Upper Limit	---	---	5.802	9.894
Weeks to First Observed Tumor	108	109	92	106

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Clitoral Gland: Carcinoma NOS[b]	0/49(0.00)	0/50(0.00)	0/49(0.00)	7/46(0.15)
P Values[c]	---	---	N.S.	P = 0.004
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	2.112
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	67
Clitoral Gland: Carcinoma NOS or Squamous-Cell Carcinoma[b]	0/49(0.00)	0/50(0.00)	1/49(0.02)	9/46(0.20)
P Values[c]	---	---	N.S.	P = 0.001
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.054	2.860
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	60	67
Clitoral Gland: Adenoma NOS or Papillary Adenoma or Carcinoma NOS or Squamous-Cell Carcinoma[b]	1/49(0.02)	2/50(0.04)	12/49(0.24)	14/46(0.30)
P Values[c]	---	---	P = 0.001	P < 0.001
Relative Risk (Control)[d]	---	---	12.000	7.609
Lower Limit	---	---	1.894	1.887
Upper Limit	---	---	499.415	65.553
Weeks to First Observed Tumor	108	104	77	57

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	12/49(0.24)	10/50(0.20)	14/49(0.29)	6/44(0.14)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.167	0.682
Lower Limit	---	---	0.560	0.221
Upper Limit	---	---	2.469	1.890
Weeks to First Observed Tumor	80	78	61	76
Uterus and Uterus/Endometrium: Carcinoma-in-Situ NOS, Undifferentiated Carcinoma, Adenocarcinoma NOS, Adenoca in Adenomatous Polyp, or Papillary Adenocarcinoma[b]	2/49(0.04)	1/50(0.02)	3/49(0.06)	5/44(0.11)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.500	5.682
Lower Limit	---	---	0.180	0.670
Upper Limit	---	---	17.316	262.045
Weeks to First Observed Tumor	108	109	106	100
Cerebrum and Brain: Astrocytoma, Glioma NOS, Oligodendroglioma, or Medulloblastoma[b]	1/49(0.02)	0/50(0.00)	2/49(0.04)	3/44(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.000	Infinite
Lower Limit	---	---	0.108	0.684
Upper Limit	---	---	115.581	Infinite
Weeks to First Observed Tumor	92	---	58	68

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Zymbal's Gland or Skin of Ear: Sebaceous Adenocarcinoma[b]	0/49(0.00)	0/50(0.00)	1/49(0.02)	4/46(0.09)
P Values[c]	---	---	N.S.	P = 0.049
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.054	1.008
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	77	75
Zymbal's Gland or Skin of Ear: Sebaceous Adenocarcinoma or Squamous-Cell Carcinoma[b]	0/49(0.00)	0/50(0.00)	3/49(0.06)	7/46(0.15)
P Values[c]	---	---	N.S.	P = 0.004
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.602	2.112
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	60	32
Mammary Gland: Adenocarcinoma NOS[b]	0/49(0.00)	0/50(0.00)	10/49(0.20)	4/46(0.09)
P Values[c]	---	---	P = 0.001	P = 0.049
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	2.976	1.008
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	84	81

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma NOS, Papillary Adenocarcinoma or Adenoma NOS[b]	2/49(0.04)	0/50(0.00)	11/49(0.22)	4/46(0.09)
P Values[c]	---	---	P = 0.007	P = 0.049
Relative Risk (Control)[d]	---	---	5.500	Infinite
Lower Limit	---	---	1.288	1.008
Upper Limit	---	---	48.873	Infinite
Weeks to First Observed Tumor	108	---	84	81
Mammary Gland: Fibroadenoma[b]	16/49(0.33)	19/50(0.38)	4/49(0.08)	0/46(0.00)
P Values[c]	---	---	P < 0.001(N)	P < 0.001(N)
Relative Risk (Control)[d]	---	---	0.250	0.000
Lower Limit	---	---	0.066	0.000
Upper Limit	---	---	0.708	0.178
Weeks to First Observed Tumor	80	106	84	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	7/49(0.14)	5/50(0.10)	0/49(0.00)	4/46(0.09)
P Values[c]	---	---	P = 0.006(N)	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.870
Lower Limit	---	---	0.000	0.183
Upper Limit	---	---	0.515	3.788
Weeks to First Observed Tumor	106	104	---	84

TABLE 4 (CONCLUDED)

[a]Treated groups received doses of 0.4 or 0.8 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 on the relative risk of the treated group to the control group.

tumors were observed in at least one of the control or 5-nitro-o-anisidine-dosed groups and where such tumors were observed in at least 5 percent of the group. Caution must be used in interpreting the low dose results since the low dose groups were from a different supplier than the low dose control groups.

For both male and female rats numerous carcinomas of the Zymbal's gland or the skin of the ear were observed in the high dose groups. For males, the Fisher exact comparisons of the high dose group to the high dose control indicated that the combined incidence of sebaceous adenocarcinomas, ceruminous carcinomas, and squamous-cell carcinomas was significantly ($P = 0.001$) greater in the high dose group. Similarly, for females the combined incidence of sebaceous adenocarcinomas and squamous-cell carcinomas were significantly ($P = 0.004$) greater in the high dose group than in the high dose control. Based upon these results the administration of 5-nitro-o-anisidine was associated with the increased incidence of carcinomas of the skin of the ear or of the Zymbal's gland in both male and female rats.

In male rats large numbers of skin tumors were observed in the dosed groups, with basal-cell carcinomas observed as early as week 48 and sebaceous adenocarcinomas observed as early as week 47. For the incidence of basal-cell carcinomas, the incidence of trichoepitheliomas, the incidence of squamous-cell carcinomas, and the incidence of sebaceous adenocarcinomas, each had a significantly ($P \leq 0.001$) greater incidence in the high dose than in the high dose control.

When the combined incidences of all carcinomas of the skin or adnexa (excluding skin of the ear) were considered, both the high dose and the low dose comparisons were significant ($P < 0.001$) with 83 percent (40/48) of the high dose, 60 percent (30/50) of the low dose, none of the 48 high dose control, and 2 percent (1/48) of the low dose control males with one or more of these tumors. Based on these results the administration of 5-nitro-o-anisidine was associated with an increased incidence of carcinomas of the skin in male rats.

In female rats numerous clitoral gland neoplasms were observed. The Fisher exact test indicated a significantly ($P = 0.004$) higher incidence of carcinomas NOS in the high dose than in the high dose control. When the combined incidence of carcinomas NOS or adenomas NOS or papillary adenomas or squamous-cell carcinomas was considered, both the low dose and the high dose Fisher exact test were significant ($P \leq 0.001$). Based upon these results, the administration of 5-nitro-o-anisidine was associated with an increased incidence of neoplasms of the clitoral gland in female rats.

For females the Fisher exact test indicated a significantly ($P = 0.001$) higher incidence of mammary adenocarcinomas NOS in the low dose than in the low dose control group. The high dose comparison had a probability level of $P = 0.049$, a marginal result. It must be reiterated, however, that the low dose rats were obtained from a different supplier than the low dose control, the high dose, and the high dose control group.

For male rats the incidence of pituitary adenomas NOS was significantly (P = 0.019) higher in the low dose than in the low dose control. The high dose comparison was not significant, however. In historical control data compiled by this laboratory for the NCI Carcinogenesis Testing Program, 35/334 (10 percent) of the untreated male Fischer 344 rats had either an adenoma NOS or a chromophobe adenoma, compared to 1/41 (2 percent) of the low dose control and 8/44 (18 percent) of the low dose group in this bioassay.

For male rats the high dose to high dose control comparison had marginal positive results both for adrenal cortical neoplasms and for preputial neoplasms. Similarly for low dose females marginal test results were noted for lung neoplasms.

For females the Fisher exact test comparison of the low dose to the low dose control group indicated a significant negative association between dose and the incidence of malignant lymphomas or leukemia. The incidence in the high dose group, however, was not significantly different from that in the high dose control.

Both for leukemia or malignant lymphomas and for interstitial-cell tumors of the testes in the males and both for pituitary adenomas NOS and for mammary fibroadenomas in the females, the possibility of a negative association between chemical administration and incidence was observed. It must be noted, however, that a relatively high mortality from tumors was observed in the dosed rats.

Thus, based upon these statistical results the administration of 5-nitro-o-anisidine was associated with the increased incidence of carcinomas of the skin and of the Zymbal's gland in male rats and of carcinomas of the Zymbal's gland and of clitoral neoplasms in female rats. There also seemed to be some possibility of an association between compound administration and the incidence of mammary adenocarcinomas in female rats.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Moderate mean body weight depression was evident in all treated groups, except dose A male mice, when compared to control groups (Figure 4). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

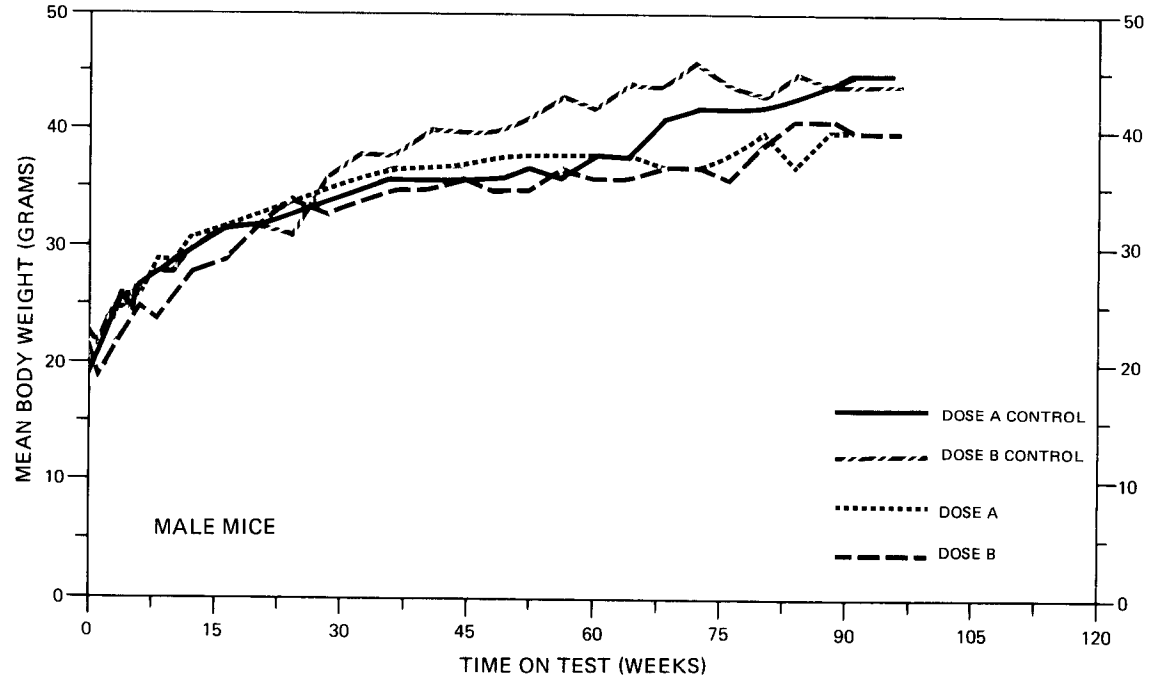
No clinical abnormalities were noted in mice of any group.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 5-nitro-o-anisidine-dosed groups are shown in Figure 5. For males there were no statistically significant differences between the mortality of the dosed and control groups. For females the Cox tests indicated significantly greater mortality in each of the dosed groups than in their respective control group.

For males five dose B control mice were sacrificed in week 49; in addition, five mice from each group but the dose B group were sacrificed in week 78. Adequate numbers of males were at risk from late-developing tumors as 88 percent (44/50) of the dose B group, 84 percent (42/50) of the dose A group, 80 percent (40/50) of the dose B control, and 86 percent (43/50) of the dose A control survived on test until the end of the study.

For females five dose B control mice were sacrificed in week 49; five mice from the dose A control, five from the dose B control, and



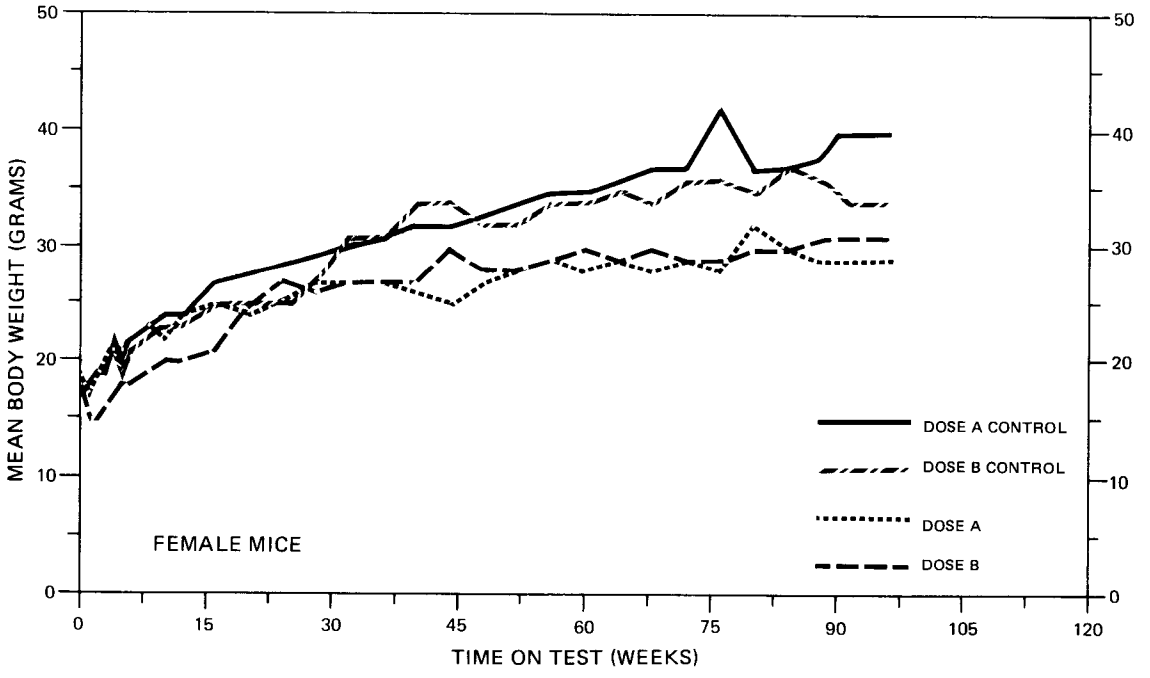


FIGURE 4
GROWTH CURVES FOR 5-NITRO-o-ANISIDINE CHRONIC STUDY MICE

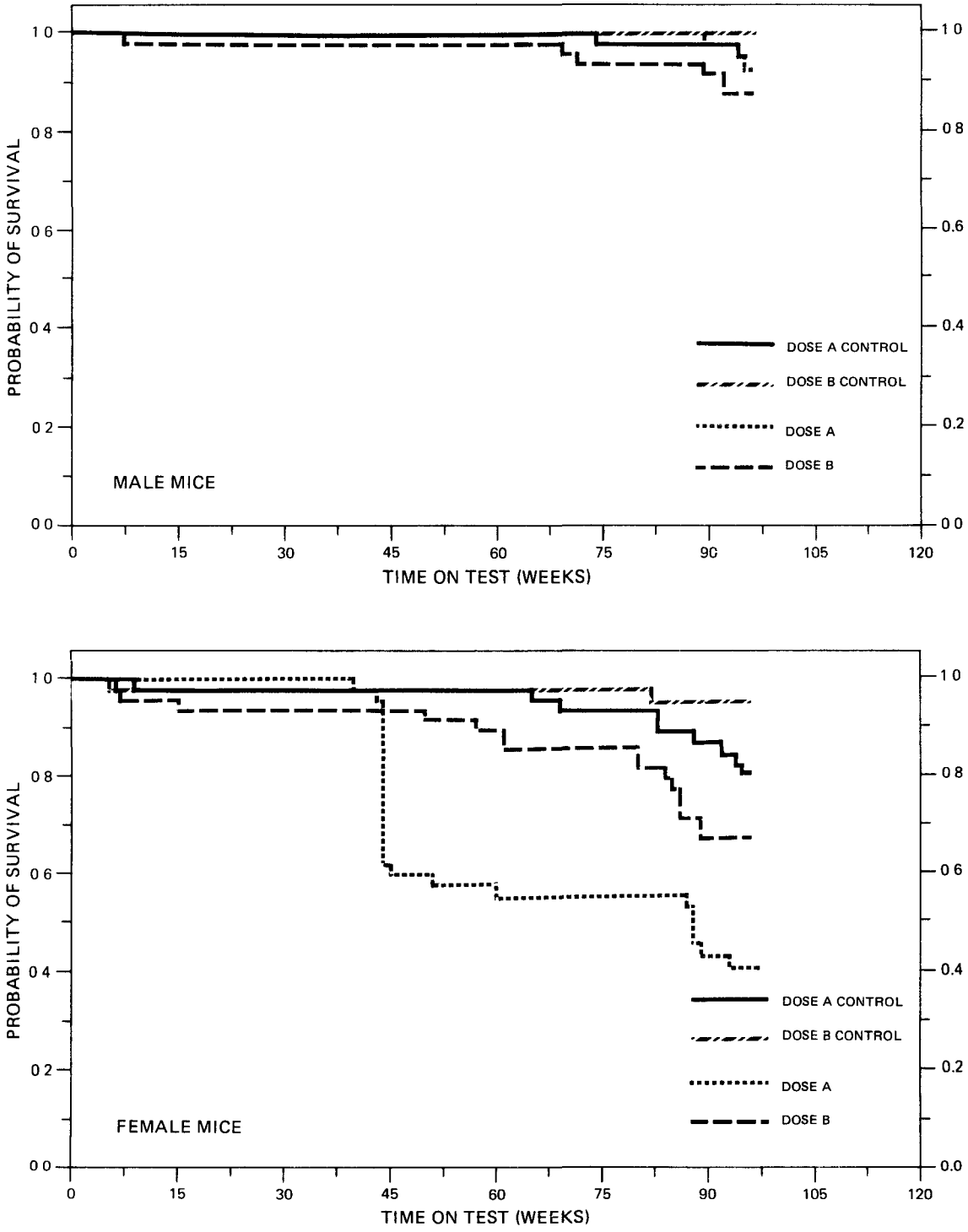


FIGURE 5
SURVIVAL COMPARISONS OF 5-NITRO-o-ANISIDINE CHRONIC STUDY MICE

six from the dose A group were sacrificed in week 78. Of the 19 dose A females that died in weeks 43 through 45, 17 had nephrosis of the kidney and 1 was autolyzed. Adequate numbers of females were at risk from late-developing tumors as 66 percent (33/50) of the dose B group, 32 percent (16/50) of the dose A group, 76 percent (38/50) of the dose B control and 72 percent (36/50) of the dose A control survived on test until the end of the study.

C. Pathology

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

The incidence of tumors of the liver in male and female mice is summarized below:

MALES	Dose A Control	Dose B Control	Dose A	Dose B
Number of animals with tissues examined histopathologically	(50)	(48)	(48)	(47)
Liver				
Hepatocellular Carcinoma	12	6	25	3
Hemangioma	1	0	0	0
Hemangiosarcoma	0	1	1	2
Nodular Hyperplasia	2	1	2	1
FEMALES				
Number of animals with tissues examined histopathologically	(47)	(50)	(41)	(43)
Liver				
Hepatocellular Carcinoma	2	1	0	8
Nodular Hyperplasia	0	0	0	1

An increased incidence of hepatocellular carcinoma as compared to controls was noted among dose B female and dose A male mice. Hepatocellular carcinoma was defined as a neoplasm within the liver parenchyma composed of hepatocytes arranged in an irregular fashion so that all traces of normal liver architecture were obscured. Cells varied in size but tended to be large with abundant, usually eosinophilic cytoplasm. Nuclei varied in size and shape both within a given tumor and between various tumors. Nuclear morphology ranged from normal to nuclei with hyperchromatism, abnormal chromatin patterns, and atypical mitoses. Occasionally, fat vacuoles were found in the cytoplasm.

With the exception of renal and hepatic lesions, the nonneoplastic lesions which occurred in both control and dosed mice were the usual types observed in aging B6C3F1 mice. There were elevated incidences of toxic nephrosis in dosed females and of hepatocyte hyperplasia and degeneration in dosed males.

Based upon this histopathologic evaluation, there appeared to be an association between liver carcinomas in dosed male and female B6C3F1 mice and the dietary administration of 5-nitro-o-anisidine.

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 tumors were observed in at least one of the control or 5-nitro-o-anisidine-dosed groups and where such tumors were observed in at

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 5-NITRO-o-ANISIDINE[a]

TOPOGRAPHY:MORPHOLOGY	DOSE A CONTROL	DOSE B CONTROL	DOSE A	DOSE B
Lung: Alveolar/Bronchiolar Carcinoma[b]	5/50(0.10)	5/49(0.10)	1/48(0.02)	1/47(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.208	0.209
Lower Limit	---	---	0.005	0.005
Upper Limit	---	---	1.768	1.767
Weeks to First Observed Tumor	95	96	96	96
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	5/50(0.10)	10/49(0.20)	5/48(0.10)	2/47(0.04)
P Values[c]	---	---	N.S.	P = 0.017(N)
Relative Risk (Control)[d]	---	---	1.042	0.209
Lower Limit	---	---	0.255	0.023
Upper Limit	---	---	4.243	0.912
Weeks to First Observed Tumor	95	96	96	96
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/50(0.10)	5/49(0.10)	5/48(0.10)	6/49(0.12)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.042	1.200
Lower Limit	---	---	0.255	0.327
Upper Limit	---	---	4.243	4.654
Weeks to First Observed Tumor	74	96	96	89

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	DOSE A CONTROL	DOSE B CONTROL	DOSE A	DOSE B
Liver: Hepatocellular Carcinoma[b]	12/50(0.24)	6/48(0.13)	25/48(0.52)	3/47(0.06)
P Values[c]	---	---	P = 0.004	N.S.
Relative Risk (Control)[d]	---	---	2.170	0.511
Lower Limit	---	---	1.202	0.087
Upper Limit	---	---	4.081	2.239
Weeks to First Observed Tumor	95	78	78	96
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	12/50(0.24)	8/48(0.17)	25/48(0.52)	3/47(0.06)
P Values[c]	---	---	P = 0.004	---
Relative Risk (Control)[d]	---	---	2.170	0.383
Lower Limit	---	---	1.202	0.069
Upper Limit	---	---	4.081	1.485
Weeks to First Observed Tumor	95	78	78	96

[a]Treated groups received time-weighted average doses of 0.8 or 0.6 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 on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 5-NITRO-o-ANISIDINE[a]

TOPOGRAPHY:MORPHOLOGY	DOSE A CONTROL	DOSE B CONTROL	DOSE A	DOSE B
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	2/46(0.04)	3/50(0.06)	0/42(0.00)	2/44(0.05)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.758
Lower Limit	---	---	0.000	0.066
Upper Limit	---	---	3.685	6.300
Weeks to First Observed Tumor	96	78	---	96
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	7/48(0.15)	2/50(0.04)	5/43(0.12)	10/45(0.22)
P Values[c]	---	---	N.S.	P = 0.008
Relative Risk (Control)[d]	---	---	0.797	5.556
Lower Limit	---	---	0.214	1.270
Upper Limit	---	---	2.692	49.760
Weeks to First Observed Tumor	83	96	78	80
Liver: Hepatocellular Carcinoma[b]	2/47(0.04)	1/50(0.02)	0/41(0.00)	8/43(0.19)
P Values[c]	---	---	N.S.	P = 0.008
Relative Risk (Control)[d]	---	---	0.000	9.302
Lower Limit	---	---	0.000	1.325
Upper Limit	---	---	3.854	401.243
Weeks to First Observed Tumor	94	96	---	80

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	DOSE A CONTROL	DOSE B CONTROL	DOSE A	DOSE B
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	5/43(0.12)	3/42(0.07)	1/31(0.03)	4/33(0.12)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.277	1.697
Lower Limit	---	---	0.006	0.307
Upper Limit	---	---	2.300	10.800
Weeks to First Observed Tumor	95	96	97	96

[a]Treated groups received time-weighted average doses of 0.8 or 0.6 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 on the relative risk of the treated group to the control group.

least 5 percent of the group. Caution must be used in interpreting results involving the dose A groups, since these dosed mice were obtained from a different supplier than the dose A control groups.

Numerous incidences of hepatocellular carcinomas were observed in both male and female mice. For males the Fisher exact test indicated a significantly ($P = 0.004$) higher incidence of hepatocellular carcinomas in the dose A group than in the dose A control. It must be noted, however, that the dosed mice were from a different supplier than the control mice. When the incidence in the dose B group was compared with the incidence in the dose B controls, it was not significant. For female mice the comparison of dose B to dose B control was significant ($P = 0.008$). In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, 51/350 (15 percent) of the male and 13/350 (4 percent) of the female untreated B6C3F1 mice had a hepatocellular carcinoma. Based upon these results, the administration of 5-nitro-o-anisidine was associated with the increased incidence of hepatocellular carcinomas in female mice.

For female mice the Fisher exact test indicated a significantly ($P = 0.008$) higher incidence of leukemia or malignant lymphomas in the dose B group than in the dose B control group. It must be noted, however, that the incidence rate of 10/45 (22 percent) observed in the dose B group did not greatly differ from the 7/48 (15 percent)

observed in the dose A control group, which came from the same supplier and was kept in the same room.

For males the Fisher exact test indicated a significantly ($P = 0.017$) lower incidence of alveolar/bronchiolar neoplasms in the dose B group than in the dose B control.

V. DISCUSSION

In both species adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

Among rats, feeding of 5-nitro-o-anisidine was associated primarily with increased incidences of tumors of the skin and its glands. Incidences of the following skin tumors: basal-cell carcinomas, trichoepitheliomas, squamous-cell carcinomas, and sebaceous adenocarcinomas--were each significant in high dose male rats. For both male and female rats, carcinomas (the combined incidences of sebaceous adenocarcinomas, ceruminous carcinomas, and squamous-cell carcinomas) of the Zymbal's gland or the skin of the ear were significant in the high dose groups. The incidences of tumors of the preputial and clitoral glands were elevated in dosed rats. The incidences of carcinomas NOS and the incidences of adenomas (the combined incidences of adenomas NOS and papillary adenomas) were each significant in the clitoral gland of dosed female rats. The incidence of mammary adenocarcinomas was significant in low dose female rats, and the incidence of pituitary adenomas was significant in low dose male rats, when each was compared to its respective control group. It should be noted that low dose rats were received from a different supplier than the low dose controls. It is, therefore, not certain that all differences in tumor incidences between low dose rats and their controls are attributable to administration of the compound.

The incidences of hepatocellular carcinomas were statistically significant in dose A male mice and in dose B female mice when compared to their respective controls. It should be noted that the dose A mice were received from a different supplier than the dose A control mice. This reduces the weight of the evidence for attributing the increase in hepatocellular carcinomas in dose A male mice to the administration of the test compound. Liver neoplasms in dose B female mice were considered to be due to the administration of 5-nitro-o-anisidine. The number of female mice with either leukemia or malignant lymphomas was significantly increased in the dose B group, when compared to the dose B controls. However, this incidence was comparable to that observed in the dose A control group and, therefore, not considered attributable to the compound.

Under the conditions of this bioassay, dietary administration of 5-nitro-o-anisidine was carcinogenic in Fischer 344 rats, causing Zymbal's gland carcinomas in both sexes, integumentary carcinomas in males, and clitoral gland neoplasms in females. The compound was also carcinogenic in female B6C3F1 mice, causing hepatocellular carcinomas.

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Review of the Bioassay of 5-Nitro-*o*-Anisidine* 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 5-Nitro-*o*-Anisidine for carcinogenicity.

The reviewer agreed with the conclusion that 5-Nitro-*o*-Anisidine was carcinogenic in both mice and rats, he pointed out a number of experimental deficiencies. Despite the flaws, he said the compound should be considered carcinogenic under the conditions of test. A motion was made by the reviewer that the report on the bioassay of 5-Nitro-*o*-Anisidine be accepted as written. The motion was accepted without objection.

Clearinghouse Members present:

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

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

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 5-NITRO-o-ANISIDINE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 5-NITRO-o-ANISIDINE

	LOW DOSE CONTROL (UNTR) 01-0079	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
ANIMALS INITIALLY IN STUDY	50	@50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	48	48	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	48	49	48
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(48)	(50)	(48)
PAPILLOMA, NOS			1 (2%)	3 (6%)
SQUAMOUS CELL PAPILLOMA	1 (2%)		1 (2%)	2 (4%)
SQUAMOUS CELL CARCINOMA	1 (2%)		3 (6%)	12 (25%)
BASAL-CELL CARCINOMA	1 (2%)		7 (14%)	30 (63%)
TRICHOEPITHELIOMA			20 (40%)	9 (19%)
SWEAT GLAND CARCINOMA				1 (2%)
SEBACEOUS ADENOMA			9 (18%)	8 (17%)
SEBACEOUS ADENOCARCINOMA			5 (10%)	21 (44%) <-
KERATOACANTHOMA			2 (4%)	2 (4%)
FIBROMA			3 (6%)	1 (2%)
FIBROSARCOMA			2 (4%)	
*SUBCUT TISSUE	(48)	(48)	(50)	(48)
SARCOMA, NOS		1 (2%)		
FIBROMA	2 (4%)	3 (6%)		
FIBROSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(48)	(48)	(49)	(48)
CARCINOMA, NOS, METASTATIC	1 (2%)			
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)	1 (2%)
SEBACEOUS ADENOCARCINOMA, METAST				1 (2%)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)		1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(48)	(50)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)		

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
<- MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN TISSUES IS COUNTED ONCE ONLY
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT ONE ANIMAL WAS FOUND TO BE A FEMALE IN A MALE GROUP.

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
LEUKEMIA, NOS	1 (2%)	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	5 (10%)	4 (8%)		
*SPLEEN	(48)	(48)	(47)	(48)
OSTEOSARCOMA, METASTATIC	1 (2%)			
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*SALIVARY GLAND	(46)	(47)	(45)	(46)
ADENOCARCINOMA, NOS		1 (2%)		
SARCOMA, NOS		1 (2%)		
*LIVER	(48)	(48)	(48)	(48)
NEOPLASTIC NODULE	1 (2%)		3 (6%)	1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)	1 (2%)		2 (4%)
*JEJUNUM	(45)	(46)	(46)	(47)
ADENOCARCINOMA, NOS			1 (2%)	
*ILEUM	(45)	(46)	(46)	(47)
SARCOMA, NOS		1 (2%)		
*COLONIC SUBMUCOSA	(44)	(46)	(45)	(39)
FIBROMA				1 (3%)
URINARY SYSTEM				
*KIDNEY	(48)	(48)	(48)	(48)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)	1 (2%)
*KIDNEY/PELVIS	(48)	(48)	(48)	(48)
TRANSITIONAL-CELL CARCINOMA				1 (2%)
*URINARY BLADDER	(46)	(43)	(48)	(48)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)		1 (2%)	
ENDOCRINE SYSTEM				
*PITUITARY	(41)	(38)	(44)	(39)
ADENOMA, NOS	1 (2%)	9 (24%)	8 (18%)	5 (13%)

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0077	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
*ADRENAL	(47)	(47)	(48)	(48)
CORTICAL ADENOMA	1 (2%)		1 (2%)	4 (8%)
CORTICAL CARCINOMA				1 (2%)
PHEOCHROMOCYTOMA	10 (21%)	7 (15%)	6 (13%)	13 (27%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)		1 (2%)
GANGLIONEUROMA	1 (2%)			
*THYROID	(39)	(48)	(47)	(47)
ADENOCARCINOMA, NOS			1 (2%)	
FOLLICULAR-CELL ADENOMA			1 (2%)	
FOLLICULAR-CELL CARCINOMA				2 (4%)
C-CELL ADENOMA			2 (4%)	1 (2%)
C-CELL CARCINOMA		1 (2%)	2 (4%)	1 (2%)
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)	
*PARATHYROID	(23)	(28)	(25)	(19)
ADENOMA, NOS		1 (4%)		
*PANCREATIC ISLETS	(45)	(46)	(44)	(46)
ISLET-CELL ADENOMA	3 (7%)		3 (7%)	
ISLET-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(48)	(50)	(48)
PAPILLARY ADENOCARCINOMA	1 (2%)			
FIBROADENOMA	1 (2%)			
*PREPUTIAL GLAND	(48)	(48)	(50)	(49)
CARCINOMA,NOS	2 (4%)			2 (4%)
SQUAMOUS CELL CARCINOMA			1 (2%)	
ADENOMA, NOS			2 (4%)	3 (6%)
CYSTADENOMA, NOS				1 (2%)
*TESTIS	(47)	(47)	(47)	(48)
INTERSTITIAL-CELL TUMOR	45 (96%)	42 (89%)	37 (79%)	16 (33%)
NERVOUS SYSTEM				
*CEREBRUM	(47)	(48)	(48)	(48)
ASTROCYTOMA				1 (2%)
*BRAIN	(47)	(48)	(48)	(48)
GLIOMA, NOS		1 (2%)		1 (2%)

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

TABLE A1 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 01-0070	CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
*CEREBRAL CORTEX	(47)	(48)	(48)	(48)
ASTROCYTOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*ZYMBAL'S GLAND	(48)	(48)	(50)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)	
SEBACEOUS ADENOCARCINOMA			1 (2%)	2 (4%)
CERUMINOUS CARCINOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(48)	(48)	(50)	(48)
MESOTHELIOMA, NOS	1 (2%)		4 (8%)	1 (2%)
MESOTHELIOMA, MALIGNANT		2 (4%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	5	6	9	5
MORIBUND SACRIFICE	5	8	38	45
SCHEDULED SACRIFICE	5	5		
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	34	30	3	
ANIMAL MISSING	1			
ANIMAL DELETED (WRONG SEX)		1		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	44	47	48
TOTAL PRIMARY TUMORS	81	80	137	156
TOTAL ANIMALS WITH BENIGN TUMORS	45	43	44	34
TOTAL BENIGN TUMORS	66	62	100	69
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	17	28	45
TOTAL MALIGNANT TUMORS	13	18	30	85
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	1	2
TOTAL SECONDARY TUMORS	3	1	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		7	2
TOTAL UNCERTAIN TUMORS	2		7	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 5-NITRO-o ANISIDINE

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	49	50	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	50	49	46
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(49)	(46)
SQUAMOUS CELL CARCINOMA			2 (4%)	3 (7%)
BASAL-CELL CARCINOMA		1 (2%)		1 (2%)
SEBACEOUS ADENOCARCINOMA			1 (2%)	2 (4%)
SARCOMA, NOS				1 (2%)
FIBROMA			1 (2%)	
FIBROSARCOMA			1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(49)	(46)
FIBROMA		1 (2%)		
FIBROSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(49)	(43)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	4 (8%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	1 (2%)
RHABDOMYOSARCOMA, METASTATIC				1 (2%)
OSTEOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(49)	(46)
MALIGNANT LYMPHOMA, NOS	2 (4%)			1 (2%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)		2 (4%)
MYELOMONOCYTIC LEUKEMIA	5 (10%)	3 (6%)		
#SPLEEN	(48)	(48)	(48)	(43)
HEMANGIOSARCOMA				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0071	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
CIRCULATORY SYSTEM				
#HEART	(49)	(50)	(48)	(43)
FIBROSARCOMA				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(49)	(50)	(45)	(43)
CARCINOMA,NOS				1 (2%)
#LIVER	(49)	(50)	(49)	(44)
NEOPLASTIC NODULE	2 (4%)			1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)			1 (2%)
#ILEUM	(49)	(48)	(49)	(43)
LEIOMYOSARCOMA		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(49)	(45)
CARCINOMA,NOS	1 (2%)			
TRANSITIONAL-CELL CARCINOMA				1 (2%)
#URINARY BLADDER	(49)	(46)	(46)	(42)
SQUAMOUS CELL CARCINOMA				1 (2%)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(44)	(40)	(46)	(41)
ADENOMA, NOS	18 (41%)	17 (43%)	10 (22%)	5 (12%)
#ADRENAL	(49)	(49)	(49)	(44)
CORTICAL ADENOMA		1 (2%)	2 (4%)	3 (7%)
CORTICAL CARCINOMA	1 (2%)			
PHEOCHROMOCYTOMA	2 (4%)	3 (6%)	3 (6%)	6 (14%)
#ADRENAL MEDULLA	(49)	(49)	(49)	(44)
GANGLIONEUROMA		1 (2%)		

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
*THYROID	(47)	(45)	(49)	(42)
FOLLICULAR-CELL CARCINOMA	1 (3%)	1 (2%)		1 (2%)
C-CELL ADENOMA	2 (5%)	1 (2%)	3 (6%)	1 (2%)
C-CELL CARCINOMA	1 (3%)	1 (2%)		
PAPILLARY CYSTADENOMA, NOS				1 (2%)
*PANCREATIC ISLETS	(47)	(48)	(44)	(43)
ISLET-CELL ADENOMA	1 (2%)	2 (4%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(49)	(46)
ADENOMA, NOS	2 (4%)			
ADENOCARCINOMA, NOS			10 (20%)	4 (9%)
PAPILLARY ADENOCARCINOMA			1 (2%)	1 (2%)
FIBROADENOMA	16 (33%)	19 (38%)	4 (8%)	
*CLITORAL GLAND	(49)	(50)	(49)	(46)
CARCINOMA,NOS				7 (15%)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
SQUAMOUS CELL CARCINOMA			1 (2%)	2 (4%)
ADENOMA, NOS	1 (2%)	2 (4%)	9 (18%)	5 (11%)
ADENOCARCINOMA, NOS			1 (2%)	
PAPILLARY ADENOMA			4 (8%)	
*VAGINA	(49)	(50)	(49)	(46)
GRANULAR-CELL TUMOR, BENIGN				1 (2%)
*UTERUS	(49)	(50)	(49)	(44)
CARCINOMA-IN-SITU, NOS				1 (2%)
UNDIFFERENTIATED CARCINOMA				1 (2%)
ADENOCARCINOMA, NOS		1 (2%)	2 (4%)	2 (5%)
ADENOMA IN ADENOMATOUS POLYP				1 (2%)
PAPILLARY ADENOCARCINOMA			1 (2%)	
SARCOMA, NOS			1 (2%)	
LEIOMYOSARCOMA	1 (2%)		2 (4%)	
ENDOMETRIAL STROMAL POLYP	12 (24%)	10 (20%)	14 (29%)	6 (14%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	1 (2%)	
*UTERUS/ENDOMETRIUM	(49)	(50)	(49)	(44)
ADENOCARCINOMA, NOS	2 (4%)			
*OVARY	(47)	(49)	(48)	(45)
GRANULOSA-CELL TUMOR		1 (2%)		

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
NERVOUS SYSTEM				
*CEREBRUM	(49)	(50)	(49)	(44)
ASTROCYTOMA				2 (5%)
#BRAIN	(49)	(50)	(49)	(44)
GLIOMA, NOS			1 (2%)	1 (2%)
OLIGODENDROGLIOMA	1 (2%)			
MEDULLOBLASTOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*ZYMBAL'S GLAND	(49)	(50)	(49)	(46)
SQUAMOUS CELL CARCINOMA			2 (4%)	2 (4%)
SEBACEOUS ADENOCARCINOMA				4 (9%)
MUSCULOSKELETAL SYSTEM				
*MUSCLE HIP/THIGH	(49)	(50)	(49)	(46)
RHABDOMYOSARCOMA				1 (2%)
BODY CAVITIES				
*PERITONEUM	(49)	(50)	(49)	(46)
MESOTHELIOMA, NOS	1 (2%)			
ALL OTHER SYSTEMS				
SITE UNKNOWN				
SQUAMOUS CELL CARCINOMA		1		
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	3	5	13	15
MORIBUND SACRIFICE	7	3	26	23
SCHEDULED SACRIFICE	5	5		
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	35	37	11	11
ANIMAL MISSING				1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	38	45	41
TOTAL PRIMARY TUMORS	73	73	84	78
TOTAL ANIMALS WITH BENIGN TUMORS	37	35	27	21
TOTAL BENIGN TUMORS	54	59	55	29
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	12	29	36
TOTAL MALIGNANT TUMORS	16	13	29	48
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		1
TOTAL SECONDARY TUMORS		1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	1		1
TOTAL UNCERTAIN TUMORS	3	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 5-NITRO-o-ANISIDINE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 5 NITRO-o-ANISIDINE

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	49	48	48
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
*LUNG	(50)	(49)	(48)	(47)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	5 (10%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		5 (10%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	5 (10%)	1 (2%)	1 (2%)
HEMANGIOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(49)	(48)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)		1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	3 (6%)		1 (2%)
MAST-CELL TUMOR				1 (2%)
GRANULOCYTIC LEUKEMIA				1 (2%)
*SPLEEN	(50)	(49)	(45)	(47)
HEMANGIOSARCOMA		1 (2%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
*LYMPH NODE	(45)	(42)	(40)	(40)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	1 (2%)		
*MESENTERIC L. NODE	(45)	(42)	(40)	(40)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			3 (8%)	2 (5%)
*PEYERS PATCH	(49)	(49)	(48)	(45)
MALIGNANT LYMPHOMA, NOS				1 (2%)
*DUODENUM	(49)	(49)	(48)	(45)
MALIGNANT LYMPHOMA, NOS			1 (2%)	

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

TABLE B1 (CONTINUED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(50)	(48)	(48)	(47)
HEPATOCELLULAR ADENOMA		2 (4%)		
HEPATOCELLULAR CARCINOMA	12 (24%)	6 (13%)	25 (52%)	3 (6%)
HEMANGIOMA	1 (2%)			
HEMANGIOSARCOMA			1 (2%)	2 (4%)
HEMANGIOSARCOMA, UNC PRIM OR MET		1 (2%)		
#STOMACH	(49)	(48)	(48)	(46)
SQUAMOUS CELL PAPILLOMA			1 (2%)	1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(40)	(41)	(38)
ADENOMA, NOS				3 (8%)
#ADRENAL	(49)	(44)	(44)	(46)
CORTICAL ADENOMA				1 (2%)
PHEOCHROMOCYTOMA		1 (2%)		
#THYROID	(40)	(45)	(47)	(47)
ADENOCARCINOMA, NOS	1 (3%)			
FOLLICULAR-CELL CARCINOMA				1 (2%)
#PANCREATIC ISLETS	(46)	(47)	(47)	(43)
ISLET-CELL ADENOMA	1 (2%)			
REPRODUCTIVE SYSTEM				
#TESTIS	(50)	(49)	(48)	(46)
INTERSTITIAL-CELL TUMOR			1 (2%)	1 (2%)
NERVOUS SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(49)	(48)	(49)
ADENOMA, NOS	1 (2%)			
PAPILLARY ADENOMA			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(49)	(48)	(49)
ACUPOFIBROSARCOMA	1 (2%)			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	2		3	6
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE	5	10	5	
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	43	39	42	44
ANIMAL MISSING		1		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	22	32	17
TOTAL PRIMARY TUMORS	27	26	40	21
TOTAL ANIMALS WITH BENIGN TUMORS	3	8	7	7
TOTAL BENIGN TUMORS	3	8	7	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	15	29	11
TOTAL MALIGNANT TUMORS	24	17	33	13
TOTAL ANIMALS WITH SECONDARY TUMORS*	1	1	5	
TOTAL SECONDARY TUMORS	1	1	6	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				1
TOTAL UNCERTAIN TUMORS				1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		1		
TOTAL UNCERTAIN TUMORS		1		

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH 5-NITRO-o-ANISIDINE

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	48	50	43	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	47	50	43	44
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(50)	(43)	(45)
FIBROSARCOMA			1 (2%)	1 (2%)
HEMANGIOSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
*LUNG	(46)	(50)	(42)	(44)
NEOPLASM, NOS				1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)		1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(50)	(43)	(45)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	2 (5%)	3 (7%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	5 (11%)
LYMPHOCYTIC LEUKEMIA	1 (2%)			
ERYTHROCYTIC LEUKEMIA	1 (2%)			
GRANULOCYTIC LEUKEMIA				1 (2%)
*SPLEEN	(47)	(49)	(38)	(43)
HEMANGIOSARCOMA	1 (2%)		1 (3%)	
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (3%)	
*MESENTERIC L. NODE	(36)	(44)	(27)	(30)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)			
*PEYERS PATCH	(45)	(48)	(33)	(41)
MALIGNANT LYMPHOMA, NOS	1 (2%)			

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

TABLE B2 (CONTINUED)

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
*KIDNEY	(45)	(50)	(42)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*LIVER	(47)	(50)	(41)	(43)
HEPATOCELLULAR CARCINOMA	2 (4%)	1 (2%)		8 (19%)
*GALLBLADDER	(48)	(50)	(43)	(45)
PAPILLOMA, NOS				1 (2%)
*STOMACH	(45)	(49)	(30)	(40)
SQUAMOUS CELL PAPILLOMA			1 (3%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
*PITUITARY	(43)	(42)	(31)	(33)
ADENOMA, NOS	5 (12%)	1 (2%)	1 (3%)	4 (12%)
CHROMOPHOBE ADENOMA		2 (5%)		
*ADRENAL	(47)	(48)	(34)	(40)
CORTICAL ADENOMA	1 (2%)			
*THYROID	(41)	(44)	(34)	(43)
FOLLICULAR-CELL ADENOMA				1 (2%)
REPRODUCTIVE SYSTEM				
*UTERUS	(43)	(47)	(32)	(36)
ADENOCARCINOMA, NOS				1 (3%)

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

TABLE B2 (CONTINUED)

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
LEIOMYOMA	1 (2%)			
#OVARY/OVIDUCT	(43)	(47)	(32)	(36)
PAPILLARY ADENOMA	1 (2%)	1 (2%)		
#OVARY	(45)	(48)	(30)	(37)
GRANULOSA-CELL TUMOR				1 (3%)
TUBULAR ADENOMA				2 (5%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(48)	(50)	(43)	(45)
ADENOMA, NOS	1 (2%)			
PAPILLARY ADENOMA		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
OMENTUM				
HEMANGIOMA				2
HEMANGIOSARCOMA	1			

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

TABLE B2 (CONCLUDED)

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	2	18	15
MORIBUND SACRIFICE	3		10	1
SCHEDULED SACRIFICE	5	10	5	
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	36	38	16	33
ANIMAL MISSING			1	
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	18	10	9	22
TOTAL PRIMARY TUMORS	22	11	9	35
TOTAL ANIMALS WITH BENIGN TUMORS	8	7	2	9
TOTAL BENIGN TUMORS	9	7	2	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	4	7	16
TOTAL MALIGNANT TUMORS	13	4	7	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	2			1
TOTAL SECONDARY TUMORS	2			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				2
TOTAL UNCERTAIN TUMORS				2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 5-NITRO-o-ANISIDINE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 5-NITRO-o-ANISIDINE

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
ANIMALS INITIALLY IN STUDY	50	@50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	48	48	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	48	49	48
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(48)	(50)	(48)
CYST, NOS				1 (2%)
EPIDERMAL INCLUSION CYST			3 (6%)	2 (4%)
SEBACEOUS CYST			3 (6%)	
ABSCESS, NOS			1 (2%)	
INFLAMMATION ACTIVE CHRONIC				1 (2%)
ATYPIA, NOS				1 (2%)
HYPERPLASIA, NOS			1 (2%)	1 (2%)
*SUBCUT TISSUE	(48)	(48)	(50)	(48)
ABSCESS, NOS				1 (2%)
METAPLASIA, OSSEOUS		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(45)	(48)	(47)	(48)
INFLAMMATION, NOS		2 (4%)		
INFLAMMATION, ACUTE/CHRONIC	18 (40%)		3 (6%)	
INFLAMMATION, CHRONIC			1 (2%)	
#LUNG/BRONCHUS	(48)	(48)	(49)	(48)
BRONCHIECTASIS	3 (6%)	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, NOS		7 (15%)		
#LUNG/BRONCHIOLE	(48)	(48)	(49)	(48)
HYPERPLASIA, FOCAL			1 (2%)	
#LUNG	(48)	(48)	(49)	(48)
CONGESTION, NOS	1 (2%)			1 (2%)
EDEMA, NOS				1 (2%)
HEMORRHAGE				1 (2%)
INFLAMMATION, FOCAL	2 (4%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
INFLAMMATION, INTERSTITIAL		4 (8%)	1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	1 (2%)	
ABSCESS, NOS	1 (2%)			1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)		
INFLAMMATION, CHRONIC			2 (4%)	
GRANULOMA, NOS	1 (2%)			
GRANULOMA, FORFIGN BODY				1 (2%)
PERIVASCULITIS				2 (4%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)			
HEMATOPOIETIC SYSTEM				
*BONE MARROW	(48)	(47)	(43)	(46)
THROMBOSIS, NOS				1 (2%)
NECROSIS, FOCAL				1 (2%)
MYELOFIBROSIS	1 (2%)			1 (2%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)			3 (7%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)			
HYPERPLASIA, MEGAKARYOCYTIC	1 (2%)			
MYELOPOIESIS				2 (4%)
*SPLEEN	(48)	(48)	(47)	(48)
FIBROSIS		1 (2%)	2 (4%)	
FIBROSIS, FOCAL			1 (2%)	
HEMOSIDEROSIS		1 (2%)		
ATROPHY, NOS				6 (13%)
LYMPHOID DEPLETION				2 (4%)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, HEMATOPOIETIC		9 (19%)		
HYPERPLASIA, ERYTHROID		10 (21%)		
HYPERPLASIA, RETICULUM CELL			1 (2%)	
HEMATOPOIESIS			4 (9%)	16 (33%)
ERYTHROPOIESIS	1 (2%)			
*LYMPH NODE	(42)	(44)	(38)	(40)
HEMORRHAGE		1 (2%)		1 (3%)
ATROPHY, NOS				3 (8%)
PLASMACYTOSIS		1 (2%)		
HYPERPLASIA, LYMPHOID		3 (7%)		
*MANDIBULAR L. NODE	(42)	(44)	(38)	(40)
DILATATION, NOS	1 (2%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
ATROPHY, NOS				1 (3%)
HYPERPLASIA, NOS	1 (2%)			
#MEDIASTINAL L.NODE	(42)	(44)	(38)	(40)
ATROPHY, NOS				2 (5%)
#PANCREATIC L.NODE	(42)	(44)	(38)	(40)
HYPERPLASIA, NOS			1 (3%)	
#MESENTERIC L. NODE	(42)	(44)	(38)	(40)
ATROPHY, NOS				1 (3%)
#THYMIC CORTEX	(24)	(23)	(34)	(32)
HEMORRHAGE				1 (3%)
CIRCULATORY SYSTEM				
#HEART	(48)	(48)	(49)	(48)
FIBROSIS, FOCAL	11 (23%)			
FIBROSIS, DIFFUSE	1 (2%)			
PERIARTERITIS				1 (2%)
#HEART/ATRIUM	(48)	(48)	(49)	(48)
THROMBOSIS, NOS				1 (2%)
#MYOCARDIUM	(48)	(48)	(49)	(48)
THROMBOSIS, NOS				1 (2%)
INFLAMMATION, INTERSTITIAL	2 (4%)	23 (48%)		
INFLAMMATION, ACUTE/CHRONIC	3 (6%)			
FIBROSIS		12 (25%)		
FIBROSIS, FOCAL	2 (4%)			
DEGENERATION, NOS	1 (2%)		2 (4%)	15 (31%)
#ENDOCARDIUM	(48)	(48)	(49)	(48)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
#CARDIAC VALVE	(48)	(48)	(49)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
*CORONARY ARTERY	(48)	(48)	(50)	(48)
PERIVASCULITIS	1 (2%)			
*PULMONARY ARTERY	(48)	(48)	(50)	(48)
MINERALIZATION	11 (23%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
THROMBOSIS, NOS				1 (2%)
MEDIAL CALCIFICATION			1 (2%)	
*MESENTERIC ARTERY	(48)	(48)	(50)	(48)
PERIARTERITIS			1 (2%)	
ARTERIOSCLEROSIS, NOS			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(46)	(47)	(45)	(46)
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, FOCAL				1 (2%)
#LIVER	(48)	(48)	(48)	(48)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, NECROTIZING	1 (2%)			1 (2%)
FIBROSIS SEPTAL LIVER		2 (4%)		
DEGENERATION, NOS			1 (2%)	
NECROSIS, NOS				2 (4%)
NECROSIS, FOCAL	8 (17%)	2 (4%)		
METAMORPHOSIS FATTY	4 (8%)		1 (2%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	8 (17%)	15 (31%)	6 (13%)	1 (2%)
ANGIECTASIS	2 (4%)	1 (2%)	1 (2%)	
ERYTHROPOIESIS	1 (2%)			
#LIVER/CENTRILOBULAR	(48)	(48)	(48)	(48)
DEGENERATION, NOS				4 (8%)
DEGENERATION, EOSINOPHILIC	2 (4%)			
NECROSIS, NOS		1 (2%)	2 (4%)	4 (8%)
METAMORPHOSIS FATTY			1 (2%)	
#LIVER/KUPFFER CELL	(48)	(48)	(48)	(48)
PIGMENTATION, NOS				1 (2%)
HYPERPIGMENTATION				1 (2%)
#LIVER/HEPATOCYTES	(48)	(48)	(48)	(48)
DEGENERATION, BALLOONING				14 (29%)
NECROSIS, NOS				1 (2%)
*BILE DUCT	(48)	(48)	(50)	(48)
INFLAMMATION, NOS		3 (6%)		
HYPERPLASIA, NOS	6 (13%)	43 (90%)		1 (2%)
*PANCREAS	(45)	(46)	(44)	(46)
INFLAMMATION, NOS		17 (37%)		

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
INFLAMMATION, ACUTE/CHRONIC	6 (13%)			
PERIARTERITIS	1 (2%)			
CYTOLOGIC DEGENERATION				1 (2%)
ATROPHY, FOCAL	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
#PANCREATIC ACINUS	(45)	(46)	(44)	(46)
METAMORPHOSIS FATTY			1 (2%)	
ATROPHY, NOS			1 (2%)	4 (9%)
HYPERTROPHY, NOS			2 (5%)	
HYPERPLASIA, FOCAL		1 (2%)		
#ESOPHAGUS	(45)	(45)	(46)	(44)
DYSPLASIA, NOS		1 (2%)		
#STOMACH	(48)	(48)	(46)	(48)
EPIDERMAL INCLUSION CYST	1 (2%)			1 (2%)
INFLAMMATION, NOS		1 (2%)		
ULCER, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, BASAL CELL		1 (2%)		
HYPERKERATOSIS		2 (4%)		
ACANTHOSIS		2 (4%)		
#GASTRIC MUCOSA	(48)	(48)	(46)	(48)
SCLEROSIS				10 (21%)
CALCIFICATION, NOS			1 (2%)	
#SMALL INTESTINE	(45)	(46)	(46)	(47)
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)	
#PEYERS PATCH	(45)	(46)	(46)	(47)
HYPERPLASIA, NOS		12 (26%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)			
#DUODENAL MUCOSA	(45)	(46)	(46)	(47)
PIGMENTATION, NOS				1 (2%)
#ILEUM	(45)	(46)	(46)	(47)
INFLAMMATION, NOS		2 (4%)		
HYPERPLASIA, LYMPHOID	1 (2%)			
#COLON	(44)	(46)	(45)	(39)
NEMATODIASIS	4 (9%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
PARASITISM		3 (7%)		
PIGMENTATION, NOS				2 (5%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
*COLONIC MUCOUS MEMBR	(44)	(46)	(45)	(39)
PIGMENTATION, NOS				1 (3%)
URINARY SYSTEM				
*KIDNEY	(48)	(48)	(48)	(48)
GLOMERULONEPHRITIS, NOS	3 (6%)	47 (98%)	9 (19%)	
INFLAMMATION, INTERSTITIAL			2 (4%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
FIBROSIS, DIFFUSE		6 (13%)		
NEPHROPATHY				1 (2%)
NEPHROSIS, NOS	41 (85%)		34 (71%)	47 (98%)
*KIDNEY/PELVIS	(48)	(48)	(48)	(48)
MINERALIZATION	1 (2%)			
HYPERPLASIA, EPITHELIAL			1 (2%)	
*URINARY BLADDER	(46)	(43)	(48)	(48)
HYPERPLASIA, EPITHELIAL		1 (2%)		
METAPLASIA, SQUAMOUS	1 (2%)			
ENDOCRINE SYSTEM				
*PITUITARY	(41)	(38)	(44)	(39)
HYPERPLASIA, NOS		1 (3%)		
HYPERPLASIA, FOCAL	3 (7%)	2 (5%)	3 (7%)	
*ADRENAL	(47)	(47)	(48)	(48)
THROMBOSIS, NOS			1 (2%)	
METAMORPHOSIS FATTY	1 (2%)			
ANGIECTASIS	3 (6%)			
*ADRENAL CORTEX	(47)	(47)	(48)	(48)
THROMBOSIS, NOS				1 (2%)
HEMORRHAGE				1 (2%)
NODULE			1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)	2 (4%)
*ADRENAL MEDULLA	(47)	(47)	(48)	(48)
HYPERPLASIA, NODULAR		1 (2%)	2 (4%)	

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL		4 (9%)		4 (8%)
#THYROID	(39)	(48)	(47)	(47)
COLLOID CYST				1 (2%)
HYPERPIGMENTATION			11 (23%)	1 (2%)
HYPERPLASIA, C-CELL	1 (3%)	3 (6%)		
HYPERPLASIA, FOLLICULAR-CELL				1 (2%)
#THYROID FOLLICLE	(39)	(48)	(47)	(47)
PIGMENTATION, NOS				39 (83%)
HYPERPIGMENTATION				1 (2%)
#PARATHYROID	(23)	(28)	(25)	(19)
HYPERPLASIA, NOS		1 (4%)		
HYPERPLASIA, DIFFUSE				1 (5%)
#PANCREATIC ISLETS	(45)	(46)	(44)	(46)
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(48)	(50)	(48)
GALACTOCELE	1 (2%)	2 (4%)		
HYPERPLASIA, NOS	3 (6%)	4 (8%)		6 (13%)
*PREPUTIAL GLAND	(48)	(48)	(50)	(48)
ATYPIA, NOS				1 (2%)
#PROSTATE	(43)	(44)	(47)	(45)
INFLAMMATION, NOS		17 (39%)	1 (2%)	
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, ACUTE	6 (14%)		8 (17%)	3 (7%)
INFLAMMATION, ACUTE FOCAL	8 (19%)		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	2 (5%)			
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
DEGENERATION, NOS			1 (2%)	
ATROPHY, NOS			2 (4%)	3 (7%)
*SEMINAL VESICLE	(48)	(48)	(50)	(48)
ATROPHY, NOS	2 (4%)		8 (16%)	8 (17%)
#TESTIS	(47)	(47)	(47)	(48)
MINERALIZATION		1 (2%)		

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
DEGENERATION, NOS	39 (83%)			2 (4%)
ATROPHY, NOS		6 (13%)		
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)	3 (6%)	5 (11%)	1 (2%)
*TESTIS/TUBULE	(47)	(47)	(47)	(48)
DEGENERATION, NOS			8 (17%)	34 (71%)
NERVOUS SYSTEM				
*BRAIN	(47)	(48)	(48)	(48)
MALACIA				1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(48)	(48)	(50)	(48)
HEMORRHAGE			1 (2%)	
PUS				1 (2%)
CATARACT			3 (6%)	
*EYE/CORNEA	(48)	(48)	(50)	(48)
INFLAMMATION, SUPPURATIVE				1 (2%)
*EYE/RETINA	(48)	(48)	(50)	(48)
DEGENERATION, NOS			2 (4%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(48)	(48)	(50)	(48)
NECROSIS, FAT			1 (2%)	1 (2%)
*PLEURA	(48)	(48)	(50)	(48)
FIBROSIS, FOCAL				1 (2%)
*MESENTERY	(48)	(48)	(50)	(48)
HYPERPLASIA, FOCAL				1 (2%)
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, ACUTE/CHRONIC	2			

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

TABLE C1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0070	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0069	HIGH DOSE 01-0121
OMENTUM				
NECROSIS, FAT		2		
SPECIAL MORPHOLOGY SUMMARY				
ANIMAL MISSING/NO NECROPSY	1			
AUTO/NECROPSY/HISTO PERF	1			
AUTO/NECROPSY/NO HISTO			1	
AUTOLYSIS/NO NECROPSY	1	1		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 5-NITRO-o-ANISIDINE

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	49	50	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	50	49	46
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(49)	(46)
EPIDERMAL INCLUSION CYST	1 (2%)			
SEBACEOUS CYST				1 (2%)
INFLAMMATION, NOS		1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(49)	(46)
MINERALIZATION		1 (2%)		
ABSCESS, NOS		1 (2%)		
RESPIRATORY SYSTEM				
*NASAL CAVITY	(49)	(50)	(49)	(46)
INFLAMMATION, ACUTE				1 (2%)
*TRACHEA	(49)	(49)	(49)	(43)
INFLAMMATION, ACUTE/CHRONIC	15 (31%)		1 (2%)	
METAPLASIA, SQUAMOUS				1 (2%)
*LUNG/BRONCHUS	(49)	(50)	(49)	(43)
BRONCHIECTASIS			2 (4%)	
INFLAMMATION, NOS		3 (6%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
*LUNG/BRONCHIOLE	(49)	(50)	(49)	(43)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, NECROTIZING				1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)	
*LUNG	(49)	(50)	(49)	(43)
CONGESTION, CHRONIC PASSIVE				1 (2%)
HEMORRHAGE				1 (2%)
INFLAMMATION, FOCAL	2 (4%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0119	LOW DOSE 02-0069	HIGH DOSE 02-0121
INFLAMMATION, INTERSTITIAL	2 (4%)	6 (12%)	2 (4%)	
PNEUMONIA, ASPIRATION			1 (2%)	
BRONCHOPNEUMONIA, ACUTE				1 (2%)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)			
HEMATOPOIETIC SYSTEM				
*BONE MARROW	(46)	(46)	(47)	(44)
HYPOPLASIA, NOS			1 (2%)	
OSTEOSCLEROSIS	1 (2%)	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	2 (5%)
HYPERPLASIA, RETICULUM CELL				3 (7%)
MYELOPOIESIS				2 (5%)
*SPLEEN	(48)	(48)	(48)	(43)
HEMORRHAGE			2 (4%)	
INFLAMMATION, NECROTIZING				1 (2%)
INFLAMMATION PROLIFERATIVE				1 (2%)
FIBROSIS			1 (2%)	
HEMOSIDEROSIS		12 (25%)		
LYMPHOID DEPLETION			1 (2%)	
HYPERPLASIA, NOS			7 (15%)	
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	25 (52%)		1 (2%)
HYPERPLASIA, ERYTHROID		19 (40%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)			1 (2%)
HEMATOPOIESIS			12 (25%)	13 (30%)
MYELOPOIESIS			1 (2%)	1 (2%)
*SPLENIC CAPSULE	(48)	(48)	(48)	(43)
HEMORRHAGIC CYST		1 (2%)		
*SPLENIC RED PULP	(48)	(48)	(48)	(43)
ATROPHY, NOS				1 (2%)
*LYMPH NODE	(42)	(47)	(43)	(43)
LYMPHOID DEPLETION				1 (2%)
PLASMACYTOSIS		1 (2%)		
HYPERPLASIA, RETICULUM CELL				1 (2%)
HYPERPLASIA, LYMPHOID		4 (9%)		
*LUMBAR LYMPH NODE	(42)	(47)	(43)	(43)
HEMORRHAGE			1 (2%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
#MESENTERIC L. NODE	(42)	(47)	(43)	(43)
INFLAMMATION, NOS				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(49)	(50)	(48)	(43)
FIBROSIS, FOCAL	1 (2%)			
FIBROSIS, DIFFUSE	1 (2%)			
#HEART/ATRIUM	(49)	(50)	(48)	(43)
THROMBOSIS, NOS			1 (2%)	1 (2%)
#MYOCARDIUM	(49)	(50)	(48)	(43)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, INTERSTITIAL	2 (4%)	23 (46%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
FIBROSIS		15 (30%)		
FIBROSIS, FOCAL	2 (4%)			
DEGENERATION, NOS			2 (4%)	7 (16%)
CALCIFICATION, NOS			1 (2%)	
#ENDOCARDIUM	(49)	(50)	(48)	(43)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#CARDIAC VALVE	(49)	(50)	(48)	(43)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#PULMONARY ARTERY	(49)	(50)	(49)	(46)
MINERALIZATION	9 (18%)			
#HEPATIC VEIN	(49)	(50)	(49)	(46)
INFLAMMATION, NOS				1 (2%)
#SUPERIOR MESENTERIC	(49)	(50)	(49)	(46)
INFLAMMATION, NOS				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(49)	(44)
ECTOPIA			1 (2%)	
HEMORRHAGE				1 (2%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
HEMORRHAGIC CYST				1 (2%)
INFLAMMATION, NECROTIZING				1 (2%)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
CIRRHOSIS, NOS			1 (2%)	
DEGENERATION, CYSTIC			1 (2%)	
DEGENERATION, EOSINOPHILIC	2 (4%)			
NECROSIS, NOS				1 (2%)
NECROSIS, FOCAL	3 (6%)	2 (4%)	1 (2%)	2 (5%)
NECROSIS, COAGULATIVE			2 (4%)	
METAMORPHOSIS FATTY	4 (8%)	6 (12%)	5 (10%)	4 (9%)
BASOPHILIC CYTO CHANGE				1 (2%)
HYPERTROPHY, FOCAL			1 (2%)	
HYPERPLASIA, FOCAL	29 (59%)	38 (76%)	3 (6%)	2 (5%)
ANGIECTASIS	1 (2%)			2 (5%)
HYPERPLASIA, ERYTHROID		1 (2%)		
HEMATOPOIESIS		2 (4%)		
#HEPATIC CAPSULE	(49)	(50)	(49)	(44)
FIBROSIS, FOCAL				1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(49)	(44)
DEGENERATION, NOS			3 (6%)	
NECROSIS, NOS			3 (6%)	2 (5%)
METAMORPHOSIS FATTY			4 (8%)	
#LIVER/PERIPORTAL	(49)	(50)	(49)	(44)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			3 (6%)	1 (2%)
#LIVER/HEPATOCYTES	(49)	(50)	(49)	(44)
NECROSIS, FOCAL			1 (2%)	
*BILE DUCT	(49)	(50)	(49)	(46)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	1 (2%)
HYPERPLASIA, NOS	5 (10%)	32 (64%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)		
#PANCREAS	(47)	(48)	(44)	(43)
THROMBOSIS, NOS				1 (2%)
INFLAMMATION, NOS		6 (13%)		
INFLAMMATION, ACUTE/CHRONIC	4 (9%)			
ATROPHY, NOS	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
#PANCREATIC ACINUS	(47)	(48)	(44)	(43)
ATROPHY, NOS			2 (5%)	2 (5%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
#STOMACH	(49)	(48)	(49)	(43)
INFLAMMATION, NOS		1 (2%)		
ULCER, NOS			2 (4%)	
ULCER, FOCAL	1 (2%)			
HYPERPLASIA, EPITHELIAL			1 (2%)	
ACANTHOSIS		2 (4%)		
#GASTRIC MUCOSA	(49)	(48)	(49)	(43)
SCLEROSIS				2 (5%)
#INTESTINAL VILLUS	(49)	(48)	(49)	(43)
PIGMENTATION, NOS				1 (2%)
#PEYERS PATCH	(49)	(48)	(49)	(43)
HYPERPLASIA, NOS		15 (31%)		1 (2%)
#COLON	(44)	(46)	(47)	(39)
NEMATODIASIS	2 (5%)			
PARASITISM		2 (4%)		
#COLONIC MUCOUS MEMBR	(44)	(46)	(47)	(39)
PIGMENTATION, NOS				1 (3%)
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(49)	(45)
MINERALIZATION	1 (2%)			
CYST, NOS			1 (2%)	
GLOMERULONEPHRITIS, NOS		43 (86%)	1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL			2 (4%)	4 (9%)
FIBROSIS, DIFFUSE		1 (2%)		
NEPHROSIS, NOS	34 (69%)		29 (59%)	24 (53%)
HYPERPLASIA, EPITHELIAL				2 (4%)
#KIDNEY/MEDULLA	(49)	(50)	(49)	(45)
HYPERPLASIA, EPITHELIAL			1 (2%)	
#KIDNEY/GLOMERULUS	(49)	(50)	(49)	(45)
INFLAMMATION, MEMBRANOUS				1 (2%)
#KIDNEY/TUBULE	(49)	(50)	(49)	(45)
PIGMENTATION, NOS				2 (4%)
#RENAL TUBULAR BASEME	(49)	(50)	(49)	(45)
CALCIFICATION, NOS			1 (2%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
#KIDNEY/PELVIS	(49)	(50)	(49)	(45)
HEMATOPOIESIS			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(44)	(40)	(46)	(41)
ABSCESS, NOS			1 (2%)	
PERIVASCULITIS		1 (3%)		
ATYPIA, NOS				1 (2%)
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL	2 (5%)	3 (8%)		1 (2%)
#ADRENAL	(49)	(49)	(49)	(44)
METAMORPHOSIS FATTY	3 (6%)	1 (2%)		
HEMATOPOIESIS			1 (2%)	
#ADRENAL CORTEX	(49)	(49)	(49)	(44)
THROMBOSIS, NOS			1 (2%)	
METAMORPHOSIS FATTY	3 (6%)			
HYPERPLASIA, FOCAL	1 (2%)		3 (6%)	5 (11%)
#ADRENAL MEDULLA	(49)	(49)	(49)	(44)
PERIVASCULAR CUFFING			1 (2%)	
HYPERPLASIA, NODULAR		3 (6%)		
HYPERPLASIA, NOS	1 (2%)			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	3 (6%)		6 (14%)
#THYROID	(49)	(45)	(49)	(42)
CYST, NOS			1 (2%)	
CYSTIC FOLLICLES		1 (2%)		
DEGENERATION, NOS			1 (2%)	
HYPERPLASIA, C-CELL		1 (2%)		3 (7%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)	
#THYROID FOLLICLE	(40)	(45)	(49)	(42)
PIGMENTATION, NOS				5 (12%)
#PANCREATIC ISLETS	(47)	(48)	(44)	(43)
HYPERPLASIA, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(49)	(46)
GALACTOCELE	9 (18%)	16 (32%)	3 (6%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		2 (4%)	
FIBROSIS				1 (2%)
HYPERPLASIA, NOS	23 (47%)	8 (16%)	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	2 (4%)			
*CLITORAL GLAND	(49)	(50)	(49)	(46)
ABSCESS, NOS				1 (2%)
*VAGINA	(49)	(50)	(49)	(46)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
*UTERUS	(49)	(50)	(49)	(44)
HYDROMETRA	6 (12%)		3 (6%)	1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
PYOMETRA			3 (6%)	
ABSCESS, NOS			4 (8%)	
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
NECROSIS, NOS			2 (4%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)		
*CERVIX UTERI	(49)	(50)	(49)	(44)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)			
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, BASAL CELL	1 (2%)			
ACANTHOSIS	1 (2%)			
*UTERUS/ENDOMETRIUM	(49)	(50)	(49)	(44)
INFLAMMATION, NOS		22 (44%)	1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, ACUTE	23 (47%)		3 (6%)	5 (11%)
ABSCESS, NOS			1 (2%)	
INFLAMMATION POLIFERATIVE				1 (2%)
HYPERPLASIA, NOS	5 (10%)	6 (12%)		1 (2%)
HYPERPLASIA, CYSTIC	5 (10%)		9 (18%)	2 (5%)
HYPERPLASIA, ADENOMATOUS		1 (2%)		
HYPERPLASIA, STROMAL			1 (2%)	
*OVARY/OVIDUCT	(49)	(50)	(49)	(44)
INFLAMMATION, NOS		10 (20%)		
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)	
INFLAMMATION, ACUTE	1 (2%)			
*OVARY	(47)	(49)	(48)	(45)
CYST, NOS	2 (4%)	8 (16%)		1 (2%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
HEMORRHAGE			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
CORPUS HEMORRHAGICUM				1 (2%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(49)	(50)	(49)	(44)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)	
#BRAIN	(49)	(50)	(49)	(44)
HEMORRHAGE			1 (2%)	
PERIVASCULITIS			1 (2%)	1 (2%)
#MEDULLA OBLONGATA	(49)	(50)	(49)	(44)
HEMORRHAGE			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(49)	(46)
INFLAMMATION, HEMORRHAGIC				1 (2%)
SYNECHIA, NOS	1 (2%)			
SYNECHIA, POSTERIOR			4 (8%)	
CATARACT	1 (2%)	1 (2%)	9 (18%)	
*EYE/CORNEA	(49)	(50)	(49)	(46)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)			
*EYE/RETINA	(49)	(50)	(49)	(46)
DEGENERATION, NOS	1 (2%)		8 (16%)	
ATROPHY, NOS		1 (2%)		
DYSPLASIA, NOS			1 (2%)	
*HARDERIAN GLAND	(49)	(50)	(49)	(46)
HYPERPLASIA, NOS		1 (2%)		
*EAR CANAL	(49)	(50)	(49)	(46)
ABSCESS, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
*VERTEBRA	(49)	(50)	(49)	(46)
OSTEOSCLEROSIS				1 (2%)

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

TABLE C2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0070	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0069	HIGH DOSE 02-0121
*STERNUM	(49)	(50)	(49)	(46)
OSTEOPETROSIS	1 (2%)			
*ABDOMINAL MUSCLE	(49)	(50)	(49)	(46)
INFLAMMATION, ACUTE FOCAL				1 (2%)
BODY CAVITIES				
*MEDIASTINUM	(49)	(50)	(49)	(46)
PERIARTERITIS	1 (2%)			
*EPI[illegible]DIUM	(49)	(50)	(49)	(46)
[illegible]AMMATION PROLIFERATIVE			1 (2%)	
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, ACUTE/CHRONIC	3			
INFLAMMATION, CHRONIC	2			
INFLAMMATION, GRANULOMATOUS				1
OMENTUM				
MINERALIZATION	1			
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED				2
ANIMAL MISSING/NO NECROPSY				1
AUTOLYSIS/NO NECROPSY	1		1	3

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 5-NITRO-o-ANISIDINE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 5-NITRO-o-ANISIDINE

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	49	48	48
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(49)	(48)	(49)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, FOCAL		3 (6%)		
INFLAMMATION, NECROTIZING		1 (2%)		
ABSCESS, NOS	2 (4%)			
FIBROSIS				1 (2%)
HYPERPLASIA, NODULAR			1 (2%)	
*SUBCUT TISSUE	(50)	(49)	(48)	(49)
NECROSIS, FAT	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(50)	(49)	(48)	(47)
BRONCHIECTASIS			1 (2%)	
INFLAMMATION, FOCAL		1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)	
#LUNG/BRONCHIOLE	(50)	(49)	(48)	(47)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC				2 (4%)
PERIVASCULITIS	1 (2%)			
#LUNG	(50)	(49)	(48)	(47)
HEMORRHAGE	2 (4%)			
INFLAMMATION, INTERSTITIAL		10 (20%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(50)	(49)	(45)	(47)
HYPERPLASIA, NOS		6 (12%)		

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

TABLE D1 (CONTINUED)

	DOSE A CONTROL(UNTR) 05-0070	DOSE B CONTROL(UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
RETICULOCYTOSIS		1 (2%)		
HYPERPLASIA, HEMATOPOIETIC		5 (10%)		
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	3 (7%)	
#SPLENIC FOLLICLES	(50)	(49)	(45)	(47)
HYPERPLASIA, NOS	2 (4%)			
#LYMPH NODE	(45)	(42)	(40)	(40)
INFLAMMATION, NOS		10 (24%)		
HYPERPLASIA, NOS		1 (2%)		
RETICULOCYTOSIS		2 (5%)		
HYPERPLASIA, LYMPHOID		3 (7%)		
#MESENTERIC L. NODE	(45)	(42)	(40)	(40)
INFLAMMATION, NOS			1 (3%)	
ANGIECTASIS				1 (3%)
HYPERPLASIA, RETICULUM CELL	1 (2%)			
HYPERPLASIA, LYMPHOID			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(49)	(49)	(48)	(47)
MINERALIZATION		1 (2%)		
PLASMACYTOSIS				1 (2%)
PERIVASCULITIS				3 (6%)
#MYOCARDIUM	(49)	(49)	(48)	(47)
DEGENERATION, NOS			1 (2%)	
#AORTIC VALVE	(49)	(49)	(48)	(47)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(49)	(48)	(47)	(46)
PERIVASCULITIS	1 (2%)			
#LIVER	(50)	(48)	(48)	(47)
INFLAMMATION, FOCAL				1 (2%)
NODULE				1 (2%)
DEGENERATION, NOS			4 (8%)	1 (2%)
NECROSIS, NOS			1 (2%)	
NECROSIS, FOCAL	1 (2%)	9 (19%)	1 (2%)	1 (2%)

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

TABLE D1 (CONTINUED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
NECROSIS, COAGULATIVE				1 (2%)
METAMORPHOSIS FATTY	2 (4%)			
HEPATOCYTOMEGALY	2 (4%)			
DEPLETION	1 (2%)			
HYPERTROPHY, NOS				3 (6%)
HYPERTROPHY, DIFFUSE			1 (2%)	
HYPERPLASIA, NODULAR	2 (4%)		2 (4%)	
HYPERPLASTIC NODULE		1 (2%)		1 (2%)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)			
HYPERPLASIA, DIFFUSE	1 (2%)			21 (45%)
ANGIECTASIS			19 (40%)	19 (40%)
#LIVER/CENTRILOBULAR	(50)	(48)	(48)	(47)
DEGENERATION, NOS			1 (2%)	
NECROSIS, NOS	1 (2%)			
#LIVER/PERIPORTAL	(50)	(48)	(48)	(47)
INFLAMMATION, NOS				3 (6%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#LIVER/KUPFFER CELL	(50)	(48)	(48)	(47)
HYPERPLASIA, NOS	1 (2%)			
#LIVER/HEPATOCYTES	(50)	(48)	(48)	(47)
DEGENERATION, NOS			20 (42%)	22 (47%)
HYPERTROPHY, NOS				2 (4%)
HYPERPLASIA, NOS				3 (6%)
HYPERPLASIA, DIFFUSE				12 (26%)
#PANCREAS	(46)	(47)	(47)	(43)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, FOCAL	1 (2%)			
#PANCREATIC ACINUS	(46)	(47)	(47)	(43)
HYPERTROPHY, FOCAL			1 (2%)	
#STOMACH	(49)	(48)	(48)	(46)
INFLAMMATION, FOCAL		2 (4%)		
INFLAMMATION, NECROTIZING		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)		
HYPERKERATOSIS		1 (2%)		
ACANTHOSIS		1 (2%)		
#GASTRIC MUCOSA	(49)	(48)	(48)	(46)
INFLAMMATION, FOCAL	1 (2%)			

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

TABLE D1 (CONTINUED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#GASTRIC SEROSA	(49)	(48)	(48)	(46)
PERIARTERITIS				1 (2%)
#PEYER'S PATCH	(49)	(49)	(48)	(45)
HYPERPLASIA, NOS	1 (2%)	7 (14%)		
#COLON	(46)	(43)	(47)	(40)
GRANULOMA, NOS	1 (2%)			
PARASITISM		3 (7%)		
URINARY SYSTEM				
#KIDNEY	(49)	(49)	(48)	(48)
GLOMERULONEPHRITIS, NOS		2 (4%)	5 (10%)	
INFLAMMATION, INTERSTITIAL	3 (6%)	16 (33%)		4 (8%)
PERIARTERITIS				1 (2%)
GLOMERULOSCLEROSIS, NOS				1 (2%)
#KIDNEY/TUBULE	(49)	(49)	(48)	(48)
DEGENERATION, NOS				1 (2%)
CALCIFICATION, FOCAL			1 (2%)	
PIGMENTATION, NOS				1 (2%)
#URINARY BLADDER	(47)	(48)	(48)	(47)
INFLAMMATION, SUPPURATIVE				1 (2%)
PERIARTERITIS				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	4 (8%)		
ENDOCRINE SYSTEM				
#ADRENAL	(49)	(44)	(44)	(46)
HYPERPLASIA, NOS		3 (7%)		
#ADRENAL/CAPSULE	(49)	(44)	(44)	(46)
HYPERPLASIA, NOS		3 (7%)		
#ADRENAL CORTEX	(49)	(44)	(44)	(46)
HYPERPLASTIC NODULE			1 (2%)	
#THYROID	(40)	(45)	(47)	(47)
FOLLICULAR CYST, NOS			2 (4%)	

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

TABLE D1 (CONTINUED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
LYMPHOCYTIC INFLAMMATORY INFILTR				3 (6%)
DEGENERATION, NOS			41 (87%)	44 (94%)
PIGMENTATION, NOS				2 (4%)
HYPERPIGMENTATION			5 (11%)	
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, EPITHELIAL				1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, PAPILLARY			1 (2%)	
HYPERPLASIA, ADENOMATOUS			1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL			3 (6%)	6 (13%)
ANGIECTASIS			1 (2%)	
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(50)	(49)	(48)	(49)
ABSCESS, NOS		1 (2%)		
HYPERPLASIA, NOS				1 (2%)
*PROSTATE	(49)	(49)	(48)	(44)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
PERIARTERITIS				1 (2%)
*SEMINAL VESICLE	(50)	(49)	(48)	(49)
INFLAMMATION, ACUTE				1 (2%)
DEGENERATION, NOS				1 (2%)
DEGENERATION, CYSTIC			1 (2%)	
HYPERPLASIA, CYSTIC			1 (2%)	
*TESTIS/TUBULE	(50)	(48)	(48)	(46)
DEGENERATION, NOS			2 (4%)	1 (2%)
CALCIFICATION, NOS				1 (2%)
*EPIDIDYMIS	(50)	(49)	(48)	(49)
INFLAMMATION, NOS		1 (2%)		
NERVOUS SYSTEM				
*BRAIN/MENINGES	(50)	(49)	(47)	(46)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
SPECIAL SENSE ORGANS				
NONE				

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

TABLE D1 (CONCLUDED)

	DOSE A CONTROL (UNTR) 05-0070	DOSE B CONTROL (UNTR) 05-0118	DOSE A 05-0071	DOSE B 05-0102
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, ACUTE		1		
OMENTUM				
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	12	5		
ANIMAL MISSING/NO NECROPSY		1		
NECROPSY PERF/NO HISTO PERFORMED				1
AUTOLYSIS/NO NECROPSY			2	1

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 5-NITRO-o-ANISIDINE

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	48	50	43	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	43	44
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(48)	(50)	(43)	(45)
ABSCESS, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(46)	(50)	(42)	(44)
INFLAMMATION, FOCAL		1 (2%)		
#LUNG/BRONCHIOLE	(46)	(50)	(42)	(44)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
HYPERPLASIA, NOS		1 (2%)		
#LUNG	(46)	(50)	(42)	(44)
INFLAMMATION, INTERSTITIAL	1 (2%)	14 (28%)		1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(46)	(49)	(35)	(40)
MYELOFIBROSIS	1 (2%)		15 (43%)	31 (78%)
MYELOSCLEROSIS				2 (5%)
#SPLEEN	(47)	(49)	(38)	(43)
PIGMENTATION, NOS			1 (3%)	
ATROPHY, NOS			1 (3%)	
HYPERTROPHY, NOS			1 (3%)	
HYPERPLASIA, NOS		9 (18%)		1 (2%)
ANGIECTASIS			1 (3%)	
HYPERPLASIA, HEMATOPOIETIC		6 (12%)		
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	3 (8%)	1 (2%)
#SPLENIC FOLLICLES	(47)	(49)	(38)	(43)
HYPERPLASIA, NOS	3 (6%)			

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

TABLE D2 (CONTINUED)

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
#HEMOLYMPH NODES	(47)	(49)	(38)	(43)
INFLAMMATION, NOS		2 (4%)		
HYPERPLASIA, NOS		1 (2%)		
#LYMPH NODE	(36)	(44)	(27)	(30)
INFLAMMATION, NOS	1 (3%)	9 (20%)		
HYPERPLASIA, NOS	1 (3%)	3 (7%)		
RETICULOCYTOSIS		1 (2%)		
HYPERPLASIA, HEMATOPOIETIC		1 (2%)		
HYPERPLASIA, PLASMA CELL	1 (3%)			
HYPERPLASIA, LYMPHOID		4 (9%)		
#ABDOMINAL LYMPH NODE	(36)	(44)	(27)	(30)
PLASMACYTOSIS	1 (3%)			
CIRCULATORY SYSTEM				
#HEART	(44)	(50)	(41)	(44)
PERIARTERITIS			2 (5%)	
ENDOCARDIOSIS			1 (2%)	
#MYOCARDIUM	(44)	(50)	(41)	(44)
INFLAMMATION, FOCAL		1 (2%)		
FIBROSIS, FOCAL	1 (2%)			
#ENDOCARDIUM	(44)	(50)	(41)	(44)
INFLAMMATION PROLIFERATIVE				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(45)	(48)	(31)	(43)
PERIVASCULITIS	3 (7%)			
PERIVASCULAR CUFFING	1 (2%)	3 (6%)		
#LIVER	(47)	(50)	(41)	(43)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
NECROSIS, FOCAL	2 (4%)	7 (14%)		
NECROSIS, COAGULATIVE			1 (2%)	
METAMORPHOSIS FATTY			1 (2%)	
HYPERPLASIA, NODULAR				1 (2%)
#LIVER/PERIPORTAL	(47)	(50)	(41)	(43)
METAMORPHOSIS FATTY			1 (2%)	

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

TABLE D2 (CONTINUED)

	DOSE A CONTROL (UNTR) 00-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
#LIVER/HEPATOCYTES	(47)	(50)	(41)	(43)
HYPERPLASIA, DIFFUSE				1 (2%)
*BILE DUCT	(48)	(50)	(43)	(45)
INFLAMMATION, ACUTE/CHRONIC	4 (8%)			
#PANCREAS	(43)	(48)	(32)	(38)
INFLAMMATION, NOS	1 (2%)	2 (4%)		
INFLAMMATION, INTERSTITIAL	1 (2%)			
PERIARTERITIS	1 (2%)			
HYPOPLASIA, NOS			1 (3%)	
#PANCREATIC ACINUS	(43)	(48)	(32)	(38)
DEGENERATION, NOS			1 (3%)	
ATROPHY, NOS	1 (2%)			
#STOMACH	(45)	(43)	(30)	(40)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, FOCAL		1 (2%)		
ULCER, FOCAL	1 (2%)			
ACANTHOSIS		2 (4%)		
METAPLASIA, SQUAMOUS				1 (3%)
#SMALL INTESTINE	(45)	(48)	(33)	(41)
INFLAMMATION, NOS			4 (12%)	
NECROSIS, NOS			2 (6%)	
ATROPHY, NOS			2 (6%)	
#S.INTESTINE/MUCOSA	(45)	(48)	(33)	(41)
NECROSIS, NOS			3 (9%)	
#PEYERS PATCH	(45)	(48)	(33)	(41)
HYPERPLASIA, NOS	1 (2%)	7 (15%)		
URINARY SYSTEM				
#KIDNEY	(45)	(50)	(42)	(43)
HYDRONEPHROSIS			4 (10%)	25 (58%)
GLOMERULONEPHRITIS, NOS	3 (7%)	4 (8%)		
GLOMERULONEPHRITIS, FOCAL	2 (4%)	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)	12 (24%)	15 (36%)	35 (81%)
GLOMERULONEPHRITIS, MEMBRANOUS	2 (4%)			
PYELONEPHRITIS, ACUTE/CHRONIC	1 (2%)			

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

TABLE D2 (CONTINUED)

	DOSE A CONTROL(UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
GLOMERULONEPHRITIS, CHRONIC	1 (2%)			
ARTERIOSCLEROSIS, NOS			1 (2%)	
NEPHROSIS, NOS			15 (36%)	32 (74%)
NEPHROSIS, TOXIC			1 (2%)	9 (21%)
#KIDNEY/GLOMERULUS	(45)	(50)	(42)	(43)
NEPHROSIS, TOXIC			12 (29%)	
#KIDNEY/TUBULE	(45)	(50)	(42)	(43)
MINERALIZATION		1 (2%)		
NEPHROSIS, NOS			4 (10%)	
NEPHROSIS, TOXIC			9 (21%)	1 (2%)
#URINARY BLADDER	(45)	(48)	(33)	(39)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
PERIARTERITIS	1 (2%)			
HYPERPLASIA, EPITHELIAL		1 (2%)		
ENDOCRINE SYSTEM				
#ADRENAL/CAPSULE	(47)	(48)	(34)	(40)
HYPERPLASIA, NOS		5 (10%)		
#ADRENAL CORTEX	(47)	(48)	(34)	(40)
NODULE		1 (2%)		
HYPERPLASIA, NOS		1 (2%)		
#THYROID	(41)	(44)	(34)	(43)
INFLAMMATION, FOCAL		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
DEGENERATION, NOS			12 (35%)	8 (19%)
HYPERPIGMENTATION			11 (32%)	
HYPERPLASIA, PAPILLARY		2 (5%)		
HYPERPLASIA, CYSTIC				1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			2 (5%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(50)	(43)	(45)
HYPERPLASIA, NOS		1 (2%)		
#UTERUS	(43)	(47)	(32)	(36)
HYDROMETRA	3 (7%)	13 (28%)	5 (16%)	4 (11%)

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

TABLE D2 (CONTINUED)

	DOSE A CONTROL (UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
ABSCESS, NOS	2 (5%)			
#UTERUS/ENDOMETRIUM	(43)	(47)	(32)	(36)
INFLAMMATION, NOS	2 (5%)	8 (17%)		
INFLAMMATION, SUPPURATIVE	2 (5%)			
INFLAMMATION, ACUTE	6 (14%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	3 (7%)			
HYPERPLASIA, NOS	1 (2%)	8 (17%)	1 (3%)	
HYPERPLASIA, CYSTIC	20 (47%)	6 (13%)	17 (53%)	28 (78%)
METAPLASIA, SQUAMOUS	1 (2%)			
#OVARY/OVIDUCT	(43)	(47)	(32)	(36)
INFLAMMATION, NOS		4 (9%)		
INFLAMMATION, SUPPURATIVE	4 (9%)			
ABSCESS, NOS	1 (2%)	1 (2%)		
#OVARY	(45)	(48)	(30)	(37)
CYST, NOS		10 (21%)		1 (3%)
INFLAMMATION, NOS		4 (8%)		
INFLAMMATION, SUPPURATIVE	6 (13%)			
INFLAMMATION, CHRONIC	1 (2%)			
ABSCESS, CHRONIC	1 (2%)			
PERIARTERITIS	1 (2%)	1 (2%)		
DEGENERATION, CYSTIC		3 (6%)		
ATROPHY, NOS				1 (3%)
HYPERPLASIA, NOS				2 (5%)
LUTEINIZATION				1 (3%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(46)	(48)	(34)	(41)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE D2 (CONCLUDED)

	DOSE A CONTROL(UNTR) 06-0070	DOSE B CONTROL (UNTR) 06-0118	DOSE A 06-0071	DOSE B 06-0102
BODY CAVITIES				
*MESENTERY	(48)	(50)	(43)	(45)
PERIARTERITIS			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(48)	(50)	(43)	(45)
PERIVASCULITIS	1 (2%)			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		3	2	1
ANIMAL MISSING/NO NECROPSY			1	
NECROPSY PERF/NO HISTO PERFORMED				1
AUTO/NECROPSY/HISTO PERF		1		
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY	2		6	5

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

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