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

BIOASSAY OF

2,4-DIAMINOANISOLE SULFATE

FOR POSSIBLE CARCINOGENICITY

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

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REPORT ON THE BIOASSAY OF 2,4-DIAMINOANISOLE SULFATE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of 2,4-diaminoanisole sulfate conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of 2,4-diaminoanisole sulfate 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), Dr. A. S. Krishna Murthy (3) and Dr. A. Russfield (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (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), and Dr. A. Chu (5), using methods selected for the Bioassay Program by Dr. J. J. Gart (7).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for

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The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (7), Mr. J. Nam (7), Dr. H. M. Pettigrew (7), and Dr. R. E. Tarone (7).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,8), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of technical-grade 2,4-diaminoanisole sulfate for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 2,4-Diaminoanisole sulfate was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The time-weighted average dietary concentrations used in the chronic bioassay were 0.12 percent for the low dose rats and 0.5 percent for the high dose rats. The dietary concentrations used for low and high dose mice were 0.12 and 0.24 percent, respectively. After a 78-week period of chemical administration, observation of the rats continued for an additional 29 weeks and observation of the mice continued for an additional 19 weeks. For each species, 49 or 50 animals of each sex were placed on test as controls.

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

In high dose male and female rat groups, the proportion of animals having one or more of the following malignant follicular-cell thyroid tumors: papillary adenocarcinomas, follicular-cell carcinomas, papillary cystadenocarcinomas, or adenocarcinomas NOS, was significantly greater than the proportion in corresponding control groups. For high dose male rats the proportion of animals having either a C-cell adenoma or a C-cell carcinoma was also significantly increased.

The incidence of malignant tumors (squamous-cell carcinomas, basal-cell carcinomas, or sebaceous adenocarcinomas) of the skin and its associated glands were significantly increased among high dose rats of both sexes.

Among high dose female mice, the combined incidence of thyroid follicular-cell adenomas and carcinomas was significantly increased. Among high dose male mice, the incidence of thyroid follicular-cell adenomas was significantly increased, but no follicular-cell carcinomas were observed.

Under the conditions of this bioassay, technical-grade 2,4-diaminoanisole sulfate was carcinogenic to both sexes of both species. In Fischer 344 rats dietary administration of the chemical induced increased incidences of malignant tumors of the skin and its associated glands and malignant thyroid tumors in each sex. In B6C3F1 mice, dietary administration of 2,4-diaminoanisole sulfate induced thyroid tumors in each sex.

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I. INTRODUCTION

2,4-Diaminoanisole sulfate (NCI No. C01989), a component of many hair dyes, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer observed among workers in the dye manufacturing industry (Wynder et al., 1963; Anthony and Thomas, 1970). Occupational exposure to several classes of chemicals, including aromatic amino-compounds, is believed to contribute to this increased cancer risk (Wynder et al., 1963), and 2,4-diaminoanisole sulfate is especially suspect because it is structurally analogous to the known carcinogen 2,4-diaminotoluene sulfate (Ito et al., 1969). The widespread exposure to 2,4-diaminoanisole sulfate among the general population and the possibility of an increased cancer risk among hairdressers (Anthony and Thomas, 1970) were additional factors in its selection for testing.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 4-methoxy-1,3-benzenediamine sulfate.* On hair dye labels this compound is commonly called 4-methoxy-m-phenylenediamine sulfate or 4-MMPD. It is also called 2,4-diamino-1-methoxybenzene sulfate; and 2,4-DAA sulfate.

2,4-Diaminoanisole sulfate is one of the most frequently used couplers in permanent hair dye formulations (Corbett and Menkart, 1973). Imines, produced within the hair shaft by the oxidation of

*The CAS registry number is 615-05-4.

a primary intermediate, such as p-phenylenediamine, react with 2,4-diaminoanisole sulfate to produce blue or purple-blue colors (Corbett, 1971; Corbett and Menkart, 1973). The maximum concentration of the compound in hair dye preparations is about 1.5 percent; however, in actual use, the dye base is diluted with an equal volume of hydrogen peroxide solution (Menkart, 1977).

2,4-Diaminoanisole sulfate can also be used as an oxidation base to dye furs (Society of Dyers and Colourists, 1971a; as cited in Urso, 1977) and as an intermediate for the production of textile dye, C.I. (Colour Index) Basic Brown 2 (Society of Dyers and Colourists, 1971b; as cited in Urso, 1977).

Specific production statistics for 2,4-diaminoanisole sulfate are not available; however, the listing of the compound in the 1977 Directory of Chemical Producers, U.S.A. (Stanford Research Institute, 1977) implies that 2,4-diaminoanisole sulfate is produced in commercial quantities (greater than 1000 pounds or $1000 in value annually). The estimated annual usage in the United States is 30,000 pounds (Menkart, 1977).

Exposure to 2,4-diaminoanisole sulfate may occur at chemical and dye production facilities and among hairdressers using dyes which contain the compound. Dermal contact occurs for all those whose hair is colored with dyes containing 2,4-diaminoanisole sulfate. About 40 percent of U.S. women are regular users of hair dyes, and approximately three out of every four dollars spent on hair coloring is spent on the

permanent type of dye (Corbett and Menkart, 1973). Additionally, exposure may result from unreacted portions of 2,4-diaminoanisole sulfate reaching rivers and streams via domestic wastewater.

2,4-Diaminoanisole sulfate can be absorbed through the skin. It has been recovered after dermal application in the urine of Rhesus monkeys and humans (Maibach, 1977).

No data concerning the effects of acute or chronic exposure to 2,4-diaminoanisole sulfate in humans are available. No evidence of carcinogenicity was found after up to 18 months of topical applications of hair dye formulations containing 2,4-diaminoanisole sulfate to 200 random-bred Swiss Webster mice of both sexes (Burnett et al., 1975). Seven topical applications of preparations containing 2,4-diaminoanisole sulfate to 60 female Charles River CD rats during gestation produced no teratogenic effects (Burnett et al., 1976).

2,4-Diaminoanisole sulfate has been found to induce frame shift reversions from a histidine-requiring mutant back to prototype in Salmonella typhimurium strain TA 1538 (Ames et al., 1975). Of nine hair dye components found to be mutagenic by Ames et al. (1975), 2,4-diaminoanisole sulfate was the most active in reverting TA 1538. Mutagenicity was also indicated by marked difference of inhibition for growth (DIG) in the DNA repair test in Escherichia coli strains B/r WP2 (trp^-) and WP100 (trp^-, $uvrA^-$, $recA^-$) (Nishioka, 1976). In a recessive lethal assay utilizing Drosophila melanogaster, 2,4-diaminoanisole sulfate exhibited weak mutagenic activity (Blijleven,

1977). Mammalian mutagenicity studies have been performed both *in vivo* and *in vitro*. In a forward mutational assay system which utilized the thymidine kinase heterozygous locus of mouse lymphoma cells, 2,4-diaminoanisole sulfate gave a weak response, causing a dose-related increase in mutation frequency and in the ratio of induced to spontaneous mutations (Palmer et al., 1977). The compound was not mutagenic to germ cells in a dominant lethal study of Charles River CD rats following intraperitoneal administration of 20 mg/kg three times weekly for 8 weeks to 20 males (Burnett et al., 1977).

II. MATERIALS AND METHODS

A. Chemicals

A single batch of technical-grade 2,4-diaminoanisole sulfate, in powder form, was purchased from American Hoechst and chemical analysis was performed by Mason Research Institute, Worcester, Massachusetts. The range of the experimentally determined melting point (135° to 138°C) was relatively narrow. No literature value was reported for this compound. Thin-layer chromatography resulted in a major spot and a single additional spot. Infrared analysis was not inconsistent with the structure of the compound.

Throughout this report the term 2,4-diaminoanisole sulfate is used to represent this technical-grade material.

B. Dietary Preparation

The basal laboratory diet for both treated and control animals was Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 2,4-Diaminoanisole sulfate was administered to the treated animals as a component of the diet.

Quantities of the chemical were weighed out and hand-blended in an aluminum bowl with an aliquot of the ground feed. Once visual homogeneity was attained, the mixture was placed in a 6 kg capacity Patterson-Kelley twin-shell stainless steel V-blender along with the remainder of the meal. The blender was sealed and operated for 20 minutes. The mixtures were placed in double plastic bags, and stored in the dark at 4°C. The mixture was prepared once weekly.

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. Mice and high dose treated and control rats were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Low dose treated and control rats were supplied by Laboratory Supply Company, Inc., Indianapolis, Indiana. Treated rats and high dose mice were received in separate shipments from their controls. Low dose treated and control mice arrived on the same day.

Upon arrival, two males and two females per species per shipment were sacrificed and examined for parasites and other signs of disease. Rats and mice to be used in the bioassay were quarantined by species for 2 weeks prior to initiation of the test. Animals were assigned to groups and distributed among cages so that average body weight per cage was approximately equal for a given species and sex.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 20° to 28°C. These rooms were not humidity controlled. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. During quarantine and for the first 13 months of study, rats were kept in galvanized-steel wire-mesh cages suspended above newspapers. Newspapers under cages were replaced daily, and cages and racks washed weekly. For the remainder of the study, all rats were housed in suspended solid-bottom polycarbonate cages equipped with disposable nonwoven fiber filter sheets. Clean bedding and cages were provided twice weekly. Corncob bedding (SAN-I-CEL®, Paxton Processing Company, Paxton, Illinois) was used for the entire period of polycarbonate caging for low dose rats and their controls. SAN-I-CEL® was also used for high dose rats and their controls during the first 8 months of polycarbonate caging. Hardwood chips (Aspen bedding, American Excelsior Company, Baltimore, Maryland) were used for these groups for the final 3 months of study. Stainless steel cage racks were cleaned once every 2 weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate cages. During quarantine and periods of chemical administration, cages were fitted with perforated stainless steel lids. During the observation period which followed, stainless steel wire bar lids were used. Both types of lids were from Lab Products, Inc., Garfield, New Jersey. Nonwoven fiber filter bonnets were used over cage lids. Low dose mice and their controls were housed ten per cage for the first 18 months of study and five per cage thereafter. The number of high dose rats per cage was reduced to five after 12 months, and the number of high dose

control rats per cage was reduced to five after 11 months. Clean cages, lids, 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 chips (Wilner Wood Products Company, Norway, Maine) were used as bedding for the first month of study for high dose mice and their controls, and for the first 8 months of study for low dose mice and their controls. SAN-I-CEL® was used for the next 12 months for all mice. Corncob bedding (Bed-o-Cobs®, The Andersons Cob Division, Maumee, Ohio) was used for the remainder of the study for low dose mice and their controls, and for the next 8 months for high dose mice and their controls. For the remainder of the study, high dose mice and their controls were provided with Aspen bedding. Reusable filter bonnets and pipe racks were sanitized every 2 weeks throughout the study.

Water was available 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 available ad libitum.

During the 78-week period of chemical administration all dosed animals were supplied with Wayne Lab-Blox® meal containing the appropriate concentrations of 2,4-diaminoanisole sulfate. Control animals had untreated meal available. Meal was supplied throughout the study to all mice and to low dose rats and their controls in Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn,

Massachusetts) containing stainless steel baffles. High dose rats and their controls were fed from Alpine feed cups for the first 11 months of study and from stainless steel gangstyle feed hoppers (Scientific Cages, Inc., Bryan, Texas) thereafter. During the untreated observation period, mice were fed pelleted Wayne Lab-Blox from a wire bar hopper incorporated into the cage lid, and rats were fed pelleted Wayne Lab-Blox on the cage floor. Food hoppers were changed on the same schedule as were cages. Food was replenished daily in Alpine feed cups.

High dose, low dose, and low dose control rats in the 2,4-diaminoanisole sulfate study were housed in a room with other rats receiving diets containing* 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 2-aminoanthraquinone (117-79-3); 3-amino-9-ethylcarbazole hydrochloride; 6-nitrobenzimidazole (94-52-0); 1-nitronaphthalene (86-57-7); and APC (8003-03-0). High dose control rats were in a room with other rats receiving diets containing amitrole (61-82-5); 2-methyl-1-nitroanthraquinone (129-15-7); and 3-nitro-p-acetophenetide (1777-84-0).

High dose mice were housed in a room with other mice receiving diets containing 5-nitro-o-anisidine (99-59-2); 2,5-toluenediamine sulfate (6369-59-1); 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 3-amino-9-ethylcarbazole hydrochloride; 6-nitrobenzimidazole (94-52-0); and 1-nitronaphthalene (86-57-7). Low dose mice and

*CAS registry numbers are given in parentheses.

all control mice were housed in a room where other mice were receiving diets containing the following compounds: amitrole (61-82-5); N,N-dimethyl-p-nitrosoaniline (138-89-6); 5-nitro-o-anisidine (99-59-2); 2,5-toluenediamine sulfate (6369-59-1); 2,4-dinitrotoluene (121-14-2); 2-aminoanthraquinone (117-79-3); 3-amino-4-ethoxyacetanilide (17026-81-2); 3-amino-9-ethylcarbazole hydrochloride; 1-amino-2-methylanthraquinone (82-28-0); 4-nitroanthranilic acid (619-17-0); 1-nitronaphthalene (86-57-7); 5-nitroacenaphthene (602-87-9); 3-nitro-p-acetophenetide (1777-84-0); and APC (8003-03-0).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 2,4-diaminoanisole sulfate for administration to treated animals in the chronic studies, subchronic toxicity studies were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. 2,4-Diaminoanisole sulfate was incorporated into the laboratory diet and supplied ad libitum to five of the six rat groups and five of the six mouse groups in concentrations of 0.075, 0.125, 0.209, 0.348, and 0.580 percent. The sixth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for 4 weeks, followed by a 2-week observation period during which animals were fed the basal diet. Survivors were sacrificed at the end of the test, and gross necropsies were performed.

The initial high concentrations chosen for administration during the chronic test were those causing no deaths, no gross compound-related abnormalities, and no mean body weight depression in excess of 15 percent relative to controls during the 6-week subchronic test.

No gross abnormalities were noted in rats. One male rat died at each of 3 dosages: 0.075, 0.125, and 0.58 percent. Only the latter death was judged compound-related. The initial high concentration chosen for rats in the chronic study was 0.125 percent, but at a later time a group of rats was placed on test at a higher concentration.

No gross abnormalities were observed in mice. One male mouse died at a concentration of 0.58 percent. The initial high concentration used for the mouse chronic study was 0.24 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 time-weighted average concentrations) are summarized in Tables 1 and 2.

The dietary concentrations of 2,4-diaminoanisole sulfate initially administered to rats in the chronic study were 0.125 and 0.06 percent. After 10 weeks, the 0.125 percent concentration was reduced to 0.12 percent in order to standardize all doses at two decimal places and facilitate dose formulation. The rat group initially receiving a concentration of 0.06 percent was sacrificed after 10 months and no histopathologic examinations were performed because the dose level

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
2,4-DIAMINOANISOLE SULFATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	2,4-DIAMINO-ANISOLE SULFATE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[a]
MALE					
LOW DOSE CONTROL	50	0	0	107	0
HIGH DOSE CONTROL	49	0	0	109	0
LOW DOSE	50	0.125 0.12 0	10 68	 29	0.12
HIGH DOSE	50	0.5 0	78	 29	0.5
FEMALE					
LOW DOSE CONTROL	50	0	0	108	0
HIGH DOSE CONTROL	50	0	0	110	0
LOW DOSE	50	0.125 0.12 0	10 68	 29	0.12
HIGH DOSE	50	0.5 0	78	 29	0.5

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
2,4-DIAMINOANISOLE SULFATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	2,4-DIAMINO-ANISOLE SULFATE CONCENTRATION (PERCENT)	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	96
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.12 0	78	19
HIGH DOSE	50	0.24 0	78	18
FEMALE				
LOW DOSE CONTROL	50	0	0	97
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.12 0	78	19
HIGH DOSE	50	0.24 0	78	18

was considered, on the basis of weight depression, to be too low. A new treated group, receiving 0.5 percent, was started approximately 11 months after the initiation of the chronic study. Throughout this report the rat groups receiving an initial concentration of 0.5 percent are referred to as the high dose groups and the rat groups receiving an initial concentration of 0.125 percent are referred to as the low dose groups. The treated rats were supplied with dosed feed for 78 weeks, followed by a 26-week observation period.

The initial dietary concentrations of 2,4-diaminoanisole sulfate administered to mice in the chronic study were 0.24 and 0.12 percent. Throughout this report those mouse groups receiving a concentration of 0.24 percent are referred to as the high dose groups and those mouse groups receiving 0.12 percent are referred to as the low dose groups. These treated mice were supplied with dosed feed for 78 weeks, followed by a 13-week observation period.

All rats and mice were approximately 6 weeks old at the time that they were placed on test. The rats that became the low dose group were placed on test one month after their controls. The new high dose rats were placed on test one month before the high dose controls. The mice that became the low dose group were placed on test at the same time as their controls. The new high dose mice were placed on test one month before the high dose control mice.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice

daily for mortality. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. 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, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

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

Tissues for which slides were prepared 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.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report

in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control

group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was

found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk

of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

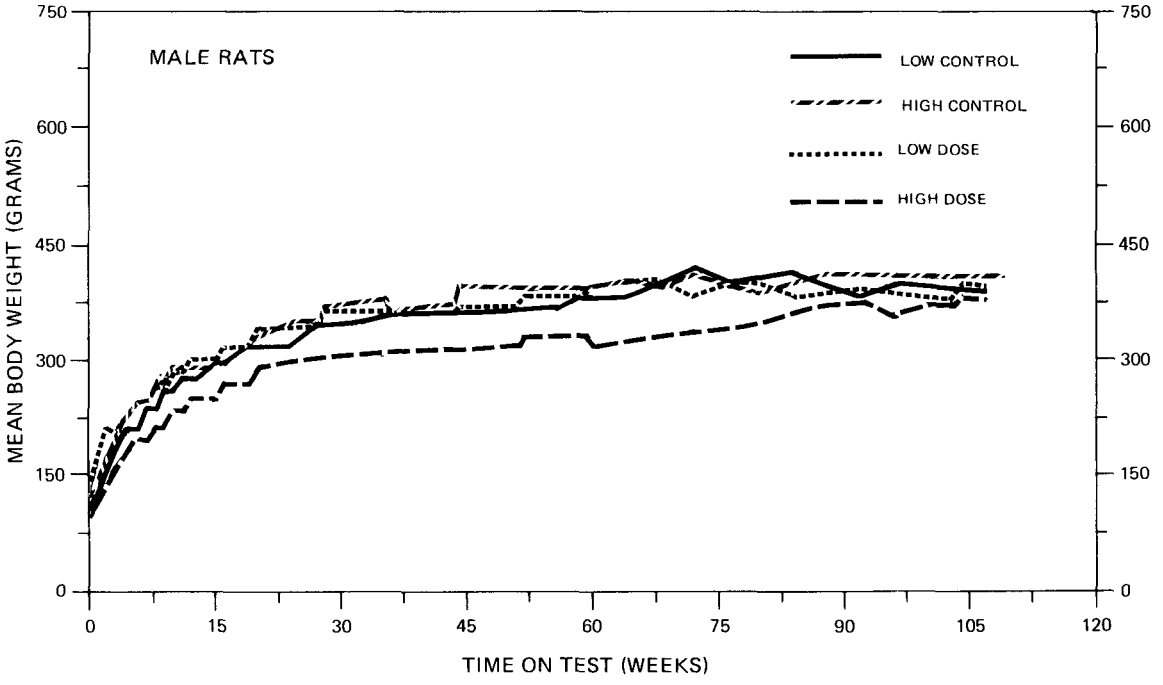
Mean body weights of high dose male and female rats were depressed relative to their controls throughout the study. No consistent depression in mean body weight was apparent for low dose male or female rats (Figure 1).

Among high dose rats, one male had a cutaneous lesion below the ear and two females had black, crusted vaginal lesions. The color of the coats of male and female high dose rats changed to a light brown. Palpable subcutaneous masses were observed in ten high dose control male rats and one high dose control female rat. Among high dose control females, white discoloration of the eye was observed in one rat, exopthalmia in a second rat, and acute alopecia in a third rat. One low dose control male had a crusted cutaneous lesion on the dorsolateral surface. No other clinical abnormalities were observed in rats of any group.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 2,4-diaminoanisole sulfate-dosed groups are shown in Figure 2.

For male rats the Cox tests for positive association between increased dosage and accelerated mortality were not significant. Five rats from each dosed and control group were sacrificed in week 78 in addition to the 10 low dose controls sacrificed in week 29. There



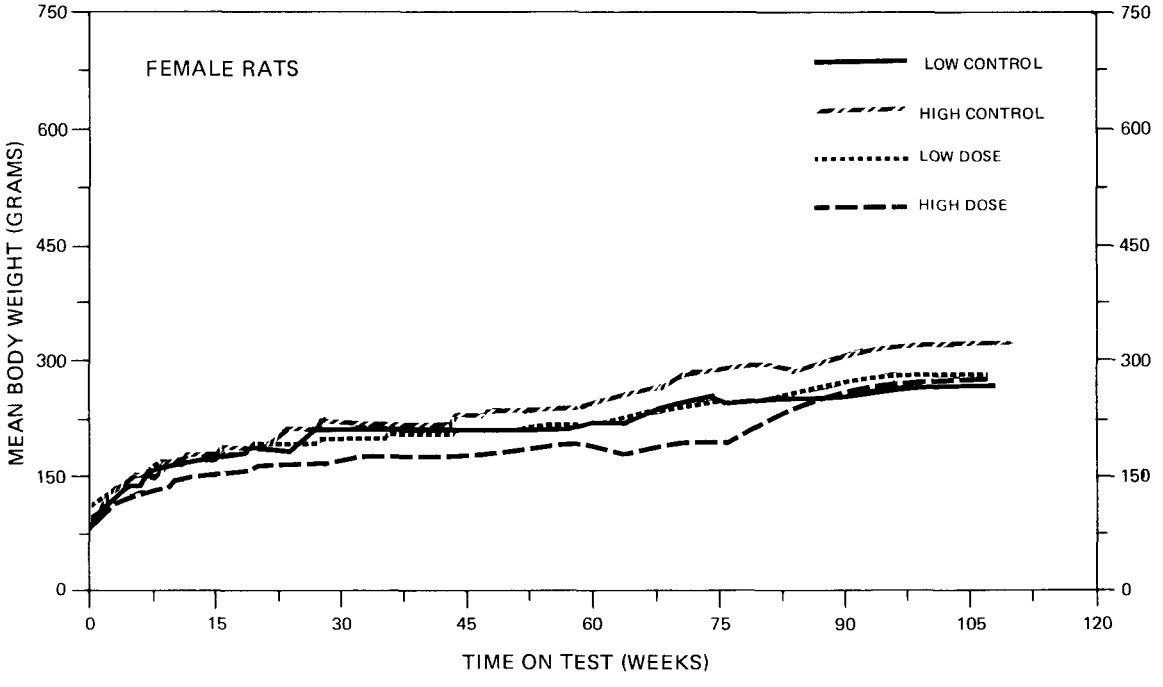
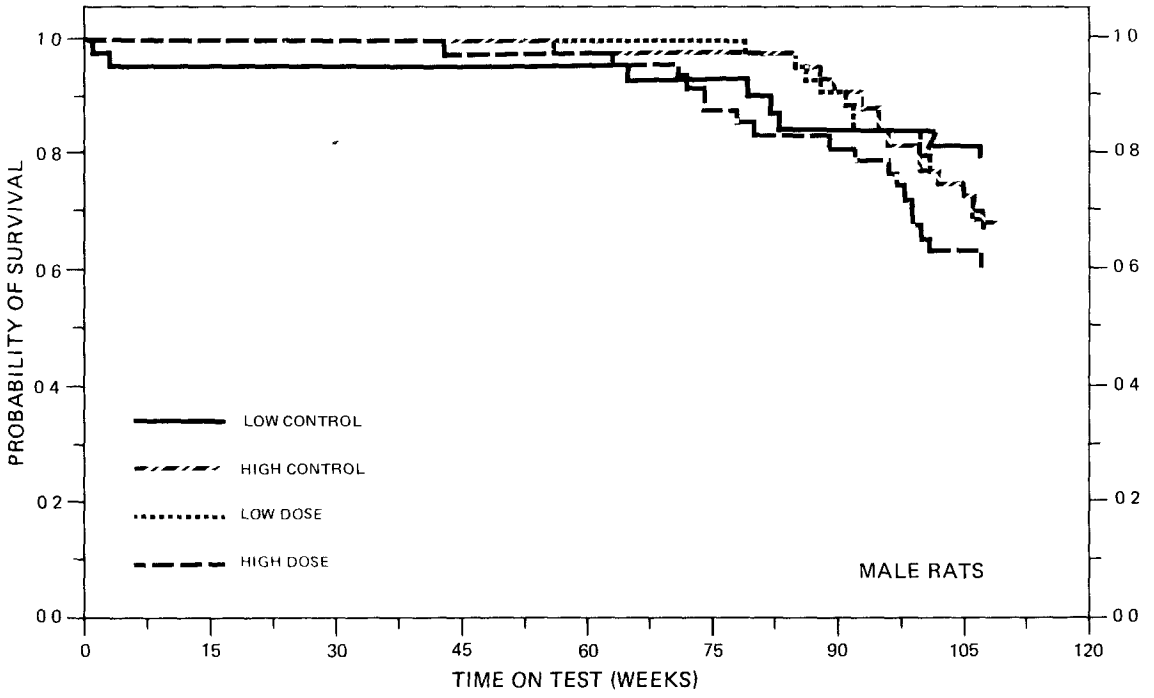


FIGURE 1
GROWTH CURVES FOR 2,4-DIAMINOANISOLE SULFATE CHRONIC STUDY RATS



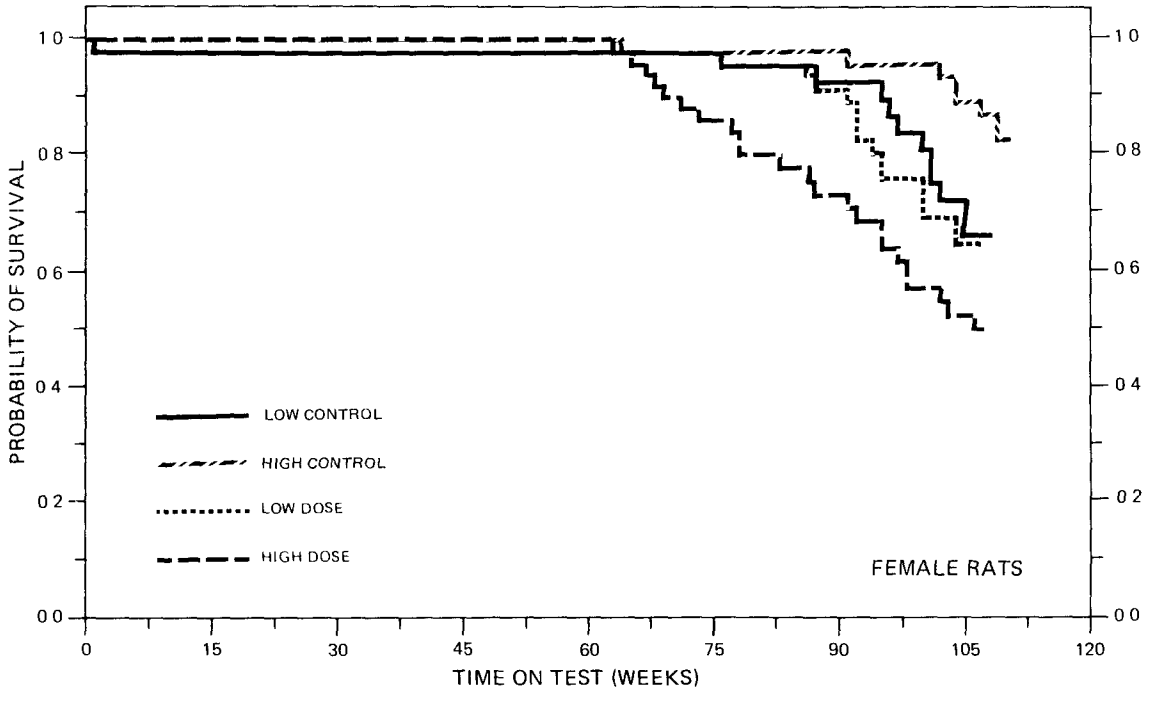


FIGURE 2
SURVIVAL COMPARISONS OF 2,4-DIAMINOANISOLE SULFATE CHRONIC STUDY RATS

were adequate numbers of male rats at risk from late-developing tumors with 54 percent (27/50) of the high dose, 60 percent (30/50) of the low dose, 61 percent (30/49) of the high dose controls, and 54 percent (27/50) of the low dose controls alive until the termination of the study.

For female rats the Cox test showed a significant ($P < 0.001$) association between increased dosage and accelerated mortality in comparing the high dose to the high dose control. Five rats from each dosed and control group were sacrificed in week 78 as well as 10 low dose controls which were sacrificed in week 29. Survival was good in all groups until about week 80. With 44 percent (22/50) of the high dose, 58 percent (29/50) of the low dose, 74 percent (37/50) of the high dose control, and 46 percent (23/50) of the low dose control animals surviving until the termination of the experiment, adequate numbers of female rats were at risk from late-developing tumors.

C. Pathology

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

A variety of neoplasms were found in both the control and treated groups (Appendix A). The incidences of most of these lesions could not be related to feeding with 2,4-diaminoanisole sulfate. However, there was an increased incidence of neoplasms of the integumentary system and of the thyroid gland in the treated rats.

Tumors of the integumentary system are summarized in Table 3. Epithelial neoplasms of the skin, preputial/clitoral gland, and Zymbal's gland/ear canal were increased in treated groups, particularly in males.

Squamous-cell carcinomas appeared grossly as hard, sometimes irregular masses which were often ulcerated and poorly demarcated from surrounding tissue. They were composed of more or less well-differentiated squamous cells which grew in whorls or strands into adjacent structures. Mitoses were often abundant. Epithelial pearl formation, hyalinization of cytoplasm, and the presence of intercellular bridges were used as criteria of squamous differentiation.

Basal-cell carcinomas appeared grossly as firm, rounded epithelial masses which were usually of small to moderate size. They were composed of small, dark undifferentiated basal cells originating from the epidermis and growing down into the dermis in masses exhibiting polarization of the outside cell layer or occasionally forming a lace-like pattern.

Sebaceous adenomas and adenocarcinomas also appeared grossly as firm masses, their color and consistency varying greatly with the degree of secondary ulceration and squamous differentiation. Microscopically, they consisted of a variable mixture of basal cells and rounded pale cells containing small clear vacuoles. When the tumor was well-differentiated with considerable histologic resemblance to normal sebaceous glands, it was classified as an adenoma. When

TABLE 3

EPITHELIAL TUMORS OF THE INTEGUMENTARY SYSTEM FOUND IN FISCHER 344 RATS

Tissue/Lesion	MALES				FEMALES			
	Low Dose Control	High Dose Control	Low Dose	High Dose	Low Dose Control	High Dose Control	Low Dose	High Dose
SKIN (Including dermis, subcutis, and tail)								
Number of Animals with Tissues Examined Histopathologically	(46)	(48)	(48)	(49)	(49)	(50)	(49)	(49)
Squamous-Cell Papilloma	0	0	1	0	0	0	0	0
Squamous-Cell Carcinoma	0	0	0	5	0	0	0	0
Basal-Cell Carcinoma	0	0	1	2	0	1	0	1
Sebaceous Adenoma	0	0	0	1	0	0	0	0
Sebaceous Adenocarcinoma	0	0	1	3	0	0	0	0
PREPUTIAL/CLITORAL GLAND								
Number of Animals with Tissues Examined Histopathologically	(46)	(48)	(48)	(49)	(49)	(50)	(49)	(49)
Adenoma NOS, Cystadenoma, or Papillary Adenoma	0	0	2	5	0	2	4	6
Carcinoma NOS	0	0	0	4	0	0	0	2
Squamous-Cell Papilloma	0	0	0	0	0	1	0	0
Squamous-Cell Carcinoma	0	0	0	0	0	0	1	0
ZYMBAL'S GLAND/EAR CANAL								
Number of Animals with Tissues Examined Histopathologically	(46)	(48)	(48)	(49)	(49)	(50)	(49)	(49)
Sebaceous Adenocarcinoma	0	0	1	4	0	0	0	7
Squamous-Cell Carcinoma	0	0	0	2	0	0	0	0

peripheral cell masses were poorly differentiated and tended to invade into adjacent tissues, they were classified as sebaceous adenocarcinomas. Particularly in the sebaceous tumors which arose in the ear canal, there was occasionally sufficient superficial squamous differentiation so as to suggest a squamous carcinoma.

Tumors of the preputial and clitoral glands were round, firm, fluctuant subcutaneous masses on the ventral surface in the genital area. When cut, they appeared as cysts which were usually filled with green pasty material. These tumors were characterized microscopically by 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. Others, with minimal squamous change, were classified as adenomas if they consisted of masses of large granulated cells with large, round, vesicular nuclei surrounding a central cavity and having a well-defined, intact outer border. If the outer border was irregular and consistent with invasion of surrounding tissue, the tumors were diagnosed as carcinomas. It was difficult to distinguish between varieties of these tumors since there was a continuous spectrum from adenoma to adenocarcinoma to squamous-cell carcinoma.

The incidence of neoplasms observed in the thyroid* are tabulated below:

MALES	Low Dose Control	High Dose Control	Low Dose	High Dose
Thyroid				
(Number of Animals with Tissues Examined Histopathologically)	(45)	(48)	(47)	(49)
Adenoma NOS	1	0	0	0
Adenocarcinoma NOS	2	0	1	14
Papillary Adenocarcinoma	0	0	0	1
Follicular-Cell Adenoma	0	0	0	1
Follicular-Cell Carcinoma	0	0	0	1
Papillary Cystadenoma NOS	0	0	0	2
Papillary Cystadenocarcinoma NOS	0	0	1	1
C-Cell Adenoma	1	0	4	8
C-Cell Carcinoma	0	1	0	3

FEMALES	Low Dose Control	High Dose Control	Low Dose	High Dose
Thyroid				
(Number of Animals with Tissues Examined Histopathologically)	(47)	(45)	(46)	(49)
Adenoma NOS	1	0	1	0
Adenocarcinoma NOS	2	0	0	4
Follicular-Cell Adenoma	0	0	0	2
Follicular-Cell Carcinoma	0	1	0	3
Papillary Cystadenoma NOS	0	0	1	0
Papillary Cystadenocarcinoma NOS	0	0	1	3
C-Cell Adenoma	1	1	2	4
C-Cell Carcinoma	0	1	0	3

The thyroids of the treated rats, especially those receiving the high dose of the compound, tended to be enlarged and dark red to black in color. Microscopically, golden brown pigment granules were found

*Follicular-cell tumors were reported as adenoma NOS, follicular-cell adenoma, papillary cystadenoma NOS, adenocarcinoma NOS, papillary adenocarcinoma, papillary cystadenocarcinoma NOS, and follicular-cell carcinoma.

within follicular cells, within macrophages, and lying free in the colloid. This hyperpigmentation was observed in 47/49 high dose males and 49/49 high dose females. A few thyroids exhibited focal lymphocytic infiltrate. In part, thyroid enlargement was due to follicular cysts (9/49 high dose males and 12/49 high dose females) or hyperplasia (either follicular or C-cell), and in part to the presence of tumors. These tumors were of two varieties, follicular-cell and C-cell origin. Feeding rats 2,4-diaminoanisole sulfate tended to increase the incidence of follicular tumors more than those of C-cell origin.

Follicular-cell tumors were usually rounded, unilateral thyroid masses having a semitranslucent red-tan or red-brown cut surface. Histologically these tumors exhibited varying degrees of differentiation and were reported as adenoma NOS, follicular-cell adenoma, papillary cystadenoma, adenocarcinoma NOS, papillary adenocarcinoma, papillary cystadenocarcinoma, and follicular-cell carcinoma. Adenomas were well-defined collections of follicles clearly differentiated from the normal thyroid tissue by increased basophilia, variation in follicle size, and increased cellularity. Papillary cystic patterns were sometimes present. There was no rigid histological differentiation between follicular adenomas and carcinomas. However, the latter tended to be larger, to have a higher nuclear/cytoplasmic ratio, and to exhibit more nuclear pleomorphism. Often, carcinomas exhibited capsular or extracapsular invasion.

C-cell tumors were usually unilateral, round thyroid masses but on section were somewhat more opaque and tended to have yellowish streaks. Microscopically, C-cell adenomas were round, well-circumscribed collections of cells having uniform ovoid nuclei and a moderate amount of indistinct pale acidophilic cytoplasm. Sometimes small cystic areas lined by flat cells and filled with colloid-like material were noted in these tumors. C-cell carcinomas tended to be larger, and both cells and nuclei occasionally assumed a spindle shape. Peripheral cells invaded the thyroid capsule and often grew beyond it.

The response of the mammary gland appeared equivocal since there was wide variation in the numbers of mammary tumors found in the low dose control females as compared with the high dose control females as shown in the following table:

	Low Dose Control	High Dose Control	Low Dose	High Dose
Mammary Gland, Mammary Duct, and Lactiferous Duct				
Number of Animals with Tissues Examined Histopathologically	(49)	(50)	(49)	(49)
Adenocarcinoma NOS	1	0	2	2
Papillary Cystadenoma NOS	0	0	1	0
Papillary Cystadenocarcinoma NOS	1	0	2	0
Fibroadenoma	4	19	16	3
Adenoma NOS	1	0	0	0

Mammary tumors were present as subcutaneous masses on the ventral surface ranging from firm to soft and fluctuant. When cut, they

sometimes exuded milky fluid, often contained within grossly visible cysts. The most frequently observed mammary neoplasm was a fibroadenoma composed of well-differentiated glands embedded in a copious fibrous connective tissue stroma. In some cases, the glands were compressed by the stroma; in others, they showed intracellular secretion vacuoles and were dilated by fluid. Often, these secretory fibroadenomas were associated with large galactoceles. A few tumors composed of masses of well-differentiated mammary glands having little associated stroma were classified as adenomas. Papillary cystic variants of adenomas were sometimes observed. Adenocarcinomas contained a high proportion of glands in comparison to stroma, and the glands tended to be poorly differentiated, sometimes breaking down into isolated cells which invaded adjacent tissue. The nuclei of the malignant tumors tended to have heavy chromatin borders, vesicular architecture, and prominent nucleoli. Mitoses were sometimes noted. Some tumor cells appeared to be lactating. Others formed papillary cystic patterns.

Both treated and control rats exhibited a spectrum of nonneoplastic degenerative and inflammatory lesions which could not be related to compound administration.

Results of this histopathologic examination indicate that under the conditions of this study, 2,4-diaminoanisole sulfate was carcinogenic to Fischer 344 rats because it increased the incidence of

integumentary neoplasms, particularly in males, and because it increased the incidence of thyroid neoplasms in male and female rats.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 4 and 5. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or 2,4-diaminoanisole sulfate-dosed groups and where such tumors were observed in at least 5 percent of the group. Because a number of low dose control rats of both sexes were sacrificed in week 29, all Fisher exact tests involving these controls have been based exclusively on rats surviving at least 30 weeks. Due to the differences in starting times between the low dose and the high dose experiments, no Cochran-Armitage tests have been performed.

Large numbers of thyroid tumors were noted in treated rats, with significant incidences of carcinomas in both male and female rats. For males the Fisher exact test showed a significant ($P = 0.001$) increase in adenocarcinomas NOS in the high dose group compared to the high dose control. For females when incidences were combined so that the numerator represented rats with either an adenocarcinoma NOS, a follicular-cell carcinoma, or a papillary cystadenocarcinoma NOS, the Fisher exact test indicated a significantly ($P = 0.006$) greater incidence in the high dose than in the high dose control group. For

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 2,4-DIAMINOANISOLE SULFATE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/35(0.03)	1/48(0.02)	4/47(0.08)	10/49(0.20)
P Values[c]	---	---	N.S.	P = 0.004
Relative Risk (Control)[d]	---	---	2.979	9.796
Lower Limit	---	---	0.314	1.484
Upper Limit	---	---	143.426	4.551
Weeks to First Observed Tumor	107	109	78	72
Thyroid: Adenocarcinoma NOS[b]	2/35(0.06)	0/48(0.00)	1/47(0.02)	14/49(0.29)
P Values[c]	---	---	N.S.	P = 0.001
Relative Risk (Control)[d]	---	---	0.372	Infinite
Lower Limit	---	---	0.007	4.279
Upper Limit	---	---	6.887	Infinite
Weeks to First Observed Tumor	107	---	107	74
Thyroid: Adenoma NOS, Follicular-Cell Adenoma, or Papillary Cystadenoma NOS[b]	1/35(0.03)	0/48(0.00)	0/47(0.00)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	Infinite
Lower Limit	---	---	0.000	0.590
Upper Limit	---	---	13.884	Infinite
Weeks to First Observed Tumor	107	---	---	72

*Includes only those rats surviving at least 30 weeks.

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Thyroid: Adenocarcinoma NOS, Papillary Adenocarcinoma, Follicular-Cell Carcinoma or Papillary Cystadenocarcinoma NOS[b]	2/35(0.06)	0/48(0.00)	2/47(0.04)	17/49(0.35)
P Values[c]	---	---	N.S.	P = 0.001
Relative Risk (Control)[d]	---	---	0.745	Infinite
Lower Limit	---	---	0.057	5.306
Upper Limit	---	---	9.877	Infinite
Weeks to First Observed Tumor	107	---	107	74
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	12/32(0.38)	9/38(0.24)	12/44(0.27)	8/40(0.20)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.727	0.844
Lower Limit	---	---	0.342	0.318
Upper Limit	---	---	1.491	2.206
Weeks to First Observed Tumor	101	85	78	74
Adrenal: Pheochromocytoma[b]	6/35(0.17)	8/47(0.17)	5/46(0.11)	9/47(0.19)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.634	1.125
Lower Limit	---	---	0.159	0.422
Upper Limit	---	---	2.163	3.061
Weeks to First Observed Tumor	107	107	107	74

*Includes only those rats surviving at least 30 weeks.

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	33/35(0.94)	42/47(0.89)	47/48(0.98)	39/49(0.80)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.963	0.891
Lower Limit	---	---	0.815	0.763
Upper Limit	---	---	1.307	1.082
Weeks to First Observed Tumor	78	78	78	71
Preputial Gland: Carcinoma NOS[b]	0/36(0.00)	0/48(0.00)	0/48(0.00)	4/49(0.08)
P Values[c]	---	---	---	N.S.
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.909
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	107
Preputial Gland: Adenoma NOS, Papillary Adenoma or Cystadenoma NOS[b]	0/36(0.00)	0/48(0.00)	2/48(0.04)	5/49(0.10)
P Values[c]	---	---	N.S.	P = 0.030
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.224	1.237
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	100	98

*Includes only those rats surviving at least 30 weeks.

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Preputial Gland: Carcinoma NOS, Adenoma NOS, Papillary Adenoma, or Cystadenoma NOS[b]	0/36(0.00)	0/48(0.00)	2/48(0.04)	8/49(0.16)
P Values[c]	---	---	N.S.	P = 0.003
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.224	2.288
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	100	98
Zymbal's Gland or Ear Canal: Sebaceous Adenocarcinoma[b]	0/36(0.00)	0/48(0.00)	1/48(0.02)	4/49(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.040	0.909
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	79	74
Zymbal's Gland or Ear Canal or Skin of Ear: Squamous-Cell Carcinoma or Sebaceous Adenocarcinoma[b]	0/36(0.00)	0/48(0.00)	1/48(0.02)	8/49(0.16)
P Values[c]	---	---	N.S.	P = 0.003
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.040	2.241
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	79	78

*Includes only those rats surviving at least 30 weeks.

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/36(0.06)	6/48(0.13)	2/48(0.04)	1/49(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.750	0.163
Lower Limit	---	---	0.057	0.004
Upper Limit	---	---	9.957	1.274
Weeks to First Observed Tumor	79	93	91	107
Body Cavities: Mesothelioma NOS or Malignant Mesothelioma[b]	0/36(0.00)	2/48(0.04)	4/48(0.08)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	1.469
Lower Limit	---	---	0.703	0.176
Upper Limit	---	---	Infinite	16.960
Weeks to First Observed Tumor	---	106	92	97
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/36(0.00)	1/48(0.02)	3/47(0.06)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	2.939
Lower Limit	---	---	0.465	0.246
Upper Limit	---	---	Infinite	151.056
Weeks to First Observed Tumor	---	109	107	98

*Includes only those rats surviving at least 30 weeks.

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Skin: Squamous-Cell Carcinoma (Excluding Skin of Ear)[b]	0/36(0.00)	0/48(0.00)	0/48(0.00)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.590
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	71
Skin: Squamous-Cell Carcinoma, Basal-Cell Carcinoma, or Sebaceous Adenocarcinoma (Excluding Skin of Ear)[b]	0/36(0.00)	0/48(0.00)	2/48(0.04)	7/49(0.14)
P Values[c]	---	---	N.S.	P = 0.007
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.224	1.904
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	107	72
Skin or Subcutaneous Tissue: Fibroma[b]	0/36(0.00)	3/48(0.06)	5/48(0.10)	2/49(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	0.653
Lower Limit	---	---	0.956	0.057
Upper Limit	---	---	Infinite	5.450
Weeks to First Observed Tumor	---	95	100	107

*Includes only those rats surviving at least 30 weeks.

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Skin or Subcutaneous Tissue: Fibrosarcoma[b]	0/36(0.00)	1/48(0.02)	1/48(0.02)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	2.939
Lower Limit	---	---	0.040	0.246
Upper Limit	---	---	Infinite	151.056
Weeks to First Observed Tumor	---	102	107	43
Pancreatic Islets: Islet-Cell Adenoma[b]	2/32(0.06)	0/46(0.00)	5/45(0.11)	0/48(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.778	---
Lower Limit	---	---	0.315	---
Upper Limit	---	---	17.842	---
Weeks to First Observed Tumor	107	---	78	---

*Includes only those rats surviving at least 30 weeks.

[a]Treated groups received time-weighted average doses of 0.12 or 0.5 percent in feed.

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

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

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

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH 2,4-DIAMINOANISOLE SULFATE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/38(0.03)	2/45(0.04)	2/46(0.04)	7/49(0.14)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.652	3.214
Lower Limit	---	---	0.090	0.654
Upper Limit	---	---	95.360	30.445
Weeks to First Observed Tumor	107	110	107	87
Thyroid: Adenocarcinoma NOS[b]	2/38(0.05)	0/45(0.00)	0/46(0.00)	4/49(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	Infinite
Lower Limit	---	---	0.000	0.854
Upper Limit	---	---	2.784	Infinite
Weeks to First Observed Tumor	107	---	---	78
Thyroid: Papillary Cystadenoma NOS or Papillary Cystadenocarcinoma NOS[b]	0/38(0.00)	0/45(0.00)	2/46(0.04)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.246	0.554
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	107	78

*Includes only those rats surviving at least 30 weeks.

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Thyroid: Adenocarcinoma NOS, Follicular-Cell Carcinoma, or Papillary Cystadenocarcinoma NOS[b]	2/38(0.05)	1/45(0.02)	1/46(0.02)	10/49(0.20)
P Values[c]	---	---	N.S.	P = 0.006
Relative Risk (Control)[d]	---	---	0.413	9.184
Lower Limit	---	---	0.007	1.395
Upper Limit	---	---	7.641	388.645
Weeks to First Observed Tumor	107	109	107	78
Pituitary: Carcinoma NOS or Adenocarcinoma NOS[b]	2/37(0.05)	0/40(0.00)	3/47(0.06)	0/38(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.181	---
Lower Limit	---	---	0.143	---
Upper Limit	---	---	13.582	---
Weeks to First Observed Tumor	107	---	92	---
Pituitary: Carcinoma NOS, Adenocarcinoma NOS, Adenoma NOS, or Chromophobe Adenoma[b]	20/37(0.54)	17/40(0.43)	20/47(0.43)	16/38(0.42)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.787	0.991
Lower Limit	---	---	0.489	0.555
Upper Limit	---	---	1.298	1.756
Weeks to First Observed Tumor	76	78	78	78

*Includes only those rats surviving at least 30 weeks.

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Adrenal: Cortical Adenoma[b]	0/37(0.00)	1/49(0.02)	0/47(0.00)	6/49(0.12)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	---	6.000
Lower Limit	---	---	---	0.769
Upper Limit	---	---	---	269.766
Weeks to First Observed Tumor	---	110	---	107
Adrenal: Pheochromocytoma[b]	2/37(0.05)	3/49(0.06)	3/47(0.06)	7/49(0.14)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.181	2.333
Lower Limit	---	---	0.136	0.570
Upper Limit	---	---	12.842	13.275
Weeks to First Observed Tumor	108	109	100	106
Mammary Gland and Ducts: Fibroadenoma[b]	4/39(0.10)	19/50(0.38)	16/49(0.35)	4/49(0.08)
P Values[c]	---	---	P = 0.011	P = 0.001(N)
Relative Risk (Control)[d]	---	---	3.184	0.215
Lower Limit	---	---	1.139	0.058
Upper Limit	---	---	12.083	0.589
Weeks to First Observed Tumor	101	107	92	107

*Includes only those rats surviving at least 30 weeks.

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Mammary: Adenocarcinoma NOS or Papillary Cystadenocarcinoma NOS[b]	2/39(0.05)	0/50(0.00)	4/49(0.08)	2/49(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.592	Infinite
Lower Limit	---	---	0.243	0.302
Upper Limit	---	---	16.921	Infinite
Weeks to First Observed Tumor	100	---	92	95
Uterus or Uterus/Endometrium: Adenocarcinoma NOS[b]	4/38(0.11)	1/50(0.02)	1/46(0.02)	3/46(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.207	3.261
Lower Limit	---	---	0.004	0.273
Upper Limit	---	---	1.978	167.332
Weeks to First Observed Tumor	95	109	92	86
Uterus: Endometrial Stromal Polyp[b]	10/38(0.26)	10/50(0.20)	18/46(0.39)	3/46(0.07)
P Values[c]	---	---	N.S.	P = 0.050(N)
Relative Risk (Control)[d]	---	---	1.487	0.326
Lower Limit	---	---	0.749	0.061
Upper Limit	---	---	3.155	1.173
Weeks to First Observed Tumor	78	78	80	65

*Includes only those rats surviving at least 30 weeks.

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Uterus or Uterus/Endometrium: Adenocarcinoma NOS; or Uterus/Endometrium: Carcinoma, Papillary Carcinoma, or Adenocarcinoma[b]	4/38(0.11)	1/50(0.02)	5/46(0.11)	6/46(0.13)
P Values[c]	---	---	N.S.	P = 0.044
Relative Risk (Control)[d]	---	---	1.033	6.522
Lower Limit	---	---	0.299	0.836
Upper Limit	---	---	6.185	292.687
Weeks to First Observed Tumor	95	109	92	86
Clitoral Gland: Adenoma NOS or Cystadenoma NOS[b]	0/39(0.00)	2/50(0.04)	4/49(0.08)	6/49(0.12)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	3.061
Lower Limit	---	---	0.743	0.581
Upper Limit	---	---	Infinite	29.826
Weeks to First Observed Tumor	---	104	80	95
Clitoral Gland: Adenoma NOS, Cystadenoma NOS or Squamous-Cell Papilloma[b]	0/39(0.00)	3/50(0.06)	4/49(0.08)	6/49(0.12)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	2.041
Lower Limit	---	---	0.743	0.464
Upper Limit	---	---	Infinite	11.991
Weeks to First Observed Tumor	---	104	80	95

*Includes only those rats surviving at least 30 weeks.

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL*	HIGH DOSE CONTROL	LOW DOSE*	HIGH DOSE
Clitoral Gland: Adenoma NOS, Cystadenoma NOS, Squamous-Cell Papilloma, Squamous-Cell Carcinoma, or Carcinoma NOS[b]	0/39(0.00)	3/50(0.06)	5/49(0.10)	8/49(0.16)
P Values[c]	---	---	P = 0.049	N.S.
Relative Risk (Control)[d]	---	---	Infinite	2.721
Lower Limit	---	---	1.012	0.699
Upper Limit	---	---	Infinite	15.105
Weeks to First Observed Tumor	---	104	80	83
Zymbal's Gland: Sebaceous Adenocarcinoma[b]	0/39(0.00)	0/50(0.00)	0/49(0.00)	7/49(0.14)
P Values[c]	---	---	---	P = 0.006
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	1.979
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	86
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/39(0.10)	5/50(0.10)	1/49(0.02)	0/49(0.00)
P Values[c]	---	---	N.S.	P = 0.030(N)
Relative Risk (Control)[d]	---	---	0.199	0.000
Lower Limit	---	---	0.004	0.000
Upper Limit	---	---	1.911	0.809
Weeks to First Observed Tumor	101	104	107	---

*Includes only those rats surviving at least 30 weeks.

TABLE 5 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 0.12 or 0.5 percent in feed.

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

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

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

males the combined incidence of C-cell adenomas and C-cell carcinomas of the thyroid was significant (P = 0.004) when comparing the high dose to the high dose control group. These results indicate that the administration of 2,4-diaminoanisole sulfate was associated with the incidence of thyroid neoplasms in both male and female rats.

For males and females a number of sebaceous adenocarcinomas of the Zymbal's gland were noted in dosed rats. For females the Fisher exact test showed that the incidence was significantly (P = 0.006) greater in the high dose group than in the high dose control group. For males, when incidences were combined so that the numerator represented rats with a sebaceous adenocarcinoma or a squamous-cell carcinoma of either the Zymbal's gland, the ear canal, or the skin of the ear, the Fisher exact test comparing high dose to high dose control was significant (P = 0.003). In historical data on untreated Fischer 344 rats compiled by this laboratory for the NCI Carcinogenesis Testing Program, 2/334 (0.01 percent) males and 0/336 females had one of these types of tumor. Based upon these results the administration of 2,4-diaminoanisole sulfate was associated with an increased incidence of Zymbal's gland/ear canal/skin of ear neoplasms in male and female rats.

In males, when incidences were combined so that the numerator represented rats with either a squamous-cell carcinoma, a basal-cell carcinoma, or a sebaceous adenocarcinoma of the skin (excluding skin of the ear), the incidence was significantly (P = 0.007) greater in

the high dose group than in the high dose control. When preputial tumor incidences in male rats were combined to include carcinomas NOS, adenomas NOS, papillary adenomas, or cystadenomas NOS, the comparison of high dose to high dose control was significant (P = 0.003). Based upon these results the administration of 2,4-diaminoanisole sulfate was associated with an increased incidence of skin tumors and of neoplasms of the preputial gland in male rats.

In the female rats the incidence of fibroadenomas of the mammary gland and ducts was significantly (P = 0.011) higher in the low dose group than in the low dose control. The comparison of high dose to high dose control, however, showed a significant (P = 0.001) negative association. Compared to the historical control data compiled by Mason Research Institute for the NCI Carcinogenesis Testing Program (105/585 [18 percent] untreated female Fischer 344 rats developed a spontaneous mammary fibroadenoma), the observed incidence was somewhat lower (4/39 or 10 percent) than expected in the low dose control and higher (19/50 or 38 percent) than expected in the high dose control.

In female rats when the incidences of uterine adenocarcinomas NOS or of uterine/endometrial carcinomas, papillary carcinomas, or adenocarcinomas were pooled, the comparison of high dose to control had a probability level of P = 0.044--a marginal result which was not significant under the Bonferroni criterion. Similarly, results for endometrial stromal polyps, malignant lymphomas or leukemias, and

clitoral neoplasms in the females and for fibromas of the integumentary system in the males were not significant under the Bonferroni inequality.

In summary, there were statistically significant incidences of neoplasms of the thyroid, of the Zymbal's gland, of the skin, and of the preputial gland in male rats and increased incidences of neoplasms of the thyroid and of the Zymbal's gland in female rats.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No marked mean body weight depression was observed in any group of mice treated with 2,4-diaminoanisole sulfate (Figure 3).

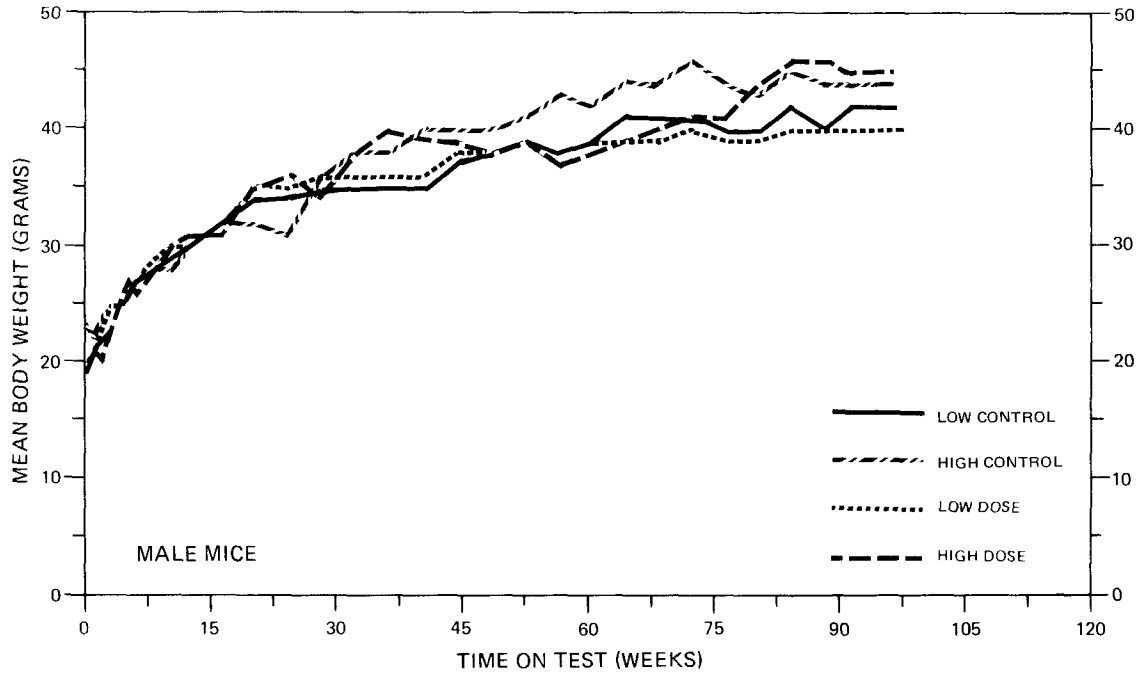
No clinical abnormalities were observed in treated or control mice during the bioassay.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 2,4-diaminoanisole sulfate-dosed groups are shown in Figure 4.

For male mice the Cox tests for positive association between increased dosage and accelerated mortality were not significant. Five mice were sacrificed from the high dose and from each control group in week 78; five additional high dose control mice were sacrificed in week 49. With 82 percent (41/50) of the high dose, 92 percent (46/50) of the low dose, 78 percent (39/50) of the high dose control, and 84 percent (42/50) of the low dose control mice alive at the termination of the study, there were adequate numbers of male mice at risk from late-developing tumors.

For female mice the Cox tests did not show a significant positive association between increased dosage and accelerated mortality. As with the males, five mice were sacrificed from the high dose and from each control group in week 78 with five additional high dose control mice having been sacrificed in week 49. There were adequate numbers



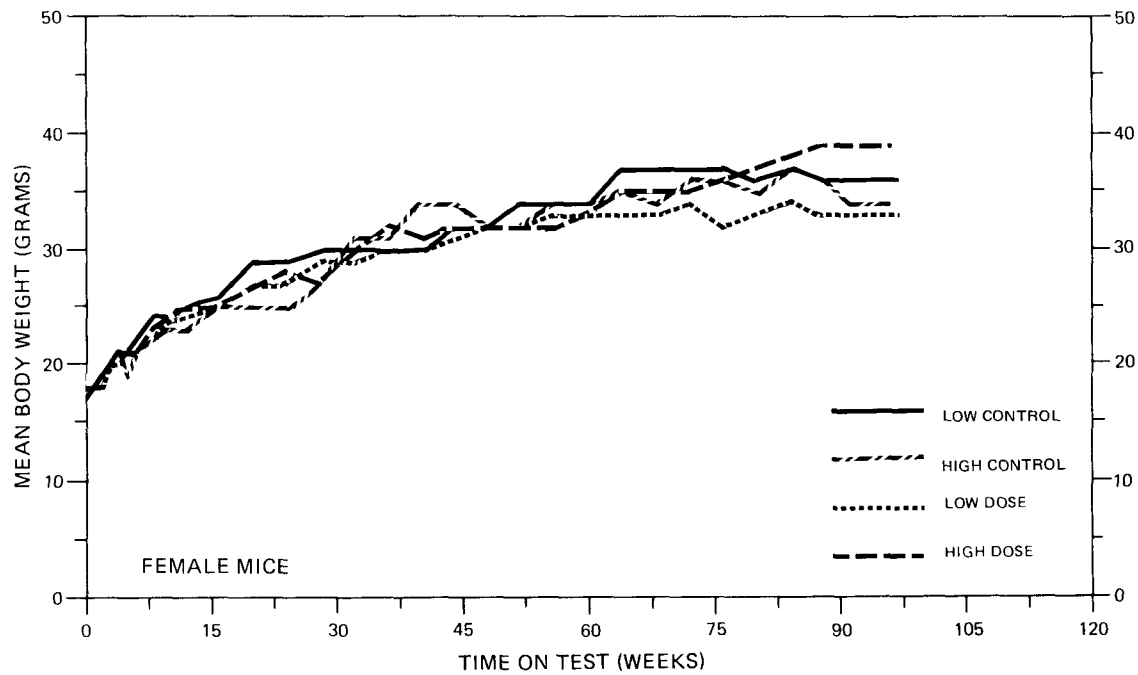
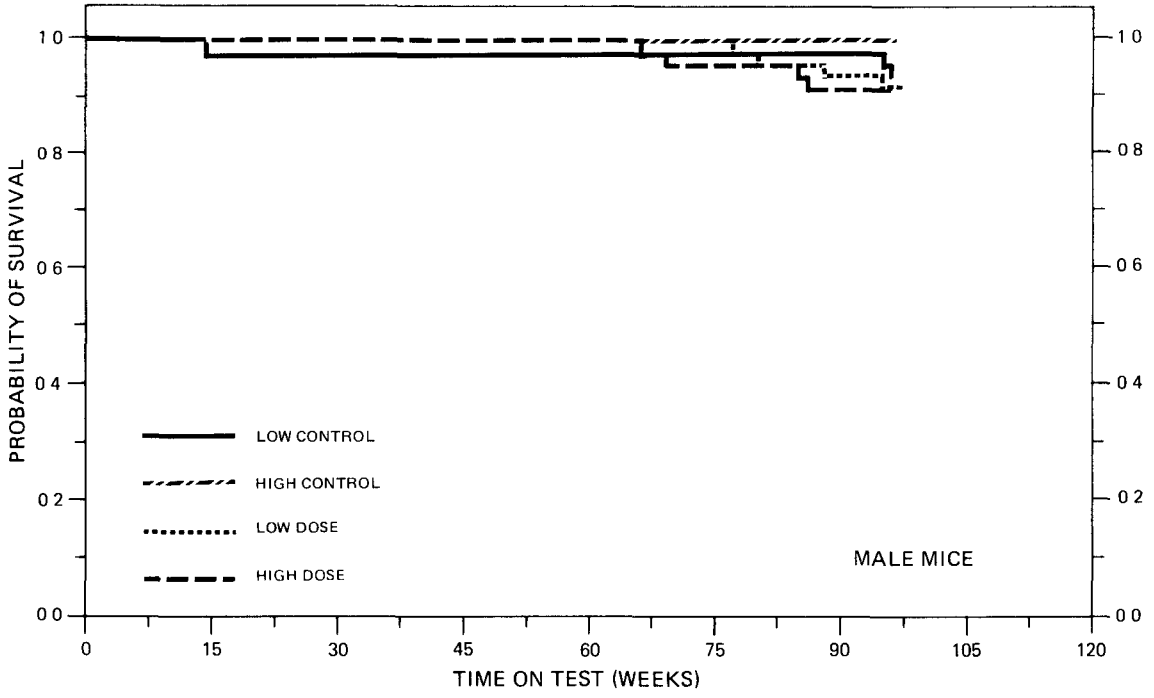


FIGURE 3
GROWTH CURVES FOR 2,4-DIAMINOANISOLE SULFATE CHRONIC STUDY MICE



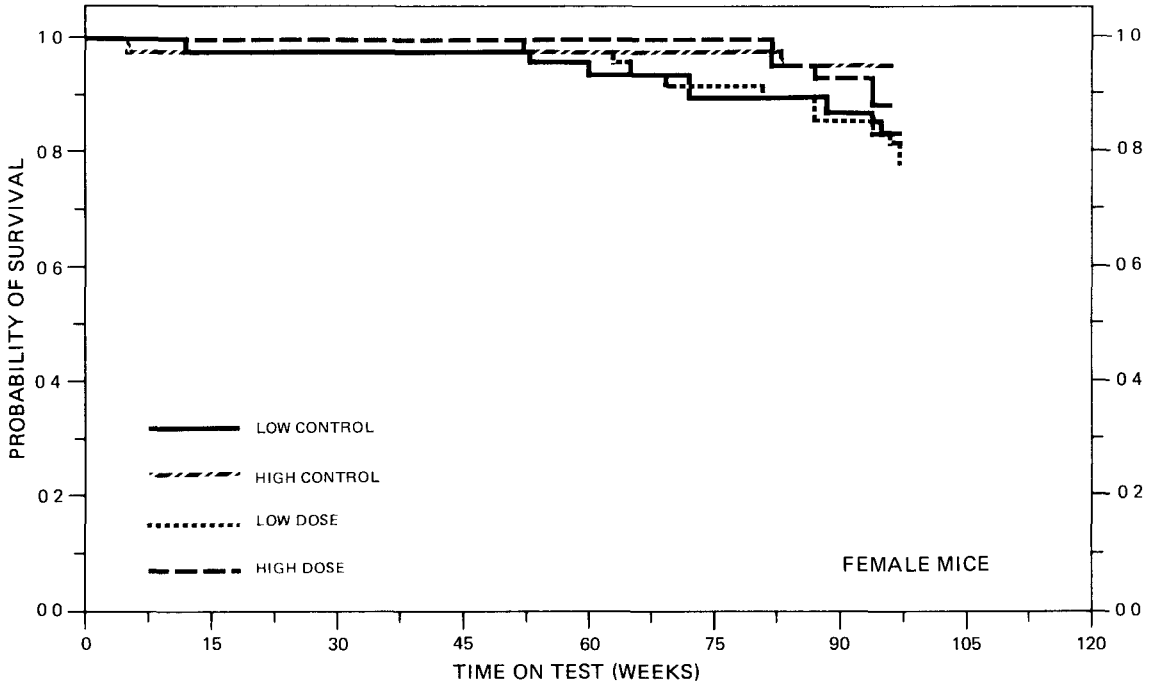


FIGURE 4
SURVIVAL COMPARISONS OF 2,4-DIAMINOANISOLE SULFATE CHRONIC STUDY MICE

of female mice at risk from late-developing tumors with 78 percent (39/50) of the high dose, 76 percent (38/50) of the low dose, 76 percent (38/50) of the high dose control, and 74 percent (37/50) of the low dose control mice surviving 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).

With the exception of thyroid and hematopoietic neoplasms, the tumors listed in Appendix B appeared with approximately equal frequency in treated and control mice or appeared in insignificant numbers.

There was an increase in follicular-cell hyperplasia and follicular-cell neoplasia in treated mice as shown in the following table:

	Low Dose Control	High Dose Control	Low Dose	High Dose
MALES				
Thyroid				
(Number of Animals with Tissues Examined Histopathologically)	(47)	(45)	(46)	(45)
Adenocarcinoma NOS	0	0	1	0
Follicular-Cell Adenoma	1	0	0	11
Hyperplasia NOS	0	0	1	0
Hyperplasia, Follicular-Cell	1	0	0	12
FEMALES				
Thyroid				
(Number of Animals with Tissues Examined Histopathologically)	(43)	(44)	(42)	(45)

Follicular-Cell Adenoma	0	0	0	6
Follicular-Cell Carcinoma	0	0	0	2
Hyperplasia NOS	0	0	1	0
Hyperplasia, Follicular-cell	0	0	3	1
Hyperplasia, Papillary	0	2	7	0
Hyperplasia, Adenomatous	0	1	0	0

Adenomas were nodular lesions composed of neoplastic follicles lined with cuboidal or columnar epithelium. These adenomas were usually better circumscribed than those lesions classified as focal hyperplasia. In the high dose mice, occasional follicular cells in adenomas contained a golden brown pigment which also appeared in the colloid.

Follicular-cell carcinomas were much larger, often involving an entire thyroid lobe and extending through the capsule into surrounding tissues. They were composed of columnar follicular cells exhibiting some degree of nuclear pleomorphism. In some areas, the carcinomas were well-differentiated, forming follicular structures and in other areas the tumor cells were more poorly differentiated.

The thyroids of the treated mice usually contained enlarged follicles filled with dense colloid and lined by flat epithelium with pyknotic nuclei. Follicular-cell hyperplasia was defined as the occurrence of a focal area in which follicular epithelium suddenly became cuboidal to columnar, the nucleus enlarged and oval in shape, and the colloid either became vacuolated or diminished in quantity. Papillary and adenomatous variants of hyperplasia were seen, and

often, especially in the male mice, it was difficult to distinguish a sharp boundary between hyperplasia and adenoma formation.

In female mice only there was an increased incidence (5/48 low dose control, 2/50 high dose control, 14/45 low dose, 9/50 high dose) of malignant lymphoma (NOS, undifferentiated, lymphocytic, histiocytic and/or mixed type) which occurred in multiple organs, spleen, mesenteric lymph node, or liver.

A variety of other nonneoplastic lesions which were observed both in control and treated mice could not be related to compound administration.

This histopathologic examination indicates that under the conditions of this study, dietary administration of 2,4-diaminoanisole sulfate increased the incidence of both thyroid follicular-cell hyperplasia and thyroid follicular-cell neoplasms in B6C3F1 mice of both sexes and possibly malignant lymphoma in female mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 6 and 7. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or 2,4-diaminoanisole sulfate-dosed groups and where such tumors were observed in at least 5 percent of the group. Because a number of high dose control mice of both sexes were sacrificed in week 49, all Fisher exact tests involving these controls have been based exclusively on mice surviving at least

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 2,4-DIAMINOANISOLE SULFATE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL*	LOW DOSE	HIGH DOSE*
Hematopoietic: Malignant Lymphoma[b]	4/48(0.08)	5/44(0.11)	6/49(0.12)	4/49(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.469	0.718
Lower Limit	---	---	0.373	0.152
Upper Limit	---	---	6.670	3.131
Weeks to First Observed Tumor	96	96	80	85
Lung: Alveolar/Bronchiolar Carcinoma[b]	6/48(0.13)	5/44(0.11)	2/48(0.04)	6/48(0.13)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.333	1.100
Lower Limit	---	---	0.034	0.302
Upper Limit	---	---	1.752	4.252
Weeks to First Observed Tumor	96	96	97	69
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	6/48(0.13)	10/44(0.23)	3/48(0.06)	12/48(0.25)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.500	1.100
Lower Limit	---	---	0.085	0.487
Upper Limit	---	---	2.194	2.556
Weeks to First Observed Tumor	96	96	97	69

*Includes only those mice surviving at least 50 weeks.

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL*	LOW DOSE	HIGH DOSE*
Liver: Hepatocellular Carcinoma[b]	7/48(0.15)	6/43(0.14)	14/49(0.29)	11/49(0.22)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.959	1.609
Lower Limit	---	---	0.814	0.600
Upper Limit	---	---	5.224	4.869
Weeks to First Observed Tumor	78	78	97	78
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	7/48(0.15)	8/43(0.19)	14/49(0.29)	12/49(0.24)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.959	1.316
Lower Limit	---	---	0.817	0.550
Upper Limit	---	---	5.224	3.368
Weeks to First Observed Tumor	78	78	97	78
Thyroid: Follicular-Cell Adenoma[b]	1/47(0.02)	0/40(0.00)	0/46(0.00)	11/45(0.24)
P Values[c]	---	---	N.S.	P < 0.001
Relative Risk (Control)[d]	---	---	0.000	Infinite
Lower Limit	---	---	0.000	2.976
Upper Limit	---	---	19.034	Infinite
Weeks to First Observed Tumor	96	---	---	78

*Includes only those mice surviving at least 50 weeks.

TABLE 6 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 0.12 or 0.24 percent in feed.

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

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

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

TABLE 7

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 2,4-DIAMINOANISOLE SULFATE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL*	LOW DOSE	HIGH DOSE*
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/46(0.02)	1/45(0.02)	3/43(0.07)	0/50(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	3.209	0.000
Lower Limit	---	---	0.270	0.000
Upper Limit	---	---	164.399	16.794
Weeks to First Observed Tumor	96	78	69	---
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	4/46(0.09)	3/45(0.07)	5/43(0.12)	4/50(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.337	1.200
Lower Limit	---	---	0.308	0.215
Upper Limit	---	---	6.314	7.805
Weeks to First Observed Tumor	96	78	69	78
Hematopoietic: Malignant Lymphoma[b]	5/48(0.10)	2/45(0.04)	14/45(0.31)	9/50(0.18)
P Values[c]	---	---	P = 0.013	P = 0.038
Relative Risk (Control)[d]	---	---	2.987	4.050
Lower Limit	---	---	1.118	0.899
Upper Limit	---	---	9.703	36.946
Weeks to First Observed Tumor	96	96	94	78

*Includes only those mice surviving at least 50 weeks.

TABLE 7 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL*	LOW DOSE	HIGH DOSE*
Pituitary: Adenoma[b]	2/42(0.05)	1/38(0.03)	5/38(0.13)	5/34(0.15)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.961	5.588
Lower Limit	---	---	0.571	0.670
Upper Limit	---	---	29.586	255.444
Weeks to First Observed Tumor	97	96	97	82
Thyroid: Follicular-Cell Adenoma[b]	0/43(0.00)	0/41(0.00)	0/42(0.00)	6/45(0.13)
P Values[c]	---	---	---	P = 0.017
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	1.468
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	78
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/43(0.00)	0/41(0.00)	0/42(0.00)	8/45(0.18)
P Values[c]	---	---	---	P = 0.004
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	2.096
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	78

*Includes only those mice surviving at least 50 weeks.

TABLE 7 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 0.12 or 0.24 percent in feed.

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

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

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

50 weeks. Due to the differences in starting times between the high dose and the low dose experiments, no Cochran-Armitage tests have been performed.

A high incidence of follicular-cell thyroid tumors were noted in both male and female treated mice. For the males the Fisher exact test indicated a significantly ($P < 0.001$) greater incidence of follicular-cell adenomas in the high dose than in the high dose control group; no follicular-cell carcinomas were observed. For the females when incidences were combined so that the numerator represented mice with either a follicular-cell adenoma or a follicular-cell carcinoma of the thyroid, the Fisher exact test again indicated a significantly ($P = 0.004$) greater incidence in the high dose than in the high dose control. Historical records collected by Mason Research Institute for untreated B6C3F1 mice in the NCI Carcinogenesis Testing Program indicated 1/350 (0.28 percent) male and 0/350 female mice with either a follicular-cell adenoma or a follicular-cell carcinoma of the thyroid.

A number of malignant lymphomas were also observed in the female mice. The Fisher exact test indicated a significantly elevated incidence in the low dose group ($P = 0.015$) compared to the low dose control group. The comparison of high dose to high dose control had a probability level of $P = 0.038$, a marginal result which was not significant under the Bonferroni criterion. In the historical data

43/350 (12 percent) of the untreated females had leukemia or a malignant lymphoma. However, other groups of control female mice at this laboratory have had incidences of malignant lymphomas of 10/49 (20 percent) and 11/50 (22 percent).

Based upon these results the administration of 2,4-diaminoanisole sulfate was associated with the incidence of follicular-cell thyroid tumors in both male and female mice and may have been associated with the incidence of malignant lymphomas in female mice.

V. DISCUSSION

In this bioassay, adequate numbers of rats and mice in all groups survived long enough to be at risk from late-developing tumors. Adverse clinical signs and depression of mean group body weight were observed in high dose rats. No growth retardation or other adverse clinical signs were observed among low dose rats or mice dosed at either level.

Follicular-cell thyroid tumors found in rats included adenomas and adenocarcinomas NOS; papillary adenocarcinomas; follicular-cell adenomas and carcinomas; and papillary cystadenomas and adenocarcinomas. For purposes of statistical analysis, incidences of malignant follicular-cell tumors of the thyroid were combined; C-cell neoplasms were analyzed separately. For high dose groups of both sexes, the proportion of rats having malignant follicular-cell tumors of the thyroid was significantly greater than in control rats. For the high dose male rats, the combined incidence of C-cell adenomas and C-cell carcinomas was significantly greater than the incidence in the corresponding control group.

An increased incidence of epithelial tumors of the integumentary system was observed among treated rats. These tumors were found in the skin, preputial gland, clitoral gland, Zymbal's gland, and ear canal. The incidence of malignant skin tumors (squamous-cell carcinoma, basal-cell carcinoma, or sebaceous adenocarcinoma) was significantly increased in the high dose male group but not in other groups

of treated rats. Malignant tumors (sebaceous adenocarcinomas or squamous-cell carcinomas) of the ear (Zymbal's gland, ear canal or skin of the ear) were significantly increased among high dose male and female rats compared to their respective controls. Among high dose male rats a significantly increased incidence of preputial gland tumors was observed including carcinomas NOS, cystadenomas, papillary adenomas, and adenomas NOS.

Among male and female mice both thyroid follicular-cell hyperplasia and thyroid follicular-cell neoplasia were related to administration of 2,4-diaminoanisole sulfate. Among high dose male mice, the incidence of follicular-cell adenomas was significantly increased, but no follicular-cell carcinomas were observed. Among high dose female mice, the combined incidence of follicular-cell adenoma and follicular-cell carcinoma was significantly increased. The eight female mice with either a follicular-cell adenoma or follicular-cell carcinoma or both included only two animals in which follicular-cell carcinoma was observed.

The incidence of malignant lymphomas was increased among female mice at both dose levels, but statistical significance was established only for the low dose group. The incidence of malignant lymphomas for the low dose controls was 5/48 (10 percent); however, other groups of untreated control female mice at this laboratory have had incidences of this lesion of 10/49 (20 percent) and 11/50 (22 percent). Thus, although the incidence of malignant lymphomas was increased among both

dose levels of female mice when compared to their respective controls, the relationship of development of this lesion to the administration of the test chemical was not clearly evident. This uncertainty is based on the variability of the incidence of these tumors in untreated control female mice and the lack of a significant dose-related effect at this site in this study.

Under the conditions of this bioassay, technical-grade 2,4-diaminoanisole sulfate was carcinogenic to both sexes of both species. In Fischer 344 rats dietary administration of the chemical induced increased incidences of malignant tumors of the skin and its associated glands and malignant thyroid tumors in each sex. In B6C3F1 mice, dietary administration of 2,4-diaminoanisole sulfate induced thyroid tumors in each sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 2,4-DIAMINOANISOLE SULFATE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED
WITH 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
ANIMALS INITIALLY IN STUDY	50	@50	50	50
ANIMALS NECROPSIED	46	48	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	48	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(48)	(49)
SQUAMOUS CELL CARCINOMA				5 (10%)
BASAL-CELL CARCINOMA			1 (2%)	2 (4%)
SEBACEOUS ADENOMA				1 (2%)
SEBACEOUS ADENOCARCINOMA			1 (2%)	3 (6%)
FIBROMA			3 (6%)	1 (2%)
FIBROSARCOMA			1 (2%)	1 (2%)
*SUBCUT TISSUE	(46)	(48)	(48)	(49)
SARCOMA, NOS		1 (2%)		
FIBROMA		3 (6%)	2 (4%)	1 (2%)
FIBROSARCOMA		1 (2%)		2 (4%)
RESPIRATORY SYSTEM				
#TRACHEA	(45)	(48)	(47)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
#LUNG	(46)	(48)	(47)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA			3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)		1 (2%)
SEBACEOUS ADENOCARCINOMA, METAST				1 (2%)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)		
FIBROSARCOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(48)	(48)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)	

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
LEUKEMIA, NOS		1 (2%)		
UNDIFFERENTIATED LEUKEMIA	1 (2%)			
MYELOMONOCYTIC LEUKEMIA		4 (8%)		1 (2%)
MONOCYTIC LEUKEMIA	1 (2%)			
*SKIN	(46)	(48)	(48)	(49)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#LYMPH NODE	(38)	(44)	(42)	(47)
ADENOCARCINOMA, NOS, METASTATIC	1 (3%)			
#THYMUS	(38)	(23)	(37)	(21)
FIBROSARCOMA			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(46)	(48)	(47)	(49)
FIBROSARCOMA			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(38)	(47)	(45)	(47)
ADENOCARCINOMA, NOS		1 (2%)		
SARCOMA, NOS		1 (2%)	1 (2%)	
#LIVER	(46)	(48)	(48)	(48)
NEOPLASTIC NODULE				1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	2 (4%)	1 (2%)
#PANCREAS	(42)	(46)	(45)	(48)
ACINAR-CELL ADENOMA				1 (2%)
#DUODENUM	(43)	(46)	(45)	(47)
FIBROSARCOMA			1 (2%)	
#ILEUM	(43)	(46)	(45)	(47)
SARCOMA, NOS		1 (2%)		
#COLON	(43)	(46)	(43)	(40)
ADENOCARCINOMA, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY/PELVIS	(46)	(48)	(48)	(49)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(38)	(44)	(40)
ADENOMA, NOS	2 (5%)	9 (24%)	12 (27%)	8 (20%)
CHROMOPHOBE ADENOMA	10 (24%)			
#ADRENAL	(43)	(47)	(46)	(47)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
PHEOCHROMOCYTOMA	6 (14%)	7 (15%)	5 (11%)	9 (19%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)		
#THYROID	(45)	(48)	(47)	(49)
ADENOMA, NOS	1 (2%)			
ADENOCARCINOMA, NOS	2 (4%)		1 (2%)	14 (29%)
PAPILLARY ADENOCARCINOMA				1 (2%)
FOLLICULAR-CELL ADENOMA				1 (2%)
FOLLICULAR-CELL CARCINOMA				1 (2%)
C-CELL ADENOMA	1 (2%)		4 (9%)	8 (16%)
C-CELL CARCINOMA		1 (2%)		3 (6%)
PAPILLARY CYSTADENOMA, NOS				2 (4%)
PAPILLARY CYSTADENOCARCINOMA, NOS			1 (2%)	1 (2%)
#PARATHYROID	(32)	(28)	(30)	(24)
ADENOMA, NOS		1 (4%)		
#PANCREATIC ISLETS	(42)	(46)	(45)	(48)
ISLET-CELL ADENOMA	2 (5%)		5 (11%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(48)	(48)	(49)
FIBROADENOMA			2 (4%)	
*PREPUTIAL GLAND	(46)	(48)	(48)	(49)
CARCINOMA, NOS				4 (8%)
ADENOMA, NOS				4 (8%)
PAPILLARY ADENOMA				1 (2%)
CYSTADENOMA, NOS			2 (4%)	
#PROSTATE	(45)	(44)	(47)	(47)
ADENOMA, NOS			1 (2%)	
PARAGANGLIOMA, NOS	1 (2%)			

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
#TESTIS	(45)	(47)	(48)	(49)
INTERSTITIAL-CELL TUMOR	33 (73%)	42 (89%)	47 (98%)	39 (80%)
NERVOUS SYSTEM				
#BRAIN	(44)	(48)	(46)	(49)
GLIOMA, NOS		1 (2%)	1 (2%)	
ASTROCYTOMA	1 (2%)			
SPECIAL SENSE ORGANS				
*EAR	(46)	(48)	(48)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
*EAR CANAL	(46)	(48)	(48)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
SEBACEOUS ADENOCARCINOMA				1 (2%)
*ZYMBAL'S GLAND	(46)	(48)	(48)	(49)
SEBACEOUS ADENOCARCINOMA			1 (2%)	3 (6%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(46)	(48)	(48)	(49)
MESOTHELIOMA, NOS			4 (8%)	2 (4%)
MESOTHELIOMA, MALIGNANT		2 (4%)		1 (2%)
*MEDIASTINUM	(46)	(48)	(48)	(49)
FIBROSARCOMA			1 (2%)	
ALL OTHER SYSTEMS				
TAIL				
SQUAMOUS CELL PAPILLOMA			1	

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

TABLE A1 (CONCLUDED)

	LOW DOSE CONTROL(UNTR) 01-0037	HIGH DOSE CONTROL(UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	6	8	7
MORIBUND SACRIFICE	2	8	7	11
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	27	30	30	27
ANIMAL MISSING				
ANIMAL DELETED(WRONG SEX)		1		
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	44	48	47
TOTAL PRIMARY TUMORS	61	80	109	129
TOTAL ANIMALS WITH BENIGN TUMORS	33	43	48	45
TOTAL BENIGN TUMORS	55	62	87	79
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	17	12	34
TOTAL MALIGNANT TUMORS	5	18	18	47
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		1
TOTAL SECONDARY TUMORS	4	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		4	3
TOTAL UNCERTAIN TUMORS	1		4	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH
2,4-DIAMINOANISOLE SULFATE

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	50	49	49
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(49)	(49)
BASAL-CELL CARCINOMA		1 (2%)		1 (2%)
FIBROSARCOMA				1 (2%)
*SUBCUT TISSUE	(49)	(50)	(49)	(49)
FIBROMA		1 (2%)	2 (4%)	1 (2%)
FIBROSARCOMA		1 (2%)		1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(48)	(49)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)		
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)		
C-CELL CARCINOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)			
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
MYELOMONOCYTIC LEUKEMIA		3 (6%)		
MONOCYTIC LEUKEMIA	2 (4%)			
#SPLEEN	(49)	(48)	(48)	(49)
HEMANGIOSARCOMA				1 (2%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
#RENAL LYMPH NODE	(41)	(47)	(43)	(41)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
CIRCULATORY SYSTEM				
NONE				

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(48)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
NEOPLASTIC NODULE				1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)			
#STOMACH	(48)	(48)	(47)	(49)
SQUAMOUS CELL PAPILLOMA				1 (2%)
#ILEUM	(47)	(48)	(46)	(47)
LEIOMYOSARCOMA		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(48)	(49)
TUBULAR-CELL ADENOMA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(40)	(47)	(38)
CARCINOMA, NOS			3 (6%)	
ADENOMA, NOS	3 (7%)	17 (43%)	18 (38%)	16 (42%)
ADENOCARCINOMA, NOS	2 (5%)			
CHROMOPHOBE ADENOMA	15 (35%)			
#ADRENAL	(46)	(49)	(47)	(49)
CORTICAL ADENOMA		1 (2%)		6 (12%)
PHEOCHROMOCYTOMA	2 (4%)	3 (6%)	3 (6%)	7 (14%)
#ADRENAL MEDULLA	(46)	(49)	(47)	(49)
GANGLIONEUROMA		1 (2%)		
#THYROID	(47)	(45)	(46)	(49)
ADENOMA, NOS	1 (2%)		1 (2%)	
ADENOCARCINOMA, NOS	2 (4%)			4 (8%)
FOLLICULAR-CELL ADENOMA				2 (4%)
FOLLICULAR-CELL CARCINOMA		1 (2%)		3 (6%)
C-CELL ADENOMA	1 (2%)	1 (2%)	2 (4%)	4 (8%)
C-CELL CARCINOMA		1 (2%)		3 (6%)
PAPILLARY CYSTADENOMA, NOS			1 (2%)	

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)	3 (6%)
#PANCREATIC ISLETS	(46)	(48)	(46)	(47)
ISLET-CELL ADENOMA		2 (4%)		
ISLET-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(49)	(49)
ADENOMA, NOS	1 (2%)			
ADENOCARCINOMA, NOS	1 (2%)		2 (4%)	2 (4%)
PAPILLARY CYSTADENOMA, NOS			1 (2%)	
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (2%)		2 (4%)	
FIBROADENOMA	4 (8%)	19 (38%)	16 (33%)	3 (6%)
*MAMMARY DUCT	(49)	(50)	(49)	(49)
FIBROADENOMA				1 (2%)
*LACTIFEROUS DUCT	(49)	(50)	(49)	(49)
FIBROADENOMA			1 (2%)	
*CLITORAL GLAND	(49)	(50)	(49)	(49)
CARCINOMA,NOS				2 (4%)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
SQUAMOUS CELL CARCINOMA			1 (2%)	
ADENOMA, NOS		2 (4%)	1 (2%)	6 (12%)
CYSTADENOMA, NOS			3 (6%)	
#UTERUS	(48)	(50)	(46)	(46)
ADENOCARCINOMA, NOS	4 (8%)	1 (2%)	1 (2%)	2 (4%)
ENDOMETRIAL STROMAL POLYP	10 (21%)	10 (20%)	18 (39%)	3 (7%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(50)	(46)	(46)
CARCINOMA,NOS			4 (9%)	2 (4%)
PAPILLARY CARCINOMA				1 (2%)
ADENOCARCINOMA, NOS				1 (2%)
SARCOMA, NOS			2 (4%)	
#OVARY	(47)	(49)	(46)	(47)
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)	
GRANULOSA-CELL TUMOR		1 (2%)	1 (2%)	
NERVOUS SYSTEM				
NONE				

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
SPECIAL SENSE ORGANS				
*EAR CANAL	(49)	(50)	(49)	(49)
FIBROMA	1 (2%)			
*ZYMBAL'S GLAND	(49)	(50)	(49)	(49)
SEBACEOUS ADENOCARCINOMA				7 (14%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(49)	(50)	(49)	(49)
MESOTHELIOMA, MALIGNANT	1 (2%)			
ALL OTHER SYSTEMS				
SITE UNKNOWN				
SQUAMOUS CELL CARCINOMA		1		
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	5	5	6	9
MORIBUND SACRIFICE	7	3	10	14
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	23	37	29	22
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	38	44	37
TOTAL PRIMARY TUMORS	56	73	87	86
TOTAL ANIMALS WITH BENIGN TUMORS	27	35	40	29
TOTAL BENIGN TUMORS	39	59	67	51
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	12	15	22
TOTAL MALIGNANT TUMORS	17	13	19	34
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1		2
TOTAL SECONDARY TUMORS	4	1		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1	1
TOTAL UNCERTAIN TUMORS		1	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 2,4-DIAMINOANISOLE SULFATE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE
TREATED WITH 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	48	49	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	48	49	49	49
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
*LUNG	(48)	(49)	(48)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)		2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA		5 (10%)	1 (2%)	7 (15%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (13%)	5 (10%)	2 (4%)	6 (13%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(49)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	3 (6%)	2 (4%)	
MALIGNANT LYMPHOMA, MIXED TYPE				2 (4%)
#SPLEEN	(47)	(49)	(48)	(48)
HEMANGIOMA	1 (2%)			
HEMANGIOSARCOMA		1 (2%)	1 (2%)	2 (4%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#LYMPH NODE	(44)	(42)	(45)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#MESENTERIC L. NODE	(44)	(42)	(45)	(45)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#SMALL INTESTINE	(48)	(49)	(47)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#PEYERS PATCH	(48)	(49)	(47)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)	

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

TABLE B1 (CONTINUED)

	LOW DOSE CONTROL(UNTR) 05-0037	HIGH DOSE CONTROL(UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(48)	(48)	(49)	(49)
HEPATOCELLULAR ADENOMA		2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	7 (15%)	6 (13%)	14 (29%)	11 (22%)
HEMANGIOMA	1 (2%)			
HEMANGIOSARCOMA, METASTATIC				1 (2%)
HEMANGIOSARCOMA, UNC PRIM OR MET		1 (2%)		
#STOMACH	(47)	(48)	(46)	(48)
SQUAMOUS CELL CARCINOMA	1 (2%)			
#SMALL INTESTINE	(48)	(49)	(47)	(47)
ADENOCARCINOMA, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(47)	(49)	(48)	(49)
TUBULAR-CELL ADENOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(40)	(40)	(43)
ADENOMA, NOS				1 (2%)
#ADRENAL	(45)	(44)	(47)	(40)
CORTICAL ADENOMA			1 (2%)	
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)	1 (3%)
#THYROID	(47)	(45)	(46)	(45)
ADENOCARCINOMA, NOS			1 (2%)	
FOLLICULAR-CELL ADENOMA	1 (2%)			11 (24%)
#PARATHYROID	(29)	(24)	(26)	(22)
ADENOMA, NOS				1 (5%)
#PANCREATIC ISLETS	(48)	(47)	(44)	(47)
ISLET-CELL ADENOMA			1 (2%)	

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

TABLE B1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
REPRODUCTIVE SYSTEM				
#TESTIS	(47)	(48)	(46)	(48)
INTERSTITIAL-CELL TUMOR				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(48)	(49)	(49)	(49)
ADENOMA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	3		4	4
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE	5	10		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	42	39	46	41
ANIMAL MISSING		1		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	22	24	33
TOTAL PRIMARY TUMORS	21	26	30	47
TOTAL ANIMALS WITH BENIGN TUMORS	2	8	5	22
TOTAL BENIGN TUMORS	3	8	5	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	15	21	21
TOTAL MALIGNANT TUMORS	18	17	25	23
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		3
TOTAL SECONDARY TUMORS		1		3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		1		
TOTAL UNCERTAIN TUMORS		1		

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED
WITH 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE CONTROL(UNTR) 06-0037	HIGH DOSE CONTROL(UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	48	50	45	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	44	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(48)	(50)	(45)	(50)
FIBROSARCOMA				1 (2%)
LEIOMYOSARCOMA	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG	(46)	(50)	(43)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (7%)	2 (4%)	2 (5%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	3 (7%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(50)	(45)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	2 (4%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE			2 (4%)	3 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		4 (9%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#SPLEEN	(46)	(49)	(44)	(50)
HEMANGIOSARCOMA	1 (2%)			
MALIGNANT LYMPHOMA, NOS			3 (7%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		2 (5%)	
#MESENTERIC L. NODE	(39)	(44)	(38)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (5%)	
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#LIVER	(47)	(50)	(42)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)

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

TABLE B2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
#THYMUS	(31)	(21)	(36)	(32)
LYMPHANGIOMA				1 (3%)
MALIGNANT LYMPHOMA, NOS	1 (3%)			
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(47)	(50)	(42)	(50)
HEPATOCELLULAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)	2 (4%)
FIBROSARCOMA	1 (2%)			
#STOMACH	(44)	(49)	(40)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
#COLON	(40)	(38)	(37)	(41)
LEIOMYOSARCOMA	1 (3%)			
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(42)	(38)	(34)
CARCINOMA, NOS	1 (2%)			
ADENOMA, NOS	2 (5%)	1 (2%)	5 (13%)	5 (15%)
CHROMOPHOBE ADENOMA		2 (5%)		
#ADRENAL	(45)	(48)	(41)	(49)
CORTICAL ADENOMA				2 (4%)
PHEOCHROMOCYTOMA	1 (2%)			
#THYROID	(43)	(44)	(42)	(45)
FOLLICULAR-CELL ADENOMA				6 (13%)
FOLLICULAR-CELL CARCINOMA				2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(50)	(45)	(50)
CARCINOMA, NOS			1 (2%)	

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

TABLE B2 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 06-0037	CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
ADENOCARCINOMA, NOS			1 (2%)	
#UTERUS	(45)	(47)	(41)	(46)
ADENOCARCINOMA, NOS			1 (2%)	
LEIOMYOSARCOMA	1 (2%)			
ENDOMETRIAL STROMAL POLYP	3 (7%)			1 (2%)
#OVARY/OVIDUCT	(45)	(47)	(41)	(46)
PAPILLARY ADENOMA		1 (2%)		
#OVARY	(45)	(48)	(40)	(43)
GRANULOSA-CELL TUMOR			1 (3%)	1 (2%)
TUBULAR ADENOMA	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(48)	(50)	(45)	(50)
PAPILLARY ADENOMA		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(48)	(50)	(45)	(50)
MESOTHELIOMA, MALIGNANT			1 (2%)	
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	2	11	3
MORIBUND SACRIFICE	2			2
SCHEDULED SACRIFICE	5	10		5
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	37	38	8	39
ANIMAL MISSING			1	
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	10	25	30
TOTAL PRIMARY TUMORS	24	11	30	34
TOTAL ANIMALS WITH BENIGN TUMORS	11	7	7	17
TOTAL BENIGN TUMORS	11	7	7	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	4	21	14
TOTAL MALIGNANT TUMORS	13	4	22	14
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	
TOTAL SECONDARY TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	1
TOTAL UNCERTAIN TUMORS			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 C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 2,4-DIAMINOANISOLE SULFATE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE	HIGH DOSE		
	CONTROL(UNTR) 01-0037	CONTROL(UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
ANIMALS INITIALLY IN STUDY	50	@50	50	50
ANIMALS NECROPSIED	46	48	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	48	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(48)	(49)
CYST, NOS				1 (2%)
EPIDERMAL INCLUSION CYST				2 (4%)
*SUBCUT TISSUE	(46)	(48)	(48)	(49)
ABSCESS, NOS				1 (2%)
METAPLASIA, OSSEOUS		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(45)	(48)	(47)	(49)
INFLAMMATION, NOS	9 (20%)	2 (4%)		
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC	10 (22%)			
#LUNG/BRONCHUS	(46)	(48)	(47)	(49)
BRONCHIECTASIS		1 (2%)		1 (2%)
INFLAMMATION, NOS		7 (15%)		
INFLAMMATION, CHRONIC	8 (17%)			
#BRONCHIAL MUCOUS GLA	(46)	(48)	(47)	(49)
ABSCESS, NOS	1 (2%)			
NECROSIS, NOS	1 (2%)			
HYPERPLASIA, ADENOMATOUS	1 (2%)			
#LUNG/BRONCHIOLE	(46)	(48)	(47)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)			
#LUNG	(46)	(48)	(47)	(49)
ATELECTASIS	1 (2%)			
CONGESTION, NOS	1 (2%)			1 (2%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
EDEMA, NOS	1 (2%)			1 (2%)
INFLAMMATION, NOS	1 (2%)			
BRONCHOPNEUMONIA, FOCAL			1 (2%)	
INFLAMMATION, FOCAL	3 (7%)			
INFLAMMATION, INTERSTITIAL	1 (2%)	4 (8%)		
INFLAMMATION, SUPPURATIVE	1 (2%)			
BRONCHOPNEUMONIA SUPPURATIVE				1 (2%)
INFLAMMATION, NECROTIZING		1 (2%)		1 (2%)
PNEUMONIA, CHRONIC MURINE	1 (2%)	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)			
PERIVASCULITIS	5 (11%)			
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, ADENOMATOUS			1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(44)	(47)	(45)	(45)
ERYTHROPOIESIS			1 (2%)	
#SPLEEN	(46)	(48)	(48)	(48)
THROMBOSIS, NOS	1 (2%)			
FIBROSIS	1 (2%)	1 (2%)		
INFARCT, HEALED	1 (2%)			
PIGMENTATION, NOS				1 (2%)
HEMOSIDEROSIS		1 (2%)		
RETICULOCYTOSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC		9 (19%)		
HYPERPLASIA, ERYTHROID	12 (26%)	10 (21%)		
HYPERPLASIA, RETICULUM CELL	8 (17%)			
HYPERPLASIA, LYMPHOID			1 (2%)	
HEMATOPOIESIS			1 (2%)	
#SPLENIC CAPSULE	(46)	(48)	(48)	(48)
INFLAMMATION, FOCAL			1 (2%)	
#SPLENIC RED PULP	(46)	(48)	(48)	(48)
INFLAMMATION PROLIFERATIVE				1 (2%)
#LYMPH NODE	(38)	(44)	(42)	(47)
HEMORRHAGE		1 (2%)		
INFLAMMATION, NOS	1 (3%)			
HYPERPLASIA, NOS	1 (3%)			
PLASMACYTOSIS		1 (2%)		
HYPERPLASIA, RETICULUM CELL	3 (8%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
HYPERPLASIA, LYMPHOID		3 (7%)		
#MEDIASTINAL L.NODE	(38)	(44)	(42)	(47)
PLASMACYTOSIS	1 (3%)			1 (2%)
#MESENTERIC L. NODE	(38)	(44)	(42)	(47)
PLASMACYTOSIS				1 (2%)
CIRCULATORY SYSTEM				
*LYMPHATIC VESSELS	(46)	(48)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
*HEART	(46)	(48)	(47)	(49)
PERIARTERITIS				1 (2%)
#MYOCARDIUM	(46)	(48)	(47)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, INTERSTITIAL	22 (48%)	23 (48%)	7 (15%)	
INFLAMMATION, CHRONIC FOCAL	3 (7%)			
FIBROSIS	7 (15%)	12 (25%)		
DEGENERATION, NOS			3 (6%)	29 (59%)
PIGMENTATION, NOS				1 (2%)
#ENDOCARDIUM	(46)	(48)	(47)	(49)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
*AORTA	(46)	(48)	(48)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
*PULMONARY ARTERY	(46)	(48)	(48)	(49)
INFLAMMATION PROLIFERATIVE				1 (2%)
HYPERTROPHY, NOS	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(38)	(47)	(45)	(47)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
#SUBMAXILLARY GLAND	(38)	(47)	(45)	(47)
PLASMACYTOSIS				1 (2%)
#LIVER	(46)	(48)	(48)	(48)
FIBROSIS SEPTAL LIVER		2 (4%)		

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
NECROSIS, FOCAL	3 (7%)	2 (4%)		
NECROSIS, COAGULATIVE	1 (2%)			
METAMORPHOSIS FATTY	1 (2%)		4 (8%)	
HYPERTROPHY, NOS			1 (2%)	
HYPERPLASIA, NODULAR			2 (4%)	
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	23 (50%)	15 (31%)	5 (10%)	
HYPERPLASIA, DIFFUSE				1 (2%)
ANGIECTASIS		1 (2%)		
#LIVER/CENTRILOBULAR	(46)	(48)	(48)	(48)
DEGENERATION, NOS			1 (2%)	
NECROSIS, NOS		1 (2%)		
#LIVER/PERIPORTAL	(46)	(48)	(48)	(48)
FIBROSIS	1 (2%)			
#LIVER/HEPATOCYTES	(46)	(48)	(48)	(48)
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS				2 (4%)
HYPERPLASIA, FOCAL			12 (25%)	11 (23%)
*BILE DUCT	(46)	(48)	(48)	(49)
INFLAMMATION, NOS	6 (13%)	3 (6%)		
HYPERPLASIA, NOS	32 (70%)	43 (90%)		
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(42)	(46)	(45)	(48)
INFLAMMATION, NOS	10 (24%)	17 (37%)		
PERIARTERITIS				1 (2%)
HYPERPLASIA, INTRADUCTAL	1 (2%)			
#PANCREATIC ACINUS	(42)	(46)	(45)	(48)
ATROPHY, NOS	4 (10%)		2 (4%)	6 (13%)
ATROPHY, FOCAL				1 (2%)
HYPERPLASIA, FOCAL		1 (2%)		
#ESOPHAGUS	(46)	(45)	(47)	(47)
DYSPLASIA, NOS		1 (2%)		
#STOMACH	(45)	(48)	(45)	(47)
EPIDERMAL INCLUSION CYST	1 (2%)			
INFLAMMATION, NOS		1 (2%)		
ULCER, NOS	2 (4%)			1 (2%)
ULCER, FOCAL			1 (2%)	

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
HYPERPLASIA, NOS	6 (13%)			
HYPERPLASIA, BASAL CELL		1 (2%)		
HYPERKERATOSIS	1 (2%)	2 (4%)		
ACANTHOSIS	1 (2%)	2 (4%)		
#SMALL INTESTINE	(43)	(46)	(45)	(47)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#S.INTESTINE/MUCOSA	(43)	(46)	(45)	(47)
PIGMENTATION, NOS				2 (4%)
#PEYERS PATCH	(43)	(46)	(45)	(47)
HYPERPLASIA, NOS	7 (16%)	12 (26%)		
#DUODENAL MUCOSA	(43)	(46)	(45)	(47)
PIGMENTATION, NOS				30 (64%)
#ILEUM	(43)	(46)	(45)	(47)
INFLAMMATION, NOS		2 (4%)		
#COLON	(43)	(46)	(43)	(40)
ULCER, FOCAL			1 (2%)	
NEMATODIASIS	3 (7%)			
PARASITISM		3 (7%)		
URINARY SYSTEM				
#KIDNEY	(46)	(48)	(48)	(49)
GLOMERULONEPHRITIS, NOS	33 (72%)	47 (98%)	45 (94%)	
INFLAMMATION, INTERSTITIAL	1 (2%)			1 (2%)
FIBROSIS, DIFFUSE		6 (13%)		
NEPHROSIS, NOS				47 (96%)
HYPERPIGMENTATION				1 (2%)
#KIDNEY/TUBULE	(46)	(48)	(48)	(49)
PIGMENTATION, NOS				2 (4%)
#KIDNEY/PELVIS	(46)	(48)	(48)	(49)
CALCIFICATION, FOCAL				1 (2%)
#URINARY BLADDER	(42)	(43)	(45)	(48)
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, EPITHELIAL	3 (7%)	1 (2%)		

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

TABLE C1 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 01-0037	CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(38)	(44)	(40)
HYPERPLASIA, NOS	3 (7%)	1 (3%)		
HYPERPLASIA, FOCAL		2 (5%)	7 (16%)	
HYPERPLASIA, CHROMOPHOBE-CELL	2 (5%)			
#ADRENAL CORTEX	(43)	(47)	(46)	(47)
HYPERTROPHY, FOCAL	1 (2%)			
HYPERPLASIA, NODULAR			4 (9%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL				2 (4%)
#ADRENAL MEDULLA	(43)	(47)	(46)	(47)
NECROSIS, NOS	1 (2%)			
CALCIFICATION, NOS	1 (2%)			
HYPERPLASIA, NODULAR	1 (2%)	1 (2%)	1 (2%)	3 (6%)
HYPERPLASIA, NOS	6 (14%)		1 (2%)	
HYPERPLASIA, FOCAL		4 (9%)	1 (2%)	1 (2%)
#THYROID	(45)	(48)	(47)	(49)
FOLLICULAR CYST, NOS				9 (18%)
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
PIGMENTATION, NOS				2 (4%)
HYPERPIGMENTATION				47 (96%)
HYPERPLASTIC NODULE				1 (2%)
HYPERPLASIA, CYSTIC				2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, C-CELL	1 (2%)	3 (6%)		3 (6%)
HYPERPLASIA, FOLLICULAR-CELL				1 (2%)
#PARATHYROID	(32)	(28)	(30)	(24)
HYPERPLASIA, NOS		1 (4%)		1 (4%)
#PANCREATIC ISLETS	(42)	(46)	(45)	(48)
HYPERPLASIA, NOS	2 (5%)	1 (2%)		2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(48)	(48)	(49)
GALACTOCELE		2 (4%)	1 (2%)	
HYPERPLASIA, NOS	5 (11%)	4 (8%)	1 (2%)	

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

TABLE C1 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 01-0037	CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
*PREPUTIAL GLAND	(46)	(48)	(48)	(49)
CYSTIC DUCTS				1 (2%)
ULCER, NOS				1 (2%)
ABSCESS, NOS	1 (2%)			
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, EPITHELIAL				1 (2%)
#PROSTATE	(45)	(44)	(47)	(47)
INFLAMMATION, NOS	21 (47%)	17 (39%)	1 (2%)	
INFLAMMATION, FOCAL	3 (7%)		5 (11%)	
INFLAMMATION, ACUTE			3 (6%)	11 (23%)
INFLAMMATION ACUTE AND CHRONIC				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
DEGENERATION, NOS				1 (2%)
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, FOCAL	5 (11%)			
HYPERPLASIA, PAPILLARY	2 (4%)			
HYPERPLASIA, ADENOMATOUS			1 (2%)	
METAPLASIA, SQUAMOUS	5 (11%)			
*SEMINAL VESICLE	(46)	(48)	(48)	(49)
ATROPHY, NOS			35 (73%)	11 (22%)
HYPERPLASIA, EPITHELIAL				1 (2%)
*COAGULATING GLAND	(46)	(48)	(48)	(49)
ATROPHY, NOS			3 (6%)	
#TESTIS	(45)	(47)	(48)	(49)
MINERALIZATION		1 (2%)		
ATROPHY, NOS	2 (4%)	6 (13%)	3 (6%)	4 (8%)
ASPERMATOGENESIS	1 (2%)			
HYPERPLASIA, INTERSTITIAL CELL	19 (42%)	3 (6%)	1 (2%)	3 (6%)
#TESTIS/TUBULE	(45)	(47)	(48)	(49)
DEGENERATION, NOS	6 (13%)		3 (6%)	19 (39%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(46)	(48)	(48)	(49)
CATARACT				1 (2%)

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

TABLE C1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0048	HIGH DOSE 01-0109
*EYE/RETINA	(46)	(48)	(48)	(49)
DEGENERATION, NOS				1 (2%)
*EYE/LACRIMAL GLAND	(46)	(48)	(48)	(49)
INFLAMMATION, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*CARTILAGE,NOS	(46)	(48)	(48)	(49)
CYST, NOS	1 (2%)			
BODY CAVITIES				
*ABDOMINAL CAVITY	(46)	(48)	(48)	(49)
NECROSIS, FAT			1 (2%)	
*PERITONEUM	(46)	(48)	(48)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
*PLEURA	(46)	(48)	(48)	(49)
INFLAMMATION, FIBRINOUS			1 (2%)	
*EPICARDIUM	(46)	(48)	(48)	(49)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
*MESENTERY	(46)	(48)	(48)	(49)
PERIARTERITIS			2 (4%)	
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT		2		
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF	1			
AUTOLYSIS/NO NECROPSY	4	1	2	1

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	50	49	49
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(49)	(49)
INFLAMMATION, NOS		1 (2%)		
GRANULOMA, FOREIGN BODY				1 (2%)
*SUBCUT TISSUE	(49)	(50)	(49)	(49)
MINERALIZATION		1 (2%)		
ABSCESS, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(49)	(48)	(48)
INFLAMMATION, NOS	9 (19%)			
INFLAMMATION, CHRONIC	10 (21%)			
POLYP, INFLAMMATORY	1 (2%)			
#LUNG/BRONCHUS	(49)	(50)	(48)	(49)
BRONCHIECTASIS	1 (2%)			2 (4%)
INFLAMMATION, NOS	1 (2%)	3 (6%)		
INFLAMMATION, CHRONIC	9 (18%)			
HYPERPLASIA, FOCAL			1 (2%)	
#LUNG/BRONCHIOLE	(49)	(50)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
#LUNG	(49)	(50)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	7 (14%)			
INFLAMMATION, INTERSTITIAL	2 (4%)	6 (12%)		
INFLAMMATION, SUPPURATIVE				1 (2%)
BRONCHOPNEUMONIA SUPPURATIVE				6 (12%)
BRONCHOPNEUMONIA NECROTIZING			1 (2%)	
ABSCESS, NOS				2 (4%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
BRONCHOPNEUMONIA, CHRONIC				1 (2%)
PERIVASCULITIS	6 (12%)			
CYTOMEGALY				1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, ADENOMATOUS			1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(46)	(43)	(45)
OSTEOSCLEROSIS		1 (2%)		
MYELOSCLEROSIS				1 (2%)
#SPLEEN	(49)	(48)	(48)	(49)
HYPERPIGMENTATION				2 (4%)
HEMOSIDEROSIS		12 (25%)	2 (4%)	
HYPERPLASIA, NOS	1 (2%)		2 (4%)	
HYPERPLASIA, HEMATOPOIETIC	3 (6%)	25 (52%)		
HYPERPLASIA, ERYTHROID	17 (35%)	19 (40%)		
HYPERPLASIA, PLASMA CELL	1 (2%)			
HYPERPLASIA, RETICULUM CELL	11 (22%)			
HEMATOPOIESIS			10 (21%)	1 (2%)
ERYTHROPOIESIS			1 (2%)	
#SPLENIC CAPSULE	(49)	(48)	(48)	(49)
HEMORRHAGIC CYST		1 (2%)		
FIBROSIS, FOCAL				1 (2%)
#LYMPH NODE	(41)	(47)	(43)	(41)
INFLAMMATION, NOS	3 (7%)			
HYPERPLASIA, NOS	2 (5%)			
PLASMACYTOSIS	3 (7%)	1 (2%)		
HYPERPLASIA, PLASMA CELL	1 (2%)			
HYPERPLASIA, LYMPHOID		4 (9%)		
#ABDOMINAL LYMPH NODE	(41)	(47)	(43)	(41)
PLASMACYTOSIS			1 (2%)	
CIRCULATORY SYSTEM				
#HEART	(49)	(50)	(48)	(48)
PERIARTERITIS				2 (4%)
PERIVASCULITIS			1 (2%)	
#MYOCARDIUM	(49)	(50)	(48)	(48)
INFLAMMATION, NOS	1 (2%)	1 (2%)		

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
INFLAMMATION, INTERSTITIAL	24 (49%)	23 (46%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	1 (2%)
FIBROSIS	5 (10%)	15 (30%)		
DEGENERATION, NOS				11 (23%)
#ENDOCARDIUM	(49)	(50)	(48)	(48)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION PROLIFERATIVE				1 (2%)
*PORTAL VEIN	(49)	(50)	(49)	(49)
THROMBUS, MURAL	1 (2%)			
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(48)	(49)
FIBROSIS	1 (2%)			
PERIVASCULITIS	1 (2%)			
NECROSIS, FOCAL	4 (8%)	2 (4%)	1 (2%)	
NECROSIS, COAGULATIVE	2 (4%)		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	6 (12%)	4 (8%)	
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASTIC NODULF				1 (2%)
HYPERPLASIA, FOCAL	22 (45%)	38 (76%)	2 (4%)	1 (2%)
HYPERPLASIA, DIFFUSE				2 (4%)
ANGIECTASIS	1 (2%)			
HYPERPLASIA, ERYTHROID		1 (2%)		
HEMATOPOIESIS		2 (4%)		
#LIVER/CENTRILOBULAR	(49)	(50)	(48)	(49)
DEGENERATION, NOS				2 (4%)
NECROSIS, NOS			1 (2%)	4 (8%)
#LIVER/PERIPORTAL	(49)	(50)	(48)	(49)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#LIVER/HEPATOCYTES	(49)	(50)	(48)	(49)
HYPERPLASIA, NOS			1 (2%)	1 (2%)
HYPERPLASIA, FOCAL			31 (65%)	28 (57%)
HYPERPLASIA, DIFFUSE				2 (4%)
*BILE DUCT	(49)	(50)	(49)	(49)
INFLAMMATION, NOS	5 (10%)	1 (2%)		

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

TABLE C2 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 02-0037	CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, NOS	27 (55%)	32 (64%)		
HYPERPLASIA, FOCAL		1 (2%)		
#PANCREAS	(46)	(48)	(46)	(47)
INFLAMMATION, NOS	7 (15%)	6 (13%)	1 (2%)	
#PANCREATIC DUCT	(46)	(48)	(46)	(47)
HYPERPLASIA, NOS	1 (2%)			
#PANCREATIC ACINUS	(46)	(48)	(46)	(47)
ATROPHY, NOS	2 (4%)		1 (2%)	6 (13%)
HYPERPLASIA, DIFFUSE				1 (2%)
#STOMACH	(48)	(48)	(47)	(49)
INFLAMMATION, NOS	2 (4%)	1 (2%)		
ULCER, NOS			1 (2%)	
INFLAMMATION, FOCAL	2 (4%)			
EROSION				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			
HYPERPLASIA, BASAL CELL			1 (2%)	
ACANTHOSIS		2 (4%)		
#GASTRIC MUCOSA	(48)	(48)	(47)	(49)
HYPERPLASIA, NOS	1 (2%)			
#PEYERS PATCH	(47)	(48)	(46)	(47)
HYPERPLASIA, NOS	6 (13%)	15 (31%)		
#DUODENAL MUCOSA	(47)	(48)	(46)	(47)
PIGMENTATION, NOS				24 (51%)
#COLON	(43)	(46)	(45)	(40)
NEMATODIASIS	3 (7%)			
PARASITISM		2 (4%)		
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(48)	(49)
HYDRONEPHROSIS	1 (2%)			
GLOMERULONEPHRITIS, NOS	33 (67%)	43 (86%)	31 (65%)	
INFLAMMATION, INTERSTITIAL	1 (2%)		1 (2%)	
GLOMERULONEPHRITIS, MEMBRANOUS	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 02-0037	CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
FIBROSIS, DIFFUSE		1 (2%)		
NEPHROSIS, NOS				23 (47%)
#KIDNEY/CORTEX	(49)	(50)	(48)	(49)
CYST, NOS			1 (2%)	
#KIDNEY/GLOMERULUS	(49)	(50)	(48)	(49)
NEPHROSIS, NOS			1 (2%)	
#KIDNEY/TUBULE	(49)	(50)	(48)	(49)
PIGMENTATION, NOS				1 (2%)
#URINARY BLADDER	(41)	(46)	(43)	(46)
INFLAMMATION, NOS	1 (2%)			
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(40)	(47)	(38)
PERIVASCULITIS		1 (3%)		
HYPERPLASIA, NOS	2 (5%)			
HYPERPLASIA, FOCAL		3 (8%)		
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)			
#ADRENAL	(46)	(49)	(47)	(49)
METAMORPHOSIS FATTY		1 (2%)		
#ADRENAL CORTEX	(46)	(49)	(47)	(49)
NODULE	1 (2%)			
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS	7 (15%)			
HYPERPLASIA, FOCAL			1 (2%)	8 (16%)
#ADRENAL MEDULLA	(46)	(49)	(47)	(49)
HYPERPLASIA, NODULAR		3 (6%)		
HYPERPLASIA, NOS	4 (9%)			
HYPERPLASIA, FOCAL		3 (6%)		4 (8%)
#THYROID	(47)	(45)	(46)	(49)
CYSTIC FOLLICLES		1 (2%)		
FOLLICULAR CYST, NOS				12 (24%)
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (2%)
HYPERPIGMENTATION				49 (100%)
HYPERPLASIA, C-CELL		1 (2%)		15 (31%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
#PANCREATIC ISLETS	(46)	(48)	(46)	(47)
HYPERPLASIA, NOS	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(49)	(49)
CALACTOCELE	5 (10%)	16 (32%)	8 (16%)	
HYPERPLASIA, NOS	17 (35%)	8 (16%)		
HYPERPLASIA, PAPILLARY	1 (2%)			
HYPERPLASIA, ADENOMATOUS			1 (2%)	
*MAMMARY DUCT	(49)	(50)	(49)	(49)
FIBROSIS			1 (2%)	
*CLITORIS	(49)	(50)	(49)	(49)
HYPERPLASIA, EPITHELIAL				1 (2%)
*CLITORAL GLAND	(49)	(50)	(49)	(49)
HYPERPLASIA, NOS				2 (4%)
#UTERUS	(48)	(50)	(46)	(46)
HYDROMETRA	3 (6%)		4 (9%)	4 (9%)
INFLAMMATION, SUPPURATIVE	1 (2%)			
PYOMETRA				2 (4%)
INFLAMMATION, ACUTE			2 (4%)	
ABSCESS, NOS	2 (4%)			
HYPERPLASIA, ADENOMATOUS	5 (10%)	1 (2%)		
POLYP, INFLAMMATORY				1 (2%)
#UTERUS/ENDOMETRIUM	(48)	(50)	(46)	(46)
INFLAMMATION, NOS	14 (29%)	22 (44%)	1 (2%)	1 (2%)
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, SUPPURATIVE	2 (4%)			1 (2%)
INFLAMMATION, ACUTE			9 (20%)	4 (9%)
INFLAMMATION, ACUTE/CHRONIC			4 (9%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)	6 (12%)	2 (4%)	
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, CYSTIC	2 (4%)		22 (48%)	5 (11%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	1 (2%)		
#OVARY/OVIDUCT	(48)	(50)	(46)	(46)
INFLAMMATION, NOS	1 (2%)	10 (20%)		1 (2%)
INFLAMMATION, SUPPURATIVE		2 (4%)		2 (4%)

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

TABLE C2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0048	HIGH DOSE 02-0109
INFLAMMATION, CHRONIC				1 (2%)
*OVARY	(47)	(49)	(46)	(47)
CYST, NOS	4 (9%)	8 (16%)	2 (4%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(49)	(49)
SYNECHIA, ANTERIOR			1 (2%)	
SYNECHIA, POSTERIOR			1 (2%)	
CATARACT		1 (2%)	1 (2%)	1 (2%)
*EYE/RETINA	(49)	(50)	(49)	(49)
DEGENERATION, NOS			1 (2%)	1 (2%)
ATROPHY, NOS		1 (2%)		
*HARDERIAN GLAND	(49)	(50)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(49)	(50)	(49)	(49)
METAPLASIA, OSSEOUS			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			1	
AUTOLYSIS/NO NECROPSY	1		1	1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 2,4-DIAMINOANISOLE SULFATE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 05-0037	CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	48	49	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	49	49	49
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(49)	(49)	(49)
HEMORRHAGE				1 (2%)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, FOCAL		3 (6%)		
INFLAMMATION, NECROTIZING		1 (2%)		
FIBROSIS	1 (2%)			
ALOPECIA	1 (2%)			
*SUBCUT TISSUE	(48)	(49)	(49)	(49)
ABSCESS, NOS			1 (2%)	3 (6%)
NECROSIS, NOS	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(48)	(49)	(48)	(48)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)	1 (2%)		
#LUNG/BRONCHIOLE	(48)	(49)	(48)	(48)
INFLAMMATION, FOCAL		1 (2%)		
#LUNG	(48)	(49)	(48)	(48)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, INTERSTITIAL	14 (29%)	10 (20%)	3 (6%)	
HYPERPLASIA, EPITHELIAL	2 (4%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM				2 (4%)
#LUNG/ALVEOLI	(48)	(49)	(48)	(48)
INFLAMMATION, FOCAL	2 (4%)			
FIBROSIS, FOCAL	1 (2%)			
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(47)	(48)	(46)	(48)
HYPERPLASIA, NOS				1 (2%)

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0208
HYPERPLASIA, DIFFUSE				15 (31%)
HYPERPLASIA, HEMATOPOIETIC				31 (65%)
#SPLEEN	(47)	(49)	(48)	(48)
INFLAMMATION, NOS	1 (2%)			
FIBROSIS, FOCAL			1 (2%)	
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, NOS	2 (4%)	6 (12%)	1 (2%)	
ANGIECTASIS			1 (2%)	
RETICULOCYTOSIS		1 (2%)		
HYPERPLASIA, HEMATOPOIETIC	2 (4%)	5 (10%)		
HYPERPLASIA, ERYTHROID	2 (4%)			
HYPERPLASIA, LYMPHOID	2 (4%)	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIESIS			1 (2%)	2 (4%)
GRANULOPOIESIS				1 (2%)
#LYMPH NODE	(44)	(42)	(45)	(45)
HEMORRHAGIC CYST	1 (2%)			
INFLAMMATION, NOS	13 (30%)	10 (24%)		
DEGENERATION, CYSTIC	1 (2%)			
HYPERPLASIA, NOS	2 (5%)	1 (2%)		
RETICULOCYTOSIS		2 (5%)		
PLASMACYTOSIS				1 (2%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)			
HYPERPLASIA, LYMPHOID	2 (5%)	3 (7%)		
MYELOID METAPLASIA	2 (5%)			
#MEDIASTINAL L.NODE	(44)	(42)	(45)	(45)
NECROSIS, NOS	1 (2%)			
PLASMACYTOSIS				1 (2%)
#ABDOMINAL LYMPH NODE	(44)	(42)	(45)	(45)
HYPERPLASIA, RETICULUM CELL			1 (2%)	
#PANCREATIC L.NODE	(44)	(42)	(45)	(45)
INFLAMMATION, NOS	1 (2%)			
#MESENTERIC L. NODE	(44)	(42)	(45)	(45)
HEMORRHAGE	1 (2%)			
INFLAMMATION, NOS	9 (20%)		2 (4%)	
INFLAMMATION, ACUTE/CHRONIC			9 (20%)	
INFLAMMATION, CHRONIC			1 (2%)	
AMYLOIDOSIS			1 (2%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)	
PLASMACYTOSIS				1 (2%)

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
HYPERPLASIA, RETICULUM CELL			1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)	1 (2%)
#THYMUS	(34)	(28)	(35)	(33)
NECROSIS, NOS	1 (3%)			
#THYMIC MEDULLA	(34)	(28)	(35)	(33)
HYPERPLASIA, LYMPHOID			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(48)	(49)	(48)	(47)
MINERALIZATION		1 (2%)		
PERIARTERITIS				3 (6%)
ARTERIOSCLEROSIS, NOS			1 (2%)	
#HEART/VENTRICLE	(48)	(49)	(48)	(47)
MELANIN	2 (4%)			
#MYOCARDIUM	(48)	(49)	(48)	(47)
INFLAMMATION, INTERSTITIAL	2 (4%)			
INFLAMMATION PROLIFERATIVE				1 (2%)
FIBROSIS	5 (10%)			
DEGENERATION, NOS			1 (2%)	
*BLOOD VESSEL	(48)	(49)	(49)	(49)
INFLAMMATION, NOS	2 (4%)			
*PULMONARY ARTERY	(48)	(49)	(49)	(49)
MINERALIZATION	2 (4%)			
*SPLENIC ARTERY	(48)	(49)	(49)	(49)
THROMBOSIS, NOS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(47)	(48)	(47)	(47)
INFLAMMATION, NOS	2 (4%)			
INFLAMMATION, ACUTE/CHRONIC			14 (30%)	
PERIVASCULAR CUFFING	1 (2%)			
#LIVER	(48)	(48)	(49)	(49)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
NECROSIS, FOCAL	13 (27%)	9 (19%)		
AMYLOIDOSIS			1 (2%)	
METAMORPHOSIS FATTY	3 (6%)		2 (4%)	1 (2%)
HYPERPLASIA, NODULAR	2 (4%)		1 (2%)	
HYPERPLASTIC NODULE		1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)			
HYPERPLASIA, DIFFUSE			1 (2%)	
ANGIECTASIS	1 (2%)			
MYELOID METAPLASIA	1 (2%)			
#LIVER/HEPATOCYTES	(48)	(48)	(49)	(49)
DEGENERATION, NOS	1 (2%)			
HYPERTROPHY, DIFFUSE				1 (2%)
*GALLBLADDER	(48)	(49)	(49)	(49)
INFLAMMATION, FOCAL	1 (2%)			
*BILE DUCT	(48)	(49)	(49)	(49)
INFLAMMATION, CHRONIC			1 (2%)	
#PANCREAS	(48)	(47)	(44)	(47)
INFLAMMATION, NOS	7 (15%)	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION ACTIVE CHRONIC			1 (2%)	
DEGENERATION, CYSTIC	1 (2%)			
METAMORPHOSIS FATTY	1 (2%)			
#PANCREATIC DUCT	(48)	(47)	(44)	(47)
CALCIFICATION, NOS				1 (2%)
HYPERPLASIA, NOS	1 (2%)			
#PANCREATIC ACINUS	(48)	(47)	(44)	(47)
HYPERTROPHY, FOCAL	1 (2%)			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)			
#STOMACH	(47)	(48)	(46)	(48)
INFLAMMATION, NOS	13 (28%)			
ULCER, NOS	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)	2 (4%)		
INFLAMMATION, INTERSTITIAL	1 (2%)			
INFLAMMATION, NECROTIZING		1 (2%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)		

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

TABLE D1 (CONTINUED)

	LOW DOSE	HIGH DOSE		
	CONTROL (UNTR) 05-0037	CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
HYPERKERATOSIS	3 (6%)	1 (2%)		
ACANTHOSIS	3 (6%)	1 (2%)		
#GASTRIC MUCOSA	(47)	(48)	(46)	(48)
HYPERPLASIA, FOCAL	1 (2%)			
#SMALL INTESTINE	(48)	(49)	(47)	(47)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
HYPERPLASIA, ADENOMATOUS				1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)	
#PEYERS PATCH	(48)	(49)	(47)	(47)
HYPERPLASIA, NOS	2 (4%)	7 (14%)	1 (2%)	
HYPERPLASIA, LYMPHOID				2 (4%)
#ILEUM	(48)	(49)	(47)	(47)
HEMORRHAGE	1 (2%)			
INFLAMMATION, NOS	2 (4%)			
AMYLOIDOSIS			1 (2%)	
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, NOS			1 (2%)	
#COLON	(45)	(43)	(46)	(39)
PARASITISM	1 (2%)	3 (7%)		
URINARY SYSTEM				
#KIDNEY	(47)	(49)	(48)	(49)
GLOMERULONEPHRITIS, NOS	6 (13%)	2 (4%)	1 (2%)	
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, INTERSTITIAL	23 (49%)	16 (33%)	15 (31%)	1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
PERIVASCULITIS			1 (2%)	
GLOMERULOSCLEROSIS, NOS			1 (2%)	1 (2%)
#KIDNEY/GLOMERULUS	(47)	(49)	(48)	(49)
AMYLOIDOSIS			1 (2%)	
#KIDNEY/TUBULE	(47)	(49)	(48)	(49)
NECROSIS, FOCAL	1 (2%)			
#KIDNEY/PELVIS	(47)	(49)	(48)	(49)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, ACUTE			1 (2%)	

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTFOL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
INFLAMMATION, ACUTF/CHRONIC			11 (23%)	
#URINARY BLADDER	(48)	(48)	(48)	(47)
INFLAMMATION, NOS	4 (8%)			
HYPERPLASIA, EPITHELIAL	9 (19%)	4 (8%)		
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(40)	(40)	(43)
HYPERPLASIA, NOS	3 (7%)			
HYPERPLASIA, FOCAL	3 (7%)			
#ADRENAL	(45)	(44)	(47)	(40)
AMYLOIDOSIS			1 (2%)	
HYPERPLASIA, NOS		3 (7%)		
#ADRENAL/CAPSULE	(45)	(44)	(47)	(40)
HYPERPLASIA, NOS		3 (7%)		
#ADRENAL CORTEX	(45)	(44)	(47)	(40)
NODULE	1 (2%)		1 (2%)	
HYPERTROPHY, FOCAL	1 (2%)		1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
#ADRENAL MEDULLA	(45)	(44)	(47)	(40)
DEGENERATION, NOS	1 (2%)			
#THYROID	(47)	(45)	(46)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, PAPILLARY	1 (2%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			12 (27%)
#THYROID FOLLICLE	(47)	(45)	(46)	(45)
DEGENERATION, NOS				44 (98%)
#PARATHYROID	(29)	(24)	(26)	(22)
HYPERPLASIA, NOS				1 (5%)
HYPERPLASIA, FOCAL				1 (5%)
#PANCREATIC ISLETS	(48)	(47)	(44)	(47)
HYPERPLASIA, NOS	2 (4%)			
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(48)	(49)	(49)	(49)
ABSCESS, NOS	2 (4%)	1 (2%)		

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
#PROSTATE	(48)	(49)	(48)	(43)
INFLAMMATION, FOCAL			1 (2%)	
INFLAMMATION, ACUTE			1 (2%)	
HYPERPLASIA, PAPILLARY			1 (2%)	
#TESTIS/TUBULE	(47)	(48)	(46)	(48)
DEGENERATION, NOS	4 (9%)		7 (15%)	
CALCIFICATION, FOCAL				1 (2%)
*EPIDIDYMIS	(48)	(49)	(49)	(49)
INFLAMMATION, NOS		1 (2%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(48)	(49)	(48)	(47)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#BRAIN	(48)	(49)	(48)	(47)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#CEREBRAL CORTEX	(48)	(49)	(48)	(47)
MINERALIZATION	3 (6%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(48)	(49)	(49)	(49)
THROMBOSIS, NOS				1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
BODY CAVITIES				
*ABDOMINAL CAVITY	(48)	(49)	(49)	(49)
NECROSIS, FAT				1 (2%)
*PLEURA	(48)	(49)	(49)	(49)
INFLAMMATION, PROLIFERATIVE				1 (2%)

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

TABLE D1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 05-0037	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0048	HIGH DOSE 05-0108
*MESENTERY	(48)	(49)	(49)	(49)
PERIARTERITIS				1 (2%)
NECROSIS, FOCAL				1 (2%)
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, ACUTE		1		
OMENTUM				
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		5	5	1
ANIMAL MISSING/NO NECROPSY		1		
AUTOLYSIS/NO NECROPSY	2		1	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 2,4-DIAMINOANISOLE SULFATE

	LOW DOSE		HIGH DOSE			
	CONTROL (UNTR) 06-0037		CONTROL (UNTR) 06-0118		LOW DOSE 06-0048	HIGH DOSE 06-0108
ANIMALS INITIALLY IN STUDY	50		50		50	50
ANIMALS MISSING					1	
ANIMALS NECROPSIED	48		50		45	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	47		50		44	50
INTEGUMENTARY SYSTEM						
*SKIN	(48)		(50)		(45)	(50)
EPIDERMAL INCLUSION CYST						1 (2%)
*SUBCUT TISSUE	(48)		(50)		(45)	(50)
MINERALIZATION	1	(2%)				
ABSCESS, NOS			1	(2%)		
FIBROSIS	1	(2%)				
RESPIRATORY SYSTEM						
#LUNG/BRONCHUS	(46)		(50)		(43)	(50)
INFLAMMATION, FOCAL	1	(2%)	1	(2%)		
#LUNG/BRONCHIOLE	(46)		(50)		(43)	(50)
HYPERPLASIA, NOS			1	(2%)		
#LUNG	(46)		(50)		(43)	(50)
INFLAMMATION, INTERSTITIAL	10	(22%)	14	(28%)	1 (2%)	
HYPERPLASIA, EPITHELIAL	3	(7%)				
HYPERPLASIA, ALVEOLAR EPITHELIUM					1 (2%)	
HEMATOPOIETIC SYSTEM						
#BONE MARROW	(45)		(49)		(41)	(48)
HYPOPLASIA, NOS						1 (2%)
HYPERPLASIA, DIFFUSE						2 (4%)
MYELOFIBROSIS	1	(2%)				29 (60%)
MYELOSCLEROSIS						11 (23%)
HYPERPLASIA, HEMATOPOIETIC					1 (2%)	38 (79%)
#SPLEEN	(46)		(49)		(44)	(50)
ATROPHY, NOS					1 (2%)	1 (2%)

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
HYPERPLASIA, NOS		9 (18%)		
ANGIECTASIS				1 (2%)
HYPERPLASIA, HEMATOPOIETIC	16 (35%)	6 (12%)		
HYPERPLASIA, ERYTHROID	6 (13%)			
HYPERPLASIA, LYMPHOID	10 (22%)	2 (4%)	3 (7%)	2 (4%)
HEMATOPOIESIS	1 (2%)			
MYELOPOIESIS	1 (2%)			
#HEMOLYMPH NODES	(46)	(49)	(44)	(50)
INFLAMMATION, NOS		2 (4%)		
HYPERPLASIA, NOS		1 (2%)		
#LYMPH NODE	(39)	(44)	(38)	(43)
CYST, NOS	1 (3%)			
INFLAMMATION, NOS	15 (38%)	9 (20%)		
HYPERPLASIA, NOS	1 (3%)	3 (7%)		
RETICULOCYTOSIS	1 (3%)	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC	2 (5%)	1 (2%)		
HYPERPLASIA, LYMPHOID		4 (9%)		
MYELOID METAPLASIA	1 (3%)			
#MEDIASTINAL L.NODE	(39)	(44)	(38)	(43)
HYPERPLASIA, LYMPHOID			1 (3%)	
#MESENTERIC L. NODE	(39)	(44)	(38)	(43)
INFLAMMATION, ACUTE/CHRONIC			2 (5%)	
HYPERPLASIA, RETICULUM CELL			2 (5%)	
#THYMUS	(31)	(21)	(36)	(32)
INFLAMMATION, NOS				1 (3%)
GRANULOMA, NOS				1 (3%)
HYPERPLASIA, LYMPHOID			1 (3%)	1 (3%)
#THYMIC MEDULLA	(31)	(21)	(36)	(32)
HYPERPLASIA, NOS			2 (6%)	
HYPERPLASIA, LYMPHOID				1 (3%)
CIRCULATORY SYSTEM				
#HEART	(46)	(50)	(43)	(50)
PERIARTERITIS				2 (4%)
#HEART/VENTRICLE	(46)	(50)	(43)	(50)
MELANIN	4 (9%)			

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
#MYOCARDIUM	(46)	(50)	(43)	(50)
INFLAMMATION, FOCAL		1 (2%)		
#ENDOCARDIUM	(46)	(50)	(43)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(45)	(48)	(40)	(50)
INFLAMMATION, NOS	2 (4%)			
INFLAMMATION, ACUTE/CHRONIC			7 (18%)	
PERIVASCULAR CUFFING	4 (9%)	3 (6%)		
#LIVER	(47)	(50)	(42)	(50)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE			1 (2%)	
NECROSIS, FOCAL	22 (47%)	7 (14%)		1 (2%)
CALCIFICATION, NOS				1 (2%)
HYPERPLASTIC NODULE	1 (2%			
HYPERPLASIA, FOCAL			1 (2%)	
ANGIECTASIS	1 (2%)			1 (2%)
HEMATOPOIESIS	3 (6%)			
#LIVER/HEPATOCYTES	(47)	(50)	(42)	(50)
HYPERTROPHY, FOCAL			1 (2%)	
*GALLBLADDER	(48)	(50)	(45)	(50)
INFLAMMATION, NOS	3 (6%)			
*BILE DUCT	(48)	(50)	(45)	(50)
INFLAMMATION, NOS	1 (2%)			
#PANCREAS	(44)	(48)	(41)	(45)
INFLAMMATION, NOS	5 (11%)	2 (4%)	1 (2%)	
PERIARTERITIS	1 (2%)			
#PANCREATIC DUCT	(44)	(48)	(41)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
#STOMACH	(44)	(49)	(40)	(49)
INFLAMMATION, NOS	7 (16%)	1 (2%)		
ULCER, NOS	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)	1 (2%)	1 (3%)	

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, EPITHELIAL	1 (2%)			
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERKERATOSIS	1 (2%)		1 (3%)	
ACANTHOSIS	1 (2%)	2 (4%)	1 (3%)	
#GASTRIC MUCOSA	(44)	(49)	(40)	(49)
HYPERPLASIA, FOCAL	1 (2%)			
#PEYERS PATCH	(44)	(48)	(39)	(49)
HYPERPLASIA, NOS	1 (2%)	7 (15%)		
URINARY SYSTEM				
#KIDNEY	(46)	(50)	(44)	(50)
HYDRONEPHROSIS			1 (2%)	
GLOMERULONEPHRITIS, NOS	14 (30%)	4 (8%)		
GLOMERULONEPHRITIS, FOCAL		1 (2%)		
INFLAMMATION, INTERSTITIAL	16 (35%)	12 (24%)	2 (5%)	4 (8%)
PERIARTERITIS				2 (4%)
GLOMERULOSCLEROSIS, NOS				2 (4%)
#KIDNEY/TUBULE	(46)	(50)	(44)	(50)
MINERALIZATION		1 (2%)		
#KIDNEY/PELVIS	(46)	(50)	(44)	(50)
INFLAMMATION, ACUTE/CHRONIC			10 (23%)	
#URINARY BLADDER	(46)	(48)	(41)	(48)
INFLAMMATION, NOS	4 (9%)			
HYPERPLASIA, EPITHELIAL	10 (22%)	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(42)	(38)	(34)
HYPERPLASIA, FOCAL	6 (14%)		1 (3%)	
#ADRENAL/CAPSULE	(45)	(48)	(41)	(49)
HYPERPLASIA, NOS		5 (10%)		
#ADRENAL CORTEX	(45)	(48)	(41)	(49)
NODULE	3 (7%)	1 (2%)	2 (5%)	
NECROSIS, NOS				1 (2%)

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS		1 (2%)	2 (5%)	
HYPERPLASIA, DIFFUSE			1 (2%)	
#THYROID	(43)	(44)	(42)	(45)
FOLLICULAR CYST, NOS	1 (2%)			
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL		1 (2%)		
PERIARTERITIS				1 (2%)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, PAPILLARY		2 (5%)	7 (17%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL			3 (7%)	1 (2%)
#THYROID FOLLICLE	(43)	(44)	(42)	(45)
DEGENERATION, NOS				44 (98%)
HYPERTROPHY, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(50)	(45)	(50)
GALACTOCELE	1 (2%)			
HYPERPLASIA, NOS	4 (8%)	1 (2%)		
#UTERUS	(45)	(47)	(41)	(46)
HYDROMETRA	1 (2%)	13 (28%)	2 (5%)	9 (20%)
PYOMETRA			1 (2%)	
ABSCESS, NOS	3 (7%)		2 (5%)	
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS	1 (2%)			
METAPLASIA, SQUAMOUS			2 (5%)	
#UTERUS/ENDOMETRIUM	(45)	(47)	(41)	(46)
HEMORRHAGIC CYST				1 (2%)
INFLAMMATION, NOS	10 (22%)	8 (17%)		
INFLAMMATION, SUPPURATIVE	4 (9%)			
INFLAMMATION, ACUTE			2 (5%)	2 (4%)
ABSCESS, NOS			2 (5%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
HYPERPLASIA, NOS	4 (9%)	8 (17%)	1 (2%)	1 (2%)
HYPERPLASIA, PAPILLARY			1 (2%)	
HYPERPLASIA, CYSTIC	18 (40%)	6 (13%)	29 (71%)	21 (46%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, STROMAL				2 (4%)

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
METAPLASIA, SQUAMOUS			1 (2%)	
#OVARY/OVIDUCT	(45)	(47)	(41)	(46)
INFLAMMATION, NOS	5 (11%)	4 (9%)		
INFLAMMATION, SUPPURATIVE			3 (7%)	1 (2%)
ABSCESS, NOS		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
#OVARY	(45)	(48)	(40)	(43)
CYST, NOS	3 (7%)	10 (21%)	6 (15%)	2 (5%)
INFLAMMATION, NOS	4 (9%)	4 (8%)	1 (3%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, SUPPURATIVE	10 (22%)		2 (5%)	
ABSCESS, NOS	4 (9%)			
INFLAMMATION, CHRONIC			6 (15%)	
SCLEROSIS				1 (2%)
PERIARTERITIS		1 (2%)		
DEGENERATION, CYSTIC	1 (2%)	3 (6%)		
NECROSIS, COAGULATIVE				1 (2%)
ATROPHY, NOS			1 (3%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(44)	(48)	(41)	(49)
INFLAMMATION, ACUTE/CHRONIC				2 (4%)
PERIARTERITIS				1 (2%)
PERIVASCULITIS				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(48)	(50)	(45)	(50)
RESORPTION	3 (6%)			
BODY CAVITIES				
*ABDOMINAL CAVITY	(48)	(50)	(45)	(50)
STEATITIS			1 (2%)	

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

TABLE D2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 06-0037	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0048	HIGH DOSE 06-0108
NECROSIS, FAT				2 (4%)
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT	1			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	3	1	
ANIMAL MISSING/NO NECROPSY			1	
AUTO/NECROPSY/HISTO PERF	2	1		
AUTO/NECROPSY/NO HISTO	1		1	
AUTOLYSIS/NO NECROPSY	2		4	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
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