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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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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 3-AMINO-4-ETHOXYACETANILIDE
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 3-amino-4-ethoxyacetanilide 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 3-amino-4-ethoxyacetanilide was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3).

Histopathologic examinations were performed by Dr. D. W. Hayden (3) and Dr. D. S. Wyand (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), using methods selected for the Carcinogenesis Testing 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

this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6), senior biologist Ms. P. Walker (6), biochemist Mr. S. C. Drill (6), chemist, Dr. N. Zimmerman (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), 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 3-amino-4-ethoxyacetanilide for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 3-Amino-4-ethoxyacetanilide was administered in the feed, at either of two concentrations, to groups of approximately 50 male and 50 female animals of each species. The dietary concentrations used in the chronic bioassay for low and high dose rats were 0.4 and 1.5 percent, respectively. The dietary concentrations used for low and high dose mice were 0.4 and 0.8 percent, respectively. After a 78-week period of chemical administration, observation of rats continued for up to 35 weeks and observation of mice continued for up to 18 weeks. For each species, 50 animals of each sex were placed on test as controls for low dose groups and approximately 50 animals of each sex were placed on test as controls for high dose groups.

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

Among rats the only clearly compound-related lesion was hemosiderosis of the thyroid gland. No neoplastic lesions were statistically significant in dosed rats.

Among mice the incidence of follicular-cell carcinomas of the thyroid gland was significant for high dose males. An elevated incidence of thyroid hyperplasia was observed in each dosed group. Hemosiderosis of the thyroid cells were found in nearly all dosed mice, but not in any control mice.

Under the conditions of this bioassay, 3-amino-4-ethoxyacetanilide was carcinogenic in male B6C3F1 mice, causing follicular-cell carcinomas of the thyroid gland. Evidence provided by this bioassay was insufficient to establish the carcinogenicity of 3-amino-4-ethoxyacetanilide in female mice or in Fischer 344 rats of either sex.

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I. INTRODUCTION

3-Amino-4-ethoxyacetanilide (NCI No. C01887), an azo dye intermediate closely related to the para aminophenol analgesics, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer reported among workers in the dye manufacturing industry (Anthony and Thomas, 1970; Wynder et al., 1963). Aromatic amines are one of several classes of chemicals believed to contribute to this increased cancer risk (Wynder et al., 1963). The structural similarity of 3-amino-4-ethoxyacetanilide to phenacetin, which may be associated with renal pelvic carcinomas in humans (Juusela, 1973), was an additional factor in the selection of this compound for testing (Weisburger, 1977).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 3-amino-4-ethoxy-N-phenylacetamide.* It is also called N-(3-amino-4-ethoxyphenyl) acetamide; and 3-amino-p-acetophenetidin.

3-Amino-4-ethoxyacetanilide is used as a chemical intermediate for the production of azo dyes for synthetic textiles, especially polyesters, but also polyamide, polyvinyl, and polyacrylonitrile fibers (Birke et al., 1974; Merian, 1965; Stanley and Farris, 1974).

Specific production figures for 3-amino-4-ethoxyacetanilide are not available; however, this compound was produced in commercial

*The CAS registry number is 17026-81-2.

quantities (in excess of 1000 pounds or $1000 in value annually) in the United States in 1975 (Stanford Research Institute, 1976). Commercial production of 3-amino-4-ethoxyacetanilide was not reported in 1976 (Stanford Research Institute, 1977). In 1974, imports of the compound through principal U.S. customs districts amounted to 11,023 pounds (U.S. International Trade Commission, 1976).

The potential for exposure to 3-amino-4-ethoxyacetanilide is greatest for workers in the dye and chemical manufacturing industries.

No information on the toxicological properties of 3-amino-4-ethoxyacetanilide is currently available; however, the para aminophenols as a class have been implicated in the production of a variety of effects on the hematopoietic system of man (Barr and Penna, 1971).

II. MATERIALS AND METHODS

A. Chemistry

Commercial-grade 3-amino-4-ethoxyacetanilide (Figure 1) was purchased from Carroll Products, Wood River Junction, Rhode Island. Chemical analysis was performed by Mason Research Institute, Worcester, Massachusetts. The melting point range of the compound was 123° to 127°C. No quantitative analyses were performed.

Throughout this report, the term 3-amino-4-ethoxyacetanilide is used to refer to the commercially available product used in this bioassay.

B. Dietary Preparation

The basal laboratory diet for both treated and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 3-Amino-4-ethoxyacetanilide was administered to the treated animals as a component of the diet.

The chemical was removed from its container and proper amounts were weighed out under an exhaust hood. The compound was hand-blended with a mortar and pestle with an aliquot of the ground feed. Once visual homogeneity was attained, the mixture was placed in a 6 kg capacity Patterson-Kelley standard model twin-shell stainless steel V-blender along with the remainder of the feed to be prepared. After 20 minutes of blending, the mixtures were placed in double plastic bags and stored in the dark at 4°C. The mixture was prepared once weekly.

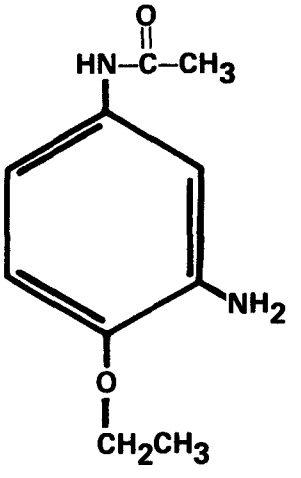


FIGURE 1
CHEMICAL STRUCTURE OF 3-AMINO-4-ETHOXYACETANILIDE

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. All rats and high dose treated and high dose control mice were received from Charles River Breeding Laboratories, Wilmington, Massachusetts. Low dose treated and low dose control mice were supplied by ARS/Sprague-Dawley, Madison, Wisconsin. Treated and control animals for both species were received in separate shipments. Upon arrival, a sample of animals was examined for parasites and other signs of disease. The remaining animals were quarantined by species for 2 weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that the 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 23° to 34°C. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. During quarantine and for the first 11 months of study, low dose (0.4 percent dietary concentration) treated and low dose control rats were housed in

wire-mesh cages (Fenco Cage Products, Boston, Massachusetts) suspended over newspapers. High dose (1.5 percent dietary concentration) treated and high dose control rats were held in wire-mesh cages for the first 13 months of study. Newspapers under cages were replaced daily and cages and racks washed weekly. For the remainder of the study, all rats were held in suspended polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) equipped with disposable nonwoven fiber filter sheets. Clean cages and bedding were provided twice weekly. SAN-I-CEL® corncob bedding (Paxton Processing Company, Paxton, Illinois) was used in polycarbonate cages for low dose rats and their controls, and for the first 7 months of polycarbonate caging for high dose rats and their controls. Aspen hardwood chip bedding (American Excelsior Company, Baltimore, Maryland) was used for the remainder of the study. Stainless steel cage racks (Fenco Cage Products) were cleaned once every 2 weeks. Disposable filters were changed at that time.

Mice were housed by sex in polycarbonate cages. During quarantine and chemical administration periods cages were fitted with perforated stainless steel lids. During the untreated observation period, wire mesh lids were used. (Cages and both types of lids were from Lab Products, Inc.) Nonwoven fiber filter bonnets were used over cage lids. High dose (0.8 percent dietary concentration) treated and control mice were housed ten per cage for the first 12 months of study and five per cage thereafter. Low dose (0.4 percent

dietary concentration) mice and their controls were housed ten per cage for the first 19 months of study and five per cage thereafter. 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 supplied for the first 10 and 9 months to the low dose treated and low dose control groups, respectively. Ab-sorb-dri® was supplied to the high dose treated and high dose control mice for the first month of study. SAN-I-CEL® was then used for 12 months, followed by a second corncob bedding, Bed-o-Cobs® (The Andersons Cob Division, Maumee, Ohio) for the next 8 months. High dose treated and high dose control mice were then supplied with Aspen bedding until the end of the study. Reusable filter bonnets and pipe racks were sanitized every 2 weeks throughout the study.

Water was available to both species from 250 ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced twice weekly, and, for rats only, refilled as needed between changes. Food and water were available ad libitum for both species.

Wayne Lab-Blox® was supplied to all animals during the quarantine and final observation periods. During the period of chemical administration, all treated animals were fed Wayne Lab-Blox® meal containing the appropriate concentration of 3-amino-4-ethoxyacetanilide. During the quarantine period, pelleted Wayne Lab-Blox® was supplied to all

animals except high dose treated and high dose control rats. During that time these rats received Wayne Lab-Blox® meal. Control animals had untreated meal available ad libitum.

The food, replenished daily, was supplied in Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) for the first 11 months of study, after which stainless steel gang-style feed hoppers (Scientific Cages, Inc., Bryan, Texas) were used to distribute meal to high dose rats and their controls. All other groups were fed from Alpine® aluminum feed cups throughout the study. Feed hoppers were changed twice weekly. Feed was replenished daily in Alpine® cups.

During the final observation period pelletted Wayne Lab-Blox® was fed to rats on the cage floors and to mice in feed hoppers incorporated into the cage lids.

Treated rats were housed in a room with other rats receiving diets containing* 1-amino-2-methylanthraquinone (82-28-0); 5-nitro-o-anisidine (99-59-2); 4-nitroanthranilic acid (619-17-0); and 5-nitroacenaphthene (602-87-9). High dose control rats were housed 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). Low dose control rats were housed in a room with other rats receiving diets containing 5-nitro-o-toluidine (99-55-8);

*CAS registry numbers are given in parentheses.

hydrazobenzene (530-50-7); 2-aminoanthraquinone (117-79-3); 3-amino-9-ethylcarbazole hydrochloride; 2,4-diaminoanisole sulfate (615-05-4); 6-nitrobenzimidazole (94-52-0); 1-nitronaphthalene (86-57-7); and APC (8003-03-0).

All treated and control mice were housed in a room with other mice receiving diets containing amitrole (61-82-5); N,N-dimethyl-p-nitrosoaniline (138-89-6); 2,5-toluenediamine sulfate (6369-59-1); 2,4-dinitrotoluene (121-14-2); 2-aminoanthraquinone (117-79-3); 3-amino-9-ethylcarbazole hydrochloride; 1-amino-2-methylanthraquinone (82-28-0); 5-nitro-o-anisidine (99-59-2); 4-nitroanthranilic acid (619-17-0); 1-nitronaphthalene (86-57-7); 5-nitroacenaphthene (602-87-9); 3-nitro-p-acetophenetide (1777-84-0); 2,4-diaminoanisole sulfate (615-05-4); and APC (8003-03-0).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 3-amino-4-ethoxyacetanilide for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. 3-Amino-4-ethoxyacetanilide was incorporated into the basal laboratory diet and supplied ad libitum to five of the six groups of each species in concentrations of 0.05, 0.09, 0.19, 0.37, and 0.74 percent. The sixth group of each species served as a control group, receiving only

the basal laboratory diet. The dosed dietary preparations were administered to rats for a period of 4 weeks, followed by 2 weeks of observation. Mice received treated feed for 4 weeks, followed by 2 weeks of observation.

The highest concentration causing no deaths, no compound-related gross abnormalities, and no mean body weight depression in excess of 15 percent relative to controls was selected as the high concentration utilized for the chronic bioassays of both species.

No deaths or compound-related abnormalities were observed in any treated or control groups.

Daily feed consumption was monitored and at the end of the observation period, all survivors were sacrificed. A dietary concentration of 0.37 percent 3-amino-4-ethoxyacetanilide produced mean body weight depressions of 11.4 and 14.7 percent in male and female rats, respectively. A dietary concentration of 0.74 percent produced mean body weight depressions of 19.4 and 2.8 percent in male and female rats, respectively.

A dietary concentration of 0.37 percent produced mean body weight depressions of 0.7 and 3.9 percent in male and female mice, respectively. A dietary concentration of 0.74 percent produced no mean body weight depression in male mice and 14.0 percent mean body weight depression in female mice.

The initial high concentration selected for administration to both species in the chronic bioassay was 0.4 percent.

F. Experimental Design

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

All rats were approximately 6 weeks old at the time the test was initiated. The initial dietary concentrations of 3-amino-4-ethoxyacetanilide were 0.4 and 0.2 percent. The rat group receiving 0.2 percent was sacrificed after 7 months and no histopathologic examinations were performed because the dose was considered, on the basis of weight depression, to be too low. At that time, a new rat group, receiving a dietary concentration of 1.5 percent, was started. Throughout this report the rats receiving a concentration of 1.5 percent are referred to as the high dose groups and those receiving a concentration of 0.4 percent are referred to as the low dose groups. Treated rats were supplied with dosed feed for a total of 78 weeks followed by an observation period of up to 35 weeks.

All mice were approximately 6 weeks old at the time the test was initiated. The initial dietary concentrations of 3-amino-4-ethoxyacetanilide were 0.4 and 0.2 percent. The mouse group receiving 0.2 percent was sacrificed after 8 months and no histopathologic examinations were performed because the dose was considered, on the basis of weight depression, to be too low. At that time, a new mouse group receiving a dietary concentration of 0.8 percent was started. Throughout this report the mice receiving a concentration of 0.8

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
3-AMINO-4-ETHOXYACETANILIDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	3-AMINO-4-ETHOXY-ACETANILIDE CONCENTRATION (PERCENT)	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	108
HIGH DOSE CONTROL	49	0	0	109
LOW DOSE	50	0.4 0	78	35
HIGH DOSE	50	1.5 0	78	28
FEMALE				
LOW DOSE CONTROL	50	0	0	109
HIGH DOSE CONTROL	50	0	0	109
LOW DOSE	48	0.4 0	78	35
HIGH DOSE	50	1.5 0	78	28

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
3-AMINO-4-ETHOXYACETANILIDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	3-AMINO-4-ETHOXY-ACETANILIDE CONCENTRATION (PERCENT)	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	93
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.4	78	
		0		16
HIGH DOSE	48	0.8	78	
		0		18
FEMALE				
LOW DOSE CONTROL	50	0	0	93
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.4	78	
		0		16
HIGH DOSE	50	0.8	78	
		0		18

percent are referred to as the high dose groups and those receiving a concentration of 0.4 percent are referred to as the low dose groups.

Treated mice were supplied with dosed feed for a total of 78 weeks followed by an observation period of up to 18 weeks.

G. Clinical and Histopathologic Examinations

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

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

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior

to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

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

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 weight depression was slightly apparent in high dose males and females (Figure 2). Subcutaneous masses were reported in 2 high dose control males and 10 high dose control females. A crusted lesion on the dorsal surface was recorded for one low dose control male. A hard cutaneous growth was observed on one low dose male. Opacity of the lens was observed in the eyes of two high dose females, and dark discoloration of one eye was observed in a third high dose female. No other clinical abnormalities were noted.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 3-amino-4-ethoxyacetanilide-dosed groups are shown in Figure 3.

For both male and female rats the Cox test did not indicate any significant positive associations between dosage and mortality. For each sex, five rats each from the high dose, the high dose control, and the low dose control groups were sacrificed in week 78. Adequate numbers of males were at risk from late-developing tumors, as 82 percent (41/50) of the high dose, 64 percent (32/50) of the low dose, 60 percent (30/50) of the high dose control, and 66 percent (33/50) of the low dose control survived on test until the end of the study. Survival among the females was also adequate, as 74 percent (37/50) of the high dose, 67 percent (32/48) of the low dose, 74 percent

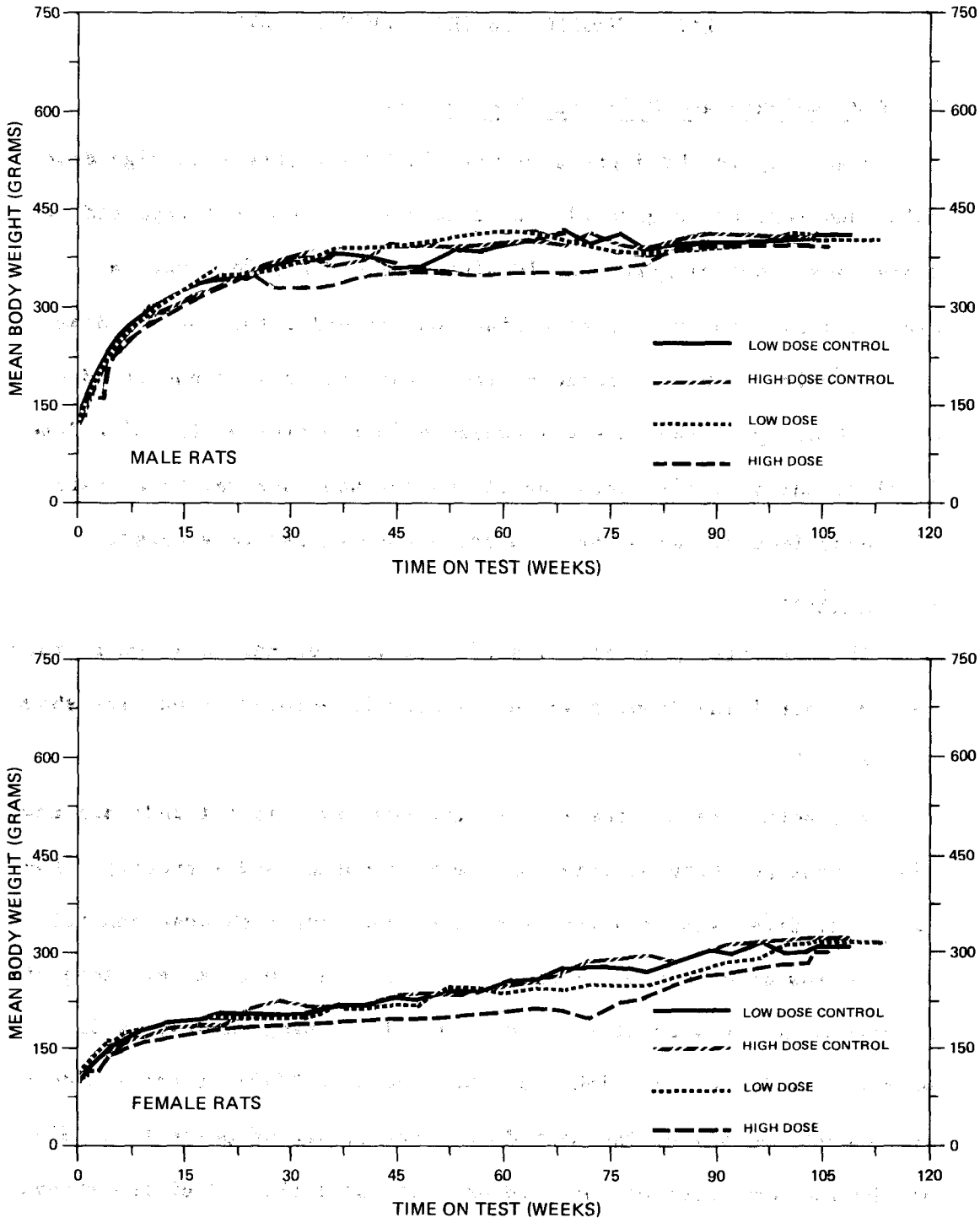


FIGURE 2
GROWTH CURVES FOR 3-AMINO-4-ETHOXYACETANILIDE CHRONIC STUDY RATS

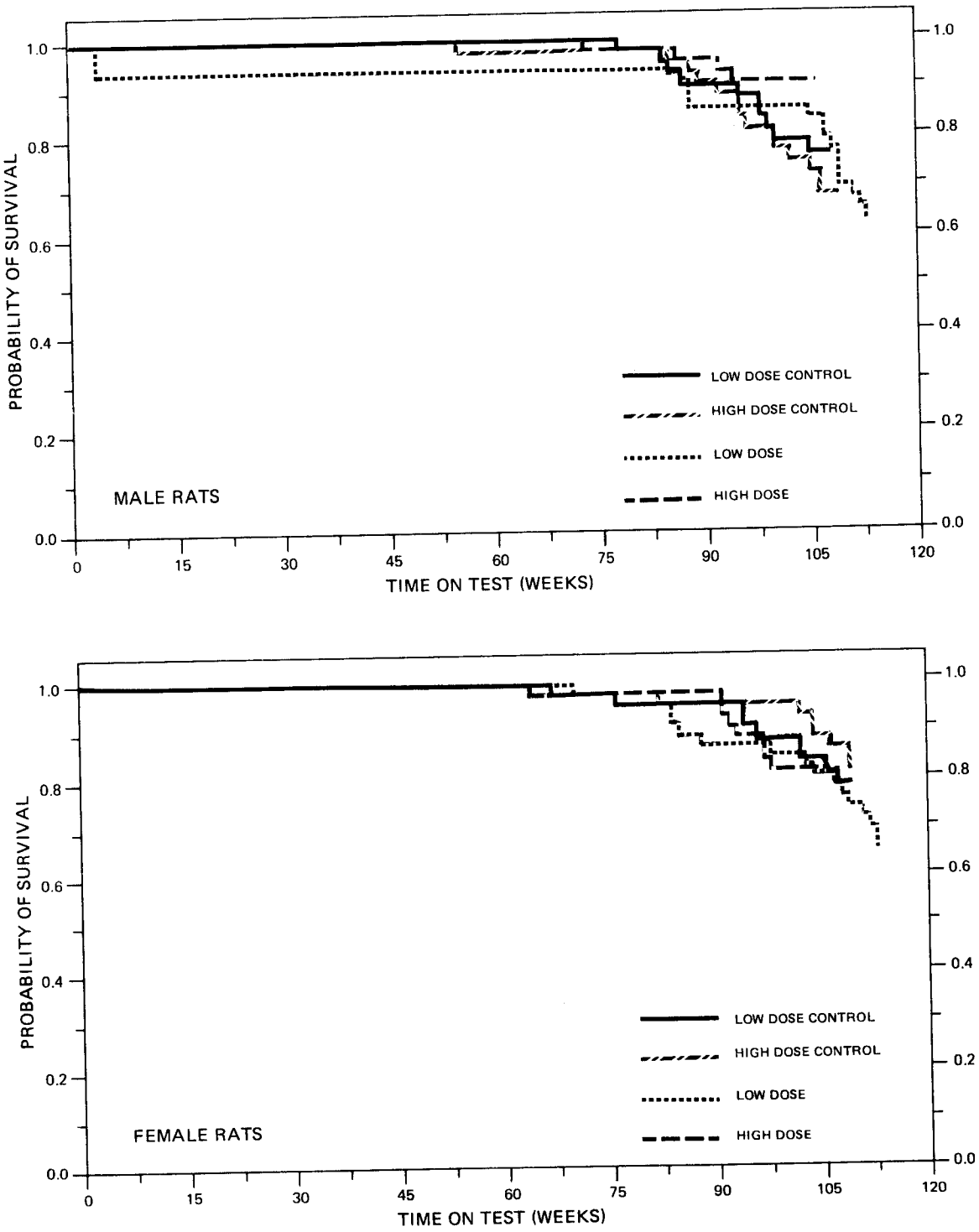


FIGURE 3
SURVIVAL COMPARISONS OF 3-AMINO-4-ETHOXYACETANILIDE CHRONIC STUDY RATS

(37/50) of the high dose control, and 68 percent (34/50) of the low dose control survived on test until the end of the study.

C. Pathology

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

The only clear-cut effects of compound feeding occurred in the thyroid gland. Proliferative and pigmentary changes observed in this organ are listed in the following table:

	Low Dose Control	Low Dose	High Dose Control	High Dose
Males				
Thyroid				
Number of Animals with Tissues Examined Histopathologically	(46)	(38)	(48)	(49)
Follicular-Cell Carcinoma	0	0	0	2
Follicular-Cell Adenoma	0	0	0	1
C-Cell Carcinoma	2	7	1	4
C-Cell Adenoma	2	2	0	0
C-Cell Hyperplasia	4	1	3	5
Hemosiderosis	0	0	0	48
Hyperplastic Nodule	0	1	0	0
Females				
Thyroid				
Number of Animals with Tissues Examined Histopathologically	(46)	(36)	(45)	(45)
Follicular-Cell Carcinoma	0	0	1	5
Papillary Cystadenoma NOS	0	0	0	1
C-Cell Carcinoma	3	5	1	3
C-Cell Adenoma	0	1	1	0
C-Cell Hyperplasia	4	0	1	4
Hemosiderosis	0	0	0	45

Hemosiderosis (the deposition of golden-brown, iron-positive pigment granules in and around thyroid follicular cells) was seen in both male and female rats receiving the high dose but was not observed in low dose animals or in any controls. There was no consistent pattern of increase in thyroid tumors or hyperplasias.

No other inflammatory or degenerative changes or tumors occurring in other organs were considered to be compound-related.

Based on the results of this histopathologic examination, 3-amino-4-ethoxyacetanilide had an effect on the thyroid of Fischer 344 rats, inducing a high incidence of hemosiderosis, but was not considered carcinogenic to this strain under the conditions of this experiment.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or 3-amino-4-ethoxyacetanilide-dosed groups and where such tumors were observed in at least 5 percent of the group.

Increased incidences of C-cell carcinomas of the thyroid were observed in dosed male rats. The Fisher exact test comparing the low dose group to the low dose control had a probability level of $P = 0.042$, a marginal result which was not significant under the Bonferroni criterion.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Skin and Subcutaneous Tissue: Fibroma[b]	7/47(0.15)	3/48(0.06)	8/49(0.16)	0/50(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.096	0.000
Lower Limit	---	---	0.378	0.000
Upper Limit	---	---	3.274	1.596
Weeks to First Observed Tumor	98	95	88	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/47(0.11)	6/48(0.13)	3/49(0.06)	1/50(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.576	0.160
Lower Limit	---	---	0.094	0.004
Upper Limit	---	---	2.786	1.249
Weeks to First Observed Tumor	84	92	111	106
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	5/47(0.11)	1/48(0.02)	5/43(0.12)	1/50(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.093	0.960
Lower Limit	---	---	0.269	0.012
Upper Limit	---	---	4.421	73.879
Weeks to First Observed Tumor	108	109	112	106

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS[b]	8/47(0.17)	9/38(0.24)	8/43(0.19)	3/41(0.07)
P Values[c]	---	---	N.S.	P = 0.043(N)
Relative Risk (Control)[d]	---	---	1.093	0.309
Lower Limit	---	---	0.392	0.058
Upper Limit	---	---	3.040	1.132
Weeks to First Observed Tumor	108	85	88	78
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	7/47(0.15)	8/47(0.17)	13/46(0.28)	8/50(0.16)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.898	0.940
Lower Limit	---	---	0.778	0.335
Upper Limit	---	---	5.096	2.641
Weeks to First Observed Tumor	108	106	88	106
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/46(0.00)	0/48(0.00)	0/38(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	---	---	---	106

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma[b]	2/46(0.04)	1/48(0.02)	7/38(0.18)	4/49(0.08)
P Values[c]	---	---	P = 0.042	N.S.
Relative Risk (Control)[d]	---	---	4.237	3.918
Lower Limit	---	---	0.867	0.407
Upper Limit	---	---	39.666	188.792
Weeks to First Observed Tumor	108	109	109	92
Thyroid: C-Cell Carcinoma or C-Cell Adenoma[b]	4/46(0.09)	1/48(0.02)	7/38(0.18)	4/49(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.118	3.918
Lower Limit	---	---	0.584	0.407
Upper Limit	---	---	9.133	188.792
Weeks to First Observed Tumor	108	109	109	92
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	4/45(0.09)	0/46(0.00)	2/40(0.05)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.563	Infinite
Lower Limit	---	---	0.053	0.290
Upper Limit	---	---	3.692	Infinite
Weeks to First Observed Tumor	85	---	112	106

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	44/47(0.94)	42/47(0.89)	46/46(1.00)	43/49(0.88)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.068	0.982
Lower Limit	---	---	0.973	0.850
Upper Limit	---	---	1.068	1.147
Weeks to First Observed Tumor	78	78	88	78
Body Cavities: Mesothelioma NOS or Mesothelioma, Malignant[b]	2/47(0.04)	2/48(0.04)	4/49(0.08)	1/50(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.918	0.480
Lower Limit	---	---	0.290	0.008
Upper Limit	---	---	20.421	8.916
Weeks to First Observed Tumor	95	106	88	106

[a]Treated groups received doses of 0.4 or 1.5 percent in feed.

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

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

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

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/48(0.10)	5/50(0.10)	0/47(0.00)	1/49(0.02)
P Values[c]	---	---	P = 0.030(N)	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.204
Lower Limit	---	---	0.000	0.005
Upper Limit	---	---	0.808	1.804
Weeks to First Observed Tumor	96	104	---	91
Pituitary: Adenoma NOS[b]	18/46(0.39)	17/40(0.43)	17/41(0.41)	12/39(0.31)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.060	0.724
Lower Limit	---	---	0.597	0.369
Upper Limit	---	---	1.858	1.383
Weeks to First Observed Tumor	94	78	85	97
Pituitary: Adenoma NOS or Carcinoma NOS[b]	20/46(0.43)	17/40(0.43)	17/41(0.41)	14/39(0.36)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.954	0.845
Lower Limit	---	---	0.550	0.453
Upper Limit	---	---	1.628	1.552
Weeks to First Observed Tumor	94	78	85	97

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Cortical Adenoma or Cortical Carcinoma[b]	4/47(0.09)	1/49(0.02)	11/46(0.24)	0/47(0.00)
P Values[c]	---	---	P = 0.040	N.S.
Relative Risk (Control)[d]	---	---	2.810	0.000
Lower Limit	---	---	0.906	0.000
Upper Limit	---	---	11.261	19.429
Weeks to First Observed Tumor	96	109	113	---
Thyroid: Follicular-Cell Carcinoma[b]	0/46(0.00)	1/45(0.02)	0/36(0.00)	5/45(0.11)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	---	5.000
Lower Limit	---	---	---	0.592
Upper Limit	---	---	---	230.761
Weeks to First Observed Tumor	---	109	---	106
Thyroid: C-Cell Carcinoma[b]	3/46(0.07)	1/45(0.02)	5/36(0.14)	3/45(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.130	3.000
Lower Limit	---	---	0.444	0.252
Upper Limit	---	---	12.838	153.831
Weeks to First Observed Tumor	109	109	113	106

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma or C-Cell Adenoma[b]	3/46(0.07)	2/45(0.04)	6/36(0.17)	3/45(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.556	1.500
Lower Limit	---	---	0.588	0.180
Upper Limit	---	---	14.751	17.256
Weeks to First Observed Tumor	109	109	113	106
Mammary Gland: Fibroadenoma[b]	14/48(0.29)	19/50(0.38)	8/47(0.17)	5/49(0.10)
P Values[c]	---	---	N.S.	P = 0.001(N)
Relative Risk (Control)[d]	---	---	0.584	0.269
Lower Limit	---	---	0.235	0.086
Upper Limit	---	---	1.343	0.674
Weeks to First Observed Tumor	76	106	85	97
Uterus: Endometrial Stromal Polyp[b]	15/47(0.32)	10/50(0.20)	15/44(0.34)	15/48(0.31)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.068	1.563
Lower Limit	---	---	0.555	0.732
Upper Limit	---	---	2.048	3.486
Weeks to First Observed Tumor	78	78	84	92

TABLE 4 (CONCLUDED)

[a]Treated groups received doses of 0.4 or 1.5 percent in feed.

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

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

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

For female rats the possibility of a negative association between compound administration and the incidence of mammary fibroadenomas was noted.

No other statistical tests for any site in either male or female rats were significant under the Bonferroni criterion. Based upon these statistical results there was no convincing evidence of the carcinogenicity of 3-amino-4-ethoxyacetanilide in male or female rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by 3-amino-4-ethoxyacetanilide that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

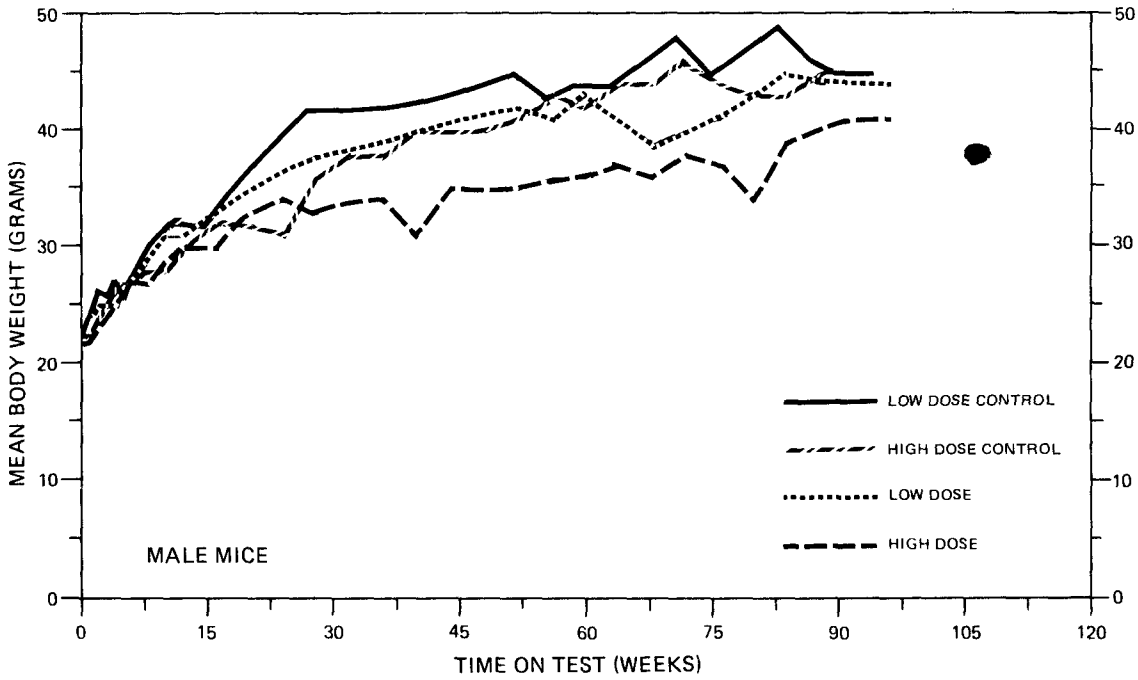
A. Body Weights and Clinical Observations

Mean body weight depression was observed in all treated groups relative to their respective controls (Figure 4). No clinical abnormalities were noted in mice of any group.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 3-amino-4-ethoxyacetanilide-dosed groups are shown in Figure 5.

For male mice the Cox test did not indicate a significantly greater mortality in either dosed group than in its respective control. For female mice no significant differences were observed. For each sex five mice from the high dose control were sacrificed in week 49 and five mice each from the high dose, the high dose control, and the low dose control were sacrificed in week 78 or 79. Adequate numbers of males were at risk from late-developing tumors as 79 percent (38/48) of the high dose, 96 percent (48/50) of the low dose, 78 percent (39/50) of the high dose control, and 78 percent (39/50) of the low dose control mice survived on test until the end of the study. For females survival was also adequate as 76 percent (38/50) of the high dose, 96 percent (48/50) of the low dose, 76 percent (38/50) of the high dose control, and 78 percent (39/50) of the low dose control mice survived on test until the end of the study.



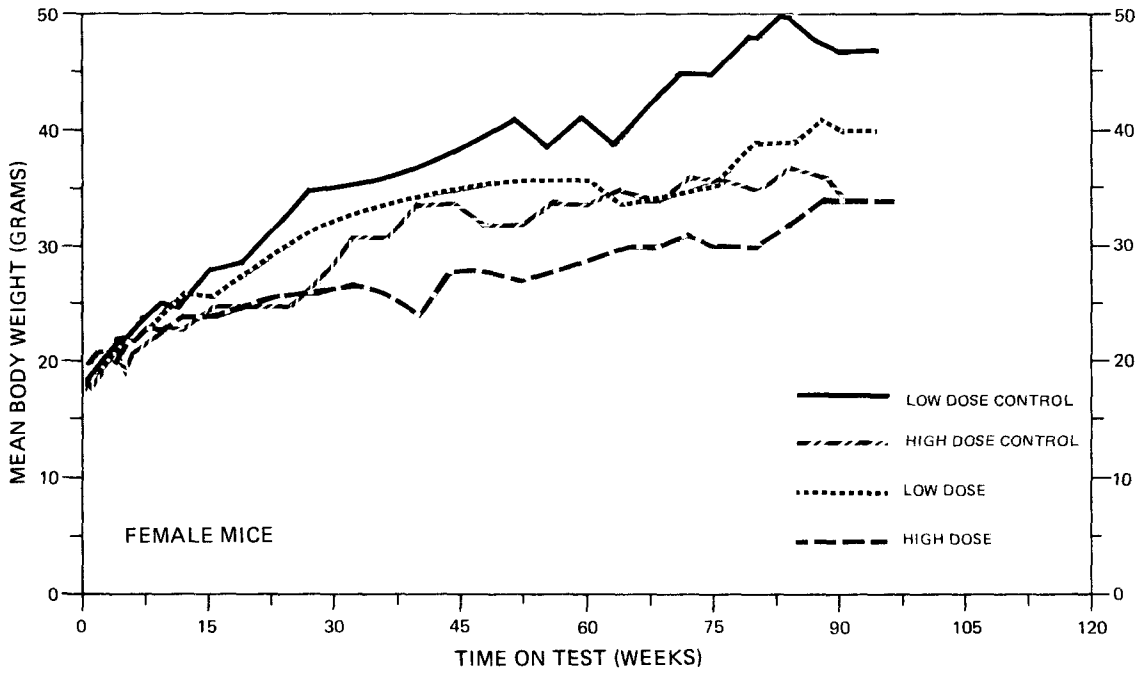
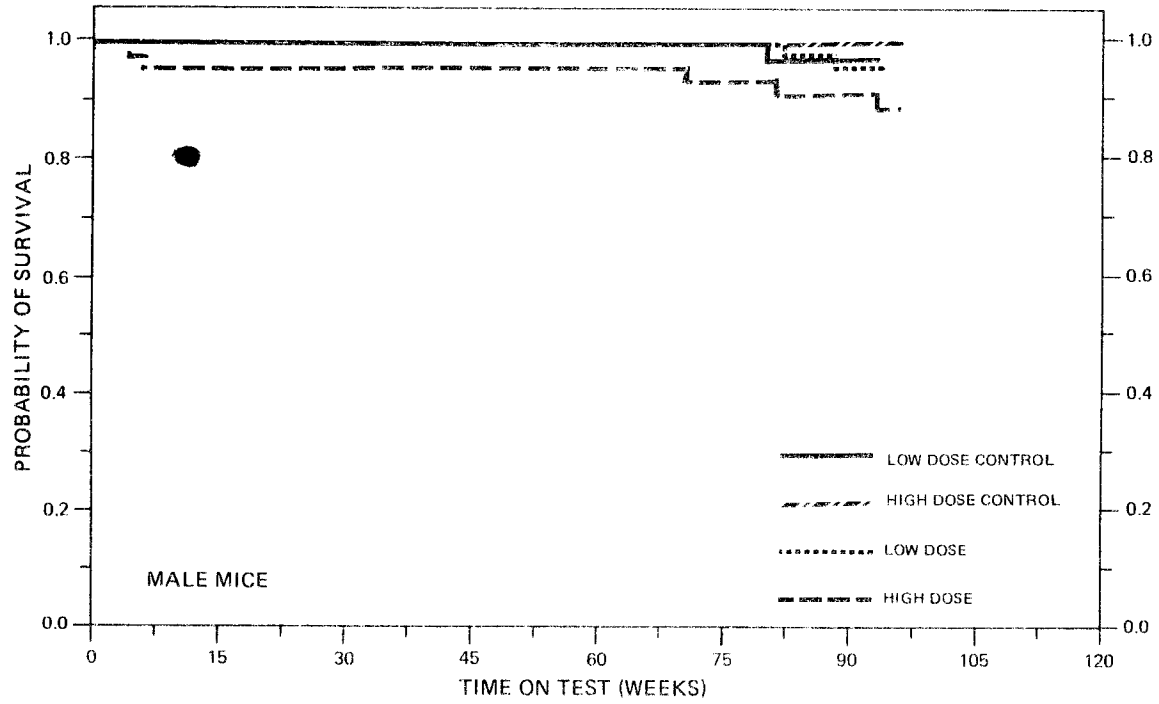


FIGURE 4
GROWTH CURVES FOR 3-AMINO-4-ETHOXYACETANILIDE CHRONIC STUDY MICE



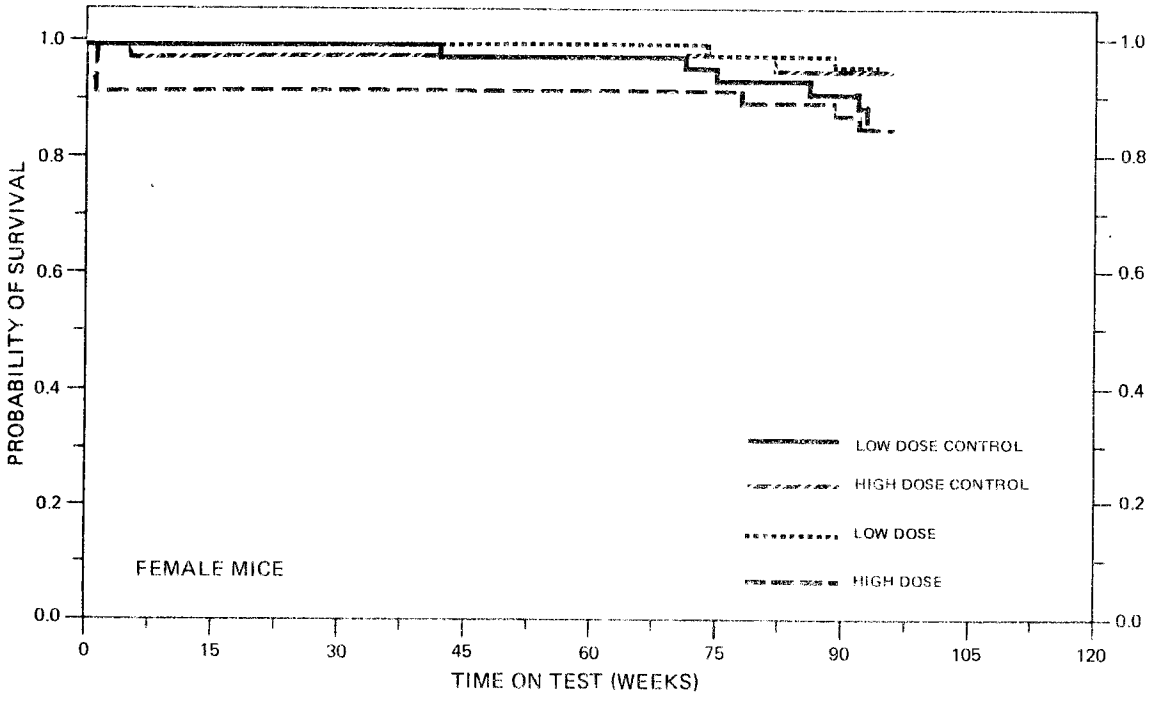


FIGURE 5
SURVIVAL COMPARISONS OF 3-AMINO-4-ETHOXYACETANILIDE CHRONIC STUDY MICE

C. Pathology

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

The only clearly compound-related changes observed occurred in the thyroid gland. Findings in this organ are summarized in the following table:

	Low Dose Control	Low Dose	High Dose Control	High Dose
Males				
Thyroid				
Number of Animals with Tissues Examined Histopathologically	(44)	(49)	(45)	(45)
Carcinoma (Adenocarcinoma NOS, or Follicular-Cell)	2	1	0	7
Adenoma (NOS or Follicular-Cell)	0	1	0	5
Hyperplasia (Adenomatous or Follicular-Cell)	0	3	0	16
Hemosiderosis	0	48	0	44
Inflammation (Lymphocytic Inflammatory Infiltration, Lipogranuloma, or Periarteritis)	0	0	0	5
Females				
Thyroid				
Number of Animals with Tissues Examined Histopathologically	(44)	(49)	(44)	(42)
Adenoma (NOS or Follicular-Cell)	0	1	0	4
Hyperplasia (Papillary, Adenomatous, or Follicular-Cell)	0	3	3	21
Hemosiderosis	0	49	0	42
Inflammation (Focal or Acute/Chronic) and Lymphocytic Inflammatory Infiltration	0	1	1	4

Thyroid carcinomas were defined as relatively large lesions composed of acinar and sometimes papillary follicles clearly differentiated from the surrounding thyroid by cytoplasmic tinctorial differences and varying degrees of nuclear pleomorphism. These lesions compressed the surrounding thyroid gland and sometimes invaded the thyroid capsule. Adenomas were smaller, better differentiated, and showed only mild nuclear atypia. Follicular-cell hyperplasia was manifested by increased cell height, increased cell density, decrease in colloid volume, and occasionally by papillary infolding of the follicle wall. Hemosiderosis consisted of the deposition of golden-brown pigment granules in and around follicular cells. In a few mice, especially at the high dose, this was accompanied by mild chronic inflammation.

Based on the results of this histopathologic examination, 3-amino-4-ethoxyacetanilide was toxic to the thyroid of B6C3F1 mice, producing hemosiderosis, and inducing proliferative follicular-cell lesions of the thyroid in mice of both sexes.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or 3-amino-4-ethoxyacetanilide-dosed groups and where such tumors were observed in at least 5 percent of the group.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	2/46(0.04)	5/49(0.10)	4/49(0.08)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.878	0.417
Lower Limit	---	---	0.284	0.041
Upper Limit	---	---	19.985	2.405
Weeks to First Observed Tumor	93	96	88	96
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	7/46(0.15)	10/49(0.20)	7/49(0.14)	3/47(0.06)
P Values[c]	---	---	N.S.	P = 0.042(N)
Relative Risk (Control)[d]	---	---	0.939	0.313
Lower Limit	---	---	0.305	0.059
Upper Limit	---	---	2.897	1.126
Weeks to First Observed Tumor	79	96	88	96
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/46(0.04)	5/49(0.10)	2/49(0.04)	3/47(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.939	0.626
Lower Limit	---	---	0.071	0.102
Upper Limit	---	---	12.495	3.025
Weeks to First Observed Tumor	93	96	93	96

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	12/46(0.26)	6/48(0.13)	13/49(0.27)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.017	0.340
Lower Limit	---	---	0.480	0.035
Upper Limit	---	---	2.190	1.790
Weeks to First Observed Tumor	93	78	88	96
Liver: Hepatocellular Carcinoma, Hepatocellular Adenoma, or Adenoma NOS[b]	12/46(0.26)	8/48(0.17)	19/49(0.39)	3/47(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.327	0.245
Lower Limit	---	---	1.088	0.047
Upper Limit	---	---	5.498	0.835
Weeks to First Observed Tumor	93	78	88	96
Thyroid: Follicular-Cell Carcinoma[b]	0/44(0.00)	0/45(0.00)	0/49(0.00)	7/45(0.16)
P Values[c]	---	---	N.S.	P = 0.006
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	1.949
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	78

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma or Adenocarcinoma NOS[b]	2/44(0.05)	0/45(0.00)	1/49(0.02)	7/45(0.16)
P Values[c]	---	---	N.S.	P = 0.006
Relative Risk (Control)[d]	---	---	0.449	Infinite
Lower Limit	---	---	0.008	1.949
Upper Limit	---	---	8.330	Infinite
Weeks to First Observed Tumor	93	---	93	78
Thyroid: Follicular-Cell Adenoma, Follicular-Cell Carcinoma, Adenocarcinoma NOS, or Adenoma NOS[b]	2/44(0.05)	0/45(0.00)	2/49(0.04)	12/45(0.27)
P Values[c]	---	---	N.S.	P = 0.004
Relative Risk (Control)[d]	---	---	0.898	Infinite
Lower Limit	---	---	0.068	3.683
Upper Limit	---	---	11.948	Infinite
Weeks to First Observed Tumor	93	---	93	78

[a]Treated groups received doses of 0.4 or 0.8 percent in feed.

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

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

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

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/46(0.02)	1/50(0.02)	4/49(0.08)	3/47(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	3.755	3.191
Lower Limit	---	---	0.391	0.267
Upper Limit	---	---	180.933	163.837
Weeks to First Observed Tumor	93	78	94	96
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	1/46(0.02)	3/50(0.06)	6/49(0.12)	3/47(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	5.633	1.064
Lower Limit	---	---	0.723	0.149
Upper Limit	---	---	253.190	7.571
Weeks to First Observed Tumor	93	78	94	96
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/47(0.11)	2/50(0.04)	7/50(0.14)	8/50(0.16)
P Values[c]	---	---	N.S.	P = 0.046
Relative Risk (Control)[d]	---	---	1.316	4.000
Lower Limit	---	---	0.387	0.851
Upper Limit	---	---	4.915	37.147
Weeks to First Observed Tumor	79	96	74	78

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	4/46(0.09)	1/50(0.02)	4/49(0.08)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.939	2.128
Lower Limit	---	---	0.185	0.105
Upper Limit	---	---	4.761	122.810
Weeks to First Observed Tumor	93	96	94	96
Pituitary: Adenoma NOS, Chromophobe Adenoma or Carcinoma NOS[b]	4/37(0.11)	3/42(0.07)	14/43(0.33)	3/39(0.08)
P Values[c]	---	---	P = 0.018	N.S.
Relative Risk (Control)[d]	---	---	3.012	1.077
Lower Limit	---	---	1.055	0.153
Upper Limit	---	---	11.502	7.585
Weeks to First Observed Tumor	79	96	94	96
Thyroid: Adenoma NOS or Follicular-Cell Adenoma[b]	0/44(0.00)	0/44(0.00)	1/49(0.02)	4/42(0.10)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.048	0.976
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	94	89

TABLE 6 (CONCLUDED)

[a]Treated groups received doses of 0.4 or 0.8 percent in feed.

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

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

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

For males numerous thyroid follicular-cell neoplasms were observed in the high dose group. The Fisher exact test indicated a significantly (P = 0.006) higher incidence of follicular-cell carcinomas of the thyroid in the high dose group than in the high dose control group. In historical data collected by this laboratory for the NCI Carcinogenesis Testing Program on untreated male B6C3F1 mice 5/350 (1 percent) had a follicular-cell neoplasm, an adenoma NOS, or an adenocarcinoma NOS of the thyroid--compared to the 2/44 (5 percent), 0/45, 2/49 (4 percent), and 12/45 (27 percent) observed in the low dose control, high dose control, low dose, and high dose group, respectively. Based upon these results the administration of 3-amino-4-ethoxyacetanilide was associated with the increased incidence of follicular-cell carcinomas of the thyroid in male mice. For females follicular-cell hyperplasia occurred in the high dose group but there was no increase in follicular tumors.

In the pituitary the Fisher exact test indicated the low dose female group had a significantly (P = 0.018) greater combined incidence of adenomas NOS, chromophobe adenomas NOS, or carcinomas NOS of the pituitary than did the low dose control group. The comparison of the high dose group to the high dose control group, however, was not significant.

No other statistical tests for either sex were significant under the Bonferroni criterion.

V. DISCUSSION

In both species adequate numbers of animals in all groups survived long enough to be at risk from late-developing tumors. Feeding of 3-amino-4-ethoxyacetanilide did not affect growth of rats or mice at the lower dose levels used in this bioassay but did slightly depress mean group body weights at the higher dose levels. Except for this slight growth depression, clinical signs indicative of toxicity were not generally observed during the bioassay.

Histopathologic examination of rats and mice indicated that the thyroid gland was the primary target organ for 3-amino-4-ethoxyacetanilide toxicity in both species. Among rats, the only clearly compound-related lesion was hemosiderosis of the thyroid gland which occurred in 48/49 (98 percent) high dose male rats and 45/45 (100 percent) high dose female rats but was not observed in other groups. Neoplastic lesions of the thyroid occurred at increased incidences in each dosed group of rats, but these increased incidences were not statistically significant.

For mice, as well as rats, the only clearly compound-related lesions occurred in the thyroid gland. The incidence of follicular-cell carcinomas of the thyroid was significant among the high dose male mice. An elevated incidence of thyroid hyperplasia was observed in each dosed group. Hemosiderosis of the thyroid gland was found in nearly every dosed mouse but not in any control mice.

Under the conditions of this bioassay, 3-amino-4-ethoxyacetanilide was carcinogenic in male B6C3F1 mice, causing follicular-cell carcinomas of the thyroid gland. Results of this bioassay do not provide sufficient evidence to establish the carcinogenicity of the compound in female mice or in Fischer 344 rats of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
ANIMALS INITIALLY IN STUDY	@50	50	50	50
ANIMALS MISSING		2		
ANIMALS NECROPSIED	48	47	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	47	46	50
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(47)	(49)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)	
KERATOACANTHOMA			1 (2%)	
SARCOMA, NOS			1 (2%)	
FIBROMA			8 (16%)	
LIPOMA			1 (2%)	
LEIOMYOSARCOMA		1 (2%)		
*SUBCUT TISSUE	(48)	(47)	(49)	(50)
SQUAMOUS CELL PAPILLOMA				1 (2%)
BASAL-CELL CARCINOMA		1 (2%)		
SARCOMA, NOS	1 (2%)			
FIBROMA	3 (6%)	7 (15%)		
FIBROSARCOMA	1 (2%)			1 (2%)
LIPOMA				2 (4%)
RESPIRATORY SYSTEM				
#LUNG	(48)	(47)	(46)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)			
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(47)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)		
LEUKEMIA,NOS	1 (2%)	1 (2%)		
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
MYELOMONOCYTIC LEUKEMIA	4 (8%)	1 (2%)	1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA			2 (4%)	

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

@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT ONE ANIMAL WAS FOUND TO BE A FEMALE IN A MALE GROUP.

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
#SPLEEN	(48)	(47)	(44)	(50)
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)		
#MEDIASTINAL L.NODE	(44)	(42)	(42)	(42)
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*CRAL CAVITY	(48)	(47)	(49)	(50)
FIBROSARCOMA		1 (2%)		
#SALIVARY GLAND	(47)	(46)	(42)	(48)
ADENOCARCINOMA, NOS	1 (2%)			
SARCOMA, NOS	1 (2%)			
#LIVER	(48)	(47)	(43)	(50)
NEOPLASTIC NODULE		5 (11%)	3 (7%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)		2 (5%)	
#PANCREAS	(46)	(45)	(40)	(47)
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)		
#STOMACH	(48)	(47)	(45)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)		
#ILEUM	(46)	(47)	(45)	(49)
SARCOMA, NOS	1 (2%)			
#COLON	(46)	(46)	(43)	(46)
MUCINOUS ADENOCARCINOMA		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(48)	(47)	(46)	(50)
LIPOMA		1 (2%)		

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

TABLE A1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
ENDOCRINE SYSTEM				
#PITUITARY	(38)	(47)	(43)	(41)
CARCINOMA,NOS				1 (2%)
ADENOMA, NOS	9 (24%)	8 (17%)	8 (19%)	3 (7%)
#ADRENAL	(47)	(47)	(46)	(50)
CORTICAL ADENOMA			1 (2%)	
PHEOCHROMOCYTOMA	7 (15%)	7 (15%)	13 (28%)	7 (14%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)			1 (2%)
GANGLIONEUROMA			1 (2%)	
NEUROBLASTOMA			1 (2%)	
#THYROID	(48)	(46)	(38)	(49)
FOLLICULAR-CELL ADENOMA				1 (2%)
FOLLICULAR-CELL CARCINOMA				2 (4%)
C-CELL ADENOMA		2 (4%)	2 (5%)	
C-CELL CARCINOMA	1 (2%)	2 (4%)	7 (18%)	4 (8%)
#PARATHYROID	(28)	(24)	(12)	(16)
ADENOMA, NOS	1 (4%)	1 (4%)	1 (8%)	
#PANCREATIC ISLETS	(46)	(45)	(40)	(47)
ISLET-CELL ADENOMA		3 (7%)	1 (3%)	2 (4%)
ISLET-CELL CARCINOMA		1 (2%)	1 (3%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(47)	(49)	(50)
ADENOCARCINOMA, NOS				1 (2%)
FIBROADENOMA			1 (2%)	
*PREPUTIAL GLAND	(48)	(47)	(49)	(50)
ADENOMA, NOS		1 (2%)		
*SEMINAL VESICLE	(48)	(47)	(49)	(50)
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)		
#TESTIS	(47)	(47)	(46)	(49)
INTERSTITIAL-CELL TUMOR	42 (89%)	44 (94%)	46 (100%)	43 (88%)
NERVOUS SYSTEM				
#BRAIN	(48)	(45)	(45)	(49)
GLIOMA, NOS	1 (2%)			

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

TABLE A1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
SPECIAL SENSE ORGANS				
*EAR CANAL	(48)	(47)	(49)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*SKULL	(48)	(47)	(49)	(50)
OSTEOMA				1 (2%)
*STERNUM	(48)	(47)	(49)	(50)
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)		
*MUSCLE OF LEG	(48)	(47)	(49)	(50)
RHABDOMYOSARCOMA				1 (2%)
BODY CAVITIES				
*BODY CAVITIES	(48)	(47)	(49)	(50)
MESOTHELIOMA, NOS			1 (2%)	1 (2%)
MESOTHELIOMA, MALIGNANT	2 (4%)	2 (4%)	3 (6%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	2	10	2
MORIBUND SACRIFICE	8	8	8	2
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	30	33	32	41
ANIMAL MISSING		2		
ANIMAL DELETED(WRONG SEX)	1			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	44	47	46	46
TOTAL PRIMARY TUMORS	80	96	108	74
TOTAL ANIMALS WITH BENIGN TUMORS	43	47	46	45
TOTAL BENIGN TUMORS	62	76	86	60
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	11	16	11
TOTAL MALIGNANT TUMORS	18	15	18	12
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		
TOTAL SECONDARY TUMORS	1	6		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		5	4	2
TOTAL UNCERTAIN TUMORS		5	4	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
ANIMALS INITIALLY IN STUDY	50	50	@50	50
ANIMALS MISSING		2		
ANIMALS NECROPSIED	50	48	47	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	46	49
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(48)	(47)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
BASAL-CELL CARCINOMA	1 (2%)			
FIBROMA			2 (4%)	
FIBROADENOMA			1 (2%)	
*SUBCUT TISSUE	(50)	(48)	(47)	(49)
FIBROMA	1 (2%)			
FIBROSARCOMA	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG	(50)	(47)	(46)	(48)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(48)	(47)	(49)
MALIGNANT LYMPHOMA, NOS		2 (4%)		
UNDIFFERENTIATED LEUKEMIA	1 (2%)			
MYELOMONOCYTIC LEUKEMIA	3 (6%)	3 (6%)		
#SPLEEN	(48)	(47)	(44)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)			
#CERVICAL LYMPH NODE	(47)	(40)	(40)	(41)
C-CELL CARCINOMA, METASTATIC				1 (2%)
#LUMBAR LYMPH NODE	(47)	(40)	(40)	(41)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)

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

@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT TWO ANIMALS WERE FOUND TO BE MALES IN A FEMALE GROUP.

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
#THYMUS	(34)	(39)	(21)	(28)
THYMOMA		1 (3%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(50)	(47)	(46)	(48)
NEOPLASTIC NODULE			5 (11%)	2 (4%)
#ILEUM	(48)	(46)	(45)	(46)
LEIOMYOSARCOMA	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(50)	(47)	(46)	(48)
TUBULAR-CELL ADENOMA				1 (2%)
#URINARY BLADDER	(46)	(47)	(43)	(48)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(46)	(41)	(39)
CARCINOMA,NOS		2 (4%)		2 (5%)
ADENOMA, NOS	17 (43%)	18 (39%)	17 (41%)	12 (31%)
#ADRENAL	(49)	(47)	(46)	(47)
CORTICAL ADENOMA	1 (2%)	3 (6%)	11 (24%)	
CORTICAL CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA	3 (6%)	1 (2%)	1 (2%)	3 (6%)
#ADRENAL MEDULLA	(49)	(47)	(46)	(47)
GANGLIONEUROMA	1 (2%)			
#THYROID	(45)	(46)	(36)	(45)
FOLLICULAR-CELL CARCINOMA	1 (2%)			5 (11%)
C-CELL ADENOMA	1 (2%)		1 (3%)	

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

TABLE A2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
C-CELL CARCINOMA	1 (2%)	3 (7%)	5 (14%)	3 (7%)
PAPILLARY CYSTADENOMA, NOS				1 (2%)
#PANCREATIC ISLETS	(48)	(46)	(40)	(47)
ISLET-CELL ADENOMA	2 (4%)		1 (3%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(48)	(47)	(49)
ADENOCARCINOMA, NOS		1 (2%)		1 (2%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)		
FIBROADENOMA	19 (38%)	14 (29%)	8 (17%)	5 (10%)
*CLITORIS	(50)	(48)	(47)	(49)
ADENOMA, NOS			1 (2%)	
*CLITORAL GLAND	(50)	(48)	(47)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
ADENOMA, NOS	2 (4%)			
*VAGINA	(50)	(48)	(47)	(49)
SARCOMA, NOS		1 (2%)		
#UTERUS	(50)	(47)	(44)	(48)
ADENOCARCINOMA, NOS	1 (2%)	2 (4%)	1 (2%)	
LEIOMYOSARCOMA			1 (2%)	
ENDOMETRIAL STROMAL POLYP	10 (20%)	15 (32%)	15 (34%)	15 (31%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		1 (2%)	
#OVARY	(49)	(46)	(46)	(47)
GRANULOSA-CELL TUMOR	1 (2%)			
GRANULOSA-CELL CARCINOMA		1 (2%)		
SERTOLI-CELL TUMOR			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(50)	(47)	(46)	(48)
ASTROCYTOMA		1 (2%)		
#CEREBRAL CORTEX	(50)	(47)	(46)	(48)
ASTROCYTOMA			1 (2%)	
#CEREBELLUM	(50)	(47)	(46)	(48)
ASTROCYTOMA			1 (2%)	1 (2%)

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

TABLE A2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
SITE UNKNOWN				
SQUAMOUS CELL CARCINOMA	1			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	5	3	6	6
MORIBUND SACRIFICE	3	6	10	2
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	37	34	32	37
ANIMAL MISSING		2		
ANIMAL DELETED(WRONG SEX)			2	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	38	42	37	30
TOTAL PRIMARY TUMORS	73	70	76	53
TOTAL ANIMALS WITH BENIGN TUMORS	35	38	35	26
TOTAL BENIGN TUMORS	59	53	61	37
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	14	9	12
TOTAL MALIGNANT TUMORS	13	17	10	14
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			2
TOTAL SECONDARY TUMORS	1			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		5	2
TOTAL UNCERTAIN TUMORS	1		5	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
ANIMALS INITIALLY IN STUDY	50	50	50	@50
ANIMAIS MISSING	1			
ANIMALS NECROPSIED	49	46	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	46	49	47
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(49)	(46)	(49)	(47)
HEMANGIOSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(49)	(46)	(49)	(47)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	5 (11%)	3 (6%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	2 (4%)	4 (8%)	2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(46)	(49)	(47)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE				2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#BONE MARROW	(48)	(46)	(49)	(47)
HEMANGIOSARCOMA				1 (2%)
#SPLEEN	(49)	(46)	(49)	(47)
HEMANGIOSARCOMA	1 (2%)			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#LYMPH NODE	(42)	(34)	(38)	(42)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#LIVER	(48)	(46)	(49)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
NONE				

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

@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT TWO ANIMALS WERE FOUND TO BE FEMALES IN A MALE GROUP.
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
DIGESTIVE SYSTEM				
#LIVER	(48)	(46)	(49)	(47)
ADENOMA, NOS			6 (12%)	1 (2%)
HEPATOCELLULAR ADENOMA	2 (4%)			
HEPATOCELLULAR CARCINOMA	6 (13%)	12 (26%)	13 (27%)	2 (4%)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA, UNC PRIM OR MET	1 (2%)			
#GASTRIC MUCOSA	(48)	(45)	(48)	(45)
ADENOCARCINOMA, NOS				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(39)	(43)	(38)
ADENOMA, NOS		1 (3%)	1 (2%)	
#ADRENAL	(44)	(44)	(48)	(42)
CORTICAL ADENOMA			1 (2%)	
PHEOCHROMOCYTOMA	1 (2%)			
#THYROID	(45)	(44)	(49)	(45)
ADENOMA, NOS			1 (2%)	
ADENOCARCINOMA, NOS		2 (5%)	1 (2%)	
FOLLICULAR-CELL ADENOMA				5 (11%)
FOLLICULAR-CELL CARCINOMA				7 (16%)
REPRODUCTIVE SYSTEM				
#TESTIS	(48)	(46)	(49)	(47)
SEMINOMA/DYSGERMINOMA		1 (2%)		
NERVOUS SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(49)	(46)	(49)	(47)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(49)	(46)	(49)	(47)
MESOTHELIOMA, NOS			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@		1	2	5
MORIBUND SACRIFICE				
SCHEDULED SACRIFICE	10	5		5
ACCIDENTALLY KILLED		3		
TERMINAL SACRIFICE	39	41	48	38
ANIMAL MISSING	1			
ANIMAL DELETED(WRONG SEX)				2

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	19	28	19
TOTAL PRIMARY TUMORS	26	26	35	25
TOTAL ANIMALS WITH BENIGN TUMORS	8	6	13	7
TOTAL BENIGN TUMORS	8	7	14	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	16	17	15
TOTAL MALIGNANT TUMORS	17	19	20	18
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		
TOTAL SECONDARY TUMORS	1	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	
TOTAL UNCERTAIN TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC	1			
TOTAL UNCERTAIN TUMORS	1			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	47	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	47	50	47
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(47)	(50)	(50)
FIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(46)	(49)	(47)
CARCINOMA, NOS, METASTATIC		1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	4 (8%)	3 (6%)
SARCOMA, NOS, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(47)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE				4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	3 (6%)	
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
LYMPHOCYTIC LEUKEMIA				1 (2%)
#SPLEEN	(49)	(45)	(50)	(47)
HEMANGIOSARCOMA		1 (2%)		
MALIGNANT LYMPHOMA, NOS			1 (2%)	
#MESENTERIC L. NODE	(44)	(27)	(41)	(40)
HEMANGIOMA				1 (3%)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#LIVER	(50)	(46)	(49)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
#PEYERS PATCH	(48)	(45)	(49)	(47)
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (2%)
#THYMUS	(21)	(21)	(34)	(32)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (3%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(50)	(46)	(49)	(47)
CARCINOMA, NOS, METASTATIC		1 (2%)		
ADENOMA, NOS			1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)	4 (9%)	4 (8%)	2 (4%)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA				1 (2%)
#STOMACH	(49)	(45)	(46)	(46)
SQUAMOUS CELL PAPILLOMA			1 (2%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(50)	(45)	(49)	(47)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(37)	(43)	(39)
CARCINOMA,NOS			1 (2%)	
ADENOMA, NOS	1 (2%)	3 (8%)	13 (30%)	3 (8%)
CHROMOPHOBE ADENOMA	2 (5%)	1 (3%)		
#ADRENAL	(48)	(44)	(49)	(47)
CORTICAL ADENOMA			1 (2%)	
#THYROID	(44)	(44)	(49)	(42)
ADENOMA, NOS			1 (2%)	
FOLLICULAR-CELL ADENOMA				4 (10%)

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
FOLLICULAR-CELL CARCINOMA				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(47)	(50)	(50)
FIBROADENOMA		1 (2%)		
#UTERUS	(47)	(43)	(49)	(43)
ENDOMETRIAL STROMAL POLYP		1 (2%)		1 (2%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)	
#UTERUS/ENDOMETRIUM	(47)	(43)	(49)	(43)
CARCINOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS			1 (2%)	
#OVARY/OVIDUCT	(47)	(43)	(49)	(43)
PAPILLARY ADENOMA	1 (2%)	1 (2%)		
INTRADUCTAL PAPILLOMA		1 (2%)		
#OVARY	(48)	(44)	(48)	(45)
PAPILLARY ADENOMA			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(47)	(50)	(50)
PAPILLARY ADENOMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(47)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)		
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	2	5	2	6
MORIBUND SACRIFICE		1		1
SCHEDULED SACRIFICE	10	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	38	39	48	38
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	17	31	21
TOTAL PRIMARY TUMORS	11	21	41	26
TOTAL ANIMALS WITH BENIGN TUMORS	7	7	18	11
TOTAL BENIGN TUMORS	7	8	21	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	11	19	14
TOTAL MALIGNANT TUMORS	4	13	20	15
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1	
TOTAL SECONDARY TUMORS		2	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
ANIMALS INITIALLY IN STUDY	@50	50	50	50
ANIMALS MISSING		2		
ANIMALS NECROPSIED	48	47	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	47	46	50
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(47)	(49)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	2 (4%)	
INFLAMMATION, NECROTIZING		1 (2%)		
INFLAMMATION, ACUTE FOCAL		1 (2%)		
*SUBCUT TISSUE	(48)	(47)	(49)	(50)
ABSCESS, NOS				1 (2%)
INFLAMMATION, GRANULOMATOUS				1 (2%)
FIBROSIS				1 (2%)
METAPLASIA, OSSEOUS	1 (2%)			
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(46)	(45)	(49)
INFLAMMATION, NOS	2 (4%)			
INFLAMMATION, CHRONIC				14 (29%)
#LUNG/BRONCHUS	(48)	(47)	(46)	(50)
BRONCHIECTASIS	1 (2%)		2 (4%)	
INFLAMMATION, NOS	7 (15%)			
ABSCESS, NOS		1 (2%)		
#LUNG	(48)	(47)	(46)	(50)
INFLAMMATION, INTERSTITIAL	4 (8%)		1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE			1 (2%)	
INFLAMMATION, NECROTIZING	1 (2%)			
PNEUMONIA, CHRONIC MURINE	1 (2%)			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM				2 (4%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(48)	(47)	(44)	(50)
FIBROSIS	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)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
INFARCT HEMORRHAGIC		1 (2%)		
HEMOSIDEROSIS	1 (2%)			2 (4%)
HYPERPLASIA, HEMATOPOIETIC	9 (19%)			
HYPERPLASIA, ERYTHROID	10 (21%)			
#LYMPH NODE	(44)	(42)	(42)	(42)
HEMORRHAGE	1 (2%)			
PLASMACYTOSIS	1 (2%)			
HYPERPLASIA, LYMPHOID	3 (7%)			
#PANCREATIC L.NODE	(44)	(42)	(42)	(42)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
#ILEOCOLIC LYMPH NODE	(44)	(42)	(42)	(42)
LYMPHADENOPATHY		1 (2%)		
CIRCULATORY SYSTEM				
#HEART	(48)	(47)	(46)	(50)
PERIARTERITIS			1 (2%)	
#MYOCARDIUM	(48)	(47)	(46)	(50)
INFLAMMATION, INTERSTITIAL	23 (48%)			
FIBROSIS	12 (25%)			
DEGENERATION, NOS		10 (21%)	11 (24%)	
*PULMONARY ARTERY	(48)	(47)	(49)	(50)
MINERALIZATION		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(47)	(46)	(42)	(48)
HYPERPLASIA, FOCAL			1 (2%)	
#LIVER	(48)	(47)	(43)	(50)
CIRRHOSIS, BILIARY			1 (2%)	
FIBROSIS SEPTAL LIVER	2 (4%)			
DEGENERATION, HYALINE		1 (2%)		
NECROSIS, FOCAL	2 (4%)	1 (2%)		
METAMORPHOSIS FATTY		3 (6%)	6 (14%)	
CYTOPLASMIC CHANGE, NOS			2 (5%)	
BASOPHILIC CYTO CHANGE			2 (5%)	1 (2%)
FOCAL CELLULAR CHANGE		12 (26%)		

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

TABLE C1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
CLEAR-CELL CHANGE				1 (2%)
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, FOCAL	15 (31%)		15 (35%)	
ANGIECTASIS	1 (2%)		1 (2%)	
#LIVER/CENTRILOBULAR	(48)	(47)	(43)	(50)
CONGESTION, PASSIVE				1 (2%)
NECROSIS, NOS	1 (2%)		1 (2%)	
NECROSIS, COAGULATIVE			1 (2%)	
*BILE DUCT	(48)	(47)	(49)	(50)
INFLAMMATION, NOS	3 (6%)			
HYPERPLASIA, NOS	43 (90%)	4 (9%)		
#PANCREAS	(46)	(45)	(40)	(47)
INFLAMMATION, NOS	17 (37%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
#PANCREATIC ACINUS	(46)	(45)	(40)	(47)
ATROPHY, NOS		3 (7%)	1 (3%)	
ATROPHY, FOCAL		1 (2%)		
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)			
#ESOPHAGUS	(45)	(46)	(46)	(47)
DYSPLASIA, NOS	1 (2%)			
#STOMACH	(48)	(47)	(45)	(50)
INFLAMMATION, NOS	1 (2%)			
ULCER, FOCAL			1 (2%)	
HYPERPLASIA, BASAL CELL	1 (2%)			
HYPERKERATOSIS	2 (4%)			
ACANTHOSIS	2 (4%)			
#GASTRIC MUCOSA	(48)	(47)	(45)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
#PEYERS PATCH	(46)	(47)	(45)	(49)
HYPERPLASIA, NOS	12 (26%)			
#ILEUM	(46)	(47)	(45)	(49)
INFLAMMATION, NOS	2 (4%)			
#COLON	(46)	(46)	(43)	(46)
PARASITISM	3 (7%)			

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

TABLE C1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
URINARY SYSTEM				
#KIDNEY	(48)	(47)	(46)	(50)
CYST, NOS		1 (2%)		
GLOMERULONEPHRITIS, NOS	47 (98%)			
INFLAMMATION, CHRONIC		39 (83%)		
FIBROSIS, DIFFUSE	6 (13%)			
NEPHROSIS, NOS			44 (96%)	30 (60%)
PIGMENTATION, NOS			1 (2%)	
#KIDNEY/TUBULE	(48)	(47)	(46)	(50)
HEMOSIDEROSIS				23 (46%)
#URINARY BLADDER	(43)	(47)	(45)	(48)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(38)	(47)	(43)	(41)
HYPERPLASIA, NOS	1 (3%)			
HYPERPLASIA, FOCAL	2 (5%)	3 (6%)	1 (2%)	
#ADRENAL	(47)	(47)	(46)	(50)
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)	
#ADRENAL CORTEX	(47)	(47)	(46)	(50)
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASTIC NODULE			1 (2%)	
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL MEDULLA	(47)	(47)	(46)	(50)
HYPERPLASIA, NODULAR	1 (2%)	3 (6%)	5 (11%)	
HYPERPLASTIC NODULE			1 (2%)	
HYPERPLASIA, FOCAL	4 (9%)		1 (2%)	3 (6%)
#THYROID	(48)	(46)	(38)	(49)
HYPERPLASTIC NODULE			1 (3%)	
HYPERPLASIA, C-CELL	3 (6%)	4 (9%)	1 (3%)	5 (10%)
#THYROID FOLLICLE	(48)	(46)	(38)	(49)
HEMOSIDEROSIS				48 (98%)
#PARATHYROID	(28)	(24)	(12)	(16)
HYPERPLASIA, NOS	1 (4%)	1 (4%)	2 (17%)	

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

TABLE C1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
#PANCREATIC ISLETS	(46)	(45)	(40)	(47)
HYPERPLASIA, NOS	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(47)	(49)	(50)
GALACTOCELE	2 (4%)	1 (2%)		
HYPERPLASIA, NOS	4 (8%)	1 (2%)	1 (2%)	
*PREPUTIAL GLAND	(48)	(47)	(49)	(50)
INFLAMMATION, ACUTE		1 (2%)		
#PROSTATE	(44)	(46)	(43)	(49)
INFLAMMATION, NOS	17 (39%)			
INFLAMMATION, ACUTE		7 (15%)	2 (5%)	1 (2%)
INFLAMMATION, ACUTE FOCAL		3 (7%)		
INFLAMMATION, ACUTE/CHRONIC		2 (4%)		
INFLAMMATION, CHRONIC			1 (2%)	
*SEMINAL VESICLE	(48)	(47)	(49)	(50)
ATROPHY, NOS			30 (61%)	
*COAGULATING GLAND	(48)	(47)	(49)	(50)
ATROPHY, NOS			8 (16%)	
#TESTIS	(47)	(47)	(46)	(49)
MINERALIZATION	1 (2%)			
DEGENERATION, NOS		1 (2%)		
ATROPHY, NOS	6 (13%)		2 (4%)	7 (14%)
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)			4 (8%)
#TESTIS/TUBULE	(47)	(47)	(46)	(49)
DEGENERATION, NOS		1 (2%)	4 (9%)	
*SCROTUM	(48)	(47)	(49)	(50)
STEATITIS				1 (2%)
NECROSIS, FAT				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				

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

TABLE C1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE CONTROL (UNTR) 01-0055	LOW DOSE 01-0057	HIGH DOSE 01-0095
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(48)	(47)	(49)	(50)
NECROSIS, FAT			1 (2%)	
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, CHRONIC				1
NECROSIS, NOS				1
CMENTUM				
NECROSIS, FAT	2			
SPECIAL MORPHOLOGY SUMMARY				
ANIMAL MISSING/NO NECROPSY		2		
AUTO/NECROPSY/NO HISTO			3	
AUTOLYSIS/NO NECROPSY	1	1	1	

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
ANIMALS INITIALLY IN STUDY	50	50	@50	50
ANIMALS MISSING		2		
ANIMALS NECROPSIED	50	48	47	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	46	49
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(48)	(47)	(49)
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
DYSPLASIA, NOS			1 (2%)	
*SUBCUT TISSUE	(50)	(48)	(47)	(49)
MINERALIZATION	1 (2%)			
ABSCESS, NOS	1 (2%)			
RESPIRATORY SYSTEM				
#TRACHEA	(49)	(47)	(41)	(46)
INFLAMMATION, NECROTIZING				1 (2%)
INFLAMMATION, CHRONIC				2 (4%)
#LUNG/BRONCHUS	(50)	(47)	(46)	(48)
BRONCHIECTASIS			1 (2%)	
INFLAMMATION, NOS	3 (6%)			
#LUNG	(50)	(47)	(46)	(48)
BRONCHOPNEUMONIA, NOS			1 (2%)	
INFLAMMATION, INTERSTITIAL	6 (12%)		1 (2%)	3 (6%)
PNEUMONIA, CHRONIC MURINE				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(46)	(45)	(46)	(46)
OSTEOSCLEROSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#SPLEEN	(48)	(47)	(44)	(47)
HEMOSIDEROSIS	12 (25%)			

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

TABLE C2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
HYPERPLASIA, HEMATOPOIETIC	25 (52%)			
HYPERPLASIA, ERYTHROID	19 (40%)			
HEMATOPOIESIS		1 (2%)	2 (5%)	
#SPLENIC CAPSULE	(48)	(47)	(44)	(47)
HEMORRHAGIC CYST	1 (2%)			
#LYMPH NODE	(47)	(40)	(40)	(41)
PLASMACYTOSIS	1 (2%)			
HYPERPLASIA, LYMPHOID	4 (9%)			
#MEDIASTINAL L.NODE	(47)	(40)	(40)	(41)
HEMOSIDEROSIS				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(50)	(47)	(45)	(48)
PERIARTERITIS			1 (2%)	
#MYOCARDIUM	(50)	(47)	(45)	(48)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, INTERSTITIAL	23 (46%)			
FIBROSIS	15 (30%)			
DEGENERATION, NOS		7 (15%)	4 (9%)	
#ENDOCARDIUM	(50)	(47)	(45)	(48)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL			1 (2%)	
*HEPATIC VEIN	(50)	(48)	(47)	(49)
PHLEBOSCLEROSIS			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(50)	(47)	(46)	(48)
DEGENERATION, NOS		1 (2%)	3 (7%)	
NECROSIS, FOCAL	2 (4%)			
METAMORPHOSIS FATTY	6 (12%)	2 (4%)	5 (11%)	1 (2%)
BASOPHILIC CYTO CHANGE			2 (4%)	3 (6%)
FOCAL CELLULAR CHANGE		25 (53%)		
HYPERPLASIA, FOCAL	38 (76%)		31 (67%)	
ANGIECTASIS			1 (2%)	
HYPERPLASIA, ERYTHROID	1 (2%)			

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

TABLE C2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
HEMATOPOIESIS	2 (4%)			
*EILE DUCT	(50)	(48)	(47)	(49)
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, NOS	32 (64%)	2 (4%)		
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(48)	(46)	(40)	(47)
INFLAMMATION, NOS	6 (13%)			
PERIARTERITIS			1 (3%)	
HYPERTROPHY, NOS			1 (3%)	
#PANCREATIC ACINUS	(48)	(46)	(40)	(47)
ATROPHY, NOS		8 (17%)		
#STOMACH	(48)	(46)	(44)	(46)
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
ACANTHOSIS	2 (4%)			
#PEYERS PATCH	(48)	(46)	(45)	(46)
HYPERPLASIA, NOS	15 (31%)			
#COLON	(46)	(45)	(44)	(45)
PARASITISM	2 (4%)			
URINARY SYSTEM				
#KIDNEY	(50)	(47)	(46)	(48)
GLOMERULONEPHRITIS, NOS	43 (86%)			
INFLAMMATION, CHRONIC		29 (62%)		
FIBROSIS, DIFFUSE	1 (2%)			
NEPHROSIS, NOS			33 (72%)	19 (40%)
POSTMORTEM CHANGE		1 (2%)		
#KIDNEY/CORTEX	(50)	(47)	(46)	(48)
CYST, NOS				1 (2%)
#KIDNEY/TUBULE	(50)	(47)	(46)	(48)
HEMOSIDEROSIS				41 (85%)
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(46)	(41)	(39)
EMBRYONAL DUCT CYST				1 (3%)

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

TABLE C2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
CYST, NOS				1 (3%)
PERIVASCULITIS	1 (3%)			
HYPERPLASIA, FOCAL	3 (8%)	1 (2%)		
#ADRENAL	(49)	(47)	(46)	(47)
METAMORPHOSIS FATTY	1 (2%)			
#ADRENAL CORTEX	(49)	(47)	(46)	(47)
CYST, NOS		1 (2%)		
DEGENERATION, NOS		3 (6%)		
METAMORPHOSIS FATTY		1 (2%)		
HYPERTROPHY, NOS			1 (2%)	
HYPERPLASIA, NODULAR		2 (4%)		
HYPERPLASTIC NODULE			1 (2%)	
HYPERPLASIA, FOCAL		3 (6%)	16 (35%)	
#ADRENAL MEDULLA	(49)	(47)	(46)	(47)
THROMBOSIS, NOS		1 (2%)		
HYPERPLASIA, NODULAR	3 (6%)			
HYPERPLASTIC NODULE				1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	1 (2%)	2 (4%)	1 (2%)
#THYROID	(45)	(46)	(36)	(45)
CYSTIC FOLLICLES	1 (2%)			1 (2%)
HYPERPLASIA, C-CELL	1 (2%)	4 (9%)		4 (9%)
#THYROID FOLLICLE	(45)	(46)	(36)	(45)
HEMOSIDEROSIS				45 (100%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(48)	(47)	(49)
CALCULUS, NOS			1 (2%)	
DILATATION/DUCTS		3 (6%)		1 (2%)
GALACTOCELE	16 (32%)	7 (15%)	3 (6%)	
HYPERPLASIA, NOS	8 (16%)	4 (8%)	1 (2%)	
*MAMMARY DUCT	(50)	(48)	(47)	(49)
FIBROSIS		2 (4%)		
*CLITORAL GLAND	(50)	(48)	(47)	(49)
INFLAMMATION, ACUTE			1 (2%)	
#UTERUS	(50)	(47)	(44)	(48)
HYDROMETRA		2 (4%)	3 (7%)	

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

TABLE C2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
HYPERPLASIA, ADENOMATOUS	1 (2%)			
#UTERUS/ENDOMETRIUM	(50)	(47)	(44)	(48)
INFLAMMATION, NOS	22 (44%)		1 (2%)	
INFLAMMATION, ACUTE		9 (19%)	5 (11%)	
INFLAMMATION, CHRONIC		1 (2%)		
HYPERPLASIA, NOS	6 (12%)			
HYPERPLASIA, CYSTIC		3 (6%)	4 (9%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, STROMAL		1 (2%)		
#OVARY/OVIDUCT	(50)	(47)	(44)	(48)
INFLAMMATION, NOS	10 (20%)			
INFLAMMATION, SUPPURATIVE	2 (4%)			
INFLAMMATION, ACUTE		3 (6%)	1 (2%)	
INFLAMMATION ACTIVE CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)		
#OVARY	(49)	(46)	(46)	(47)
CYST, NOS	8 (16%)			
INFLAMMATION, CHRONIC		1 (2%)		
#OVARY/FOLLICLE	(49)	(46)	(46)	(47)
HYPERPLASIA, NOS		1 (2%)		
NERVOUS SYSTEM				
*CHOROID PLEXUS	(50)	(48)	(47)	(49)
INFLAMMATION, FOCAL			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE	(50)	(48)	(47)	(49)
CATARACT	1 (2%)		1 (2%)	
*EYE/RETINA	(50)	(48)	(47)	(49)
ATROPHY, NOS	1 (2%)			
*EYE/CRYSTALLINE LENS	(50)	(48)	(47)	(49)
CALCIFICATION, NOS				1 (2%)
*HARDERIAN GLAND	(50)	(48)	(47)	(49)
HYPERPLASIA, NOS	1 (2%)			

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

TABLE C2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE CONTROL (UNTR) 02-0055	LOW DOSE 02-0057	HIGH DOSE 02-0095
MUSCULOSKELETAL SYSTEM				
*BONE	(50)	(48)	(47)	(49)
OSTEOSCLEROSIS		1 (2%)		
*STERNUM	(50)	(48)	(47)	(49)
OSTEOSCLEROSIS			1 (2%)	
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(48)	(47)	(49)
NECROSIS, FAT			1 (2%)	
*PERITONEUM	(50)	(48)	(47)	(49)
NECROSIS, FAT			1 (2%)	
*PLEURA	(50)	(48)	(47)	(49)
INFLAMMATION, CHRONIC		1 (2%)		
*EPICARDIUM	(50)	(48)	(47)	(49)
INFLAMMATION, CHRONIC		1 (2%)		
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, CHRONIC FOCAL				1
CMENTUM				
NECROSIS, FAT	1			
SPECIAL MORPHOLOGY SUMMARY				
ANIMAL MISSING/NO NECROPSY		2		
AUTO/NECROPSY/HISTO PERF				1
AUTO/NECROPSY/NO HISTO		1	1	
AUTOLYSIS/NO NECROPSY			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 3-AMINO-4-ETHOXYACETANILIDE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
ANIMALS INITIALLY IN STUDY	50	50	50	@50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	46	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	46	49	47
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(46)	(49)	(47)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	3 (6%)			
INFLAMMATION, NECROTIZING	1 (2%)			
GRANULOMA, PYOGENIC		1 (2%)	1 (2%)	
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(49)	(46)	(49)	(47)
INFLAMMATION, FOCAL	1 (2%)	1 (2%)		
#LUNG/BRONCHIOLE	(49)	(46)	(49)	(47)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, FOCAL	1 (2%)			
#LUNG	(49)	(46)	(49)	(47)
EMPHYSEMA, NOS		1 (2%)		
HEMORRHAGE		1 (2%)		
INFLAMMATION, INTERSTITIAL	10 (20%)	7 (15%)	2 (4%)	1 (2%)
INFLAMMATION, HEMORRHAGIC			1 (2%)	
PERIARTERITIS				1 (2%)
PERIVASCULAR CUFFING				1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM				1 (2%)
#LUNG/ALVEOLI	(49)	(46)	(49)	(47)
INFLAMMATION, NOS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(46)	(49)	(47)
MEGAKARYOCYTOSIS				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 TWO ANIMALS WERE FOUND TO BE FEMALES IN A MALE GROUP.

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
#SPLEEN	(49)	(46)	(49)	(47)
HYPERPLASIA, NOS	6 (12%)			
RETICULOCYTOSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC	5 (10%)			
HYPERPLASIA, ERYTHROID		1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		7 (14%)	1 (2%)
HEMATOPOIESIS		1 (2%)		1 (2%)
#LYMPH NODE	(42)	(34)	(38)	(42)
HEMORRHAGE		1 (3%)		
INFLAMMATION, NOS	10 (24%)			
HYPERPLASIA, NOS	1 (2%)	1 (3%)		
RETICULOCYTOSIS	2 (5%)			
HYPERPLASIA, LYMPHOID	3 (7%)			
#MANDIBULAR L. NODE	(42)	(34)	(38)	(42)
HYPERPLASIA, NOS			3 (8%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (3%)		
HYPERPLASIA, LYMPHOID			2 (5%)	
#MEDIASTINAL L.NODE	(42)	(34)	(38)	(42)
HYPERPLASIA, NOS			2 (5%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#PANCREATIC L.NODE	(42)	(34)	(38)	(42)
LYMPHANGIECTASIS			1 (3%)	
#MESENTERIC L. NODE	(42)	(34)	(38)	(42)
LYMPHANGIECTASIS			2 (5%)	
THROMBOSIS, NOS		1 (3%)		
HEMORRHAGE		1 (3%)		
HYPERPLASIA, NOS			2 (5%)	
ANGIECTASIS				8 (19%)
HYPERPLASIA, RETICULUM CELL			2 (5%)	
HYPERPLASIA, LYMPHOID				2 (5%)
#THYMUS	(28)	(21)	(35)	(30)
HYPERPLASIA, LYMPHOID			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(49)	(46)	(49)	(47)
MINERALIZATION	1 (2%)			

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
CALCIFICATION, FOCAL			1 (2%)	
#ENDOCARDIUM	(49)	(46)	(49)	(47)
INFLAMMATION PROLIFERATIVE		1 (2%)		
*CORONARY ARTERY	(49)	(46)	(49)	(47)
FIBROSIS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(37)	(49)	(46)
PERIVASCULITIS			1 (2%)	
PERIVASCULAR CUFFING		5 (14%)		
ATROPHY, FOCAL				1 (2%)
#SUBMAXILLARY GLAND	(48)	(37)	(49)	(46)
PERIVASCULITIS			1 (2%)	
#LIVER	(48)	(46)	(49)	(47)
INFLAMMATION, NECROTIZING		1 (2%)		
NECROSIS, FOCAL	9 (19%)	2 (4%)	2 (4%)	
NECROSIS, HEMORRHAGIC		1 (2%)		
METAMORPHOSIS FATTY		8 (17%)	6 (12%)	1 (2%)
HYPERTROPHY, NOS			1 (2%)	
HYPERPLASTIC NODULE	1 (2%)			
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	10 (20%)	
HYPERPLASIA, DIFFUSE			1 (2%)	
#LIVER/PERIPORTAL	(48)	(46)	(49)	(47)
INFLAMMATION, ACUTE/CHRONIC				3 (6%)
*GALLBLADDER	(49)	(46)	(49)	(47)
HYPERPLASIA, ADENOMATOUS				1 (2%)
*BILE DUCT	(49)	(46)	(49)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
#PANCREAS	(47)	(44)	(49)	(47)
DILATATION/DUCTS				1 (2%)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL		2 (5%)		
INFLAMMATION, INTERSTITIAL		1 (2%)		
LIPOGRANULOMA			1 (2%)	

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
HYPERPLASIA, FOCAL		2 (5%)		
#PANCREATIC ACINUS	(47)	(44)	(49)	(47)
ATROPHY, NOS				1 (2%)
ATROPHY, FOCAL		1 (2%)	1 (2%)	
#ESOPHAGUS	(49)	(46)	(49)	(46)
INFLAMMATION, NOS				1 (2%)
#STOMACH	(48)	(45)	(48)	(45)
INFLAMMATION, NOS		2 (4%)		
INFLAMMATION, FOCAL	2 (4%)			1 (2%)
INFLAMMATION, NECROTIZING	1 (2%)			
INFLAMMATION, ACUTE		1 (2%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)	
HYPERPLASIA, EPITHELIAL		2 (4%)		
HYPERPLASIA, FOCAL	1 (2%)			
HYPERPLASIA, ADENOMATOUS		2 (4%)		
HYPERKERATOSIS	1 (2%)			
ACANTHOSIS	1 (2%)			
METAPLASIA, NOS				1 (2%)
#GASTRIC MUCOSA	(48)	(45)	(48)	(45)
ECTOPIA			1 (2%)	
METAPLASIA, NOS				1 (2%)
#PEYERS PATCH	(49)	(46)	(49)	(46)
HYPERPLASIA, NOS	7 (14%)			
HYPERPLASIA, LYMPHOID			1 (2%)	
#COLON	(43)	(41)	(44)	(38)
PARASITISM	3 (7%)			
URINARY SYSTEM				
#KIDNEY	(49)	(46)	(49)	(47)
CALCULUS, NOS			36 (73%)	
GLOMERULONEPHRITIS, NOS	2 (4%)	2 (4%)		11 (23%)
GLOMERULONEPHRITIS, FOCAL		1 (2%)		2 (4%)
INFLAMMATION, INTERSTITIAL	16 (33%)	7 (15%)		1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
PERIARTERITIS				2 (4%)
METAMORPHOSIS FATTY			2 (4%)	
HYPERPLASIA, TUBULAR CELL			3 (6%)	

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
HYPERPLASIA, FOCAL				1 (2%)
METAPLASIA, OSSEOUS		1 (2%)		
#RENAL PAPILLA	(49)	(46)	(49)	(47)
HYPERPLASIA, NOS			1 (2%)	
#KIDNEY/TUBULE	(49)	(46)	(49)	(47)
METAMORPHOSIS FATTY			33 (67%)	
DYSPLASIA, NOS				1 (2%)
#KIDNEY/PELVIS	(49)	(46)	(49)	(47)
INFLAMMATION, ACUTE/CHRONIC		3 (7%)		
#URINARY BLADDER	(48)	(46)	(48)	(47)
HYPERPLASIA, EPITHELIAL	4 (8%)	2 (4%)		
ENDOCRINE SYSTEM				
#PITUITARY	(40)	(39)	(43)	(38)
HYPERPLASIA, FOCAL		1 (3%)		
#ADRENAL	(44)	(44)	(48)	(42)
NECROSIS, FOCAL		1 (2%)		
HYPERPLASIA, NOS	3 (7%)			
#ADRENAL/CAPSULE	(44)	(44)	(48)	(42)
HYPERPLASIA, NOS	3 (7%)			
#ADRENAL CORTEX	(44)	(44)	(48)	(42)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS		2 (5%)	6 (13%)	
HYPERPLASIA, FOCAL		14 (32%)	1 (2%)	
#THYROID	(45)	(44)	(49)	(45)
FOLLICULAR CYST, NOS				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR				2 (4%)
LIPOGRANULOMA				1 (2%)
PERIARTERITIS				2 (4%)
DEGENERATION, NOS			37 (76%)	
DEGENERATION PIGMENTARY			8 (16%)	
HYPERPIGMENTATION			3 (6%)	
HYPERPLASIA, ADENOMATOUS			3 (6%)	3 (7%)
HYPERPLASIA, FOLLICULAR-CELL				13 (29%)

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
#THYROID FOLLICLE	(45)	(44)	(49)	(45)
DEGENERATION, NOS				4 (9%)
HYPERPIGMENTATION				40 (89%)
#PARATHYROID	(24)	(17)	(16)	(27)
CYST, NOS		1 (6%)		
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(49)	(46)	(49)	(47)
ABSCESS, NOS	1 (2%)			
#PROSTATE	(49)	(46)	(49)	(45)
HYPERPLASIA, EPITHELIAL		1 (2%)		
#TESTIS	(48)	(46)	(49)	(47)
HYPERPLASIA, INTERSTITIAL CELL			2 (4%)	
#TESTIS/TUBULE	(48)	(46)	(49)	(47)
DEGENERATION, NOS		3 (7%)		1 (2%)
*EPIDIDYMIS	(49)	(46)	(49)	(47)
INFLAMMATION, NOS	1 (2%)			
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(49)	(46)	(49)	(47)
HYPOPLASIA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(49)	(46)	(49)	(47)
NECROSIS, FAT		1 (2%)		

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

TABLE D1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE CONTROL (UNTR) 05-0030	LOW DOSE 05-0057	HIGH DOSE 05-0094
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, NECROTIZING			1	
INFLAMMATION, ACUTE	1			
CMENTUM				
NECROSIS, FAT	1			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	5	2		
ANIMAL MISSING/NO NECROPSY	1			
ACCIDENTAL DEATH		3		
AUTOLYSIS/NO NECROPSY		1	1	1

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

TABLE D-2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 3-AMINO-4-ETHOXYACETANILIDE

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	47	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	47	50	47
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(47)	(50)	(50)
ABSCESS, NOS	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(50)	(46)	(49)	(47)
INFLAMMATION, FOCAL	1 (2%)			
#LUNG/BRONCHIOLE	(50)	(46)	(49)	(47)
INFLAMMATION, NOS				1 (2%)
HYPERPLASIA, NOS	1 (2%)			
#LUNG	(50)	(46)	(49)	(47)
INFLAMMATION, INTERSTITIAL	14 (28%)	2 (4%)	7 (14%)	1 (2%)
PERIVASCULITIS				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)	
#LUNG/ALVEOLI	(50)	(46)	(49)	(47)
EMPHYSEMA, NOS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(45)	(49)	(46)
HYPOPLASIA, NOS		1 (2%)		
MYELOFIBROSIS		1 (2%)		5 (11%)
MYELOSCLEROSIS			2 (4%)	
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#SPLEEN	(49)	(45)	(50)	(47)
HYPERPLASIA, NOS	9 (18%)			
LYMPHOCYTOSIS		2 (4%)		

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
HYPERPLASIA, HEMATOPOIETIC	6 (12%)			
HYPERPLASIA, RETICULUM CELL			1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)	3 (7%)	4 (8%)	4 (9%)
HEMATOPOIESIS		2 (4%)		3 (6%)
#HEMOLYMPH NODES	(49)	(45)	(50)	(47)
INFLAMMATION, NOS	2 (4%)			
HYPERPLASIA, NOS	1 (2%)			
#LYMPH NODE	(44)	(27)	(41)	(40)
INFLAMMATION, NOS	9 (20%)			
HYPERPLASIA, NOS	3 (7%)			
RETICULOCYTOSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC	1 (2%)			
HYPERPLASIA, LYMPHOID	4 (9%)			
#MANDIBULAR L. NODE	(44)	(27)	(41)	(40)
HYPERPLASIA, NOS			2 (5%)	
#MEDIASTINAL L.NODE	(44)	(27)	(41)	(40)
HYPERPLASIA, RETICULUM CELL			1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)	
#PANCREATIC L.NODE	(44)	(27)	(41)	(40)
HYPERPLASIA, RETICULUM CELL		1 (4%)		
#MESENTERIC L. NODE	(44)	(27)	(41)	(40)
LYMPHANGIECTASIS				3 (8%)
HYPERPLASIA, LYMPHOID				1 (3%)
#THYMUS	(21)	(21)	(34)	(32)
HYPERPLASIA, LYMPHOID			1 (3%)	1 (3%)
CIRCULATORY SYSTEM				
#HEART	(50)	(46)	(49)	(47)
PERIARTERITIS				1 (2%)
#HEART/ATRIUM	(50)	(46)	(49)	(47)
CALCIFICATION, FOCAL		1 (2%)		
#MYOCARDIUM	(50)	(46)	(49)	(47)
INFLAMMATION, FOCAL	1 (2%)			
#ENDOCARDIUM	(50)	(46)	(49)	(47)
INFLAMMATION, FOCAL			1 (2%)	

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(29)	(49)	(44)
PERIVASCULAR CUFFING	3 (6%)	1 (3%)		
#SUBMAXILLARY GLAND	(48)	(29)	(49)	(44)
PERIVASCULITIS			2 (4%)	
#LIVER	(50)	(46)	(49)	(47)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
PERIVASCULITIS				1 (2%)
NECROSIS, FOCAL	7 (14%)	1 (2%)		
NECROSIS, COAGULATIVE		1 (2%)		1 (2%)
CALCIFICATION, FOCAL			1 (2%)	
HYPERPLASIA, NODULAR		2 (4%)	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	
ANGIECTASIS		1 (2%)		
#LIVER/PERIPORTAL	(50)	(46)	(49)	(47)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)		
#PANCREAS	(48)	(39)	(49)	(46)
DILATATION/DUCTS				2 (4%)
INFLAMMATION, NOS	2 (4%)			
HYPOPLASIA, NOS			1 (2%)	
#PANCREATIC DUCT	(48)	(39)	(49)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (3%)		
#PANCREATIC ACINUS	(48)	(39)	(49)	(46)
HYPOPLASIA, NOS				1 (2%)
ATROPHY, NOS				1 (2%)
#STOMACH	(49)	(45)	(46)	(46)
INFLAMMATION, NOS	1 (2%)	3 (7%)		
INFLAMMATION, FOCAL	1 (2%)		1 (2%)	
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
ACANTHOSIS	2 (4%)			
#PEYERS PATCH	(48)	(45)	(49)	(47)
HYPERPLASIA, NOS	7 (15%)	1 (2%)		

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
HYPERPLASIA, LYMPHOID			1 (2%)	
#DUODENUM	(48)	(45)	(49)	(47)
ECTOPIA		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(50)	(45)	(49)	(47)
CALCULUS, NOS			3 (6%)	
GLOMERULONEPHRITIS, NOS	4 (8%)	2 (4%)		22 (47%)
GLOMERULONEPHRITIS, FOCAL	1 (2%)	1 (2%)		
INFLAMMATION, INTERSTITIAL	12 (24%)	9 (20%)		
CALCIFICATION, FOCAL			1 (2%)	
#KIDNEY/TUBULE	(50)	(45)	(49)	(47)
MINERALIZATION	1 (2%)			
#KIDNEY/PELVIS	(50)	(45)	(49)	(47)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)	
*URETER	(50)	(47)	(50)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
#URINARY BLADDER	(48)	(42)	(49)	(45)
HYPERPLASIA, EPITHELIAL	1 (2%)			
ENDOCRINE SYSTEM				
#PITUITARY	(42)	(37)	(43)	(39)
HYPERPLASIA, FOCAL			1 (2%)	1 (3%)
#ADRENAL/CAPSULE	(48)	(44)	(49)	(47)
HYPERPLASIA, NOS	5 (10%)			
#ADRENAL CORTEX	(48)	(44)	(49)	(47)
NODULE	1 (2%)	1 (2%)		
METAMORPHOSIS FATTY			1 (2%)	
HYPERPLASIA, NOS	1 (2%)	2 (5%)	12 (24%)	
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL MEDULLA	(48)	(44)	(49)	(47)
INFLAMMATION, FIBRINOUS			1 (2%)	
#THYROID	(44)	(44)	(49)	(42)
INFLAMMATION, FOCAL	1 (2%)			

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
LYMPHOCYTIC INFLAMMATORY INFILTR				4 (10%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
DEGENERATION, NOS			36 (73%)	
DEGENERATION PIGMENTARY			1 (2%)	
HYPERPIGMENTATION			12 (24%)	
HYPERPLASIA, PAPILLARY	2 (5%)		1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)	21 (50%)
#THYROID FOLLICLE	(44)	(44)	(49)	(42)
DEGENERATION, NOS				42 (100%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(47)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)			
#UTERUS	(47)	(43)	(49)	(43)
HYDROMETRA	13 (28%)	4 (9%)	7 (14%)	7 (16%)
HEMATOMETRA				1 (2%)
METAPLASIA, SQUAMOUS		1 (2%)		
#UTERUS/ENDOMETRIUM	(47)	(43)	(49)	(43)
INFLAMMATION, NOS	8 (17%)	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE				3 (7%)
ABSCESS, NOS				1 (2%)
HYPERPLASIA, NOS	8 (17%)		2 (4%)	
HYPERPLASIA, CYSTIC	6 (13%)	33 (77%)	33 (67%)	16 (37%)
DYSPLASIA, NOS				1 (2%)
#OVARY/OVIDUCT	(47)	(43)	(49)	(43)
INFLAMMATION, NOS	4 (9%)			
ABSCESS, NOS	1 (2%)			
#OVARY	(48)	(44)	(48)	(45)
CYST, NOS	10 (21%)	5 (11%)	1 (2%)	3 (7%)
INFLAMMATION, NOS	4 (8%)			
ABSCESS, NOS				2 (4%)
SCLEROSIS			1 (2%)	
PERIARTERITIS	1 (2%)			
DEGENERATION, NOS			1 (2%)	
DEGENERATION, CYSTIC	3 (6%)			
NERVOUS SYSTEM				
#BRAIN/MENINGES	(48)	(45)	(49)	(47)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)

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

TABLE D2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE CONTROL (UNTR) 06-0030	LOW DOSE 06-0057	HIGH DOSE 06-0094
*CEREBRUM	(48)	(45)	(49)	(47)
CYST, NOS				1 (2%)
GRANULOMA, NOS				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(47)	(50)	(50)
NECROSIS, FAT			1 (2%)	
*PLEURA	(50)	(47)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
*MESENTERY	(50)	(47)	(50)	(50)
ABSCESS, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	3	1		1
AUTO/NECROPSY/HISTO PERF	1	1	1	
AUTO/NECROPSY/NO HISTO				3
AUTOLYSIS/NO NECROPSY		3		

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

Review of the Bioassay of 3-Amino-4-Ethoxyacetanilide*
for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup of the
Clearinghouse on Environmental Carcinogens

April 26, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/ Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 3-Amino-4-Ethoxyacetanilide for carcinogenicity.

The primary reviewer considered the study well conducted and adequate to give a level of safety assurance. Although he did not attach great importance to the thyroid tumors found only in the male mice, he agreed that they appeared to be treatment related. The primary reviewer recommended that additional data be obtained on the significance of the thyroid lesions. He concluded that 3-Amino-4-Ethoxyacetanilide probably does not pose a carcinogenic risk to humans.

The secondary reviewer said that 3-Amino-4-Ethoxyacetanilide was carcinogenic in treated male mice, inducing follicular-cell carcinomas of the thyroid. She pointed out a thyroid effect in the other treatment groups, hemosiderosis being a common finding. Based on the results of the study, the secondary reviewer recommended that no statement could be made regarding the carcinogenic risk to humans of 3-Amino-4-Ethoxyacetanilide.

A discussion ensued as to whether the thyroid lesions resulted from an indirect or direct effect. A Subgroup member suggested that the 3-Amino-4-Ethoxyacetanilide may interfer with the production of thyroxin. He added that 3-Amino-4-Ethoxyacetanilide would not appear to pose a carcinogenic risk to man.

A motion was approved unanimously that the report on the bioassay of 3-Amino-4-Ethoxyacetanilide be accepted as written.

Members present were:

Michael Shimkin (Acting Chairman), University of California at San Diego
(David Clayson, Eppley Institute for Cancer Research, submitted a written review)
Joseph Highland, Environmental Defense Fund
George Roush, Jr., Monsanto Company
Louise Strong, University of Texas Health Sciences Center
John Weisburger, American Health Foundation

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

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