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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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BIOASSAY OF

3-AMINO-9-ETHYLCARBAZOLE (HYDROCHLORIDE)

FOR POSSIBLE CARCINOGENICITY

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

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FOREWORD: This report presents the results of the bioassay of 3-amino-9-ethylcarbazole (hydrochloride) 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 greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as 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 that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: The bioassay of 3-amino-9-ethylcarbazole (hydrochloride) was conducted by EG&G 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 bioassay was conducted under the supervision of Drs. A. Handler[1] and E. Smith[2], principal investigators, and Mr. G. Wade[3]. NCI project officers were Drs. E. K. Weisburger[4], T. Cameron[4], and N. P. Page[4,5]. The program manager was Mr. J. Baker[3]. Ms. A. Good[3] supervised the technicians in charge of animal care, and Ms. E. Zepp[3] supervised the preparation of the feed mixtures and collected samples of the diets for analysis. Ms. D. Bouthot[3] kept all daily records of the test, and Ms. R. Monson[3] prepared a report based on these records. Histopathologic examinations were performed by Drs. A. S. K. Murthy[3]

and D. Hayden[3], and the diagnoses included in this report represent their interpretations.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute, Rockville, Maryland[6]. The statistical analyses were performed by Dr. J. R. Joiner[7] and Ms. P. L. Yong[7], using methods selected for the bioassay program by Dr. J. J. Gart[8].

The melting point of the test chemical and the analysis of the dosed feed mixtures used in this bioassay were performed by Dr. M. Hagopian[3]. Chemicals were analyzed under the direction of Dr. E. Murrill[9]. The results of the analyses were reviewed by Dr. C. W. Jameson[7] and Dr. S. S. Olin[7].

This report was prepared at Tracor Jitco[7] under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Waitz, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

The following scientists at NCI were responsible for evaluating the bioassay, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Dawn G. Goodman[10], Dr. Richard A. Griesemer, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire[11], Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of 3-amino-9-ethylcarbazole (hydrochloride) for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice. Both the free amine form and the hydrochloride salt were used.

Groups of 50 rats of each sex and 50 mice of each sex were administered the test chemical at one of two doses, either 800 or 2,000 ppm for rats and either 800 or 1,200 ppm for mice, for 78 weeks. The rats were then observed for an additional 26-29 weeks, and the mice for an additional 16-17 weeks. Controls consisted of groups of 50 untreated rats of each sex and 50 untreated mice of each sex; separate controls were used for the groups of animals administered the different doses. All surviving rats were killed at 104-110 weeks; all surviving mice were killed at 94-97 weeks.

Since the suppliers of the low-dose rats and mice differed from those of the corresponding low-dose controls, while the suppliers for the high-dose rats and mice were the same as those of the corresponding high-dose controls, comparisons of high-dose groups with their corresponding controls were the more appropriate. Furthermore, since the low-dose animals did not receive the same regimen of administration of the test compound as that received by the high-dose animals, and since tests using the low-dose groups were not performed concurrently with those using the high-dose groups, analyses of dose-related trends were not possible. Although the interpretation of results of the study was based primarily on comparisons of high-dose groups with their respective controls, the results obtained with the low-dose groups, regardless of the indicated complicating factors, supported the interpretation.

Neoplasms of the liver were observed in significant incidences in rats and mice of both sexes. In male rats, hepatocellular carcinomas alone were significantly higher ($P \leq 0.020$) in both the low- and high-dose groups. When neoplastic nodules of the liver were combined with hepatocellular carcinomas, the combination occurred at significant incidences ($P \leq 0.012$) in the low- and high-dose male rats and in the high-dose female rats

(males: low-dose controls 0/36, low-dose 12/42; high-dose controls 1/48, high-dose 22/48; females: high-dose controls 0/50, high-dose 6/48). Hepatocellular carcinomas alone similarly occurred at significant incidences ($P < 0.001$) in the low- and high-dose male and female mice (males: low-dose controls 7/48, low-dose 32/44; high-dose controls 6/44, high-dose 41/49; females: low-dose controls 1/47, low-dose 37/43; high-dose controls 1/45, high-dose 43/49).

Papillomas or carcinomas of the integumentary system occurred at significant incidences ($P \leq 0.013$) in both the low- and high-dose male rats (low-dose controls 0/36, low-dose 8/44; high-dose controls 0/48, high-dose 6/48); these tumors also occurred in low- and high-dose female rats, but not at incidences high enough to be statistically significant (low-dose controls 0/39, low-dose 4/44; high-dose controls 0/50, high-dose 4/49).

Carcinomas of the Zymbal's glands of the ear occurred at significant incidences ($P \leq 0.045$) in the low- and high-dose male and female rats (males: low-dose controls 0/36, low-dose 5/44; high-dose controls 0/48, high-dose 7/48; females: low-dose controls 0/39, low-dose 10/44; high-dose controls 0/50, high-dose 12/49). These tumors were first observed as early as week 47 on study.

Adenocarcinomas of the uterus or endometrium occurred at a significant incidence ($P = 0.002$) only in the high-dose female rats (high-dose controls 1/50, high-dose 11/49); these tumors also occurred in the low-dose females, but not at an incidence high enough to be statistically significant (low-dose controls 4/38, low-dose 11/43).

It is concluded that under the conditions of this bioassay, 3-amino-9-ethylcarbazole (hydrochloride) was carcinogenic for the liver, inducing hepatocellular carcinomas in Fischer 344 rats and B6C3F1 mice of both sexes. Other tumors induced in the rats were carcinomas or papillomas of the integumentary system in males, carcinomas of the Zymbal's gland of the ear in males and females, and adenocarcinomas of the uterus.

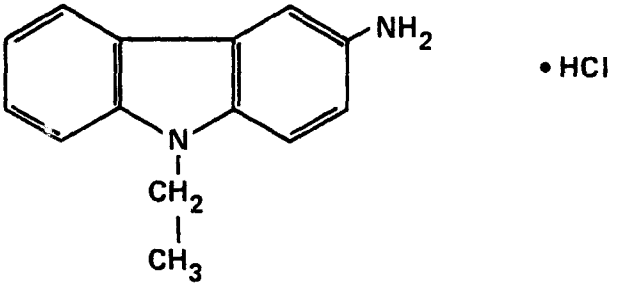
TABLE OF CONTENTS

APPENDIXES

TABLES

FIGURES

I. INTRODUCTION



3-amino-9-ethylcarbazole (hydrochloride)

3-Amino-9-ethylcarbazole (CAS 132-32-1; NCI C01898), is an aromatic amine dye intermediate that has been used industrially in the manufacture of C. I. Pigment Violet 23 and C. I. Direct Blue 108 (Society of Dyers and Colourists, 1971). It is also used in histochemical laboratories in a colorimetric assay for the enzyme peroxidase (Feinstein and Lindahl, 1973) and may be supplanting benzidine as a biological stain (Kaplow, 1975). Approximately 10,604 pounds were imported to the United States for these uses in 1974 (United States International Trade Commission, 1976), and over 1,000 pounds per year are now manufactured domestically according to recent estimates (Stanford Research Institute, 1977).

3-Amino-9-ethylcarbazole in its free amine form or as the hydrochloride salt (C03043) is one in a series of aromatic amine dye intermediates that were selected for study in the Carcinogenesis Testing Program because of the apparent increase in the incidence of cancer among dye workers (Wynder et al., 1963; Anthony and Thomas, 1970).

II. MATERIALS AND METHODS

A. Chemical

3-Amino-9-ethylcarbazole and its hydrochloride salt were obtained from Carroll Products, Wood River Junction, Rhode Island. The melting point range of the batch of 3-amino-9-ethylcarbazole used in the chronic studies was 80-85°C, significantly below that of 127° reported in the literature (Society of Dyers and Colourists, 1971). The hydrochloride salt used in the chronic studies decomposed above 210°C. Perchloric acid titration of one amine function also indicated a lower purity of 92.1 $\pm$ 0.2% for the free amine and 98.8 $\pm$ 0.4% purity for the hydrochloride salt. The salt was shown to be the monohydrochloride using the Buchler-Cotlove chloridometer. Gas-liquid chromatography indicated three major impurities in the free amine, accounting for 4.5% of the total peak area, and three major impurities in the hydrochloride salt, accounting for 1.8% of the peak area. Thin-layer chromatography showed two minor and four trace impurities in the free amine and two minor and three trace impurities in the hydrochloride salt. Infrared and nuclear magnetic resonance spectra of both the free amine and the hydrochloride salt were consistent with the structures.

Bulk chemicals were stored at 4°C in the original containers.

In the chronic feeding studies, the free amine form of the test chemical was administered to the low-dose rats through week 18 and to the low-dose mice through week 1 (see tables 1 and 2). Thereafter, these animals received the hydrochloride salt of the amine. The high-dose rats and mice received the hydrochloride salt for the entire period of the study. Since it is considered that the amine is converted systemically to the salt form, the term 3-amino-9-ethylcarbazole hydrochloride is used to represent the test chemical used in the chronic feeding studies.

B. Dietary Preparation

3-Amino-9-ethylcarbazole or its hydrochloride salt was incorporated into powdered Wayne® Lab Blox animal feed (Allied Mills, Inc., Chicago, Ill.) for administration during the bioassay. The chemical was removed from its container, sifted, and weighed out under an exhaust hood, then mixed by hand with an aliquot of feed in a mortar until visual uniformity was reached. This premix was then mixed with the remaining feed in a Patterson-Kelly twin-shell blender for 20 minutes. Test diets were prepared once per week and used within 1 week of preparation. The diets were sealed in double plastic bags and stored at 4°C.

During the chronic studies, the concentration of 3-amino-9-ethylcarbazole or its hydrochloride salt was measured in selected batches of formulated diets. The results are summarized in Appendix G. At each dietary concentration, the mean of the analytical concentrations for the samples tested was within 20% of the theoretical concentration, and the coefficient of variation was < 18%.

C. Animals

For the subchronic studies, Fischer 344 rats were obtained from Charles River Breeding Laboratories, Inc, Wilmington, Massachusetts, and C57BL/6 mice were obtained from Southern Animal Farms, Prattville, Alabama.

For the chronic studies, Fischer 344 rats and B6C3F1 mice were used. Charles River Laboratories supplied the male rats that were administered the high dose of the test chemical, the female rats that were administered both high and low doses, and the male and female rats which were used as controls for the high-dose groups. A. R. Schmidt, Madison, Wisconsin, supplied the group of male rats that were administered the low dose of the test chemical, and Laboratory Supply Company, Indianapolis, Indiana, supplied the male and female rats which were used as the controls for the low-dose groups.

Charles River Laboratories supplied the male and female B6C3F1 mice that were administered the high dose of the test chemical and the male and female mice that were used as controls. A. R. Schmidt supplied the male and female mice that were administered the low dose.

All animals were received at 28 days of age and were quarantined for approximately 2 weeks prior to the start of the bioassay. At the end of the quarantine period, animals were assigned to control or dosed groups in such a way that the mean weights of animals in each cage were approximately the same.

D. Animal Maintenance

All animals were housed by species in temperature-controlled rooms. The temperature range was 23-34°C. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron filters, providing six changes of room air per hour. Fluorescent lighting provided illumination on a 12-hour daily cycle.

Rats were maintained separately according to sex, with five animals per cage. During quarantine and for the first 13 months of the bioassay, the rats were housed in galvanized or stainless steel wire mesh cages (Fenco Cage Products, Boston, Mass.), suspended above newspapers. The newspapers were replaced every day, and the cages and racks were washed every week. For the

remainder of the bioassay, the rats were housed in suspended polycarbonate cages (Lab Products, Inc., Garfield, N. J.), equipped with disposable nonwoven fiber filter sheets. Clean bedding and cages were provided twice per week. Sanicel® corncob bedding (Paxton Processing Co., S. Lancaster, Mass.) was provided for the first 8 months in the polycarbonate housing for the high-dose rats, for the first 7 months for the high-dose control rats, and for the entire period for the low-dose rats and their controls. The high-dose rats and their controls were provided with Aspen-bed® hardwood chip bedding (American Excelsior, Summerville, Mass.) for the remainder of the bioassay. The racks for the stainless steel cages were cleaned once every 2 weeks, and the disposable filters were replaced at that time.

Mice were maintained separately according to sex, at first with 10 animals per cage, using shoe-box-type polycarbonate cages (Lab Products, Inc.). During quarantine and the period of administration of the test chemical, the cages were fitted with perforated stainless steel lids. During the observation periods that followed, stainless steel wire bar lids were used. Both types of lids were obtained from Lab Products, Inc. Filtek® nonwoven fiber filter bonnets (Lab Products, Inc.) were used over the cage lids. After 12 months of the study, the high-dose mice were housed five per cage, and after 11 months, their controls

were housed five per cage; after 18 months of the study, the low-dose mice and their controls were similarly housed five per cage. The cages, lids, and bedding were changed three times per week when the cage populations were 10 per cage and twice per week when the cage populations were reduced to five per cage. Absorb-dri® hardwood chip bedding (Lab Products, Inc.) was used for 1 month for the high-dose mice and their controls and for 8 months for the low-dose mice and their controls. Sanicel® corncob bedding was used for 12 months. Bed-o-cob bedding (Anderson Cob Mills, Inc., Maumee, Ohio) was then used for 8 months for the high-dose mice and their controls and to the end of the bioassay for the low-dose mice and their controls. The high-dose mice and their controls were provided with Aspen-bed® bedding for the remainder of the study. Reusable filter bonnets and pipe racks were sanitized every 2 weeks throughout the study.

All equipment that was sanitized was washed with Dubois Serve Detergent and rinsed at 82°C.

Tap water (0.75-1.0 ppm chlorine) was provided ad libitum from 250-ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. The bottles were replaced twice per week, and, for the rats only, filled as needed between changes.

Wayne® Lab diet was used throughout the bioassay. Pelleted Wayne® Lab Blox was fed during the quarantine period to the low-dose mice and their controls and to the low-dose rats and their controls. Other groups were fed Wayne® Lab Blox meal during quarantine. All animals received the meal during administration of the test chemical. The meal was distributed in Alpine aluminum feed cups (Curtin-Matheson Scientific, Inc., Woburn, Mass.) for the high-dose rats and their controls for the first 11 months of the study and for all other groups for the entire study. After 11 months, the high-dose rats and their controls were fed from stainless steel gang-style hoppers (Scientific Cages, Inc., Bryan, Tex.). During the observation periods that followed administration of the test chemical, all animals were fed Wayne® Lab Blox pellets on the floors of the cages.

Rats and mice were housed in separate rooms. All rats except the high-dose male and female controls were housed in a single room with rats administered the following compounds in feed:

(CAS 99-55-8) 5-nitro-o-toluidine
(CAS 122-66-7) hydrazobenzene
(CAS 117-79-3) 2-aminoanthraquinone
(CAS 94-52-0) 5-nitro-1H-benzimidazole
(CAS 86-57-7) 1-nitronaphthalene
(CAS 615-05-4) 4-methoxy-m-phenylenediamine
(CAS 8003-03-0) aspirin: phenacetin: caffeine (APC)

The high-dose male and female control rats were housed in another room with rats administered the following compounds in feed:

(CAS 61-82-5) 3-amino-s-triazole (positive control)
(CAS 129-15-7) 2-methyl-1-nitroanthraquinone
(C01978) 3'-nitro-p-acetophenetide

All control and low-dose male and female mice were housed in a room with mice administered one of the following compounds in feed:

(CAS 61-82-5) 3-amino-s-triazole (positive control)
(CAS 138-89-6) N,N-dimethyl-p-nitrosoaniline
(CAS 6369-59-1) toluene-2,5-diamine sulfate
(CAS 121-14-2) 2,4-dinitrotoluene
(CAS 117-79-3) 2-aminoanthraquinone
(C01887) 3-amino-4-ethoxyacetanilide
(CAS 82-28-0) 1-amino-2-methylanthraquinone
(CAS 99-59-2) 5-nitro-o-anisidine
(CAS 619-17-0) 4-nitroanthranilic acid
(CAS 86-57-7) 1-nitronaphthalene
(CAS 602-87-9) 5-nitroacenaphthene
(C01978) 3'-nitro-p-acetophenetide
(CAS 615-05-4) 4-methoxy-m-phenylenediamine
(CAS 8003-03-0) aspirin: phenacetin: caffeine (APC)

Male and female high-dose mice were housed in another room, with mice administered one of the following compounds in feed:

(CAS 6369-59-1) toluene-2,5-diamine sulfate
(CAS 99-55-8) 5-nitro-o-toluidine
(CAS 122-66-7) hydrazobenzene
(CAS 94-52-0) 5-nitro-1H-benzimidazole
(CAS 99-59-2) 5-nitro-o-anisidine
(CAS 86-57-7) 1-nitronaphthalene
(CAS 615-05-4) 4-methoxy-m-phenylenediamine

E. Subchronic Studies

Six-week subchronic studies were conducted using Fischer 344 rats and C57BL/6 mice to estimate the maximum tolerated doses of 3-amino-9-ethylcarbazole, on the basis of which two concentrations (hereinafter referred to as "low doses" and "high doses") were determined for the chronic studies. The free amine form of the test chemical was administered in the diet for 4 weeks at concentrations of 40, 100, 250, 600, or 1,440 ppm. Five males and five females of each species received the chemical at one of each of the concentrations, and five males and five females of each species were given basal diets. All animals were killed and necropsied at the end of 6 weeks.

At the end of the studies, no differences in mean body weight gains in various dosed male rats could be attributed to administration of the test compound. Depressions in mean body weight gains in dosed female rats compared to controls ranged from 5-9% at doses of 40-600 ppm, and was 13% at 1,440 ppm. In the mice, mean body weight gains were depressed from 7-12% in all the male groups, but no consistent pattern of weight gain depression was seen in the female groups. There were no deaths in any of the animals.

On the basis of these data, initial doses of 300 and 600 ppm for the free amine (equivalent to 400 and 800 ppm when calculated and administered as the hydrochloride salt) were selected as the low and high doses, respectively, to be administered to rats and mice in the chronic studies.

F. Chronic Studies

The test groups, doses administered, and times on study of the chronic studies are shown in tables 1 and 2.

Rats and mice that had been designated to be administered a low dose of 300 ppm (free amine) were killed at weeks 49 and 32, respectively, because these doses had no effect on the mean body weights. The original high-dose groups then became the low-dose groups, and new high-dose groups of rats and mice were started concurrently at doses of 2,000 and 1,200 ppm (hydrochloride salt) for the rats and the mice, respectively.

The free amine, which was administered to the low-dose rats through week 18 and to the low-dose mice during week 1, was replaced by equimolar concentrations of the hydrochloride salt because of concern that the free amine might be unstable in the feed. The high-dose rats and mice received the hydrochloride salt for the entire period of administration of the chemical.

Table 1. 3-Amino-9-Ethylcarbazole Hydrochloride
Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals[a]	3-Amino-9-Ethylcarbazole Hydrochloride in Diet[b] (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Low-Dose[c,d]	50	800	78	26-27
Low-Dose Control[e]	50	0		107
High-Dose[f,g]	50	2,000	78	28-29
High-Dose Control[g]	50	0		109
Female				
Low-Dose[c,h]	50	800	78	27-28
Low-Dose Control[e]	50	0		107-108
High-Dose[f,g]	50	2,000	78	29
High-Dose Control[g]	50	0		109-110

[a]Rats were 41-44 days of age when placed on study.

[b]Diets were available ad libitum 7 days per week.

[c]The test chemical was administered to the low-dose groups as the free amine (600 ppm) for the first 18 weeks, then as the hydrochloride salt for the remaining 60 weeks. The dose in the above table is calculated on the basis of the weight of the hydrochloride salt.

[d]The rats used in the low-dose male group were obtained from A. R. Schmidt, Madison, Wisconsin.

Table 1. 3-Amino-9-Ethylcarbazole Hydrochloride
Chronic Feeding Studies in Rats

(continued)

[e]The rats used in the low-dose control groups were obtained from Laboratory Supply Company, Indianapolis, Indiana.

[f]The test chemical was administered to the high-dose groups as the hydrochloride salt for the entire study.

[g]The rats used in the high-dose and corresponding control groups were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The high-dose and corresponding control groups were started 50-51 weeks after the low-dose and corresponding control groups.

[h]The female rats used in the low-dose group were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts.

Table 2. 3-Amino-9-Ethylcarbazole Hydrochloride
Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals[a]	3-Amino-9-Ethylcarbazole Hydrochloride in Diet[b] (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Low-Dose[c]	50	800	78	16-17
Low-Dose Control[d]	50	0		96
High-Dose[d,e]	50	1,200	78	17
High-Dose Control[d]	50	0		96
Female				
Low-Dose[c]	50	800	78	17
Low-Dose Control[d]	50	0		97
High-Dose[d,e]	50	1,200	78	17
High-Dose Control[d]	50	0		96

[a]Mice were 41-44 days of age when placed on study.

[b]Diets were available *ad libitum* 7 days per week.

[c]The test chemical was administered to the low-dose groups as the free amine (600 ppm) for the first week, then as the hydrochloride salt for the remaining 77 weeks. The dose in the above table is calculated on the basis of the weight of the hydrochloride salt. The mice used in the low-dose groups were obtained from A. R. Schmidt, Madison, Wisconsin.

Table 2. 3-Amino-9-Ethylcarbazole Hydrochloride
Chronic Feeding Studies in Mice

(continued)

[d]The mice used in the high-dose groups and in all control groups were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The high-dose and corresponding control groups were started about 33 weeks after the low-dose and corresponding control groups were placed on study.

[e]The test chemical was administered as the hydrochloride salt for the entire study.

G. Clinical and Pathologic Examinations

Inspection for mortality and morbidity was carried out twice daily. Body weights were recorded every 2 weeks for the first 12 weeks and every month thereafter. Clinical observations were recorded every month.

Moribund animals and animals that survived to the end of the bioassay were killed using CO_2 anesthesia and necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization. The following tissues were examined microscopically: tissue masses, abnormal regional lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gall bladder (mice), pancreas, spleen, kidney, adrenal, bladder, seminal vesicles/prostate/testis (males), ovary/uterus (females), nasal cavity, brain, pituitary, eyes, external and middle ear, and spinal cord. Peripheral blood smears were prepared from each animal whenever possible. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnoses.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals may have been missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study 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 appropriate 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) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for 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 is 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) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed 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) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions (Armitage, 1971), was not used.

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

on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was 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 dosed 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 dosed 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 dosed 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% of a large number of identical experiments, the true ratio of the risk in a dosed 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 ($P < 0.025$ 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. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of high-dose male and female rats were lower than those of corresponding controls throughout the bioassay (figure 1). The mean body weight of the low-dose males was slightly lower than that of the corresponding controls during the latter part of the bioassay, and the mean body weight of the low-dose females was essentially unaffected. Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation. No other clinical signs related to administration of the test chemical were observed.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed 3-amino-9-ethylcarbazole hydrochloride at the doses used in this bioassay, together with those of the corresponding controls, are shown in figure 2. In each sex, the result of the Cox test comparing the survival of the low-dose group with its controls is significant ($P \leq 0.002$), indicating increased mortality in the dosed groups. In females, the result of the Cox test comparing the high-dose group with its controls is also significant ($P < 0.001$), but in male rats the

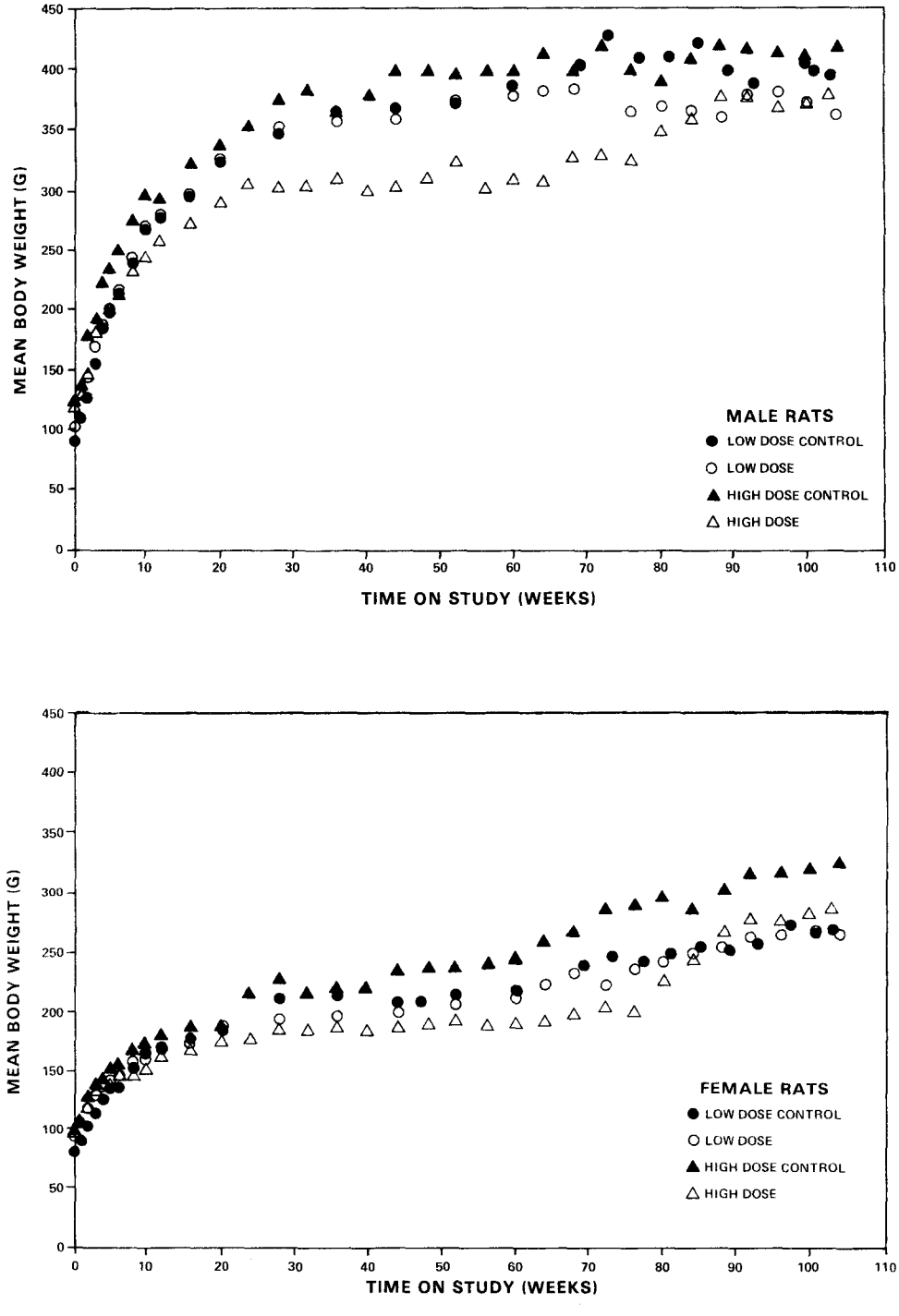


Figure 1. Growth Curves For Rats Fed 3-Amino-9-Ethylcarbazole Hydrochloride In The Diet

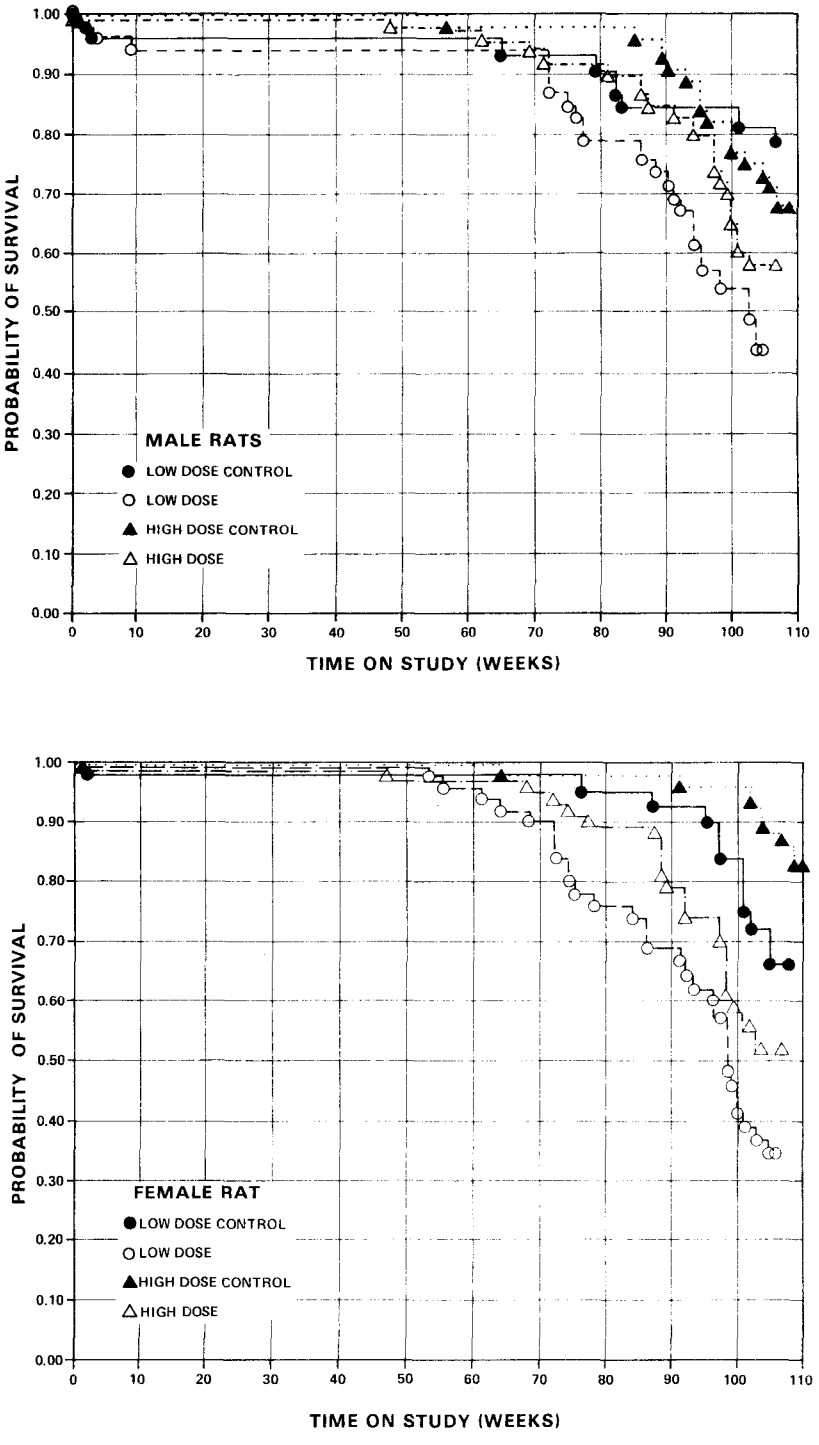


Figure 2. Survival Curves For Rats Fed 3-Amino-9-Ethylcarbazole Hydrochloride In The Diet

survival of the high-dose group was not significantly different from that of the controls.

In male rats, 37/50 (74%) of the low-dose group and 37/50 (74%) of the low-dose control group were alive at week 78 on study. In the low-dose control group, 10 animals were killed at week 29 and 5 at week 78; in the low-dose group, 3 animals were reported as missing, 1 at week 1 and 2 at week 2; 5 low-dose animals were killed at week 78. Forty-six out of 50 (92%) of the high-dose group and 48/49 (98%) of the high-dose control group were alive at week 78 on study; 5 animals of each group were killed at week 78.

In female rats, 39/50 (78%) of the low-dose animals and 38/50 (76%) of the low-dose controls were alive at week 78 on study. In the low-dose control group, 10 animals were killed at week 29 and 5 at week 78; in the low-dose group, 5 animals were killed at week 78. Forty-five out of 50 (90%) of the high-dose group and 49/50 (98%) of the high-dose control animals were alive at week 78 on study; 5 animals of each group were killed at week 78.

Sufficient numbers of rats of each sex were at risk for development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1-A4; findings on nonneoplastic lesions are summarized in Appendix C, tables C1-C4.

The occurrence of neoplasms of the skin, auditory sebaceous gland, preputial/clitoral glands, liver, mammary gland, uterus, and intestine in Fischer 344 rats appeared to be related to administration of 3-amino-9-ethylcarbazole hydrochloride.

Epithelial neoplasms of the skin not localized to any particular site were found in dosed rats of each sex, but in only one control animal — a female. The types and incidences of the tumors of the skin are summarized in the following tabulation:

MALE RATS	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Number of animals necropsied	(46)	(48)	(44)	(48)
Skin and Subcutis				
Squamous-Cell Papilloma			3	2
Squamous-Cell Carcinoma			3	3
Basal-Cell Carcinoma			4	1
Sebaceous Adenoma			1	
Adenoma, NOS*				2

*Not otherwise specified

FEMALE RATS	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Number of animals necropsied	(49)	(50)	(44)	(49)
Skin and Subcutis				
Squamous-Cell Papilloma			1	1
Squamous-Cell Carcinoma			3	3
Basal-Cell Carcinoma		1		
Sebaceous Adenocarcinoma				1

Squamous-cell papilloma was a papillary growth of the squamous epithelium with hyperkeratosis. Squamous-cell carcinomas in a few dosed rats had grown into the subcutaneous tissue. An occasional cell nest was seen in the lumen of lymphatics or blood vessels. The neoplastic cells formed keratin pearls which varied in size and shape. Many of the cells were anaplastic, and their cytoplasm was eosinophilic. Keratohyalin granules were present only in some cells. Nuclei were large, and mitotic figures numerous. This tumor metastasized to the lung in two rats (one high-dose male, one control female). Basal-cell carcinomas extended down to the panniculus adiposus and were ulcerated at the surface. Tumor cells were lobulated or closely packed, and the cytoplasm was basophilic. Nuclei were hyperchromatic, and there were many mitotic figures. Keratin pearls and hair follicles in some tumors suggested differentiation. Unlike the

squamous-cell carcinoma, cells in this tumor did not exhibit much pleomorphism.

Neoplasms of the auditory sebaceous gland occurred in 5/44 low-dose males and 7/48 high-dose males; 10/44 low-dose females and 12/49 high-dose females; and in none of the controls. Thirteen tumors were considered to be carcinomas, NOS, and 21 to be squamous-cell carcinomas. The morphologies of these tumors were similar to those described by Pliss (1973). Sebaceous carcinoma in one rat metastasized to the lung.

Adenocarcinomas of the uterus were found in 5/98 combined control and 22 dosed female rats (11/43 low-dose, 11/49 high-dose). Papillary ingrowths of the epithelium filled the lumen and had invaded into the myometrium. Transformed glands were adjacent to each other with little supporting stroma. Tumor cells were arranged in acini or syncitia. The cytoplasm of these cells was basophilic. Vacuolization and/or bright eosinophilic droplets were seen in some cells. Nuclear pleomorphism was not marked. Nuclei were vesicular with prominent nucleoli. Both normal and abnormal mitotic figures were numerous. Large areas of necrosis and inflammatory cells replaced part of the tumor parenchyma. The uterine adenocarcinomas in three rats had metastasized to the lung.

Carcinomas and adenocarcinomas of the mammary gland occurred in 10 dosed female rats (8/44 low-dose, 3/49 high-dose) and 2/89 control female rats. These tumors were solitary or multiple and were comprised of glandular structures of varying sizes or of closely packed cells. Stroma was scant between the transformed acini. Secretory material was found in the lumen of some glands. Tumor cells were cuboidal and the cytoplasm was eosinophilic or vacuolated. Both normal and abnormal mitotic figures were numerous. In a few tumors, central necrosis was found in nests of densely packed cells. A mammary adenocarcinoma had metastasized to the lung and liver in one dosed rat.

Tumors of the preputial gland were found in 2/44 low-dose, 5/48 high-dose, and in none of the control male rats. Tumors of the clitoral gland were found in 6/44 low-dose, 7/49 high-dose, and 3/99 control female rats.

The incidences of neoplastic nodules of the liver and hepatocellular carcinomas in control and dosed rats are summarized in the following tabulation:

MALE RATS	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Number of Animals with Tissue Examined Microscopically	(46)	(48)	(42)	(48)
Liver				
Hepatocellular Carcinoma		1	6	8
Hepatocellular Carcinoma and Neoplastic Nodule		1	12	22
FEMALE RATS				
Number of Animals with Tissue Examined Microscopically	(49)	(50)	(43)	(48)
Liver				
Hepatocellular Carcinoma	2		1	3
Hepatocellular Carcinoma and Neoplastic Nodule	2		1	6

Neoplastic nodules of the liver were small, and compressed the adjacent parenchyma in areas. The cells were large with acidophilic cytoplasm and hyperchromatic nuclei. A few mitotic figures were present. Hepatocellular carcinomas involved a part or an entire lobe of the liver. The lobular architecture was distorted. Liver plates were several cells thick. There was a pleomorphism in the size of transformed hepatocytes. The cytoplasm of the cells was acidophilic or vacuolated. The nuclei were large, and the nucleoli were prominent. Mitotic figures

were numerous. Cholangiolar tumors were associated with hepatocellular carcinomas in two male rats of the high-dose group. No metastases were found.

The incidences of adenomatous polyps and adenocarcinomas of the small intestine and colon are summarized in the following tabulation:

MALE RATS	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Number of Animals with Tissue Examined Microscopically	(43)	(46)	(41)	(46)
Small Intestine				
Adenomatous Polyp			1	
Adenocarcinoma			3	1
Colon				
Adenomatous Polyp				1
Adenocarcinoma			1	1
Adenocarcinoma in Adenomatous Polyp			1	
FEMALE RATS				
Number of Animals with Tissue Examined Microscopically	(47)	(48)	(40)	(46)
Small Intestine				
Adenomatous Polyp			2	
Adenocarcinoma			2	

Adenomatous polyps had a pedicle and were supported by fibrovascular stroma. Glands varied in size in these polyps. Cells lining these glands were piled up in areas, and the cytoplasm was

more basophilic than in cells of the adjacent normal mucosa. Adenocarcinomas were either polypoid or sessile and infiltrated into the submucosa. Glands were closely packed and exhibited pleomorphism in shape and size; a few were cystic. Neoplastic cells were either columnar or cuboidal in shape, and the cytoplasm was basophilic. Only a few of the neoplastic cells stained positive with the PAS stain, and Paneth cell granules stained bright red in tumors of the small intestine. Nuclei were hyperchromatic and mitotic figures were numerous. In some of the tumors, there were areas of necrosis and clusters of inflammatory cells.

A variety of nonneoplastic lesions occurred in both dosed and control animals. The incidence, distribution, and severity of these lesions were similar to those known to occur spontaneously in aged Fischer 344 rats.

Based on the histopathologic examination, 3-amino-9-ethylcarbazole hydrochloride was considered to be carcinogenic to Fischer 344 rats under the conditions of this study, since there was an increased incidence of neoplasms of the skin in males, mammary gland and uterus in females, and auditory sebaceous glands, preputial/clitoral glands, liver, and intestines in males and females.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more than one group. No Cochran-Armitage tests were made, because the low- and high-dose groups were not tested concurrently. The 10 low-dose control animals of each sex that were killed at week 29 on study were deducted from the denominators of the incidences in the controls.

When the incidences of all animals with carcinomas or papillomas in the integumentary system were combined for analysis, the results of the Fisher exact test indicated a significantly higher incidence of these tumors in both the male high-dose (6/48 [13%], P = 0.013) and the male low-dose (8/44 [18%], P = 0.006) groups than in the respective controls. These tumors did not appear in statistically significant incidences in female dosed groups, although they were present in both the female high-dose group (4/49 [8%]) and the female low-dose group (4/44 [9%]), compared with 0/50 and 0/39 in the two control groups.

The results of the Fisher exact test on the incidence in the male rats of hepatocellular carcinomas show that the incidences in the low- and high-dose groups are significantly higher than those in

the corresponding control groups (P = 0.020 and P = 0.015, respectively). The incidences of the combination of neoplastic nodules and hepatocellular carcinomas in the low- and high-dose groups are also significantly higher than those in the corresponding control groups ($P < 0.001$). In the female rats, the combined incidence of neoplastic nodules of the liver and hepatocellular carcinomas is significantly higher (P = 0.012) in the high-dose group than in the corresponding control group.

The Fisher exact comparison of the incidence of adenocarcinomas of the uterus or endometrium in the high-dose group of female rats with that in the corresponding control group shows a P value of 0.002.

In either the male or female rats, carcinomas or squamous-cell carcinomas of the Zymbal's gland occurred exclusively in the dosed groups. In the male rats, the results of the Fisher exact test show that the incidences in the low- and high-dose groups are significantly higher than those in their corresponding controls (P = 0.045 and P = 0.006, respectively). In the females, the results of the Fisher exact test comparing the incidence in each dosed group with that in its control group are significant ($P \leq 0.001$).

No other tumors occurred at significantly higher incidences in dosed groups of rats than in controls. A significant result (P = 0.018) in the negative direction is observed in the comparison of the incidence of interstitial-cell tumors in low-dose male rats with that in its control group. Historical records show that groups of this strain of rat usually show incidences of this tumor from 75 to 100%.

In summary, the statistical analysis of the data for rats indicates an association of the administration of this chemical with the incidences of squamous-cell carcinomas or papillomas of the integumentary system in both sexes, hepatocellular carcinomas in male rats, the combination of neoplastic nodules of the liver and hepatocellular carcinomas in both sexes of rats, and carcinomas of the Zymbal's gland in both sexes. In addition, the high-dose female rats had a significant increase in adenocarcinomas of the uterus.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of high-dose male and female mice were lower than those of corresponding controls throughout the bioassay (figure 3). The mean body weight of the low-dose females was slightly lower than that of the controls during the latter part of the bioassay, but the mean body weight of the low-dose males was essentially unaffected. Fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation. No other clinical signs related to administration of the test chemical were observed.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed 3-amino-9-ethylcarbazole hydrochloride at the doses used in this bioassay, together with those of the corresponding controls, are shown in figure 4. In male mice, the results of the Cox tests comparing the survival of the low- and high-dose groups with their respective controls were both significant (low-dose $P = 0.034$; high-dose $P = 0.006$). In female mice, the result of the Cox test comparing the low-dose group with its control is not significant, but the result of the

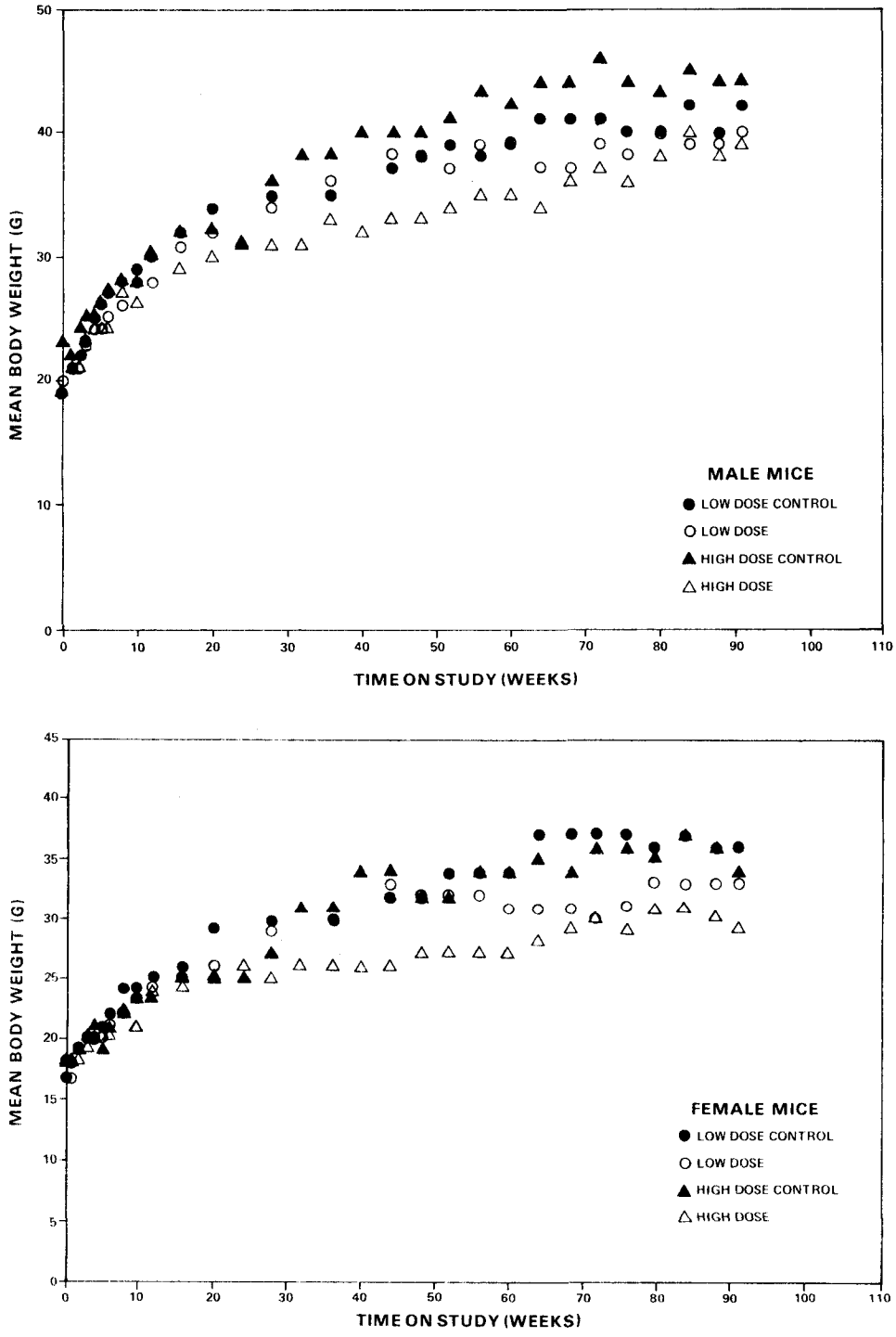


Figure 3. Growth Curves For Mice Fed 3-Amino-9-Ethylcarbazole Hydrochloride In The Diet

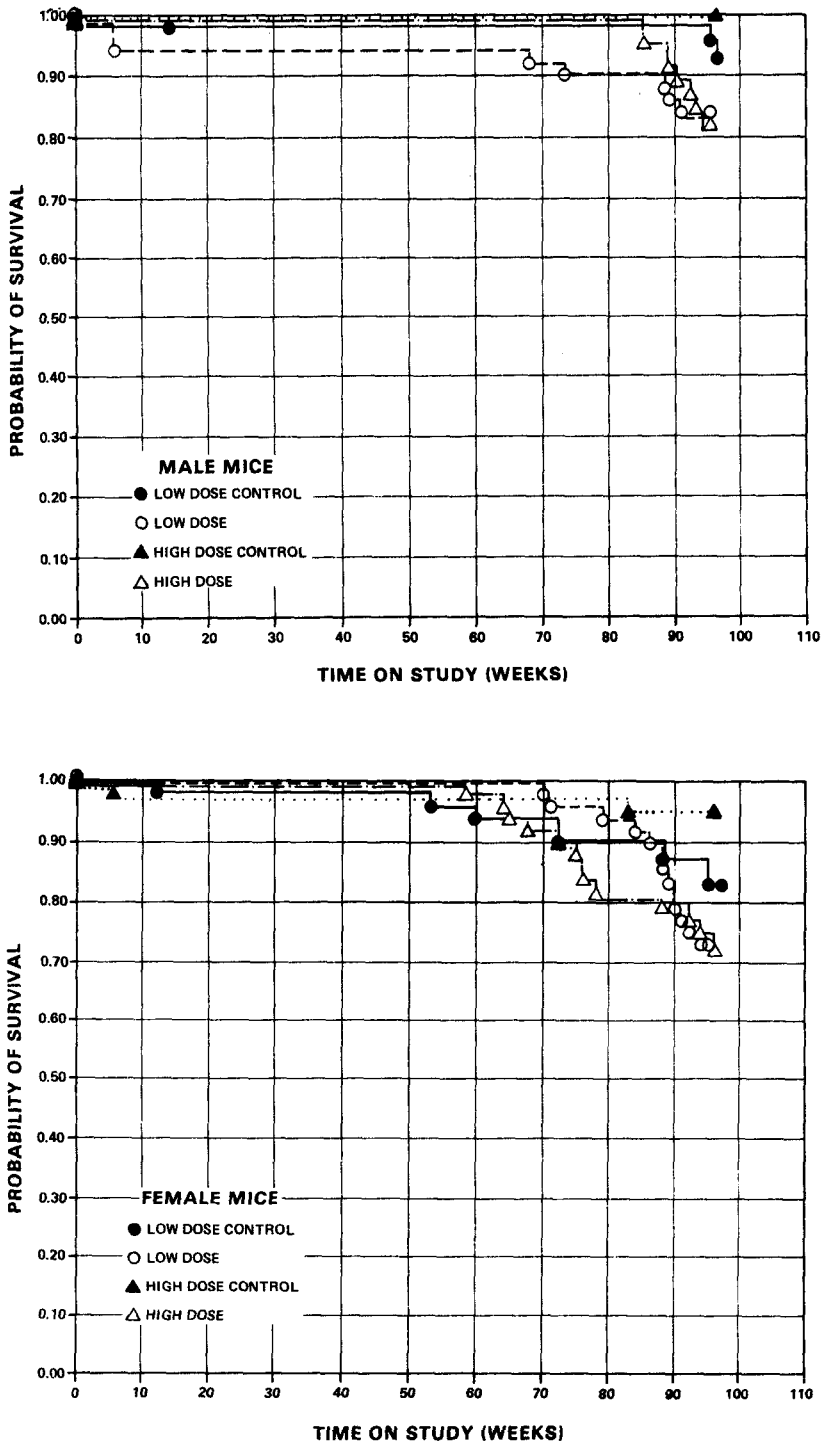


Figure 4. Survival Curves For Mice Fed 3-Amino-9-Ethylcarbazole Hydrochloride In The Diet

comparison of the high-dose group with its controls indicates increased mortality in that dosed group (P = 0.004).

In male mice, 42/50 (84%) of the low-dose group and 44/50 (88%) of the low-dose control group were alive at week 94. In the low-dose control group, five animals were killed at week 78, and in the low-dose group, one animal was reported missing at week 16. Thirty-eight out of 50 (76%) of the high-dose group and 40/50 (80%) of the high-dose control group were alive at week 95. In the high-dose control group, five animals were killed at week 49 and five at week 78; in the high-dose group, five animals were killed at week 78.

In female mice, 35/50 (70%) of the low-dose group and 39/50 (78%) of the low-dose control group were alive at week 95. In the low-dose control group, five animals were killed at week 78, and in the low-dose group, two animals were reported as missing, one at week 20 and one at week 76. Thirty-two out of 50 (64%) of the high-dose group and 38/50 (76%) of the high-dose control group were alive at week 95. In the high-dose control group, five animals were killed at week 49 and five at week 78; in the high-dose group, five animals were killed at week 78 and one animal was reported as missing at week 11.

Sufficient numbers of mice of each sex were at risk for development of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1-B4; findings on nonneoplastic lesions are summarized in Appendix D, tables D1-D4.

A dose-related increase in the incidence of hepatocellular carcinomas was found in mice administered 3-amino-9-ethylcarbazole hydrochloride. The following tabulation summarizes the occurrence of these tumors in the various groups of animals and the numbers of animals in which pulmonary metastases were found:

MALE MICE	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Number of Animals with Tissue Examined Microscopically	(48)	(48)	(44)	(49)
Hepatocellular Carcinoma	7	6	32	41
Pulmonary Metastases		1		3
FEMALE MICE				
Number of Animals with Tissue Examined Microscopically	(47)	(50)	(43)	(49)
Hepatocellular Carcinoma	1	1	37	43
Pulmonary Metastases			2	5

Hepatic tumors involved a part or an entire lobe of the liver. The normal lobular architecture of the liver was not preserved. Sinusoids in these areas were distended. A moderate pleomorphism in the size of transformed hepatocytes was evident. The cytoplasm was acidophilic, and in some animals it was vacuolated, suggesting fatty infiltration. Nuclei were hyperchromatic and were occasionally bizarre. Mitotic figures were numerous. Small areas of necrosis, accompanied by inflammatory cells, were scattered in the tumor parenchyma.

Adenomatous polyps of the gall bladder were found in three dosed male mice, one in the low-dose group and two in the high-dose group. None were found in the controls. These polyps were characterized by papillary-like fronds of the columnar epithelium supported by a thin fibrovascular stroma. Many of the epithelial cells contained secretory material on the luminal side, and piling of cells was noted in areas.

A variety of nonneoplastic lesions were observed, but the incidence, distribution, and severity of these lesions were similar to those known to occur spontaneously in aged B6C3F1 mice.

Based on the histopathologic examination, 3-amino-9-ethyl-carbazole hydrochloride was considered to be carcinogenic in

B6C3F1 mice under the conditions of this study, since there was a dose-related increase in the incidence of hepatocellular carcinomas in both the males and the females.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group. No Cochran-Armitage tests were made, because the low- and high-dose groups were not tested concurrently. The results of the five high-dose control animals of each sex that were killed at week 49 are not included in the analysis.

In both the male and female mice, the results of the Fisher exact test show that the incidence of hepatocellular carcinomas in each of the dosed groups is significantly higher ($P < 0.001$) than that in the corresponding control group.

The historical records of the bioassay program at this laboratory indicate that the mean incidence of hepatocellular carcinoma in control male B6C3F1 mice is 49/350 (14%) with 24/54 (44%) being the highest incidence of this tumor in any control group of male mice, compared with 32/44 (73%) in the low-dose group and 41/49 (84%) in the high-dose group of this bioassay.

This historical record also indicates that the mean incidence of hepatocellular carcinoma is 13/350 (4%) with 7/54 (13%) being the highest incidence of this tumor in any control group of female mice, compared with 37/43 (86%) in the low-dose group and 43/49 (88%) in the high-dose group of this bioassay. The incidences in both the low- and high-dose groups are significantly high ($P < 0.001$) when they are compared with that in the historical-control group.

The statistical conclusion is that the incidence of hepatocellular carcinomas in mice is associated with the administration of 3-amino-9-ethylcarbazole hydrochloride. There is no other incidence of tumors in either sex that shows a statistical difference in any dosed group compared with its control group.

V. DISCUSSION

The toxicity of 3-amino-9-ethylcarbazole hydrochloride for Fischer 344 rats and B6C3F1 mice was shown by markedly lower mean body weights in high-dose male and female rats and mice and by slightly lower mean body weights in low-dose male mice and low-dose female mice, when comparisons are made with corresponding untreated controls. The survival rate of the dosed groups of rats and mice was lower than that of the untreated controls; however, a sufficient number of animals survived to be at risk for development of late-appearing tumors. No other clinical signs were observed that could be related to administration of the test chemical.

Since the suppliers of the low-dose rats and mice differed from those of the corresponding low-dose controls, while the suppliers for the high-dose rats and mice were the same as those of the corresponding high-dose controls, comparisons of high-dose groups with their corresponding controls were the more appropriate. Furthermore, since the low-dose animals did not receive the same regimen of administration of the test compound as that received by the high-dose animals, and since tests using the low-dose groups were not performed concurrently with those using the high-dose groups, analyses of dose-related trends were not possible. Although the interpretation of results of the study

was based primarily on comparisons of high-dose groups with their respective controls, the results obtained with the low-dose groups, regardless of the indicated complicating factors, supported the interpretation.

Neoplasms of the liver were observed in significant incidences in rats and mice of both sexes. In male rats hepatocellular carcinomas alone were significantly higher ($P \leq 0.020$) in both the low- and high-dose groups. When neoplastic nodules of the liver were combined with hepatocellular carcinomas, the combination occurred at significant incidences ($P \leq 0.012$) in the low- and high-dose male rats and in the high-dose female rats (males: low-dose controls 0/36, low-dose 12/42; high-dose controls 1/48, high-dose 22/48; females: high-dose controls 0/50, high-dose 6/48). Hepatocellular carcinomas alone similarly occurred at significant incidences ($P < 0.001$) in the low- and high-dose male and female mice (males: low-dose controls 7/48, low-dose 32/44; high-dose controls 6/44, high-dose 41/49; females: low-dose controls 1/47, low-dose 37/43; high-dose controls 1/45, high-dose 43/49).

Papillomas or carcinomas of the integumentary system occurred at significant incidences ($P \leq 0.013$) in both low- and high-dose male rats (low-dose controls 0/36, low-dose 8/44; high-dose controls 0/48, high-dose 6/48); these tumors also occurred in

low- and high-dose female rats, but not at incidences high enough to be statistically significant (low-dose controls 0/39, low-dose 4/44; high-dose controls 0/50, high-dose 4/49).

In both male and female rats, carcinomas of the Zymbal's glands of the ear occurred only in the dosed groups. In male rats the incidences in the low- and high-dose groups were higher ($P = 0.045$ and $P = 0.006$, respectively) than in their corresponding controls (males: low-dose controls 0/36, low-dose 5/44; high-dose controls 0/48, high-dose 7/48). In females the incidences in each group were significant ($P \leq 0.001$), compared with corresponding controls (females: low-dose controls 0/39, low-dose 10/44; high-dose controls 0/50, high-dose 12/49). These tumors were first observed as early as week 47 on study.

Adenocarcinomas of the uterus or endometrium occurred at a significant incidence ($P = 0.002$) only in the high-dose female rats (high-dose controls 1/50, high-dose 11/49); these tumors also occurred in the low-dose females, but not at an incidence high enough to be statistically significant (low-dose controls 4/38, low-dose 11/43).

Carcinomas and adenocarcinomas of the mammary gland were observed in 7/44 low-dose female rats and 3/49 high-dose females, but in only 2/39 low-dose female controls and 0/50 high-dose female

controls. The incidences of the tumors in the dosed groups were not high enough, however, to be statistically significant when compared with incidences in corresponding control groups.

Adenomatous polyps or adenocarcinomas of the small intestine were observed in 4/41 low-dose male rats, 1/46 high-dose males, and 4/40 low-dose females. The same tumors were observed in the colons of 2/41 low-dose and 2/46 high-dose males. None were observed at either site in the control male or female rats. Similarly, adenomas of the preputial gland were observed in 1/44 (2%) low-dose and 4/48 (8%) high-dose male rats, but in none of the controls, and adenomas of the clitoris or clitoral gland occurred in 3/44 (7%) low-dose and 3/49 (6%) high-dose females, but in only 2/99 (2%) of the controls. Although the incidences of these different tumors were not statisticaly significant, their historical spontaneous incidences in similar bioassays performed on other test chemicals at the same laboratory were very low (1/334 [0.3%] for adenomatous polyps or adenocarcinomas of the small intestine or colon in males and 0/336 in females, only 4/334 [1%] for adenomas of the preputial gland in males, and only 3/336 [0.9%] for adenomas of the clitoris or clitoral gland in females). Thus, the occurrence of these tumors in the dosed groups of rats in the present bioassay may have been associated with administration of 3-amino-9-ethylcarbazole hydrochloride.

It is concluded that under the conditions of this bioassay, 3-amino-9-ethylcarbazole hydrochloride was carcinogenic for the liver, inducing hepatocellular carcinomas in Fischer 344 rats and B6C3F1 mice of both sexes. Other tumors induced in the rats were carcinomas or papillomas of the integumentary system in males, carcinomas of the Zymbal's gland of the ear in males and females, and adenocarcinomas of the uterus.

VI. BIBLIOGRAPHY

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		3
ANIMALS NECROPSIED	46	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	46	43
INTEGUMENTARY SYSTEM		
*SKIN	(46)	(44)
NEOPLASM, NOS		1 (2%)
SQUAMOUS CELL PAPILLOMA		3 (7%)
SQUAMOUS CELL CARCINOMA		3 (7%)
BASAL-CELL CARCINOMA		4 (9%)
SEBACEOUS ADENOMA		1 (2%)
*SUBCUT TISSUE	(46)	(44)
FIBROMA		1 (2%)
FIBROSARCOMA		1 (2%)
RESPIRATORY SYSTEM		
#TRACHEA	(45)	(40)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	
#LUNG/BRONCHUS	(46)	(43)
PAPILLOMA, NOS		1 (2%)
#LUNG	(46)	(43)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (5%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(46)	(44)
MALIGNANT LYMPHOMA, NOS		1 (2%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)	
MYELOMONOCYTIC LEUKEMIA		4 (9%)
MONOCYTIC LEUKEMIA	1 (2%)	1 (2%)

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

A1. MALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
#LYMPH NODE	(38)	(34)
ADENOCARCINOMA, NOS, METASTATIC	1 (3%)	
CIRCULATORY SYSTEM		
NONE		
DIGESTIVE SYSTEM		
#LIVER	(46)	(42)
NEOPLASTIC NODULE		6 (14%)
HEPATOCELLULAR CARCINOMA		6 (14%)
#SMALL INTESTINE	(43)	(41)
ADENOCARCINOMA, NOS		1 (2%)
ADENOMATOUS POLYP, NOS		1 (2%)
MUCINOUS CYSTADENOCARCINOMA		1 (2%)
LEIOMYOSARCOMA		1 (2%)
#JEJUNUM	(43)	(41)
CYSTADENOCARCINOMA, NOS		1 (2%)
LEIOMYOSARCOMA		1 (2%)
#COLON	(43)	(38)
ADENOCARCINOMA, NOS		1 (3%)
ADENOCA IN ADENOMATOUS POLYP		1 (3%)
URINARY SYSTEM		
NONE		
ENDOCRINE SYSTEM		
#PITUITARY	(41)	(37)
ADENOMA, NOS	2 (5%)	5 (14%)
CHROMOPHOBE ADENOMA	10 (24%)	7 (19%)
#ADRENAL	(43)	(43)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	
PHEOCHROMOCYTOMA	6 (14%)	4 (9%)

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

A1. MALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
GANGLIONEUROMA		1 (2%)
#THYROID	(45)	(40)
ADENOMA, NOS	1 (2%)	1 (3%)
ADENOCARCINOMA, NOS	2 (4%)	
FOLLICULAR-CELL ADENOMA		1 (3%)
FOLLICULAR-CELL CARCINOMA		2 (5%)
C-CELL ADENOMA	1 (2%)	1 (3%)
#PANCREATIC ISLETS	(42)	(39)
ISLET-CELL ADENOMA	2 (5%)	4 (10%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(46)	(44)
FIBROADENOMA		1 (2%)
*PREPUTIAL GLAND	(46)	(44)
ADENOMA, NOS		1 (2%)
SEBACEOUS ADENOMA		1 (2%)
#PROSTATE	(45)	(41)
PARAGANGLIOMA, NOS	1 (2%)	
#TESTIS	(45)	(43)
INTERSTITIAL-CELL TUMOR	33 (73%)	32 (74%)
NERVOUS SYSTEM		
#BRAIN	(44)	(42)
ASTROCYTOMA	1 (2%)	
SPECIAL SENSE ORGANS		
*ZYMBAL'S GLAND	(46)	(44)
CARCINOMA,NOS		1 (2%)
SQUAMOUS CELL CARCINOMA		4 (9%)
MUSCULOSKELETAL SYSTEM		
NONE		

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

A1. MALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
BODY CAVITIES		
*BODY CAVITIES	(46)	(44)
MESOTHELIOMA, NOS		2 (5%)
ALL OTHER SYSTEMS		
TAIL		
BASAL-CELL CARCINOMA		
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	6	7
MORIBUND SACRIFICE	2	17
SCHEDULED SACRIFICE	15	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	27	18
ANIMAL MISSING		3
@ INCLUDES AUTOLYZED ANIMALS		
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	40
TOTAL PRIMARY TUMORS	61	112
TOTAL ANIMALS WITH BENIGN TUMORS	33	38
TOTAL BENIGN TUMORS	55	68
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	26
TOTAL MALIGNANT TUMORS	5	35
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	
TOTAL SECONDARY TUMORS	4	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	9
TOTAL UNCERTAIN TUMORS	1	9
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 MALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	@50	50
ANIMALS NECROPSIED	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	48
INTEGUMENTARY SYSTEM		
*SKIN	(48)	(48)
SQUAMOUS CELL PAPILLOMA		2 (4%)
SQUAMOUS CELL CARCINOMA		2 (4%)
BASAL-CELL CARCINOMA		1 (2%)
ADENOMA, NOS		1 (2%)
*SUBCUT TISSUE	(48)	(48)
SQUAMOUS CELL CARCINOMA		1 (2%)
ADENOMA, NOS		1 (2%)
SARCOMA, NOS	1 (2%)	
FIBROMA	3 (6%)	5 (10%)
FIBROSARCOMA	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG	(48)	(48)
CARCINOMA, NOS, METASTATIC		1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	3 (6%)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(48)	(48)
MALIGNANT LYMPHOMA, NOS	1 (2%)	
LEUKEMIA,NOS	1 (2%)	
UNDIFFERENTIATED LEUKEMIA		1 (2%)
MYELOMONOCYTIC LEUKEMIA	4 (8%)	3 (6%)
#LYMPH NODE	(44)	(33)
SQUAMOUS CELL CARCINOMA, METASTA		1 (3%)

\# 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.

A2. MALE RATS (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
CIRCULATORY SYSTEM		
#HEART/VENTRICLE	(48)	(48)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(47)	(45)
ADENOCARCINOMA, NOS	1 (2%)	
SARCOMA, NOS	1 (2%)	
#LIVER	(48)	(48)
BILE DUCT ADENOMA		1 (2%)
NEOPLASTIC NODULE		14 (29%)
HEPATOCELLULAR CARCINOMA	1 (2%)	8 (17%)
*BILE DUCT	(48)	(48)
BILE DUCT CARCINOMA		1 (2%)
#STOMACH	(48)	(42)
SQUAMOUS CELL PAPILLOMA		1 (2%)
#JEJUNUM	(46)	(46)
CYSTADENOCARCINOMA, NOS		1 (2%)
#ILEUM	(46)	(46)
SARCOMA, NOS	1 (2%)	
#COLON	(46)	(38)
ADENOCARCINOMA, NOS		1 (3%)
ADENOMATOUS POLYP, NOS		1 (3%)
URINARY SYSTEM		
#KIDNEY	(48)	(48)
TRANSITIONAL-CELL CARCINOMA		1 (2%)
TUBULAR-CELL ADENOMA		1 (2%)
#URINARY BLADDER	(43)	(42)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)
ENDOCRINE SYSTEM		
#PITUITARY	(38)	(41)
ADENOMA, NOS	9 (24%)	10 (24%)

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

A2. MALE RATS (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
CHROMOPHOBE ADENOMA		1 (2%)
#ADRENAL	(47)	(48)
CORTICAL ADENOMA		1 (2%)
PHEOCHROMOCYTOMA	7 (15%)	9 (19%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	1 (2%)
#THYROID	(48)	(47)
NEOPLASM, NOS		1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)
C-CELL CARCINOMA	1 (2%)	2 (4%)
#PARATHYROID	(28)	(23)
ADENOMA, NOS	1 (4%)	
#PANCREATIC ISLETS	(46)	(43)
ISLET-CELL ADENOMA		4 (9%)
REPRODUCTIVE SYSTEM		
*PREPUTIAL GLAND	(48)	(48)
CARCINOMA,NOS		1 (2%)
ADENOMA, NOS		4 (8%)
#TESTIS	(47)	(47)
INTERSTITIAL-CELL TUMOR	42 (89%)	40 (85%)
NERVOUS SYSTEM		
#BRAIN	(48)	(47)
GLIOMA, NOS	1 (2%)	
ASTROCYTOMA		1 (2%)
OLIGODENDROGLIOMA		1 (2%)
SPECIAL SENSE ORGANS		
*ZYMBAL'S GLAND	(48)	(48)
CARCINOMA,NOS		4 (8%)
SQUAMOUS CELL CARCINOMA		3 (6%)
MUSCULOSKELETAL SYSTEM		
NONE		

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

A2. MALE RATS (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
BODY CAVITIES		
*BODY CAVITIES	(48)	(48)
MESOTHELIOMA, NOS		3 (6%)
MESOTHELIOMA, MALIGNANT	2 (4%)	
ALL OTHER SYSTEMS		
SITE UNKNOWN		
CARCINOMA,NOS		1
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	6	6
MORIBUND SACRIFICE	8	13
SCHEDULED SACRIFICE	5	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	30	26
ANIMAL MISSING		
ANIMAL DELETED(WRONG SEX)	1	
@ INCLUDES AUTOLYZED ANIMALS		
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	44	47
TOTAL PRIMARY TUMORS	80	141
TOTAL ANIMALS WITH BENIGN TUMORS	43	43
TOTAL BENIGN TUMORS	62	85
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	32
TOTAL MALIGNANT TUMORS	18	38
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3
TOTAL SECONDARY TUMORS	1	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		18
TOTAL UNCERTAIN TUMORS		18
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 A3.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET(LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	49	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	43
INTEGUMENTARY SYSTEM		
*SKIN	(49)	(44)
SQUAMOUS CELL PAPILLOMA		1 (2%)
SQUAMOUS CELL CARCINOMA		2 (5%)
*SUBCUT TISSUE	(49)	(44)
SQUAMOUS CELL CARCINOMA		1 (2%)
SARCOMA, NOS		2 (5%)
FIBROMA		2 (5%)
FIBROSARCOMA		1 (2%)
RESPIRATORY SYSTEM		
#LUNG	(49)	(43)
CARCINOMA, NOS, METASTATIC		1 (2%)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	3 (7%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)
SARCOMA, NOS, METASTATIC		1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(49)	(44)
MALIGNANT LYMPHOMA, NOS		1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	
MYELOMONOCYTIC LEUKEMIA		1 (2%)
MONOCYTIC LEUKEMIA	2 (4%)	
#LYMPH NODE	(41)	(36)
SARCOMA, NOS, METASTATIC		1 (3%)
#RENAL LYMPH NODE	(41)	(36)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	

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

A3. FEMALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
CIRCULATORY SYSTEM		
NONE		
DIGESTIVE SYSTEM		
#LIVER	(49)	(43)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)	
HEPATOCELLULAR CARCINOMA	2 (4%)	1 (2%)
#PANCREAS	(46)	(39)
CARCINOMA, NOS, METASTATIC		1 (3%)
#STOMACH	(48)	(41)
CARCINOMA, NOS, METASTATIC		1 (2%)
#SMALL INTESTINE	(47)	(40)
ADENOMATOUS POLYP, NOS		1 (3%)
MUCINOUS CYSTADENOCARCINOMA		1 (3%)
#ILEUM	(47)	(40)
ADENOCARCINOMA, NOS		1 (3%)
ADENOMATOUS POLYP, NOS		1 (3%)
#COLON	(43)	(35)
ADENOCARCINOMA, NOS		1 (3%)
URINARY SYSTEM		
NONE		
ENDOCRINE SYSTEM		
#PITUITARY	(43)	(30)
ADENOMA, NOS	3 (7%)	2 (7%)
ADENOCARCINOMA, NOS	2 (5%)	
CHROMOPHOBE ADENOMA	15 (35%)	13 (43%)
#ADRENAL	(46)	(43)
PHEOCHROMOCYTOMA	2 (4%)	1 (2%)
#THYROID	(47)	(40)
ADENOMA, NOS	1 (2%)	

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

A3. FEMALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
ADENOCARCINOMA, NOS	2 (4%)	1 (3%)
C-CELL ADENOMA	1 (2%)	2 (5%)
#THYROID FOLLICLE	(47)	(40)
PAPILLARY CYSTADENOMA, NOS		1 (3%)
#PANCREATIC ISLETS	(46)	(39)
ISLET-CELL ADENOMA		1 (3%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(49)	(44)
CARCINOMA,NOS		1 (2%)
ADENOMA, NOS	1 (2%)	
ADENOCARCINOMA, NOS	1 (2%)	4 (9%)
PAPILLARY ADENOCARCINOMA		1 (2%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (2%)	2 (5%)
FIBROADENOMA	4 (8%)	4 (9%)
*CLITORIS	(49)	(44)
CARCINOMA,NOS		1 (2%)
*CLITORAL GLAND	(49)	(44)
SQUAMOUS CELL PAPILLOMA		1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)
ADENOMA, NOS		3 (7%)
#UTERUS	(48)	(43)
NEOPLASM, NOS		2 (5%)
ADENOCARCINOMA, NOS	4 (8%)	11 (26%)
LEIOMYOSARCOMA		1 (2%)
ENDOMETRIAL STROMAL POLYP	10 (21%)	11 (26%)
#OVARY	(47)	(43)
CARCINOMA, NOS, METASTATIC		1 (2%)
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
*EAR CANAL	(49)	(44)
FIBROMA	1 (2%)	

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

A3. FEMALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
*ZYMBAL'S GLAND	(49)	(44)
CARCINOMA,NOS		5 (11%)
SQUAMOUS CELL CARCINOMA		5 (11%)
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
*BODY CAVITIES	(49)	(44)
MESOTHELIOMA, MALIGNANT	1 (2%)	
ALL OTHER SYSTEMS		
SITE UNKNOWN		
LEIOMYOSARCOMA		1
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	5	15
MORIBUND SACRIFICE	7	15
SCHEDULED SACRIFICE	15	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	23	15
ANIMAL MISSING		

@ INCLUDES AUTOLYZED ANIMALS

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

A3. FEMALE RATS (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	40
TOTAL PRIMARY TUMORS	56	97
TOTAL ANIMALS WITH BENIGN TUMORS	27	31
TOTAL BENIGN TUMORS	39	48
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	34
TOTAL MALIGNANT TUMORS	17	47
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	3
TOTAL SECONDARY TUMORS	4	7
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2
TOTAL UNCERTAIN TUMORS		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		
TOTAL UNCERTAIN TUMORS		

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

TABLE A4.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49
INTEGUMENTARY SYSTEM		
*SKIN	(50)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)
SQUAMOUS CELL CARCINOMA		3 (6%)
BASAL-CELL CARCINOMA	1 (2%)	
SEBACEOUS ADENOCARCINOMA		1 (2%)
*SUBCUT TISSUE	(50)	(49)
FIBROMA	1 (2%)	1 (2%)
FIBROSARCOMA	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG	(50)	(48)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(50)	(49)
UNDIFFERENTIATED LEUKEMIA	1 (2%)	
MYELOMONOCYTIC LEUKEMIA	3 (6%)	4 (8%)
LYMPHOCYTIC LEUKEMIA		2 (4%)
#SPLEEN	(48)	(48)
UNDIFFERENTIATED LEUKEMIA	1 (2%)	
CIRCULATORY SYSTEM		
NONE		

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

A4. FEMALE RATS (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
DIGESTIVE SYSTEM		
#LIVER	(50)	(48)
NEOPLASTIC NODULE		3 (6%)
HEPATOCELLULAR CARCINOMA		3 (6%)
#ILEUM	(48)	(46)
LEIOMYOSARCOMA	1 (2%)	
URINARY SYSTEM		
#URINARY BLADDER	(46)	(43)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)
ENDOCRINE SYSTEM		
#PITUITARY	(40)	(39)
ADENOMA, NOS	17 (43%)	19 (49%)
CHROMOPHOBE ADENOMA		1 (3%)
#ADRENAL	(49)	(47)
CORTICAL ADENOMA	1 (2%)	3 (6%)
PHEOCHROMOCYTOMA	3 (6%)	4 (9%)
#ADRENAL MEDULLA	(49)	(47)
GANGLIONEUROMA	1 (2%)	
#THYROID	(45)	(44)
FOLLICULAR-CELL ADENOMA		1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	
C-CELL ADENOMA	1 (2%)	1 (2%)
C-CELL CARCINOMA	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(48)	(47)
ISLET-CELL ADENOMA	2 (4%)	
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(49)
ADENOCARCINOMA, NOS		3 (6%)
FIBROADENOMA	19 (38%)	11 (22%)

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

A4. FEMALE RATS (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
*CLITORIS	(50)	(49)
CARCINOMA,NOS		1 (2%)
SQUAMOUS CELL CARCINOMA		2 (4%)
ADENOMA, NOS		3 (6%)
*CLITORAL GLAND	(50)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)	
SQUAMOUS CELL CARCINOMA		1 (2%)
ADENOMA, NOS	2 (4%)	
#UTERUS	(50)	(49)
ADENOCARCINOMA, NOS	1 (2%)	10 (20%)
ENDOMETRIAL STROMAL POLYP	10 (20%)	5 (10%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)
#OVARY	(49)	(47)
GRANULOSA-CELL TUMOR	1 (2%)	
NERVOUS SYSTEM		
#BRAIN	(50)	(48)
ASTROCYTOMA		2 (4%)
SPECIAL SENSE ORGANS		
*ZYMBAL'S GLAND	(50)	(49)
CARCINOMA,NOS		3 (6%)
SQUAMOUS CELL CARCINOMA		9 (18%)
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		

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

A4. FEMALE RATS (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
ALL OTHER SYSTEMS		
*MULTIPLE ORGANS	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)
SITE UNKNOWN		
SQUAMOUS CELL CARCINOMA	1	
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	5	7
MORIBUND SACRIFICE	3	15
SCHEDULED SACRIFICE	5	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	37	23
ANIMAL MISSING		
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	38	45
TOTAL PRIMARY TUMORS	73	106
TOTAL ANIMALS WITH BENIGN TUMORS	35	34
TOTAL BENIGN TUMORS	59	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	35
TOTAL MALIGNANT TUMORS	13	48
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1
TOTAL SECONDARY TUMORS	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3
TOTAL UNCERTAIN TUMORS	1	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		
TOTAL UNCERTAIN TUMORS		

@ INCLUDES AUTOLYZED ANIMALS

* 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 FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		1
ANIMALS NECROPSIED	48	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	44
INTEGUMENTARY SYSTEM		
*SKIN	(48)	(44)
HEMANGIOSARCOMA		1 (2%)
RESPIRATORY SYSTEM		
#LUNG	(48)	(42)
ALVEOLAR/BRONCHIOLAR ADENOMA		5 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (13%)	1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(48)	(44)
MALIGNANT LYMPHOMA, NOS	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	2 (5%)
#SPLEEN	(47)	(43)
HEMANGIOMA	1 (2%)	1 (2%)
#LIVER	(48)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)
CIRCULATORY SYSTEM		
NONE		
DIGESTIVE SYSTEM		
#LIVER	(48)	(44)
HEPATOCELLULAR CARCINOMA	7 (15%)	32 (73%)

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

B1. MALE MICE (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
HEMANGIOMA	1 (2%)	
*GALLBLADDER	(48)	(44)
ADENOMATOUS POLYP, NOS		1 (2%)
#STOMACH	(47)	(42)
SQUAMOUS CELL CARCINOMA	1 (2%)	
URINARY SYSTEM		
NONE		
ENDOCRINE SYSTEM		
#THYROID	(47)	(35)
FOLLICULAR-CELL ADENOMA	1 (2%)	
REPRODUCTIVE SYSTEM		
NONE		
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		

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

B1. MALE MICE (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	3	7
MORIBUND SACRIFICE		1
SCHEDULED SACRIFICE	5	
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	42	41
ANIMAL MISSING		1
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	35
TOTAL PRIMARY TUMORS	21	44
TOTAL ANIMALS WITH BENIGN TUMORS	2	7
TOTAL BENIGN TUMORS	3	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	33
TOTAL MALIGNANT TUMORS	18	37
TOTAL ANIMALS WITH SECONDARY TUMORS#		
TOTAL SECONDARY TUMORS		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		
TOTAL UNCERTAIN TUMORS		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		
TOTAL UNCERTAIN TUMORS		

@ INCLUDES AUTOLYZED ANIMALS

* 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 MALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING	1	
ANIMALS NECROPSIED	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50
INTEGUMENTARY SYSTEM		
NONE		
RESPIRATORY SYSTEM		
#LUNG	(49)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	3 (6%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	2 (4%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)
#SPLEEN	(49)	(49)
HEMANGIOSARCOMA	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	
#LYMPH NODE	(42)	(39)
HEPATOCELLULAR CARCINOMA, METAST		1 (3%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	1 (3%)
#PEYERS PATCH	(49)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)
#KIDNEY	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)
CIRCULATORY SYSTEM		
NONE		

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

B2. MALE MICE (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
DIGESTIVE SYSTEM		
#LIVER	(48)	(49)
HEPATOCELLULAR ADENOMA	2 (4%)	
HEPATOCELLULAR CARCINOMA	6 (13%)	41 (84%)
HEMANGIOSARCOMA, UNC PRIM OR MET	1 (2%)	
*GALLBLADDER	(49)	(50)
ADENOMATOUS POLYP, NOS		2 (4%)
*RECTUM	(49)	(50)
ADENOCARCINOMA, NOS		1 (2%)
URINARY SYSTEM		
NONE		
ENDOCRINE SYSTEM		
#ADRENAL	(44)	(47)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)
#THYROID	(45)	(46)
FOLLICULAR-CELL ADENOMA		3 (7%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)
REPRODUCTIVE SYSTEM		
#TESTIS	(48)	(49)
INTERSTITIAL-CELL TUMOR		1 (2%)
*EPIDIDYMIS	(49)	(50)
HIBERNOMA		1 (2%)
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
NONE		

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

B2. MALE MICE (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@		7
MORIBUND SACRIFICE		1
SCHEDULED SACRIFICE	10	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	39	37
ANIMAL MISSING	1	

@ INCLUDES AUTOLYZED ANIMALS

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

B2. MALE MICE (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	45
TOTAL PRIMARY TUMORS	26	64
TOTAL ANIMALS WITH BENIGN TUMORS	8	13
TOTAL BENIGN TUMORS	8	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	44
TOTAL MALIGNANT TUMORS	17	51
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	4
TOTAL SECONDARY TUMORS	1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		
TOTAL UNCERTAIN TUMORS		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC	1	
TOTAL UNCERTAIN TUMORS	1	

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

TABLE B3.

SUMMARY OF TH INCIDENCE OF NEOPLASMS IN FEMALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		2
ANIMALS NECROPSIED	48	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	43
INTEGUMENTARY SYSTEM		
*SUBCUT TISSUE	(48)	(45)
FIBROSARCOMA		2 (4%)
LEIOMYOSARCOMA	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG	(46)	(42)
HEPATOCELLULAR CARCINOMA, METAST		2 (5%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (7%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	3 (7%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(48)	(45)
MALIGNANT LYMPHOMA, NOS	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	1 (2%)
#SPLEEN	(46)	(40)
HEMANGIOSARCOMA	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	
#LYMPH NODE	(39)	(35)
MALIGNANT LYMPHOMA, NOS		1 (3%)
#THYMUS	(31)	(17)
MALIGNANT LYMPHOMA, NOS	1 (3%)	
CIRCULATORY SYSTEM		
NONE		

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

B3. FEMALE MICE (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
DIGESTIVE SYSTEM		
#LIVER	(47)	(43)
HEPATOCELLULAR CARCINOMA	1 (2%)	37 (86%)
FIBROSARCOMA	1 (2%)	
*GALLBLADDER	(48)	(45)
PAPILLARY ADENOMA		1 (2%)
#STOMACH	(44)	(37)
SQUAMOUS CELL PAPILLOMA	1 (2%)	
#COLON	(40)	(37)
LEIOMYOSARCOMA	1 (3%)	
URINARY SYSTEM		
NONE		
ENDOCRINE SYSTEM		
#PITUITARY	(42)	(29)
CARCINOMA,NOS	1 (2%)	
ADENOMA, NOS	2 (5%)	1 (3%)
#ADRENAL	(45)	(40)
CORTICAL ADENOMA		1 (3%)
PHEOCHROMOCYTOMA	1 (2%)	3 (8%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(48)	(45)
ADENOCARCINOMA, NOS		1 (2%)
#UTERUS	(45)	(39)
LEIOMYOSARCOMA	1 (2%)	
ENDOMETRIAL STROMAL POLYP	3 (7%)	
#OVARY	(45)	(39)
TUBULAR ADENOMA	1 (2%)	
NERVOUS SYSTEM		
NONE		

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

B3. FEMALE MICE (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	6	10
MORIBUND SACRIFICE	2	3
SCHEDULED SACRIFICE	5	
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	37	35
ANIMAL MISSING		2

@ INCLUDES AUTOLYZED ANIMALS

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

B3. FEMALE MICE (LOW DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	38
TOTAL PRIMARY TUMORS	24	52
TOTAL ANIMALS WITH BENIGN TUMORS	11	7
TOTAL BENIGN TUMORS	11	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	37
TOTAL MALIGNANT TUMORS	13	45
TOTAL ANIMALS WITH SECONDARY TUMORS#		2
TOTAL SECONDARY TUMORS		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		
TOTAL UNCERTAIN TUMORS		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		
TOTAL UNCERTAIN TUMORS		

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

TABLE B4.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		1
ANIMALS NECROPSIED	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49
INTEGUMENTARY SYSTEM		
*SUBCUT TISSUE	(50)	(49)
SARCOMA, NOS		1 (2%)
RESPIRATORY SYSTEM		
#LUNG	(50)	(48)
HEPATOCELLULAR CARCINOMA, METAST		5 (10%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM		
*MULTIPLE ORGANS	(50)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)
*HEMATOPOIETIC SYSTEM	(50)	(49)
NEOPLASM, NOS		1 (2%)
#LIVER	(50)	(49)
KUPFFER-CELL SARCOMA		3 (6%)
CIRCULATORY SYSTEM		
NONE		
DIGESTIVE SYSTEM		
#LIVER	(50)	(49)
HEPATOCELLULAR CARCINOMA	1 (2%)	43 (88%)

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

B4. FEMALE MICE (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
#STOMACH	(49)	(44)
SQUAMOUS CELL PAPILLOMA		1 (2%)
URINARY SYSTEM		
#KIDNEY	(50)	(45)
TUBULAR-CELL ADENOMA		1 (2%)
#URINARY BLADDER	(48)	(43)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)
ENDOCRINE SYSTEM		
#PITUITARY	(42)	(33)
ADENOMA, NOS	1 (2%)	
CHROMOPHOBE ADENOMA	2 (5%)	
REPRODUCTIVE SYSTEM		
#OVARY/OVIDUCT	(47)	(35)
PAPILLARY ADENOMA	1 (2%)	
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
*HARDERIAN GLAND	(50)	(49)
PAPILLARY ADENOMA	1 (2%)	
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
*BODY CAVITIES	(50)	(49)
MESOTHELIOMA, MALIGNANT		1 (2%)

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

B4. FEMALE MICE (HIGH DOSE AND CONTROL): NEOPLASMS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
ALL OTHER SYSTEMS		
NONE		
ANIMAL DISPOSITION SUMMARY		
ANIMALS INITIALLY IN STUDY	50	50
NATURAL DEATH@	2	11
MORIBUND SACRIFICE		2
SCHEDULED SACRIFICE	10	5
ACCIDENTALLY KILLED		
TERMINAL SACRIFICE	38	31
ANIMAL MISSING		1
@ INCLUDES AUTOLYZED ANIMALS		
TUMOR SUMMARY		
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	46
TOTAL PRIMARY TUMORS	11	58
TOTAL ANIMALS WITH BENIGN TUMORS	7	6
TOTAL BENIGN TUMORS	7	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	44
TOTAL MALIGNANT TUMORS	4	51
TOTAL ANIMALS WITH SECONDARY TUMORS#		5
TOTAL SECONDARY TUMORS		5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1
TOTAL UNCERTAIN TUMORS		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		
TOTAL UNCERTAIN TUMORS		
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS		
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN		

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		3
ANIMALS NECROPSIED	46	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	46	43
INTEGUMENTARY SYSTEM		
*SKIN	(46)	(44)
INFLAMMATION, NOS		1 (2%)
ULCER, NOS		2 (5%)
*SUBCUT TISSUE	(46)	(44)
FIBROSIS		1 (2%)
RESPIRATORY SYSTEM		
#TRACHEA	(45)	(40)
INFLAMMATION, NOS	9 (20%)	8 (20%)
INFLAMMATION, CHRONIC	10 (22%)	
#LUNG/BRONCHUS	(46)	(43)
BRONCHIECTASIS		2 (5%)
INFLAMMATION, NOS		1 (2%)
INFLAMMATION, CHRONIC	8 (17%)	
#BRONCHIAL MUCOUS GLA	(46)	(43)
ABSCESS, NOS	1 (2%)	
NECROSIS, NOS	1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)	
#LUNG/BRONCHIOLE	(46)	(43)
INFLAMMATION, NOS	1 (2%)	5 (12%)
INFLAMMATION, FOCAL	1 (2%)	
#LUNG	(46)	(43)
ATELECTASIS	1 (2%)	
CONGESTION, NOS	1 (2%)	
EDEMA, NOS	1 (2%)	
BRONCHOPNEUMONIA, NOS		1 (2%)

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

C1. MALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, FOCAL	3 (7%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)	11 (26%)
INFLAMMATION, SUPPURATIVE	1 (2%)	
INFLAMMATION, NECROTIZING		
PNEUMONIA, CHRONIC MURINE	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	
PERIVASCULITIS	5 (11%)	
HYPERPLASIA, NOS		1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)
HEMATOPOIETIC SYSTEM		
#SPLEEN	(46)	(42)
THROMBOSIS, NOS	1 (2%)	
FIBROSIS	1 (2%)	
FIBROSIS, FOCAL		2 (5%)
INFARCT, HEALED	1 (2%)	
HEMOSIDEROSIS		4 (10%)
RETICULOCYTOSIS	1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		4 (10%)
HYPERPLASIA, ERYTHROID	12 (26%)	8 (19%)
HYPERPLASIA, RETICULUM CELL	8 (17%)	
#LYMPH NODE	(38)	(34)
INFLAMMATION, NOS	1 (3%)	1 (3%)
NECROSIS, CENTRAL		1 (3%)
HYPERPLASIA, NOS	1 (3%)	3 (9%)
HYPERPLASIA, RETICULUM CELL	3 (8%)	
#MEDIASTINAL L.NODE	(38)	(34)
PLASMACYTOSIS	1 (3%)	
CIRCULATORY SYSTEM		
*LYMPHATIC VESSELS	(46)	(44)
INFLAMMATION, NOS	1 (2%)	
#MYOCARDIUM	(46)	(43)
INFLAMMATION, NOS	1 (2%)	12 (28%)
INFLAMMATION, INTERSTITIAL	22 (48%)	21 (49%)
INFLAMMATION, CHRONIC FOCAL	3 (7%)	
FIBROSIS	7 (15%)	17 (40%)

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

C1. MALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
*AORTA	(46)	(44)
MINERALIZATION		1 (2%)
INFLAMMATION, NOS		1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	
*PULMONARY ARTERY	(46)	(44)
MINERALIZATION		5 (11%)
HYPERTROPHY, NOS	1 (2%)	
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(38)	(38)
PERIVASCULITIS		1 (3%)
HYPERPLASIA, FOCAL		1 (3%)
#LIVER	(46)	(42)
NECROSIS, FOCAL	3 (7%)	4 (10%)
NECROSIS, COAGULATIVE	1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	8 (19%)
HYPERPLASIA, FOCAL	23 (50%)	19 (45%)
HEMATOPOIESIS		1 (2%)
#LIVER/PERIPORTAL	(46)	(42)
FIBROSIS	1 (2%)	1 (2%)
*BILE DUCT	(46)	(44)
INFLAMMATION, NOS	6 (13%)	
HYPERPLASIA, NOS	32 (70%)	17 (39%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)
#PANCREAS	(42)	(39)
INFLAMMATION, NOS	10 (24%)	18 (46%)
DEGENERATION, CYSTIC		1 (3%)
HYPERPLASIA, INTRADUCTAL	1 (2%)	1 (3%)
#PANCREATIC DUCT	(42)	(39)
INFLAMMATION, NOS		1 (3%)
HYPERPLASIA, NOS		2 (5%)
#PANCREATIC ACINUS	(42)	(39)
ATROPHY, NOS	4 (10%)	3 (8%)
HYPERPLASIA, FOCAL		1 (3%)
#STOMACH	(45)	(42)
EPIDERMAL INCLUSION CYST	1 (2%)	

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

C1. MALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
INFLAMMATION, NOS		7 (17%)
ULCER, NOS	2 (4%)	
HYPERPLASIA, NOS	6 (13%)	3 (7%)
HYPERPLASIA, FOCAL		1 (2%)
HYPERKERATOSIS	1 (2%)	2 (5%)
ACANTHOSIS	1 (2%)	3 (7%)
#SMALL INTESTINE	(43)	(41)
INFLAMMATION, FOCAL		1 (2%)
#PEYERS PATCH	(43)	(41)
HYPERPLASIA, NOS	7 (16%)	5 (12%)
#COLON	(43)	(38)
NEMATODIASIS	3 (7%)	
PARASITISM		1 (3%)
URINARY SYSTEM		
#KIDNEY	(46)	(42)
GLOMERULONEPHRITIS, NOS	33 (72%)	40 (95%)
INFLAMMATION, INTERSTITIAL	1 (2%)	
ABSCESS, NOS		1 (2%)
FIBROSIS		1 (2%)
#URINARY BLADDER	(42)	(40)
INFLAMMATION, NOS	1 (2%)	4 (10%)
HYPERPLASIA, EPITHELIAL	3 (7%)	8 (20%)
ENDOCRINE SYSTEM		
#PITUITARY	(41)	(37)
HYPERPLASIA, NOS	3 (7%)	
HYPERPLASIA, CHROMOPHOBE-CELL	2 (5%)	
#ADRENAL CORTEX	(43)	(43)
HYPERTROPHY, FOCAL	1 (2%)	
HYPERPLASIA, NOS	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)
#ADRENAL MEDULLA	(43)	(43)
NECROSIS, NOS	1 (2%)	
CALCIFICATION, NOS	1 (2%)	

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

C1. MALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
HYPERPLASIA, NODULAR	1 (2%)	2 (5%)
HYPERPLASIA, NOS	6 (14%)	1 (2%)
#THYROID	(45)	(40)
HYPERPLASIA, ADENOMATOUS	1 (2%)	1 (3%)
HYPERPLASIA, C-CELL	1 (2%)	1 (3%)
#PARATHYROID	(32)	(24)
HYPERPLASIA, NOS		1 (4%)
#PANCREATIC ISLETS	(42)	(39)
HYPERPLASIA, NOS	2 (5%)	3 (8%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(46)	(44)
GALACTOCELE		1 (2%)
HYPERPLASIA, NOS	5 (11%)	9 (20%)
*PREPUTIAL GLAND	(46)	(44)
ABSCESS, NOS	1 (2%)	
HYPERPLASIA, NOS	1 (2%)	1 (2%)
#PROSTATE	(45)	(41)
INFLAMMATION, NOS	21 (47%)	16 (39%)
INFLAMMATION, FOCAL	3 (7%)	2 (5%)
HYPERPLASIA, NOS		1 (2%)
HYPERPLASIA, FOCAL	5 (11%)	2 (5%)
HYPERPLASIA, PAPILLARY	2 (4%)	
METAPLASIA, SQUAMOUS	5 (11%)	3 (7%)
#TESTIS	(45)	(43)
MINERALIZATION		4 (9%)
ATROPHY, NOS	2 (4%)	11 (26%)
ASPERMATOGENESIS	1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	19 (42%)	14 (33%)
#TESTIS/TUBULE	(45)	(43)
MINERALIZATION		1 (2%)
DEGENERATION, NOS	6 (13%)	5 (12%)
NERVOUS SYSTEM		
NONE		

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

C1. MALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
SPECIAL SENSE ORGANS		
*EYE	(46)	(44)
CATARACT		
*EYE/RETINA	(46)	(44)
ATROPHY, NOS		
*EAR CANAL	(46)	(44)
NECROSIS, NOS		1 (2%)
KERATIN-PEARL FORMATION		1 (2%)
*WAX GLAND	(46)	(44)
KERATIN-PEARL FORMATION		1 (2%)
MUSCULOSKELETAL SYSTEM		
*CARTILAGE,NOS	(46)	(44)
CYST, NOS	1 (2%)	
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
SPECIAL MORPHOLOGY SUMMARY		
ANIMAL MISSING/NO NECROPSY		3
AUTO/NECROPSY/HISTO PERF	1	1
AUTO/NECROPSY/NO HISTO		1
AUTOLYSIS/NO NECROPSY	4	3

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	@50	50
ANIMALS NECROPSIED	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	48
INTEGUMENTARY SYSTEM		
*SKIN	(48)	(48)
INFLAMMATION, NOS		1 (2%)
INFLAMMATION, NECROTIZING		3 (6%)
*SUBCUT TISSUE	(48)	(48)
ABSCESS, NOS		1 (2%)
FIBROSIS		1 (2%)
METAPLASIA, OSSEOUS	1 (2%)	
RESPIRATORY SYSTEM		
#TRACHEA	(48)	(47)
INFLAMMATION, NOS	2 (4%)	2 (4%)
#LUNG/BRONCHUS	(48)	(48)
BRONCHIECTASIS	1 (2%)	1 (2%)
INFLAMMATION, NOS	7 (15%)	3 (6%)
METAPLASIA, SQUAMOUS		1 (2%)
#LUNG	(48)	(48)
INFLAMMATION, INTERSTITIAL	4 (8%)	16 (33%)
INFLAMMATION, NECROTIZING	1 (2%)	2 (4%)
PNEUMONIA, CHRONIC MURINE	1 (2%)	
GRANULOMA, FOREIGN BODY		1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	6 (13%)
HEMATOPOIETIC SYSTEM		
#BONE MARROW	(47)	(46)
MEGAKARYOCYTOSIS		2 (4%)
#SPLEEN	(48)	(48)
INFLAMMATION, NOS		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.

C2. MALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
FIBROSIS	1 (2%)	
HEMOSIDEROSIS	1 (2%)	10 (21%)
HYPERPLASIA, HEMATOPOIETIC	9 (19%)	16 (33%)
HYPERPLASIA, ERYTHROID	10 (21%)	23 (48%)
#LYMPH NODE	(44)	(33)
HEMORRHAGE	1 (2%)	
INFLAMMATION, NOS		1 (3%)
HYPERPLASIA, NOS		3 (9%)
RETICULOCYTOSIS		4 (12%)
LYMPHOCYTOSIS		1 (3%)
PLASMACYTOSIS	1 (2%)	
HYPERPLASIA, LYMPHOID	3 (7%)	1 (3%)
CIRCULATORY SYSTEM		
#MYOCARDIUM	(48)	(48)
INFLAMMATION, INTERSTITIAL	23 (48%)	35 (73%)
FIBROSIS	12 (25%)	26 (54%)
*PULMONARY ARTERY	(48)	(48)
MINERALIZATION		2 (4%)
DIGESTIVE SYSTEM		
#LIVER	(48)	(48)
FIBROSIS SEPTAL LIVER	2 (4%)	
NECROSIS, FOCAL	2 (4%)	
METAMORPHOSIS FATTY		6 (13%)
HYPERPLASIA, FOCAL	15 (31%)	8 (17%)
ANGIECTASIS	1 (2%)	4 (8%)
HEMATOPOIESIS		1 (2%)
#LIVER/CENTRILOBULAR	(48)	(48)
NECROSIS, NOS	1 (2%)	
*BILE DUCT	(48)	(48)
INFLAMMATION, NOS	3 (6%)	
HYPERPLASIA, NOS	43 (90%)	22 (46%)
#PANCREAS	(46)	(43)
INFLAMMATION, NOS	17 (37%)	12 (28%)
#PANCREATIC DUCT	(46)	(43)
HYPERPLASIA, NOS		2 (5%)

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

C2. MALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
#PANCREATIC ACINUS	(46)	(43)
HYPERTROPHY, NOS		1 (2%)
HYPERTROPHY, FOCAL		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	3 (7%)
#ESOPHAGUS	(45)	(38)
DYSPLASIA, NOS	1 (2%)	
#STOMACH	(48)	(42)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, FOCAL		1 (2%)
HYPERPLASIA, FOCAL		3 (7%)
HYPERPLASIA, BASAL CELL	1 (2%)	4 (10%)
HYPERKERATOSIS	2 (4%)	1 (2%)
ACANTHOSIS	2 (4%)	1 (2%)
#PEYERS PATCH	(46)	(46)
HYPERPLASIA, NOS	12 (26%)	12 (26%)
#ILEUM	(46)	(46)
INFLAMMATION, NOS	2 (4%)	
#COLON	(46)	(38)
PARASITISM	3 (7%)	1 (3%)
URINARY SYSTEM		
#KIDNEY	(48)	(48)
GLOMERULONEPHRITIS, NOS	47 (98%)	48 (100%)
INFLAMMATION, INTERSTITIAL		1 (2%)
FIBROSIS, DIFFUSE	6 (13%)	19 (40%)
GLOMERULOSCLEROSIS, NOS		2 (4%)
HYPERPLASIA, TUBULAR CELL		1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)
#URINARY BLADDER	(43)	(42)
HYPERPLASIA, EPITHELIAL	1 (2%)	2 (5%)
ENDOCRINE SYSTEM		
#PITUITARY	(38)	(41)
HYPERPLASIA, NOS	1 (3%)	1 (2%)

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

C2. MALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
HYPERPLASIA, FOCAL	2 (5%)	2 (5%)
#ADRENAL MEDULLA	(47)	(48)
HYPERPLASIA, NODULAR	1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	4 (9%)	1 (2%)
#THYROID	(48)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)
HYPERPLASIA, C-CELL	3 (6%)	1 (2%)
#PARATHYROID	(28)	(23)
HYPERPLASIA, NOS	1 (4%)	3 (13%)
#PANCREATIC ISLETS	(46)	(43)
HYPERPLASIA, NOS	1 (2%)	
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(48)	(48)
GALACTOCELE	2 (4%)	
HYPERPLASIA, NOS	4 (8%)	9 (19%)
*PREPUTIAL GLAND	(48)	(48)
NECROSIS, NOS		1 (2%)
#PROSTATE	(44)	(44)
INFLAMMATION, NOS	17 (39%)	20 (45%)
*SEMINAL VESICLE	(48)	(48)
HYPERPLASIA, PAPILLARY		1 (2%)
#TESTIS	(47)	(47)
MINERALIZATION	1 (2%)	1 (2%)
ATROPHY, NOS	6 (13%)	7 (15%)
HYPERPLASIA, NOS		2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)	4 (9%)
#TESTIS/TUBULE	(47)	(47)
MINERALIZATION		2 (4%)
DEGENERATION, NOS		2 (4%)
NERVOUS SYSTEM		
#BRAIN	(48)	(47)
MINERALIZATION		1 (2%)

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

C2. MALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
*BONE	(48)	(48)
OSTEOSCLEROSIS		1 (2%)
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
OMENTUM		
NECROSIS, NOS		1
NECROSIS, FAT	2	
SPECIAL MORPHOLOGY SUMMARY		
AUTOLYSIS/NO NECROPSY	1	2

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

TABLE C3.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	49	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	43
INTEGUMENTARY SYSTEM		
*SKIN	(49)	(44)
INFLAMMATION, NOS		1 (2%)
ULCER, NOS		2 (5%)
RESPIRATORY SYSTEM		
#TRACHEA	(48)	(42)
INFLAMMATION, NOS	9 (19%)	3 (7%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)
INFLAMMATION, CHRONIC	10 (21%)	
POLYP, INFLAMMATORY	1 (2%)	
#LUNG/BRONCHUS	(49)	(43)
BRONCHIECTASIS	1 (2%)	1 (2%)
INFLAMMATION, NOS	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	9 (18%)	
#LUNG/BRONCHIOLE	(49)	(43)
INFLAMMATION, NOS	1 (2%)	
#LUNG	(49)	(43)
EDEMA, NOS		1 (2%)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, FOCAL	7 (14%)	
INFLAMMATION, INTERSTITIAL	2 (4%)	14 (33%)
FIBROSIS, DIFFUSE		1 (2%)
PERIVASCULITIS	6 (12%)	
METAMORPHOSIS FATTY		1 (2%)
HYPERPLASIA, NOS		1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (5%)
#LUNG/ALVEOLI	(49)	(43)
FIBROSIS, FOCAL		2 (5%)

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

C3. FEMALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
HEMATOPOIETIC SYSTEM		
#SPLEEN	(49)	(43)
INFLAMMATICN, NOS		1 (2%)
INFARCT, NOS		1 (2%)
HEMOSIDEROSIS		3 (7%)
HYPERPLASIA, NOS	1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	3 (6%)	19 (44%)
HYPERPLASIA, ERYTHROID	17 (35%)	16 (37%)
HYPERPLASIA, PLASMA CELL	1 (2%)	
HYPERPLASIA, RETICULUM CELL	11 (22%)	
ERYTHROPOIESIS		1 (2%)
#LYMPH NODE	(41)	(26)
INFLAMMATION, NOS	3 (7%)	6 (17%)
HYPERPLASIA, NOS	2 (5%)	3 (8%)
PLASMACYTOSIS	3 (7%)	1 (3%)
HYPERPLASIA, HEMATOPOIETIC		2 (6%)
HYPERPLASIA, PLASMA CELL	1 (2%)	1 (3%)
HYPERPLASIA, LYMPHOID		2 (6%)
#MEDIASTINAL L.NODE	(41)	(36)
PLASMACYTOSIS		3 (8%)
CIRCULATORY SYSTEM		
#MYOCARDIUM	(49)	(43)
INFLAMMATION, NOS	1 (2%)	11 (26%)
INFLAMMATION, INTERSTITIAL	24 (49%)	16 (37%)
FIBROSIS	5 (10%)	4 (9%)
*PULMONARY ARTERY	(49)	(44)
MINERALIZATION		1 (2%)
*PORTAL VEIN	(49)	(44)
THROMBUS, MURAL	1 (2%)	
DIGESTIVE SYSTEM		
#LIVER	(49)	(43)
INFLAMMATION, NOS		3 (7%)
FIBROSIS	1 (2%)	2 (5%)

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

C3. FEMALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
PERIVASCULITIS	1 (2%)	
DEGENERATION, NOS		1 (2%)
NECROSIS, FOCAL	4 (8%)	3 (7%)
NECROSIS, COAGULATIVE	2 (4%)	3 (7%)
METAMORPHOSIS FATTY	1 (2%)	5 (12%)
HYPERPLASIA, NODULAR	1 (2%)	
HYPERPLASIA, FOCAL	22 (45%)	25 (58%)
ANGIECTASIS	1 (2%)	1 (2%)
HEMATOPOIESIS		1 (2%)
*BILE DUCT	(49)	(44)
INFLAMMATION, NOS	5 (10%)	
HYPERPLASIA, NOS	27 (55%)	15 (34%)
#PANCREAS	(46)	(39)
INFLAMMATION, NOS	7 (15%)	14 (36%)
HYPERPLASIA, INTRADUCTAL		2 (5%)
#PANCREATIC DUCT	(46)	(39)
HYPERPLASIA, NOS	1 (2%)	2 (5%)
#PANCREATIC ACINUS	(46)	(39)
ATROPHY, NOS	2 (4%)	4 (10%)
#STOMACH	(48)	(41)
INFLAMMATION, NOS	2 (4%)	2 (5%)
INFLAMMATION, FOCAL	2 (4%)	
HYPERPLASIA, NOS		1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	
HYPERPLASIA, FOCAL		2 (5%)
ACANTHOSIS		2 (5%)
#GASTRIC MUCOSA	(48)	(41)
HYPERPLASIA, NOS	1 (2%)	
#PEYERS PATCH	(47)	(40)
HYPERPLASIA, NOS	6 (13%)	4 (10%)
#COLON	(43)	(35)
NEMATODIASIS	3 (7%)	
PARASITISM		2 (6%)
URINARY SYSTEM		
#KIDNEY	(49)	(43)
HYDRONEPHROSIS	1 (2%)	1 (2%)

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

C3. FEMALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
GLOMERULONEPHRITIS, NOS	33 (67%)	28 (65%)
PYELONEPHRITIS, NOS		1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)	8 (19%)
GLOMERULONEPHRITIS, MEMBRANOUS	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		1 (2%)
HYPERPLASIA, ERYTHROID		1 (2%)
#KIDNEY/CORTEX	(49)	(43)
CYST, NOS		1 (2%)
#URINARY BLADDER	(41)	(39)
INFLAMMATION, NOS	1 (2%)	
HYPERPLASIA, EPITHELIAL		4 (10%)
ENDOCRINE SYSTEM		
#PITUITARY	(43)	(30)
HYPERPLASIA, NOS	2 (5%)	
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)	
#ADRENAL	(46)	(43)
METAMORPHOSIS FATTY		1 (2%)
HYPERPLASIA, FOCAL		1 (2%)
#ADRENAL CORTEX	(46)	(43)
FIBRIN BODY		1 (2%)
NODULE	1 (2%)	
HYPERPLASIA, NOS	7 (15%)	1 (2%)
HYPERPLASIA, FOCAL		3 (7%)
#ADRENAL MEDULLA	(46)	(43)
HYPERPLASIA, NOS	4 (9%)	
#THYROID	(47)	(40)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	
#PANCREATIC ISLETS	(46)	(39)
HYPERPLASIA, NOS	1 (2%)	
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(49)	(44)
GALACTOCELE	5 (10%)	3 (7%)

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

C3. FEMALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
HYPERPLASIA, NOS	17 (35%)	13 (30%)
HYPERPLASIA, PAPILLARY	1 (2%)	
*CLITORAL GLAND	(49)	(44)
ABSCESS, NOS		1 (2%)
*VAGINA	(49)	(44)
NECROSIS, HEMORRHAGIC		1 (2%)
HYPERPLASIA, NOS		1 (2%)
#UTERUS	(48)	(43)
HYDROMETRA	3 (6%)	
HEMORRHAGE		3 (7%)
INFLAMMATION, SUPPURATIVE	1 (2%)	
ABSCESS, NOS	2 (4%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)
HYPERPLASIA, ADENOMATOUS	5 (10%)	3 (7%)
POLYP, INFLAMMATORY		1 (2%)
#UTERUS/ENDOMETRIUM	(48)	(43)
INFLAMMATION, NOS	14 (29%)	12 (28%)
INFLAMMATION, FOCAL	1 (2%)	
INFLAMMATION, SUPPURATIVE	2 (4%)	7 (16%)
HYPERPLASIA, NOS	1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)
HYPERPLASIA, CYSTIC	2 (4%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	
#OVARY/OVIDUCT	(48)	(43)
INFLAMMATION, NOS	1 (2%)	1 (2%)
#OVARY	(47)	(43)
CYST, NOS	4 (9%)	1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)	
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
*EAR CANAL	(49)	(44)
KERATIN-PEARL FORMATION		1 (2%)

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

C3. FEMALE RATS (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
SPECIAL MORPHOLOGY SUMMARY		
AUTO/NECROPSY/NO HISTO		1
AUTOLYSIS/NO NECROPSY	1	6

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

TABLE C4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49
INTEGUMENTARY SYSTEM		
*SKIN	(50)	(49)
EPIDERMAL INCLUSION CYST		2 (4%)
INFLAMMATION, NOS	1 (2%)	
*SUBCUT TISSUE	(50)	(49)
MINERALIZATION	1 (2%)	
ABSCESS, NOS	1 (2%)	
RESPIRATORY SYSTEM		
#TRACHEA	(49)	(45)
INFLAMMATION, NOS		1 (2%)
#LUNG/BRONCHUS	(50)	(48)
INFLAMMATION, NOS	3 (6%)	
INFLAMMATION, FOCAL		2 (4%)
#LUNG	(50)	(48)
INFLAMMATION, INTERSTITIAL	6 (12%)	13 (27%)
FIBROSIS, FOCAL		1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	3 (6%)
METAPLASIA, SQUAMOUS		1 (2%)
HEMATOPOIETIC SYSTEM		
#BONE MARROW	(46)	(45)
OSTEOSCLEROSIS	1 (2%)	
#SPLEEN	(48)	(48)
INFLAMMATION, NOS		5 (10%)
FIBROSIS		1 (2%)

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

C4. FEMALE RATS(HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
HEMOSIDEROSIS	12 (25%)	18 (38%)
HYPERPLASIA, HEMATOPOIETIC	25 (52%)	21 (44%)
HYPERPLASIA, ERYTHROID	19 (40%)	28 (58%)
#SPLENIC CAPSULE	(48)	(48)
HEMORRHAGIC CYST	1 (2%)	
#LYMPH NODE	(47)	(27)
INFLAMMATION, NOS		2 (7%)
HYPERPLASIA, NOS		3 (11%)
PLASMACYTOSIS	1 (2%)	1 (4%)
HYPERPLASIA, LYMPHOID	4 (9%)	3 (11%)
CIRCULATORY SYSTEM		
#MYOCARDIUM	(50)	(48)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, INTERSTITIAL	23 (46%)	22 (46%)
FIBROSIS	15 (30%)	13 (27%)
#ENDOCARDIUM	(50)	(48)
INFLAMMATION, NOS	1 (2%)	
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(50)	(44)
HYPERPLASIA, FOCAL		1 (2%)
#LIVER	(50)	(48)
NECROSIS, FOCAL	2 (4%)	4 (8%)
NECROSIS, COAGULATIVE		1 (2%)
METAMORPHOSIS FATTY	6 (12%)	6 (13%)
CYTOPLASMIC VACUOLIZATION		3 (6%)
HYPERPLASIA, FOCAL	38 (76%)	16 (33%)
HYPERPLASIA, ERYTHROID	1 (2%)	
HEMATOPOIESIS	2 (4%)	1 (2%)
#LIVER/PERIPORTAL	(50)	(48)
FIBROSIS		1 (2%)
#LIVER/HEPATOCYTES	(50)	(48)
DEGENERATION, NOS		1 (2%)
*BILE DUCT	(50)	(49)
INFLAMMATION, NOS	1 (2%)	2 (4%)

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

C4. FEMALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
HYPERPLASIA, NOS	32 (64%)	27 (55%)
HYPERPLASIA, FOCAL	1 (2%)	
#PANCREAS	(48)	(47)
INFLAMMATION, NOS	6 (13%)	12 (26%)
#PANCREATIC DUCT	(48)	(47)
HYPERPLASIA, NOS		1 (2%)
#STOMACH	(48)	(46)
INFLAMMATION, NOS	1 (2%)	3 (7%)
DEGENERATION, NOS		1 (2%)
HYPERPLASIA, NOS		1 (2%)
HYPERPLASIA, FOCAL		2 (4%)
HYPERPLASIA, BASAL CELL		6 (13%)
HYPERKERATOSIS		5 (11%)
ACANTHOSIS	2 (4%)	6 (13%)
#PEYERS PATCH	(48)	(46)
HYPERPLASIA, NOS	15 (31%)	6 (13%)
#COLON	(46)	(28)
PARASITISM	2 (4%)	
URINARY SYSTEM		
#KIDNEY	(50)	(49)
GLOMERULONEPHRITIS, NOS	43 (86%)	45 (92%)
FIBROSIS, DIFFUSE	1 (2%)	
#URINARY BLADDER	(46)	(43)
HYPERPLASIA, EPITHELIAL		6 (14%)
ENDOCRINE SYSTEM		
#PITUITARY	(40)	(39)
PERIVASCULITIS	1 (3%)	
HYPERPLASIA, FOCAL	3 (8%)	
#ADRENAL	(49)	(47)
METAMORPHOSIS FATTY	1 (2%)	
#ADRENAL CORTEX	(49)	(47)
LIPOIDOSIS		1 (2%)

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

C4. FEMALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
HYPERTROPHY, FOCAL		1 (2%)
#ADRENAL MEDULLA	(49)	(47)
HYPERPLASIA, NODULAR	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	
#THYROID	(45)	(44)
CYSTIC FOLLICLES	1 (2%)	
HYPERPLASIA, PAPILLARY		2 (5%)
HYPERPLASIA, C-CELL	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(48)	(47)
HYPERPLASIA, NOS		1 (2%)
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(49)
GALACTOCELE	16 (32%)	6 (12%)
HYPERPLASIA, NOS	8 (16%)	13 (27%)
#UTERUS	(50)	(49)
HEMORRHAGE		1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	2 (4%)
#UTERUS/ENDOMETRIUM	(50)	(49)
INFLAMMATION, NOS	22 (44%)	22 (45%)
INFLAMMATION, NECROTIZING		1 (2%)
HYPERPLASIA, NOS	6 (12%)	8 (16%)
HYPERPLASIA, CYSTIC		2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	
#OVARY/OVIDUCT	(50)	(49)
INFLAMMATION, NOS	10 (20%)	2 (4%)
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)
#OVARY	(49)	(47)
CYST, NOS	8 (16%)	6 (13%)
HYPERPLASIA, NOS		3 (6%)
NERVOUS SYSTEM		
NONE		

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

C4. FEMALE RATS (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
SPECIAL SENSE ORGANS		
*EYE	(50)	(49)
CATARACT	1 (2%)	
*EYE/RETINA	(50)	(49)
ATROPHY, NOS	1 (2%)	1 (2%)
*HARDERIAN GLAND	(50)	(49)
HYPERPLASIA, NOS	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
OMENTUM		
NECROSIS, FAT	1	2
SPECIAL MORPHOLOGY SUMMARY		
AUTO/NECROPSY/HISTO PERF		1
AUTOLYSIS/NO NECROPSY		1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		1
ANIMALS NECROPSIED	48	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	44
INTEGUMENTARY SYSTEM		
*SKIN	(48)	(44)
FIBROSIS	1 (2%)	
ALOPECIA	1 (2%)	
*SUBCUT TISSUE	(48)	(44)
ABSCESS, NOS		2 (5%)
NECROSIS, NOS	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG/BRONCHUS	(48)	(42)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, FOCAL	1 (2%)	2 (5%)
#LUNG	(48)	(42)
EDEMA, NOS		1 (2%)
HEMORRHAGE		1 (2%)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, FOCAL		1 (2%)
INFLAMMATION, INTERSTITIAL	14 (29%)	8 (19%)
HYPERPLASIA, EPITHELIAL	2 (4%)	
#LUNG/ALVEOLI	(48)	(42)
INFLAMMATION, FOCAL	2 (4%)	
FIBROSIS, FOCAL	1 (2%)	
HEMATOPOIETIC SYSTEM		
#SPLEEN	(47)	(43)
INFLAMMATION, NOS	1 (2%)	
HYPERPLASIA, NOS	2 (4%)	13 (30%)

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

D1. MALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
HYPERPLASIA, HEMATOPOIETIC	2 (4%)	5 (12%)
HYPERPLASIA, ERYTHROID	2 (4%)	5 (12%)
HYPERPLASIA, LYMPHOID	2 (4%)	
#LYMPH NODE	(44)	(36)
HEMORRHAGIC CYST	1 (2%)	
INFLAMMATION, NOS	13 (30%)	18 (50%)
DEGENERATION, CYSTIC	1 (2%)	
HYPERPLASIA, NOS	2 (5%)	
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	1 (3%)
HYPERPLASIA, RETICULUM CELL		1 (3%)
HYPERPLASIA, LYMPHOID	2 (5%)	2 (6%)
MYELOID METAPLASIA	2 (5%)	
#MEDIASTINAL L.NODE	(44)	(36)
NECROSIS, NOS	1 (2%)	
#PANCREATIC L.NODE	(44)	(36)
INFLAMMATION, NOS	1 (2%)	
#MESENTERIC L. NODE	(44)	(36)
HEMORRHAGE	1 (2%)	
INFLAMMATION, NOS	9 (20%)	
#THYMUS	(34)	(16)
NECROSIS, NOS	1 (3%)	
CIRCULATORY SYSTEM		
#HEART/VENTRICLE	(48)	(42)
MELANIN	2 (4%)	
#MYOCARDIUM	(48)	(42)
INFLAMMATION, INTERSTITIAL	2 (4%)	
FIBROSIS	5 (10%)	
*BLOOD VESSEL	(48)	(44)
INFLAMMATION, NOS	2 (4%)	1 (2%)
*AORTA	(48)	(44)
INFLAMMATION, NOS		1 (2%)
*PULMONARY ARTERY	(48)	(44)
MINERALIZATION	2 (4%)	

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

D1. MALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(47)	(41)
INFLAMMATION, NOS	2 (4%)	
PERIVASCULAR CUFFING	1 (2%)	
#LIVER	(48)	(44)
DEGENERATION, NOS		1 (2%)
NECROSIS, FOCAL	13 (27%)	11 (25%)
METAMORPHOSIS FATTY	3 (6%)	
HYPERPLASIA, NODULAR	2 (4%)	
HYPERPLASTIC NODULE		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	
HYPERPLASIA, DIFFUSE		2 (5%)
ANGIECTASIS	1 (2%)	
MYELOID METAPLASIA	1 (2%)	
#LIVER/HEPATOCYTES	(48)	(44)
DEGENERATION, NOS	1 (2%)	
*GALLBLADDER	(48)	(44)
INFLAMMATION, NOS		7 (16%)
INFLAMMATION, FOCAL	1 (2%)	
HYPERPLASIA, PAPILLARY		4 (9%)
*BILE DUCT	(48)	(44)
HYPERPLASIA, NOS		2 (5%)
#PANCREAS	(48)	(43)
INFLAMMATION, NOS	7 (15%)	1 (2%)
INFLAMMATION, FOCAL	1 (2%)	
DEGENERATION, CYSTIC	1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	
#PANCREATIC DUCT	(48)	(43)
HYPERPLASIA, NOS	1 (2%)	
#PANCREATIC ACINUS	(48)	(43)
HYPERTROPHY, NOS		1 (2%)
HYPERTROPHY, FOCAL	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	
#STOMACH	(47)	(42)
INFLAMMATION, NOS	13 (28%)	2 (5%)

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

D1. MALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
ULCER, NOS	1 (2%)	
INFLAMMATION, FOCAL	1 (2%)	3 (7%)
INFLAMMATION, INTERSTITIAL	1 (2%)	
HYPERPLASIA, NOS	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	
HYPERKERATOSIS	3 (6%)	4 (10%)
ACANTHOSIS	3 (6%)	5 (12%)
#GASTRIC MUCOSA	(47)	(42)
HYPERPLASIA, FOCAL	1 (2%)	
#PEYERS PATCH	(48)	(43)
HYPERPLASIA, NOS	2 (4%)	5 (12%)
#ILEUM	(48)	(43)
HEMORRHAGE	1 (2%)	
INFLAMMATION, NOS	2 (4%)	
#COLON	(45)	(36)
PARASITISM	1 (2%)	
URINARY SYSTEM		
#KIDNEY	(47)	(44)
GLOMERULONEPHRITIS, NOS	6 (13%)	7 (16%)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, INTERSTITIAL	23 (49%)	18 (41%)
#KIDNEY/TUBULE	(47)	(44)
NECROSIS, FOCAL	1 (2%)	
#URINARY BLADDER	(48)	(42)
INFLAMMATION, NOS	4 (8%)	
HYPERPLASIA, EPITHELIAL	9 (19%)	5 (12%)
ENDOCRINE SYSTEM		
#PITUITARY	(42)	(34)
HYPERPLASIA, NOS	3 (7%)	
HYPERPLASIA, FOCAL	3 (7%)	
#ADRENAL	(45)	(43)
NODULE		2 (5%)

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

D1. MALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
#ADRENAL/CAPSULE	(45)	(43)
HYPERPLASIA, NOS		6 (14%)
#ADRENAL CORTEX	(45)	(43)
NODULE	1 (2%)	1 (2%)
HYPERTROPHY, FOCAL	1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)	
#ADRENAL MEDULLA	(45)	(43)
DEGENERATION, NOS	1 (2%)	
#THYROID	(47)	(35)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	
HYPERPLASIA, PAPILLARY	1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	
#PANCREATIC ISLETS	(48)	(43)
HYPERPLASIA, NOS	2 (4%)	
REPRODUCTIVE SYSTEM		
*PREPUTIAL GLAND	(48)	(44)
ABSCESS, NOS	2 (4%)	
#TESTIS	(47)	(43)
HYPERPLASIA, INTERSTITIAL CELL		4 (9%)
#TESTIS/TUBULE	(47)	(43)
DEGENERATION, NOS	4 (9%)	
NERVOUS SYSTEM		
#BRAIN	(48)	(43)
MINERALIZATION		1 (2%)
#CEREBRAL CORTEX	(48)	(43)
MINERALIZATION	3 (6%)	
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
NONE		

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

D1. MALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
SPECIAL MORPHOLOGY SUMMARY		
ANIMAL MISSING/NO NECROPSY		1
AUTO/NECROPSY/HISTO PERF		1
AUTOLYSIS/NO NECROPSY	2	5

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING	1	
ANIMALS NECROPSIED	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50
INTEGUMENTARY SYSTEM		
*SKIN	(49)	(50)
INFLAMMATION, NOS	1 (2%)	
INFLAMMATION, FOCAL	3 (6%)	
INFLAMMATION, NECROTIZING	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG/BRONCHUS	(49)	(49)
INFLAMMATION, FOCAL	1 (2%)	
#LUNG/BRONCHIOLE	(49)	(49)
INFLAMMATION, FOCAL	1 (2%)	
#LUNG	(49)	(49)
INFLAMMATION, INTERSTITIAL	10 (20%)	6 (12%)
HYPERPLASIA, EPITHELIAL		1 (2%)
HEMATOPOIETIC SYSTEM		
#SPLEEN	(49)	(49)
HYPERPLASIA, NOS	6 (12%)	1 (2%)
RETICULOCYTOSIS	1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	5 (10%)	1 (2%)
HYPERPLASIA, ERYTHROID		3 (6%)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)
#LYMPH NODE	(42)	(39)
CONGESTION, NOS		1 (3%)
INFLAMMATION, NOS	10 (24%)	3 (8%)
HYPERPLASIA, NOS	1 (2%)	
RETICULOCYTOSIS	2 (5%)	1 (3%)

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

D2. MALE MICE (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
HYPERPLASIA, HEMATOPOIETIC		4 (10%)
HYPERPLASIA, RETICULUM CELL		1 (3%)
HYPERPLASIA, LYMPHOID	3 (7%)	2 (5%)
CIRCULATORY SYSTEM		
#HEART	(49)	(49)
MINERALIZATION	1 (2%)	
#MYOCARDIUM	(49)	(49)
INFLAMMATION, NOS		2 (4%)
DIGESTIVE SYSTEM		
#LIVER	(48)	(49)
FIBROSIS SEPTAL LIVER		1 (2%)
NECROSIS, FOCAL	9 (19%)	3 (6%)
METAMORPHOSIS FATTY		1 (2%)
HYPERPLASTIC NODULE	1 (2%)	3 (6%)
*GALLBLADDER	(49)	(50)
INFLAMMATION, NOS		1 (2%)
HYPERPLASIA, PAPILLARY		2 (4%)
*BILE DUCT	(49)	(50)
HYPERPLASIA, NOS		1 (2%)
#PANCREAS	(47)	(44)
INFLAMMATION, NOS	1 (2%)	
#STOMACH	(48)	(48)
INFLAMMATION, FOCAL	2 (4%)	
INFLAMMATION, NECROTIZING	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	
HYPERKERATOSIS	1 (2%)	
ACANTHOSIS	1 (2%)	
#PEYERS PATCH	(49)	(47)
HYPERPLASIA, NOS	7 (14%)	2 (4%)
#COLON	(43)	(39)
PARASITISM	3 (7%)	2 (5%)

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

D2. MALE MICE (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
URINARY SYSTEM		
#KIDNEY	(49)	(50)
POLYCYSTIC KIDNEY		1 (2%)
GLOMERULONEPHRITIS, NOS	2 (4%)	16 (32%)
INFLAMMATION, INTERSTITIAL	16 (33%)	2 (4%)
HYPERPLASIA, TUBULAR CELL		1 (2%)
#URINARY BLADDER	(48)	(49)
HYPERPLASIA, EPITHELIAL	4 (8%)	1 (2%)
ENDOCRINE SYSTEM		
#ADRENAL	(44)	(47)
HYPERPLASIA, NOS	3 (7%)	2 (4%)
#ADRENAL/CAPSULE	(44)	(47)
HYPERPLASIA, NOS	3 (7%)	
#ADRENAL CORTEX	(44)	(47)
HYPERTROPHY, FOCAL		1 (2%)
#THYROID	(45)	(46)
HYPERPLASIA, FOLLICULAR-CELL		2 (4%)
#PANCREATIC ISLETS	(47)	(44)
HYPERPLASIA, NOS		3 (7%)
REPRODUCTIVE SYSTEM		
*PREPUTIAL GLAND	(49)	(50)
ABSCESS, NOS	1 (2%)	1 (2%)
#TESTIS	(48)	(49)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)
#TESTIS/TUBULE	(48)	(49)
DEGENERATION, NOS		2 (4%)
*EPIDIDYMIS	(49)	(50)
INFLAMMATION, NOS	1 (2%)	
NERVOUS SYSTEM		
NONE		

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

D2. MALE MICE (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
NONE		
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
ADIPOSE TISSUE		
INFLAMMATION, ACUTE	1	
OMENTUM		
NECROSIS, FAT	1	
SPECIAL MORPHOLOGY SUMMARY		
NO LESION REPORTED	5	
ANIMAL MISSING/NO NECROPSY	1	
AUTO/NECROPSY/HISTO PERF		2

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

TABLE D3.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (LOW DOSE AND CONTROL)

	LOW DOSE CONTROL	LOW DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		2
ANIMALS NECROPSIED	48	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	43
INTEGUMENTARY SYSTEM		
*SUBCUT TISSUE	(48)	(45)
MINERALIZATION	1 (2%)	
FIBROSIS	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG/BRONCHUS	(46)	(42)
INFLAMMATION, FOCAL	1 (2%)	
#LUNG	(46)	(42)
INFLAMMATION, INTERSTITIAL	10 (22%)	7 (17%)
HYPERPLASIA, EPITHELIAL	3 (7%)	
HEMATOPOIETIC SYSTEM		
#BONE MARROW	(45)	(41)
MYELOFIBROSIS	1 (2%)	
#SPLEEN	(46)	(40)
HYPERPLASIA, NOS		14 (35%)
HYPERPLASIA, HEMATOPOIETIC	16 (35%)	6 (15%)
HYPERPLASIA, ERYTHROID	6 (13%)	5 (13%)
HYPERPLASIA, LYMPHOID	10 (22%)	
HEMATOPOIESIS	1 (2%)	
MYELOPOIESIS	1 (2%)	
#LYMPH NODE	(39)	(35)
CYST, NOS	1 (3%)	
INFLAMMATION, NOS	15 (38%)	18 (51%)
HYPERPLASIA, NOS	1 (3%)	1 (3%)
RETICULOCYTOSIS	1 (3%)	

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

D3. FEMALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
LYMPHOCYTOSIS		1 (3%)
HYPERPLASIA, HEMATOPOIETIC	2 (5%)	
MYELOID METAPLASIA	1 (3%)	
CIRCULATORY SYSTEM		
#HEART/VENTRICLE	(46)	(42)
MELANIN	4 (9%)	
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(45)	(37)
INFLAMMATION, NOS	2 (4%)	
PERIVASCULAR CUFFING	4 (9%)	
#LIVER	(47)	(43)
INFLAMMATION, NOS	1 (2%)	
NECROSIS, FOCAL	22 (47%)	3 (7%)
NECROSIS, COAGULATIVE		1 (2%)
METAMORPHOSIS FATTY		1 (2%)
HYPERPLASTIC NODULE	1 (2%)	2 (5%)
ANGIECTASIS	1 (2%)	
HEMATOPOIESIS	3 (6%)	
*GALLBLADDER	(48)	(45)
INFLAMMATION, NOS	3 (6%)	
HYPERPLASIA, PAPILLARY		2 (4%)
*BILE DUCT	(48)	(45)
INFLAMMATION, NOS	1 (2%)	
HYPERPLASIA, NOS		1 (2%)
#PANCREAS	(44)	(41)
INFLAMMATION, NOS	5 (11%)	
PERIARTERITIS	1 (2%)	
#PANCREATIC DUCT	(44)	(41)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	
#STOMACH	(44)	(37)
INFLAMMATION, NOS	7 (16%)	
ULCER, NOS	1 (2%)	
INFLAMMATION, FOCAL	1 (2%)	3 (8%)

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

D3. FEMALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
HYPERPLASIA, NOS	1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)	
HYPERKERATOSIS	1 (2%)	2 (5%)
ACANTHOSIS	1 (2%)	2 (5%)
#GASTRIC MUCOSA	(44)	(37)
HYPERPLASIA, FOCAL	1 (2%)	
#PEYERS PATCH	(44)	(40)
HYPERPLASIA, NOS	1 (2%)	1 (3%)
URINARY SYSTEM		
#KIDNEY	(46)	(43)
GLOMERULONEPHRITIS, NOS	14 (30%)	6 (14%)
INFLAMMATION, INTERSTITIAL	16 (35%)	9 (21%)
#URINARY BLADDER	(46)	(34)
INFLAMMATION, NOS	4 (9%)	3 (9%)
HYPERPLASIA, EPITHELIAL	10 (22%)	2 (6%)
ENDOCRINE SYSTEM		
#PITUITARY	(42)	(29)
HYPERPLASIA, FOCAL	6 (14%)	
#ADRENAL/CAPSULE	(45)	(40)
HYPERPLASIA, NOS		2 (5%)
#ADRENAL CORTEX	(45)	(40)
NODULE	3 (7%)	
#THYROID	(43)	(37)
FOLLICULAR CYST, NOS	1 (2%)	
INFLAMMATION, NOS	1 (2%)	
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(48)	(45)
GALACTOCELE	1 (2%)	
HYPERPLASIA, NOS	4 (8%)	3 (7%)

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

D3. FEMALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
#UTERUS	(45)	(39)
HYDROMETRA	1 (2%)	3 (8%)
ABSCESS, NOS	3 (7%)	1 (3%)
FIBROSIS	1 (2%)	
#UTERUS/ENDOMETRIUM	(45)	(39)
INFLAMMATION, NOS	10 (22%)	1 (3%)
INFLAMMATION, SUPPURATIVE	4 (9%)	1 (3%)
HYPERPLASIA, NOS	4 (9%)	4 (10%)
HYPERPLASIA, CYSTIC	18 (40%)	19 (49%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	
#OVARY/OVIDUCT	(45)	(39)
INFLAMMATION, NOS	5 (11%)	
#OVARY	(45)	(39)
CYST, NOS	3 (7%)	2 (5%)
INFLAMMATION, NOS	4 (9%)	1 (3%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	
INFLAMMATION, SUPPURATIVE	10 (22%)	
ABSCESS, NOS	4 (9%)	
DEGENERATION, CYSTIC	1 (2%)	
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
*EYE	(48)	(45)
CATARACT		1 (2%)
*HARDERIAN GLAND	(48)	(45)
HYPERPLASIA, PAPILLARY		1 (2%)
MUSCULOSKELETAL SYSTEM		
*BONE	(48)	(45)
INFLAMMATION, NOS		2 (4%)
RESORPTION	3 (6%)	
BODY CAVITIES		
NONE		

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

D3. FEMALE MICE (LOW DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	LOW DOSE
ALL OTHER SYSTEMS		
OMENTUM		
NECROSIS, FAT	1	1
SPECIAL MORPHOLOGY SUMMARY		
NO LESION REPORTED	1	
ANIMAL MISSING/NO NECROPSY		2
AUTO/NECROPSY/HISTO PERF	2	1
AUTO/NECROPSY/NO HISTO	1	2
AUTOLYSIS/NO NECROPSY	2	3

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

TABLE D4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET (HIGH DOSE AND CONTROL)

	HIGH DOSE CONTROL	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS MISSING		1
ANIMALS NECROPSIED	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49
INTEGUMENTARY SYSTEM		
*SUBCUT TISSUE	(50)	(49)
ABSCESS, NOS	1 (2%)	
RESPIRATORY SYSTEM		
#LUNG/BRONCHUS	(50)	(48)
INFLAMMATION, FOCAL	1 (2%)	
#LUNG/BRONCHIOLE	(50)	(48)
HYPERPLASIA, NOS	1 (2%)	
#LUNG	(50)	(48)
INFLAMMATION, INTERSTITIAL	14 (28%)	6 (13%)
HYPERPLASIA, EPITHELIAL		1 (2%)
HEMATOPOIETIC SYSTEM		
#SPLEEN	(49)	(46)
GROWTH, ALTERATION		1 (2%)
HYPERPLASIA, NOS	9 (18%)	3 (7%)
HYPERPLASIA, HEMATOPOIETIC	6 (12%)	1 (2%)
HYPERPLASIA, ERYTHROID		4 (9%)
HYPERPLASIA, LYMPHOID	2 (4%)	
#HEMOLYMPH NODES	(49)	(46)
INFLAMMATION, NOS	2 (4%)	
HYPERPLASIA, NOS	1 (2%)	
#LYMPH NODE	(44)	(35)
INFLAMMATION, NOS	9 (20%)	4 (11%)
HYPERPLASIA, NOS	3 (7%)	

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

D4. FEMALE MICE (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
RETICULOCYTOSIS	1 (2%)	1 (3%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)	
HYPERPLASIA, LYMPHOID	4 (9%)	
CIRCULATORY SYSTEM		
*CARDIOVASCULAR SYSTE	(50)	(49)
PERIVASCULITIS		1 (2%)
#MYOCARDIUM	(50)	(49)
INFLAMMATION, FOCAL	1 (2%)	
*AORTA	(50)	(49)
INFLAMMATION, NOS		2 (4%)
DIGESTIVE SYSTEM		
#SALIVARY GLAND	(48)	(46)
PERIVASCULAR CUFFING	3 (6%)	
#LIVER	(50)	(49)
NECROSIS, FOCAL	7 (14%)	
HYPERPLASTIC NODULE		2 (4%)
#PANCREAS	(48)	(43)
INFLAMMATION, NOS	2 (4%)	1 (2%)
#STOMACH	(49)	(44)
INFLAMMATION, NOS	1 (2%)	1 (2%)
INFLAMMATION, FOCAL	1 (2%)	1 (2%)
ACANTHOSIS	2 (4%)	3 (7%)
#PEYERS PATCH	(48)	(44)
HYPERPLASIA, NOS	7 (15%)	2 (5%)
#COLON	(38)	(35)
PARASITISM		1 (3%)
URINARY SYSTEM		
#KIDNEY	(50)	(45)
GLOMERULONEPHRITIS, NOS	4 (8%)	9 (20%)

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

D4. FEMALE MICE (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
GLOMERULONEPHRITIS, FOCAL	1 (2%)	
INFLAMMATION, INTERSTITIAL	12 (24%)	5 (11%)
#KIDNEY/TUBULE	(50)	(45)
MINERALIZATION	1 (2%)	
#URINARY BLADDER	(48)	(43)
INFLAMMATION, NOS		2 (5%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)
HYPERPLASIA, PAPILLARY		1 (2%)
ENDOCRINE SYSTEM		
#ADRENAL	(48)	(46)
HYPERPLASIA, NOS		5 (11%)
#ADRENAL/CAPSULE	(48)	(46)
HYPERPLASIA, NOS	5 (10%)	
#ADRENAL CORTEX	(48)	(46)
NODULE	1 (2%)	
HYPERPLASIA, NOS	1 (2%)	
#THYROID	(44)	(42)
INFLAMMATION, FOCAL	1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)
HYPERPLASIA, PAPILLARY	2 (5%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	
REPRODUCTIVE SYSTEM		
*MAMMARY GLAND	(50)	(49)
HYPERPLASIA, NOS	1 (2%)	
#UTERUS	(47)	(35)
HYDROMETRA	13 (28%)	2 (6%)
#UTERUS/ENDOMETRIUM	(47)	(35)
INFLAMMATION, NOS	8 (17%)	1 (3%)
HYPERPLASIA, NOS	8 (17%)	2 (6%)
HYPERPLASIA, CYSTIC	6 (13%)	2 (6%)
#OVARY/OVIDUCT	(47)	(35)
INFLAMMATION, NOS	4 (9%)	

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

D4. FEMALE MICE (HIGH DOSE AND CONTROL): NONNEOPLASTIC LESIONS (CONTINUED)

	HIGH DOSE CONTROL	HIGH DOSE
ABSCESS, NOS	1 (2%)	
#OVARY	(48)	(40)
CYST, NOS	10 (21%)	2 (5%)
HEMORRHAGE		1 (3%)
INFLAMMATION, NOS	4 (8%)	
PERIARTERITIS	1 (2%)	
DEGENERATION, CYSTIC	3 (6%)	
HYPERPLASIA, CYSTIC		1 (3%)
NERVOUS SYSTEM		
NONE		
SPECIAL SENSE ORGANS		
NONE		
MUSCULOSKELETAL SYSTEM		
*BONE	(50)	(49)
INFLAMMATION, NOS		1 (2%)
BODY CAVITIES		
NONE		
ALL OTHER SYSTEMS		
NONE		
SPECIAL MORPHOLOGY SUMMARY		
NO LESION REPORTED	3	
ANIMAL MISSING/NO NECROPSY		1
AUTO/NECROPSY/HISTO PERF	1	

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Integumentary System:				
Squamous-cell Carcinoma[b]	0/36 (0)	0/48 (0)	3/44 (7)	3/48 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.497	0.602
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	78	86
Integumentary System: Squamous-cell				
Papilloma or Carcinoma[b]	0/36 (0)	0/48 (0)	6/44 (14)	5/48 (10)
P Values[c,d]			P = 0.023	P = 0.028
Relative Risk[e]			Infinite	Infinite
Lower limit			1.324	1.263
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	72	86

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Integumentary System: Basal-cell Carcinoma of the Skin[b]	0/36 (0)	0/48 (0)	4/44 (9)	1/48 (2)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.767	0.053
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	86	106
Integumentary System: Basal-cell or Squamous-cell Carcinoma or Squamous-cell Papilloma[b]	0/36 (0)	0/48 (0)	8/44 (18)	6/48 (13)
P Values[c,d]			P = 0.006	P = 0.013
Relative Risk[e]			Infinite	Infinite
Lower Limit			1.892	1.602
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	72	86

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Integumentary System: Fibroma in Subcutaneous Tissue[b]	0/36 (0)	3/48 (6)	1/44 (2)	5/48 (10)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	1.667
Lower Limit			0.044	0.345
Upper Limit			Infinite	10.203
Weeks to First Observed Tumor	--	95	78	103
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/36 (0)	1/48 (2)	1/43 (2)	3/48 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	3.000
Lower Limit			0.045	0.252
Upper Limit			Infinite	154.112
Weeks to First Observed Tumor	--	109	95	106

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	0/36 (0)	1/48 (2)	3/43 (7)	5/48 (10)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	5.000
Lower Limit			0.509	0.590
Upper Limit			Infinite	231.143
Weeks to First Observed Tumor	--	109	95	91
Hematopoietic System: Lymphoma or Leukemia[b]	2/36 (4)	6/48 (13)	6/44 (14)	4/48 (8)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			2.455	0.667
Lower Limit			0.474	0.147
Upper Limit			23.746	2.628
Weeks to First Observed Tumor	79	93	94	100

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	0/36 (0)	1/48 (2)	6/42 (14)	8/48 (17)
P Values[c,d]			P = 0.020	P = 0.015
Relative Risk[e]			Infinite	8.000
Lower Limit			1.388	1.138
Upper Limit			Infinite	346.323
Weeks to First Observed Tumor	--	109	72	78
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	0/36 (0)	1/48 (2)	12/42 (29)	22/48 (46)
P Values[c,d]			P < 0.001	P < 0.001
Relative Risk[e]			Infinite	22.000
Lower Limit			3.185	3.844
Upper Limit			Infinite	873.814
Weeks to First Observed Tumor	--	109	72	78

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Adenoma, NOS[b]	12/32 (38)	9/38 (24)	12/37 (32)	11/41 (27)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.865	1.133
Lower Limit			0.420	0.483
Upper Limit			1.802	2.744
Weeks to First Observed Tumor	101	85	78	94
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	6/35 (17)	8/47 (17)	4/43 (9)	10/48 (31)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.543	1.224
Lower Limit			0.122	0.478
Upper Limit			2.109	3.257
Weeks to First Observed Tumor	107	107	78	101

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma[b]	0/35 (0)	0/48 (0)	2/40 (5)	1/47 (2)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.262	0.055
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	105	106
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	0/35 (0)	0/48 (0)	3/40 (8)	1/47 (2)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.533	0.055
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	103	106

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	2/34 (6)	0/46 (0)	4/39 (10)	4/43 (9)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			1.744	Infinite
Lower Limit			0.269	0.994
Upper Limit			18.348	Infinite
Weeks to First Observed Tumor	--	--	105	97
Preputial Gland: Adenoma, NOS[b]	0/36 (0)	0/48 (0)	1/44 (2)	4/48 (8)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.044	0.929
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	105	97

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor[b]	33/35 (94)	42/47 (89)	32/43 (74)	40/47 (85)
P Values[c,d]			P = 0.018(N)	N.S.
Relative Risk[e]			0.789	0.952
Lower Limit			0.709	0.819
Upper Limit			0.986	1.130
Weeks to First Observed Tumor	78	78	72	78
Zymbal's Gland: Carcinoma, NOS[b]	0/36 (0)	0/48 (0)	1/44 (2)	4/48 (8)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.044	0.929
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	104	48

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Zymbal's Gland: Squamous-cell Carcinoma[b]	0/36 (0)	0/48 (0)	4/44 (9)	3/48 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.767	0.602
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	72	78
Zymbal's Gland: Carcinoma, NOS, or Squamous-cell Carcinoma[b]	0/36 (0)	0/48 (0)	5/44 (11)	7/48 (15)
P Values[c,d]			P = 0.045	P = 0.006
Relative Risk[e]			Infinite	Infinite
Lower Limit			1.044	1.944
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	72	48

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Body Cavities: Mesothelioma, NOS, or Mesothelioma, Malignant[b]	0/36 (0)	2/48 (4)	2/44 (5)	3/48 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	1.500
Lower Limit			0.244	0.180
Upper Limit			Infinite	17.302
Weeks to First Observed Tumor	--	106	86	91

[a]Dosed groups received 800 or 2,000 ppm.

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

[c]Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with its matched control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Integumentary System:				
Squamous-cell Carcinoma[b]	0/39 (0)	0/50 (0)	3/44 (7)	3/49 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.537	0.614
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	78	98
Integumentary System: Squamous-cell Papilloma or Carcinoma[b]	0/39 (0)	0/50 (0)	4/44 (9)	4/49 (8)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.829	0.946
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	78	98

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue[b]	0/39 (0)	1/50 (2)	2/44 (5)	1/49 (2)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	1.020
Lower Limit			0.264	0.013
Upper Limit			Infinite	78.488
Weeks to First Observed Tumor	--	102	78	107
Integumentary System: Sarcoma, NOS[b]	0/39 (0)	0/50 (0)	2/44 (5)	0/49 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	--
Lower Limit			0.264	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	84	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	1/39 (3)	1/50 (2)	4/43 (9)	6/48 (13)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			3.628	6.250
Lower Limit			0.381	0.801
Upper Limit			174.220	280.829
Weeks to First Observed Tumor	107	110	93	97
Hematopoietic System: Lymphoma or Leukemia[b]	4/39 (10)	5/50 (10)	2/44 (5)	6/49 (12)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.443	1.224
Lower Limit			0.042	0.333
Upper Limit			2.914	4.751
Weeks to First Observed Tumor	101	104	72	98

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	2/39 (5)	0/50 (0)	1/43 (2)	3/48 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.453	Infinite
Lower Limit			0.008	0.626
Upper Limit			8.373	Infinite
Weeks to First Observed Tumor	97	--	92	78
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	2/39 (5)	0/50 (0)	1/43 (2)	6/48 (13)
P Values[c,d]			N.S.	P = 0.012
Relative Risk[e]			0.453	Infinite
Lower Limit			0.008	1.667
Upper Limit			8.373	Infinite
Weeks to First Observed Tumor	97	--	92	78

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, or Chromophobe Adenoma[b]	18/37 (49)	17/40 (43)	15/30 (50)	20/39 (51)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			1.028	1.207
Lower Limit			0.589	0.717
Upper Limit			1.741	2.034
Weeks to First Observed Tumor	76	78	64	77
Pituitary: Adenocarcinoma, NOS[b]	2/37 (3)	0/40 (0)	0/30 (0)	0/39 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.000	--
Lower Limit			0.000	--
Upper Limit			4.099	--
Weeks to First Observed Tumor	107	--	--	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Adrenal: Cortical Adenoma[b]	0/37 (0)	1/49 (2)	0/43 (0)	3/47 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			--	3.128
Lower Limit			--	0.262
Upper Limit			--	160.605
Weeks to First Observed Tumor	--	110	--	88
Adrenal: Pheochromocytoma[b]	2/37 (5)	3/49 (6)	1/43 (2)	4/47 (9)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.430	1.390
Lower Limit			0.007	0.248
Upper Limit			7.940	9.029
Weeks to First Observed Tumor	108	109	105	107

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Mammary Gland:				
Adenocarcinoma, NOS[b]	1/39 (3)	0/50 (0)	4/44 (9)	3/49 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			3.545	Infinite
Lower Limit			0.372	0.614
Upper Limit			170.387	Infinite
Weeks to First Observed Tumor	101	--	64	74
Mammary Gland: Fibroadenoma[b]	4/39 (10)	19/50 (38)	4/44 (9)	11/49 (22)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.886	0.591
Lower Limit			0.177	0.286
Upper Limit			4.460	1.160
Weeks to First Observed Tumor	101	107	68	92

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Mammary Gland: Papillary Cystadenocarcinoma, NOS[b]	1/39 (3)	0/50 (0)	2/44 (5)	0/49 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			1.773	--
Lower Limit			0.096	--
Upper Limit			102.188	--
Weeks to First Observed Tumor	107	--	78	--
Mammary Gland: Carcinoma, NOS, Adenocarcinoma, NOS, Papillary Adenocarcinoma, or Papillary Cystadenocarcinoma, NOS[b]	2/39 (5)	0/50 (0)	8/44 (18)	3/49 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			3.545	Infinite
Lower Limit			0.765	0.614
Upper Limit			32.681	Infinite
Weeks to First Observed Tumor	101	--	64	74

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Clitoris or Clitoral Gland:				
Adenoma, NOS[b]	0/39 (0)	2/50 (4)	3/44 (7)	3/49 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	1.531
Lower Limit			0.537	0.183
Upper Limit			Infinite	17.671
Weeks to First Observed Tumor	--	104	78	99
Uterus: Neoplasm, NOS[b]	0/38 (0)	0/50 (0)	2/43 (5)	0/49 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	--
Lower Limit			0.264	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	103	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Clitoris or Clitoral Gland:				
Carcinoma, NOS, or Squamous-cell Carcinoma[b]	0/39 (0)	0/50 (0)	2/44 (5)	4/49 (8)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			0.264	0.946
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	99	77
Uterus or Endometrium:				
Adenocarcinoma, NOS[b]	4/38 (11)	1/50 (2)	11/43 (26)	11/49 (22)
P Values[c,d]			N.S.	P = 0.002
Relative Risk[e]			2.430	11.224
Lower Limit			0.796	1.736
Upper Limit			9.650	470.753
Weeks to First Observed Tumor	95	109	74	92

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	10/38 (26)	10/50 (20)	11/43 (26)	5/49 (10)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.972	0.510
Lower Limit			0.425	0.147
Upper Limit			2.267	1.511
Weeks to First Observed Tumor	78	78	72	68
Uterus: Endometrial Stromal Polyp or Sarcoma[b]	10/38 (26)	11/50 (22)	11/43 (26)	5/49 (10)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.972	0.464
Lower Limit			0.425	0.135
Upper Limit			2.267	1.331
Weeks to First Observed Tumor	78	78	72	68

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Zymbal's Gland: Carcinoma, NOS[b]	0/39 (0)	0/50 (0)	5/44 (11)	3/49 (6)
P Values[c,d]			P = 0.037	N.S.
Relative Risk[e]			Infinite	Infinite
Lower Limit			1.127	0.614
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	68	88
Zymbal's Gland: Squamous-cell Carcinoma[b]	0/39 (0)	0/50 (0)	5/44 (11)	9/49 (18)
P Values[c,d]			P = 0.037	P = 0.001
Relative Risk[e]			Infinite	Infinite
Lower Limit			1.127	2.684
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	72	47

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Zymbal's Gland: Carcinoma, NOS, or Squamous-cell Carcinoma[b]	0/39 (0)	0/50 (0)	10/44 (23)	12/49 (24)
P Values[c,d]			P = 0.001	P < 0.001
Relative Risk[e]			Infinite	Infinite
Lower Limit			2.661	3.742
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	68	47

[a]Dosed groups received 800 or 2,000 ppm.

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

[c]Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with its matched control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	6/48 (13)	5/44 (11)	1/42 (2)	3/49 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.190	0.539
Lower Limit			0.004	0.088
Upper Limit			1.477	2.605
Weeks to First Observed Tumor	96	96	94	78
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	6/48 (13)	10/44 (23)	6/42 (14)	7/49 (14)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			1.143	0.629
Lower Limit			0.329	0.223
Upper Limit			3.946	1.669
Weeks to First Observed Tumor	96	96	94	78

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Hematopoietic System:				
Lymphoma[b]	4/48 (8)	5/44 (11)	3/44 (7)	5/50 (10)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.818	0.880
Lower Limit			0.126	0.217
Upper Limit			4.560	3.582
Weeks to First Observed Tumor	96	96	94	95
Hematopoietic System:				
Lymphoma or Leukemia[b]	4/48 (8)	5/44 (11)	3/44 (7)	6/50 (12)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.818	1.056
Lower Limit			0.126	0.289
Upper Limit			4.558	4.090
Weeks to First Observed Tumor	96	96	94	89

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	7/48 (15)	6/44 (14)	32/44 (73)	41/49 (84)
P Values[c,d]			P < 0.001	P < 0.001
Relative Risk[e]			4.987	6.136
Lower Limit			2.527	3.102
Upper Limit			10.814	13.256
Weeks to First Observed Tumor	78	78	68	78
Liver: Hepatocellular Adenoma or Carcinoma[b]	7/48 (15)	8/44 (18)	32/44 (73)	41/49 (84)
P Values[c,d]			P < 0.001	P < 0.001
Relative Risk[e]			4.987	4.602
Lower Limit			2.527	2.569
Upper Limit			10.814	8.447
Weeks to First Observed Tumor	78	78	68	78

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma[b]	1/47 (2)	0/40 (0)	0/35 (0)	3/46 (7)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.000	Infinite
Lower Limit			0.000	0.527
Upper Limit			24.848	Infinite
Weeks to First Observed Tumor	96	--	--	95
Thyroid: Follicular-cell Adenoma or Papillary Cystadenoma, NOS[b]	1/47 (2)	0/40 (0)	0/35 (0)	4/46 (9)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.000	Infinite
Lower Limit			0.000	0.812
Upper Limit			24.848	Infinite
Weeks to First Observed Tumor	96	--	--	78

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

[a]Dosed groups received doses of 800 or 1,200 ppm.

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

[c]Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with its matched-control group when $P < 0.05$; otherwise, not significant (N.S. is indicated.

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/46 (2)	1/45 (2)	3/42 (7)	1/48 (2)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			3.286	0.938
Lower Limit			0.276	0.012
Upper Limit			168.212	72.085
Weeks to First Observed Tumor	97	78	88	95
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	4/46 (9)	3/45 (7)	4/42 (10)	4/48 (8)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			1.095	1.250
Lower Limit			0.217	0.224
Upper Limit			5.515	8.117
Weeks to First Observed Tumor	97	78	86	75

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Hematopoietic System:				
Lymphoma[b]	5/48 (10)	2/45 (4)	2/45 (4)	2/49 (4)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.427	0.918
Lower Limit			0.042	0.069
Upper Limit			2.455	12.222
Weeks to First Observed Tumor	97	96	89	65
Hematopoietic System:				
Kupffer-cell Sarcoma[b]	0/48 (0)	0/45 (0)	0/45 (0)	3/49 (6)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			--	Infinite
Lower Limit			--	0.554
Upper Limit			--	Infinite
Weeks to First Observed Tumor	--	--	--	78

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	1/47 (2)	1/45 (2)	37/43 (86)	43/49 (88)
P Values[c,d]			P < 0.001	P < 0.001
Relative Risk[e]			40.442	39.490
Lower Limit			7.935	7.832
Upper Limit			1373.351	1336.021
Weeks to First Observed Tumor	97	96	79	58
Pituitary: Adenoma, NOS[b]	2/42 (5)	1/38 (3)	1/29 (3)	0/33 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.724	0.000
Lower Limit			0.013	0.000
Upper Limit			13.163	21.280
Weeks to First Observed Tumor	97	96	90	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	0/42 (0)	2/28 (5)	0/29 (0)	0/33 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			--	0.000
Lower Limit			--	0.000
Upper Limit			--	3.841
Weeks to First Observed Tumor	--	96	--	--
Pituitary: Adenoma, NOS, or Chromophobe Adenoma[b]	2/42 (5)	3/38 (8)	1/29 (3)	0/33 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.724	0.000
Lower Limit			0.013	0.000
Upper Limit			13.163	1.887
Weeks to First Observed Tumor	97	96	90	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

Topography: Morphology	Low-Dose Control	High-Dose Control	Low Dose	High Dose
Adrenal: Pheochromocytoma[b]	1/45 (2)	0/43 (0)	3/40 (8)	0/46 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			3.375	--
Lower Limit			0.284	--
Upper Limit			172.561	--
Weeks to First Observed Tumor	97	--	88	--
Uterus: Endometrial Stromal Polyp[b]	3/45 (7)	0/43 (0)	0/39 (0)	0/35 (0)
P Values[c,d]			N.S.	N.S.
Relative Risk[e]			0.000	--
Lower Limit			0.000	--
Upper Limit			1.905	--
Weeks to First Observed Tumor	53	--	--	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered 3-Amino-9-Ethylcarbazole Hydrochloride in the Diet[a]

(continued)

[a]Dosed groups received doses of 800 or 1,200 ppm.

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

[c]Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of theat dosed group with its matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

[e]The 95% confidence interval of the relative risk between each dosed group and the specified control group.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR 3-AMINO-9-ETHYLCARBAZOLE HYDROCHLORIDE AND ITS HYDROCHLORIDE SALT

APPENDIX G

Analysis of Formulated Diets for 3-Amino-9-Ethylcarbazole and Its Hydrochloride Salt

Duplicate 2-g samples of the diet mixture were each shaken with 50 ml 95% ethanol for 15 minutes. The mixture was allowed to settle overnight, and the absorbance of the supernatant, after appropriate dilution, was measured at 306 nm against a "blank" extracted from 2 g of feed from the same lot used to prepare the diet mixture. Concentrations were determined by comparison with standard solutions. Recoveries were determined from duplicate spiked feed samples worked up simultaneously with each set of diet mixtures. Typical recoveries from spiked feed samples (1,000 ppm) were 98% for the free amine and 88% for the hydrochloride.

Theoretical Concentrations in Diet (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
300	6	340	12.98	280-400
600	6	710	6.61	660-800
400*	4	350	17.89	300-410
800*	4	730	11.89	650-800

*Hydrochloride salt

Review of the Bioassay of 3-Amino-9-Ethylcarbazole (Hydrochloride)* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 3-Amino-9-Ethylcarbazole (Hydrochloride) for carcinogenicity.

The reviewer noted that some carbazole compounds have been shown to be carcinogens. Besides a statistically significant incidence of liver tumors induced in both treated rats and mice, several other tumor types were found at increased rates in rats, including lung tumors. The reviewer said that the experimental design and study appeared to be adequate to define the carcinogenicity of the compound. In view of the results, the reviewer stated that the compound should be considered to pose a potential carcinogenic risk to man. He moved that the report on the

bioassay of 3-Amino-9-Ethylcarbazole (Hydrochloride) be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

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

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

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