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BIOASSAY OF 1H-BENZOTRIAZOLE FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
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Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioassay of 1H-benzotriazole 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: This bioassay of 1H-benzotriazole was conducted by EG&G Mason Research Institute, Worcester, Massachusetts, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI Carcinogenesis Testing Program.

The bioassay was conducted under the supervision of Drs. A. Handler[1] and E. Smith[2], and Mr. G. Wade[3]. NCI project officers were Drs. E. 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. Dr. A. Russfield[3], pathologist, supervised the performance of the necropsies. Histopathologic evaluations were

performed by Drs. R. Fleischman[3] and A. S. K. Murthy[3], and the diagnoses included in this report represent their interpretation.

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], using methods selected for the bioassay program by Dr. J. J. Gart[8].

Chemicals used in this bioassay were analyzed under the direction of Dr. E. Murrill[9], and dosed feed mixtures were analyzed by Dr. M. Hagopian[3]. The analytical results were reviewed by Dr. S. S. Olin[7]. The chemical structure was supplied by NCI.

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 other 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, Dr. Richard A. Griesemer, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire[10], Dr. Sherman Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of 1H-benzotriazole for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered 1H-benzotriazole at one of two time-weighted average doses, either 6,700 or 12,100 ppm, for 78 weeks. Except for five control and five high-dose rats of each sex, which were killed at week 78, all animals surviving at that time were observed for 26-27 additional weeks. Controls consisted of groups of 50 untreated rats of each sex and were observed for 105-106 weeks. All rats surviving to weeks 104-106 were then killed.

Groups of 50 mice of each sex were administered 1H-benzotriazole at one of two time-weighted average doses, either 11,700 or 23,500 ppm, for 104 weeks, then observed for 2 additional weeks. Controls consisted of groups of 50 untreated mice of each sex and were observed for 109 weeks. All mice surviving to weeks 106-109 were then killed.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls throughout most of the bioassay. Survival of animals in dosed and control groups of both rats and mice was at least 60%, and sufficient numbers of animals were at risk for development of late-appearing tumors.

In male rats, neoplastic nodules of the liver occurred at a statistically significant incidence (P = 0.024) in the high-dose group when compared with the control group (controls 0/48, low-dose 0/46, high-dose 5/45 [11%]). The incidence of this tumor in control Fischer 344 rats used in similar bioassays of other test chemicals at the same laboratory has varied from 0 to 11%, with 2/13 historical-control groups having incidences of 10-11%. Since the incidence in the high-dose group is no higher than has been observed in some control groups, these tumors cannot be clearly associated with administration of the test chemical.

Brain tumors occurred in three dosed male rats, in one dosed female rat, and in none of the controls. The occurrence of this rare tumor in dosed animals of each sex is suggestive of, but not considered as sufficient evidence of, carcinogenicity.

In female rats, the incidence of endometrial stromal polyps in the low-dose group was significantly higher (P = 0.010) than that in the corresponding controls (controls 2/48, low-dose 10/45, high-dose 8/50). However, the incidence in the high-dose group was not significant, and when the incidences of endometrial stromal polyps and endometrial stromal sarcomas were combined, they were not significant in either the low- or high-dose groups. Thus, these tumors cannot be associated with administration of the chemical.

In male mice, no tumors occurred in dosed groups at incidences that were significantly higher than those in controls.

In female mice, alveolar/bronchiolar carcinomas occurred at a statistically significant incidence (P = 0.001) only in the low-dose group when compared with the control group (controls 0/49, low-dose 9/49 [18%], high-dose 3/49 [6%]). The incidence in the high-dose group was not significant, and the data did not show a dose-related trend. It should be noted that the incidence of these tumors in control B6C3F1 female mice from other bioassays at this laboratory has varied from 0 to 7%, with a mean of 4%. Therefore, the occurrence of this tumor in the female mice cannot be clearly related to the administration of the test chemical.

In female B6C3F1 mice there was an increased incidence of alveolar/bronchiolar carcinomas, suggesting a possible carcinogenic effect of 1H-benzotriazole. In Fischer 344 rats there was an increased incidence of brain tumors, suggesting a possible carcinogenic effect. However, there was no convincing evidence that under the conditions of this bioassay 1H-benzotriazole was carcinogenic in B6C3F1 mice or Fischer 344 rats of either sex.

TABLE OF CONTENTS

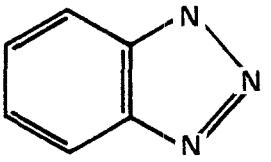
APPENDIXES

TABLES

FIGURES

I. INTRODUCTION

1H-Benzotriazole (CAS 95-14-7; NCI C03521), also commonly called 1,2,3-benzotriazole, is an anti-corrosive chemical used primarily on copper, but also on iron, steel, cadmium, chromium, zinc, and silver-nickel alloys (Sherwin-Williams Chemicals, 1976).



1H-BENZOTRIAZOLE

Like other amine anticorrosives, 1H-benzotriazole can form covalent and coordinate-covalent linkages with metals, which prevent attack by corrosive agents (Bregman, 1963; Sherwin-Williams Chemicals, 1976).

As an anticorrosive, 1H-benzotriazole is used in metal working, in art restoration, and in the construction industry as a tarnish remover and a protective coating (Sherwin-Williams Chemicals, 1976). It functions as a corrosion inhibitor in water cooling systems such as automobile radiators and boilers (Union Carbide, 1966), and in dry cleaning equipment (Levy et al., 1967). It is included in some formulations of automatic dishwasher detergents to prevent tarnishing of metal pots and silverware, and to inhibit the corrosion of metal machine parts (Donaldson, 1971). 1H-Benzotriazole is used in synthetic greases, lubricants, and

hydraulic fluids to prevent the oxidation of these materials which is catalyzed by metal ions. In the electronics industry, it is used to treat packing materials for copper electronic parts (Green, 1969), and to extend the life of polymers that are used as insulators for copper wire (Hansen, 1968).

Other than as an anticorrosive, 1H-benzotriazole is used in electrolytic processing, where the stripping of metals from copper cathodes is eased by pretreatment of the cathode with 1H-benzotriazole (Anaconda American Brass, 1965). In photographic processing, 1H-benzotriazole acts as an antifogging agent in silver-halide emulsions (Sahyun, 1971), restraining the developer and preventing the blackening or fogging of the image due to overdevelopment (West, 1973).

1H-Benzotriazole was selected for study in the Carcinogenesis Testing Program in part because of its use in dishwashing detergents and the possibility that such use could lead to contamination of water supplies.

II. MATERIALS AND METHODS

A. Chemical

Two lots of 1H-benzotriazole were obtained from Aldrich Chemical Company, Milwaukee, Wisconsin, and were stored at 4°C. Lot No. 122917 was used during the subchronic studies, and Lot No. 030737 during the chronic studies. The identity and purity of both lots were determined by analytical procedures. Both lots gave a single homogeneous peak with high-pressure liquid chromatography, and a trace impurity by thin-layer chromatography. Karl Fischer analysis indicated a water content of less than 0.1%. Nonaqueous titration of the amine function with perchloric acid gave a purity of 100.5 $\pm$ 1.0% for Lot No. 030737. Elemental analyses of both lots (C, H, N) were consistent with $C_6H_5N_3$, the molecular formula of the chemical. The melting point of Lot No. 030737 was 97.5-98.5°C, and that of Lot No. 122917 was 96.8-98.9°C; these values were consistent with that of 98-99°C reported previously (Fagel and Ewing, 1951). Infrared, ultraviolet, and nuclear magnetic resonance spectra for both lots were consistent with the structure of 1H-benzotriazole and identical to the spectra in the literature (Fagel and Ewing, 1951; Sadtler Standard Spectra, 1966). Aldrich Chemical Company specifies this material to have a purity of greater than 99%.

B. Dietary Preparation

Diets were prepared once per week by first mixing a weighed amount of chemical with an aliquot of ground Wayne® Lab Blox animal feed (Allied Mills, Inc., Chicago, Ill.) in a mortar. When this premix appeared homogeneous, it was placed in a Patterson-Kelly twin-shell blender with the remaining feed and mixed for 20 minutes. Diets containing 1H-benzotriazole were stored in double plastic bags at 4°C and used within 1 week of preparation.

Selected samples from diets containing 10,000 or 20,000 ppm 1H-benzotriazole were extracted and analyzed by ultraviolet spectrophotometry at intervals of 2-6 weeks after mixing. Concentrations were all within 25% of the theoretical values, but were consistently low. On the basis of temperature-dependent stability analyses performed at Midwest Research Institute, it was concluded that 1H-benzotriazole was stable in feed for 2 weeks at 25°C.

C. Animals

For the subchronic and the chronic studies, male and female Fischer 344 rats and male and female B6C3F1 mice were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The control rats and mice were received earlier

than, and were placed on test prior to, animals in the dosed groups. On arrival at the laboratory, the mice were examined and showed evidence of intestinal parasites. The animals were administered piperazine adipate in the drinking water at 3.0 g/l for two 3-day periods, with an interval of 3 days between the periods. The rats appeared to be normal and were not administered the piperazine adipate. All animals were quarantined for 2 weeks and then were assigned to control or dosed groups so that the means of the weights of the animals in each cage within a particular group were approximately equal. Dosed rats were 42 days of age, control rats were 43 days of age, and both dosed and control mice were 44 days of age when placed on study.

D. Animal Maintenance

Animal rooms were maintained at temperatures ranging from 23-34°C. Air was filtered through Tri-Dek® 15/40 denier dacron filters and air flow was maintained at a velocity permitting six changes of room air per hour. Rooms were illuminated by fluorescent light for 12 hours per day.

Rats were housed five per cage in galvanized steel wire-mesh cages (Fenco Cage Products, Boston, Mass.). Cages were suspended over drop trays lined with newspaper; no filters were used.

Cages and racks were sanitized every week and paper in the drop trays was replaced daily. After the first 52 weeks on study, rats were transferred to suspended solid polycarbonate cages (Lab Products, Inc., Garfield, N. J.), in which they were also housed five per cage. These cages were equipped with disposable nonwoven fiber filter sheets (Webrex®). The polycarbonate cages were sanitized and supplied with fresh bedding twice per week. A corn cob bedding (Sanicel®, Paxton Processing Co., S. Lancaster, Mass.) or a hardwood chip bedding (Aspen-bed®, American Excelsior, Sommerville, Mass.) was used in the rat cages.

Mice were housed 10 per cage in polycarbonate cages equipped with nonwoven fiber filter bonnets (Filtek, Lab Products, Inc., Garfield, N. J.). The number of animals per cage was reduced to five during the last 8 weeks of the chronic studies. Cages and stainless steel perforated lids were sanitized three times per week during the time the mice were housed 10 per cage, and twice per week during the time the mice were housed 5 per cage. Fresh bedding composed of either corn cobs (Sanicel®; Bed-o-Cobs®, Anderson Cob Mills, Inc., Maumee, Ohio) or hardwood chips (Aspen-bed®) was furnished at these times. The filter bonnets were sanitized every 2 weeks. Cage racks for the mice were sanitized every 2 weeks.

There was no rotation of the cages within the racks or of the

racks within the rooms. 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 in 250-ml glass bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced twice per week and were refilled as needed. Sipper tubes and stoppers were cleaned once per week by being soaked in a disinfectant (Environ, Vestal Laboratories, St. Louis, Mo.), and rinsed before use. Controls were fed Wayne® Lab Blox animal feed, and dosed animals were given the same product, which had been mixed with the test chemical. All diets were available ad libitum 7 days per week in Alpine® aluminum feed cups (Curtin-Matheson Scientific, Inc., Woburn, Mass.) or in stainless steel gang hoppers (Scientific Cages, Inc., Bryan, Texas).

All control and dosed rats were housed in the same room as rats being administered one of the following compounds:

Feed Studies

(CAS 53-96-3) fluorenylacetamide
(CAS 120-71-8) 5-methyl-o-anisidine
(CAS 2438-88-2) 2,3,5,6-tetrachloro-4-nitroanisole
(CAS 95-83-0) 4-chloro-o-phenylenediamine
(CAS 5131-60-2) 4-chloro-m-phenylenediamine

Dosed mice were housed in the same room as rats and mice administered one of the following compounds:

Feed Studies

(CAS 2243-62-1) 1,5-naphthalenediamine
(CAS 1465-25-4) N-1-naphthylethylenediamine dihydrochloride

Control mice were housed in the same room as mice administered one of the following compounds:

Feed Studies

(CAS 122-66-77) hydrazobenzene
(CAS 2438-88-2) 2,3,5,6-tetrachloro-4-nitroanisole
(CAS 126-72-7) tris(2,3-dibromopropyl)phosphate
(CAS 1465-25-4) N-1-naphthylethylenediamine dihydrochloride
(CAS 615-66-7) 2-chloro-p-phenylenediamine sulfate
(CAS 142-04-1) aniline hydrochloride

E. Subchronic Studies

Subchronic feeding studies were conducted with Fischer 344 rats and B6C3F1 mice to estimate the maximum tolerated doses of 1H-benzotriazole, on the basis of which two concentrations (hereinafter referred to as "low doses" and "high doses") were determined for the chronic studies. 1H-Benzotriazole was administered in the diet 7 days per week for 8 weeks at doses of 300, 1,000, 3,000, 10,000, or 30,000 ppm. Five males and five females of each species were tested at each dose, and five males and five females of each species served as untreated controls. At the end of the studies, all animals were killed by CO_2 inhalation and necropsied.

In comparison with the controls, mean weight depressions in male

and female rats receiving the chemical were no greater than 12% at each dose ranging from 300 to 10,000 ppm; mean weight depressions increased sharply to 40 and 34% for males and females, respectively, at 30,000 ppm. No deaths occurred before termination of the study. The low and high doses for the chronic studies using rats were set at 10,000 and 20,000 ppm.

In the mice, no effects on mean body weights were seen at doses up to 10,000 ppm, but a slight weight depression of approximately 5% was seen in both sexes at 30,000 ppm. No deaths occurred in the mice before termination of the study. The low and high doses for the chronic studies using mice were set at 20,000 and 40,000 ppm.

F. Chronic Studies

The test groups, doses administered, and times on study of the chronic feeding studies are shown in tables 1 and 2. For both rats and mice, dosage changes were based on weight differences between the dosed and control groups and not on clinical signs or mortality.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity. Body weights were recorded every 2 weeks for the first 12 weeks

Table 1. Chronic Feeding Studies of 1H-Benzotriazole in Rats

Sex and Test Group	Initial No. of Animals[a]	1H-Benzotriazole in Diet[b] (ppm)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)	Time-Weighted Average Dose[c] (ppm)
Male					
Control[d]	50	0		105-106	
Low-Dose	50	10,000	27		
		5,000	51	26-27	6,700
High-Dose	50	20,000	1		
		5,000	7		
		20,000	19		
		10,000	51	27	12,100
Female					
Control[d]	50	0		106	
Low-Dose	50	10,000	27		
		5,000	51	27	6,700
High-Dose	50	20,000	1		
		5,000	7		
		20,000	19		
		10,000	51	27	12,100

[a]Rats were 42 or 43 days of age when placed on study.

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

[c]Time-weighted average dose = $\frac{\Sigma \text{(dose in ppm x no. of weeks at that dose)}}{\Sigma \text{(no. of weeks receiving each dose)}}$

[d]Controls were placed on study 4 weeks earlier than dosed animals.

Table 2. Chronic Feeding Studies of 1H-Benzotriazole in Mice

Sex and Test Group	Initial No. of Animals[a]	1H-Benzotriazole in Diet[b] (ppm)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)	Time-Weighted Average Dose[c] (ppm)
Male					
Control[d]	50	0		109	
Low-Dose	50	20,000	18		
		10,000	86	2	11,700
High-Dose	50	40,000	18		
		20,000	86	2	23,500
Female					
Control[d]	50	0		109	
Low-Dose	50	20,000	18		
		10,000	86	2	11,700
High-Dose	50	40,000	18		
		20,000	86	2	23,500

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

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

[c]Time-weighted average dose = $\frac{\Sigma(\text{dose in ppm} \times \text{no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

[d]Controls were placed on study 14 weeks earlier than dosed animals.

and every month thereafter. Clinical observations were recorded every month. Animals that were moribund and those that survived to the termination of the bioassay were killed using CO_2 anesthesia and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically whenever possible: 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. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

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

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

was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which 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 the dosed male and female rats were lower than those of the corresponding controls throughout most of the bioassay. A dose-related effect was generally indicated by the data for each sex, except for the last 24 weeks in the females when the mean body weights of both the low- and high-dose groups gradually rose toward those of the controls (figure 1). Fluctuation in the growth curve may be due to dose changes.

Eye discoloration or inflammation or both were found in one low-dose male, one high-dose male, two high-dose females, and two control males. One high-dose male had inflammation of the posterior ventral surface. Alopecia was noted in one control male. None of these clinical signs could be clearly related to administration of the test chemical.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and females rats fed 1H-benzotriazole in the diet at the doses of this bioassay, together with those of the controls, are shown in figure 2.

In male rats, the result of the Tarone test for dose-related

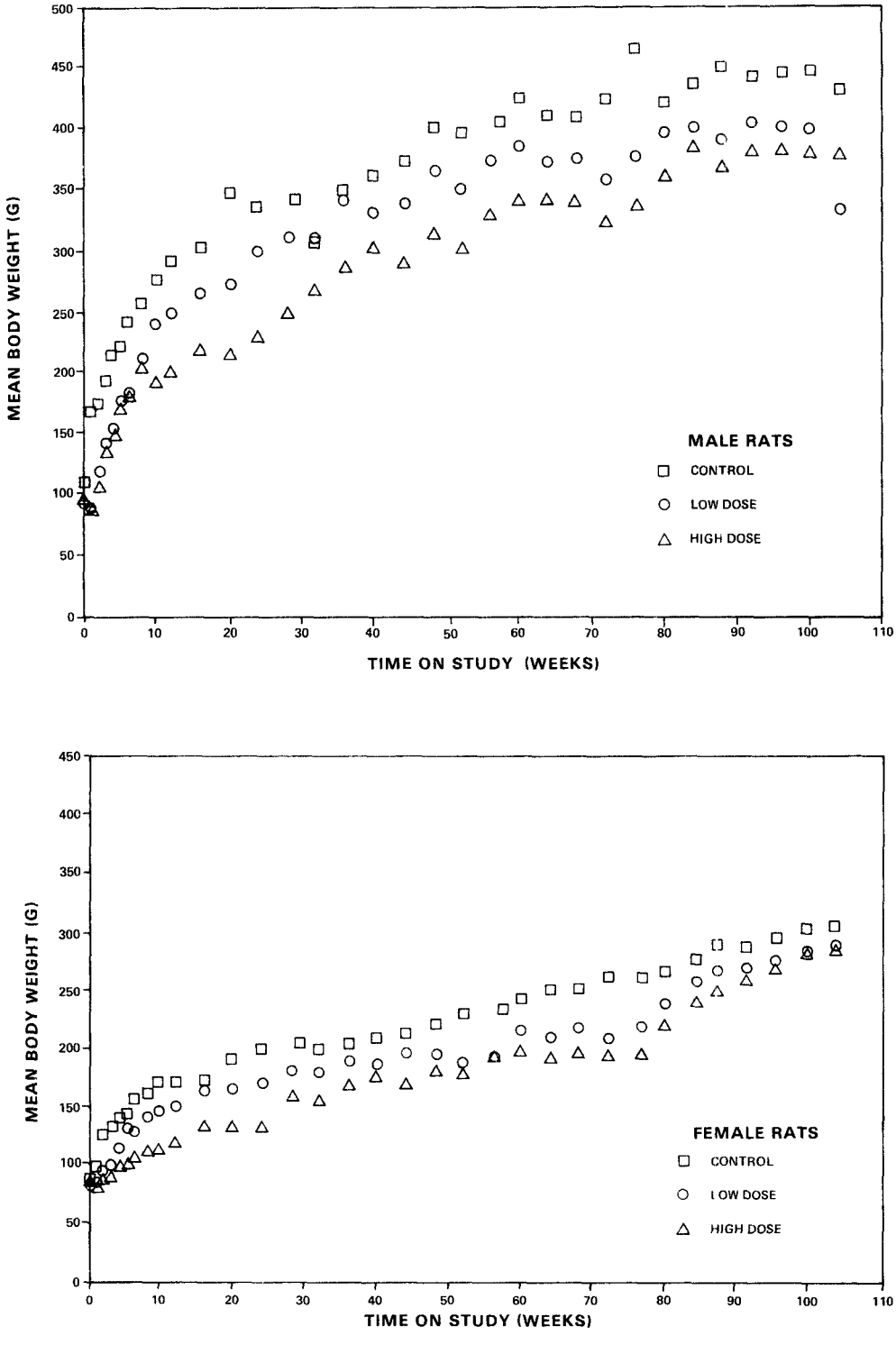


Figure 1. Growth Curves For Rats Fed 1H-Benzotriazole In The Diet

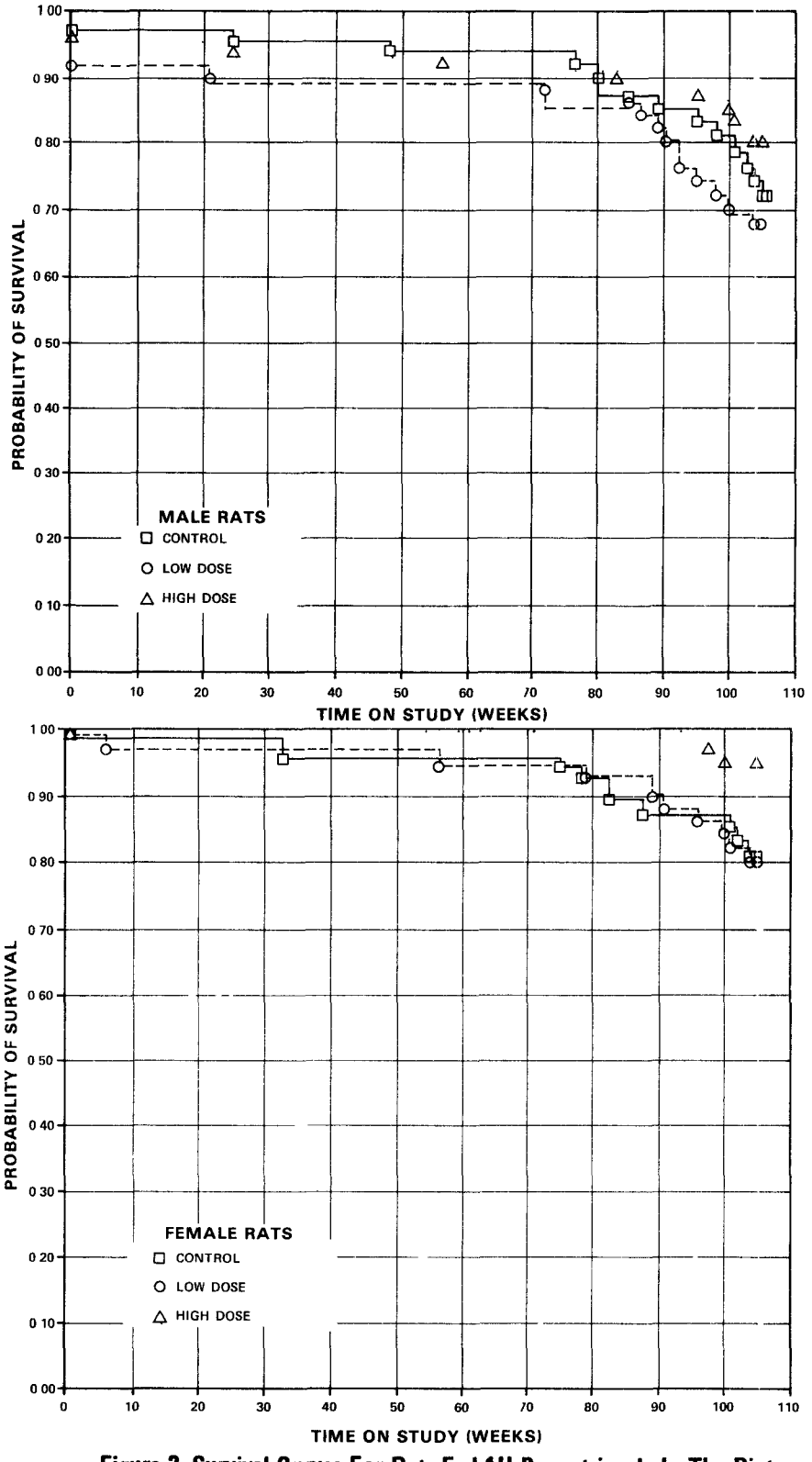


Figure 2. Survival Curves For Rats Fed 1H-Benzotriazole In The Diet

trend in mortality is not significant. In females, the result of the Tarone test is significant (P = 0.049), but in a negative direction.

In males, 36/50 (72%) of the high-dose group, 34/50 (68%) of the low-dose group, and 32/50 (64%) of the controls were alive at the end of the bioassay. In females, 43/50 (86%) of the high-dose group, 40/50 (80%) of the low-dose group, and 36/50 (72%) of the controls were alive at the end of the bioassay. In each sex, five animals in the high-dose and control groups were killed at week 78. Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

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

Hepatic lesions observed in male and female rats consisted of neoplastic nodules of the liver in five males and two females from the high-dose groups. No animals in the control or low-dose groups had neoplastic nodules. Morphologic features of the neoplastic nodules were similar to those described in the literature (Squire and Levitt, 1975). Neoplastic nodules were spherical lesions up to several liver lobules in size composed of

plates of hepatocytes which were sharply demarcated and compressed the adjacent normal parenchyma. Hepatocytes within these nodules showed varying degrees of cytoplasmic change, including clear cell, eosinophilic, and basophilic alterations. Mitotic figures and varying degrees of nuclear atypia including multinucleation and hyperchromasia were noted.

Brain lesions observed in rats as early as week 21 consisted of an oligodendroglioma in one low-dose male and gliomas in two low-dose males and one high-dose female. These tumors were not present in the control animals.

In female rats a non-dose-related increase in the incidence of C-cell adenomas and carcinomas of the thyroid was noted. The incidence in the controls was 0/43, the low-dose group 5/43, and the high-dose group 3/50.

Most of the remaining neoplasms occurred randomly in control and dosed groups, and their incidences and types, with few exceptions, were similar to those observed historically in Fischer 344 rats. With the possible exception of the liver in male rats and the brain in male and female rats, no particular organ or system seemed to be the target of this chemical. One high-dose female had a rare and unusual neoplasm which appeared to be a primary nonchromaffin paraganglioma of the heart (Scotti,

1971). The mass was visible microscopically in the wall of the left ventricle and was composed of sheets of cells arranged in small organoid-like packets. The cells had large oval and round vesicular nuclei, high nuclear cytoplasmic ratios, and a light gray-blue cytoplasm. The endocrine-like appearance of the mass suggested it might be a chemodectoma, since all efforts to demonstrate chromaffin granules were negative.

A variety of degenerative, proliferative, and inflammatory lesions were observed in the control and dosed rats, but none were believed to be related to administration of 1H-benzotriazole.

Although administration of this chemical may be associated with neoplastic nodules of the liver in male Fischer 344 rats, there was no convincing evidence, based on the histopathologic examination, that administration of 1H-benzotriazole was carcinogenic under the conditions of this bioassay.

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 of one group and at an incidence of at least 5% in one or more than one group.

In male rats, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of neoplastic nodules of the liver is significant (P = 0.008), and the results of the Fisher exact test show that the incidence in the high-dose group (5/45, 11%) is significantly higher (P = 0.024) than that in the controls (0/48). At this laboratory, 2/13 historical-control groups have shown incidences of 10-11% of this neoplasm, although the average incidence in the controls is 2%. No other type of liver tumor is observed.

In females, the results of the Cochran-Armitage test for positive dose-associated trend are not significant for any of the incidences of tumors listed. The results of the Fisher exact test show that the incidence of endometrial stromal polyps in the low-dose group is significantly higher (P = 0.010) than that in the corresponding controls. The incidence in the high-dose group is not significant. When the incidences of endometrial stromal polyps and of endometrial stromal sarcomas are combined for analyses, the results of the Fisher exact test are no longer significant in either the low- or high-dose groups. The incidence of C-cell adenomas or carcinomas of the thyroid is higher in the low-dose group than in the control group, but the probability level of 0.028 resulting from the Fisher exact test is above the 0.025 level required for significance when multiple

comparison is considered. The incidence in the high-dose group is not significant.

Significant results in the negative direction are observed in the incidences of pituitary and adrenal tumors in female rats, due to higher incidences in the controls than in the dosed groups.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male and female mice were lower than those of the corresponding controls throughout most of the bioassay, and a dose-related effect was indicated by the data for each sex (figure 3). 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.

Alopecia was noted in 1 low-dose female, 2 high-dose females, 27 control males, and 30 control females. One control male and one control female showed distention of the stomach. A low-dose male had swelling and inflammation in the anal region, and one high-dose male had an abscess in the same area. One high-dose female exhibited poor balance in the month before termination of the study. None of these clinical signs could be clearly related to administration of the test chemical.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed 1H-benzotriazole in the diet at the doses of this bioassay, together with those of the controls, are shown in figure 4.

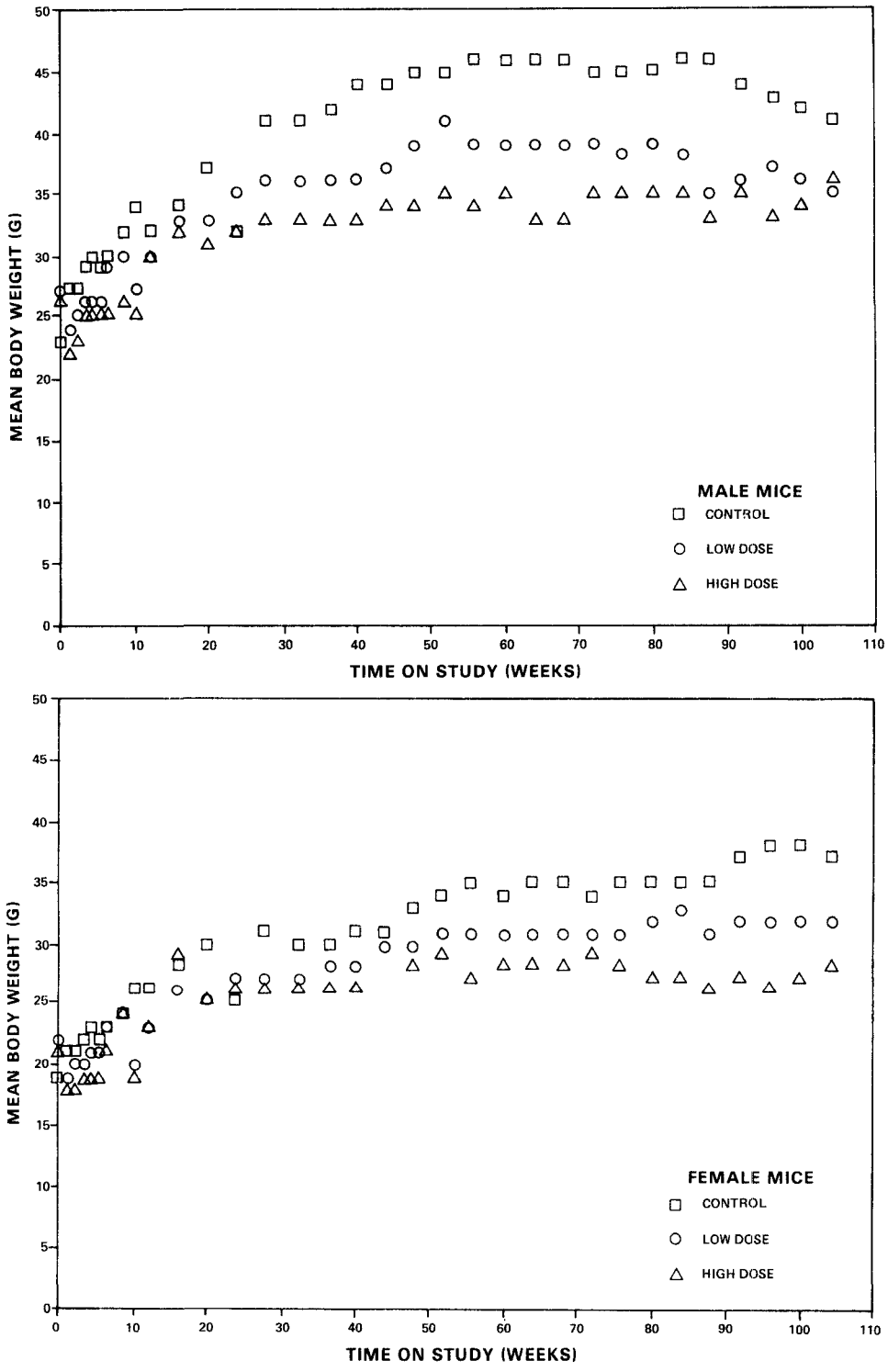


Figure 3. Growth Curves For Mice Fed 1H-Benzotriazole In The Diet

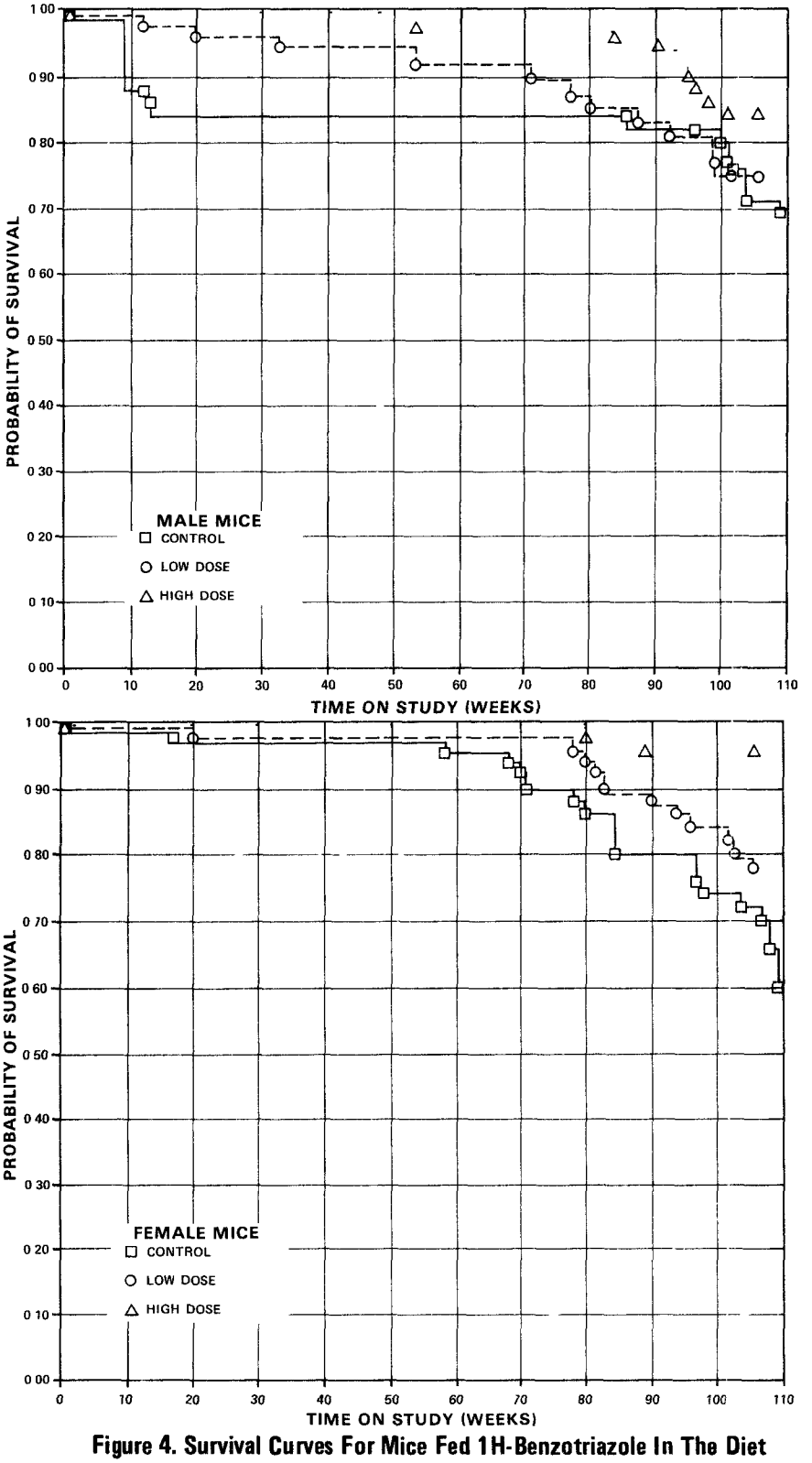


Figure 4. Survival Curves For Mice Fed 1H-Benzotriazole In The Diet

In male mice, the result of the Tarone test for dose-related trend in mortality is not significant. In females, the result of the Tarone test is significant (P = 0.002), but in a negative direction.

In males, 42/50 (84%) of the high-dose group, 36/50 (72%) of the low-dose group, and 33/50 (66%) of the controls were alive at the end of the bioassay. In females, 47/50 (94%) of the high-dose group, 39/50 (78%) of the low-dose group, and 30/50 (60%) of the controls were alive at the end of the bioassay. 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 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

In female mice, a non-dose-related increase in the incidence of alveolar/bronchiolar adenomas and carcinomas was noted. The incidence in the controls was 0/49, the low-dose group 10/49, and the high-dose group 4/49.

The remaining neoplasms occurred randomly in control and dosed groups, and their incidence and type, with few exceptions, were

similar to those observed historically in B6C3F1 mice. No particular organ or system seemed to be the target of this chemical.

A variety of degenerative, proliferative, and inflammatory lesions were seen in the control and dosed mice.

Based on the histopathologic examination, there was no evidence for the carcinogenicity of 1H-benzotriazole in the B6C3F1 mouse under the conditions of this bioassay.

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.

In male mice, the results of the Cochran-Armitage test for positive dose-related trend and those of the Fisher exact test for higher incidence in the dosed groups than in the control group are not significant.

In female mice, the results of the Cochran-Armitage test for positive dose-associated trend are not significant for any of the incidences of tumors listed. The results of the Fisher exact test show that the incidences of alveolar/bronchiolar carcinomas

and of the combination of alveolar/bronchiolar adenomas or carcinomas in the low-dose group are higher than those in the corresponding controls (P = 0.001 in each case); however, the incidences in the high-dose group are not significant. The incidence of alveolar/bronchiolar carcinomas in historical-control female mice in this laboratory is 10/275 (3.6%). The incidence of this tumor in historical-control groups has varied from 0-7%. The association of these lung tumors with administration of the chemical is equivocal, in the absence of a significant incidence in the high-dose female group and in both of the dosed groups of male mice.

Significant results in the negative direction are observed in the combined incidence of lymphomas in male mice, due to the higher incidence of malignant lymphomas in the controls than in either dosed group. A negative result is also observed in the incidence of hepatocellular carcinomas in male mice, but when the incidences of hepatocellular adenomas or carcinomas in male mice are combined, statistical results are not significant. In female mice, a negative result is observed in the incidences of malignant lymphomas, but when all lymphomas are combined, results are no longer significant.

In some of the 95% confidence intervals of relative risk, shown in the tables, one is included; this indicates the absence of

significant results. It should also be noted that some of the intervals have upper limits greater than one, indicating the theoretical possibility of the induction of tumors by 1H-benzotriazole, which could not be detected under the conditions of this test.

V. DISCUSSION

The toxicity of 1H-benzotriazole for Fischer 344 rats and B6C3F1 mice was shown by consistently lowered mean body weights of all dosed groups when compared with corresponding control groups. No other clinical signs were observed that were related to administration of the test chemical. Survival was not decreased in any of the dosed groups compared with respective control groups, and in the female rats or mice, survival in the dosed groups was slightly higher than in the control groups. The survival in the dosed and control groups of both rats and mice was at least 60%, and sufficient numbers of animals were at risk for development of late-appearing tumors.

In male rats, neoplastic nodules of the liver occurred at a statistically significant incidence ($P = 0.024$) in the high-dose group when compared with the control group (controls 0/48, low-dose 0/46, high-dose 5/45 [11%]), and the data showed a dose-related trend ($P = 0.008$). The incidence of this tumor in control Fischer 344 rats used in similar bioassays of other test chemicals at the same laboratory has varied from 0 to 11%, with 2/13 historical-control groups having incidences of 10-11%. Since the incidence in the high-dose group is no higher than has been observed in some control groups, these tumors cannot be clearly associated with administration of the test chemical.

Brain tumors occurred in 3/44 (7%) low-dose males, as compared with 0/46 controls. This tumor was also present in 1/50 (2%) high-dose females, as compared with 0/50 controls. The occurrence of brain tumors in dosed males and females is suggestive of, but not considered as sufficient evidence of, carcinogenicity. The suggestion of carcinogenicity is supported by the absence of these lesions in the concurrent controls and by the historical record of the low incidence of brain tumors (0/250 males and 1/249 females) in control Fischer 344 rats at this laboratory.

In female rats, the incidence of endometrial stromal polyps in the low-dose group was significantly higher ($P = 0.010$) than that in the corresponding controls (controls 2/48, low-dose 10/45, high-dose 8/50). However, the incidence in the high-dose group was not significant, and when the incidences of endometrial stromal polyps and endometrial stromal sarcomas were combined, they were not significant in either the low- or high-dose groups. Thus, these tumors cannot be associated with administration of the chemical.

In male mice, no tumors occurred in dosed groups at incidences that were significantly higher than those in controls.

In female mice, alveolar/bronchiolar carcinomas occurred at a

statistically significant incidence (P = 0.001) only in the low-dose group when compared with the control group (controls 0/49, low-dose 9/49 [18%], high-dose 3/49 [6%]). The incidence in the high-dose groups was not significant and the data did not show a dose-related trend. It should be noted that the incidence of these tumors in control B6C3F1 female mice from other bioassays at this laboratory has varied from 0 to 7%, with a mean of 4%. Therefore, the occurrence of this tumor in the female mice cannot be clearly related to the administration of the test chemical.

1H-Benzotriazole has been reported not to be carcinogenic when total doses of 900-1,000 mg were administered to Wistar rats by weekly subcutaneous injection at a level of 0.1 g/kg body weight in a vehicle consisting of colloidal Infusin or species-nonspecific serum (Vasil'eva, 1970); when a total dose of 92 mg was similarly administered to hybrid (C57BL x CBA)F1 mice, leukemia was induced at an incidence (13.7%) that was significantly higher than that (3.4%) in untreated controls, but not higher than that (11.1%) in vehicle controls.

In female B6C3F1 mice there was an increased incidence of alveolar/bronchiolar carcinomas, suggesting a possible carcinogenic effect of 1H-benzotriazole. In Fischer 344 rats there was an increased incidence of brain tumors, suggesting a

possible carcinogenic effect. However, there was no convincing evidence that under the conditions of this bioassay 1H-benzotriazole was carcinogenic in B6C3F1 mice or Fischer 344 rats of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED 1H-BENZOTRIAZOLE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	46	46
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
FIBROMA		2 (4%)	1 (2%)
LIPOMA		2 (4%)	
*SUBCUT TISSUE	(48)	(50)	(50)
FIBROMA	3 (6%)		
FIBROSARCOMA	2 (4%)		
RESPIRATORY SYSTEM			
#LUNG	(48)	(46)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	2 (4%)
FIBROSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
UNDIFFERENTIATED LEUKEMIA	2 (4%)		
MYELOMONOCYTIC LEUKEMIA		5 (10%)	3 (6%)
#SPLEEN	(48)	(44)	(46)
MYELOMONOCYTIC LEUKEMIA	4 (8%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(48)	(46)	(45)
NEOPLASTIC NODULE			5 (11%)
URINARY SYSTEM			
#KIDNEY	(48)	(45)	(46)
LIPOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(40)	(45)
ADENOMA, NOS	10 (22%)	5 (13%)	4 (9%)
#ADRENAL	(46)	(44)	(46)
PHEOCHROMOCYTOMA	4 (9%)	3 (7%)	3 (7%)
#THYROID	(43)	(40)	(44)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	3 (7%)		1 (2%)
C-CELL CARCINOMA	2 (5%)	1 (3%)	1 (2%)
#PARATHYROID	(25)	(21)	(8)
ADENOMA, NOS	1 (4%)		
#PANCREATIC ISLETS	(44)	(44)	(46)
ISLET-CELL ADENOMA		3 (7%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(48)	(50)	(50)
CARCINOMA,NOS			1 (2%)
#TESTIS	(48)	(43)	(46)
INTERSTITIAL-CELL TUMOR	37 (77%)	38 (88%)	38 (83%)
NERVOUS SYSTEM			
#BRAIN	(46)	(44)	(46)
OSTEOSARCOMA, METASTATIC	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
GLIOMA, NOS		2 (5%)	
OLIGODENDROGLIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKULL	(48)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*BODY CAVITIES	(48)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	11	5
MORIBUND SACRIFICE	5	5	4
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	34	36
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	42	43	40
TOTAL PRIMARY TUMORS	74	64	61
TOTAL ANIMALS WITH BENIGN TUMORS	40	42	40
TOTAL BENIGN TUMORS	61	54	48
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	10	8
TOTAL MALIGNANT TUMORS	12	10	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		
TOTAL SECONDARY TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		5
TOTAL UNCERTAIN TUMORS	1		5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
*SUBCUT TISSUE	(50)	(48)	(50)
SARCOMA, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)		1 (2%)
MYELOMONOCYTIC LEUKEMIA		2 (4%)	
#SPLEEN	(50)	(48)	(50)
MYELOMONOCYTIC LEUKEMIA	2 (4%)		
#LIVER	(50)	(48)	(50)
LEUKEMIA,NOS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(47)	(50)
PARAGANGLIOMA, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NEOPLASTIC NODULE			2 (4%)
#STOMACH	(49)	(48)	(50)
PAPILLOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
#COLON	(40)	(46)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
URINARY SYSTEM			
#URINARY BLADDER	(47)	(47)	(49)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(46)	(47)
ADENOMA, NOS	16 (40%)	9 (20%)	8 (17%)
CHROMOPHOBE ADENOMA	1 (3%)		
#ADRENAL	(48)	(48)	(50)
PHEOCHROMOCYTOMA	6 (13%)	2 (4%)	1 (2%)
#THYROID	(43)	(43)	(50)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA		4 (9%)	
C-CELL CARCINOMA		1 (2%)	3 (6%)
#PANCREATIC ISLETS	(46)	(48)	(49)
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(50)
ADENOMA, NOS		2 (4%)	
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	
FIBROADENOMA	6 (12%)	2 (4%)	2 (4%)
*CLITORAL GLAND	(50)	(48)	(50)
ADENOMA, NOS			1 (2%)
#UTERUS	(48)	(45)	(50)
ADENOCARCINOMA, NOS	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROMA	2 (4%)		
ENDOMETRIAL STROMAL POLYP	2 (4%)	10 (22%)	8 (16%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)		2 (4%)
#UTERUS/ENDOMETRIUM	(48)	(45)	(50)
ADENOCARCINOMA, NOS			1 (2%)
#OVARY/PAROVARIAN	(48)	(45)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(47)	(50)
GLIOMA, NOS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(48)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALL OTHER SYSTEMS			
THORAX			
SARCOMA, NOS		1	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	7	5	
MORIBUND SACRIFICE	2	5	2
SCHEDULED SACRIFICE	5		5
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	40	43
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	27	27	30
TOTAL PRIMARY TUMORS	42	36	35
TOTAL ANIMALS WITH BENIGN TUMORS	23	23	20
TOTAL BENIGN TUMORS	33	30	21
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	6	10
TOTAL MALIGNANT TUMORS	9	6	11
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			6
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			3
TOTAL UNCERTAIN TUMORS			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED 1H-BENZOTRIAZOLE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2	2	
ANIMALS NECROPSIED	39	45	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	39	44	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(39)	(43)	(46)
HEPATOCELLULAR CARCINOMA, METAST	2 (5%)	3 (7%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (5%)	2 (5%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (5%)	5 (12%)	5 (11%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(39)	(45)	(48)
MALIGNANT LYMPHOMA, NOS	11 (28%)	1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#SPLEEN	(38)	(43)	(46)
ANGIOSARCOMA		1 (2%)	2 (4%)
MALIGNANT LYMPHOMA, NOS	1 (3%)		
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#MESENTERIC L. NODE	(36)	(35)	(43)
ANGIOSARCOMA			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)	1 (3%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (3%)	1 (2%)
#LIVER	(39)	(43)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
#SMALL INTESTINE	(37)	(42)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(39)	(43)	(47)
HEPATOCELLULAR ADENOMA		1 (2%)	2 (4%)
HEPATOCELLULAR CARCINOMA	12 (31%)	11 (26%)	5 (11%)
ANGIOSARCOMA		1 (2%)	
#STOMACH	(37)	(42)	(45)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(27)	(39)	(30)
ADENOMA, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
#TESTIS	(38)	(42)	(47)
INTERSTITIAL-CELL TUMOR		1 (2%)	
HEMANGIOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(39)	(45)	(48)
RHABDOMYOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	13	8	8
MORIBUND SACRIFICE	2	4	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	33	36	42
ANIMAL MISSING	2	2	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	24	23	18
TOTAL PRIMARY TUMORS	29	27	24
TOTAL ANIMALS WITH BENIGN TUMORS	2	5	4
TOTAL BENIGN TUMORS	2	5	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	20	15
TOTAL MALIGNANT TUMORS	27	22	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	3	
TOTAL SECONDARY TUMORS	2	3	
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 B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(49)	(50)
*FIBROSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		9 (18%)	3 (6%)
LIPOSARCOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	10 (20%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	4 (8%)	
MALIGNANT LYMPHOMA, MIXED TYPE		2 (4%)	
#SPLEEN	(45)	(47)	(50)
HEMANGIOSARCOMA	1 (2%)		
ANGIOSARCOMA		2 (4%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
#PANCREATIC L.NODE	(44)	(42)	(44)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#MESENTERIC L. NODE	(44)	(42)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#LIVER	(46)	(48)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#JEJUNUM	(42)	(47)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(46)	(48)	(49)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)	2 (4%)	
URINARY SYSTEM			
#KIDNEY	(46)	(48)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(34)	(36)	(38)
ADENOMA, NOS	3 (9%)	2 (6%)	
#ADRENAL	(46)	(45)	(46)
PHEOCHROMOCYTOMA	3 (7%)		
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#THYROID	(44)	(42)	(38)
FOLLICULAR-CELL ADENOMA	2 (5%)	1 (2%)	1 (3%)
FOLLICULAR-CELL CARCINOMA	2 (5%)		1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(49)	(50)
PAPILLARY ADENOCARCINOMA		1 (2%)	
#UTERUS	(44)	(46)	(46)
ENDOMETRIAL STROMAL POLYP	1 (2%)	1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	
ANGIOSARCOMA		1 (2%)	
#OVARY	(44)	(44)	(45)
PAPILLARY CYSTADENOCARCINOMA,NOS		1 (2%)	
TUBULAR ADENOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	17	6	2
MORIBUND SACRIFICE	3	5	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	30	39	47
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	25	14
TOTAL PRIMARY TUMORS	28	33	15
TOTAL ANIMALS WITH BENIGN TUMORS	9	6	3
TOTAL BENIGN TUMORS	10	6	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	23	11
TOTAL MALIGNANT TUMORS	18	27	12
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			

* 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 1H-BENZOTRIAZOLE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	46	46
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, FOCAL			1 (2%)
ABSCESS, NOS		1 (2%)	
HYPERKERATOSIS			1 (2%)
ACANTHOSIS			1 (2%)
*SUBCUT TISSUE	(48)	(50)	(50)
ABSCESS, NOS	3 (6%)		
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(48)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#TRACHEA	(29)	(43)	(45)
INFLAMMATION, CHRONIC		2 (5%)	
#LUNG/BRONCHUS	(48)	(46)	(46)
BRONCHIECTASIS		3 (7%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)	
#LUNG	(48)	(46)	(46)
HEMORRHAGE		2 (4%)	
BRONCHOPNEUMONIA, FOCAL			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	1 (2%)
BRONCHOPNEUMONIA, ACUTE			1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
PERIVASCULITIS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(46)	(45)	(45)
HYPOPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(48)	(44)	(46)
INFARCT, NOS	1 (2%)	1 (2%)	
ATROPHY, NOS		1 (2%)	
#MANDIBULAR L. NODE	(43)	(43)	(43)
HYPERPLASIA, LYMPHOID			1 (2%)
#PANCREATIC L.NODE	(43)	(43)	(43)
HEMORRHAGE		1 (2%)	
ATROPHY, NOS		1 (2%)	
#THYMUS	(32)	(41)	(40)
HEMORRHAGE		1 (2%)	
ATROPHY, NOS		4 (10%)	
HYPERPLASIA, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(48)	(46)	(45)
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS			1 (2%)
FIBROSIS, FOCAL		1 (2%)	
FIBROSIS, DIFFUSE			1 (2%)
DEGENERATION, NOS		1 (2%)	
#ENDOCARDIUM	(48)	(46)	(45)
INFLAMMATION, FOCAL		1 (2%)	
*AORTA	(48)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	2 (4%)
DIGESTIVE SYSTEM			
#LIVER	(48)	(46)	(45)
FIBROSIS, FOCAL		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRRHOSIS, PORTAL		1 (2%)	
NECROSIS, FOCAL		2 (4%)	1 (2%)
METAMORPHOSIS FATTY	2 (4%)	1 (2%)	
NUCLEAR ALTERATION			1 (2%)
BASOPHILIC CYTO CHANGE		13 (28%)	11 (24%)
EOSINOPHILIC CYTO CHANGE		5 (11%)	11 (24%)
CLEAR-CELL CHANGE		4 (9%)	6 (13%)
HYPERPLASIA, FOCAL	3 (6%)		
ANGIECTASIS			1 (2%)
#LIVER/CENTRILOBULAR	(48)	(46)	(45)
METAMORPHOSIS FATTY		1 (2%)	
*BILE DUCT	(48)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PANCREAS	(44)	(44)	(46)
INFLAMMATION, NOS	2 (5%)		
INFLAMMATION, FOCAL		2 (5%)	
INFLAMMATION, CHRONIC			2 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	3 (7%)
#PERIESOPHAGEAL TISSU	(42)	(39)	(35)
CYST, NOS			1 (3%)
#STOMACH	(48)	(45)	(44)
INFLAMMATION, NOS		1 (2%)	
PERIARTERITIS		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
HYPERPLASIA, BASAL CELL			1 (2%)
#GASTRIC SUBMUCOSA	(48)	(45)	(44)
EDEMA, NOS		1 (2%)	
#COLON	(42)	(44)	(42)
PARASITISM		2 (5%)	6 (14%)
URINARY SYSTEM			
#KIDNEY	(48)	(45)	(46)
CYST, NOS		1 (2%)	
HEMORRHAGE			1 (2%)
FIBROSIS, FOCAL			1 (2%)
NEPHROPATHY	35 (73%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NEPHROSIS, NOS		40 (89%)	36 (78%)
#RENAL PAPILLA	(48)	(45)	(46)
MINERALIZATION		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(40)	(45)
CYST, NOS		2 (5%)	
HEMORRHAGE		2 (5%)	
HYPERPLASIA, FOCAL	1 (2%)	2 (5%)	5 (11%)
#ADRENAL MEDULLA	(46)	(44)	(46)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	3 (7%)		
#THYROID	(43)	(40)	(44)
HYPERPLASIA, C-CELL		3 (8%)	2 (5%)
#PANCREATIC ISLETS	(44)	(44)	(46)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
#PROSTATE	(45)	(43)	(45)
INFLAMMATION, ACUTE		3 (7%)	9 (20%)
INFLAMMATION, ACUTE FOCAL		21 (49%)	12 (27%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#TESTIS	(48)	(43)	(46)
MINERALIZATION	1 (2%)		
GRANULOMA, SPERMATIC		1 (2%)	
DEGENERATION, NOS			2 (4%)
ATROPHY, NOS	4 (8%)	1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)	1 (2%)	4 (9%)
*EPIDIDYMIS	(48)	(50)	(50)
ABSCESS, NOS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(46)	(44)	(46)
INFLAMMATION, NOS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFARCT, NOS			1 (2%)
CORPORA AMYLACEA			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(48)	(50)	(50)
SYNECHIA, ANTERIOR		1 (2%)	
CATARACT	1 (2%)	1 (2%)	
*EYE/RETINA	(48)	(50)	(50)
ATROPHY, NOS	2 (4%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(48)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
PERIARTERITIS			1 (2%)
*MESENTERY	(48)	(50)	(50)
PERIARTERITIS		1 (2%)	
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, ACUTE/CHRONIC			1
INFLAMMATION, CHRONIC		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1
AUTO/NECROPSY/HISTO PERF	1	1	
AUTO/NECROPSY/NO HISTO		4	4
AUTOLYSIS/NO NECROPSY	2		

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(50)	(48)	(50)
INFLAMMATION, NOS	1 (2%)		
#LUNG/BRONCHUS	(50)	(48)	(50)
BRONCHIECTASIS		5 (10%)	
INFLAMMATION, ACUTE FOCAL		2 (4%)	
#LUNG/BRONCHIOLE	(50)	(48)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
#LUNG	(50)	(48)	(50)
HEMORRHAGE			2 (4%)
INFLAMMATION, NOS	1 (2%)		
BRONCHOPNEUMONIA, FOCAL			1 (2%)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
BRONCHOPNEUMONIA, ACUTE		1 (2%)	
INFLAMMATION, ACUTE FOCAL			2 (4%)
ABSCESS, NOS	2 (4%)		1 (2%)
PNEUMONIA, CHRONIC MURINE	1 (2%)		
GRANULOMA, NOS	1 (2%)		3 (6%)
GRANULOMA, FOREIGN BODY		1 (2%)	
INFLAMMATION, NECRO GRAN		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (4%)
#LUNG/ALVEOLI	(50)	(48)	(50)
INFLAMMATION, ACUTE		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(48)	(50)
ATROPHY, NOS			1 (2%)
HEMATOPOIESIS	7 (14%)		
#MESENTERIC L. NODE	(43)	(47)	(48)
DILATATION, NOS		2 (4%)	1 (2%)
ATROPHY, NOS			1 (2%)
#THYMUS	(31)	(42)	(38)
ATROPHY, NOS			1 (3%)
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(50)	(47)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#CARDIAC VALVE	(50)	(47)	(50)
INFLAMMATION, CHRONIC			2 (4%)
*AORTA	(50)	(48)	(50)
PERIARTERITIS			1 (2%)
*PULMONARY ARTERY	(50)	(48)	(50)
MINERALIZATION			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(50)
ECTOPIA		1 (2%)	
NECROSIS, FOCAL			1 (2%)
METAMORPHOSIS FATTY	4 (8%)	1 (2%)	
NUCLEAR ALTERATION			1 (2%)
BASOPHILIC CYTO CHANGE		28 (58%)	37 (74%)
EOSINOPHILIC CYTO CHANGE		1 (2%)	
CLEAR-CELL CHANGE		3 (6%)	4 (8%)
HYPERPLASIA, FOCAL	9 (18%)		
ANGIECTASIS			1 (2%)
*BILE DUCT	(50)	(48)	(50)
INFLAMMATION, FOCAL		2 (4%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(46)	(48)	(49)
INFLAMMATION, CHRONIC FOCAL		4 (8%)	
FIBROSIS, FOCAL		1 (2%)	
#STOMACH	(49)	(48)	(50)
HYPERPLASIA, PAPILLARY	1 (2%)		
#COLON	(40)	(46)	(50)
PARASITISM			2 (4%)
URINARY SYSTEM			
#KIDNEY	(49)	(48)	(50)
HYDRONEPHROSIS			1 (2%)
CYST, NOS		1 (2%)	1 (2%)
GLOMERULONEPHRITIS, NOS	1 (2%)		
NEPHROPATHY	18 (37%)		
NEPHROSIS, NOS		16 (33%)	17 (34%)
#RENAL PAPILLA	(49)	(48)	(50)
MINERALIZATION		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#KIDNEY/PELVIS	(49)	(48)	(50)
MINERALIZATION		7 (15%)	3 (6%)
HYPERPLASIA, EPITHELIAL		4 (8%)	13 (26%)
HYPERPLASIA, CYSTIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(46)	(47)
MINERALIZATION	1 (3%)		
HEMORRHAGE		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
#ADRENAL	(48)	(48)	(50)
METAMORPHOSIS FATTY		1 (2%)	
#ADRENAL CORTEX	(48)	(48)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(43)	(43)	(50)
HYPERPLASIA, C-CELL	1 (2%)	1 (2%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PARATHYROID	(31)	(15)	(14)
HYPERPLASIA, NODULAR	1 (3%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(50)
GALACTOCELE	2 (4%)	1 (2%)	3 (6%)
HYPERPLASIA, NOS	1 (2%)	4 (8%)	1 (2%)
*CLITORAL GLAND	(50)	(48)	(50)
ABSCESS, NOS			1 (2%)
#UTERUS	(48)	(45)	(50)
HYDROMETRA		4 (9%)	4 (8%)
HEMORRHAGE			1 (2%)
ABSCESS, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
AMYLOIDOSIS			1 (2%)
#UTERUS/ENDOMETRIUM	(48)	(45)	(50)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, ACUTE		11 (24%)	12 (24%)
HYPERPLASIA, CYSTIC		4 (9%)	4 (8%)
#OVARY/OVIDUCT	(48)	(45)	(50)
INFLAMMATION, ACUTE		4 (9%)	2 (4%)
#OVARY/PAROVARIAN	(48)	(45)	(50)
CYST, NOS		2 (4%)	1 (2%)
#OVARY	(49)	(45)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS	1 (2%)		
DEGENERATION, CYSTIC	2 (4%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(47)	(50)
INFARCT, FOCAL		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(48)	(50)
SYNECHIA, POSTERIOR			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*EYE/CORNEA	(50)	(48)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*EYE/IRIS	(50)	(48)	(50)
INFLAMMATION, ACUTE		1 (2%)	
*EYE/CRYSTALLINE LENS	(50)	(48)	(50)
CATARACT			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, CHRONIC		2	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	11	2	2
AUTO/NECROPSY/HISTO PERF	1		
AUTOLYSIS/NO NECROPSY		2	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED 1H-BENZOTRIAZOLE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2	2	
ANIMALS NECROPSIED	39	45	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	39	44	48
INTEGUMENTARY SYSTEM			
*SKIN	(39)	(45)	(48)
EPIDERMAL INCLUSION CYST	1 (3%)		
INFLAMMATION, DIFFUSE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	1 (3%)		
FIBROSIS	1 (3%)		
FIBROSIS, FOCAL		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(38)	(41)	(38)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#LUNG/BRONCHUS	(39)	(43)	(46)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#LUNG	(39)	(43)	(46)
HEMORRHAGE		1 (2%)	5 (11%)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		4 (9%)	
#LUNG/ALVEOLI	(39)	(43)	(46)
INFLAMMATION, FOCAL			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(36)	(43)	(46)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(38)	(43)	(46)
ATROPHY, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
HYPERPLASIA, LYMPHOID	1 (3%)	3 (7%)	1 (2%)
HEMATOPOIESIS	1 (3%)		
ERYTHROPOIESIS	3 (8%)		
#MANDIBULAR L. NODE	(36)	(35)	(43)
HYPERPLASIA, PLASMA CELL	1 (3%)		
#PANCREATIC L.NODE	(36)	(35)	(43)
INFLAMMATION, ACUTE		1 (3%)	
NECROSIS, FOCAL		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	
#MESENTERIC L. NODE	(36)	(35)	(43)
THROMBOSIS, NOS		1 (3%)	
HEMORRHAGE		13 (37%)	13 (30%)
NECROSIS, NOS			1 (2%)
HYPERPLASIA, NOS	4 (11%)		
HYPERPLASIA, LYMPHOID	4 (11%)		
HEMATOPOIESIS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(39)	(43)	(44)
PERIARTERITIS			2 (5%)
*CORONARY ARTERY	(39)	(45)	(48)
HYPERTROPHY, NOS			1 (2%)
*MESENTERIC ARTERY	(39)	(45)	(48)
HYPERTROPHY, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(39)	(43)	(47)
HEMORRHAGE			1 (2%)
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		2 (5%)	
ABSCESS, CHRONIC		1 (2%)	
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL			2 (4%)
METAMORPHOSIS FATTY			1 (2%)
BASOPHILIC CYTO CHANGE			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL	3 (8%)	1 (2%)	
HEMATOPOIESIS			1 (2%)
#STOMACH	(37)	(42)	(45)
GRANULOMA, FOREIGN BODY			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#JEJUNUM	(37)	(42)	(45)
AMYLOIDOSIS	1 (3%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
#ILEUM	(37)	(42)	(45)
AMYLOIDOSIS	2 (5%)		
#COLON	(37)	(41)	(44)
PARASITISM		4 (10%)	2 (5%)
URINARY SYSTEM			
#KIDNEY	(39)	(43)	(47)
GLOMERULONEPHRITIS, CHRONIC			1 (2%)
NEPHROSIS, NOS		21 (49%)	2 (4%)
GLOMERULOSCLEROSIS, NOS	3 (8%)		
#KIDNEY/CORTEX	(39)	(43)	(47)
SCAR	1 (3%)		
#KIDNEY/GLOMERULUS	(39)	(43)	(47)
AMYLOIDOSIS	2 (5%)		
ENDOCRINE SYSTEM			
#PITUITARY	(27)	(39)	(30)
HYPERPLASIA, FOCAL			1 (3%)
#ADRENAL	(36)	(39)	(44)
AMYLOIDOSIS	2 (6%)		
#ADRENAL CORTEX	(36)	(39)	(44)
HYPERPLASIA, FOCAL		1 (3%)	
#THYROID	(38)	(39)	(36)
CYSTIC FOLLICLES	1 (3%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AMYLOIDOSIS	1 (3%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (5%)	1 (3%)	
#PARATHYROID	(28)	(15)	(18)
HYPERPLASIA, NOS	1 (4%)		
#PANCREATIC ISLETS	(36)	(41)	(44)
HYPERPLASIA, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(38)	(42)	(47)
HYPERPLASIA, INTERSTITIAL CELL			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(39)	(45)	(48)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
*PERITONEUM	(39)	(45)	(48)
HYPERPLASIA, MESOTHELIAL			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(39)	(45)	(48)
PERIARTERITIS		2 (4%)	
AMYLOIDOSIS	1 (3%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	1	10
ANIMAL MISSING/NO NECROPSY	2	2	
AUTO/NECROPSY/HISTO PERF		1	1
AUTO/NECROPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY	9	3	2

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED 1H-BENZOTRIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)		
*SUBCUT TISSUE	(49)	(49)	(50)
ABSCESS, CHRONIC		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(49)	(49)	(49)
PERIVASCULITIS			1 (2%)
#LUNG	(49)	(49)	(49)
EDEMA, INTERSTITIAL		1 (2%)	
HEMORRHAGE			2 (4%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL		3 (6%)	3 (6%)
FIBROSIS, FOCAL		1 (2%)	
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(40)	(47)	(48)
MYELOFIBROSIS		21 (45%)	13 (27%)
#SPLEEN	(45)	(47)	(50)
NECROSIS, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	5 (11%)	
HEMATOPOIESIS		1 (2%)	
ERYTHROPOIESIS	4 (9%)		
#LYMPH NODE OF THORAX	(44)	(42)	(44)
HYPERPLASIA, NOS	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC L.NODE	(44)	(42)	(44)
HEMATOPOIESIS	1 (2%)		
#LUMBAR LYMPH NODE	(44)	(42)	(44)
HYPERPLASIA, NOS	1 (2%)		
#MESENTERIC L. NODE	(44)	(42)	(44)
HEMORRHAGE		9 (21%)	4 (9%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#RENAL LYMPH NODE	(44)	(42)	(44)
HYPERPLASIA, NOS		1 (2%)	
HEMATOPOIESIS	1 (2%)		
#THYMUS	(19)	(37)	(40)
CYST, NOS			1 (3%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(49)	(49)	(50)
DEGENERATION, NOS		1 (2%)	
*AORTA	(49)	(49)	(50)
MINERALIZATION		1 (2%)	
*PULMONARY ARTERY	(49)	(49)	(50)
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
*PANCREATIC ARTERY,	(49)	(49)	(50)
HYPERPLASIA, NOS			1 (2%)
*MESENTERIC ARTERY	(49)	(49)	(50)
HYPERPLASIA, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(46)	(48)	(49)
METAMORPHOSIS FATTY			1 (2%)
HYPERPLASTIC NODULE	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
HEMATOPOIESIS	1 (2%)	1 (2%)	
#PANCREAS	(38)	(47)	(46)
CYSTIC DUCTS			2 (4%)
#PANCREATIC DUCT	(38)	(47)	(46)
INFLAMMATION, CHRONIC			1 (2%)
#PANCREATIC ACINUS	(38)	(47)	(46)
ATROPHY, NOS			1 (2%)
#STOMACH	(41)	(46)	(49)
HYPERPLASIA, FOCAL		1 (2%)	
#JEJUNUM	(42)	(47)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#ILEUM	(42)	(47)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#COLON	(40)	(47)	(47)
PARASITISM		1 (2%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(46)	(48)	(50)
MULTIPLE CYSTS		1 (2%)	
NEPHROSIS, NOS		25 (52%)	3 (6%)
GLOMERULOSCLEROSIS, NOS	2 (4%)		
#URINARY BLADDER	(43)	(44)	(48)
PERIARTERITIS			2 (4%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(46)	(45)	(46)
METAMORPHOSIS FATTY		2 (4%)	
#THYROID	(44)	(42)	(38)
CYSTIC FOLLICLES		1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (5%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#UTERUS	(44)	(46)	(46)
HYDROMETRA		12 (26%)	9 (20%)
PYOMETRA		1 (2%)	
#UTERUS/ENDOMETRIUM	(44)	(46)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
HYPERPLASIA, CYSTIC	30 (68%)	17 (37%)	7 (15%)
#OVARY	(44)	(44)	(45)
MINERALIZATION		1 (2%)	1 (2%)
CYST, NOS	7 (16%)	2 (5%)	4 (9%)
HEMORRHAGE			1 (2%)
HEMORRHAGIC CYST	4 (9%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	2 (5%)		
NERVOUS SYSTEM			
#BRAIN	(46)	(46)	(49)
EPIDERMAL INCLUSION CYST			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(49)	(50)
ABSCESS, NOS	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(49)	(50)
PERIARTERITIS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AMYLOIDOSIS		1 (2%)	
ADIPOSE TISSUE			
STEATITIS	1		
NECROSIS, FAT	1		
OMENTUM			
INFLAMMATION, CHRONIC FOCAL		1	
NECROSIS, FOCAL		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	2	9
AUTO/NECROPSY/HISTO PERF	3	2	
AUTOLYSIS/NO NECROPSY	1	1	

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED 1H-BENZOTRIAZOLE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 1H-Benzotriazole in the Diet[a]

Topography: Morphology	Control	Low Dose	High Dose
Integumentary System: Fibroma[b]	3/48 (6)	2/50 (4)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.640	0.320
Lower Limit		0.055	0.006
Upper Limit		5.345	3.822
Weeks to First Observed Tumor	105	89	83
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	3/48 (6)	1/46 (2)	2/46 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.348	0.696
Lower Limit		0.007	0.060
Upper Limit		4.143	5.792
Weeks to First Observed Tumor	105	104	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia[b]	7/48 (15)	5/50 (10)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.686	0.411
Lower Limit		0.184	0.072
Upper Limit		2.334	1.687
Weeks to First Observed Tumor	80	92	101
Liver: Neoplastic Nodule[b]	0/48 (0)	0/46 (0)	5/45 (11)
P Values[c,d]	P = 0.008	N.S.	P = 0.024
Relative Risk[f]		--	Infinite
Lower Limit		--	1.348
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	101

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma, NOS[b]	10/45 (22)	5/40 (13)	4/45 (9)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.563	0.400
Lower Limit		0.164	0.098
Upper Limit		1.639	1.273
Weeks to First Observed Tumor	103	85	105
Adrenal: Pheochromocytoma[b]	4/46 (9)	3/44 (7)	3/46 (7)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.784	0.750
Lower Limit		0.121	0.116
Upper Limit		4.367	4.186
Weeks to First Observed Tumor	78	72	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma[b]	2/43 (5)	1/40 (3)	1/44 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.538	0.489
Lower Limit		0.009	0.008
Upper Limit		9.907	9.035
Weeks to First Observed Tumor	95	104	105
Thyroid: C-cell Adenoma or Carcinoma[b]	5/43 (12)	1/40 (3)	2/44 (5)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.215	0.391
Lower Limit		0.005	0.039
Upper Limit		1.806	2.242
Weeks to First Observed Tumor	95	104	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	0/44 (0)	3/44 (7)	0/46 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.013		
Relative Risk[f]		Infinite	--
Lower Limit		0.604	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	100	--
Testis: Interstitial-cell Tumor[b]	37/48 (77)	38/43 (88)	38/46 (83)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.146	1.072
Lower Limit		0.925	0.856
Upper Limit		1.354	1.318
Weeks to First Observed Tumor	78	89	78

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Brain: Glioma, NOS, or Oligodendroglioma[b]	0/46 (0)	3/44 (7)	0/46 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.012		
Relative Risk[f]		Infinite	--
Lower Limit		0.631	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	21	--

[a]Dosed groups received time-weighted average doses of 6,700 or 12,100 ppm.

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

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$, otherwise, not significant (N.S.) is indicated. 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 the 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 probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 1H-Benzotriazole in the Diet[a]

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia[b]	4/50 (8)	3/48 (6)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.781	0.250
Lower Limit		0.120	0.005
Upper Limit		4.374	2.411
Weeks to First Observed Tumor	102	101	97
Pituitary: Adenoma, NOS[b]	16/40 (40)	9/46 (20)	8/47 (17)
P Values[c,d]	P = 0.010 (N)	P = 0.032 (N)	P = 0.016 (N)
Relative Risk[f]		0.489	0.426
Lower Limit		0.218	0.179
Upper Limit		1.039	0.936
Weeks to First Observed Tumor	101	65	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, or Chromophobe Adenoma[b]	17/40 (43)	9/46 (20)	8/47 (17)
P Values[c,d]	P = 0.005 (N)	P = 0.019 (N)	P = 0.008 (N)
Relative Risk[f]		0.460	0.401
Lower Limit		0.208	0.171
Upper Limit		0.962	0.867
Weeks to First Observed Tumor	101	65	105
Adrenal: Pheochromocytoma[b]	6/48 (13)	2/48 (4)	1/50 (2)
P Values[c,d]	P = 0.025 (N)	N.S.	N.S.
Relative Risk[f]		0.333	0.160
Lower Limit		0.034	0.004
Upper Limit		1.754	1.249
Weeks to First Observed Tumor	106	105	78

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma[b]	0/43 (0)	1/43 (2)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		Infinite	Infinite
Lower Limit		0.054	0.519
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105
Thyroid: C-cell Adenoma or Carcinoma[b]	0/43 (0)	5/43 (12)	3/50 (6)
P Values[c,d]	N.S.	P = 0.028	N.S.
Relative Risk[f]		Infinite	Infinite
Lower Limit		1.268	0.519
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma[b]	6/50 (12)	2/48 (4)	2/50 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.347	0.333
Lower Limit		0.036	0.034
Upper Limit		1.829	1.758
Weeks to First Observed Tumor	106	89	105
Uterus: Endometrial Stromal Polyp[b]	2/48 (4)	10/45 (22)	8/50 (16)
P Values[c,d]	N.S.	P = 0.010	N.S.
Relative Risk[f]		5.333	3.840
Lower Limit		1.222	0.818
Upper Limit		47.758	35.654
Weeks to First Observed Tumor	106	91	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp or Sarcoma[b]	4/48 (8)	10/45 (22)	9/50 (18)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		2.667	2.160
Lower Limit		0.835	0.651
Upper Limit		10.849	9.012
Weeks to First Observed Tumor	106	91	105

[a]Dosed groups received time-weighted average doses of 6,700 or 12,100 ppm.

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

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$, otherwise, not significant (N.S.) is indicated. 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 the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 1H-Benzotriazole in the Diet[a]

(continued)

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

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED 1H-BENZOTRIAZOLE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 1H-Benzotriazole in the Diet[a]

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	2/39 (5)	5/43 (12)	5/46 (11)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		2.267	2.120
Lower Limit		0.398	0.371
Upper Limit		22.762	21.333
Weeks to First Observed Tumor	109	106	95
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	4/39 (10)	7/43 (16)	5/46 (11)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.587	1.060
Lower Limit		0.440	0.246
Upper Limit		6.878	5.005
Weeks to First Observed Tumor	109	106	95

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Malignant			
Lymphoma, NOS[b]	12/39 (31)	1/45 (2)	0/48 (0)
P Values[c,d]	P < 0.001 (N)	P < 0.001 (N)	P < 0.001 (N)
Departure from Linear Trend[e]	P = 0.015		
Relative Risk[f]		0.072	0.000
Lower Limit		0.002	0.000
Upper Limit		0.453	0.220
Weeks to First Observed Tumor	101	53	--
Hematopoietic System: Malignant			
Lymphoma, Histiocytic Type[b]	1/39 (3)	1/45 (2)	4/48 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.867	3.250
Lower Limit		0.011	0.340
Upper Limit		66.545	156.521
Weeks to First Observed Tumor	109	106	106

Table F1. Analyses of the Incidence of Primary Tumors in Male mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: All Lymphomas[b]	13/39 (33)	4/45 (9)	6/48 (13)
P Values[c,d]	P = 0.011 (N)	P = 0.006 (N)	P = 0.019 (N)
Departure from Linear Trend[e]	P = 0.043		
Relative Risk[f]		0.267	0.375
Lower Limit		0.069	0.130
Upper Limit		0.782	0.953
Weeks to First Observed Tumor	101	53	106
All Sites: Angiosarcoma[b]	0/39 (0)	2/45 (4)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		Infinite	Infinite
Lower Limit		0.258	0.492
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	99	106

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	12/39 (31)	11/43 (26)	5/47 (11)
P Values[c,d]	P = 0.016 (N)	N.S.	P = 0.019 (N)
Relative Risk[f]		0.831	0.346
Lower Limit		0.379	0.105
Upper Limit		1.816	0.955
Weeks to First Observed Tumor	86	71	106
Liver: Hepatocellular Adenoma or Carcinoma[b]	12/39 (31)	12/43 (28)	7/47 (15)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.907	0.484
Lower Limit		0.426	0.180
Upper Limit		1.941	1.200
Weeks to First Observed Tumor	86	71	106

[a]Dosed groups received time-weighted average doses of 11,700 or 23,500 ppm.

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

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$, otherwise, not significant (N.S.) is indicated. 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 the 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 probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 1H-Benzotriazole in the Diet[a]

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/49 (0)	9/49 (18)	3/49 (6)
P Values[c,d]	N.S.	P = 0.001	N.S.
Departure from Linear Trend[e]	P = 0.002		
Relative Risk[f]		Infinite	Infinite
Lower Limit		2.631	0.602
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	20	80
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	0/49 (0)	10/49 (20)	4/49 (8)
P Values[c,d]	N.S.	P = 0.001	N.S.
Departure from Linear Trend[e]	P = 0.002		
Relative Risk[f]		Infinite	Infinite
Lower Limit		2.976	0.928
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	20	80

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Malignant			
Lymphoma, NOS[b]	12/49 (24)	0/49 (0)	1/50 (2)
P Values[c,d]	P < 0.001 (N)	P < 0.001 (N)	P = 0.001 (N)
Departure from Linear Trend[e]	P = 0.007		
Relative Risk[f]		0.000	0.082
Lower Limit		0.000	0.002
Upper Limit		0.272	0.518
Weeks to First Observed Tumor	58	--	89
Hematopoietic System: Malignant			
Lymphoma, Histiocytic Type[b]	1/49 (2)	5/49 (10)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		5.000	3.920
Lower Limit		0.589	0.407
Upper Limit		231.287	188.989
Weeks to First Observed Tumor	109	20	106

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, Mixed Type[b]	0/49 (0)	3/49 (6)	0/50 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.013		
Relative Risk[f]		Infinite	--
Lower Limit		0.602	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	106	--
Hematopoietic System: All Lymphomas[b]	13/49 (27)	8/49 (16)	7/50 (14)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.615	0.528
Lower Limit		0.243	0.195
Upper Limit		1.451	1.295
Weeks to First Observed Tumor	58	20	89

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma, NOS[b]	3/34 (9)	2/36 (6)	0/38 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.630	0.000
Lower Limit		0.055	0.000
Upper Limit		5.162	1.472
Weeks to First Observed Tumor	109	106	--
Adrenal: Pheochromocytoma or Pheochromocytoma Malignant[b]	4/46 (9)	0/45 (0)	0/46 (0)
P Values[c,d]	P = 0.015 (N)	N.S.	N.S.
Relative Risk[f]		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.099	1.076
Weeks to First Observed Tumor	68	--	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma[b]	2/44 (5)	0/42 (0)	1/38 (3)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.000	0.579
Lower Limit		0.000	0.010
Upper Limit		3.524	10.653
Weeks to First Observed Tumor	107	--	106
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	4/44 (9)	1/42 (2)	2/38 (5)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.262	0.579
Lower Limit		0.005	0.055
Upper Limit		2.505	3.789
Weeks to First Observed Tumor	80	106	106

[a]Dosed groups received time-weighted average doses of 11,700 or 23,500 ppm.

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 1H-Benzotriazole in the Diet[a]

(continued)

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$, otherwise, not significant (N.S.) is indicated. 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 the 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 probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

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

Review of the Bioassay of 1*H*-Benzotriazole* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

April 26, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/ Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 1*H*-Benzotriazole for carcinogenicity.

The primary reviewer agreed with the conclusion in the report that, under the conditions of test, there was no clear evidence demonstrating the carcinogenicity of 1*H*-Benzotriazole in rats or mice. After a brief description of the experimental design, he said that the weight gain and survival among the animals were acceptable. A few gliomas were observed among treated rats, a brain tumor rarely found in control animals. He suggested that if a follow-up study is warranted, it should be conducted in new-born animals, since they are particularly susceptible to the induction of CNS tumors. Although an increased incidence of lung tumors were found in one sex of mice at the low dose level, the primary reviewer opined that the results could be discounted since these tumors usually are induced in both sexes and in a dose-related fashion.

The secondary reviewer commented on the lower incidence of pituitary tumors in treated rats as compared to control animals. A Subgroup member added that the number of lymphomas also were lower among treated rats of both sexes.

A motion was made that the report on the bioassay of 1*H*-Benzotriazole be accepted as written. It was further moved that 1*H*-Benzotriazole probably poses no carcinogenic risk to man. The motion was seconded and approved unanimously.

Members present were:

Michael Shimkin (Acting Chairman), University of California at San Diego
Joseph Highland, Environmental Defense Fund
George Roush, Jr., Monsanto Company
Louise Strong, University of Texas Health Sciences Center
John Weisburger, American Health Foundation

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

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