National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 53
1978

BIOASSAY OF 2-AMINO-5-NITROTHIAZOLE FOR POSSIBLE CARCINOGENICITY

CAS No. 121-66-4

NCI-CG-TR-53

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

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DHEW Publication No. (NIH) 78-1359

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FOREWORD: This report presents the results of the bioassay of 2-amino-5-nitrothiazole 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 environmental 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 2-amino-5-nitrothiazole was conducted by The Dow Chemical Company, Indianapolis, Indiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design and doses were determined by Dr. E. K. Weisburger[1]. Dr. C. G. Gerbig[2] supervised the preparation of the diets and was responsible for animal care. Histopathologic examinations were performed by Dr. J. L. Emerson[2,3], the principal investigator, and the diagnoses included in this report represent his interpretation. Dr. Emerson also prepared a preliminary draft of sections of this report.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[4]. The statistical analyses were performed by Dr. J. R. Joiner[5], using methods selected for the bioassay program by Dr. J. J. Gart[6]. Chemicals used in this bioassay were analyzed under the direction of Dr. E. Murrill[7], and the analytical results were reviewed by Dr. S. S. Olin[5]. The structural formula was supplied by NCI[1].

This report was prepared at Tracor Jitco[5] under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. Marshall Steinberg, Director of the Bioassay Program; Dr. L. A. Campbell, Deputy Director for Science; Drs. J. F. Robens and C. H. Williams, toxicologists; 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.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of NCI[6]: Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh M. Pettigrew, and Dr. Robert E. Tarone.

The following other scientists at NCI[1] were responsible for evaluating the bioassay experiment, 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[8], and Dr. Jerrold M. Ward.

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SUMMARY

A bioassay of 2-amino-5-nitrothiazole for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were fed 2-amino-5-nitrothiazole at one of the following doses, either 300 or 600 ppm for rats, and either 50 or 100 ppm for mice. The rats were dosed for 110 weeks, followed by 1 week of observation; the mice were dosed for 104 weeks. Matched controls consisted of 50 untreated rats and 50 untreated mice of each sex. All surviving rats were killed at week 111, all surviving mice at week 104.

The mean body weights of the groups of rats and mice fed 2-amino-5-nitrothiazole in the diet were slightly lower than those of the controls throughout most of the period of administration. No other clinical signs related to administration of the chemical were noted. There was a dose-related trend in mortality only in the male rats; however, sufficient numbers of rats were at risk in all groups for development of late-appearing tumors.

In male rats, there was a significant dose-related trend ($P = 0.044$) in the incidences of malignant lymphomas, lymphocytic leukemias, or undifferentiated leukemias, although the results of direct comparisons of incidences in each of the dosed groups with those in the controls were not significant. There was also a significant dose-related trend in the incidence of granulocytic leukemia in the male rats ($P = 0.014$) and a significantly increased incidence of this tumor ($P = 0.023$) in the high-dose group (matched controls 2/50, low-dose 4/50, high-dose 9/49). When the incidences of all neoplasms of the hematopoietic system (lymphomas and all leukemias) were combined, greater significance was attained for both the dose-related trend ($P = 0.001$) and the direct comparison ($P = 0.002$) of the incidence of the high-dose group with that in the matched controls (controls 13/50, low-dose 19/50, high-dose 28/49). The reliability of the incidence of hematopoietic tumors in the male controls was supported by that for male controls observed in a similar bioassay of another test

chemical at the same laboratory (13/50). The incidences of the combined hematopoietic tumors in the dosed female rats were not significant when compared with the incidence in the matched controls.

In female rats, there was a significant dose-related trend in the incidence of chromophobe adenomas of the pituitary ($P = 0.016$) and a higher incidence ($P = 0.021$) in the high-dose group than in the matched controls (controls 19/45, low-dose 29/47, high-dose 29/44). The incidence of this lesion in dosed male rats was much lower than that in dosed females, and the dose-related trend ($P = 0.048$) was only marginally significant (controls 3/46, low-dose 3/45, high-dose 8/43). The incidences of chromophobe adenomas of the pituitary which were observed in control groups of rats used in a similar bioassay of another test chemical at the same laboratory were 13/49 (27%) for the males and 26/50 (52%) for the females. Because of the variability in incidences of the tumor among different control groups, the occurrence of chromophobe adenomas of the pituitary in the dosed female rats cannot be clearly associated with the administration of 2-amino-5-nitrothiazole.

Also in female rats, there was a higher incidence of endometrial stromal polyps of the uterus in the low-dose group ($P = 0.023$) than in the matched controls (controls 2/50, low-dose 9/49, high-dose 3/50). Since, however, only three high-dose animals had this tumor, the occurrence of uterine tumors in the low-dose group cannot be clearly associated with administration of the test chemical.

In the mice, no neoplasms were observed at a statistically significant incidence in the dosed groups when compared with the controls.

It is concluded that under the conditions of this bioassay, the occurrence of tumors of the hematopoietic system, i.e., lymphoma and granulocytic leukemia, in dosed male Fischer 344 rats was associated with administration of 2-amino-5-nitrothiazole. 2-Amino-5-nitrothiazole was not carcinogenic in female Fischer 344 rats or in male or female B6C3F1 mice.

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I. INTRODUCTION

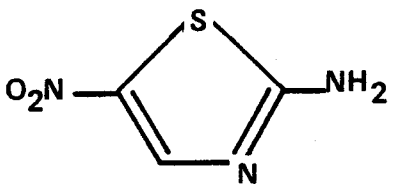
2-Amino-5-nitrothiazole (CAS 121-66-4; NCI C03065) is an antiprotozoal drug for animals which is now used in the form of the acetyl derivative to control histomoniasis (blackhead) in turkeys. The use of acetyl-2-amino-5-nitrothiazole in animal feed and the allowable residues in food products from treated animals (0.1 ppm) are regulated by the Food and Drug Administration (FDA, 1976). Nitrothiazole compounds are structurally related to the nitrofurans, and derivatives of both compounds have chemotherapeutic uses. The nitrothiazoles have shown schistosomicidal, anthelmintic, and amoebicidal activity (Rollo, 1975), whereas the nitrofurans are primarily antibacterial agents (Morris et al., 1969; Fingl, 1975). Some nitrofurans (4-substituted 2-hydrazinothiazoles) have shown carcinogenic activity in rats, causing primarily mammary gland tumors (Cohen et al., 1975).

2-Amino-5-nitrothiazole was selected for testing for carcinogenicity in the bioassay program because of its structural relationship to the carcinogenic nitrofurans.

II. MATERIALS AND METHODS

A. Chemical

2-AMINO-5-NITROTHIAZOLE



2-Amino-5-nitrothiazole was obtained from Eastman Kodak Co., Rochester, New York, in a single batch (Lot No. 672-1) which was used during all phases of the studies. This batch was 99.0 ± 0.5% pure as determined by polarographic analysis.

Elemental analysis (C, H, N, S) agreed with theoretical values for $C_3H_3N_3O_2S$, the molecular formula for 2-amino-5-nitrothiazole. High-pressure liquid chromatography (uv detector) showed one impurity which accounted for 0.9% of the total peak area. Nuclear magnetic resonance and infrared spectra were consistent with reference spectra for the structure of 2-amino-5-nitrothiazole.

Analyses performed after completion of the bioassay showed no detectable change in the purity of the test chemical.

B. Dietary Preparation

Diets containing 2-amino-5-nitrothiazole were prepared by blending a 10% premix with sufficient finely ground Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) for 20 minutes in a 20-kg Patterson-Kelly Twin Shell Blender to obtain the appropriate concentration. Dietary preparations were stored in plastic-lined fiber drums at approximately 4°C for no longer than 14-17 days.

The stability of 2-amino-5-nitrothiazole in feed over a 14-day interval at 4°C was confirmed by analysis at Midwest Research Institute using the standard method of the Association of Official Analytical Chemists (Horwitz, 1970) for the assay of 2-amino-5-nitrothiazole in feed. The concentrations of 2-amino-5-nitrothiazole in selected batches of prepared diets were checked during the chronic study, using the same analytical method.

C. Animals

Rats and mice of each sex, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were

used in these bioassays. The rats were of the Fischer 344 strain obtained from A. R. Schmidt/Sprague-Dawley, Madison, Wisconsin, and the mice were B6C3F1 hybrids obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. On arrival at the laboratory, all animals were quarantined (rats for 7 days, mice for 14 days) and were then assigned to control or dosed groups. Rats were earmarked and mice were toe-clipped to allow individual identification.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature was maintained at 21-26°C, and the relative humidity was maintained at 45-55%. The room air was changed 15 times per hour. Illumination was provided by fluorescent light for 14 hours per day. Food and deionized chlorinated well water were supplied ad libitum.

Rats in the chronic study were housed individually, first in suspended cages made of stainless-steel wire mesh (Ford Fence Co., Indianapolis, Ind.), and at week 45 in suspended filtered polycarbonate cages (Maryland Plastics, Federalsburg, Md.) equipped with an automatic watering system and lined with autoclaved Absorb-Dri® bedding (Lab Products, Inc., Garfield, N. J.). The cages were changed, washed, and sanitized at 82°C twice per

week. The feeders were changed, washed, and sterilized once per week, and the cage filters were changed every 2 weeks.

Mice were housed five per cage in filtered prebedded cages made of disposable polypropylene (Lab Products, Inc., Garfield, N.J.). The cages were changed twice per week and the used cages were incinerated. Feeders, water bottles, and cage lids were also changed twice per week, and cage filters were changed once per week. Feeders and sipper tubes were washed and sterilized prior to use. Water bottles and cage lids were sanitized at 82°C.

Rats and mice were housed in separate rooms. The animal racks were rotated once per week, but the cages were kept in fixed positions on the racks. The rats fed 2-amino-5-nitrothiazole were housed in the same room as rats fed the positive control, N-2-fluorenylacetamide (CAS 53-96-3) and rats that received 3-nitropropionic acid (CAS 504-88-1) by gavage. The mice fed 2-amino-5-nitrothiazole were housed in the same room as mice fed N,N′-dicyclohexylthiourea (CAS 1212-29-9), proflavine hydrochloride (CAS 952-23-8), 1,3-dichloro-5,5-dimethylhydantoin (CAS 118-52-5), or N-2-fluorenylacetamide, and mice receiving 3-nitropropionic acid by gavage. Untreated controls were housed in the same room with respective dosed animals.

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses of 2-amino-5-nitrothiazole, on the basis of which low and high concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration in the chronic studies. In the subchronic studies, 2-amino-5-nitrothiazole was added to the animal feed in concentrations ranging from 375 to 4,000 ppm for rats and from 30 to 500 ppm for mice. The chemical was provided in feed to dosed groups of five male and five female animals of each species for 6 weeks, and the animals were given basal diets for the last 2 weeks of the study.

In male rats, mean body weight gain was 92% of that of the matched controls at 750 ppm, 75% at 1,500 ppm, 53% at 3,000 ppm, and 43% at 4,000 ppm. In females, mean body weight gain was 93% of that of the matched controls at 750 ppm, 81% at 1,500 ppm, 53% at 3,000 ppm, and 43% at 4,000 ppm. No deaths occurred among rats, and the only gross pathologic changes were slightly enlarged thyroids in rats tested at the two highest doses. The low and high doses for the chronic studies using rats were set at 300 and 600 ppm.

No effects on growth were observed in male mice. One male at 140 ppm died. In female mice, mean body weight gain was unaffected

at 30 ppm. Mean body weight gain was 82% of that of the controls at 60 ppm, 96% at 140 ppm, 61% at 260 ppm, and 57% at 500 ppm. Hydronephrosis was found in a total of seven mice of both sexes among all groups, and pyelonephritis in one mouse. The low and high doses for the chronic studies using mice were set at 50 and 100 ppm.

F. Designs of Chronic Studies

The designs of the chronic studies are shown in tables 1 and 2.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity and weighed every 14 days during the first 3 months and every 28 days thereafter. Clinical observations were recorded once per week. Animals that were moribund at the time of the daily examinations were killed and necropsied; however, some moribund animals were isolated from their cage-mates for a few days prior to being killed.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and animals found dead. The following tissues were microscopically examined: skin, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart,

Table 1. Design of 2-Amino-5-Nitrothiazole Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals[a]	2-Amino-5-Nitrothiazole in Diet[b] (ppm)	Time on Study[c] Dosed (weeks)	Time on Study[c] Observed (weeks)
Male				
Matched-Control	50	0		111
Low-Dose	50	300	110	1
High-Dose	50	600	110	1
Female				
Matched-Control	50	0		111
Low-Dose	50	300	110	1
High-Dose	50	600	110	1

[a]All animals were 50 days of age when placed on study.

[b]Diets containing 2-amino-5-nitrothiazole were administered 7 days per week.

[c]All animals were started on study on the same day.

Table 2. Design of 2-Amino-5-Nitrothiazole Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals[a]	2-Amino-5-Nitrothiazole in Diet[b] (ppm)	Time on Study[c] Dosed (weeks)	Time on Study[c] Observed (weeks)
Male				
Matched-Control	50	0		104
Low-Dose	50	50	104	
High-Dose	50	100	104	
Female				
Matched-Control	50	0		104
Low-Dose	50	50	104	
High-Dose	50	100	104	

[a]All animals were 53 days of age when placed on study.

[b]Diets containing 2-amino-5-nitrothiazole were administered 7 days per week.

[c]All animals were started on study on the same day.

salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, colon, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, testis or ovary, prostate or uterus, brain, and eyes. Peripheral blood smears were prepared from each animal whenever possible. Occasionally, additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals were 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 descrip-

tive 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 with 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 rats of each sex were slightly less than weights of the controls in a dose-related manner (figure 1). Fluctuations 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.

Early during the second year of the study, approximately 75% of the rats developed acute swellings of the cervical salivary glands. The clinical appearance was consistent with that of sialodacryoadenitis. Control animals as well as dosed animals developed this condition, which lasted for approximately 2 weeks. The animals ate less feed, developed rough coats, and in some cases, lost weight. Unilateral cataracts were observed at the end of the first year and through the second year in both control and dosed animals.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed 2-amino-5-nitrothiazole in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2.

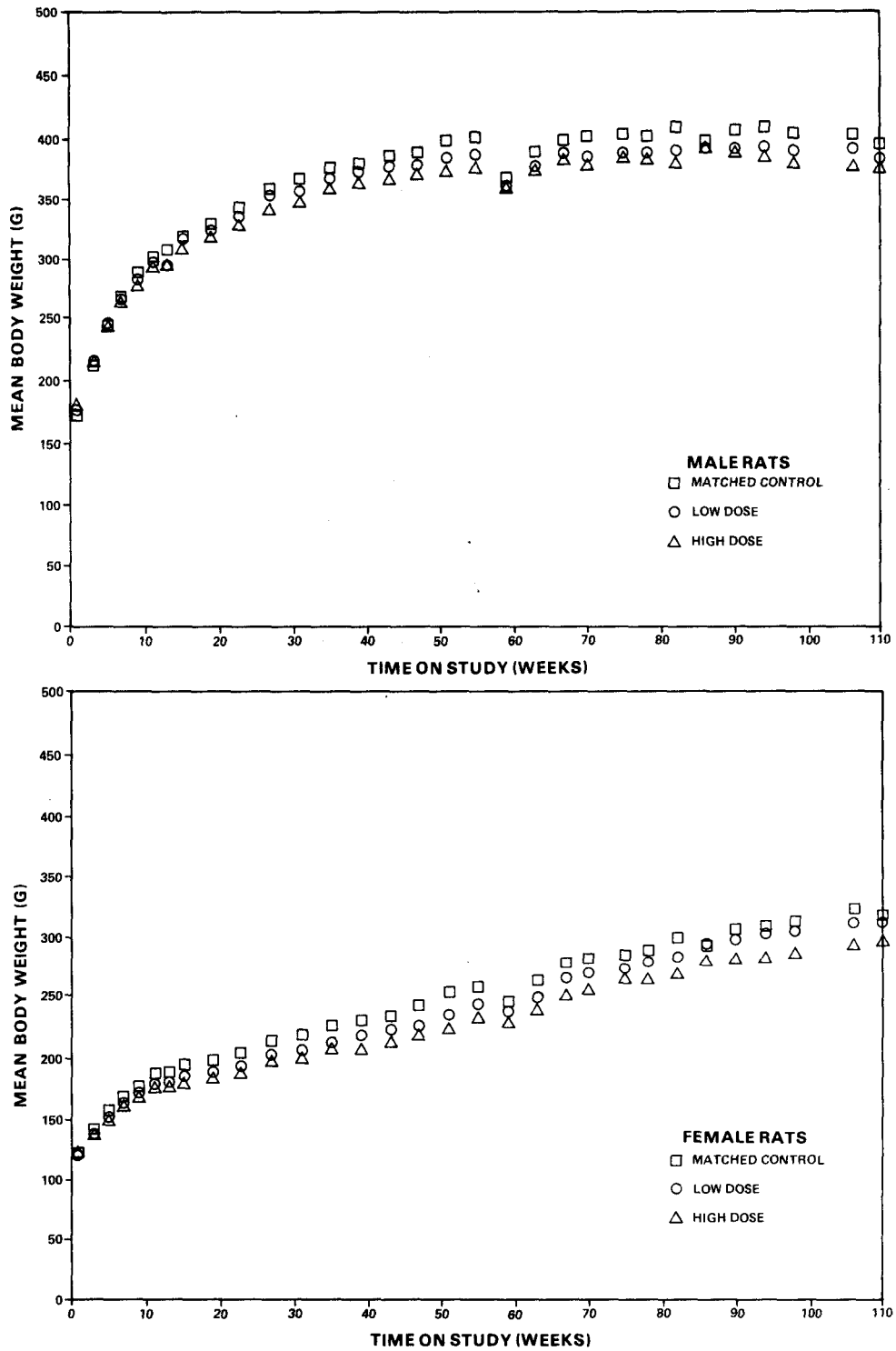


Figure 1. Growth Curves for Rats Fed 2-Amino-5-Nitrothiazole in the Diet

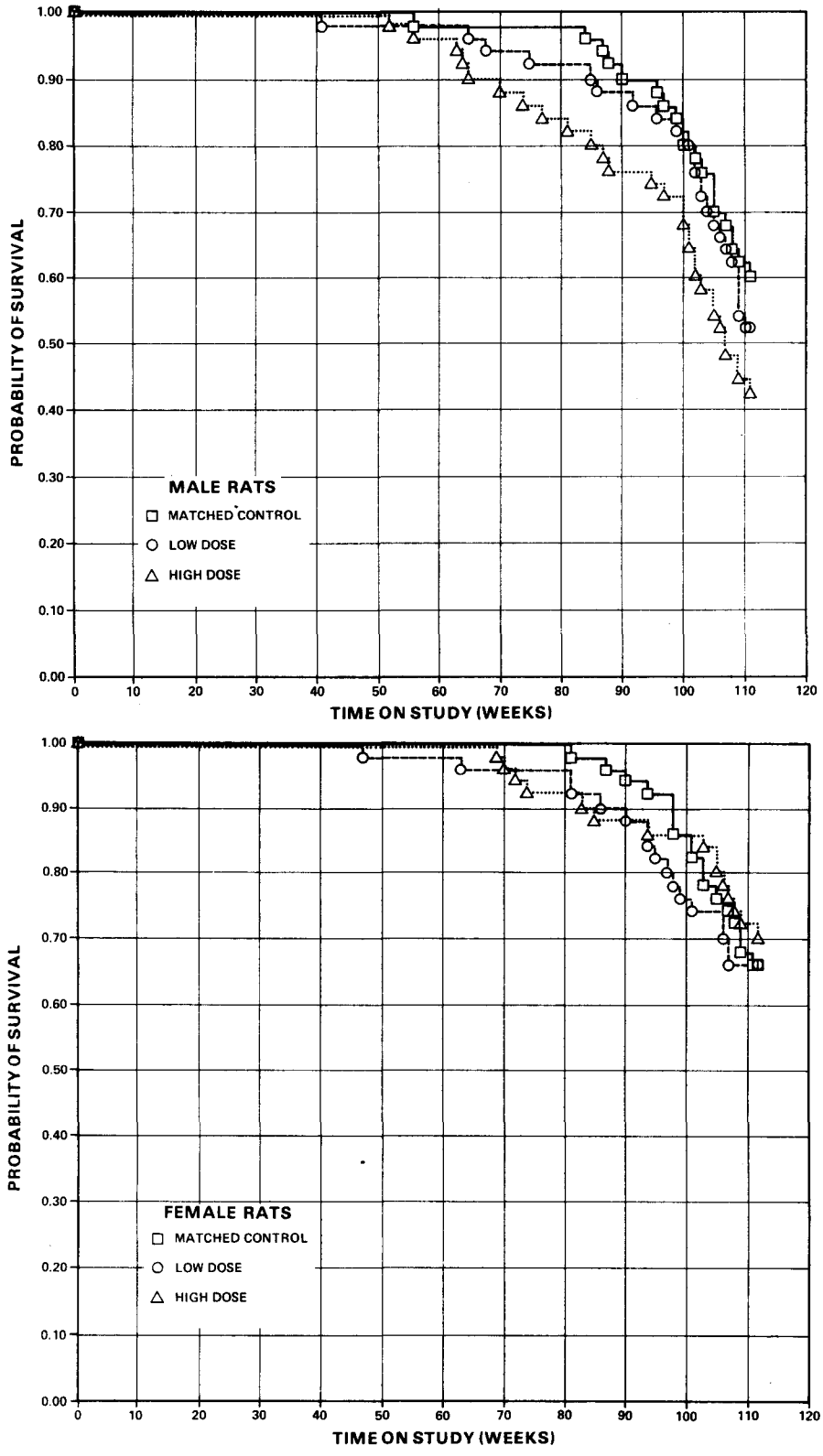


Figure 2. Survival Curves for Rats Fed 2-Amino-5-Nitrothiazole in the Diet

In male rats, there was a dose-related positive trend (P = 0.042) in mortality; however, 27/50 (54%) of the high-dose males lived at least 2 years. There was no dose-related trend in mortality in the female rats, and over 65% of all the female rats (35/50 [70%] high-dose, 33/50 [66%] low-dose, 33/50 [66%] matched controls) lived to the end of the study. 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.

A variety of neoplasms were observed in both the control and dosed groups, each of which has been previously encountered as a spontaneous lesion in the rat. Some types of neoplasms occurred only in rats of dosed groups, or with a greater frequency in dosed groups when compared with controls; the converse was also true.

The incidences of undifferentiated and lymphocytic types of malignant lymphoma, leukemia, and granulocytic leukemia of the spleen or multiple organs increased in the dosed male groups. This trend was not as evident in the females. The incidences of lymphoma and leukemia were as follows:

Males	Matched Control	Low Dose	High Dose
Number of animals with tissue examined microscopically	50	50	49
Malignant Lymphoma, Undifferentiated	5* (10%)	8 (16%)	10 (20%)
Malignant Lymphoma, Lymphocytic	4 (8%)	4 (8%)	8 (16%)
Malignant Lymphoma, Histiocytic	0	1 (2%)	0
Malignant Lymphoma, NOS, (not otherwise specified)	0	1 (2%)	0
Lymphocytic Leukemia	4 (8%)	4 (8%)	6 (12%)
Granulocytic Leukemia	2 (4%)	4 (8%)	9 (18%)
Total number of animals with Lymphoma or Leukemia	13 (26%)	19 (38%)	28 (57%)
Females			
Number of animals with tissue examined microscopically	50	50	50
Malignant Lymphoma, Undifferentiated	4 (8%)	10 (20%)	7 (14%)
Malignant Lymphoma, Lymphocytic	1 (2%)	1 (2%)	1 (2%)
Lymphocytic Leukemia	1 (2%)	1 (2%)	2 (4%)
Granulocytic Leukemia	2 (4%)	2 (4%)	1 (2%)
Total number of animals with Lymphoma or Leukemia	7 (14%)	14 (28%)	10 (20%)

*Includes three animals with undifferentiated leukemia.

The undifferentiated malignant lymphoma was considered to be the same as that described by Moloney et al. (1970). Many of the high-dose animals died or were killed in moribund condition because of the leukemia.

The nonneoplastic lesions consisted of degenerative, proliferative, and inflammatory changes that are commonly observed in aging rats (Sass et al., 1975). These conditions occurred in a random fashion and did not appear to be related to administration of the test chemical.

Focal myocarditis ranging from acute to chronic occurred in 8/48 (17%) control males, 22/49 (45%) low-dose males, 21/48 (43%) high-dose males; 3/48 (6%) control females, 11/47 (23%) low-dose females, and 16/49 (33%) high-dose females. Although the incidence was greater in dosed groups than in controls, it was not considered to be related to administration of the test chemical, since it is a common finding in aged rats.

The incidence of endometrial stromal polyps of the uterus was higher in the low-dose females than in the control and high-dose females (controls 2/50 [4%], low-dose 9/49 [18%], high-dose 3/50 [6%]). However, this benign proliferative lesion was not associated with an increased incidence of malignant tumors in the uterus.

Suppurative inflammation of the preputial glands of male and female rats was observed in all groups. A low incidence of adenoma of the preputial gland was present in all groups.

The increased incidence of pituitary angiectasis in dosed female rats was associated with an increased incidence of chromophobe adenoma of the pituitary gland.

There was a dose-related increase in the incidence of hematopoietic neoplasms in male rats. The incidence of the undifferentiated type of malignant lymphoma was lower than that previously reported for this strain (Turusov, 1973), but the onset was earlier.

In the judgment of the pathologist, 2-amino-5-nitrothiazole administered to Fischer 344 rats was carcinogenic for males, but not the females, under the conditions of this study.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more than one group.

In male rats, the results of the Cochran-Armitage test for positive dose-related trend in the combined incidence of malignant

lymphoma, lymphocytic leukemia, or undifferentiated leukemia are significant (P = 0.044), but the results of the Fisher exact test are not. The results of the Cochran-Armitage test for the incidence of granulocytic leukemia are significant (P = 0.014), and the results of the Fisher exact test show that the incidence in the high-dose group is significantly higher (P = 0.023) than that in the controls. In the analyses of the incidence of any type of leukemia or lymphoma, the results of the Cochran-Armitage test are significant (P = 0.001), and the results of the Fisher exact test show a higher incidence of these tumors in the high-dose group (P = 0.002) than in the matched controls. The statistical conclusion is that the occurrence of neoplasms of the hematopoietic system in male rats is associated with 2-amino-5-nitrothiazole at the doses used in this study. There were two groups of controls at this laboratory. The group matched with 2-amino-5-nitrothiazole had an incidence of 13/50 (26%) hematopoietic tumors and the other group had 14/50 (28%).

In female rats, the results of the Cochran-Armitage test for positive dose-related trend in proportions for chromophobe adenoma of the pituitary are significant (P = 0.016), and the results of the Fisher exact test show significantly greater incidences of this tumor in the high-dose group (P = 0.021) than in the matched controls. The results of the Fisher exact

comparison of the incidences in the low-dose and control animals show a P value of 0.048, which is above the 0.025 level required when multiple comparison is considered. The high incidence seen in the matched controls (19/45, 42%) indicates a high spontaneous rate of this type of tumor in these animals. The incidence of this tumor in the second female control group at this laboratory was 26/50 (52%). In male rats, the results of the Cochran-Armitage test for the incidence of this tumor indicates a probability level of 0.048, but the results of the Fisher exact test are not significant.

In the analyses of endometrial stromal polyp of the uterus in female rats, although the results of the Cochran-Armitage test for positive dose-related trend in incidences are not significant at the 0.05 level, there is a significant departure from linear trend (P = 0.009), due to the greater incidence of this tumor in the low-dose group (9/49) than in the high-dose group (3/50). The results of the Fisher exact test show a significantly higher incidence of this tumor in the low-dose group than in the matched controls (P = 0.023), but the incidence in the high-dose group is not significant.

In male rats, the incidences of alveolar/bronchiolar adenoma of the lung and interstitial-cell tumor of the testis were higher in the control group than in the dosed groups. This may have

occurred because the dosed animals did not live as long as the control animals.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male mice were slightly lower than those of the corresponding controls in a dose-related manner throughout the study. Toward the end of the study mean body weights of the female mice at both doses were lower than those of the corresponding controls (figure 3). Fluctuations in a growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation.

During the first year of the study, the dosed mice were generally comparable to the controls in appearance and behavior. Focal alopecia, focal dermatitis, and small palpable nodules in the perineal area associated with fighting were observed in increasing numbers of male mice, beginning at week 34.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed 2-amino-5-nitrothiazole in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4.

In male mice, the results of the Tarone test for dose-related trend in mortality are not significant; at least 66% of the

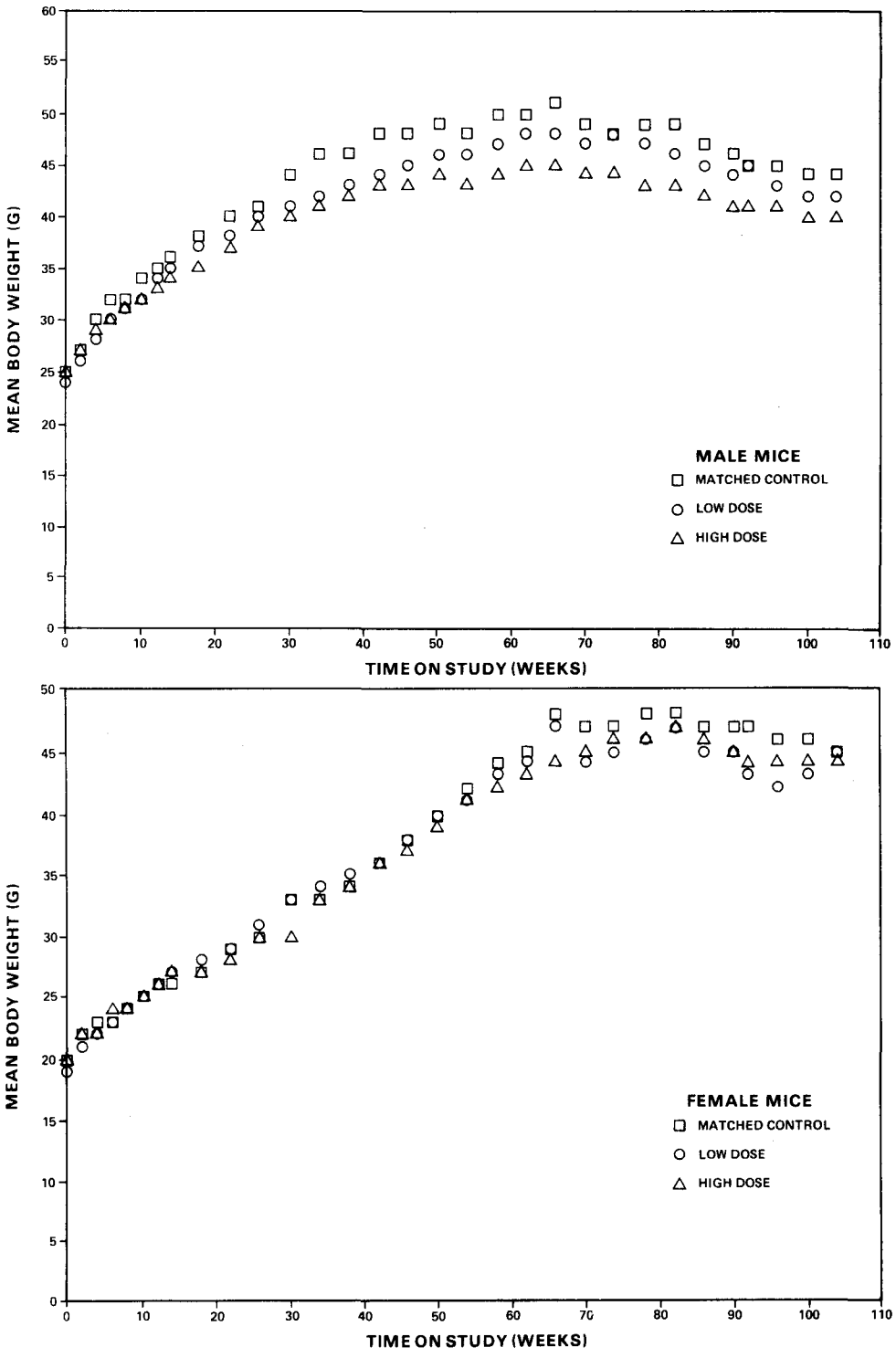


Figure 3. Growth Curves for Mice Fed 2-Amino-5-Nitrothiazole in the Diet

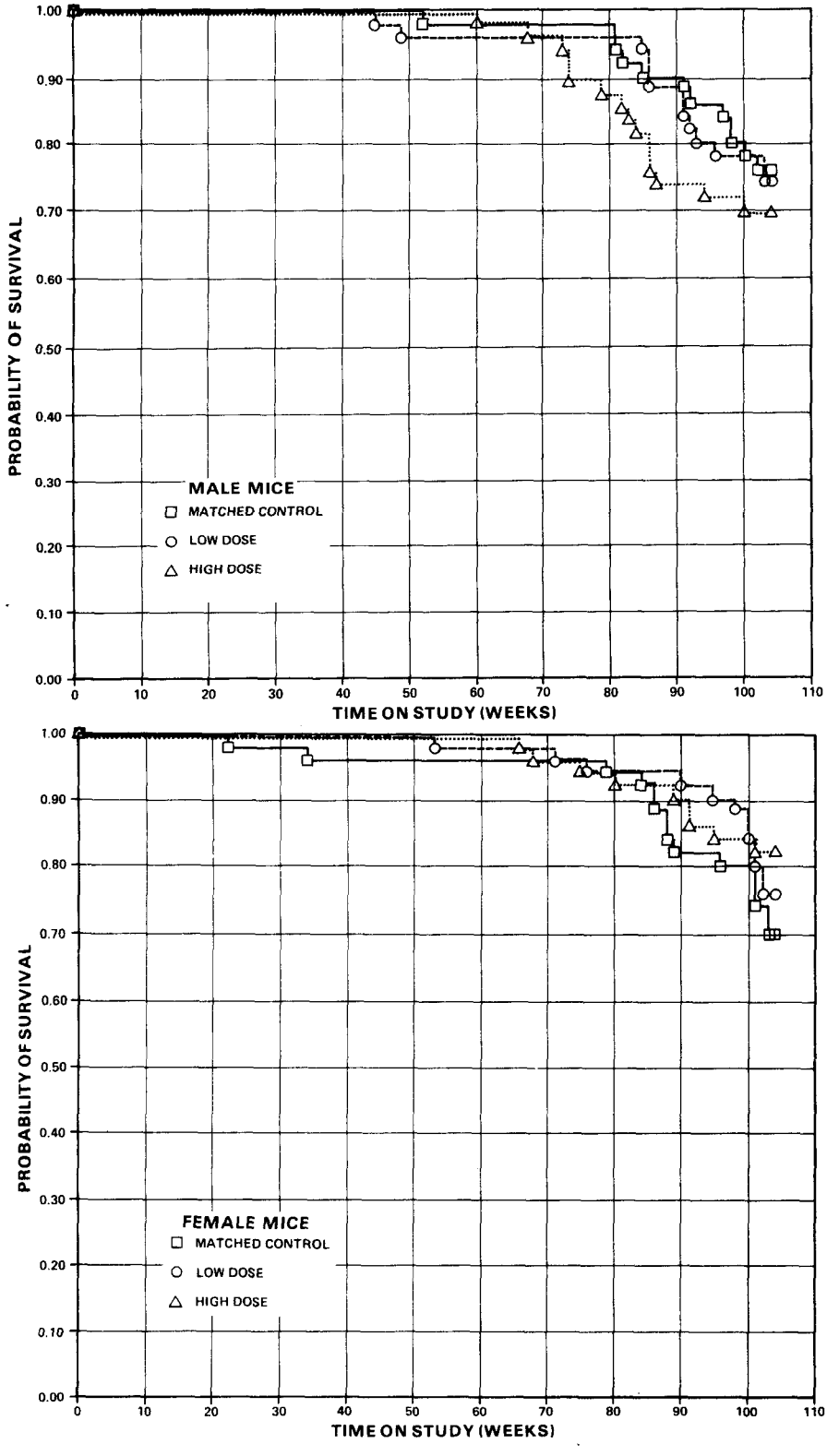


Figure 4. Survival Curves for Mice Fed 2-Amino-5-Nitrothiazole in the Diet

animals (33/50 [66%] high-dose, 37/50 [74%] low-dose, 38/50 [76%] matched controls) lived to the end of the study. In the male high-dose group, two animals were reported missing. There is no positive dose-related trend in mortality in the female mice, and at least 70% of every female group (41/50 [82%] high-dose, 38/50 [76%] low-dose, 35/50 [70%] matched controls) lived to the end of the study. 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.

A variety of neoplasms were observed in both the control and dosed groups, each of which has been encountered previously as a spontaneous lesion in the mouse.

The incidences of hepatocellular carcinoma, adenoma, and hyperplasia were as follows:

Males	Matched Control	Low Dose	High Dose
Number of animals with tissue examined microscopically	49	50	48
Hepatocellular Carcinoma	16 (33%)	11 (22%)	11 (23%)
Hepatocellular Adenoma	4 (8%)	6 (12%)	4 (8%)
Hyperplasia, Nodular or Hyperplastic Nodule	1 (2%)	1 (2%)	1 (2%)
Females			
Number of animals with tissue examined microscopically	49	50	50
Hepatocellular Carcinoma	1 (2%)	2 (4%)	4 (8%)
Hepatocellular Adenoma	1 (2%)	4 (8%)	1 (2%)
Hyperplasia, Nodular	0 (0%)	1 (2%)	0 (0%)

The incidence of proliferative hepatocellular lesions was greater in males than in females, but there was no indication that these lesions were related to administration of the test chemical.

Other lesions that occurred among dosed and control groups were also considered to be spontaneous. Some types of neoplasms occurred only in mice of dosed groups, or with a greater frequency in dosed groups when compared with controls; the converse was also true.

Several chronic inflammatory, degenerative, and proliferative conditions were observed in all groups. These conditions occurred in a random fashion and were considered to be of common occurrence, spontaneous, and not related to administration of the test chemical.

Based on the histologic examination, there was no evidence for the carcinogenicity of 2-amino-5-nitrothiazole in B6C3F1 mice 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 with an incidence of at least 5% in one or more than one group.

The results of the Cochran-Armitage test for positive dose-related trend in the incidence of alveolar/bronchiolar adenoma of the lung in female mice ($P = 0.048$) and the incidence of combined alveolar/bronchiolar adenoma and carcinoma of the lung in female mice ($P = 0.034$) are significant. However, the results of the Fisher exact test are not significant for these tumors.

In female mice, the incidences of hematopoietic tumors in the dosed groups are lower than that in the control group. These

significant trends in the negative direction cannot be explained by low survival in the dosed groups, since the survivals of the dosed and control groups of female mice are comparable.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by 2-amino-5-nitrothiazole, which could not be detected under the conditions of this test.

V. DISCUSSION

The mean body weights of the groups of rats and mice administered 2-amino-5-nitrothiazole in this bioassay were slightly lower than those of the controls throughout most of the period of administration. No clinical signs related to administration of the test chemical were noted. There was a dose-related trend in mortality only in the male rats; however, sufficient numbers of rats and mice were at risk in all groups for development of late-appearing tumors.

In male rats, there was a significant dose-related trend ($P = 0.044$) in the incidences of malignant lymphomas, lymphocytic leukemias, or undifferentiated leukemias, although the results of direct comparisons of incidences in each of the dosed groups with those in the controls were not significant. There was also a significant dose-related trend in the incidence of granulocytic leukemia in the male rats ($P = 0.014$) and a significantly increased incidence of this tumor ($P = 0.023$) in the high-dose group (matched controls 2/50, low-dose 4/50, high-dose 9/49). When the incidences of all neoplasms of the hematopoietic system (lymphomas and all leukemias) were combined, greater significance was attained for both the dose-related trend ($P = 0.001$) and the direct comparison ($P = 0.002$) of the incidence in the high-dose group with that in the matched controls (controls 13/50, low-dose

19/50, high-dose 28/49). The reliability of the incidence of hematopoietic tumors in the male controls was supported by that for male controls observed in a similar bioassay of another test chemical at the same laboratory (13/50). The incidences of the combined hematopoietic tumors in the dosed female rats were not significant when compared with the incidence in the matched controls.

In female rats, there was a significant dose-related trend in the incidence of chromophobe adenomas of the pituitary (P = 0.016) and a higher incidence (P = 0.021) in the high-dose group than in the matched controls (controls 19/45, low-dose 29/47, high-dose 29/44). The incidence of this lesion in dosed male rats was much lower than that in dosed females, and the dose-related trend (P = 0.048) was only marginally significant (controls 3/46, low-dose 3/45, high-dose 8/43). The incidences of chromophobe adenomas of the pituitary which were observed in control groups of rats used in a similar bioassay of another test chemical at the same laboratory were 13/49 (27%) for the males and 26/50 (52%) for the females. Because of this variability in incidences of the tumor among different control groups, the occurrence of chromophobe adenomas of the pituitary in the dosed female rats cannot be clearly associated with the administration of 2-amino-5-nitrothiazole.

Also in female rats, there was a higher incidence of endometrial stromal polyps of the uterus in the low-dose group (P = 0.023) than in the matched controls (controls 2/50, low-dose 9/49, high-dose 3/50). Since, however, only three high-dose animals had this tumor, the occurrence of uterine tumors in the low-dose group cannot be clearly associated with administration of the test chemical.

In previous work, Cohen et al. (1975) administered 2-amino-5-nitrothiazole in the diet to Sprague-Dawley rats at 1,000 ppm for 46 weeks. Tumors of the mammary gland, kidney, pelvis, and lungs resulted, but the incidences were low. No increased incidences of tumors in these specific organs were observed in the present bioassay.

In the mice, no neoplasms were observed at a statistically significant incidence in the dosed groups when compared with the controls.

It is concluded that under the conditions of this bioassay, the occurrence of tumors of the hematopoietic system, i.e., lymphoma and granulocytic leukemia, in dosed male Fischer 344 rats was associated with administration of 2-amino-5-nitrothiozole. 2-Amino-5-nitrothiazole was not carcinogenic in female Fischer 344 rats or in male or female B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)		1 (2%)
TRICHOEPITHELIOMA	1 (2%)		
SEBACEOUS ADENOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(49)
FIBROMA	1 (2%)	1 (2%)	
FIBROSARCOMA	1 (2%)	1 (2%)	1 (2%)
LIPOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
C-CELL CARCINOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)	7 (14%)	9 (18%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	4 (8%)	8 (16%)
UNDIFFERENTIATED LEUKEMIA	2 (4%)		
LYMPHOCYTIC LEUKEMIA	4 (8%)	4 (8%)	6 (12%)
GRANULOCYTIC LEUKEMIA	2 (4%)	4 (8%)	9 (18%)
#SPLEEN	(49)	(47)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
#LYMPH NODE	(41)	(41)	(42)
FOLLICULAR-CELL CARCINOMA, METAS		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(37)	(41)	(31)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(48)
ANITSCHKOW-CELL SARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
*PALATE	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*TONGUE	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#LIVER	(49)	(49)	(49)
NEOPLASTIC NODULE		1 (2%)	
HEPATOCELLULAR CARCINOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(45)	(43)
CHROMOPHOBE ADENOMA	3 (7%)	3 (7%)	8 (19%)
#ADRENAL	(49)	(47)	(48)
CORTICAL ADENOMA		1 (2%)	
CORTICAL CARCINOMA	1 (2%)		
PHEOCHROMOCYTOMA	4 (8%)	4 (9%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#THYROID	(46)	(48)	(46)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	3 (6%)	3 (7%)
C-CELL ADENOMA	3 (7%)	7 (15%)	4 (9%)
C-CELL CARCINOMA	1 (2%)		1 (2%)
#PARATHYROID	(37)	(31)	(31)
ADENOMA, NOS		1 (3%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ISLETS	(49)	(44)	(45)
ISLET-CELL ADENOMA	4 (8%)	4 (9%)	3 (7%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOMA, NOS			1 (2%)
FIBROMA			1 (2%)
FIBROADENOMA	1 (2%)	1 (2%)	4 (8%)
*PREPUTIAL GLAND	(50)	(50)	(49)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	2 (4%)	1 (2%)	1 (2%)
#TESTIS	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR	48 (96%)	48 (96%)	41 (84%)
*SCROTUM	(50)	(50)	(49)
FIBROSARCOMA		1 (2%)	
NERVOUS SYSTEM			
#MIDBRAIN	(50)	(50)	(49)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(49)
OSTEOMA		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(49)
MESOTHELIOMA, MALIGNANT		1 (2%)	
*PERITONEUM	(50)	(50)	(49)
MESOTHELIOMA, NOS	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*TUNICA VAGINALIS	(50)	(50)	(49)
MESOTHELIOMA, NOS		1 (2%)	
MESOTHELIOMA, MALIGNANT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
MESOTHELIOMA, MALIGNANT	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	15	16	15
MORIBUND SACRIFICE	5	8	14
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	30	26	21
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	48	46
TOTAL PRIMARY TUMORS	99	105	107
TOTAL ANIMALS WITH BENIGN TUMORS	48	48	42
TOTAL BENIGN TUMORS	72	73	66
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	26	31
TOTAL MALIGNANT TUMORS	26	30	41
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	
TOTAL SECONDARY TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	
TOTAL UNCERTAIN TUMORS	1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SEBACEOUS ADENOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
SEBACEOUS ADENOMA		1 (2%)	
SEBACEOUS ADENOCARCINOMA			1 (2%)
FIBROMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
LIPOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE	4 (8%)	10 (20%)	6 (12%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA	1 (2%)	1 (2%)	2 (4%)
GRANULOCYTIC LEUKEMIA	2 (4%)	1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(50)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#LYMPH NODE	(44)	(39)	(34)
C-CELL CARCINOMA, METASTATIC	2 (5%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
NONE			
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(47)	(44)
CARCINOMA,NOS		1 (2%)	
CHROMOPHOBE ADENOMA	19 (42%)	29 (62%)	29 (66%)
#ADRENAL	(49)	(49)	(50)
PHEOCHROMOCYTOMA	3 (6%)		
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(50)	(47)	(48)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		
C-CELL ADENOMA	3 (6%)	4 (9%)	3 (6%)
C-CELL CARCINOMA	2 (4%)	3 (6%)	5 (10%)
#PARATHYROID	(37)	(34)	(30)
ADENOMA, NOS		1 (3%)	1 (3%)
#PANCREATIC ISLETS	(49)	(50)	(48)
ISLET-CELL ADENOMA	1 (2%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS	1 (2%)	3 (6%)	1 (2%)
PAPILLARY ADENOCARCINOMA			2 (4%)
FIBROADENOMA	12 (24%)	12 (24%)	14 (28%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	2 (4%)	2 (4%)	2 (4%)
#UTERUS	(50)	(49)	(50)
LEIOMYOMA	1 (2%)	1 (2%)	
ENDOMETRIAL STROMAL POLYP	2 (4%)	9 (18%)	3 (6%)
#OVARY	(50)	(49)	(48)
GRANULOSA-CELL TUMOR		1 (2%)	
SERTOLI-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(49)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
#BRAIN	(49)	(49)	(49)
CARCINOMA, NOS, METASTATIC		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
LUMBOSACRAL REGION			
LIPOSARCOMA	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@	4	7	8
MORIBUND SACRIFICE	13	10	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	33	33	35
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	40	44	44
TOTAL PRIMARY TUMORS	59	86	78
TOTAL ANIMALS WITH BENIGN TUMORS	35	40	38
TOTAL BENIGN TUMORS	45	62	56
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	21	19
TOTAL MALIGNANT TUMORS	14	23	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	2	1
TOTAL SECONDARY TUMORS	3	4	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN

MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			2
ANIMALS NECROPSIED	49	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	48
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(48)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
SEBACEOUS ADENOMA		2 (4%)	
*SUBCUT TISSUE	(49)	(50)	(48)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
FIBROMA		1 (2%)	
FIBROSARCOMA	2 (4%)	2 (4%)	3 (6%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(48)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	3 (6%)	2 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	10 (20%)	10 (20%)	11 (23%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	4 (8%)	2 (4%)	1 (2%)
CORTICAL CARCINOMA, METASTATIC	1 (2%)	1 (2%)	
FIBROSARCOMA, METASTATIC		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	5 (10%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
GRANULOCYTIC LEUKEMIA			3 (6%)
MONOCYTIC LEUKEMIA			2 (4%)
GRANULOCYTIC SARCOMA	1 (2%)		
#SPLEEN	(46)	(43)	(46)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	4 (9%)	3 (6%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(40)	(33)	(29)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (3%)	1 (3%)	
#LIVER	(49)	(50)	(48)
GRANULOCYTIC LEUKEMIA	1 (2%)		
#SMALL INTESTINE	(47)	(44)	(45)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(48)
HEPATOCELLULAR ADENOMA	4 (8%)	6 (12%)	4 (8%)
HEPATOCELLULAR CARCINOMA	16 (33%)	11 (22%)	11 (23%)
CORTICAL CARCINOMA, METASTATIC	1 (2%)	1 (2%)	
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA	2 (4%)	1 (2%)	3 (6%)
ANGIOSARCOMA		1 (2%)	2 (4%)
#PANCREAS	(48)	(46)	(45)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(48)	(47)	(48)
ADENOCARCINOMA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(46)	(49)	(46)
CORTICAL CARCINOMA	1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(43)	(39)	(40)
FOLLICULAR-CELL ADENOMA		1 (3%)	
#PANCREATIC ISLETS	(48)	(46)	(45)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#TESTIS	(47)	(48)	(46)
INTERSTITIAL-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(50)	(48)
PAPILLARY ADENOMA	1 (2%)		
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(48)
CORTICAL CARCINOMA, METASTATIC	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	10	12	13
MORIBUND SACRIFICE	2	1	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	37	33
ANIMAL MISSING			2

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	39	32	34
TOTAL PRIMARY TUMORS	54	53	45
TOTAL ANIMALS WITH BENIGN TUMORS	15	18	15
TOTAL BENIGN TUMORS	17	23	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	31	25	24
TOTAL MALIGNANT TUMORS	37	30	28
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	5	1
TOTAL SECONDARY TUMORS	6	9	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(47)	(48)	(49)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	2 (4%)	7 (14%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	11 (22%)	3 (6%)	6 (12%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	6 (12%)	2 (4%)	1 (2%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
LYMPHOCYTIC LEUKEMIA	2 (4%)		1 (2%)
GRANULOCYTIC LEUKEMIA	1 (2%)		
#SPLEEN	(47)	(49)	(49)
HEMANGIOSARCOMA		3 (6%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
#LYMPH NODE	(38)	(39)	(35)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (3%)	
#MESENTERIC L. NODE	(38)	(39)	(35)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	1 (3%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)		
#LUNG	(47)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SMALL INTESTINE	(48)	(47)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#KIDNEY	(49)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#THYMUS	(38)	(43)	(41)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
GRANULOCYTIC SARCOMA			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (2%)	4 (8%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)	2 (4%)	4 (8%)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA	1 (2%)	1 (2%)	1 (2%)
#DUODENUM	(48)	(47)	(50)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(42)	(43)
CHROMOPHOBE ADENOMA	2 (5%)	6 (14%)	6 (14%)
#THYROID	(40)	(44)	(43)
FOLLICULAR-CELL ADENOMA			2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROADENOMA			1 (2%)
*UTERUS	(47)	(49)	(50)
SARCOMA, NOS			1 (2%)
LEIOMYOSARCOMA	2 (4%)	1 (2%)	
ENDOMETRIAL STROMAL POLYP		1 (2%)	
HEMANGIOMA		1 (2%)	
*OVARY	(39)	(47)	(46)
LUTEOMA		1 (2%)	
GRANULOSA-CELL TUMOR	1 (3%)		
TERATOMA, BENIGN		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	9	6
MORIBUND SACRIFICE	1	3	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	35	38	41
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	31	28
TOTAL PRIMARY TUMORS	31	40	45
TOTAL ANIMALS WITH BENIGN TUMORS	3	16	16
TOTAL BENIGN TUMORS	5	17	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	19	21
TOTAL MALIGNANT TUMORS	25	23	26
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
CYST, NOS	1 (2%)		
HYPERKERATOSIS	2 (4%)		
*SUBCUT TISSUE	(50)	(50)	(49)
ULCER, NOS		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		
#TRACHEA	(49)	(47)	(49)
INFLAMMATION, NOS	17 (35%)	14 (30%)	9 (18%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	3 (6%)		1 (2%)
#LUNG/BRONCHUS	(50)	(50)	(48)
BRONCHIECTASIS	4 (8%)	4 (8%)	1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	8 (16%)	19 (38%)	20 (42%)
#LUNG	(50)	(50)	(48)
ATELECTASIS	1 (2%)		
CONGESTION, NOS	2 (4%)	2 (4%)	
HEMORRHAGE		1 (2%)	
BRONCHOPNEUMONIA, NOS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, 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
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE		1 (2%)	
BRONCHOPNEUMONIA ACUTE SUPPURATI	1 (2%)		1 (2%)
PNEUMONIA, CHRONIC MURINE	12 (24%)	5 (10%)	2 (4%)
FIBROSIS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
PIGMENTATION, NOS	1 (2%)		1 (2%)
HEMOSIDEROSIS	1 (2%)		
ALVEOLAR MACROPHAGES	5 (10%)	2 (4%)	2 (4%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
#LUNG/ALVEOLI	(50)	(50)	(48)
CONGESTION, NOS	1 (2%)		
EDEMA, NOS	1 (2%)	1 (2%)	
HEMORRHAGE	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(49)	(48)
HYPOPLASIA, NOS		1 (2%)	
HYPERPLASIA, NOS	4 (8%)	1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	4 (8%)	8 (16%)	11 (23%)
HYPERPLASIA, ERYTHROID	1 (2%)		
HYPERPLASIA, GRANULOCYTIC		3 (6%)	7 (15%)
ERYTHROPOIESIS		1 (2%)	
#SPLEEN	(49)	(47)	(49)
RUPTURE		1 (2%)	
CONGESTION, NOS	1 (2%)	2 (4%)	1 (2%)
FIBROSIS	1 (2%)		
NECROSIS, FOCAL		1 (2%)	2 (4%)
HEMOSIDEROSIS	23 (47%)	31 (66%)	18 (37%)
ATROPHY, NOS	1 (2%)		
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, RETICULUM CELL			2 (4%)
HEMATOPOIESIS	25 (51%)	31 (66%)	18 (37%)
ERYTHROPOIESIS		2 (4%)	2 (4%)
GRANULOPOIESIS	1 (2%)	1 (2%)	5 (10%)
#LYMPH NODE	(41)	(41)	(42)
HEMOSIDEROSIS	1 (2%)		
#MESENTERIC L. NODE	(41)	(41)	(42)
HYPERPLASIA, 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
#THYMUS	(37)	(41)	(31)
LYMPHANGIECTASIS		1 (2%)	
HEMOSIDEROSIS		2 (5%)	1 (3%)
ANGIECTASIS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(48)
FIBROSIS, FOCAL		1 (2%)	
#HEART/ATRIUM	(48)	(49)	(48)
THROMBOSIS, NOS		1 (2%)	
#MYOCARDIUM	(48)	(49)	(48)
INFLAMMATION, FOCAL	2 (4%)	2 (4%)	
INFLAMMATION, INTERSTITIAL		1 (2%)	2 (4%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS	4 (8%)	1 (2%)	
FIBROSIS, FOCAL	1 (2%)	16 (33%)	18 (38%)
SCAR		1 (2%)	
DEGENERATION, NOS	6 (13%)	1 (2%)	
NECROSIS, FOCAL			1 (2%)
#ENDOCARDIUM	(48)	(49)	(48)
INFLAMMATION, FOCAL	2 (4%)		
*PULMONARY ARTERY	(50)	(50)	(49)
MEDIAL CALCIFICATION		1 (2%)	
CALCIFICATION, FOCAL			2 (4%)
#HEPATIC SINUSOID	(49)	(49)	(49)
CONGESTION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(49)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
CIRRHOSIS, NOS		1 (2%)	
DEGENERATION, CYSTIC		1 (2%)	
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL		1 (2%)	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
METAMORPHOSIS FATTY	1 (2%)	7 (14%)	8 (16%)
PIGMENTATION, NOS		1 (2%)	
FOCAL CELLULAR CHANGE		2 (4%)	2 (4%)
PHAGOCYTIC CELL	1 (2%)		
ANGIECTASIS			3 (6%)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	4 (8%)		
ERYTHROPOIESIS		1 (2%)	
#LIVER/CENTRILOBULAR	(49)	(49)	(49)
METAMORPHOSIS FATTY	2 (4%)	2 (4%)	3 (6%)
PIGMENTATION, NOS	1 (2%)		
#LIVER/HEPATOCYTES	(49)	(49)	(49)
DEGENERATION, NOS			1 (2%)
*BILE DUCT	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	2 (4%)	2 (4%)
HYPERPLASIA, FOCAL	18 (36%)	26 (52%)	28 (57%)
#PANCREAS	(49)	(44)	(45)
EDEMA, NOS	1 (2%)		
PERIARTERITIS	1 (2%)		
#PANCREATIC DUCT	(49)	(44)	(45)
HYPERPLASIA, FOCAL	2 (4%)	5 (11%)	3 (7%)
#STOMACH	(49)	(50)	(47)
ULCER, NOS	1 (2%)		1 (2%)
ULCER, FOCAL	1 (2%)	3 (6%)	
INFLAMMATION, SUPPURATIVE			1 (2%)
EROSION	1 (2%)	1 (2%)	
#GASTRIC MUCOSA	(49)	(50)	(47)
EROSION		1 (2%)	
#CARDIAC STOMACH	(49)	(50)	(47)
ULCER, FOCAL			2 (4%)
#PEYERS PATCH	(49)	(49)	(43)
HYPERPLASIA, LYMPHOID	5 (10%)	4 (8%)	4 (9%)
#ILEUM	(49)	(49)	(43)
MUCOCELE	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
#COLON	(32)	(33)	(31)
NEMATODIASIS	3 (9%)	3 (9%)	1 (3%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
CAST, NOS	1 (2%)		
CONGESTION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)	8 (16%)	2 (4%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	8 (16%)	6 (12%)	5 (10%)
INFLAMMATION, CHRONIC FOCAL	26 (52%)	16 (33%)	18 (37%)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)	2 (4%)	2 (4%)
GLOMERULOSCLEROSIS, NOS	1 (2%)		
PIGMENTATION, NOS			2 (4%)
#KIDNEY/CORTEX	(50)	(49)	(49)
INFARCT, FOCAL		1 (2%)	1 (2%)
PIGMENTATION, NOS		5 (10%)	2 (4%)
#KIDNEY/TUBULE	(50)	(49)	(49)
CAST, NOS	1 (2%)		2 (4%)
DEGENERATION, HYALINE		1 (2%)	
PIGMENTATION, NOS	3 (6%)	1 (2%)	2 (4%)
#CONVOLUTED TUBULES	(50)	(49)	(49)
PIGMENTATION, NOS		2 (4%)	2 (4%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#U. BLADDER/SUBMUCOSA	(47)	(42)	(43)
HEMORRHAGE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(45)	(43)
CYST, NOS	1 (2%)	1 (2%)	
MULTIPLE CYSTS		1 (2%)	
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
HEMORRHAGIC CYST			1 (2%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL			1 (2%)
ANGIECTASIS	2 (4%)	2 (4%)	4 (9%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL	(49)	(47)	(48)
ANGIECTASIS	1 (2%)	1 (2%)	
#ADRENAL CORTEX	(49)	(47)	(48)
HYPERPLASIA, NODULAR	1 (2%)		
#ADRENAL MEDULLA	(49)	(47)	(48)
HYPERPLASIA, NODULAR	2 (4%)		
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	4 (9%)	2 (4%)
#THYROID	(46)	(48)	(46)
CYSTIC FOLLICLES		1 (2%)	4 (9%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
NECROSIS, NOS			1 (2%)
HYPERPLASIA, C-CELL	23 (50%)	29 (60%)	29 (63%)
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
GALACTOCELE			1 (2%)
*PENIS	(50)	(50)	(49)
PROLAPSE			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(49)
ULCER, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	2 (4%)		
#PROSTATE	(44)	(42)	(42)
INFLAMMATION, DIFFUSE			1 (2%)
INFLAMMATION, SUPPURATIVE	2 (5%)		
#TESTIS	(50)	(50)	(49)
NECROSIS, NOS		1 (2%)	
CALCIFICATION, DYSTROPHIC		1 (2%)	
ATROPHY, NOS	32 (64%)	19 (38%)	31 (63%)
ATROPHY, FOCAL	7 (14%)	19 (38%)	4 (8%)
ASPERMATOGENESIS	4 (8%)	2 (4%)	5 (10%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		4 (8%)
#TESTIS/TUBULE	(50)	(50)	(49)
CALCIFICATION, 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
CALCIFICATION, FOCAL		2 (4%)	2 (4%)
*EPIDIDYMIS	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
NERVOUS SYSTEM			
*NEURON	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#BRAIN/MENINGES	(50)	(50)	(49)
THROMBOSIS, NOS	1 (2%)		
#BRAIN	(50)	(50)	(49)
HEMORRHAGE			1 (2%)
GLIOSIS			1 (2%)
DEGENERATION, NOS			1 (2%)
#BRAIN STEM	(50)	(50)	(49)
HEMORRHAGE			1 (2%)
NECROSIS, NOS	1 (2%)		
#MIDBRAIN	(50)	(50)	(49)
NECROSIS, NOS	1 (2%)		
MALACIA	1 (2%)		
*SPINAL CORD	(50)	(50)	(49)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
*SCIATIC NERVE	(50)	(50)	(49)
DEGENERATION, MYELIN			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)		
CATARACT	13 (26%)	5 (10%)	7 (14%)
*EYE/CORNEA	(50)	(50)	(49)
INFLAMMATION, INTERSTITIAL	1 (2%)		
*LENS CAPSULE	(50)	(50)	(49)
DEGENERATION, 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
CALCIFICATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(49)
ATROPHY, NOS			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(49)
NECROSIS, FAT	1 (2%)		
*PERITONEUM	(50)	(50)	(49)
EFFUSION, NOS		1 (2%)	
*PERITONEAL CAVITY	(50)	(50)	(49)
RETENTION FLUID		1 (2%)	
*PLEURA	(50)	(50)	(49)
HYDROTHORAX	1 (2%)		
*MESENTERY	(50)	(50)	(49)
STEATITIS		1 (2%)	
NECROSIS, FAT	2 (4%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, FOCAL	1		
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY			1

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
NECROSIS, FOCAL	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(49)	(50)	(49)
INFLAMMATION, NOS	17 (35%)	26 (52%)	14 (29%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
NECROSIS, NOS			2 (4%)
METAPLASIA, SQUAMOUS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	1 (2%)
#LUNG/BRONCHUS	(50)	(50)	(50)
BRONCHIECTASIS	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, FOCAL			1 (2%)
HYPERPLASIA, LYMPHOID	27 (54%)	25 (50%)	31 (62%)
#LUNG	(50)	(50)	(50)
BRONCHOPNEUMONIA, NOS	1 (2%)		
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL			2 (4%)
PNEUMONIA, CHRONIC MURINE	5 (10%)	3 (6%)	
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
PERIVASCULAR CUFFING	2 (4%)		
HEMOSIDEROSIS		1 (2%)	
ALVEOLAR MACROPHAGES	2 (4%)	2 (4%)	2 (4%)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#LUNG/ALVEOLI	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)
EDEMA, NOS		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			
*BLOOD	(50)	(50)	(50)
ANEMIA, NOS		1 (2%)	
#BONE MARROW	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
MYELOFIBROSIS		1 (2%)	
HEMATOPOIETIC TISSUE DISORDER		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	3 (6%)	7 (14%)	5 (10%)
HYPERPLASIA, GRANULOCYTIC	2 (4%)		
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
NECROSIS, COAGULATIVE			1 (2%)
HEMOSIDEROSIS	34 (68%)	34 (68%)	39 (78%)
ATROPHY, NOS		1 (2%)	1 (2%)
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)	1 (2%)	
HEMATOPOIESIS	40 (80%)	39 (78%)	35 (70%)
ERYTHROPOIESIS		2 (4%)	1 (2%)
GRANULOPOIESIS			1 (2%)
#LYMPH NODE	(44)	(39)	(34)
HEMOSIDEROSIS	1 (2%)		
#MANDIBULAR L. NODE	(44)	(39)	(34)
LYMPHANGIECTASIS			1 (3%)
#CERVICAL LYMPH NODE	(44)	(39)	(34)
CONGESTION, NOS	1 (2%)		
HEMOSIDEROSIS	1 (2%)		
#THYMUS	(39)	(37)	(36)
PERIARTERITIS			1 (3%)
HEMOSIDEROSIS	1 (3%)	1 (3%)	4 (11%)
CIRCULATORY SYSTEM			
#HEART	(48)	(47)	(49)
PERIARTERITIS		1 (2%)	1 (2%)
#HEART/ATRIUM	(48)	(47)	(49)
THROMBOSIS, NOS		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
#MYOCARDIUM	(48)	(47)	(49)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, INTERSTITIAL		6 (13%)	5 (10%)
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL	2 (4%)	5 (11%)	12 (24%)
*PULMONARY ARTERY	(50)	(50)	(50)
CALCIFICATION, FOCAL		1 (2%)	
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERKERATOSIS			1 (2%)
#LIVER	(49)	(49)	(49)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS			1 (2%)
NODULE			1 (2%)
ADHESION, NOS		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
NECROSIS, COAGULATIVE			1 (2%)
METAMORPHOSIS FATTY	9 (18%)	9 (18%)	4 (8%)
PIGMENTATION, NOS		1 (2%)	
FOCAL CELLULAR CHANGE			1 (2%)
ANGIECTASIS	3 (6%)	1 (2%)	4 (8%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	1 (2%)	2 (4%)	1 (2%)
ERYTHROPOIESIS	1 (2%)		
#LIVER/CENTRILOBULAR	(49)	(49)	(49)
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	2 (4%)	2 (4%)	
#LIVER/PERIPORTAL	(49)	(49)	(49)
METAMORPHOSIS FATTY	1 (2%)		2 (4%)
#LIVER/HEPATOCYTES	(49)	(49)	(49)
NECROSIS, FOCAL		1 (2%)	
*BILE DUCT	(50)	(50)	(50)
INFLAMMATION, FOCAL		3 (6%)	
HYPERPLASIA, NOS		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
HYPERPLASIA, FOCAL	15 (30%)	16 (32%)	19 (38%)
#PANCREAS	(49)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
ADHESION, NOS		1 (2%)	
#PANCREATIC DUCT	(49)	(50)	(48)
HYPERPLASIA, FOCAL	5 (10%)	9 (18%)	7 (15%)
#STOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
ULCER, FOCAL			1 (2%)
EROSION			1 (2%)
NECROSIS, FOCAL			1 (2%)
#CARDIAC STOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
ULCER, FOCAL		1 (2%)	
#PEYERS PATCH	(49)	(48)	(48)
HYPERPLASIA, LYMPHOID	4 (8%)	10 (21%)	3 (6%)
#COLON	(35)	(40)	(28)
NEMATODIASIS	5 (14%)	6 (15%)	4 (14%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
INFLAMMATION, INTERSTITIAL	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	12 (24%)	5 (10%)	3 (6%)
NEPHROSIS, NOS	1 (2%)		
CALCIFICATION, FOCAL			1 (2%)
PIGMENTATION, NOS	2 (4%)	2 (4%)	
#KIDNEY/CORTEX	(49)	(50)	(50)
CYST, NOS		1 (2%)	1 (2%)
PIGMENTATION, NOS	17 (35%)	28 (56%)	36 (72%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#KIDNEY/TUBULE	(49)	(50)	(50)
CAST, NOS		1 (2%)	
PIGMENTATION, NOS	2 (4%)	5 (10%)	
#CONVOLUTED TUBULES	(49)	(50)	(50)
CAST, NOS	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
HYALINE MEMBRANE	1 (2%)		
METAMORPHOSIS FATTY		1 (2%)	
PIGMENTATION, NOS		3 (6%)	2 (4%)
#KIDNEY/PELVIS	(49)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		1 (2%)
#URINARY BLADDER	(35)	(43)	(44)
CALCULUS, NOS	1 (3%)		
INFLAMMATION, CHRONIC	1 (3%)		
HYPERPLASIA, EPITHELIAL	1 (3%)		
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(47)	(44)
CYST, NOS	1 (2%)		
HEMORRHAGE	2 (4%)		2 (5%)
HEMORRHAGIC CYST	2 (4%)	1 (2%)	
HEMOSIDEROSIS	1 (2%)	2 (4%)	2 (5%)
HYPERPLASIA, NOS	3 (7%)	2 (4%)	
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)	
ANGIECTASIS	3 (7%)	22 (47%)	23 (52%)
#ADRENAL	(49)	(49)	(50)
DEGENERATION, NOS	1 (2%)		
ANGIECTASIS	3 (6%)	10 (20%)	18 (36%)
#ADRENAL CORTEX	(49)	(49)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
NECROSIS, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(49)	(49)	(50)
CYST, NOS			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
#THYROID	(50)	(47)	(48)
CYSTIC FOLLICLES	1 (2%)		4 (8%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
HYPERPLASIA, C-CELL	39 (78%)	33 (70%)	36 (75%)
HYPERPLASIA, FOLLICULAR-CELL		2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	5 (10%)	8 (16%)	6 (12%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS		1 (2%)	
METAPLASIA, SQUAMOUS			1 (2%)
ADENOSIS	1 (2%)	1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	7 (14%)	2 (4%)	1 (2%)
ABSCESS, NOS			1 (2%)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
*VAGINA	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#UTERUS	(50)	(49)	(50)
HYDROMETRA		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
NECROSIS, NOS		1 (2%)	
PIGMENTATION, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
CYST, NOS	1 (2%)	1 (2%)	4 (8%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, FOCAL		1 (2%)	
ULCER, FOCAL	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, SUPPURATIVE	8 (16%)	6 (12%)	3 (6%)
INFLAMMATION, VESICULAR		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, CYSTIC	2 (4%)	1 (2%)	1 (2%)
#OVARY/OVIDUCT	(50)	(49)	(50)
INFLAMMATION, NOS			5 (10%)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, SUPPURATIVE	5 (10%)	7 (14%)	1 (2%)
#OVARY	(50)	(49)	(48)
CYST, NOS	9 (18%)	7 (14%)	11 (23%)
FOLLICULAR CYST, NOS		2 (4%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(49)
NECROSIS, NOS			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
NECROSIS, FOCAL			1 (2%)
MALACIA	1 (2%)		
#CEREBELLUM	(49)	(49)	(49)
NECROSIS, FOCAL			1 (2%)
*SPINAL CORD	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
CATARACT	11 (22%)	16 (32%)	21 (42%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)		
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
FIBROSIS			1 (2%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, FAT			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
ALL OTHER SYSTEMS			
DIAPHRAGM			
HERNIA, NOS	1	2	2
ADIPOSE TISSUE			
INFLAMMATION, NOS			4
OMENTUM			
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			2
ANIMALS NECROPSIED	49	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	48
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(48)
CYST, NOS	1 (2%)		
ULCER, NOS			1 (2%)
ULCER, FOCAL			1 (2%)
INFLAMMATION, SUPPURATIVE		2 (4%)	
INFLAMMATION, VESICULAR		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, NOS			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(49)	(49)	(48)
METAPLASIA, SQUAMOUS	1 (2%)		
HYPERPLASIA, LYMPHOID	11 (22%)	4 (8%)	
#LUNG	(49)	(49)	(48)
CONGESTION, NOS	1 (2%)		1 (2%)
EDEMA, NOS			1 (2%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
ALVEOLAR MACROPHAGES		1 (2%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIETIC SYSTEM			
*BLOOD	(49)	(50)	(48)
ANEMIA, NOS		1 (2%)	
#BONE MARROW	(46)	(44)	(48)
HYPERPLASIA, HEMATOPOIETIC	2 (4%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, GRANULOCYTIC	2 (4%)	2 (5%)	
#SPLEEN	(46)	(48)	(46)
HEMORRHAGE	1 (2%)		
AMYLOIDOSIS			1 (2%)
HEMOSIDEROSIS			1 (2%)
ANGIECTASIS	1 (2%)		
LEUKEMOID REACTION		1 (2%)	1 (2%)
LYMPHOCYTOSIS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)	5 (10%)	
HEMATOPOIESIS	24 (52%)	28 (58%)	28 (61%)
ERYTHROPOIESIS	2 (4%)		
GRANULOPOIESIS	1 (2%)		
#LYMPH NODE	(40)	(33)	(29)
INFLAMMATION, NOS		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	
HEMATOPOIESIS	1 (3%)		
#MANDIBULAR L. NODE	(40)	(33)	(29)
HYPERPLASIA, LYMPHOID		2 (6%)	
#MEDIASTINAL L. NODE	(40)	(33)	(29)
HYPERPLASIA, LYMPHOID			1 (3%)
#MESENTERIC L. NODE	(40)	(33)	(29)
THROMBOSIS, NOS	1 (3%)		
CONGESTION, NOS	3 (8%)	2 (6%)	1 (3%)
#THYMUS	(35)	(20)	(31)
HYPERPLASIA, LYMPHOID			1 (3%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(49)	(49)	(48)
INFLAMMATION, INTERSTITIAL			1 (2%)
#CARDIAC VALVE	(49)	(49)	(48)
MELANIN			1 (2%)
*PULMONARY ARTERY	(49)	(50)	(48)
INFLAMMATION, 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
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(43)	(47)	(44)
FIBROSIS		1 (2%)	
#LIVER	(49)	(50)	(48)
CYST, NOS			1 (2%)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
FIBROSIS, FOCAL	1 (2%)		
DEGENERATION, HYALINE			1 (2%)
NECROSIS, FOCAL			1 (2%)
AMYLOIDOSIS			1 (2%)
METAMORPHOSIS FATTY	4 (8%)	1 (2%)	3 (6%)
PIGMENTATION, NOS		1 (2%)	
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, NODULAR		1 (2%)	1 (2%)
HYPERPLASTIC NODULE	1 (2%)		
ANGIECTASIS	1 (2%)	1 (2%)	
LEUKEMOID REACTION		1 (2%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
HYPERPLASIA, RETICULUM CELL			2 (4%)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#HEPATIC CAPSULE	(49)	(50)	(48)
HEMATOMA, NOS	1 (2%)		
#LIVER/CENTRILOBULAR	(49)	(50)	(48)
METAMORPHOSIS FATTY	1 (2%)		1 (2%)
#LIVER/PERIPORTAL	(49)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
#LIVER/HEPATOCYTES	(49)	(50)	(48)
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS		1 (2%)	
NECROSIS, COAGULATIVE		1 (2%)	
*BILE DUCT	(49)	(50)	(48)
CYST, NOS			2 (4%)
INFLAMMATION, NOS		2 (4%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, FOCAL			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			2 (4%)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
HYPERPLASIA, NOS	4 (8%)	3 (6%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
#PANCREAS	(48)	(46)	(45)
CYSTIC DUCTS	1 (2%)		
EDEMA, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
FIBROSIS	1 (2%)		
NECROSIS, NOS	1 (2%)		
#PANCREATIC DUCT	(48)	(46)	(45)
CYST, NOS		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
#SMALL INTESTINE	(47)	(44)	(45)
INFLAMMATION, NOS			1 (2%)
NECROSIS, NOS			1 (2%)
#PEYERS PATCH	(47)	(44)	(45)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID	2 (4%)	2 (5%)	4 (9%)
#COLON	(22)	(36)	(35)
INFLAMMATION, NOS			1 (3%)
NEMATODIASIS	4 (18%)	5 (14%)	2 (6%)
URINARY SYSTEM			
#KIDNEY	(48)	(47)	(48)
PYELONEPHRITIS, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		
INFLAMMATION, INTERSTITIAL	1 (2%)	1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
FIBROSIS	1 (2%)		
PERIARTERITIS		1 (2%)	
INFARCT, NOS		1 (2%)	
AMYLOIDOSIS			1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
HYPERPLASIA, NODULAR		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, LYMPHOID	1 (2%)	1 (2%)	
#KIDNEY/CORTEX	(48)	(47)	(48)
FIBROSIS, FOCAL		1 (2%)	
INFARCT, NOS	1 (2%)		
#KIDNEY/TUBULE	(48)	(47)	(48)
DEGENERATION, HYALINE		1 (2%)	1 (2%)
#URINARY BLADDER	(47)	(49)	(44)
CALCULUS, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
PERIARTERITIS		1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(31)	(45)	(36)
CYST, NOS			2 (6%)
#ADRENAL/CAPSULE	(46)	(49)	(46)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	28 (61%)	35 (71%)	34 (74%)
#ADRENAL CORTEX	(46)	(49)	(46)
HYPERPLASIA, NOS	2 (4%)		
#ADRENAL MEDULLA	(46)	(49)	(46)
HYPERPLASIA, NOS			1 (2%)
#THYROID	(43)	(39)	(40)
CYSTIC FOLLICLES	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	2 (5%)	2 (5%)	
#PANCREATIC ISLETS	(48)	(46)	(45)
HYPERPLASIA, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(49)	(50)	(48)
DILATATION, NOS		1 (2%)	
CYST, NOS			4 (8%)
INFLAMMATION, SUPPURATIVE	2 (4%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PROSTATE	(39)	(33)	(35)
INFLAMMATION, SUPPURATIVE		1 (3%)	1 (3%)
*SEMINAL VESICLE	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
#TESTIS	(47)	(48)	(46)
ATROPHY, NOS		1 (2%)	3 (7%)
ATROPHY, FOCAL		1 (2%)	1 (2%)
ASPERMATOGENESIS	1 (2%)	1 (2%)	
*EPIDIDYMIS	(49)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		3 (6%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
CALCIFICATION, FOCAL		1 (2%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(48)
PUS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
DEGENERATION, NOS		1 (2%)	
CATARACT		2 (4%)	
PHTHISIS BULBI			1 (2%)
*EYE/CORNEA	(49)	(50)	(48)
INFLAMMATION, INTERSTITIAL			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(50)	(48)
DEGENERATION, NOS			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(48)
HEMORRHAGE			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
FIBROSIS		1 (2%)	
NECROSIS, FAT		1 (2%)	1 (2%)
*PERITONEUM	(49)	(50)	(48)
HEMOPERITONEUM		1 (2%)	
INFLAMMATION, NOS			1 (2%)
NECROSIS, FOCAL	1 (2%)		
*PLEURA	(49)	(50)	(48)
HYDROTHORAX			1 (2%)
*MESENTERY	(49)	(50)	(48)
NECROSIS, FAT	2 (4%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, NOS	2		
FIBROSIS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
ANIMAL MISSING/NO NECROPSY			2
AUTOLYSIS/NO NECROPSY	1		

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, NOS			1 (2%)
HYPERKERATOSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
EDEMA, NOS			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#LUNG/BRONCHUS	(47)	(48)	(49)
HYPERPLASIA, LYMPHOID	18 (38%)	1 (2%)	3 (6%)
#LUNG	(47)	(48)	(49)
INFLAMMATION, FOCAL	1 (2%)		
ALVEOLAR MACROPHAGES			3 (6%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LUNG/ALVEOLI	(47)	(48)	(49)
CONGESTION, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(46)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC	3 (7%)	2 (4%)	1 (2%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)		
#SPLEEN	(47)	(49)	(49)
THROMBOSIS, 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
HEMOSIDEROSIS		2 (4%)	
ANGIECTASIS		2 (4%)	
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, LYMPHOID	6 (13%)	5 (10%)	13 (27%)
HEMATOPOIESIS	19 (40%)	35 (71%)	23 (47%)
MYELOPOIESIS	1 (2%)		
#LYMPH NODE	(38)	(39)	(35)
HYPERPLASIA, LYMPHOID	1 (3%)		
#MESENTERIC L. NODE	(38)	(39)	(35)
INFLAMMATION, GRANULOMATOUS	1 (3%)		
#THYMUS	(38)	(43)	(41)
HYPERPLASIA, LYMPHOID	1 (3%)	1 (2%)	
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(49)	(50)	(50)
MELANIN		1 (2%)	
#MYOCARDIUM	(49)	(50)	(50)
INFLAMMATION, INTERSTITIAL		1 (2%)	
#CARDIAC VALVE	(49)	(50)	(50)
MELANIN			1 (2%)
*UTERINE ARTERY	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#HEPATIC SINUSOID	(49)	(50)	(50)
CONGESTION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
PELIOSIS HEPATIS		1 (2%)	1 (2%)
DEGENERATION, HYALINE		1 (2%)	
NECROSIS, FOCAL	1 (2%)	1 (2%)	
METAMORPHOSIS FATTY	2 (4%)		4 (8%)
HEMOSIDEROSIS		1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
FOCAL CELLULAR CHANGE			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, NODULAR		1 (2%)	
ANGIECTASIS		1 (2%)	1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (2%)	1 (2%)	2 (4%)
HYPERPLASIA, LYMPHOID	2 (4%)		
HEMATOPOIESIS	3 (6%)	3 (6%)	1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(50)
NECROSIS, FOCAL		1 (2%)	
#LIVER/HEPATOCYTES	(49)	(50)	(50)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	2 (4%)
*BILE DUCT	(50)	(50)	(50)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
#PANCREAS	(44)	(50)	(49)
HEMATOPOIESIS		1 (2%)	
#PANCREATIC DUCT	(44)	(50)	(49)
DISTENTION		1 (2%)	
CYST, NOS		2 (4%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#PEYERS PATCH	(48)	(47)	(50)
HYPERPLASIA, LYMPHOID		3 (6%)	5 (10%)
#DUODENUM	(48)	(47)	(50)
INFLAMMATION, NOS			1 (2%)
#COLON	(36)	(40)	(46)
NEMATODIASIS		1 (3%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
GLOMERULONEPHRITIS, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, LYMPHOID	10 (20%)	1 (2%)	3 (6%)
#KIDNEY/CORTEX	(49)	(50)	(50)
SCAR	1 (2%)		
DEGENERATION, HYALINE	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
#KIDNEY/TUBULE	(49)	(50)	(50)
DEGENERATION, HYALINE			1 (2%)
#CONVOLUTED TUBULES	(49)	(50)	(50)
PIGMENTATION, NOS		1 (2%)	
#URINARY BLADDER	(30)	(44)	(40)
PERIARTERITIS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(42)	(43)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
ANGIECTASIS		1 (2%)	2 (5%)
#ADRENAL	(48)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
#ADRENAL/CAPSULE	(48)	(49)	(50)
HYPERPLASIA, FOCAL	43 (90%)	45 (92%)	45 (90%)
#ADRENAL CORTEX	(48)	(49)	(50)
HEMORRHAGE			1 (2%)
CYTOLOGIC DEGENERATION			2 (4%)
#THYROID	(40)	(44)	(43)
CYSTIC FOLLICLES	1 (3%)		
HYPERPLASIA, FOLLICULAR-CELL	6 (15%)	7 (16%)	8 (19%)
#PARATHYROID	(16)	(18)	(8)
CYST, NOS			1 (13%)
MELANIN			1 (13%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
METAPLASIA, SQUAMOUS			1 (2%)
#UTERUS	(47)	(49)	(50)
HYDROMETRA			1 (2%)
HEMORRHAGE			1 (2%)
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
#UTERUS/ENDOMETRIUM	(47)	(49)	(50)
CYST, NOS		2 (4%)	
INFLAMMATION, SUPPURATIVE	3 (6%)		2 (4%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	19 (40%)	27 (55%)	37 (74%)
#OVARY/OVIDUCT	(47)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, SUPPURATIVE	3 (6%)		
NECROSIS, NOS	1 (2%)		
#OVARY/PAROVARIAN	(47)	(49)	(50)
FIBROSIS			1 (2%)
NECROSIS, FAT			1 (2%)
#OVARY	(39)	(47)	(46)
CYST, NOS	4 (10%)	10 (21%)	7 (15%)
FOLLICULAR CYST, NOS		3 (6%)	
MULTIPLE CYSTS		2 (4%)	
PAROVARIAN CYST		1 (2%)	4 (9%)
HEMORRHAGE		1 (2%)	
HEMATOMA, NOS		1 (2%)	
HEMORRHAGIC CYST	1 (3%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC	1 (3%)		
NECROSIS, FAT		1 (2%)	
#OVARY/FOLLICLE	(39)	(47)	(46)
HEMORRHAGE		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(47)	(49)	(50)
PERIVASCULAR CUFFING			1 (2%)
#CEREBRUM	(47)	(49)	(50)
ATROPHY, NOS		1 (2%)	
#BRAIN	(47)	(49)	(50)
PERIVASCULAR CUFFING			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
CATARACT			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
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
DEGENERATION, NOS		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
CYST, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	
*PLEURA	(50)	(50)	(50)
HYDROTHORAX	1 (2%)	1 (2%)	
*MESENTERY	(50)	(50)	(50)
STEATITIS			1 (2%)
FIBROSIS			1 (2%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, FAT			2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
ADIPOSE TISSUE			
INFLAMMATION, FOCAL		1	
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF	1		

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	3/50 (6)	0/50 (0)	0/48 (0)
P Values[c,d]	P = 0.039 (N)	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.663	1.730
Weeks to First Observed Tumor	102	--	--
Hematopoietic System: Malignant Lymphoma, Lymphocytic Leukemia, or Undifferentiated Leukemia[b]	11/50 (22)	15/50 (30)	19/49 (39)
P Values[c,d]	P = 0.044	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.364	1.763
Lower Limit		0.653	0.897
Upper Limit		2.943	3.629
Weeks to First Observed Tumor	96	85	64

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Granulocytic Leukemia[b]	2/50 (4)	4/50 (8)	9/49 (18)
P Values[c,d]	P = 0.014	N.S.	P = 0.023
Relative Risk (Matched Control)[f]		2.000	4.592
Lower Limit		0.301	1.015
Upper Limit		21.316	41.883
Weeks to First Observed Tumor	90	68	97
Hematopoietic System: All Lymphoma or Leukemia[b]	13/50 (26)	19/50 (38)	28/49 (57)
P Values[c,d]	P = 0.001	N.S.	P = 0.002
Relative Risk (Matched Control)[f]		1.462	2.198
Lower Limit		0.773	1.269
Upper Limit		2.839	3.929
Weeks to First Observed Tumor	90	68	64

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	3/46 (7)	3/45 (7)	8/43 (19)
P Values[c,d]	P = 0.048	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.022	2.853
Lower Limit		0.143	0.738
Upper Limit		7.254	15.707
Weeks to First Observed Tumor	111	105	77
Adrenal: Pheochromocytoma[b]	4/49 (8)	4/47 (9)	1/48 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.043	0.255
Lower Limit		0.207	0.005
Upper Limit		5.284	2.457
Weeks to First Observed Tumor	88	85	111

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma[b]	1/46 (2)	3/48 (6)	3/46 (7)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.875	3.000
Lower Limit		0.241	0.252
Upper Limit		147.682	153.954
Weeks to First Observed Tumor	111	101	106
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	1/46 (2)	3/48 (6)	4/46 (9)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.875	4.000
Lower Limit		0.241	0.414
Upper Limit		147.682	192.454
Weeks to First Observed Tumor	111	101	106

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma[b]	3/46 (7)	7/48 (15)	4/46 (9)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.236	1.333
Lower Limit		0.549	0.238
Upper Limit		12.700	8.645
Weeks to First Observed Tumor	111	109	85
Thyroid: C-cell Adenoma or Carcinoma[b]	4/46 (9)	7/48 (15)	5/46 (11)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.677	1.250
Lower Limit		0.459	0.286
Upper Limit		7.336	5.923
Weeks to First Observed Tumor	111	109	85

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	4/49 (8)	4/44 (9)	3/45 (7)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.114	0.817
Lower Limit		0.220	0.126
Upper Limit		5.626	4.558
Weeks to First Observed Tumor	88	111	107
Mammary Gland: Fibroadenoma[b]	1/50 (2)	1/50 (2)	4/49 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	4.082
Lower Limit		0.013	0.422
Upper Limit		76.970	196.666
Weeks to First Observed Tumor	111	111	102

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor[b]	48/50 (96)	48/50 (96)	41/49 (84)
P Values[c,d]	P = 0.020 (N)	N.S.	P = 0.043 (N)
Relative Risk (Matched Control)[f]		1.000	0.872
Lower Limit		0.931	0.806
Upper Limit		1.074	1.016
Weeks to First Observed Tumor	84	68	85
All Sites: Mesothelioma[b]	2/50 (4)	3/50 (6)	0/49 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.500	0.000
Lower Limit		0.180	0.000
Upper Limit		17.329	3.448
Weeks to First Observed Tumor	105	92	--

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

[a]Dosed groups received 300 or 600 ppm.

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

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

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma or Lymphocytic Leukemia[b]	5/50 (10)	12/50 (24)	9/50 (18)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.400	1.800
Lower Limit		0.857	0.586
Upper Limit		8.071	6.377
Weeks to First Observed Tumor	98	47	69
Hematopoietic System: All Lymphoma or Leukemia[b]	7/50 (14)	14/50 (28)	10/50 (20)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.000	1.429
Lower Limit		0.832	0.535
Upper Limit		5.348	4.071
Weeks to First Observed Tumor	98	47	69

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	19/45 (42)	29/47 (62)	29/44 (66)
P Values[c,d]	P = 0.016	P = 0.048	P = 0.021
Relative Risk (Matched Control)[f]		1.461	1.561
Lower Limit		0.944	1.015
Upper Limit		2.273	2.380
Weeks to First Observed Tumor	90	94	70
Adrenal: Pheochromocytoma[b]	3/49 (6)	0/49 (0)	0/50 (0)
P Values[c,d]	P = 0.036 (N)	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.662	1.629
Weeks to First Observed Tumor	107	--	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma[b]	2/50 (4)	3/47 (6)	5/48 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.596	2.604
Lower Limit		0.191	0.451
Upper Limit		18.399	26.304
Weeks to First Observed Tumor	111	99	111
Thyroid: C-cell Adenoma or Carcinoma[b]	5/50 (10)	5/47 (11)	8/48 (17)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.064	1.667
Lower Limit		0.261	0.520
Upper Limit		4.329	6.036
Weeks to First Observed Tumor	111	99	106

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Adenocarcinoma, NOS[b]	1/50 (2)	3/50 (6)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		3.000	1.000
Lower Limit		0.250	0.013
Upper Limit		154.270	76.970
Weeks to First Observed Tumor	98	111	111
Mammary Gland: Fibroadenoma[b]	12/50 (24)	12/50 (24)	14/50 (28)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	1.167
Lower Limit		0.458	0.558
Upper Limit		2.192	2.477
Weeks to First Observed Tumor	94	90	107

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	2/50 (4)	9/49 (18)	3/50 (6)
P Values[c,d]	N.S.	P = 0.023	N.S.
Departure from Linear Trend[e]	P = 0.009		
Relative Risk (Matched Control)[f]		4.592	1.500
Lower Limit		1.018	0.181
Upper Limit		41.883	17.329
Weeks to First Observed Tumor	111	63	111

[a]Dosed groups received 300 or 600 ppm.

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

[c]Beneath the incidence of tumors in the matched-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 matched-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 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED 2-AMINO-5-NITROTHIAZOLE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Subcutaneous Tissue: Fibrosarcoma[b]	2/49 (4)	2/50 (4)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.980	1.531
Lower Limit		0.074	0.183
Upper Limit		13.058	17.665
Weeks to First Observed Tumor	77	99	79
Lung: Alveolar/Bronchiolar Adenoma[b]	10/49 (20)	10/49 (20)	11/48 (23)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	1.123
Lower Limit		0.412	0.479
Upper Limit		2.430	2.666
Weeks to First Observed Tumor	81	82	64

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	4/49 (8)	2/49 (4)	1/48 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.500	0.255
Lower Limit		0.047	0.005
Upper Limit		3.315	2.457
Weeks to First Observed Tumor	100	100	80
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	14/49 (29)	12/49 (24)	12/48 (25)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.857	0.875
Lower Limit		0.406	0.414
Upper Limit		1.784	1.820
Weeks to First Observed Tumor	81	82	64

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Granulocytic Leukemia[b]	1/49 (2)	0/50 (0)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	3.063
Lower Limit		0.000	0.257
Upper Limit		18.285	157.336
Weeks to First Observed Tumor	88	--	104
Hematopoietic System: Lymphoma[b]	6/49 (12)	8/50 (16)	2/48 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.307	0.340
Lower Limit		0.430	0.035
Upper Limit		4.243	1.791
Weeks to First Observed Tumor	87	81	100

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: All Neoplasms[b]	8/49 (16)	8/50 (16)	7/48 (15)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.980	0.893
Lower Limit		0.349	0.299
Upper Limit		2.757	2.594
Weeks to First Observed Tumor	87	81	78
All Sites: Hemangiosarcoma[b]	5/49 (10)	4/50 (8)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.784	0.613
Lower Limit		0.165	0.101
Upper Limit		3.426	2.963
Weeks to First Observed Tumor	81	92	82

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	16/49 (33)	11/50 (22)	11/48 (23)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.674	0.702
Lower Limit		0.317	0.330
Upper Limit		1.381	1.437
Weeks to First Observed Tumor	94	99	70
Liver: Hepatocellular Adenoma or Carcinoma[b]	20/49 (41)	16/50 (32)	15/48 (31)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.784	0.766
Lower Limit		0.436	0.418
Upper Limit		1.392	1.376
Weeks to First Observed Tumor	94	99	70

[a]Dosed groups received 50 or 100 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 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

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

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	2/47 (4)	2/48 (4)	7/49 (14)
P Values[c,d]	P = 0.048	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.979	3.357
Lower Limit		0.074	0.682
Upper Limit		13.027	31.811
Weeks to First Observed Tumor	100	100	101
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	2/47 (4)	4/48 (8)	8/49 (16)
P Values[c,d]	P = 0.034	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.958	3.837
Lower Limit		0.296	0.820
Upper Limit		20.832	35.590
Weeks to First Observed Tumor	100	96	101

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma, Undifferentiated Leukemia, or Lymphocytic Leukemia[b]	20/50 (40)	12/50 (24)	11/50 (22)
P Values[c,d]	P = 0.030(N)	N.S.	P = 0.041(N)
Relative Risk (Matched Control)[f]		0.600	0.550
Lower Limit		0.303	0.269
Upper Limit		1.141	1.069
Weeks to First Observed Tumor	75	94	76
Hematopoietic System: All Neoplasms[b]	21/50 (42)	12/50 (24)	12/50 (24)
P Values[c,d]	P = 0.032(N)	P = 0.044(N)	P = 0.044(N)
Relative Risk (Matched Control)[f]		0.571	0.571
Lower Limit		0.291	0.291
Upper Limit		1.074	1.074
Weeks to First Observed Tumor	75	94	76

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma[b]	1/50 (2)	4/50 (8)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		4.000	4.000
Lower Limit		0.412	0.412
Upper Limit		192.807	192.807
Weeks to First Observed Tumor	100	72	65
Liver: Hepatocellular Carcinoma[b]	1/49 (2)	2/50 (4)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.960	3.920
Lower Limit		0.105	0.405
Upper Limit		113.312	188.989
Weeks to First Observed Tumor	100	91	101

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma[b]	2/49 (4)	6/50 (12)	5/50 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.940	2.450
Lower Limit		0.555	0.424
Upper Limit		28.662	24.778
Weeks to First Observed Tumor	100	91	101
Pituitary: Chromophobe Adenoma[b]	2/43 (5)	6/42 (14)	6/43 (14)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		3.071	3.000
Lower Limit		0.589	0.574
Upper Limit		29.705	29.042
Weeks to First Observed Tumor	100	98	72

[a]Dosed groups received 50 or 100 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 2-Amino-5-Nitrothiazole in the Diet[a]

(continued)

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

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

Review of the Bioassay of 2-Amino-5-Nitrothiazole for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

March 6, 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 2-Amino-5-Nitrothiazole for carcinogenicity.

The primary reviewer for the report on the bioassay of 2-Amino-5-Nitrothiazole agreed with the conclusion that the compound was associated with granulocytic leukemia in treated male rats. It was not carcinogenic in female rats or either sex of mice, under the conditions of test. After a brief description of the experimental design and conditions of test, he noted the negative dose-related trend with respect to hematopoetic tumors in treated female mice. He pointed out increases in a number of tumors observed in treated animals, although none were clearly associated with the administration of 2-Amino-5-Nitrothiazole.

The secondary reviewer observed that granulocytic leukemia was not sex linked. Therefore, it was unusual to find it in one sex and not the other. He suggested that the observed incidence might be within a normal statistical variation. Another Subgroup member said that leukemia might be expected to occur with greater frequency among females as a result of a hormonal influence.

It was noted by a Subgroup member that the "real-life significance may be quite minimal" with respect to the carcinogenicity of 2-Amino-5-Nitrothiazole.

A motion was made that the report be accepted as written. The motion was seconded and approved unanimously. A second motion was passed unanimously that the record show that the results were unusual with respect to the induction of granulocytic leukemias in only one sex of treated rats.

Members present were:

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Arnold Brown, Mayo Clinic
Lawrence Garfinkel, American Cancer Society
E. Cuyler Hammond, American Cancer Society
Joseph Highland, Environmental Defense Fund
Henry Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
Sheldon Samuels, Industrial Union Department, AFL-CIO
Michael Shimkin, University of California at San Diego
John Weisburger, American Health Foundation
Sidney Wolfe, Health Research Group

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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.

*U.S. GOVERNMENT PRINTING OFFICE:1978 260-899/3106 1-3

DHEW Publication No. (NIH) 78-1359