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

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CONTRIBUTORS: This report presents the results of the bioassay of ethionamide for possible carcinogenicity, conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Southern Research Institute, Birmingham, Alabama, 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 Drs. D. P. Griswold[1], J. D. Prejean[1], E. K. Weisburger[2], and J. H. Weisburger[2,3]. Ms. J. Belzer and Mr. I. Brown[1] were responsible for the care and feeding of the laboratory animals. Data management and retrieval were performed by Ms. C. A. Dominick[1]. Histopathologic examinations were performed by Drs. S. D. Kosanke[1] and J. C. Peckham[1], and the diagnoses included in this report represent their interpretation.

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. C. W. Jameson[5].

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.

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SUMMARY

A bioassay of the chemotherapeutic drug ethionamide for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice.

Groups of 35 rats and 34 or 35 mice of each sex were administered ethionamide at one of the following doses, either 1,500 or 3,000 ppm for the rats and either 1,000 or 2,000 ppm for the mice. The animals were treated 5 days per week for 78 weeks, then observed for an additional 25 or 26 weeks. Matched controls consisted of groups of 15 untreated rats and 15 untreated mice of each sex. All surviving animals were killed at 103 or 104 weeks.

Mean body weights of the treated rats and mice were lower than those of the corresponding matched controls during most or all of the study. Survival in the rats was sufficient to allow development of late-appearing tumors. In the mice, survival of the high-dose males (27%), matched-control males (7%), and low-dose females (37%) to the end of the study was low, and the deaths were associated with suppurative lung lesions. However, tests for dose-related trend in mortality were not significant in either sex, and 47% or more of all groups of mice except control males were alive at 78 weeks.

In the rats, a variety of neoplasms were observed in treated and control groups of each sex. The lesions were of types commonly found in Fischer 344 rats, and none of the incidences of tumors in dosed animals were statistically significant when compared with controls.

In the mice, the incidences of malignant lymphoma were slightly higher in dosed than in control mice (males: controls 2/15, low-dose 8/34, high-dose 4/34; females: controls 2/15, low-dose 4/31, high-dose 10/34). The incidences were not significant by any of the statistical tests used, including the Tarone and Cox tests using the life-table method.

It is concluded that under the conditions of this bioassay, ethionamide was not carcinogenic in either Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

Ethionamide (CAS 536-33-4; NCI C01694) is a synthetic antitubercular drug. It is tuberculostatic for Mycobacterium tuberculosis and atypical mycobacteria, the etiological agents for tuberculosis (Weinstein, 1975). Use of ethionamide is reserved for cases that have become resistant to treatment with primary drugs. This practice has been adopted because of allergic reactions, gastro-intestinal disturbances, and the relatively high risk of liver damage associated with ethionamide treatment (Weinstein, 1975; Smith, 1977). After absorption, ethionamide is distributed widely in tissues and plasma, as well as in the cerebrospinal fluid, making it useful for treating meningeal infections (Smith, 1977). The adult dose ranges from 0.5 to 1.0 g/day for a period of 1 to 2 years.

Ethionamide was selected for screening in the carcinogenesis bioassay program in an attempt to evaluate the carcinogenicity of certain drugs that are used for prolonged periods of time in humans.

II. MATERIALS AND METHODS

A. Chemical

Ethionamide (2-ethylthioisonicotinamide) was obtained in two batches from the Ives Laboratories, Inc., New York, N.Y. The purity of the batch used in the chronic studies (Lot No. 24) was determined to be 98.9 $\pm$ 1.2% by thiourea titration at Midwest Research Institute. No attempt was made to identify or quantitate impurities. The melting point of Lot No. 24 was 159.5-163.5°C (literature: 161-163.5°C). Elemental analyses (C, H, N, S) were correct for $C_8H_{10}N_2S$, the molecular formula of ethionamide. The identity was confirmed by nuclear magnetic resonance, infrared, and ultraviolet spectra, which were in agreement with the structure and matched the spectra in the literature.

The chemical used for the chronic studies was stored in a cold room at 5°C.

B. Dietary Preparation

Test diets were prepared every 2 weeks by mixing a known amount of sifted ethionamide with a small amount of Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) in a portable mixer, then adding this mixture to the required amount of animal

meal and mixing in a twin-shell blender for 10 minutes. The prepared diets were stored at room temperature in sealed plastic containers. No concentration or stability analyses of the chemical in the feed were performed.

C. Animals

Animals used in the bioassay were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. For the subchronic studies, male Sprague-Dawley rats and male Swiss mice were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The animals were approximately 40 days of age when received at the laboratory, and were quarantined for 5 days as an acclimation period prior to the start of the subchronic study.

For the chronic studies, Fischer 344 rats of each sex were obtained from Harlan Industries, Cumberland, Indiana, and B6C3F1 mice of each sex were obtained from A. R. Schmidt, Madison, Wisconsin. The rats were 30 days of age when received and the mice were 36 days of age. All animals were quarantined for an acclimation period (rats for 11 days, mice for 34 days). Those animals with no visible signs of disease were then assigned to control or dosed groups and earmarked for individual identification.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 20-24°C, and the relative humidity was maintained at 40-60%. Room air was changed 15 times per hour and passed through both intake and exhaust fiberglass roughing filters. In addition to natural light, illumination was provided by fluorescent light for 9 hours per day. Food and water were supplied daily and were made available ad libitum.

Rats and mice were housed five per cage in solid-bottom stainless steel cages (Hahn Roofing and Sheet Metal Co., Birmingham, Ala.). The bottoms of the rat cages were lined with Iso-Dri® hardwood chips (Carworth, Edison, N.J.), and the cage tops were covered with disposable filter bonnets; mouse cages were provided with Sterolit® clay bedding (Englehard Mineral and Chemical Co., New York, N.Y.). Bedding was replaced once per week; cages, water bottles, feeders were sanitized at 82°C once per week; racks were cleaned once per week.

The rats and mice were housed in separate rooms. Control animals were housed with respective dosed animals. Animals dosed with ethionamide were maintained in the same rooms as animals of the same species being dosed with the following chemicals:

RATS

Feed Studies

4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide
(acetohexamide) (CAS 968-81-0)
anthranilic acid (CAS 118-92-3)
1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide) (CAS 64-77-7)
4-chloro-N-((propylamino)carbonyl)benzenesulfonamide
(chlorpropamide) (CAS 94-20-2)
5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine
(pyrimethamine) (CAS 58-14-0)
2,6-diamino-3-(phenylazo)pyridine hydrochloride
(phenazopyridine hydrochloride) (CAS 136-40-3)
L-tryptophan (CAS 73-22-3)
N-9H-fluoren-2-ylacetamide (CAS 53-96-3)
N-(p-toluenesulfonyl)-N′-hexamethyleniminourea
(tolazamide) (CAS 1156-19-0)
1-phenethylbiguanide hydrochloride (phenformin) (CAS 114-86-3)
pyrazinecarboxamide (pyrazinamide) (CAS 98-96-4)
4,4′-sulfonyldianiline (dapsone) (CAS 80-08-0)
4,4′-thiodianiline (CAS 139-65-1)

MICE

Feed Studies

4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide
(acetohexamide) (CAS 968-81-0)
anthranilic acid (CAS 118-92-3)
1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide) (CAS 64-77-7)
4-chloro-N-((propylamino)carbonyl)benzenesulfonamide
(chlorpropamide) (CAS 94-20-2)
5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine
(pyrimethamine) (CAS 58-14-0)
2,6-diamino-3-(phenylazo)pyridine hydrochloride
(phenazopyridine hydrochloride) (CAS 136-40-3)
L-tryptophan (CAS 73-22-3)
N-9H-fluoren-2-ylacetamide (CAS 53-96-3)
N-(p-toluenesulfonyl)-N′-hexamethyleniminourea
(tolazamide) (CAS 1156-19-0)
1-phenethylbiguanide hydrochloride (phenformin) (CAS 114-86-3)
pyrazinecarboxamide (pyrazinamide) (CAS 98-96-4)
4,4′-sulfonyldianiline (dapsone) (CAS 80-08-0)
4,4′-thiodianiline (CAS 139-65-1)

Gavage Studies

cholesterol (p-(bis(2-chloroethyl)amino)phenyl)acetate (phenesterin) (CAS 3546-10-9)
estradiol bis((p-(bis(2-chloroethyl)amino)phenyl)acetate) (estradiol mustard) (CAS 22966-79-6)

Intraperitoneal Injection Studies

4′-(9-acridinylamino)methansulfon-m-aniside monohydrochloride (MAAM) (NSC 141549)
acronycine (CAS 7008-42-6)
5-azacytidine (CAS 320-67-2)
beta-2′-deoxy-6-thioguanosine monohydrate (beta-TGdR) (CAS 789-61-7)
1,4-butanediol dimethanesulfonate (busulfan) (CAS 55-98-1)
emetine dihydrochloride tetrahydrate (CAS 316-42-7)
3,3′-iminobis-1-propanol dimethanesulfonate (ester) hydrochloride [IPD] (CAS 3458-22-8)
(±)-4,4′-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione (ICRF-159) (CAS 21416-87-5)
N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide (isophosphamide) (CAS 3778-73-2)
N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzylamine hydrochloride (phenoxybenzamine) (CAS 63-92-3)
N-(1-methylethyl)-4-((2-methylhydrazino)methyl)benzamide monohydrochloride (procarbazine) (CAS 366-70-1)
tris(1-aziridinyl)phosphine sulfide (thio-TEPA) (CAS 52-24-4)
2,4,6-tris(dimethylamino)-s-triazine (CAS 645-05-6)

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses of ethionamide, 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. Ethionamide was administered in the diet for 45 days to male Sprague-Dawley rats at doses of 1,200, 3,000, 6,000, 15,000, or 30,000 ppm and to male Swiss mice at doses of 2,000, 5,000,

10,000, 25,000, or 50,000 ppm. Following administration of the chemical, all animals were observed for an additional 45 days. Five animals of each species were tested at each dose, and 10 animals of each species were maintained as untreated controls.

All rats treated at 15,000 and 30,000 ppm died, and one animal treated at 6,000 ppm died. The mean body weight gains of dosed animals when compared with controls were 75% at 6,000 ppm, 82% at 3,000 ppm, and approximately same as controls at 1,200 ppm. The low and high doses for the chronic studies using rats were set at 1,500 and 3,000 ppm.

In mice, all animals treated at 25,000 and 50,000 ppm died, and two animals dosed at 10,000 ppm died. The mean body weight gains were unaffected in mice treated at 10,000 ppm and below. No gross abnormalities were seen in any animals at necropsy. The low and high doses for the chronic studies using mice were set at 1,000 and 2,000 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 animals that were moribund were killed and necropsied, except for

Table 1. Design of Ethionamide Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals[a]	Ethionamide in Diet (ppm)[b]	Time on Study	
			Dosed[c] (weeks)	Observed (weeks)
MALE				
Matched-Control	15	0		104
Low-Dose	35	1,500	78	26
High-Dose	34	3,000	78	25
FEMALE				
Matched-Control	15	0		104
Low-Dose	35	1,500	78	26
High-Dose	35	3,000	78	26

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

[b]Dosed animals were fed test diets 5 days per week and control diets 2 days per week.

[c]All rats were placed on study on the same day.

Table 2. Design of Ethionamide Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals[a]	Ethionamide in Diet (ppm)[b]	Time on Study	
			Dosed[c] (weeks)	Observed (weeks)
MALE				
Matched-Control	15	0		104
Low-Dose	35	1,000	78	26
High-Dose	34	2,000	78	26
FEMALE				
Matched-Control	15	0		104
Low-Dose	35	1,000	78	26
High-Dose	35	2,000	78	26

[a]Mice were 70 days of age when placed on study.

[b]Dosed animals were fed test diets 5 days per week and control diets 2 days per week.

[c]All mice were placed on study on the same day.

those dying prior to day 100, due, presumably, to toxicity of the test chemical. Rats and mice were weighed individually every 2 weeks to week 75, then approximately once per month for the remainder of the study. Palpation for masses was carried out at each weighing.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, muscle, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder and bile duct (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, brain, and sensory organs. 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 missing, cannibalized, or judged to be in such an advanced state

of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

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

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes

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

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

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

a control group with that of a group of treated animals at each dose level. When results for a number of treated groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) 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 treated group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a

treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result ($P < 0.025$ 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 both the low- and high-dose male rats were lower than those of the matched controls (figure 1). Mean body weights of the high-dose females were lower throughout the study, while those of the low-dose females were similar to those of the controls for the first 50 weeks, and lower thereafter. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variation. No other signs of toxicity related to chemical administration were recorded in rats.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed ethionamide in the diet at the doses of this experiment, together with those of the controls, are shown in figure 2.

The results of the Tarone test for positive dose-related trend in mortality are not significant in either sex. In male rats, 19/34 (56%) of the high-dose group, 20/35 (57%) of the low-dose group, and 9/15 (60%) of the matched controls lived to the end of the study. The females survived longer than the males, with 25/35

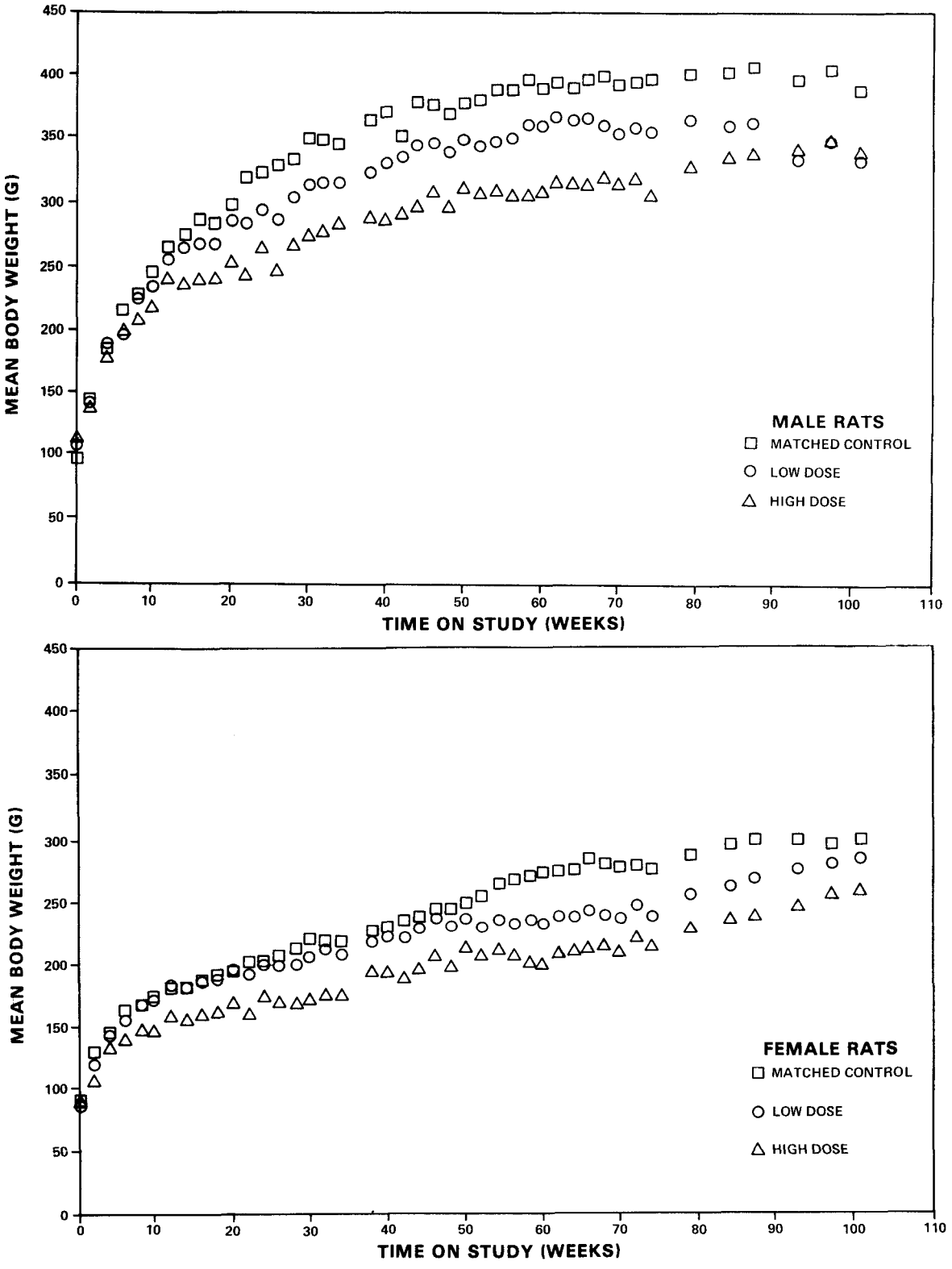
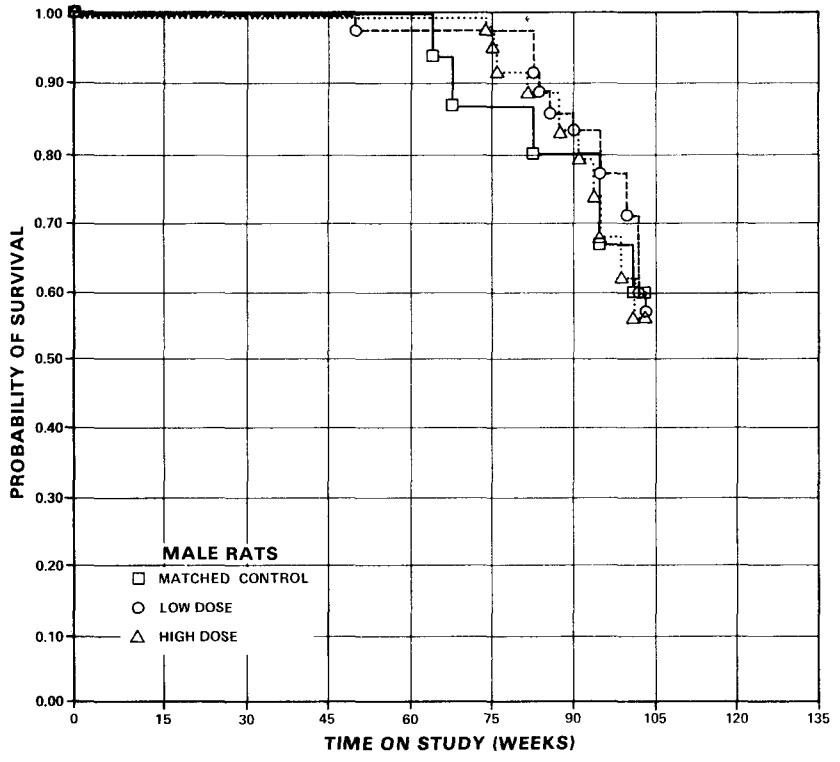


Figure 1. Growth Curves for Rats Fed Ethionamide in the Diet



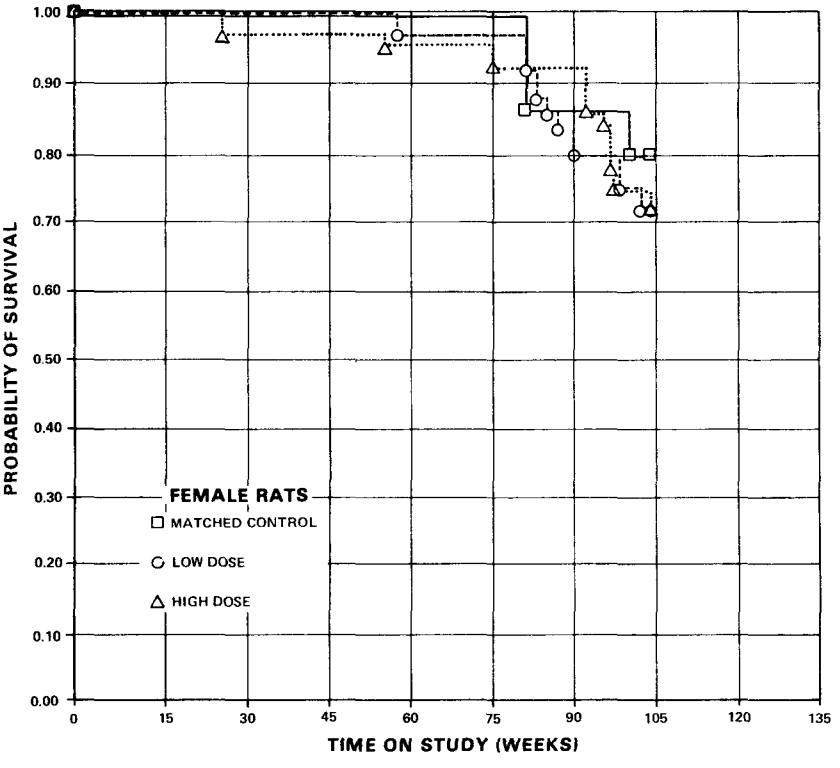


Figure 2. Survival Curves for Rats Fed Ethionamide in the Diet

(71%) of the high-dose group, 25/35 (71%) of the low-dose group and 12/15 (80%) of the matched controls living to termination of the study. The high survival in the different groups allowed development of late-appearing tumors and provided a sufficient number of rats of each sex for meaningful statistical analyses of the incidences of tumors that appeared during the 104-week bioassay.

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 treated groups. These lesions, and their frequency, however, are not uncommon in this strain of rat independent of any chemical administration. The majority of tumors observed were benign.

In addition to the neoplastic lesions, a number of degenerative, proliferative, and inflammatory changes were encountered also in animals of the control and treated groups (Appendix C). These nonneoplastic lesions are commonly seen in aged Fischer 344 rats.

In the judgment of the pathologists, ethionamide was not

carcinogenic in Fischer 344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in 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 and of the Fisher exact test for direct comparisons of control and dosed groups in the positive direction are not significant in either sex. In male rats, the incidence of leukemia has a significant trend in the negative direction. In female rats, fibroadenoma of the mammary gland appears at a significantly higher incidence in the matched-control group than in either dosed group. In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals except the incidence of fibroadenoma of the mammary gland in high-dose female rats has an upper limit greater than one, indicating the theoretical possibility of the induction of

tumors by ethionamide, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of both the low- and high-dose male and female mice were lower than those of the matched controls from week 10 to week 70 (figure 3). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variation. No other signs of toxicity related to chemical administration were observed in the mice.

To control respiratory disease, mice in the colony were treated with oxytetracycline in the drinking water at 0.6 mg/ml during week 54 and at 0.3 mg/ml during week 55. Also, propylene glycol was vaporized in the mouse rooms for about 2 months beginning at week 54.

B. Survival (Mice)

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

The results of the Tarone test for positive dose-related trend in mortality are not significant in either sex. In male mice, 9/34

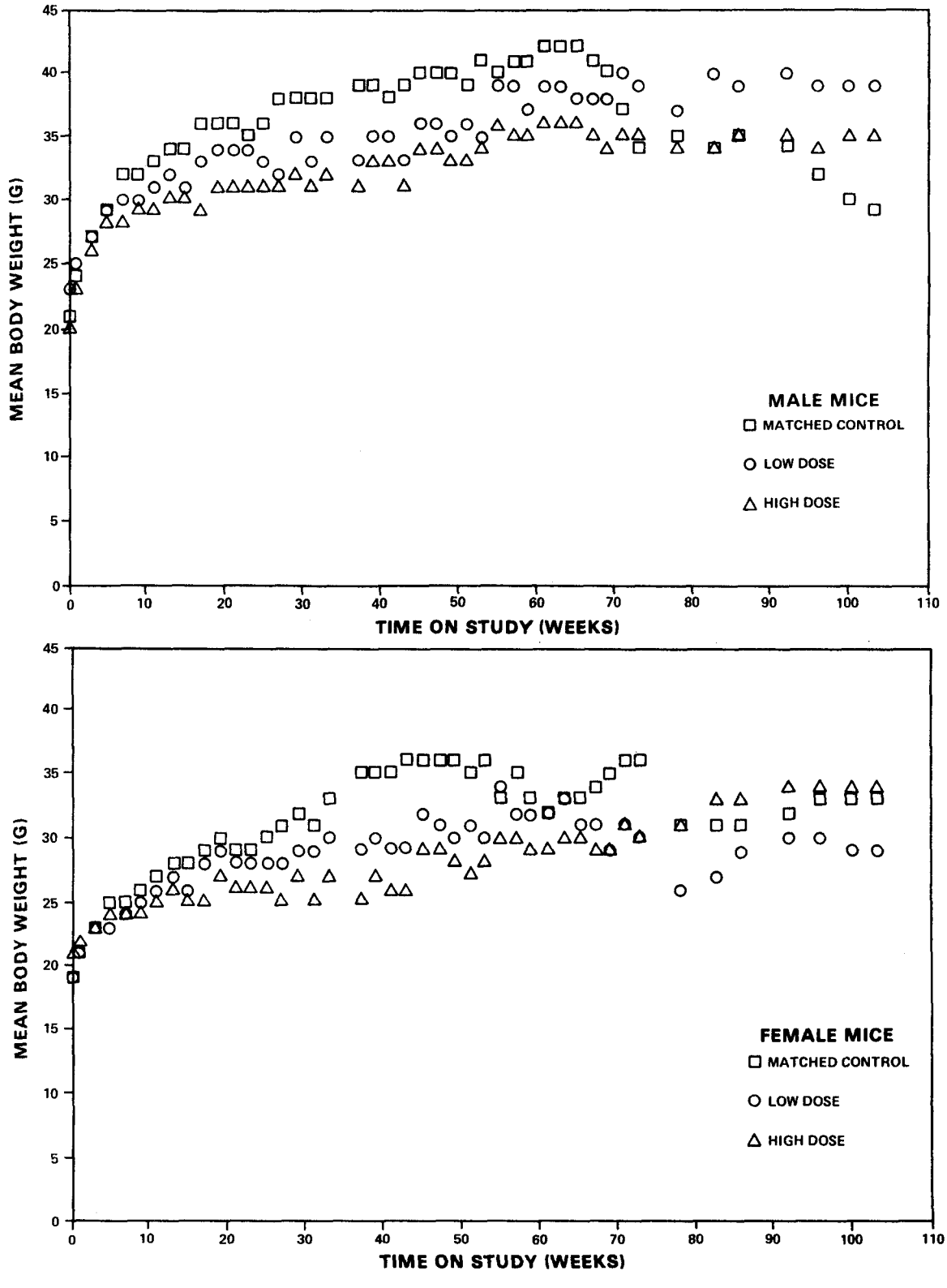


Figure 3. Growth Curves for Mice Fed Ethionamide in the Diet

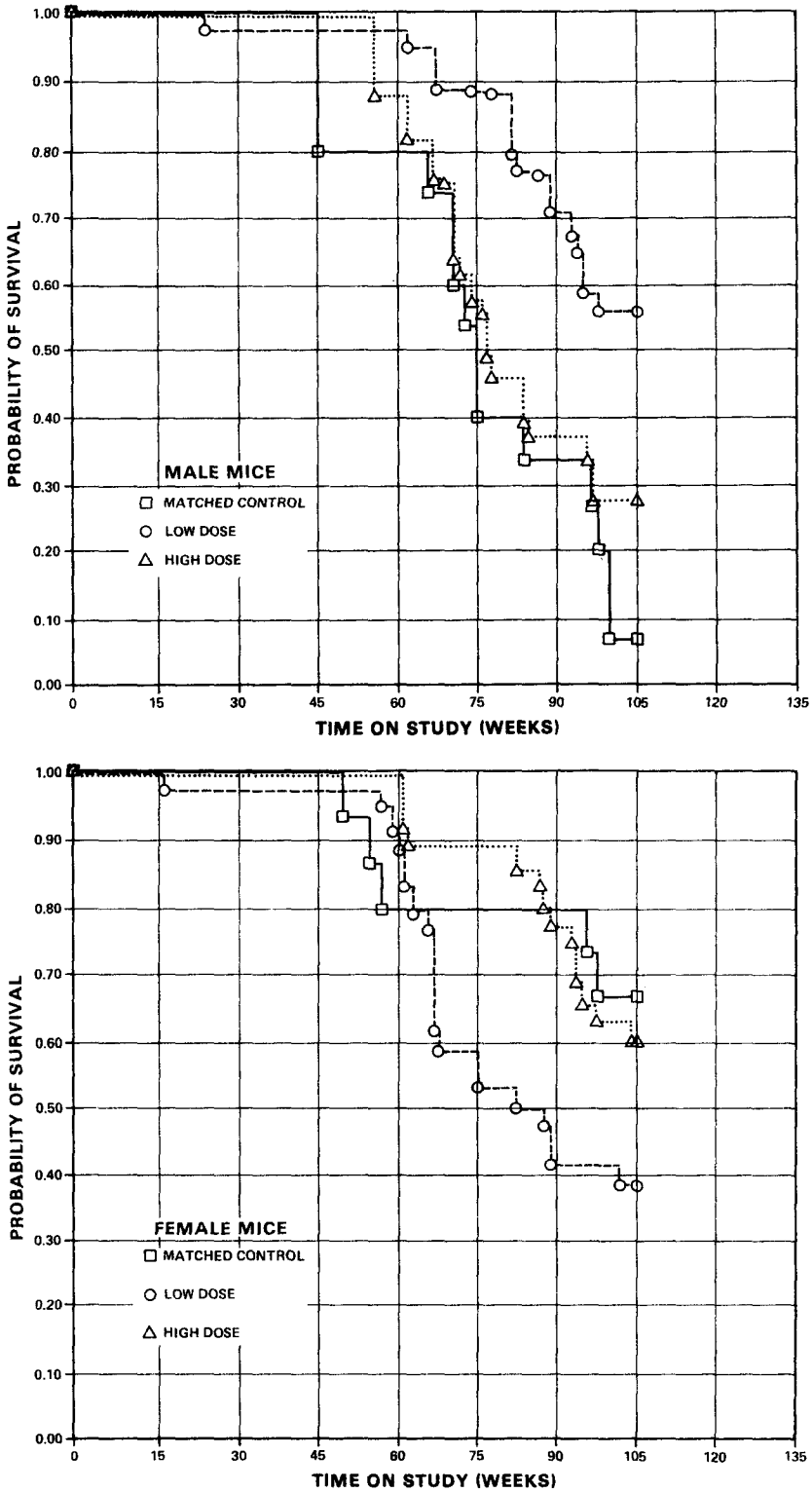


Figure 4. Survival Curves for Mice Fed Ethionamide in the Diet

(26%) of the high-dose group, 19/35 (54%) of the low-dose group, and only 1/15 (7%) of the matched controls lived to the end of the study. In female mice, 21/35 (60%) of the high-dose group, 13/35 (37%) of the low-dose group, and 10/15 (67%) of the matched controls survived to termination of the study. In male mice, all the high-dose animals, 33 of the low-dose animals, and 13 of the controls were alive at week 52. By week 78, 16 of the high-dose animals, 29 of the low-dose animals, and 6 of the controls were still alive. In females, all the high-dose animals, 33 of the low-dose animals, and 14 of the controls were alive at week 52. By week 78, 31 of the high-dose animals, 18 of the low-dose animals, and 12 of the controls were still alive.

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.

Excluding the lymphoreticular tumors, the neoplasms listed in Appendix B appeared with greater frequency in the control mice.

The incidence of lymphoreticular neoplasms, which was higher in the dosed than in the control groups, was the highest in the

low-dose males and high-dose females. The incidences of these lesions were as follows:

MALE

	Untreated Control	Low Dose	High Dose
Number of mice necropsied	(15)	(34)	(34)
Brain*	(15)	(34)	(32)
malignant lymphoma, histiocytic type	0	0	2
Trigeminal ganglion			
malignant lymphoma, mixed type	0	0	1
Multiple organs, lymphoreticular			
malignant lymphoma, NOS (not otherwise specified)	0	1	0
malignant lymphoma, lymphocytic or lymphoblastic (undifferentiated) type	1	0	1
malignant lymphoma, histiocytic type	1	6	0
Spleen*	(15)	(34)	(34)
malignant lymphoma, histiocytic type	0	1	0
Total number of animals with tumors	2	8	4

*Number of mice with tissue examined microscopically

FEMALE

	Untreated Control	Low Dose	High Dose
Number of mice necropsied	(15)	(31)	(34)
Multiple organs, lymphoreticular			
malignant lymphoma, NOS	0	0	1
malignant lymphoma, lymphocytic or lymphoblastic (undifferentiated) type	0	2	3
malignant lymphoma, histiocytic type	2	0	4
Spleen*	(14)	(31)	(33)
malignant lymphoma, histiocytic type	0	0	1
Pancreatic lymph node*	(12)	(26)	(30)
malignant lymphoma, lymphoblastic (undifferentiated) type	0	0	1
malignant lymphoma, mixed type	0	1	0
Mesenteric lymph node*	(12)	(26)	(30)
malignant lymphoma, lymphoblastic (undifferentiated) type	0	1	0
Total number of animals with tumors	2	4	10

*Number of mice with tissue examined microscopically

The brains of three animals and the trigeminal nerve of one animal had lymphomatous infiltrates. The neoplastic cells were lymphoid in appearance, having a large pleomorphic nucleus that stained basophilic and a minimal amount of eosinophilic cytoplasm. Within the brain, the cellular infiltrate involved the choroid plexuses and meninges most often. The perineural tissues of the trigeminal nerve as well as the nerve itself were infiltrated with these neoplastic lymphoid cells.

The malignant lymphomas were classified as lymphocytic, histiocytic, or mixed types. The lymphocytic type was comprised of cells having a small, darkly basophilic to large, lightly basophilic vesicular nucleus and a rim of eosinophilic cytoplasm. Malignant lymphomas composed of lymphoblastic or undifferentiated cells were also included in the lymphocytic type. The histiocytic type was comprised primarily of cells with a large open-faced vesicular nucleus, distinct eosinophilic nucleolus, and an abundant eosinophilic cytoplasm. However, some histiocytic tumors contained many cells having a smaller, pleomorphic nucleus that was often elliptical or indented. The mixed type was a combination of the lymphocytic and histiocytic cell types. The malignant lymphomas, NOS, had cellular distortion which prevented further classification.

The malignant lymphomas were either generalized, involving several organs, or solitary, involving only one organ. The generalized lymphomas usually involved the spleen, liver, and one or more lymph nodes. The solitary lymphomas involved the spleen, pancreatic lymph nodes, or mesenteric lymph nodes.

In addition to the neoplastic lesions, a number of degenerative, proliferative, and inflammatory changes were encountered also in animals of the dosed and control groups (Appendix D). These nonneoplastic lesions are commonly seen in aged B6C3F1 mice;

however, the suppurative lesions involving the lungs were associated with increased deaths, which were especially prominent in the low-dose females, high-dose males, and control males.

In this bioassay the incidence of lymphoreticular neoplasms was slightly higher in the dosed mice, particularly the females, than in the controls. Because the differences in incidences between dosed and control groups were small, in the judgment of the pathologists, ethionamide was not considered to be carcinogenic.

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 in 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 and of the Fisher exact test for direct comparisons of control and dosed groups are not significant in either sex. Due to the early mortality, the life-table method is used to analyze the incidence of lymphoma in both males and females (figure 5). In this life-table analysis, neither the results of the Tarone test using three groups nor the results of the Cox test for comparison of each treated group with the control group were significant in either sex.

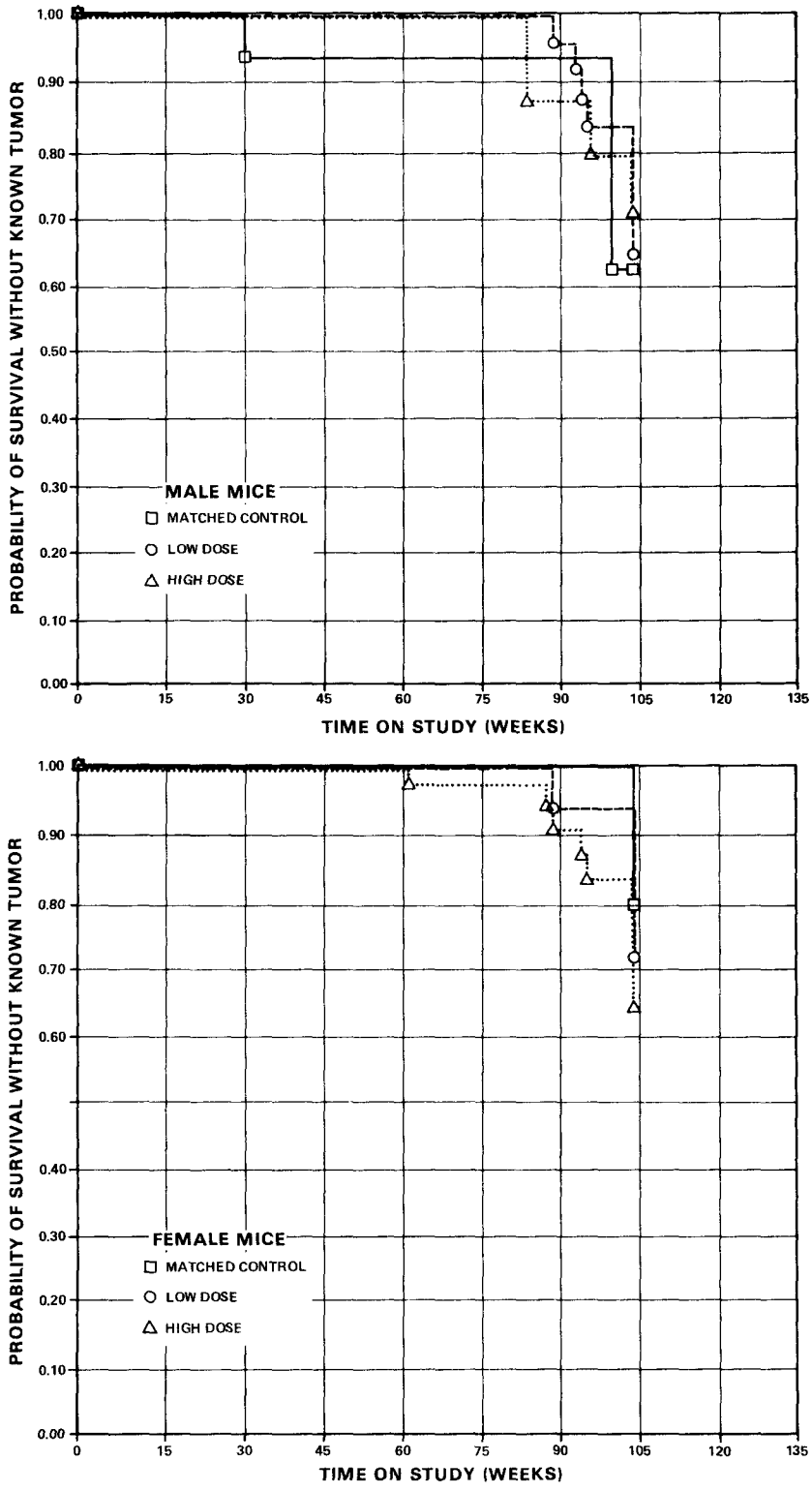


Figure 5. Life Table for Mice Fed Ethionamide in the Diet: Lymphoma

The current historical records of this laboratory indicate an overall incidence of malignant lymphoma of 35/586 (6%) in male mice and 51/588 (9%) in female mice. The incidences within individual control groups range from 0/20 to 4/14 (28%) in male mice and from 0/20 to 6/15 (40%) in female mice.

In each of the 95% confidence intervals of 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 ethionamide, which could not be detected under the conditions of this test.

V. DISCUSSION

The mean body weights of the low- and high-dose rats and mice fed diets containing ethionamide were lower than those of the corresponding matched controls during most or all of the bioassay. Survival in the rats was sufficient to allow development of late-appearing tumors. Tests for dose-related trend in mortality were not significant in either rats or mice. In the mice, a high incidence of suppurative lung lesions were associated with decreased life spans, particularly for low-dose females, high-dose males, and matched-control males. While only 1 control, 19 low-dose, and 9 high-dose male mice and only 10 control, 13 low-dose, and 21 high-dose female mice lived to the end of the study, at week 78 there were 6, 29, and 16 males and 12, 18, and 31 females in the respective groups.

In the rats, a variety of neoplasms were observed in treated and matched-control groups of both sexes. The lesions were of types commonly found in Fischer 344 rats, and none of the incidences of tumors were statistically significant.

In the mice, the incidences of malignant lymphoma were slightly higher in dosed than in control mice (males: controls 2/15, low-dose 8/34, high-dose 4/34; females: controls 2/15, low-dose 4/31, high-dose 10/34. The incidences were not significant by

any of the statistical tests used, including the Tarone and Cox tests using the life-table method; also, they are within the ranges of 0/20 to 4/14 (28%) observed in this laboratory for individual groups of historical-control male B6C3F1 mice (overall incidence of 35/586, or 6%) and within the range of 0/20 to 6/15 (40%) for individual groups of historical-control female B6C3F1 mice (overall incidence of 51/588, or 9%).

One long-term study with ethionamide has been reported (Biancifiori et al., 1964). Female BALB/c/Cb/Se mice were given intragastric instillations of 0.1 ml of 2% ethionamide in propylene glycol 6 days per week for 50 weeks. Seven of the 33 dosed mice developed thyroid tumors between 28 and 69 weeks, compared with 0/18 surviving controls receiving propylene glycol alone and 0/47 untreated controls. Five of the tumors were papillary carcinomas and two were epidermoid carcinomas. In the present bioassay, no lesions of the thyroid were found in the dosed rats or mice at an incidence above that in the matched controls.

It is concluded that under the conditions of this bioassay, ethionamide was not carcinogenic in either Fischer 344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED ETHIONAMIDE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	34
ANIMALS NECROPSIED	15	35	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	35	33
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(35)	(33)
SQUAMOUS CELL PAPILLOMA		1 (3%)	
*SUBCUT TISSUE	(15)	(35)	(33)
FIBROMA		2 (6%)	
FIBROSARCOMA		1 (3%)	
RESPIRATORY SYSTEM			
#LUNG	(15)	(35)	(33)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (7%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(15)	(35)	(33)
UNDIFFERENTIATED LEUKEMIA	2 (13%)	4 (11%)	1 (3%)
GRANULOCYTIC LEUKEMIA	1 (7%)		
MONOCYTIC LEUKEMIA		1 (3%)	
#THYMUS	(14)	(35)	(31)
THYMOMA	1 (7%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(15)	(35)	(33)
HEPATOCELLULAR ADENOMA		1 (3%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA			1 (3%)
URINARY SYSTEM			
#KIDNEY	(15)	(35)	(33)
CARCINOMA,NOS		1 (3%)	
ENDOCRINE SYSTEM			
#PITUITARY	(14)	(34)	(29)
CHROMOPHOBE ADENOMA	1 (7%)	1 (3%)	
#ADRENAL	(15)	(35)	(33)
PHEOCHROMOCYTOMA, MALIGNANT	1 (7%)		
#THYROID	(15)	(35)	(30)
C-CELL ADENOMA	3 (20%)	2 (6%)	1 (3%)
C-CELL CARCINOMA			1 (3%)
#PANCREATIC ISLETS	(15)	(35)	(33)
ISLET-CELL ADENOMA		1 (3%)	
ISLET-CELL CARCINOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(15)	(35)	(33)
ADENOMA, NOS	1 (7%)		
#TESTIS	(15)	(34)	(33)
INTERSTITIAL-CELL TUMOR	13 (87%)	32 (94%)	31 (94%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(15)	(35)	(33)
SQUAMOUS CELL PAPILLOMA	1 (7%)		
*ZYMBAL'S GLAND	(15)	(35)	(33)
SQUAMOUS CELL PAPILLOMA		1 (3%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(15)	(35)	(33)
MESOTHELIOMA, NOS		1 (3%)	
ALL OTHER SYSTEMS			
THORAX			
SARCOMA, NOS	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	15	35	34
NATURAL DEATH@	2	2	7
MORIBUND SACRIFICE	4	13	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	20	19
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	34	31
TOTAL PRIMARY TUMORS	26	50	35
TOTAL ANIMALS WITH BENIGN TUMORS	14	33	31
TOTAL BENIGN TUMORS	21	41	32
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	8	3
TOTAL MALIGNANT TUMORS	5	8	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS NECROPSIED	15	35	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	35	35
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(15)	(35)	(35)
FIBROMA	1 (7%)	2 (6%)	1 (3%)
FIBROSARCOMA			1 (3%)
RESPIRATORY SYSTEM			
#LUNG	(14)	(35)	(35)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (3%)
OSTEOSARCOMA, METASTATIC		1 (3%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(15)	(35)	(35)
UNDIFFERENTIATED LEUKEMIA		2 (6%)	4 (11%)
LYMPHOCYTIC LEUKEMIA	1 (7%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(15)	(35)	(35)
HEPATOCELLULAR ADENOMA		1 (3%)	3 (9%)
URINARY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(11)	(30)	(32)
CHROMOPHOBE ADENOMA	2 (18%)	7 (23%)	3 (9%)
CHROMOPHOBE CARCINOMA		3 (10%)	
#THYROID	(15)	(34)	(34)
C-CELL ADENOMA		4 (12%)	3 (9%)
C-CELL CARCINOMA	1 (7%)	1 (3%)	1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(15)	(35)	(35)
ADENOCARCINOMA, NOS			1 (3%)
FIBROADENOMA	5 (33%)	3 (9%)	2 (6%)
*PREPUTIAL GLAND	(15)	(35)	(35)
CARCINOMA,NOS	1 (7%)		
ADENOMA, NOS		1 (3%)	
#UTERUS	(15)	(34)	(35)
ADENOCARCINOMA, NOS			2 (6%)
ENDOMETRIAL STROMAL POLYP	5 (33%)	10 (29%)	15 (43%)
#OVARY	(15)	(34)	(35)
FIBROMA			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(15)	(35)	(35)
SQUAMOUS CELL PAPILLOMA			1 (3%)
*ZYMBAL'S GLAND	(15)	(35)	(35)
SQUAMOUS CELL PAPILLOMA			1 (3%)
MUSCULOSKELETAL SYSTEM			
*BONE	(15)	(35)	(35)
OSTEOSARCOMA		1 (3%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	15	35	35
NATURAL DEATH@	1	5	3
MORIBUND SACRIFICE	2	5	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	12	25	25
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	26	25
TOTAL PRIMARY TUMORS	16	35	40
TOTAL ANIMALS WITH BENIGN TUMORS	11	23	21
TOTAL BENIGN TUMORS	13	28	31
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	6	8
TOTAL MALIGNANT TUMORS	3	7	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE FED ETHIONAMIDE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	34
ANIMALS MISSING		1	
ANIMALS NECROPSIED	15	34	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	34	34
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(15)	(33)	(34)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (7%)	5 (15%)	1 (3%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (7%)		1 (3%)
HEMATOPOIETIC SYSTEM			
#BRAIN	(15)	(34)	(32)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (6%)
*TRIGEMINAL GANGLION	(15)	(34)	(34)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (3%)
*MULTIPLE ORGANS	(15)	(34)	(34)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (7%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (3%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (7%)	6 (18%)	
#SPLEEN	(15)	(34)	(34)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(14)	(34)	(33)
HEPATOCELLULAR ADENOMA	1 (7%)	3 (9%)	2 (6%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	2 (14%)	3 (9%)	2 (6%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(14)	(31)	(33)
FOLLICULAR-CELL ADENOMA			1 (3%)
REPRODUCTIVE SYSTEM			
#TESTIS	(15)	(32)	(33)
INTERSTITIAL-CELL TUMOR		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	15	35	34
NATURAL DEATH@	6	8	6
MORIBUND SACRIFICE	8	7	18
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	1	19	9
ANIMAL MISSING		1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	16	10
TOTAL PRIMARY TUMORS	7	20	11
TOTAL ANIMALS WITH BENIGN TUMORS	2	8	4
TOTAL BENIGN TUMORS	2	9	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	10	6
TOTAL MALIGNANT TUMORS	5	11	7
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS MISSING		1	
ANIMALS NECROPSIED	15	31	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	31	34
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(15)	(31)	(34)
SARCOMA, NOS			1 (3%)
RESPIRATORY SYSTEM			
#LUNG	(15)	(30)	(33)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (7%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (3%)
OSTEOSARCOMA, METASTATIC		1 (3%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(15)	(31)	(34)
MALIGNANT LYMPHOMA, NOS			1 (3%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (3%)	2 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	1 (3%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (13%)		4 (12%)
#SPLEEN	(14)	(31)	(33)
HEMANGIOSARCOMA	1 (7%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
#MANDIBULAR L. NODE	(12)	(26)	(30)
HEMANGIOMA	1 (8%)		
#PANCREATIC L.NODE	(12)	(26)	(30)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (3%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (4%)	
#MESENTERIC L. NODE	(12)	(26)	(30)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (4%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#DUODENUM	(14)	(31)	(31)
ADENOMATOUS POLYP, NOS		1 (3%)	
#COLON	(15)	(31)	(31)
LEIOMYOSARCOMA			1 (3%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(14)	(31)	(34)
FOLLICULAR-CELL ADENOMA		1 (3%)	1 (3%)
FOLLICULAR-CELL CARCINOMA	1 (7%)		
REPRODUCTIVE SYSTEM			
#UTERUS	(14)	(31)	(34)
SARCOMA, NOS		1 (3%)	
#UTERUS/ENDOMETRIUM	(14)	(31)	(34)
ADENOMA, NOS			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	15	35	35
NATURAL DEATH@	1	5	7
MORIBUND SACRIFICE	4	16	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	10	13	21
ANIMAL MISSING		1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	14
TOTAL PRIMARY TUMORS	6	7	15
TOTAL ANIMALS WITH BENIGN TUMORS	2	2	2
TOTAL BENIGN TUMORS	2	2	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	5	13
TOTAL MALIGNANT TUMORS	4	5	13
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED ETHIONAMIDE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	34
ANIMALS NECROPSIED	15	35	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	35	33
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(35)	(33)
EPIDERMAL INCLUSION CYST		1 (3%)	
ULCER, NOS		2 (6%)	
INFLAMMATION, SUPPURATIVE			1 (3%)
*SUBCUT TISSUE	(15)	(35)	(33)
INFLAMMATION, CHRONIC		1 (3%)	
RESPIRATORY SYSTEM			
#TRACHEA	(15)	(35)	(33)
INFLAMMATION, SUPPURATIVE	4 (27%)	6 (17%)	7 (21%)
#LUNG	(15)	(35)	(33)
PNEUMONIA, CHRONIC MURINE	3 (20%)	4 (11%)	6 (18%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(15)	(34)	(33)
HEMORRHAGE		1 (3%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(15)	(35)	(33)
INFLAMMATION, INTERSTITIAL			2 (6%)
DIGESTIVE SYSTEM			
#LIVER	(15)	(35)	(33)
INFLAMMATION, SUPPURATIVE		1 (3%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC			1 (3%)
CYTOPLASMIC VACUOLIZATION			1 (3%)
#STOMACH	(15)	(35)	(33)
ULCER, NOS			1 (3%)
#GASTRIC MUCOSA	(15)	(35)	(33)
MINERALIZATION			1 (3%)
URINARY SYSTEM			
#KIDNEY	(15)	(35)	(33)
INFLAMMATION, CHRONIC	12 (80%)	34 (97%)	33 (100%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#PROSTATE	(15)	(34)	(33)
INFLAMMATION, SUPPURATIVE			3 (9%)
#TESTIS	(15)	(34)	(33)
INFLAMMATION, NECROTIZING		1 (3%)	
*EPIDIDYMIS	(15)	(35)	(33)
GRANULOMA, SPERMATIC			1 (3%)
NERVOUS SYSTEM			
*PERIPHERAL NERVE	(15)	(35)	(33)
INFLAMMATION, CHRONIC		1 (3%)	
#BRAIN	(15)	(35)	(30)
HEMORRHAGE	1 (7%)		
MALACIA	1 (7%)	1 (3%)	1 (3%)
SPECIAL SENSE ORGANS			
*EYE	(15)	(35)	(33)
INFLAMMATION, SUPPURATIVE		1 (3%)	1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*EYE/CORNEA	(15)	(35)	(33)
ULCER, NOS		1 (3%)	
INFLAMMATION, CHRONIC SUPPURATIV			2 (6%)
MUSCULOSKELETAL SYSTEM			
*BONE	(15)	(35)	(33)
FIBROUS OSTEODYSTROPHY		1 (3%)	3 (9%)
EXOSTOSIS			1 (3%)
*JOINT	(15)	(35)	(33)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(15)	(35)	(33)
STEATITIS	1 (7%)		
*MESENTERY	(15)	(35)	(33)
PERIARTERITIS			3 (9%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(15)	(35)	(33)
MINERALIZATION		1 (3%)	5 (15%)
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 ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS NECROPSIED	15	35	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	35	35
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(35)	(35)
INFLAMMATION, SUPPURATIVE		1 (3%)	
RESPIRATORY SYSTEM			
#TRACHEA	(15)	(34)	(35)
INFLAMMATION, SUPPURATIVE	1 (7%)	2 (6%)	9 (26%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
#LUNG	(14)	(35)	(35)
PNEUMONIA, CHRONIC MURINE		4 (11%)	7 (20%)
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
#MYOCARDIUM	(15)	(35)	(35)
INFLAMMATION, INTERSTITIAL			1 (3%)
DIGESTIVE SYSTEM			
#LIVER	(15)	(35)	(35)
INFLAMMATION, CHRONIC			3 (9%)
CYTOPLASMIC VACUOLIZATION			3 (9%)
URINARY SYSTEM			
#KIDNEY	(15)	(35)	(35)
HYDRONEPHROSIS			1 (3%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	7 (47%)	26 (74%)	22 (63%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(15)	(35)	(35)
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)		
#UTERUS	(15)	(34)	(35)
DECIDUAL ALTERATION, NOS	1 (7%)	1 (3%)	
#UTERUS/ENDOMETRIUM	(15)	(34)	(35)
INFLAMMATION, SUPPURATIVE	4 (27%)	3 (9%)	6 (17%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	1 (3%)
#OVARY	(15)	(34)	(35)
INFLAMMATION, SUPPURATIVE		1 (3%)	1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*MIDDLE EAR	(15)	(35)	(35)
INFLAMMATION, SUPPURATIVE			1 (3%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	3	4

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED ETHIONAMIDE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	34
ANIMALS MISSING		1	
ANIMALS NECROPSIED	15	34	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	34	34
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(15)	(34)	(34)
INFLAMMATION, FOCAL		1 (3%)	
RESPIRATORY SYSTEM			
#TRACHEA	(15)	(34)	(34)
INFLAMMATION, SUPPURATIVE			1 (3%)
#LUNG/BRONCHIOLE	(15)	(33)	(34)
INFLAMMATION, ACUTE SUPPURATIVE			1 (3%)
#LUNG	(15)	(33)	(34)
INFLAMMATION, INTERSTITIAL		1 (3%)	
INFLAMMATION, SUPPURATIVE			3 (9%)
BRONCHOPNEUMONIA SUPPURATIVE	8 (53%)	4 (12%)	16 (47%)
INFLAMMATION, GRANULOMATOUS			1 (3%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(15)	(34)	(34)
ANGIECTASIS		1 (3%)	
HYPERPLASIA, RETICULUM CELL			2 (6%)
#MESENTERIC L. NODE	(13)	(30)	(28)
LYMPHANGIECTASIS		1 (3%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(15)	(33)	(33)
INFLAMMATION, INTERSTITIAL	2 (13%)		7 (21%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(14)	(34)	(33)
NECROSIS, COAGULATIVE		1 (3%)	
HYPERPLASIA, NODULAR	1 (7%)	1 (3%)	
ANGIECTASIS			1 (3%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(14)	(31)	(33)
FOLLICULAR CYST, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
#MEDULLA OBLONGATA	(15)	(34)	(32)
HEMORRHAGE			1 (3%)
SPECIAL SENSE ORGANS			
*EAR CANAL	(15)	(34)	(34)
INFLAMMATION, SUPPURATIVE		1 (3%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	12	4
ANIMAL MISSING/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 ETHIONAMIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	35	35
ANIMALS MISSING		1	
ANIMALS NECROPSIED	15	31	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	31	34
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(15)	(30)	(33)
HYPERPLASIA, LYMPHOID			1 (3%)
#LUNG	(15)	(30)	(33)
BRONCHOPNEUMONIA, NOS			1 (3%)
PNEUMONIA, ASPIRATION	1 (7%)		
INFLAMMATION, SUPPURATIVE	2 (13%)		
BRONCHOPNEUMONIA SUPPURATIVE	8 (53%)	16 (53%)	2 (6%)
HYPERPLASIA, LYMPHOID		3 (10%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(15)	(30)	(31)
MYELOFIBROSIS	1 (7%)		
#SPLEEN	(14)	(31)	(33)
HYPERPLASIA, LYMPHOID			1 (3%)
#MESENTERIC L. NODE	(12)	(26)	(30)
HYPERPLASIA, LYMPHOID			1 (3%)
#THYMUS	(14)	(29)	(34)
HYPERPLASIA, LYMPHOID		1 (3%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(15)	(31)	(34)
HYPERPLASIA, NODULAR			1 (3%)
#PANCREAS	(14)	(31)	(32)
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)		
URINARY SYSTEM			
#KIDNEY	(15)	(31)	(34)
INFLAMMATION, CHRONIC			1 (3%)
#U.BLADDER/SUBMUCOSA	(14)	(29)	(33)
HYPERPLASIA, LYMPHOID			1 (3%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(14)	(31)	(34)
INFLAMMATION, SUPPURATIVE	1 (7%)	4 (13%)	2 (6%)
HYPERPLASIA, CYSTIC	3 (21%)	8 (26%)	14 (41%)
#UTERUS/MYOMETRIUM	(14)	(31)	(34)
FIBROSIS	1 (7%)		
#OVARY	(14)	(31)	(34)
INFLAMMATION, NOS		1 (3%)	
INFLAMMATION, SUPPURATIVE	1 (7%)	1 (3%)	2 (6%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*MIDDLE EAR	(15)	(31)	(34)
INFLAMMATION, NOS			1 (3%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (7%)		1 (3%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(15)	(31)	(34)
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		5	6
ANIMAL MISSING/NO NECROPSY		1	
AUTOLYSIS/NO NECROPSY		3	1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED ETHIONAMIDE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Ethionamide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma[b]	0/15 (0)	2/35 (6)	0/33 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	--
Lower Limit		0.135	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	100	--
Hematopoietic System: Leukemia[b]	3/15 (20)	5/35 (14)	1/33 (3)
P Values[c,d]	P = 0.048(N)	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.714	0.152
Lower Limit		0.166	0.003
Upper Limit		4.179	1.737
Weeks to First Observed Tumor	95	83	99

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Ethionamide in the Dieta

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma[b]	3/15 (20)	2/35 (6)	1/30 (3)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.286	0.167
Lower Limit		0.027	0.003
Upper Limit		2.289	1.901
Weeks to First Observed Tumor	68	104	103
Thyroid: C-cell Adenoma or Carcinoma[b]	3/15 (20)	2/35 (6)	2/30 (7)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.286	0.333
Lower Limit		0.027	0.032
Upper Limit		2.289	2.649
Weeks to First Observed Tumor	68	104	101

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Ethionamide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor[b]	13/15 (87)	32/34 (94)	31/33 (94)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.086	1.084
Lower Limit		0.908	0.905
Upper limit		1.315	1.315
Weeks to First Observed Tumor	83	83	74

[a]Treated groups received doses of 1,500 or 3,000 ppm in feed.

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

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Ethionamide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma[b]	1/15 (7)	2/35 (6)	1/35 (3)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.857	0.429
Lower Limit		0.050	0.006
Upper Limit		49.128	32.715
Weeks to First Observed Tumor	82	99	96
Hematopoietic System: Leukemia[b]	1/15 (7)	2/35 (6)	4/35 (11)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.857	1.714
Lower Limit		0.050	0.196
Upper Limit		49.128	81.832
Weeks to First Observed Tumor	101	99	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Ethionamide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma[b]	0/15 (0)	1/35 (3)	3/35 (9)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	Infinite
Lower Limit		0.024	0.273
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	104
Pituitary: Chromophobe Carcinoma[b]	0/11 (0)	3/30 (10)	0/32 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.046		
Relative Risk (Matched Control)[f]		Infinite	--
Lower Limit		0.243	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	84	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Ethionamide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma[b]	2/11 (18)	10/30 (33)	3/32 (9)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.833	0.516
Lower Limit		0.503	0.072
Upper Limit		15.522	5.706
Weeks to First Observed Tumor	104	82	104
Thyroid: C-cell Adenoma or Carcinoma[b]	1/15 (7)	5/34 (15)	4/34 (12)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.206	1.765
Lower Limit		0.286	0.201
Upper Limit		100.914	84.138
Weeks to First Observed Tumor	104	104	96

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Ethionamide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma[b]	5/15 (33)	3/35 (9)	2/35 (6)
P Values[c,d]	P = 0.013(N)	P = 0.043(N)	P = 0.020(N)
Relative Risk (Matched Control)[f]		0.257	0.171
Lower Limit		0.048	0.019
Upper Limit		1.168	0.933
Weeks to First Observed Tumor	101	104	104
Uterus: Endometrial Stromal Polyp[b]	5/15 (33)	10/34 (29)	15/35 (43)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.882	1.286
Lower Limit		0.351	0.571
Upper Limit		2.823	3.812
Weeks to First Observed Tumor	101	84	75

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Ethionamide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Adenocarcinoma, NOS[b]	0/15 (0)	0/34 (0)	2/35 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	Infinite
Lower Limit		--	0.135
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	97

[a]Treated groups received doses of 1,500 or 3,000 ppm in feed.

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

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS

IN MICE FED ETHIONAMIDE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Ethionamide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	2/15 (13)	5/33 (15)	2/34 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.136	0.441
Lower Limit		0.220	0.036
Upper Limit		11.095	5.706
Weeks to First Observed Tumor	75	83	96
Hematopoietic System: Malignant Lymphoma[b]	2/15 (13)	8/34 (24)	4/34 (12)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.765	0.882
Lower Limit		0.421	0.147
Upper Limit		15.787	9.103
Weeks to First Observed Tumor	45	89	94

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Ethionamide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	2/14 (14)	3/34 (9)	2/33 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.618	0.424
Lower Limit		0.083	0.035
Upper Limit		6.904	5.471
Weeks to First Observed Tumor	45	87	96
Liver: Hepatocellular Adenoma or Carcinoma[b]	3/14 (21)	6/34 (18)	4/33 (12)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.824	0.566
Lower Limit		0.215	0.115
Upper Limit		4.588	3.496
Weeks to First Observed Tumor	45	78	78

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Ethionamide in the Diet[a]

(continued)

[a]Treated groups received doses of 1,000 or 2,000 ppm in feed.

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

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Ethionamide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Malignant Lymphoma[b]	2/15 (13)	4/31 (13)	10/34 (29)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.968	2.206
Lower Limit		0.162	0.565
Upper Limit		9.933	19.069
Weeks to First Observed Tumor	104	89	61

[a]Treated groups received doses of 1,000 or 2,000 ppm in feed.

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

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

Review of the Bioassay of Ethionamide* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

January 18, 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 laboratory animal sciences, 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 Ethionamide for carcinogenicity.

The primary reviewer briefly described the conditions under which Ethionamide was tested and noted that the bioassay was conducted in the same room and at the same time that other chemicals were studied. She pointed out the inadequate number of control animals which resulted from an undersized initial group and excessive mortality. Although comparisons were made with pooled control animals, the control data was not given in the report. The primary reviewer commented on the increased but not statistically significant incidence of malignant lymphomas in treated mice, and in particular those associated with the central nervous system. She felt that the tumors may take on additional significance if compared with the program-wide controls. The primary reviewer recommended that a judgment on the mouse study be deferred until such an analysis could be performed. Despite the shortcomings and experimental limitations of the rat study, she said that it was sufficiently adequate to conclude that Ethionamide was not carcinogenic, under the conditions of test.

A Program staff member confirmed that the treated animals were compared with pooled controls but that the data were not incorporated into the report. In regard to the mouse lymphomas, another Staff member commented that an analysis did not show a dose-related effect. It was recommended to defer any conclusion on the mouse portion of the study until the Subgroup members had the opportunity to review the lymphoma incidence among the pooled controls.

It was moved that the staff's conclusion on the rat portion of the study be accepted. The motion was seconded and approved by all the Subgroup members except Mr. Garfinkel, who opposed it on the basis that the study was inadequate due to too few animals.

Members Present Were:

Arnold Brown (Acting Chairman), Mayo Clinic
Lawrence Garfinkel, American Cancer Society
Joseph Highland, Environmental Defense Fund
Charles Kensler, Arthur D. Little Company
Verald K. Rowe, Dow Chemical, U.S.A.
Sheldon Samuels, Industrial Union Department, AFL-CIO
Louise Strong, University of Texas Health Sciences Center
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.

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