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BIOASSAY OF
ETHYL TELLURAC
FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
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Bethesda, Maryland 20205

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FOREWORD: This report presents the results of the bioassay of ethyl tellurac conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals that are carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of ethyl tellurac was conducted by the NCI Frederick Cancer Research Center (FCRC) (1), Frederick, Maryland, operated for NCI (2) by Litton Bionetics, Inc.

The manager of the bioassay at FCRC was Dr. B. Ulland, the toxicologist was Dr. E. Gordon, and Drs. R. Cardy and D. Creasia compiled the data. Ms. S. Toms was responsible for management of data, Mr. D. Cameron for management of histopathology, Mr. L. Callahan for management of the computer branch, and Mr. R. Cypher for management of the facilities. Mr. A. Butler performed the computer services. Necropsies were performed by Drs. B. Ulland, R. Schueler, R. Ball, and R. Cardy. Histopathologic evaluations were performed by Drs. J. F. Hardisty (3) and C. E. Gilmore (3), and the diagnoses included in this report represent their interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). The statistical analyses were

performed by Dr. J. R. Joiner (5) and Ms. P. L. Yong (5), using methods selected for the bioassay program by Dr. J. J. Gart (6).

The chemicals used in this bioassay were analyzed at FCRC (1) by Dr. W. Zielinsky. The chemical narrative and analyses were reviewed and approved by Dr. W. Lijinsky (1).

This report was prepared at Tracor Jitco (5) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A Owen, Ms. M. S. King, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI were responsible for evaluating the bioassay, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of technical-grade ethyl tellurac for possible carcinogenicity was conducted by administering the preparation in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered ethyl tellurac at one of two doses, either 300 or 600 ppm for the males and either 150 or 300 ppm for the females, for 105 weeks. Matched controls consisted of 20 untreated rats of each sex. All surviving rats were killed at 105 weeks.

Groups of 50 mice of each sex were administered ethyl tellurac at one of two doses, initially either 2,500 or 5,000 ppm. Due to signs of toxicity in the dosed animals, these doses were reduced to 500 and 2,000 ppm, respectively, starting at week 41 for the males and at week 38 for the females. The reduced doses were maintained for 66 weeks for the males; for the females, the reduced doses were raised after 3 weeks to 2,000 and 5,000 ppm, respectively, and maintained at these levels for 66 weeks. The time-weighted average doses for the males were either 1,255 or 3,132 ppm; for the females, either 2,132 or 4,915 ppm. Matched controls consisted of 20 untreated mice of each sex. All surviving mice were killed at 106 weeks.

Mean body weights of the dosed groups of rats or mice were lower than those of corresponding controls throughout most or all of the bioassay. No other clinical signs in the rats or mice were clearly related to administration of the test chemical. Survival of the rats and the mice was not affected by the chemical, and sufficient numbers of all groups were at risk for the development of late-appearing tumors.

In the male rats, mesotheliomas occurred at incidences that were dose related ($P = 0.012$); in direct comparisons, the incidences of the tumors in the individual dosed groups were not significantly higher than that in the control group (controls 0/20, low-dose 2/49, high-dose 8/50). However, the historical-control data at this laboratory indicate an incidence of 12/416 (2.9%) in male F344 rats compared with 8/50 (16%) in the male high-dose group in this study.

In the female rats, no tumors occurred at incidences that were related to administration of the test chemical.

In both male and female mice, adenomas of the lacrimal (harderian) gland of the eye occurred in the dosed groups, but not in the corresponding controls (males: controls 0/17, low-dose 16/46,

high-dose 10/49; females: controls 0/20, low-dose 6/50, high-dose 5/49). The incidences in the dosed groups were not high enough to show statistically significant dose-related trends. However, in direct comparisons of dosed and control groups of male mice, the incidence was statistically significant in the low-dose males (P = 0.003). In female mice, direct comparisons of dosed and control groups indicated that the incidence of this tumor was not statistically significant.

It is concluded that under the conditions of this bioassay, ethyl tellurac was not carcinogenic for F344 rats or B6C3F1 mice of either sex. The incidence of mesotheliomas in dosed male rats and the incidence of adenomas of the lacrimal (harderian) gland of the eye in dosed mice of either sex provided evidence which was suggestive but under the conditions of the bioassay insufficient to establish the carcinogenicity of ethyl tellurac in these animals.

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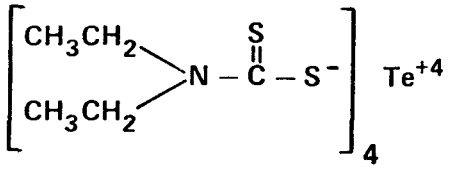
I. INTRODUCTION

Ethyl tellurac (CAS 20941-65-5 and 30145-38-1; NCI C02857) is the common name for tellurium diethyldithiocarbamate. It is used in rubber processing where it functions to accelerate the rate of vulcanization or formation of sulfur bridges between rubber polymers that produces modulus or rigidity in the finished product (LeBras, 1957).



Ethyl tellurac

Ethyl tellurac belongs to a class of rubber accelerators that are extremely fast-acting and have been termed "ultra-accelerators" (Harris and Trivette, 1964). In addition to shortening the curing time, the ultra-accelerators are active at low temperatures and can be used, for example, in rubber cements (Shaver, 1965). While the mechanism by which ethyl tellurac catalyzes vulcanization is not completely understood, it seems probable that tellurium, a group VI relative of sulfur, replaces it in the crosslink so that the linkage now resembles S-Te-S, instead of S-S-S (Ambelang, 1964). Tellurium is more capable of absorbing

the thermal energy generated by vulcanization, and prevents these linkages from undergoing reversion, or breakdown, which normally occurs if curing proceeds too far (Dunkel et al., 1959).

Natural rubber, styrene-butadiene-rubber, nitrile and butyl rubber (Del Gatto, 1968) and ethylene-propylene-diene rubber are compounded with ethyl tellurac in a ratio of 1 to 2 parts accelerator per 100 parts rubber (Winspear, 1958). Some thiazole accelerators are used in conjunction with ethyl tellurac (Del Gatto, 1968).

Production data are not reported for ethyl tellurac alone, although the class of which it is a member, the dithiocarbamates, accounted for 15% of the acyclic rubber-processing chemicals that were sold in 1976 (United States International Trade Commission, 1977).

Ethyl tellurac was tested by Innes et al. (1969) in a large-scale screen of industrial compounds for carcinogenic activity. Since the results of this preliminary bioassay in mice suggested but did not clearly associate the incidence of lung tumors with administration of the test chemical, ethyl tellurac was selected for further testing in the Carcinogenesis Testing Program.

II. MATERIALS AND METHODS

A. Chemical

Ethyl tellurac (tellurium diethyldithiocarbamate; $C_{20}H_{40}N_4S_8Te$) was obtained as technical-grade, nonformulated material from R. T. Vanderbilt Co. The material is a fine, dark-yellow powder. Atomic absorption spectrometric analysis showed the presence of 18.3% tellurium in the test material (manufacturer's specification: 17.5 to 19.5% tellurium). This value was slightly higher than the theoretical level of tellurium in ethyl tellurac (17.7%). The high purity of the test material was validated by elemental analysis (experimental: 32.7% carbon, 5.7% hydrogen, 7.7% nitrogen; theoretical: 33.3% carbon, 5.6% hydrogen, 7.8% nitrogen). Thin-layer chromatography of the test material on silylated silica showed only a single spot, with no impurities. The material had a melting point of 115°C (literature: 108 to 118°C) and an infrared spectrum consistent with the chemical structure for ethyl tellurac. Mass spectral analysis showed the absence of a molecular ion, and a base peak at 60 m/e. Atomic absorption analysis also showed the presence of 0.004% selenium, 0.03% lead, 0.05% zinc, and 0.02% sodium.

B. Dietary Preparation

Appropriate mixtures of dosed feed were prepared fresh every 1 to 1-1/2 weeks in 6 to 12-kg batches. A known weight of the chemical was first mixed with an equal weight of autoclaved Wayne® Sterilizable Lab Meal with 4% fat (Allied Mills, Inc., Chicago, Ill.), using a mortar and pestle. The mixing was continued with second and third additions of feed, and final mixing was performed with the remaining quantity of feed for a minimum of 15 minutes in a Patterson-Kelly twin-shell blender. The diets were routinely stored at 5°C until used.

C. Animals

Male and female F344 (Fischer) rats and B6C3F1 mice were obtained as 4-week-old weanlings, all within 3 days of the same age, from the NCI Frederick Cancer Research Center animal farm (Frederick, Md.). The animals were housed within the test facility for 2 weeks and then were assigned four rats to a cage and five mice to a cage on a weight basis for each cage of animals of a given species and sex. Male rats used in the chronic study weighed 90 to 105 g; the female rats, 80 to 95 g; the male mice, 18 to 22 g; and the female mice, 17 to 21 g. Individual animals were identified by ear punch.

D. Animal Maintenance

The animals were housed in polycarbonate cages (Lab Products Inc., Garfield, N. J.), 19 x 10-1/2 x 8 inches for the rats and 11-1/2 x 7-1/2 x 5 inches for the mice. The cages were suspended from aluminum racks (Scientific Cages, Inc., Bryan, Tex.) and were covered by nonwoven polyester-fiber 12-mil-thick filter paper (Hoeltge, Inc., Cincinnati, Ohio). The bedding used was Absorb-dri® hardwood chips (Northeastern Products, Inc., Warrenburg, N. Y). The feed supplied was presterilized Wayne® Sterilizable Lab Meal, provided ad libitum in suspended stainless steel hoppers and replenished as required, at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from glass bottles. Sipper tubes (Lab Products, Inc.) suspended through the tops of the cages.

The contaminated bedding was disposed of through an enclosed vacuum line that led to a holding tank from which the bedding was fed periodically into an incinerator. The cages were sanitized at 82 to 88°C in a tunnel-type cagewasher (Industrial Washing Machine Corp., Mataway, N. J.) twice per week, using the detergents, Clout® (Pharmacal Research Laboratories, Greenwich, Conn.) or Oxford D'Chlor (Oxford Chemicals, Atlanta, Ga.). The feed hoppers were sanitized twice per month in the same equipment. The glass

bottles and sipper tubes were sanitized at 82 to 88°C in a tunnel-type bottle washer (Consolidated Equipment Supply Co., Mercersburg, Pa.) three times per week, using a Calgen Commercial Division detergent (St. Louis, Mo.). The racks for the cages were sanitized at or above 82°C in a rack washer (Consolidated Equipment Co.) once per month, using the Calgen Commercial Division detergent, and the filter paper was changed at the same time.

The air in the animal rooms was maintained at 22 to 24°C and 45 to 55% relative humidity. Fresh air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake and through a "Z"-type roughing filter of 30% efficiency and a bag system of 90 to 95% efficiency at the exhaust (American Air Filters, Louisville, Ky.; Mine Safety Appliances, Pittsburgh, Pa.) and was not recirculated. Room air was changed 15 times per hour. The air pressure was maintained negative to a clean hallway and positive to a return hallway. Fluorescent lighting was provided automatically on a 12-hour-per-day cycle.

Rats administered ethyl tellurac and their corresponding controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 97-77-8) ethyl tuads
(CAS 19010-66-3) lead dimethyldithiocarbamate

Mice administered ethyl tellurac and their corresponding controls were housed in the same room as mice on feeding studies of the following chemicals:

(CAS 103-33-3) azobenzene
(CAS 72-56-0) p,p'-ethyl-DDD
(CAS 298-00-0) methyl parathion
(CAS 85-44-9) phthalic anhydride
(CAS 51-03-6) piperonyl butoxide
(CAS 88-06-2) 2,4,6-trichlorophenol
(CAS 128-66-5) C. I. vat yellow 4

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of ethyl tellurac, on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were selected for administration in the chronic studies. Groups of five rats and of five mice of each sex were fed diets containing ethyl tellurac at one of several doses, and groups of five controls of each species and sex were administered basal diet only for 7 weeks, rollowed by 1 week of additional observation. Each animal was weighed twice per week. At the end of the subchronic studies, all animals were killed using CO_2 and necropsied.

Based on these studies, the low and high doses for chronic studies using male rats were set at 300 and 600 ppm; for female rats, at 150 and 300 ppm. For chronic studies using mice, the low and high doses were set at 2,500 and 5,000 ppm for both males and females.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 1 and 2.

Due to excessive depression of weight in both dosed male and dosed female mice, the doses were reduced starting at week 41 for the males and at week 38 for the females. For the males, the lowered doses were retained for the remainder of the administration of the chemical; for the females, they were increased after 3 weeks, as indicated.

Table 1. Ethyl Tellurac Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Ethyl Tellurac in Diet (b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	20	0	105
Low-Dose	50	300	105
High-Dose	50	600	105
Female			
Matched-Control	20	0	105
Low-Dose	50	150	105
High-Dose	50	300	105

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum 7 days per week.

Table 2. Ethyl Tellurac Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Ethyl Tellurac in Diet (b) (ppm)	Time on Study (weeks)	Time-Weighted Average Dose (c) (ppm)
Male				
Matched-Control	20	0	106	
Low-Dose	50	2,500	40	
		500	66	1,255
High-Dose	50	5,000	40	
		2,000	66	3,132
Female				
Matched-Control	20	0	106	
Low-Dose	50	2,500	37	
		500	3	
		2,000	66	2,132
High-Dose	50	5,000	37	
		2,000	3	
		5,000	66	4,915

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum 7 days per week.

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

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Observations for sick, tumor-bearing, and moribund animals were recorded daily. Clinical examination and palpation for masses were performed each month, and the animals were weighed at least once per month. Moribund animals and those that survived to the end of the bioassay were killed using CO_2 and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (parotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum and cerebellum), and all tissue masses. Peripheral blood smears also were made for all animals, whenever possible.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

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

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

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 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 less than 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 less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of the dosed male and female rats were lower than those of corresponding matched controls throughout the bioassay (figure 1). In the males, the depression in weight was slightly greater in the high-dose group than in the low-dose group; in the females, the weights of the low- and high-dose groups were essentially the same. No other clinical signs were observed that were clearly related to administration of the test chemical.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered ethyl tellurac in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. In each sex, the result of the Tarone test for dose-related trend in mortality is not significant.

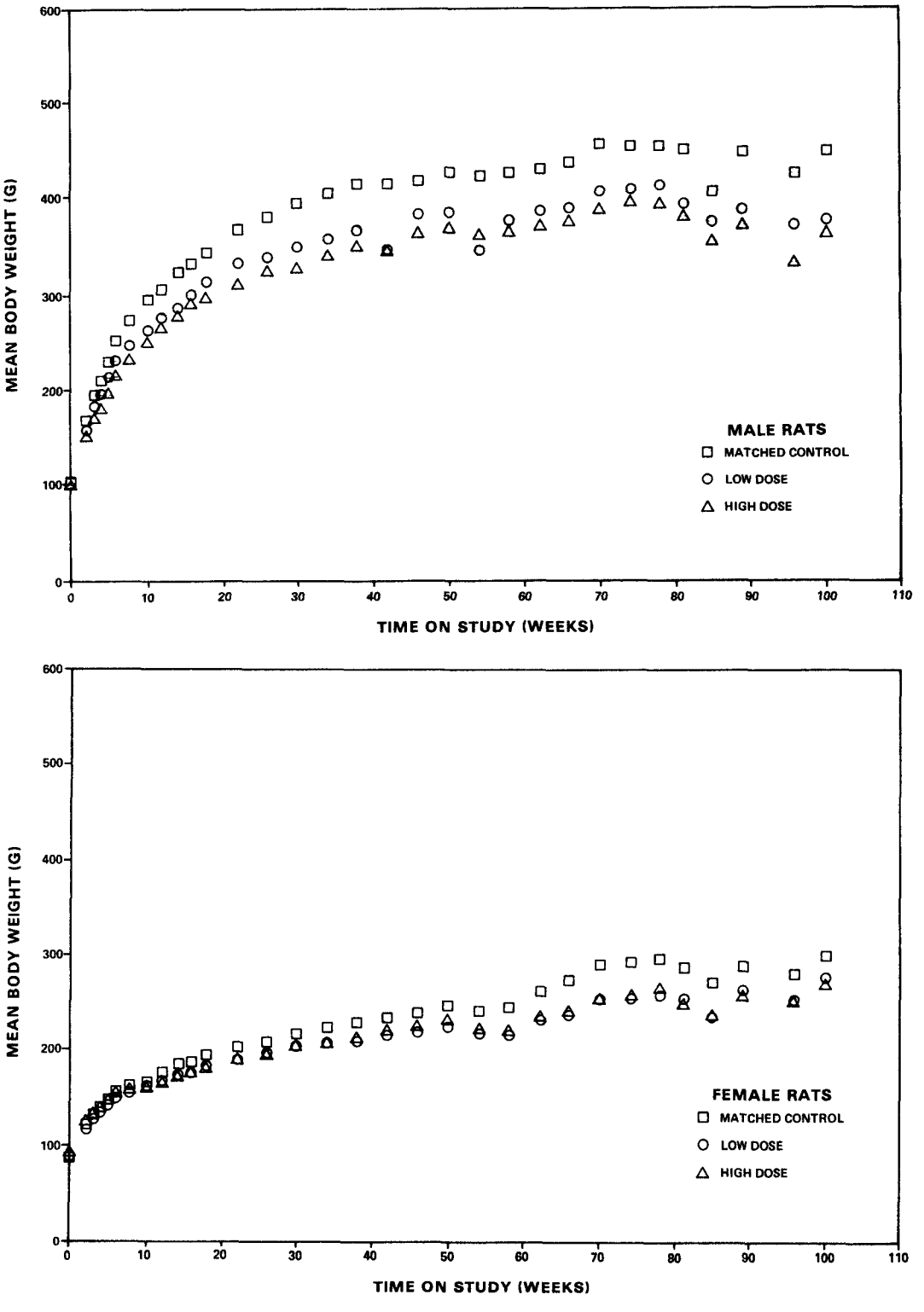


Figure 1. Growth Curves for Rats Administered Ethyl Tellurac in the Diet

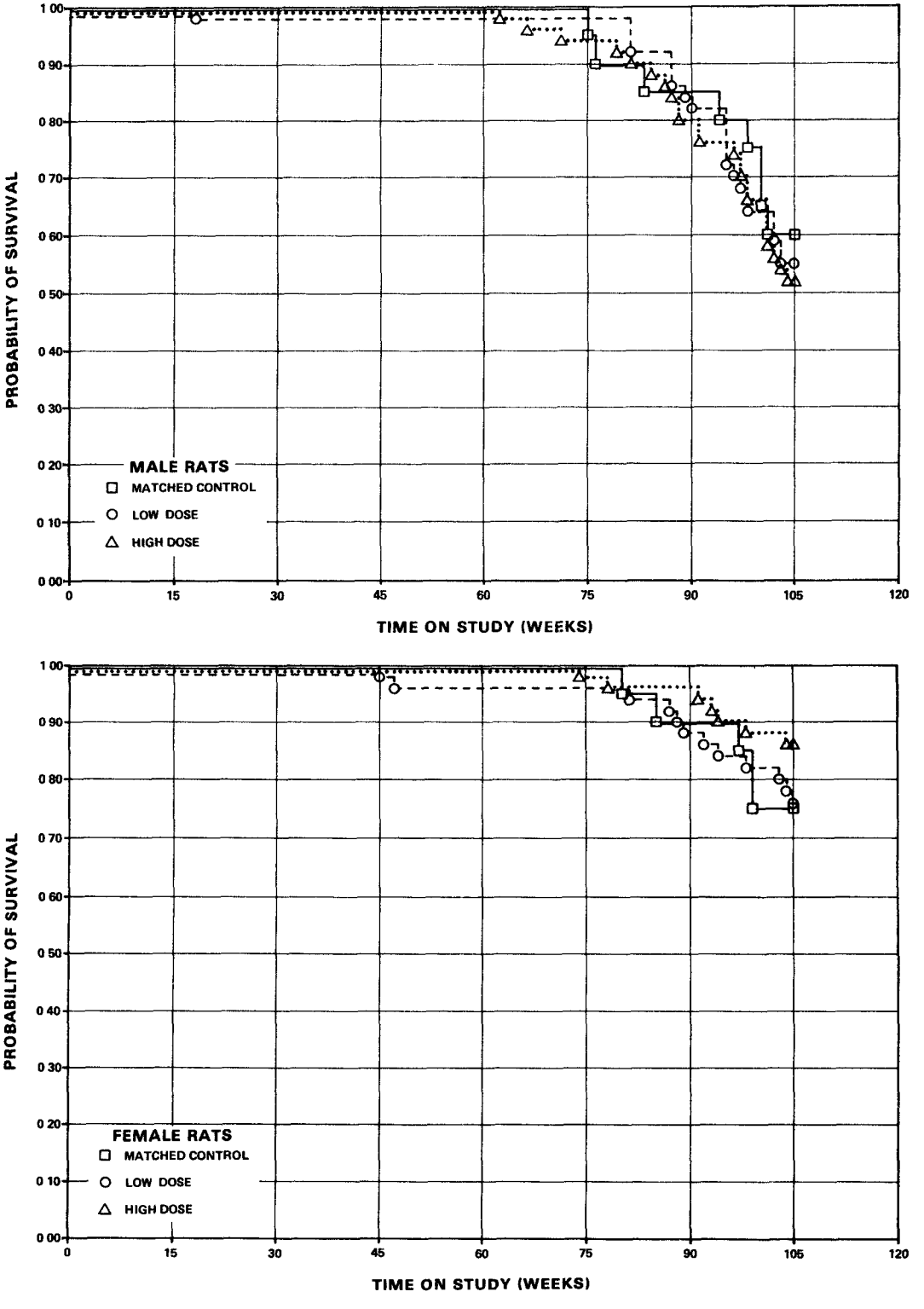


Figure 2. Survival Curves for Rats Administered Ethyl Tellurac in the Diet

In male rats, 26/50 (52%) of the high-dose group, 27/50 (54%) of the low-dose group, and 12/20 (60%) of the control group lived to the end of the bioassay. In females, 43/50 (86%) of the high-dose group, 38/52 (76%) of the low-dose group, and 15/20 (75%) of the control group lived to the end of the bioassay.

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.

With the exception of the mesotheliomas observed in the dosed male rats and the high incidence of malignant lymphoma in all groups, the neoplasms that were observed had similar incidences in control and dosed groups. The nature and incidence of these neoplasms are consistent with the occurrence of similar neoplasms in aged F344 rats.

Malignant mesotheliomas were present in 2/49 of the low-dose male

rats and 8/50 of the high-dose male rats. These neoplasms were nodular growths arising from the serous membranes linking the peritoneal cavity and scrotum. Microscopically, they were characterized as papillary projections consisting of a fibrous core covered by large, atypical, mesothelial cells.

There was a high incidence of tumors of the hematopoietic system in both control and dosed rats as shown in the following tabulation:

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Animals Necropsied	20	49	50	20	50	50
Malignant Lymphoma	7 (35%)	27 (55%)	24 (48%)	4 (20%)	14 (28%)	15 (30%)
Erythrocytic Leukemia					1 (2%)	

The most frequent hematopoietic neoplasms encountered were malignant lymphomas. Most of these neoplasms were composed of undifferentiated lymphoreticular cells and involved several organs; spleen and liver were the organs most frequently involved, followed by the lung, lymph nodes, and thymus. Malignant lymphomas (also called mononuclear-cell or monocytic leukemia) frequently occur as in aging F344 rats; there appears to be little difference between the low- and high-dose groups in the incidences of the malignant lymphomas in this bioassay.

Several inflammatory, degenerative, and proliferative lesions commonly seen in aged F344 rats occurred with approximately equal frequency in dosed and control animals.

Based on the histopathologic examination, an increase in the number of malignant mesotheliomas in male F344 rats may be associated with the administration of ethyl tellurac under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

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

Four mesotheliomas of the body cavities were observed in the male high-dose group, but none in the low-dose group or the controls. The result of the Cochran-Armitage test for positive dose-related trend is significant ($P = 0.041$), but those of the Fisher exact test are not significant. The results of the statistical tests on the incidence of mesothelioma of the tunica vaginalis are not significant. When mesotheliomas of all sites are considered

together, the result of the Cochran-Armitage test is significant (P = 0.012) but those of the Fisher exact test remain not significant. The historical-control data at this laboratory indicate an incidence of 12/416 (2.9%) in male F344 rats, compared with 8/50 (16%) in the male high-dose groups of this study.

In females, the result of the Cochran-Armitage test for the incidence of adenomas of the pituitary is not significant. An indicated departure from linear trend is observed, because the incidence in the low-dose group is greater than that in the high-dose group. The Fisher exact test shows that the incidence in the low-dose group is significantly higher (P = 0.012) than that in the control group, but this significance is not confirmed by the incidence in the high-dose group.

In male rats, the results of the Cochran-Armitage test and Fisher exact test for the incidence of lymphoma are not significant. When the life-table method is applied, the result of the Tarone test is also not significant. The historical records of this laboratory show an incidence of lymphoma and leukemia of 91/416 (22%) among untreated F344 male rats compared with 24/50 (48%) in the high-dose groups of male rats in this study.

Significant results in the negative direction are observed in the incidence of cortical adenomas or carcinomas of the adrenal and the incidence of islet-cell adenomas in male rats, in which the incidences in the control group exceed those in the dosed groups.

In summary, the occurrence of mesotheliomas in male rats may be associated with the administration of ethyl tellurac.

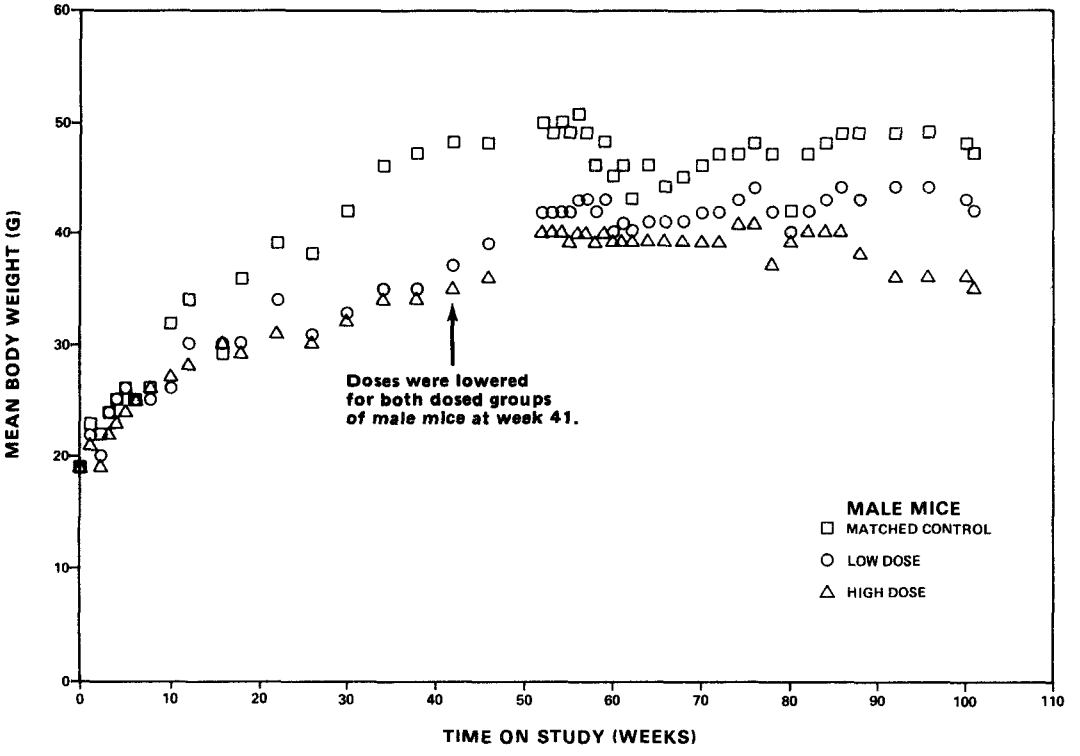
IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male and female mice were much lower than those of corresponding matched controls throughout most of the bioassay (figure 3). The depression in weight was slightly greater in the high-dose groups than in the low-dose groups. Tissue masses were observed in dosed females at higher incidences than in corresponding controls, but no other clinical signs in either the males or females were related to administration of the test chemical.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered ethyl tellurac in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. In each sex, the result of the Tarone test for dose-related trend in mortality is not significant.



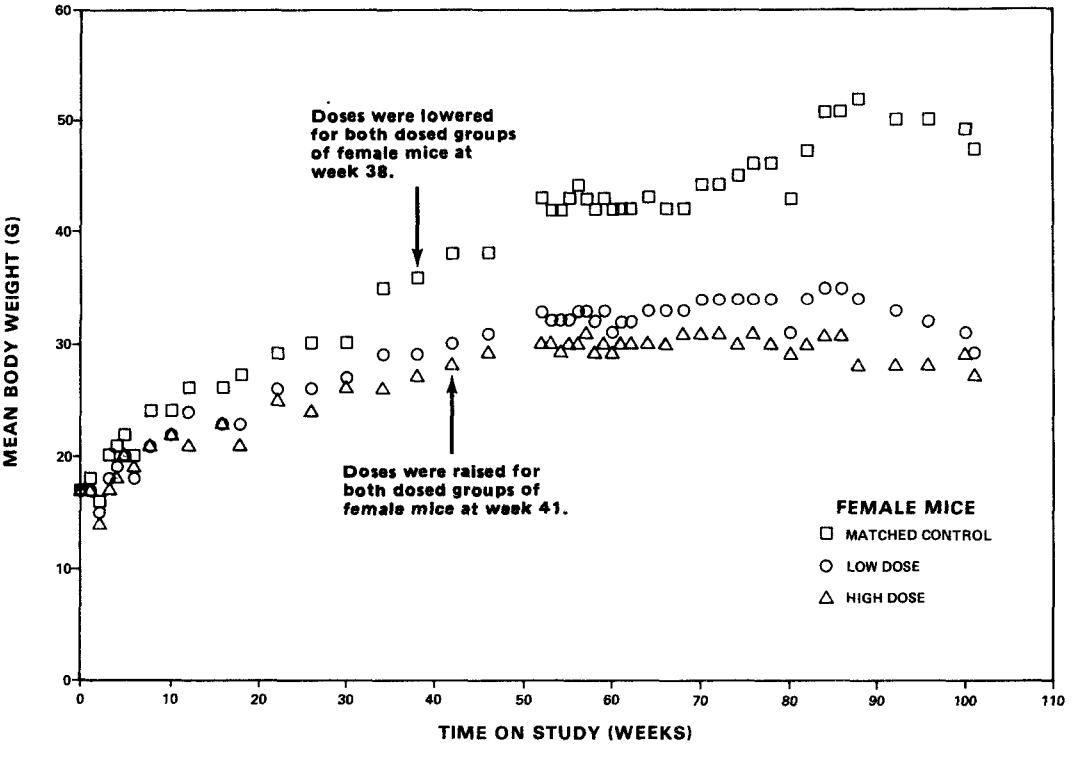
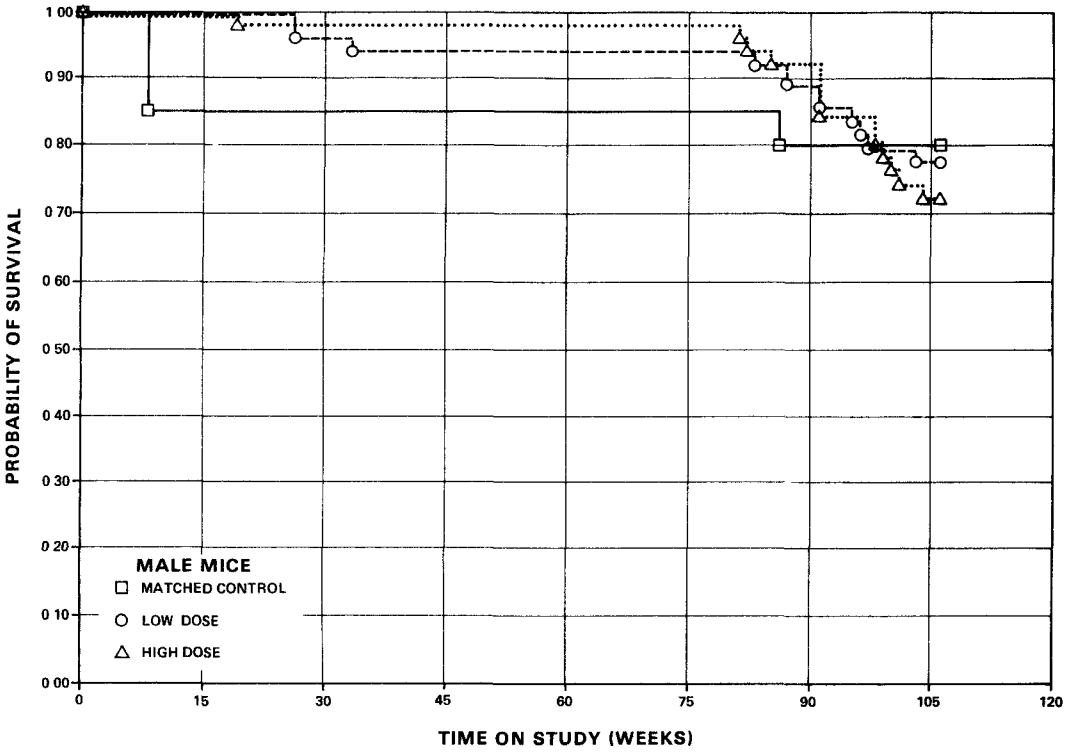


Figure 3. Growth Curves for Mice Administered Ethyl Tellurac in the Diet



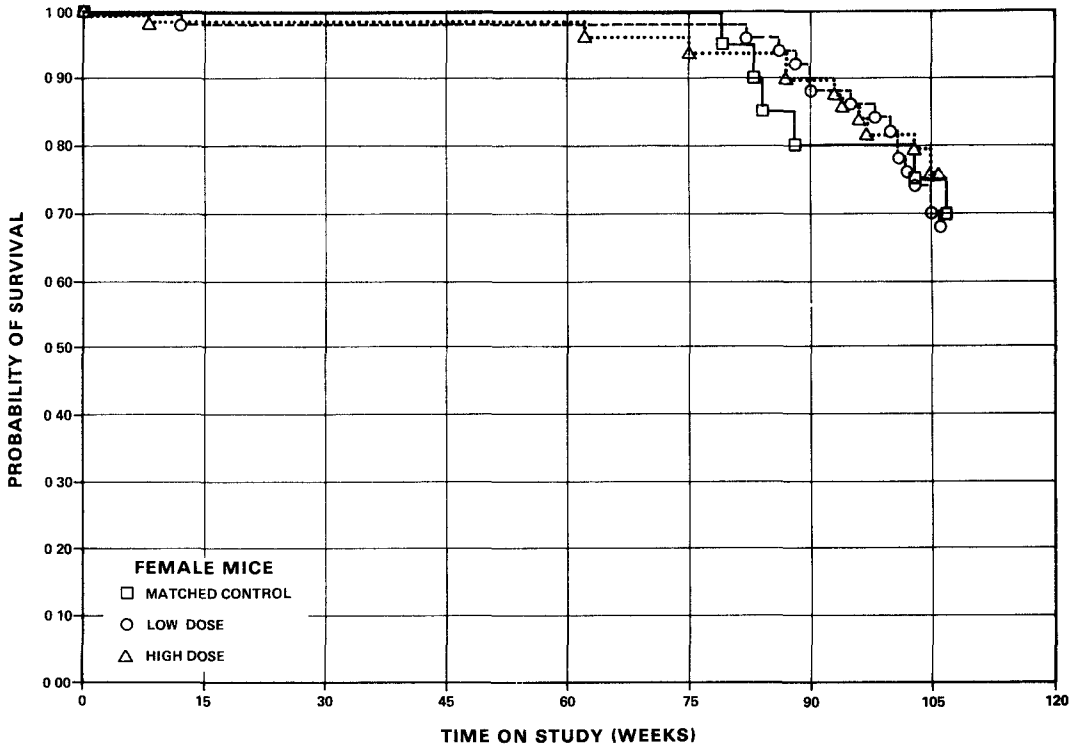


Figure 4. Survival Curves for Mice Administered Ethyl Tellurac in the Diet

In male mice, 36/50 (72%) of the high-dose group, 37/50 (74%) of the low-dose group, and 16/20 (80%) of the control group lived to the end of the bioassay. In females, 37/50 (74%) of the high-dose group, 34/50 (68%) of the low-dose group, and 14/20 (70%) of the control group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the 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.

The majority of neoplasms observed in dosed mice were observed in incidences similar to those of the controls except for tumors of the lacrimal (harderian) gland in male and female mice, tumors of the lung in male mice, and tumors of the liver in female mice.

Adenomas of the lacrimal (harderian) gland were noted grossly as masses adjacent to the eyes; the glands were not examined microscopically unless such a mass was observed grossly. None

were found in the control mice but several were present in dosed animals (males: low-dose 16/46 or 35%, high-dose 10/49 or 20%; females: low-dose 6/50 or 12%, high-dose 5/49 or 10%). The adenomas of the lacrimal gland consisted of clearly defined areas of proliferating epithelial cells arranged in fronds supported by thin fibrous trabeculae and without evidence of invasion.

Hepatocellular carcinomas were observed more frequently in dosed females than in female controls.

	Controls	Low Dose	High Dose
Male	8/17 (47%)	15/46 (33%)	16/49 (33%)
Female	1/19 (5%)	7/49 (14%)	10/48 (21%)

Metastases of the tumor to lung and/or lymph nodes occurred in one control male and in two males in the dosed groups.

Alveolar/bronchiolar adenomas or carcinomas were observed in increased incidences in dosed male mice (controls 0/17, low-dose 16/46, high-dose 11/46). The carcinomas were distinguished from the adenomas by their hyperchromatic staining, increased number of mitoses, and solid growth.

In addition to the neoplastic lesions, degenerative, proliferative,

and inflammatory lesions occurred that were similar in number and kind to those naturally occurring lesions found in aged B6C3F1 mice.

Based on the histopathologic examinations, an increased incidence of adenoma of the lacrimal (harderian) gland in both male and female B6C3F1 mice, and neoplasms of the lung in male mice and of the liver in female mice may be associated with the administration of ethyl tellurac under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In male mice, the results of the Fisher exact test applied to the incidence of animals with alveolar/bronchiolar adenomas or carcinomas are significant ($P = 0.003$ and $P = 0.022$, for the low-dose and high-dose, respectively). The result of the Cochran-Armitage test is not significant, but a departure from linear trend is indicated, because the incidence in the low-dose is higher than that in the high-dose group. The incidence in the control group (0/17) may,

however, have been unusually low, since the incidence of these tumors in historical controls at this laboratory is 78/422 (18%). Thus, the occurrence of the alveolar/bronchiolar carcinomas or adenomas in the dosed male mice cannot clearly be related to administration of the test chemical.

The result of the Cochran-Armitage test for the incidence of adenomas of the lacrimal (harderian) gland of the eye in male mice is not significant. An indicated departure from linear trend is observed, because the incidence in the low-dose group is greater than that in the high-dose group. The Fisher exact comparisons of the incidences in the low- and high-dose groups with that of the control group show P values of 0.003 and 0.039, respectively. The latter is above the 0.025 level for significance when the Bonferroni inequality criterion is used for multiple comparison. The historical-control data at this laboratory, however, indicate an incidence of 10/422 (2.4%) in male B6C3F1 mice, compared with 10/49 (20%) in the high-dose male group in this study.

In females, the incidence of adenomas of the lacrimal (harderian) gland is 0/20 in the control group, 6/50 (12%) in the low-dose group, and 5/49 (10%) in the high-dose group. The results of the Cochran-Armitage test and of the Fisher exact test are not significant. The historical-control data at this laboratory

indicate an incidence of 2/440 (0.5%) in female B6C3F1 mice. Using this rate of tumors as a parameter (Fears et al., 1977) and assuming a binomial distribution, the probability level of the occurrence of 5 or more such tumors out of a possible 49 animals is less than 0.001.

In summary, the incidence of adenoma of the lacrimal (harderian) gland of the eye in mice of each sex is associated with the administration of ethyl tellurac.

V. DISCUSSION

Mean body weights of both rats and mice administered technical-grade ethyl tellurac were lower than those of controls under the conditions of the bioassay, and the depressions were greater in the mice than in the rats. No other clinical signs were observed that clearly were related to administration of the test chemical. Survivals of the rats and mice were unaffected by the ethyl tellurac and were 76% or greater in all groups at week 90 of the bioassay; thus, sufficient numbers of dosed and control rats and mice of each sex were at risk for the development of late-appearing tumors.

In the male rats, mesotheliomas were observed on the peritoneal surfaces of multiple abdominal organs and on the tunica vaginalis. These tumors occurred at incidences that were dose related ($P = 0.012$); in direct comparisons, the incidences of the tumors in the individual dosed groups were not significantly higher than that in the control group (controls 0/20, low-dose 2/49, high-dose 8/50). However, the historical-control data at this laboratory indicate an incidence of 12/416 (2.9%) in male F344 rats compared with 8/50 (16%) in the male high-dose groups of this study.

No tumors occurred in female rats that could clearly be associated with administration of the test chemical.

In the male mice, alveolar/bronchiolar carcinomas or adenomas occurred in the dosed groups, but not in the control group (controls 0/17; low-dose 16/46, or 35%; high-dose 11/46, or 25%). In direct comparisons of dosed and control groups, the incidences were statistically significant in both the low-dose ($P = 0.003$) and the high-dose ($P = 0.022$) groups. The incidence in the control group may, however, have been unusually low, since the incidence of these tumors in historical-control male mice at this laboratory is 78/422 (18%). Thus, the occurrence of the alveolar/bronchiolar carcinomas or adenomas in the dosed male mice cannot be clearly related to administration of the test chemical.

In both the male and female mice, adenomas of the lacrimal (harderian) gland of the eye occurred in the dosed groups, but not in the corresponding controls (males: controls 0/17, low-dose 16/46, high-dose 10/49; females: controls 0/20, low-dose 6/50, high-dose 5/49). The incidences in the dosed groups were not high enough to show statistically significant dose-related trends. However, in direct comparisons of dosed and control groups of male mice the incidence was statistically

significant in the low-dose males (P = 0.003) and the historical-control data at this laboratory indicate an incidence of 10/422 (2.4%) in male B6C3F1 mice, compared with 16/46 (35%) in the low-dose and 10/49 (20%) in the high-dose male groups in this study. In female mice, direct comparisons of dosed and control groups indicated that the incidences of adenomas of the lacrimal (harderian) gland were not statistically significant.

In other tests for tumorigenicity, it was reported that when the chemical was administered at 46.4 mg/kg by stomach tube for 4 weeks, then in the diet at 149 ppm for 18 months, to each of two different strains of hybrid mice (C57BL/6 X C3H/Anf and C57BL/6 X AKR), an elevated incidence of lung tumors in 7/36 dosed animals as compared with 12/172 in controls (P = 0.02) was observed in the second strain (Innes et al., 1969). The data were considered as inconclusive.

It is concluded that under the conditions of this bioassay, ethyl tellurac was not carcinogenic for F344 rats or B6C3F1 mice of either sex. The incidence of mesotheliomas in dosed male rats and the incidence of adenomas of the lacrimal (harderian) gland of the eye in dosed mice of either sex provided evidence which was suggestive but under the conditions of the bioassay insufficient to establish the carcinogenicity of ethyl tellurac in these animals.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)	1 (2%)	
SEBACEOUS ADENOMA			1 (2%)
*SUBCUT TISSUE	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA			2 (4%)
FIBROMA	1 (5%)	3 (6%)	3 (6%)
LIPOMA			1 (2%)
OSTEOSARCOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST	1 (5%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA, METAS		1 (2%)	
OSTEOSARCOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	4 (8%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	6 (30%)	26 (53%)	20 (40%)
#SPLEEN	(19)	(49)	(48)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (5%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(47)
NEOPLASTIC NODULE		1 (2%)	
HEPATOCELLULAR CARCINOMA	1 (5%)	1 (2%)	
#STOMACH	(18)	(49)	(47)
FIBROSARCOMA	1 (6%)		
#SMALL INTESTINE	(17)	(49)	(47)
LEIOMYOSARCOMA		1 (2%)	
#COLON	(17)	(49)	(46)
ADENOMATOUS POLYP, NOS		1 (2%)	
LEIOMYOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
#KIDNEY/CORTEX	(20)	(49)	(48)
ADENOMA, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(45)	(45)
ADENOMA, NOS	7 (37%)	9 (20%)	7 (16%)
#ADRENAL	(20)	(48)	(48)
CORTICAL ADENOMA	2 (10%)		
CORTICAL CARCINOMA	1 (5%)		
PHEOCHROMOCYTOMA	1 (5%)	1 (2%)	3 (6%)
#THYROID	(20)	(49)	(47)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)
FOLLICULAR-CELL CARCINOMA		3 (6%)	2 (4%)
C-CELL ADENOMA		4 (8%)	
C-CELL CARCINOMA	1 (5%)		1 (2%)
#PANCREATIC ISLETS	(16)	(48)	(48)
ISLET-CELL ADENOMA	3 (19%)	2 (4%)	1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
ADENOCARCINOMA, NOS	1 (5%)		
FIBROSARCOMA		1 (2%)	
FIBROADENOMA		2 (4%)	
#TESTIS	(20)	(48)	(49)
INTERSTITIAL-CELL TUMOR	16 (80%)	40 (83%)	43 (88%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(49)	(48)
MENINGIOMA			1 (2%)
#BRAIN	(20)	(49)	(48)
ASTROCYTOMA	1 (5%)		1 (2%)
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(49)	(50)
SARCOMA, NOS			1 (2%)
BODY CAVITIES			
*BODY CAVITIES	(20)	(49)	(50)
MESOTHELIOMA, NOS			4 (8%)
*TUNICA VAGINALIS	(20)	(49)	(50)
MESOTHELIOMA, NOS		2 (4%)	4 (8%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	8	17	21
MORIBUND SACRIFICE		5	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	12	27	26
ANIMAL MISSING		1	
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	48	47
TOTAL PRIMARY TUMORS	46	104	104
TOTAL ANIMALS WITH BENIGN TUMORS	19	43	44
TOTAL BENIGN TUMORS	30	64	63
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	32	28
TOTAL MALIGNANT TUMORS	16	37	33
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	
TOTAL SECONDARY TUMORS	2	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		3	8
TOTAL UNCERTAIN TUMORS		3	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
KERATOACANTHOMA		1 (2%)	
FIBROSARCOMA		2 (4%)	
*SUBCUT TISSUE	(20)	(50)	(50)
LIPOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (5%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)		3 (6%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
C-CELL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)	2 (4%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	4 (20%)	12 (24%)	13 (26%)
ERYTHROCYTIC LEUKEMIA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
NEOPLASTIC NODULE			1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
#LARGE INTESTINE	(20)	(49)	(50)
ADENOMATOUS POLYP, NOS			1 (2%)
LEIOMYOSARCOMA	1 (5%)		
URINARY SYSTEM			
#URINARY BLADDER	(19)	(46)	(49)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(47)	(49)
ADENOMA, NOS	2 (10%)	19 (40%)	9 (18%)
#ADRENAL	(19)	(49)	(50)
CORTICAL ADENOMA			1 (2%)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA	1 (5%)	1 (2%)	2 (4%)
#THYROID	(20)	(48)	(48)
FOLLICULAR-CELL ADENOMA		2 (4%)	
FOLLICULAR-CELL CARCINOMA		1 (2%)	
C-CELL ADENOMA	3 (15%)	3 (6%)	7 (15%)
C-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(20)	(48)	(50)
ISLET-CELL ADENOMA	1 (5%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
PAPILLARY CYSTADENOCARCINOMA,NOS		1 (2%)	1 (2%)
FIBROMA			1 (2%)
FIBROADENOMA	3 (15%)	8 (16%)	9 (18%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(20)	(48)	(49)
ENDOMETRIAL STROMAL POLYP	4 (20%)	3 (6%)	7 (14%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)
#OVARY	(20)	(47)	(49)
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)		
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(50)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	10	3
MORIBUND SACRIFICE	2	2	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	15	38	43
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	40	39
TOTAL PRIMARY TUMORS	22	60	64
TOTAL ANIMALS WITH BENIGN TUMORS	12	27	30
TOTAL BENIGN TUMORS	16	38	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	20	22
TOTAL MALIGNANT TUMORS	6	22	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	
TOTAL SECONDARY TUMORS	1	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		2	
ANIMALS NECROPSIED	17	46	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	17	46	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(17)	(46)	(49)
FIBROSARCOMA		1 (2%)	
HEMANGIOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(17)	(46)	(46)
HEPATOCELLULAR CARCINOMA, METAST	1 (6%)	2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		14 (30%)	11 (24%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(17)	(46)	(49)
MALIGNANT LYMPHOMA, NOS	1 (6%)	1 (2%)	1 (2%)
#SPLEEN	(14)	(44)	(46)
HEMANGIOSARCOMA	1 (7%)		1 (2%)
MALIGNANT LYMPHOMA, NOS			3 (7%)
#MESENTERIC L. NODE	(17)	(43)	(43)
HEPATOCELLULAR CARCINOMA, METAST	1 (6%)		
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#PANCREAS	(17)	(46)	(46)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#SMALL INTESTINE	(17)	(46)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
*MESENTERY	(17)	(46)	(49)
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
CIRCULATORY SYSTEM			
#HEART	(17)	(46)	(46)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(17)	(46)	(49)
HEPATOCELLULAR CARCINOMA	8 (47%)	15 (33%)	16 (33%)
HEMANGIOSARCOMA			1 (2%)
#PANCREAS	(17)	(46)	(46)
HEMANGIOMA			1 (2%)
#ESOPHAGUS	(17)	(46)	(45)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#SMALL INTESTINE	(17)	(46)	(49)
ADENOCARCINOMA, NOS		4 (9%)	
URINARY SYSTEM			
#KIDNEY	(17)	(46)	(49)
CORTICAL CARCINOMA, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(17)	(45)	(47)
CORTICAL ADENOMA		1 (2%)	1 (2%)
CORTICAL CARCINOMA			1 (2%)
#THYROID	(17)	(45)	(44)
ADENOCARCINOMA, NOS			1 (2%)
FOLLICULAR-CELL ADENOMA		1 (2%)	
#PANCREATIC ISLETS	(17)	(46)	(46)
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(16)	(44)	(48)
CARCINOMA,NOS			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(17)	(46)	(49)
ADENOMA, NOS		16 (35%)	10 (20%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(17)	(46)	(49)
HEMANGIOSARCOMA			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	11	14
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	37	36
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*	10	39	35
TOTAL PRIMARY TUMORS	10	63	50
TOTAL ANIMALS WITH BENIGN TUMORS		18	12
TOTAL BENIGN TUMORS		21	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	30	33
TOTAL MALIGNANT TUMORS	10	42	38
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	3
TOTAL SECONDARY TUMORS	2	2	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	49	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(49)
FIBROSARCOMA		3 (6%)	
LIPOMA		2 (4%)	
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	1 (2%)
NEUROFIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(46)	(45)
PAPILLOMA, NOS		1 (2%)	
#LUNG	(19)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	4 (8%)	6 (13%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (11%)	5 (10%)	6 (13%)
OSTEOSARCOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	4 (20%)	4 (8%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	
#SPLEEN	(19)	(48)	(48)
HEMANGIOMA			3 (6%)
HEMANGIOSARCOMA		2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MANDIBULAR L. NODE	(18)	(43)	(46)
MALIGNANT LYMPHOMA, NOS			2 (4%)
#MESENTERIC L. NODE	(18)	(43)	(46)
MALIGNANT LYMPHOMA, NOS		2 (5%)	1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(19)	(49)	(48)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#SMALL INTESTINE	(19)	(48)	(45)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#KIDNEY	(19)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(19)	(49)	(48)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(48)
CARCINOMA, NOS, METASTATIC			1 (2%)
HEPATOCELLULAR CARCINOMA	1 (5%)	7 (14%)	10 (21%)
HEMANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(48)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	2 (4%)
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(46)	(46)
CORTICAL ADENOMA		3 (7%)	4 (9%)
#THYROID	(18)	(46)	(44)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(48)	(46)
LEIOMYOSARCOMA		1 (2%)	
#OVARY	(19)	(46)	(43)
GRANULOSA-CELL TUMOR		1 (2%)	2 (5%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(50)	(49)
ADENOMA, NOS		6 (12%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
*PUBIS	(20)	(50)	(49)
OSTEOSARCOMA	1 (5%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(49)
NEOPLASM, NOS		1 (2%)	
*PERITONEUM	(20)	(50)	(49)
MESOTHELIOMA, NOS		1 (2%)	
*ABDOMINAL VISCERA	(20)	(50)	(49)
NEUROFIBROSARCOMA, METASTATIC			1 (2%)
ALL OTHER SYSTEMS			
THORAX			
ALVEOLAR/BRONCHIOLAR CA, METASTA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	16	12
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	34	37
ANIMAL MISSING			1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	36	35
TOTAL PRIMARY TUMORS	9	53	51
TOTAL ANIMALS WITH BENIGN TUMORS	1	14	17
TOTAL BENIGN TUMORS	1	17	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	28	22
TOTAL MALIGNANT TUMORS	8	33	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		3
TOTAL SECONDARY TUMORS	1		3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		3	2
TOTAL UNCERTAIN TUMORS		3	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
EPIDERMAL INCLUSION CYST	2 (10%)		
*SUBCUT TISSUE	(20)	(49)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(20)	(49)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
#LUNG	(20)	(49)	(48)
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (15%)	4 (8%)	7 (15%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#ALVEOLAR EPITHELIUM	(20)	(49)	(48)
FOAM-CELL		3 (6%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(49)	(48)
EMBOLUS, SEPTIC			1 (2%)
INFARCT, NOS	1 (5%)	1 (2%)	
HEMOSIDEROSIS		3 (6%)	1 (2%)
LYMPHOID DEPLETION			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	3 (6%)	2 (4%)
HEMATOPOIESIS	1 (5%)	12 (24%)	5 (10%)
#MANDIBULAR L. NODE	(20)	(49)	(48)
LYMPHANGIECTASIS	1 (5%)	1 (2%)	3 (6%)
HYPERPLASIA, LYMPHOID		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
#MESENTERIC L. NODE	(20)	(49)	(48)
LYMPHANGIECTASIS	1 (5%)		
NECROSIS, FOCAL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#RENAL LYMPH NODE	(20)	(49)	(48)
HEMOSIDEROSIS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(19)	(49)	(48)
ENDOCARDITIS, BACTERIAL		1 (2%)	
PERIARTERITIS			1 (2%)
ENDOCARDIOSIS			1 (2%)
#HEART/ATRIUM	(19)	(49)	(48)
THROMBOSIS, NOS		2 (4%)	4 (8%)
#MYOCARDIUM	(19)	(49)	(48)
INFLAMMATION, FOCAL	1 (5%)		
FIBROSIS	2 (11%)		1 (2%)
FIBROSIS, FOCAL			1 (2%)
*PULMONARY ARTERY	(20)	(49)	(50)
MEDIAL CALCIFICATION	1 (5%)		
*MESENTERIC ARTERY	(20)	(49)	(50)
ARTERIOSCLEROSIS, NOS		1 (2%)	1 (2%)
*PORTAL VEIN	(20)	(49)	(50)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(47)
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
FIBROSIS		2 (4%)	
NECROSIS, FOCAL		9 (18%)	3 (6%)
METAMORPHOSIS FATTY	1 (5%)	1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION		5 (10%)	2 (4%)
HEPATOCYTOMEGALY	2 (11%)	3 (6%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL	2 (11%)	3 (6%)	
ANGIECTASIS			1 (2%)
HEMATOPOIESIS		2 (4%)	
NODULAR REGENERATION			1 (2%)
#PORTAL TRACT	(19)	(49)	(47)
FIBROSIS			1 (2%)
#LIVER/CENTRILOBULAR	(19)	(49)	(47)
NECROSIS, NOS			4 (9%)
NECROSIS, DIFFUSE			1 (2%)
CYTOPLASMIC VACUOLIZATION		3 (6%)	4 (9%)
#LIVER/PERIPORTAL	(19)	(49)	(47)
FIBROSIS		2 (4%)	3 (6%)
CYTOPLASMIC VACUOLIZATION		2 (4%)	
#LIVER/HEPATOCYTES	(19)	(49)	(47)
NECROSIS, FOCAL		1 (2%)	4 (9%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
*BILE DUCT	(20)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS	14 (70%)	39 (80%)	33 (66%)
#PANCREATIC ACINUS	(16)	(48)	(48)
ATROPHY, NOS	2 (13%)	1 (2%)	3 (6%)
ATROPHY, FOCAL	3 (19%)	15 (31%)	4 (8%)
#STOMACH	(18)	(49)	(47)
ULCER, NOS	1 (6%)	1 (2%)	
ULCER, ACUTE	1 (6%)	1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
#SMALL INTESTINE	(17)	(49)	(47)
CYST, NOS		1 (2%)	
#LARGE INTESTINE	(17)	(49)	(46)
NEMATODIASIS		3 (6%)	
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(48)
HYDRONEPHROSIS		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
EMBOLUS, SEPTIC			1 (2%)
PYELONEPHRITIS, ACUTE		2 (4%)	
INFLAMMATION, CHRONIC	15 (75%)	23 (47%)	23 (48%)
#KIDNEY/CORTEX	(20)	(49)	(48)
INFARCT, FOCAL		1 (2%)	
#KIDNEY/GLOMERULUS	(20)	(49)	(48)
THROMBOSIS, NOS		1 (2%)	
#KIDNEY/TUBULE	(20)	(49)	(48)
CYST, NOS			1 (2%)
PIGMENTATION, NOS			1 (2%)
HEMOSIDEROSIS			2 (4%)
#URINARY BLADDER	(17)	(47)	(46)
CALCULUS, NOS	1 (6%)		
CAST, NOS			5 (11%)
HEMORRHAGIC CYST		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(45)	(45)
CYST, NOS			1 (2%)
HEMORRHAGE			1 (2%)
#ADRENAL	(20)	(48)	(48)
NECROSIS, FOCAL		1 (2%)	
#ADRENAL CORTEX	(20)	(48)	(48)
EMBOLUS, SEPTIC			1 (2%)
LIPOIDOSIS	1 (5%)	2 (4%)	
HYPERPLASIA, FOCAL	1 (5%)	1 (2%)	
#THYROID	(20)	(49)	(47)
CYST, NOS			4 (9%)
CYSTIC FOLLICLES		3 (6%)	
HYPERPLASIA, C-CELL	8 (40%)	12 (24%)	7 (15%)
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
#THYROID FOLLICLE	(20)	(49)	(47)
HYPERPLASIA, CYSTIC	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
GALACTOCELE		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS		3 (6%)	4 (8%)
*PREPUTIAL GLAND	(20)	(49)	(50)
ABSCESS, NOS	1 (5%)	1 (2%)	
#PROSTATE	(17)	(48)	(47)
CAST, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE	7 (41%)	5 (10%)	2 (4%)
INFLAMMATION, ACUTE SUPPURATIVE		3 (6%)	2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
#TESTIS	(20)	(48)	(49)
INFARCT, NOS	1 (5%)		
ATROPHY, NOS	1 (5%)	3 (6%)	1 (2%)
ASPERMATOGENESIS		1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	1 (5%)	1 (2%)	2 (4%)
#TESTIS/TUBULE	(20)	(48)	(49)
ATROPHY, DISUSE		1 (2%)	
*EPIDIDYMIS	(20)	(49)	(50)
RETENTION OF CONTENT			1 (2%)
STEATITIS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(48)
MINERALIZATION			2 (4%)
EPIDERMAL INCLUSION CYST			1 (2%)
HEMORRHAGE		4 (8%)	3 (6%)
GLIOSIS		1 (2%)	
INFARCT, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(49)	(50)
STEATITIS		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
PERIARTERITIS			2 (4%)
*TUNICA VAGINALIS	(20)	(49)	(50)
STEATITIS	1 (5%)		1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
AMYLOIDOSIS			1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY		1	
AUTO/NECROPSY/HISTO PERF			1

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(20)	(49)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
#LUNG	(20)	(49)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		3 (6%)	5 (10%)
HYPERPLASIA, LYMPHOID	1 (5%)		
#ALVEOLAR EPITHELIUM	(20)	(49)	(50)
FOAM-CELL		3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(20)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (5%)		
#BONE MARROW	(20)	(49)	(50)
FIBROSIS		2 (4%)	
#SPLEEN	(20)	(49)	(50)
HEMOSIDEROSIS	5 (25%)	3 (6%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	3 (15%)	9 (18%)	6 (12%)
#MANDIBULAR L. NODE	(20)	(49)	(50)
LYMPHANGIECTASIS			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
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (5%)	1 (2%)	3 (6%)
#CARDIAC VALVE	(20)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEMORRHAGE			1 (2%)
GRANULOMA, NOS		1 (2%)	
CHOLANGIOFIBROSIS		1 (2%)	
NECROSIS, FOCAL		1 (2%)	2 (4%)
METAMORPHOSIS FATTY	1 (5%)	2 (4%)	
HEPATOCYTOMEGALY	2 (10%)	8 (16%)	10 (20%)
HYPERPLASIA, FOCAL	10 (50%)	23 (47%)	35 (70%)
HEMATOPOIESIS	1 (5%)		
REGENERATIVE NODULE		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(49)	(50)
CYTOPLASMIC VACUOLIZATION		4 (8%)	2 (4%)
#LIVER/PERIPORTAL	(20)	(49)	(50)
FIBROSIS		1 (2%)	
*BILE DUCT	(20)	(50)	(50)
INFLAMMATION, NOS			4 (8%)
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, CHRONIC		6 (12%)	16 (32%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, NOS	3 (15%)	10 (20%)	10 (20%)
#PANCREAS	(20)	(48)	(50)
PERIARTERITIS	1 (5%)		
NECROSIS, FAT		1 (2%)	
#PANCREATIC ACINUS	(20)	(48)	(50)
ATROPHY, NOS		1 (2%)	1 (2%)
ATROPHY, FOCAL	1 (5%)	7 (15%)	10 (20%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(20)	(49)	(50)
CYST, NOS		1 (2%)	
#LARGE INTESTINE	(20)	(49)	(50)
NEMATODIASIS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	5 (25%)	12 (24%)	11 (22%)
NEPHROSIS, CHOLEMIC		1 (2%)	
#KIDNEY/TUBULE	(20)	(49)	(50)
MINERALIZATION	1 (5%)	1 (2%)	
PIGMENTATION, NOS			2 (4%)
REGENERATION, NOS	1 (5%)		
#URINARY BLADDER	(19)	(46)	(49)
INFLAMMATION, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(47)	(49)
CYST, NOS	1 (5%)	5 (11%)	4 (8%)
ANGIECTASIS	2 (10%)	1 (2%)	2 (4%)
#ADRENAL	(19)	(49)	(50)
LIPOIDOSIS			2 (4%)
#ADRENAL CORTEX	(19)	(49)	(50)
ATROPHY, DIFFUSE		1 (2%)	
HYPERPLASIA, NODULAR	1 (5%)		
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL		2 (4%)	1 (2%)
HYPERPLASIA, DIFFUSE			1 (2%)
#ADRENAL MEDULLA	(19)	(49)	(50)
ANGIECTASIS	1 (5%)		
#THYROID	(20)	(48)	(48)
GRANULOMA, 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
HYPERPLASIA, C-CELL	8 (40%)	10 (21%)	31 (65%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
GALACTOCELE		1 (2%)	1 (2%)
HYPERPLASIA, NOS	2 (10%)		
#UTERUS/ENDOMETRIUM	(20)	(48)	(49)
CYST, NOS	1 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC		3 (6%)	1 (2%)
#OVARY/PAROVARIAN	(20)	(48)	(49)
HEMATOMA, NOS			1 (2%)
#OVARY	(20)	(47)	(49)
CYSTIC FOLLICLES	1 (5%)	5 (11%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(50)	(50)
THROMBOSIS, NOS	1 (5%)		
#BRAIN	(20)	(50)	(50)
MINERALIZATION			1 (2%)
HYDROCEPHALUS, NOS	1 (5%)		
HEMORRHAGE	1 (5%)	2 (4%)	2 (4%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
CATARACT		1 (2%)	
*EYE/CRYSTALLINE LENS	(20)	(50)	(50)
CATARACT	1 (5%)	1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
STEATITIS	1 (5%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
GRANULATION, TISSUE		1 (2%)	
PERIARTERITIS		2 (4%)	
ALL OTHER SYSTEMS			
OMENTUM			
STEATITIS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
AUTO/NECROPSY/HISTO PERF		1	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		2	
ANIMALS NECROPSIED	17	46	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	17	46	49
INTEGUMENTARY SYSTEM			
*SKIN	(17)	(46)	(49)
CYST, NOS			1 (2%)
*SUBCUT TISSUE	(17)	(46)	(49)
ABSCESS, NOS			2 (4%)
RESPIRATORY SYSTEM			
#TRACHEA	(17)	(46)	(45)
HEMATOPOIESIS		1 (2%)	
#LUNG	(17)	(46)	(46)
HEMORRHAGE			2 (4%)
INFLAMMATION, NOS			1 (2%)
PIGMENTATION, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(17)	(46)	(49)
HYPOPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(14)	(44)	(46)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	3 (21%)	7 (16%)	10 (22%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(17)	(46)	(49)
INFLAMMATION, FOCAL		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
NECROSIS, FOCAL			1 (2%)
HYPERPLASIA, NODULAR	1 (6%)	1 (2%)	4 (8%)
ANGIECTASIS		2 (4%)	
HEMATOPOIESIS			1 (2%)
#PANCREAS	(17)	(46)	(46)
CYSTIC DUCTS		1 (2%)	
ATROPHY, NOS		1 (2%)	
#STOMACH	(17)	(45)	(49)
INFLAMMATION, FOCAL			2 (4%)
#SMALL INTESTINE	(17)	(46)	(49)
POLYP		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(17)	(46)	(49)
HYDRONEPHROSIS		2 (4%)	
INFLAMMATION, INTERSTITIAL	1 (6%)		
#KIDNEY/CORTEX	(17)	(46)	(49)
CYST, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(15)	(39)	(38)
CYST, NOS			1 (3%)
#THYROID	(17)	(45)	(44)
CYSTIC FOLLICLES			1 (2%)
#PANCREATIC ISLETS	(17)	(46)	(46)
HYPERPLASIA, NOS	2 (12%)		1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(17)	(46)	(49)
CYST, NOS	1 (6%)		
*SEMINAL VESICLE	(17)	(46)	(49)
CAST, 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
#TESTIS	(16)	(46)	(48)
ATROPHY, NOS	2 (13%)	4 (9%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(17)	(46)	(46)
MINERALIZATION	7 (41%)	22 (48%)	21 (46%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	1	4
ANIMAL MISSING/NO NECROPSY		2	
AUTO/NECROPSY/HISTO PERF			1
AUTOLYSIS/NO NECROPSY	3	2	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	49	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(19)	(49)	(48)
HYPERPLASIA, NOS		3 (6%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#LUNG	(19)	(49)	(48)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(48)	(46)
HYPOPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(19)	(48)	(48)
ANGIECTASIS	1 (5%)		
HYPERPLASIA, LYMPHOID		2 (4%)	
HEMATOPOIESIS	7 (37%)	10 (21%)	9 (19%)
#THYMUS	(19)	(46)	(46)
HYPERPLASIA, LYMPHOID			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(48)
CYST, 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
INFLAMMATION, FOCAL	1 (5%)		
NECROSIS, FOCAL		2 (4%)	
INFARCT, HEALED			1 (2%)
HYPERPLASIA, NODULAR	1 (5%)	3 (6%)	4 (8%)
ANGIECTASIS	1 (5%)	1 (2%)	3 (6%)
#PANCREAS	(19)	(48)	(42)
CYSTIC DUCTS	1 (5%)		1 (2%)
ATROPHY, NOS		1 (2%)	2 (5%)
#STOMACH	(19)	(48)	(47)
INFLAMMATION, NOS	1 (5%)		
INFLAMMATION, FOCAL	1 (5%)		
#SMALL INTESTINE	(19)	(48)	(45)
POLYP, INFLAMMATORY			1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(48)
PERIVASCULAR CUFFING	2 (11%)	2 (4%)	1 (2%)
#KIDNEY/CORTEX	(19)	(49)	(48)
CYST, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(43)	(38)
CYST, NOS		1 (2%)	
#ADRENAL CORTEX	(19)	(46)	(46)
HYPERPLASIA, NODULAR			1 (2%)
#THYROID	(18)	(46)	(44)
CYSTIC FOLLICLES		2 (4%)	2 (5%)
ATROPHY, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(48)	(46)
POLYP, INFLAMMATORY	1 (5%)		
#UTERUS/ENDOMETRIUM	(19)	(48)	(46)
CYST, NOS	8 (42%)	8 (17%)	3 (7%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(19)	(46)	(43)
CYST, NOS	3 (16%)	6 (13%)	11 (26%)
NERVOUS SYSTEM			
#BRAIN	(19)	(48)	(48)
MINERALIZATION	4 (21%)	24 (50%)	25 (52%)
HYDROCEPHALUS, NOS		2 (4%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1
ANIMAL MISSING/NO NECROPSY			1
AUTO/NECROPSY/HISTO PERF		1	1
AUTO/NECROPSY/NO HISTO	1	1	1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED ETHYL TELLURAC IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	1/20 (5)	3/49 (6)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.224	1.200
Lower Limit		0.108	0.106
Upper Limit		62.958	61.724
Weeks to First Observed Tumor	105	95	102
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	0/20 (0)	1/49 (2)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.023	0.261
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma (b)	7/20 (35)	27/49 (55)	24/50 (48)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.574	1.371
Lower Limit		0.835	0.713
Upper Limit		3.604	3.217
Weeks to First Observed Tumor	98	82	62
Pituitary: Adenoma, NOS (b)	7/19 (37)	9/45 (20)	7/45 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.543	0.422
Lower Limit		0.222	0.155
Upper Limit		1.500	1.241
Weeks to First Observed Tumor	101	95	101

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Adrenal: Cortical Carcinoma or Adenoma (b)	3/20 (15)	0/48 (0)	0/48 (0)
P Values (c,d)	P = 0.005 (N)	P = 0.023 (N)	P = 0.023 (N)
Departure from Linear Trend (e)	P = 0.016		
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		0.686	0.686
Weeks to First Observed Tumor	75	--	--
Adrenal: Pheochromocytoma (b)	1/20 (5)	1/48 (2)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.417	1.250
Lower Limit		0.006	0.110
Upper Limit		32.058	64.251
Weeks to First Observed Tumor	105	105	84

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma (b)	0/20 (0)	3/49 (6)	2/47 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.255	0.131
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	87	105
Thyroid: Follicular-cell Carcinoma or Adenoma (b)	0/20 (0)	4/49 (8)	3/47 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.394	0.266
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	87	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell			
Carcinoma or Adenoma (b)	1/20 (5)	4/49 (8)	1/47 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.633	0.426
Lower Limit		0.179	0.006
Upper Limit		78.704	32.720
Weeks to First Observed Tumor	105	105	101
Pancreatic Islets: Islet-cell			
Adenoma (b)	3/16 (19)	2/48 (4)	1/48 (2)
P Values (c,d)	P = 0.027 (N)	N.S.	P = 0.045 (N)
Relative Risk (f)		0.222	0.111
Lower Limit		0.021	0.002
Upper Limit		1.808	1.296
Weeks to First Observed Tumor	105	105	103

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor (b)	16/20 (80)	40/48 (83)	43/49 (88)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.042	1.097
Lower Limit		0.830	0.880
Upper Limit		1.432	1.457
Weeks to First Observed Tumor	76	82	62
Body Cavities: Mesothelioma, NOS (b)	0/20 (0)	0/49 (0)	4/50 (8)
P Values (c,d)	P = 0.041	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.386
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	96

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Tunica Vaginalis: Mesothelioma, NOS (b)	0/20 (0)	2/49 (4)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.125	0.386
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	82	88
All Sites: Mesothelioma, NOS (b)	0/20 (0)	2/49 (4)	8/50 (16)
P Values (c,d)	P = 0.012	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Upper Limit		0.125	0.952
Lower Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	82	88

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Ethyl Tellurac 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 control group is the probability level for the Cochran-Armitage test when P is less than 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 is less than 0.05; otherwise, not significant (N.S.) is indicated.

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

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Ethyl Tellurac in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	2/20 (10)	0/49 (0)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.040		
Relative Risk (f)		0.000	0.600
Lower Limit		0.000	0.076
Upper Limit		1.372	6.860
Weeks to First Observed Tumor	105	--	98
Hematopoietic System: Lymphoma or Leukemia (b)	4/20 (20)	15/50 (30)	16/50 (32)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.500	1.600
Lower Limit		0.566	0.613
Upper Limit		5.627	5.950
Weeks to First Observed Tumor	97	47	74

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	2/20 (10)	19/47 (40)	9/49 (18)
P Values (c,d)	N.S.	P = 0.012	N.S.
Departure from Linear Trend (e)	P = 0.003		
Relative Risk (f)		4.043	1.837
Lower Limit		1.134	0.434
Upper Limit		33.427	16.572
Weeks to First Observed Tumor	99	81	91
Thyroid: Follicular-cell Carcinoma or Adenoma (b)	0/20 (0)	3/48 (6)	0/48 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.044		
Relative Risk (f)		Infinite	--
Lower Limit		0.261	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	105	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell			
Carcinoma or Adenoma (b)	3/20 (15)	4/48 (8)	7/48 (15)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.556	0.972
Lower Limit		0.106	0.255
Upper Limit		3.546	5.422
Weeks to First Observed Tumor	105	105	105
Mammary Gland: Fibroadenoma (b)	3/20 (15)	8/50 (16)	9/50 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.067	1.200
Lower Limit		0.295	0.346
Upper Limit		5.813	6.408
Weeks to First Observed Tumor	80	92	104

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	4/20 (20)	3/48 (6)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.313	0.714
Lower Limit		0.051	0.211
Upper Limit		1.708	3.052
Weeks to First Observed Tumor	80	105	105

(a) Dosed groups received 150 or 300 ppm.

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

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

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

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED ETHYL TELLURAC IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Ethyl Tellurac in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/17 (0)	14/46 (30)	11/46 (24)
P Values (c,d)	N.S.	P = 0.006	P = 0.022
Departure from Linear Trend (e)	P = 0.021		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.703	1.296
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	87	82
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	0/17 (0)	16/46 (35)	11/46 (24)
P Values (c,d)	N.S.	P = 0.003	P = 0.022
Departure from Linear Trend (e)	P = 0.007		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.976	1.296
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	87	82

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma (b)	1/17 (6)	6/46 (13)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.217	1.388
Lower Limit		0.306	0.154
Upper Limit		99.570	66.919
Weeks to First Observed Tumor	86	91	91
All Sites: Hemangiosarcoma (b)	1/17 (6)	1/46 (4)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.370	1.041
Lower Limit		0.005	0.093
Upper Limit		28.408	53.527
Weeks to First Observed Tumor	106	106	85

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma (b)	1/17 (6)	2/46 (4)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.739	1.388
Lower Limit		0.042	0.154
Upper Limit		42.678	66.919
Weeks to First Observed Tumor	106	106	85
Liver: Hepatocellular Carcinoma (b)	8/17 (47)	15/46 (33)	16/49 (33)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.693	0.694
Lower Limit		0.362	0.367
Upper Limit		1.592	1.585
Weeks to First Observed Tumor	106	96	81

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Small Intestine: Adenocarcinoma, NOS (b)	0/17 (0)	4/46 (9)	0/49 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.029		
Relative Risk (f)		Infinite	--
Lower Limit		0.361	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	106	--
Eye/Lacrimal Gland: Adenoma, NOS (b)	0/17 (0)	16/46 (35)	10/49 (20)
P Values (c,d)	N.S.	P = 0.003	P = 0.039
Departure from Linear Trend (e)	P = 0.004		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.976	1.089
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	106	106

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

(a) Dosed groups received time-weighted average doses of 1,255 or 3,132 ppm.

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

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

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

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Ethyl Tellurac in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma of the Subcutaneous Tissue (b)	0/20 (0)	3/50 (6)	0/49 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.250	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	101	--
Lung: Alveolar/Bronchiolar Carcinoma (b)	2/19 (11)	5/49 (10)	6/48 (13)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.969	1.188
Lower Limit		0.180	0.242
Upper Limit		9.685	11.426
Weeks to First Observed Tumor	106	101	97

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	3/19 (16)	9/49 (18)	12/48 (25)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.163	1.583
Lower Limit		0.338	0.502
Upper Limit		6.195	8.066
Weeks to First Observed Tumor	106	95	97
Hematopoietic System: Lymphoma (b)	4/20 (20)	11/50 (22)	9/49 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.100	0.918
Lower Limit		0.384	0.300
Upper Limit		4.321	3.730
Weeks to First Observed Tumor	83	82	75

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangioma (b)	0/20 (0)	1/50 (2)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.022	0.255
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	100	94
All Sites: Hemangiosarcoma (b)	0/20 (0)	4/50 (8)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.386	0.023
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	103	93

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangioma or Hemangiosarcoma (b)	0/20 (0)	5/50 (10)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.525	0.394
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	100	93
Liver: Hepatocellular Carcinoma (b)	1/19 (5)	7/49 (14)	10/48 (21)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.714	3.958
Lower Limit		0.393	0.639
Upper Limit		119.544	167.483
Weeks to First Observed Tumor	106	86	62

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Adrenal: Cortical Adenoma (b)	0/19 (0)	3/46 (7)	4/46 (9)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.259	0.400
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	106	97
Ovary: Granulosa-cell Tumor (b)	0/19 (0)	1/46 (2)	2/43 (5)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.023	0.136
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	106	106

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Ethyl Tellurac in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Eye/Lacrimal Gland: Adenoma, NOS (b)	0/20 (0)	6/50 (12)	5/49 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.667	0.536
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	106	106

(a) Dosed groups received time-weighted average doses of 2,132 or 4,915 ppm.

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

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

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

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

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

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

December 13, 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 on the Institute's bioassay program to identify and 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, and State health officials. 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 Ethyl Tellurac.

The reviewer for the report on the bioassay of Ethyl Tellurac briefly described the experimental design, and said that the statistical analysis required the use of historic controls, because of the small matched control group size. A dose-related increase of mesotheliomas occurred in treated rats, although it was not statistically significant. The reviewer questioned if the finding was sufficient to call it "suggestive of carcinogenicity," as concluded in the report. An increase in the incidence of adenomas of the lacrimal gland was also found in treated mice, which was statistically significant when compared to historic controls. The reviewer opined that the findings were probably not adequate for basing a firm conclusion of carcinogenicity.

A discussion ensued in which there was general agreement that the evidence supported a conclusion that an effect was induced by Ethyl Tellurac. However, the effect was not sufficiently strong or of such a nature to conclude that the compound was carcinogenic. One Subgroup member emphasized that the major finding was benign tumors of the lacrimal gland in mice. Since the natural progression of this tumor type is unknown, he argued that it was not possible to draw any conclusion on the carcinogenicity of Ethyl Tellurac. He recommended that a revised conclusion not include the term "carcinogenic." It was agreed that the Program staff would revise the language in the report's conclusion so as to reflect the substance of the Subgroup's discussion.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

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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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