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BIOASSAY OF TETRAETHYLTHIURAM DISULFIDE FOR POSSIBLE CARCINOGENICITY

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

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FOREWORD: This report presents the results of the bioassay of tetraethylthiuram disulfide 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 a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a 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 found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of tetraethylthiuram disulfide was conducted at 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. Histopathologic evaluations for rats and mice were performed by Dr. R. U. Turnquist. The diagnoses included in this report represent his interpretations.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (3). Statistical analyses were performed by Dr. J. R. Joiner (4) and Ms. P. L. Yong (4), using methods selected for the bioassay program by Dr. J. J. Gart (5). The chemicals used in this bioassay were analyzed at FCRC by Dr. W. Zielinsky (1). The chemical analyses were reviewed and approved by Dr. W. Lijinsky (1).

This report was prepared at Tracor Jitco (4) 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 experiment, 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 technical-grade of tetraethylthiuram disulfide for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered tetraethylthiuram disulfide in the diet at one of two doses, either 300 or 600 ppm, for 107 weeks. Groups of 50 mice of each sex were administered the test chemical at one of two doses, either 500 or 2,000 ppm for the males and either 100 or 500 ppm for the females, for 108 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the ends of the periods of administration of the test chemical.

Mean body weights of the dosed rats and mice of each sex were lower than those of corresponding controls and were dose related throughout most of the bioassay. Mortality was not significantly affected by administration of the test chemical to either the rats or the mice, except for the female rats, in which the mortality was higher in the control group than in the dosed groups; however, the survival at the end of the bioassay was 65% or greater in all dosed and control groups of rats and mice of either sex, and sufficient numbers of animals were at risk in each group for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in dosed groups than in corresponding control groups.

It is concluded that under the conditions of this bioassay, tetraethylthiuram disulfide was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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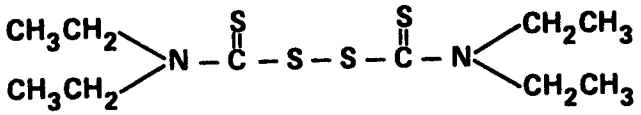
I. INTRODUCTION



TETRAETHYLTHIURAM DISULFIDE

Tetraethylthiuram disulfide (CAS 97-77-8; NCI C02959), is known in the rubber industry as ethyl tuads, where it is used in compounding natural rubber and the synthetic elastomers isobutylene-isoprene, butadiene, styrene-butadiene, isoprene, and nitrile-butadiene rubber (Del Gatto, 1968). It is used both as a rubber accelerator and vulcanizing agent, as an activator of thiazole accelerators, and as a plasticizer in neoprene (Shaver, 1968; Barnhart, 1968). Current estimates indicate that 510,000 to 550,000 kilograms of chemical are produced annually world wide (International Agency for Research on Cancer, 1977).

Pharmaceutical-grade tetraethylthiuram disulfide is known as disulfiram (National Formulary, 1975). The severe

cardiovascular effects that are experienced when persons taking this compound ingest alcohol were investigated in 1947 by Danish physicians, whose work led to the use of disulfiram in certain cases of chronic alcoholism (Hald et al., 1948). This acetaldehyde syndrome, or hypersensitivity to alcohol, is characterized by vasodilatation, a fall in blood pressure, flushes, headaches, and respiratory difficulty (Ritchie, 1975). High blood levels of acetaldehyde result from the inhibition of aldehyde dehydrogenase, which catalyzes the final step in the metabolism of ethanol to acetic acid, (Goldstein et al., 1974). Disulfiram also inhibits dopamine β-hydroxylase, which is essential for the metabolism of dopamine to norepinephrine; it has also been found to inhibit microsomal enzymes in the liver (Schmähl et al., 1976).

The acute oral LD_{50} for disulfiram has been reported to be 8.6 g/kg in Wistar rats (Child and Crump, 1952), and 12 g/kg in white mice (Kirchheim, 1951). Some investigators have noted ataxia, hypothermia and flaccid paralysis in severely poisoned animals (Child and Crump, 1952), and others have reported ataxia in animals fed 2,500 ppm for 8 weeks (Fitzhugh et al., 1952).

Chronic testing of tetraethylthiuram disulfide in hybrid mice was carried out by NCI in the 1960's because of its extensive use in industry (Innes et al., 1969). They obtained an increased

incidence of tumors that could not clearly be associated with administration of the test chemical; thus the compound was selected for study by the Carcinogenesis Testing Program using an expanded bioassay.

II. MATERIALS AND METHODS

A. Chemical

Technical-grade tetraethylthiuram disulfide was obtained from R. T. Vanderbilt as an off-white solid. Its purity was estimated by high-pressure liquid chromatography to be 94.6%, with eight impurities (one greater than 1%). The material had a melting point range of 68 to 70°C, (literature: 72°C; Del Gatto, 1968), and its infrared spectrum was consistent with its chemical structure. Mass spectral analysis showed no molecular ion, and a base peak at 60 m/e. Elemental analysis showed 40.6% carbon, 6.6% hydrogen, and 9.6% nitrogen (theoretical: 40.5% C, 6.7% H, and 9.4% N).

B. Dietary Preparation

Test diets containing tetraethylthiuram disulfide were prepared fresh every 1 to 1-1/2 weeks in 6- to 12-kilogram batches at appropriate doses. 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 with an intensifer bar. Uniformity of the mixtures was established by comparative analysis of samples taken from three different locations within the blender.

The diets were stored at 7°C in plastic bags 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. The animals were housed within the test facility for 2 weeks and then 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. For use in the chronic study, the male rats weighed 90 to 105 g, averaging at least 100 g; the female rats, 80 to 95 g, averaging at least 90 g; the male mice, 18 to 22 g, averaging at least 19.5 g; and the female mice, 17 to 21 g, averaging at least 18.5 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 at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from glass bottles. Sipper tubes (Lab Products, Inc.) were 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 twice per week and the feed hoppers twice per month at 82 to 88°C in a tunnel-type cagewasher (Industrial Washing Corp., Mataway, N.J.), using the detergents, Clout® (Pharmacal Research Laboratories, Greenwich, Conn.) or Oxford D'Chlor (Oxford Chemicals, Atlanta, Ga.). 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 Supply Co.) once per month, using the Calgen Commercial Division detergent, and the filter paper was changed at the same time.

Animal rooms were maintained at 22 to 24°C and 45 to 55% relative humidity. Incoming air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake, and was expelled without recirculation 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.). The 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 tetraethylthiuram disulfide and their corresponding controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 20941-65-5) ethyl tellurac
(CAS 19010-66-3) lead dimethyldithiocarbamate

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

(CAS 128-37-0) butylated hydroxytoluene (BHT)
(CAS 128-4-7) sodium diethyldithiocarbamate
(CAS 3165-93-3) 4-chloro-o-toluidine hydrochloride
(CAS 195-53-4) o-toluidine hydrochloride

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of tetraethylthiuram disulfide, on the basis of which two concentrations (referred to in this report as as "low" and "high" doses) were selected for administration in the chronic studies. Groups of 5 rats of each sex and groups of 10 male mice and 5 female mice were fed diets containing tetraethylthiuram disulfide at one of several doses for 7 weeks, and groups of 5 or 10 control animals, respectively, of each species and sex were administered basal diet only. Each animal was weighed twice per week.

Table 1 shows the number of animals in each dosed group at the

end of the course of administration and the mean body weights of dosed animals at week 7, expressed as percentages of mean body weights of controls. At the end of the subchronic studies, all animals were killed using CO_2 and necropsied.

Ten percent depression in body weight was the major criterion for estimation of MTD's since survival was adequate in all groups. The doses required to produce this response were determined by the following procedure: first, least squares regressions of mean body weights versus days on study were used to estimate mean body weights of each of the dosed groups at day 49. Next, probits of the percent weights of dosed groups at day 49 relative to weights of corresponding control groups were plotted against the logarithms of the doses, and least squares regressions fitted to the data were used to estimate the doses required to induce 10% depression in weight.

The low and high doses for chronic studies using male and female rats were set at 300 and 600 ppm; using male mice, 500 and 2,000 ppm, and using female mice, 100 and 500 ppm.

Table 1. Tetraethylthiuram Disulfide Subchronic Feeding Studies in Rats and Mice

Dose (ppm)	Male		Female	
	Survival (a)	Mean Weight at Week 7 as % of Control	Survival (a)	Mean Weight at Week 7 as % of Control
RATS				
0	5/5	100	5/5	100
1,500	5/5	78	5/5	83
2,200	5/5	75	5/5	75
3,200	5/5	69	5/5	75
4,600	5/5	63	5/5	63
6,800	4/5	51	5/5	58
MICE				
0	10/10	100		
2,000	10/10	82		
3,000	9/10	85		
4,000	10/10	80		
4,500	10/10	80		
5,000	10/10	81		
6,000	10/10	77		
8,000	10/10	78		
0			5/5	100
250			5/5	98
500			4/5	92
1,000			5/5	89
1,500			5/5	83
2,000			5/5	91
2,500			5/5	91
5,000			5/5	88
10,000			5/5	74

(a) Number surviving/number in group.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3.

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Observations on 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 animals 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% buffered 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

Table 2. Tetraethylthiuram Disulfide Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Tetraethyl-thiuram Disulfide in Diet (b) (ppm)	Time on Study (weeks)
Males			
Matched-Control	20	0	107
Low-Dose	50	300	107
High-Dose	50	600	107
Females			
Matched-Control	20	0	107
Low-Dose	50	300	107
High-Dose	50	600	107

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

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

Table 3. Tetraethylthiuram Disulfide Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Tetraethyl-thiuram Disulfide in Diet (b) (ppm)	Time on Study (weeks)
Males			
Matched-Control	20	0	108
Low-Dose	50	500	108
High-Dose	50	2,000	108
Females			
Matched-Control	20	0	108
Low-Dose	50	100	108
High-Dose	50	500	108

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

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

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 by autolysis or severe cannibalization. A few tissues from some animals were not examined, particularly from those animals that may have died early, been missing, or been in advanced states of cannibalization or autolysis. 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 included 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 statisticlly 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 for the departure from linearity test, which is only reported when its two-tailed P values is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

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

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first observed 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 dosed male and female rats were lower than those of corresponding controls and were dose related throughout the bioassay (figure 1). Other clinical signs occurred at comparable frequencies in the dosed and control groups of animals.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered tetraethylthiuram disulfide in the diet at the doses of this bioassay, together with those for the matched controls, are shown in the Kaplan and Meier curves in figure 2. In male rats, the result of the Tarone test for dose-related trend in mortality is not significant. In females, the result of the Tarone test is significant ($P = 0.005$), but in the negative direction.

In male rats, 36/50 (72%) of the high-dose group, 39/50 (78%) of the low-dose group, and 13/20 (65%) of the control group lived to

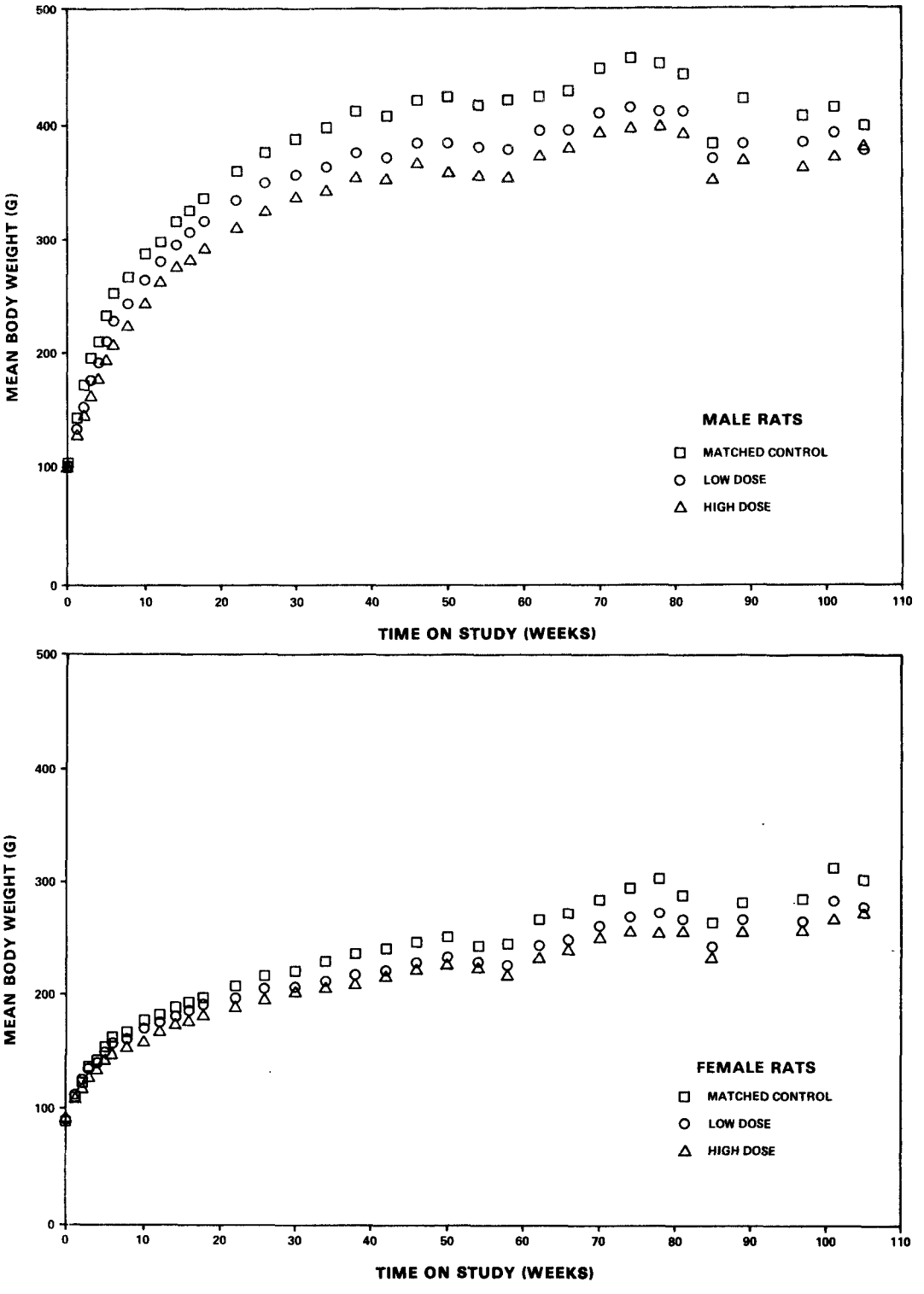


Figure 1. Growth Curves for Rats Administered Tetraethylthiuram disulfide in the Diet

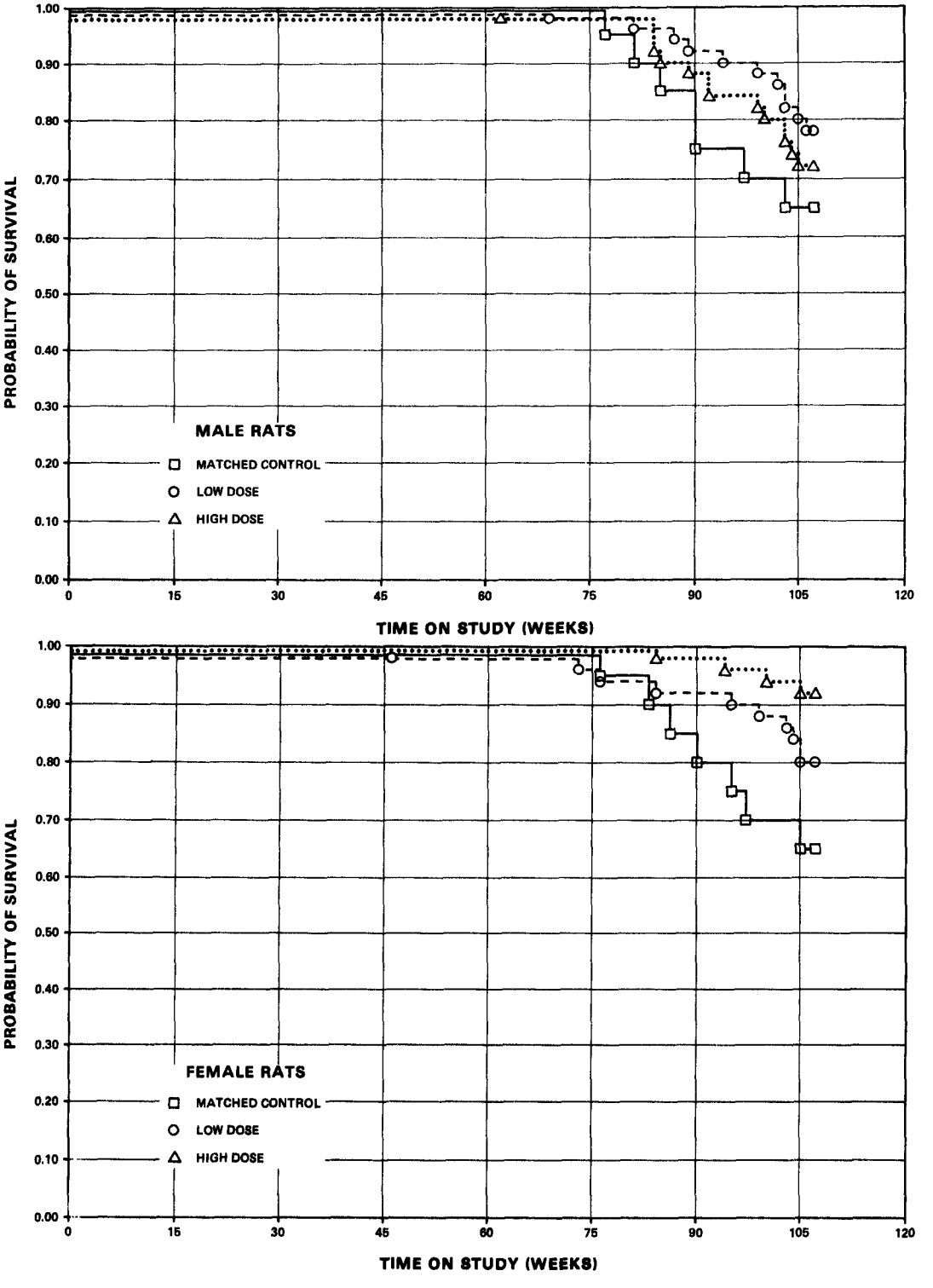


Figure 2. Survival Curves for Rats Administered Tetraethylthiuram disulfide in the Diet

the end of the bioassay. In females, 46/50 (92%) of the high-dose group, 40/50 (80%) of the low-dose group, and 13/20 (65%) 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.

A variety of neoplastic changes were noted in the control and dosed rats. There was no apparent relationship between the incidence of neoplasms and the administration of the test compound.

Several nonneoplastic changes were observed in the dosed and control groups. These findings included degenerative, inflammatory, and cystic lesions which are usually observed in aged male and female rats.

Based on the histopathologic examination, there was no evidence for the carcinogenicity of tetraethylthiuram disulfide 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 groups.

The results of the Cochran Armitage test for positive dose-related trend in tumor incidence and the results of the Fisher exact test comparing the tumor incidences in the control group with those in each dosed group in the positive direction are not significant in either sex.

Significant results in the negative direction are observed in the incidences of pituitary tumors in each sex of rat and in the incidences of tumors of the pituitary, the thyroid, and the mammary gland in female rats.

In each of the 95% confidence intervals for relative risk, shown

in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that some of the intervals have an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by tetraethylthiuram disulfide, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed male and female mice were lower than those of corresponding controls and were dose related throughout most of the bioassay (figure 3). Other clinical signs occurred at comparable incidences in dosed and control groups.

B. Survival (Mice)

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

In male mice, 46/50 (92%) of the high-dose group, 43/50 (86%) of the low-dose group, and 13/20 (65%) of the control group lived to the end of the bioassay. In females, 44/50 (88%) of the high-dose

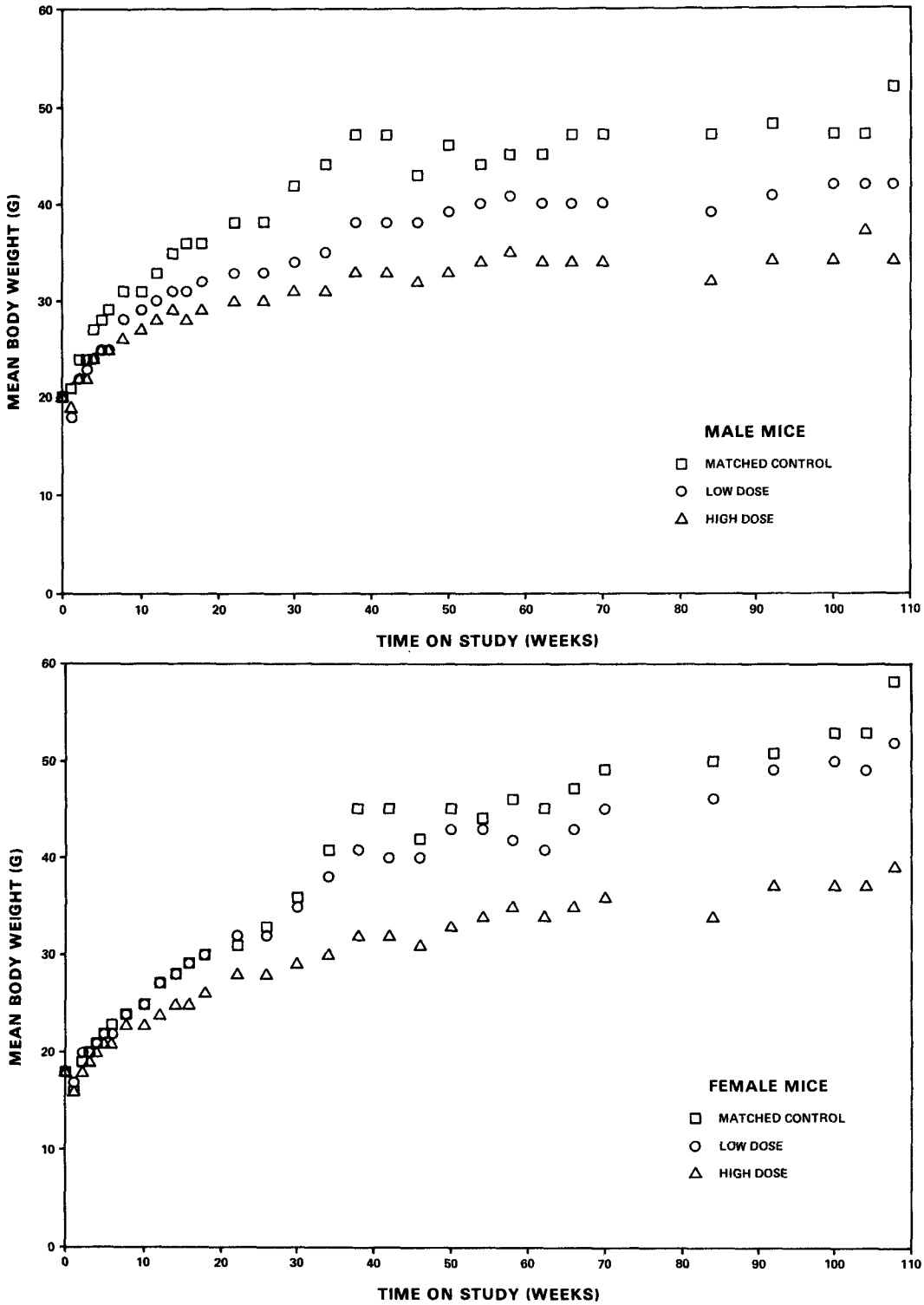


Figure 3. Growth Curves for Mice Administered Tetraethylthiuram disulfide in the Diet

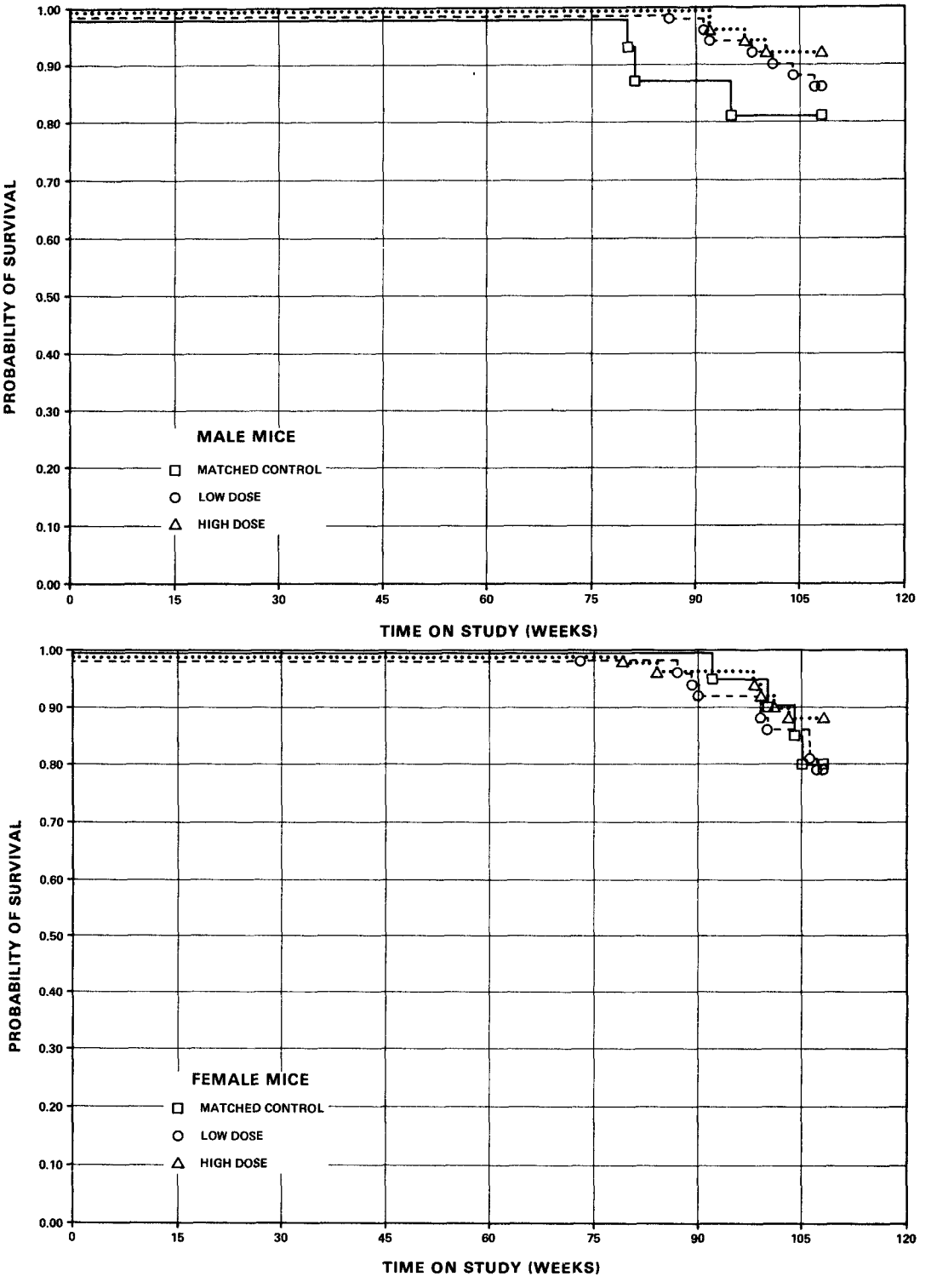


Figure 4. Survival Curves for Mice Administered Tetraethylthiuram disulfide in the Diet

group, 39/50 (78%) of the low-dose group, and 16/20 (80%) 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 neolasms 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 incidence and type of neoplasms observed in control and dosed animals were those commonly seen in B6C3F1 mice.

The large number of degenerative, proliferative, and inflammatory lesions which were detected in animals of the dosed and control groups are commonly seen in aged B6C3F1 mice.

Based on the histopathologic examination, there was no evidence for the carcinogenicity of tetraethylthiuram disulfide 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 female mice, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of animals with either alveolar/bronchiolar adenoma or carcinoma is significant ($P = 0.036$), but the results of the Fisher exact test are not significant.

Significant results in the negative direction are observed in the combined incidence of alveolar/bronchiolar adenoma and carcinoma and in the combined incidence of hepatocellular adenoma or carcinoma in male mice, in which the incidences in the control group exceed those in the dosed groups.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors

by tetraethylthiuram disulfide, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of the dosed rats and mice of each sex were lower than those of the corresponding controls and were dose related throughout most of the bioassay. Mortality was not significantly affected by administration of the test chemical to either the rats or the mice; however, for female rats mortality was higher in the control group than in the dosed groups. Survival at the end of the bioassay was 65% or greater in all dosed and control groups of rats and mice of either sex, and sufficient numbers of animals were at risk in each group for the development of late-appearing tumors.

Alveolar/bronchiolar adenomas or carcinomas occurred in the female mice at incidences that were dose related ($P = 0.036$); however, in direct comparisons the incidences of these tumors in the individual dosed groups were not significantly higher than that in the control group. Thus, the occurrence of tumors of the lung in the female mice cannot be clearly related to the administration of the test chemical.

No tumors occurred in rats or male mice at incidences that were

significantly higher in dosed groups than in corresponding control groups.

In previous tests for tumorigenicity, tetraethylthiuram disulfide was administered by stomach tube daily for 3 weeks at 100 mg/kg body weight, and then in the diet at 323 ppm for 18 months, to hybrid mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR). An elevated incidence of hepatomas in 8/17 dosed mice compared with 8/79 controls (P less than 0.001) was observed in the males of the first hybrid (NTIS, 1968, Innes et al., 1969; International Agency for Research on Cancer, 1977). When the test chemical was administered by stomach tube twice weekly for an unspecified number of weeks at 500 mg/kg body weight to Sprague-Dawley rats, no tumors developed in any of the animals except two animals that developed interstitial-cell tumors of the testis (Schmahl et al., 1976). Administration of tetraethylthiuram disulfide to rats or mice has been reported to reduce the toxicities of N-nitrosodimethylamine and of N-nitrosodiethylamine in these species and to reduce the incidences of liver tumor induction but not that of other types of tumors induced by the two nitrosamines in these species (Schmähl et al., 1976). On the other hand, it must be noted that tetraethylthiuram disulfide can react with nitrite to form N-nitrosodiethylamines (Lijinsky, 1972). It has also been reported to inhibit neoplasia of the forestomach caused in mice

by polycyclic aromatic hydrocarbons and neoplasia of the large intestine caused in mice by dimethylhydrazine (Wattenberg, 1975). In NIOSH-sponsored research currently in progress, laboratory rats exposed to 20 ppm ethylene dibromide by inhalation (the current TWA OSHA exposure standard) and also receiving a diet containing 0.05% tetraethylthiuram disulfide have high mortality levels as well as a high incidence of tumors (including hemangiosarcomas of the liver, spleen, and kidney) compared with animals exposed to ethylene dibromide alone.

It is concluded that under the conditions of this bioassay, tetraethylthiuram disulfide was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED 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 (5%)		
*SUBCUT TISSUE	(20)	(50)	(50)
KERATOACANTHOMA			1 (2%)
FIBROMA			1 (2%)
FIBROSARCOMA		1 (2%)	
OSTEOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (5%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)	5 (10%)	6 (12%)
LEUKEMIA,NOS	1 (5%)	5 (10%)	7 (14%)
MONOCYTIC LEUKEMIA	3 (15%)	6 (12%)	
#SPLEEN	(20)	(50)	(49)
FIBROSARCOMA, METASTATIC		1 (2%)	
OSTEOSARCOMA, METASTATIC		1 (2%)	
#MANDIBULAR L. NODE	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
#THYMUS	(15)	(37)	(47)
CARCINOMA,NOS	1 (7%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
HEPATOCELLULAR ADENOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
CARCINOMA,NOS		1 (2%)	
NEPHROBLASTOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(46)	(45)
CHROMOPHOBE ADENOMA	13 (65%)	11 (24%)	7 (16%)
CHROMOPHOBE CARCINOMA			1 (2%)
#ADRENAL	(20)	(50)	(49)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(20)	(50)	(49)
C-CELL ADENOMA	2 (10%)	4 (8%)	1 (2%)
#PANCREATIC ISLETS	(20)	(50)	(48)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA	1 (5%)		
#TESTIS	(20)	(50)	(48)
INTERSTITIAL-CELL TUMOR	13 (65%)	41 (82%)	33 (69%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(50)	(49)
MENINGIOMA			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*CEREBRUM	(20)	(50)	(49)
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
*EAR CANAL	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*BONE/UPPER EXTREMITY	(20)	(50)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
NEUROFIBROMA		1 (2%)	
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS	1 (5%)	2 (4%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	6	7
MORIBUND SACRIFICE	1	5	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	39	36
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	18	48	41
TOTAL PRIMARY TUMORS	40	85	67
TOTAL ANIMALS WITH BENIGN TUMORS	18	44	37
TOTAL BENIGN TUMORS	31	62	47
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	20	17
TOTAL MALIGNANT TUMORS	8	21	20
TOTAL ANIMALS WITH SECONDARY TUMORS#		3	2
TOTAL SECONDARY TUMORS		4	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	2	
TOTAL UNCERTAIN TUMORS	1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED 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%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (2%)	1 (2%)
LEUKEMIA,NOS		2 (4%)	6 (12%)
MONOCYTIC LEUKEMIA	2 (10%)	3 (6%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR ADENOMA			1 (2%)
URINARY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(48)
CHROMOPHOBE ADENOMA	16 (80%)	12 (24%)	20 (42%)
#ADRENAL	(20)	(50)	(50)
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
#THYROID	(20)	(50)	(50)
C-CELL ADENOMA	2 (10%)	1 (2%)	
#PANCREATIC ISLETS	(20)	(49)	(50)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)		
FIBROADENOMA	3 (15%)	3 (6%)	
#UTERUS	(20)	(50)	(49)
CARCINOMA,NOS	1 (5%)		
ENDOMETRIAL STROMAL POLYP	3 (15%)	7 (14%)	6 (12%)
NERVOUS SYSTEM			
#CEREBRUM	(20)	(50)	(50)
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	6	2
MORIBUND SACRIFICE	5	4	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	40	46
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	28	33
TOTAL PRIMARY TUMORS	31	34	38
TOTAL ANIMALS WITH BENIGN TUMORS	17	24	26
TOTAL BENIGN TUMORS	26	26	29
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	8	9
TOTAL MALIGNANT TUMORS	5	8	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADIMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	4		
ANIMALS NECROPSIED	16	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	16	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(16)	(50)	(50)
CYSTADENOMA, NOS		1 (2%)	
*SUBCUT TISSUE	(16)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(16)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (13%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (13%)	7 (14%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(16)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE	2 (13%)	1 (2%)	3 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
LYMPHOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(16)	(50)	(49)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#CERVICAL LYMPH NODE	(16)	(50)	(49)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
#PANCREAS	(16)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(16)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(16)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (6%)	2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA	4 (25%)	4 (8%)	3 (6%)
HEMANGIOSARCOMA	1 (6%)		
#ESOPHAGUS	(16)	(50)	(50)
KERATOACANTHOMA		1 (2%)	
#STOMACH	(16)	(50)	(50)
KERATOACANTHOMA		1 (2%)	
#SMALL INTESTINE	(16)	(50)	(48)
ADENOMATOUS POLYP, NOS			1 (2%)
#DUODENUM	(16)	(50)	(48)
ADENOMATOUS POLYP, NOS			1 (2%)
ADENOCA IN ADENOMATOUS POLYP			1 (2%)
URINARY SYSTEM			
#KIDNEY	(16)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
ENDOCRINE SYSTEM			
#THYROID	(16)	(50)	(49)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(16)	(50)	(50)
PAPILLARY ADENOMA			1 (2%)
CYSTADENOMA, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	7	4
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	43	46
ANIMAL MISSING	4		

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	21	18
TOTAL PRIMARY TUMORS	12	30	19
TOTAL ANIMALS WITH BENIGN TUMORS	3	9	6
TOTAL BENIGN TUMORS	3	11	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	14	13
TOTAL MALIGNANT TUMORS	9	19	13
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED 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			
*SUBCUT TISSUE	(20)	(49)	(50)
RHABDOMYOSARCOMA	1 (5%)		
AMELOBLASTOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA			5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	4 (8%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	2 (10%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE	3 (15%)	4 (8%)	4 (8%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)	1 (2%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (5%)		
LYMPHOCYTIC LEUKEMIA		2 (4%)	
#MANDIBULAR L. NODE	(20)	(48)	(49)
ISLET-CELL CARCINOMA, METASTATIC			1 (2%)
#LUNG	(20)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
#THYMUS	(20)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEPATOCELLULAR ADENOMA		2 (4%)	
HEPATOCELLULAR CARCINOMA		1 (2%)	
HEMANGIOSARCOMA	1 (5%)		
#DUODENUM	(20)	(48)	(50)
ADENOMATOUS POLYP, NOS			2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID FOLLICLE	(20)	(48)	(49)
CYSTADENOMA, NOS		1 (2%)	
#PANCREATIC ISLETS	(20)	(48)	(49)
ISLET-CELL CARCINOMA	1 (5%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
FIBROMA			1 (2%)
#UTERUS	(20)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
#OVARY	(20)	(48)	(50)
CYSTADENOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(20)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
ISLET-CELL CARCINOMA, METASTATIC	1 (5%)		
HEMANGIOSARCOMA		1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	10	6
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	39	44
ANIMAL MISSING		1	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	18	20
TOTAL PRIMARY TUMORS	13	19	23
TOTAL ANIMALS WITH BENIGN TUMORS		3	10
TOTAL BENIGN TUMORS		3	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	15	12
TOTAL MALIGNANT TUMORS	13	16	13
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED 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)
EPIDERMAL INCLUSION CYST	1 (5%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
FIBROSIS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, ADENOMATOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(50)	(49)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
#MANDIBULAR L. NODE	(20)	(50)	(49)
INFLAMMATION, ACUTE			1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(49)
DEGENERATION, NOS			1 (2%)
*PANCREATIC ARTERY,	(20)	(50)	(50)
HYPERTROPHY, NOS	1 (5%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(20)	(50)	(49)
NECROSIS, FOCAL	1 (5%)		
METAMORPHOSIS FATTY	2 (10%)		
#PANCREAS	(20)	(50)	(48)
PERIARTERITIS	1 (5%)		
#STOMACH	(20)	(50)	(49)
EROSION		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
INFLAMMATION, CHRONIC	7 (35%)	1 (2%)	
INFARCT, NOS		1 (2%)	
HEMOFUSCIN		1 (2%)	
#KIDNEY/TUBULE	(20)	(50)	(49)
PIGMENTATION, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(46)	(45)
MULTIPLE CYSTS			1 (2%)
#ADRENAL	(20)	(50)	(49)
METAMORPHOSIS FATTY	1 (5%)		
#THYROID	(20)	(50)	(49)
CYST, NOS	1 (5%)		
MULTIPLE CYSTS		1 (2%)	
REPRODUCTIVE SYSTEM			
#TESTIS	(20)	(50)	(48)
ATROPHY, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(50)	(49)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
GRANULOMA, NOS		1 (2%)	
#BRAIN	(20)	(50)	(49)
HEMORRHAGE			1 (2%)
NECROSIS, FOCAL			1 (2%)
SPECIAL SENSE ORGANS			
*EYE ANTERIOR CHAMBER	(20)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*EYE/CORNEA	(20)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
*EYELID	(20)	(50)	(50)
INFLAMMATION WITH FIBROSIS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	2
AUTO/NECROPSY/HISTO PERF	1	1	6

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED 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)
EPIDERMAL INCLUSION CYST	2 (10%)		
INFLAMMATION, SUPPURATIVE	1 (5%)		
NECROSIS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(50)	(50)
MYELOFIBROSIS		1 (2%)	
#SPLEEN	(20)	(50)	(50)
INFARCT, NOS		1 (2%)	
HEMATOPOIESIS	1 (5%)	1 (2%)	
CIRCULATORY SYSTEM			
*PULMONARY ARTERY	(20)	(50)	(50)
MINERALIZATION			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(50)	(49)
INFLAMMATION, CHRONIC	1 (5%)		
#LIVER	(20)	(50)	(50)
INFLAMMATION WITH FIBROSIS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
METAMORPHOSIS FATTY			1 (2%)
BASOPHILIC CYTO CHANGE	1 (5%)	2 (4%)	3 (6%)
#PANCREAS	(20)	(49)	(50)
INFLAMMATION, ACUTE		1 (2%)	
ATROPHY, FOCAL			1 (2%)
#STOMACH	(20)	(50)	(50)
ULCER, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
INFLAMMATION, CHRONIC	3 (15%)		1 (2%)
NEPHROSIS, NOS		1 (2%)	2 (4%)
HEMOFUSCIN		1 (2%)	1 (2%)
#URINARY BLADDER	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)		
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(49)	(48)
CYST, NOS			2 (4%)
#ADRENAL MEDULLA	(20)	(50)	(50)
METAMORPHOSIS FATTY		1 (2%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(50)	(49)
HEMORRHAGE		2 (4%)	
NECROSIS, FOCAL		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(50)	(49)
CYST, NOS		1 (2%)	
MULTIPLE CYSTS		3 (6%)	2 (4%)
HYPERPLASIA, NOS		1 (2%)	
#OVARY	(20)	(50)	(49)
CYST, NOS	2 (10%)		
MULTIPLE CYSTS			1 (2%)
NERVOUS SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE ANTERIOR CHAMBER	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*EYE POSTERIOR CHAMBE	(20)	(50)	(50)
HEMORRHAGE		1 (2%)	
*EYE/CORNEA	(20)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	15	14
AUTO/NECROPSY/HISTO PERF		4	2

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	4		
ANIMALS NECROPSIED	16	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	16	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(16)	(50)	(50)
ULCER, NOS		1 (2%)	1 (2%)
FIBROSIS			1 (2%)
PARAKERATOSIS			1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*BLOOD	(16)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#SPLEEN	(16)	(50)	(49)
HYPERPLASIA, LYMPHOID		4 (8%)	1 (2%)
HEMATOPOIESIS		4 (8%)	6 (12%)
#LYMPH NODE	(16)	(50)	(49)
HYPERPLASIA, LYMPHOID		8 (16%)	1 (2%)
#MANDIBULAR L. NODE	(16)	(50)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#CELIAC LYMPH NODE	(16)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(16)	(50)	(49)
FIBROSIS, FOCAL	1 (6%)		
HYPERPLASIA, LYMPHOID	3 (19%)	9 (18%)	5 (10%)
#THYMUS	(16)	(50)	(49)
CYST, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NODULAR		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(16)	(50)	(50)
METAMORPHOSIS FATTY			1 (2%)
ANGIECTASIS	1 (6%)		
#LIVER/CENTRILOBULAR	(16)	(50)	(50)
METAMORPHOSIS FATTY		1 (2%)	
#LIVER/PERIPORTAL	(16)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#PEYERS PATCH	(16)	(50)	(48)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		10 (20%)	
#COLON	(16)	(50)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(16)	(50)	(50)
ABSCESS, NOS		1 (2%)	
INFLAMMATION WITH FIBROSIS		1 (2%)	
FIBROSIS		1 (2%)	
FIBROSIS, FOCAL		2 (4%)	
INFARCT, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(16)	(50)	(50)
HYPERTROPHY, FOCAL		1 (2%)	
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(16)	(50)	(50)
CYST, NOS	1 (6%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		7	17
ANIMAL MISSING/NO NECROPSY	4		
AUTO/NECROPSY/HISTO PERF	2	3	3

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

	MATCHED 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			
*SUBCUT TISSUE	(20)	(49)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(50)
HYPERPLASIA, LYMPHOID	3 (15%)	10 (20%)	5 (10%)
HEMATOPOIESIS	4 (20%)	14 (29%)	1 (2%)
#LYMPH NODE	(20)	(48)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	3 (6%)
#MANDIBULAR L. NODE	(20)	(48)	(49)
HYPERPLASIA, LYMPHOID	2 (10%)	7 (15%)	3 (6%)
#MESENTERIC L. NODE	(20)	(48)	(49)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HYPERPLASIA, LYMPHOID	4 (20%)	9 (19%)	10 (20%)
#RENAL LYMPH NODE	(20)	(48)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(20)	(48)	(49)
HYPERPLASIA, NODULAR		2 (4%)	
HYPERPLASIA, NOS		1 (2%)	2 (4%)
HYPERPLASIA, RETICULUM CELL		4 (8%)	
HYPERPLASIA, LYMPHOID			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(20)	(48)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
INFLAMMATION, NOS	1 (5%)		
CIRRHOSIS, PORTAL			1 (2%)
NECROSIS, COAGULATIVE			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	1 (2%)
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(49)	(50)
METAMORPHOSIS FATTY		1 (2%)	
#PANCREAS	(20)	(48)	(49)
ATROPHY, NOS		1 (2%)	
#STOMACH	(20)	(48)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#INTESTINAL VILLUS	(20)	(48)	(50)
HYPERTROPHY, FOCAL		1 (2%)	
#PEYERS PATCH	(20)	(48)	(50)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	6 (12%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
HYDRONEPHROSIS			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
#KIDNEY/TUBULE	(20)	(49)	(50)
NEPHROSIS, NOS			1 (2%)
ENDOCRINE SYSTEM			
NONE			

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(20)	(49)	(50)
CYST, NOS		5 (10%)	17 (34%)
MULTIPLE CYSTS	5 (25%)	13 (27%)	3 (6%)
HEMORRHAGE	1 (5%)		
#OVARY	(20)	(48)	(50)
CYST, NOS	2 (10%)	1 (2%)	2 (4%)
FOLLICULAR CYST, NOS		1 (2%)	2 (4%)
POLYCYSTIC OVARY	2 (10%)	2 (4%)	1 (2%)
#OVARY/FOLLICLE	(20)	(48)	(50)
HEMORRHAGIC CYST		4 (8%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(48)	(46)
INFLAMMATION, NOS	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
*MESENTERY	(20)	(49)	(50)
GRANULOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	2	5
ANIMAL MISSING/NO NECROPSY		1	
AUTO/NECROPSY/HISTO PERF	3	6	3

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED TETRAETHYLTHIURAM DISULFIDE IN THE DIET

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

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	2/20 (10)	3/50 (6)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.600	0.612
Lower Limit		0.076	0.078
Upper Limit		6.860	6.996
Weeks to First Observed Tumor	81	107	107
Hematopoietic System: Lymphoma or Leukemia (b)	5/20 (25)	16/50 (32)	13/50 (26)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.280	1.040
Lower Limit		0.538	0.416
Upper Limit		3.983	3.341
Weeks to First Observed Tumor	77	81	99

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Carcinoma or Adenoma (b)	13/20 (65)	11/46 (24)	8/45 (18)
P Values (c,d)	P = 0.001 (N)	P = 0.002 (N)	P less than 0.001 (N)
Departure From Linear Trend (e)	P = 0.049		
Relative Risk (f)		0.368	0.274
Lower Limit		0.206	0.135
Upper Limit		0.735	0.593
Weeks to First Observed Tumor	77	89	84
Thyroid: C-cell Adenoma (b)	2/20 (10)	4/50 (8)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.800	0.204
Lower Limit		0.128	0.004
Upper Limit		8.436	3.754
Weeks to First Observed Tumor	107	107	105

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor (b)	13/20 (65)	41/50 (82)	33/48 (69)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.262	1.058
Lower Limit		0.908	0.740
Upper Limit		1.884	1.696
Weeks to First Observed Tumor	90	102	100

(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 trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P 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 Tetraethylthiuram Disulfide in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	2/20 (10)	0/50 (0)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.044		
Relative Risk (f)		0.000	0.400
Lower Limit		0.000	0.032
Upper Limit		1.345	5.277
Weeks to First Observed Tumor	107	--	107
Hematopoietic System: Lymphoma or Leukemia (b)	3/20 (15)	6/50 (12)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.800	1.067
Lower Limit		0.195	0.295
Upper Limit		4.615	5.813
Weeks to First Observed Tumor	90	76	107

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	16/20 (80)	12/49 (24)	20/48 (42)
P Values (c,d)	P = 0.035 (N)	P less than 0.001 (N)	P = 0.004 (N)
Departure from Linear Trend (e)	P less than 0.001		
Relative Risk (f)		0.306	0.521
Lower Limit		0.205	0.385
Upper Limit		0.548	0.842
Weeks to First Observed Tumor	76	104	100
Thyroid: C-cell Adenoma (b)	2/20 (10)	1/50 (2)	0/50 (0)
P Values (c,d)	P = 0.035 (N)	N.S.	N.S.
Relative Risk (f)		0.200	0.000
Lower Limit		0.004	0.000
Upper Limit		3.681	1.345
Weeks to First Observed Tumor	107	107	--

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	3/20 (15)	3/50 (6)	0/50 (0)
P Values (c,d)	P = 0.010 (N)	N.S.	P = 0.021 (N)
Relative Risk (f)		0.400	0.000
Lower Limit		0.060	0.000
Upper Limit		2.802	0.659
Weeks to First Observed Tumor	83	76	--
Uterus: Endometrial Stromal Polyp (b)	3/20 (15)	7/50 (14)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.933	0.816
Lower Limit		0.245	0.199
Upper Limit		5.215	4.706
Weeks to First Observed Tumor	107	107	107

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Tetraethylthiuram Disulfide 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 trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P 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 TETRAETHYLTHIURAM DISULFIDE IN THE DIET

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

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	2/16 (13)	7/50 (14)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.120	0.480
Lower Limit		0.250	0.062
Upper Limit		10.462	5.464
Weeks to First Observed Tumor	108	101	108
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	4/16 (25)	11/50 (22)	4/50 (8)
P Values (c,d)	P = 0.020 (N)	N.S.	N.S.
Relative Risk (f)		0.880	0.320
Lower Limit		0.320	0.070
Upper Limit		3.416	1.569
Weeks to First Observed Tumor	108	101	92

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Tetraethylthiuram Disulfide in the Diet (a)
(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma (b)	1/16 (6)	3/50 (6)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.960	0.320
Lower Limit		0.086	0.004
Upper Limit		49.396	24.645
Weeks to First Observed Tumor	108	108	108
Hematopoietic System: Lymphoma or Leukemia (b)	2/16 (13)	5/50 (10)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.800	0.640
Lower Limit		0.152	0.105
Upper Limit		7.969	6.719
Weeks to First Observed Tumor	80	92	108

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	4/16 (25)	4/50 (8)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.320	0.240
Lower Limit		0.070	0.041
Upper Limit		1.569	1.300
Weeks to First Observed Tumor	108	104	108
Liver: Hepatocellular Carcinoma or Adenoma (b)	5/16 (31)	6/50 (12)	4/50 (8)
P Values (c,d)	P = 0.049 (N)	N.S.	P = 0.032 (N)
Relative Risk (f)		0.384	0.256
Lower Limit		0.120	0.061
Upper Limit		1.424	1.071
Weeks to First Observed Tumor	108	104	108

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

(continued)

(a) Dosed groups received 500 or 2,000 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 trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P 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 Tetraethylthiuram Disulfide in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	1/20 (5)	4/49 (8)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.633	1.633
Lower Limit		0.179	0.179
Upper Limit		78.704	78.704
Weeks to First Observed Tumor	108	108	108
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	1/20 (5)	4/49 (8)	9/49 (18)
P Values (c,d)	P = 0.036	N.S.	N.S.
Relative Risk (f)		1.633	3.673
Lower Limit		0.179	0.573
Upper Limit		78.704	157.154
Weeks to First Observed Tumor	108	108	108

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

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	5/20 (25)	8/49 (16)	7/50 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.653	0.560
Lower Limit		0.222	0.180
Upper Limit		2.293	2.029
Weeks to First Observed Tumor	108	87	99
Liver: Hepatocellular Carcinoma or Adenoma (b)	0/20 (0)	3/49 (6)	0/50 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.255	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	108	--

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

(continued)

(a) Dosed groups received 100 or 500 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 trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P 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 Tetraethylthiuram Disulfide* 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 Tetraethylthiuram Disulfide for carcinogenicity.

After a brief description of the experimental design, the reviewer for the report on the bioassay of Tetraethylthiuram Disulfide said that the study appeared to have been properly conducted. Although the size of the matched control groups was too small, the reviewer opined that this shortcoming was not significant. Based on the results of the bioassay, she concluded that the compound did not pose a carcinogenic risk to man. It was moved that the report on the bioassay of Tetraethylthiuram Disulfide be accepted as written. The motion was seconded and approved without objection.

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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