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BIOASSAY OF

THIO-TEPA

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
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Bethesda, Maryland 20014

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

CONTRIBUTORS: This bioassay of thio-TEPA was conducted by Southern Research Institute, Birmingham, Alabama, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design and doses were determined by Drs. D. P. Griswold[1], J. D. Prejean[1], E. K. Weisburger[2], and J. H. Weisburger[2,3]. Ms. J. Belzer[1] and Mr. I. Brown[1] were responsible for the care of the laboratory animals and administration of the test chemical. Data management and retrieval were performed by Ms. C. A. Dominick[1]. Histopathologic examinations were performed by Drs. S. D. Kosanke[1] and J. C. Peckham[1], and the diagnoses included in this report represent their interpretation.

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

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

The following other 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. Dawn G. Goodman, Dr. Richard A. Griesemer, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire[8], Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of thio-TEPA for possible carcinogenicity was conducted by administering the test chemical by intraperitoneal injection to Sprague-Dawley rats and B6C3F1 mice.

Groups of 31-39 rats of each sex were administered thio-TEPA in phosphate-buffered saline at one of three doses, either 0.7, 1.4, or 2.8 mg/kg body weight, three times per week for a maximum of 52 weeks, then observed for additional periods of time. The maximum time on study (administration of chemical and observation) was 86 weeks. The groups at the low dose were started 69 weeks after those at the mid and high doses, because of high mortalities observed in the groups at the higher doses. Matched controls consisted of groups of 10 untreated rats and 10 vehicle-control rats of each sex. Pooled-control groups also were used. Surviving control rats were killed at 82-87 weeks; surviving dosed rats were killed at 81 or 82 weeks.

Groups of 35 mice of each sex were administered thio-TEPA at one of two doses, either 1.15 or 2.3 mg/kg body weight, three times per week for a maximum of 52 weeks, then observed for a maximum additional period of 34 weeks. Matched controls consisted of groups of 15 untreated mice and 15 vehicle-control mice of each sex. Pooled controls also were used. Surviving control and dosed mice were killed at 86 or 87 weeks.

Thio-TEPA was toxic to both rats and mice, causing decreased mean body weight gains and early deaths in the mid- and high-dose rats and in the high-dose mice. Because of the early deaths, statistical analyses were based only on time-adjusted incidences of tumors. Since all high-dose male and female rats had died by 21 weeks, microscopic evaluation of tissues was performed only on the low- and mid-dose animals.

In rats, the incidence of combined neoplasms of the hematopoietic system (lymphoma, lymphocytic leukemia, or granulocytic leukemia) was significant in the males in both the low-dose ($P = 0.020$) and mid-dose ($P = 0.001$) groups, using pooled controls (pooled

controls 0/29, low-dose 6/34; pooled controls 0/30, mid-dose 6/16).

Squamous-cell carcinoma of the skin or ear canal occurred at a significant incidence in the male rats in both the low-dose ($P = 0.009$) and mid-dose ($P = 0.023$) groups, using pooled controls (pooled controls 0/29, low-dose 7/33; pooled controls 0/30, mid-dose 3/13) and in the mid-dose females ($P < 0.001$), using pooled controls (pooled controls 0/28, mid-dose 8/21); in addition, two low-dose females had such tumors, with none occurring in the corresponding low-dose controls.

The incidence of adenocarcinoma of the uterus was significant in the mid-dose female rats ($P = 0.001$), using pooled controls (pooled controls 0/28, mid-dose 7/21); in addition, two low-dose females had adenocarcinoma of the uterus, with no such tumor occurring in the corresponding low-dose controls.

In rats, neuroepitheliomas (neuroblastomas) or nasal carcinomas occurred in three low-dose males, two low-dose females, and two mid-dose females. Although these are not statistically significant incidences, these tumors did not occur among control animals and no such tumors have occurred in 380 Sprague-Dawley control rats of each sex in other bioassays at the same laboratory. Thus, they may be associated with administration of the chemical.

In the high-dose groups of both male and female mice, but not in the low-dose groups, the incidences of lymphoma or lymphocytic leukemia were significantly higher ($P < 0.001$) for each sex than those of either the vehicle or pooled controls (males: vehicle controls 1/8, pooled controls 1/18, low-dose 2/24, high-dose 26/28; females: vehicle controls 0/14, pooled controls 0/29, low-dose 5/26, high-dose 32/32).

In the low-dose male mice squamous-cell carcinoma was found in the skin of seven animals, in the preputial glands of six

animals, and in the ear canal of two animals. A carcinoma of the preputial gland was also found in a high-dose male. When the incidences of the tumors at the different sites were combined, the incidence in the low-dose group was statistically significant using either the vehicle ($P = 0.004$) or the pooled ($P < 0.001$) controls (vehicle controls 0/8, pooled controls 0/18, low-dose 14/24, high-dose 1/2).

It is concluded that under the conditions of this bioassay, thio-TEPA was carcinogenic in both Sprague-Dawley rats and B6C3F1 mice. In the rats, the chemical induced squamous-cell carcinoma of the skin or ear canal in both males and females, and hematopoietic neoplasms in the males; in the mice, it induced lymphoma or lymphocytic leukemia in both sexes and squamous-cell carcinoma in the skin and associated glands of males.

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FIGURES

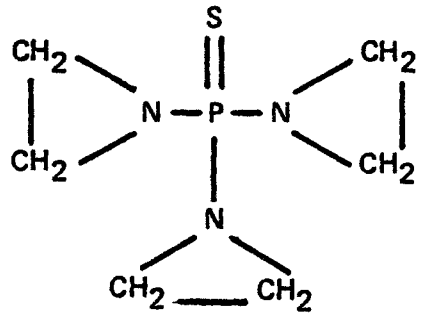
I. INTRODUCTION

Thio-TEPA (CAS 52-24-4; NSC 6396; NCI C01649) is an ethyleneimine alkylating agent that was introduced in 1953 for clinical use in cancer chemotherapy. Following oxidative desulfurization of thio-TEPA, the three ethylenimine groups that the chemical contains become activated to ethylenimonium ions (Montgomery and Struck, 1973; Lederle Laboratories, 1977). The presence of several such groups raises the possibility that the drug will bind to more than one site on the DNA molecule and will have increased cytotoxic effects (Calabresi and Parks, 1975).

At one time thio-TEPA was an important therapeutic drug in the management of ovarian carcinoma (Calabresi and Welch, 1962). It has been used effectively in the treatment of Hodgkins disease, bronchogenic carcinoma, bladder cancer, retinoblastoma, and breast cancer and for the control of pleural, pericardial, and peritoneal neoplastic effusions (Wheeler, 1973; Carter and Slavik, 1974; Calabresi and Parks, 1975). In the pulmonary tumor response test in strain A mice (Shimkin et al., 1966), thio-TEPA showed weak activity. On the basis of these results, the drug was retested in a lifetime carcinogen bioassay. This drug is one of a series of anticancer agents that were selected for testing because they may be administered chronically in humans.

II. MATERIALS AND METHODS

A. Chemical



Thio-TEPA

Thio-TEPA is the common name for tris(1-aziridinyl)phosphine sulfide, manufactured by Lederle Laboratories, Pearl River, New York. Lederle Lot No. D9878, which conformed to USP specifications, was used during the chronic study. The purity of this lot was 98.0 ± 1.0% as determined by titration of the aziridine groups with tetrabutylammonium iodide and perchloric acid. Elemental analysis for sulfur was slightly high (18.2 ± 0.6% vs. 17.0% theoretical), but may have been affected by phosphorus; analysis of carbon, hydrogen, nitrogen, and phosphorus verified the chemical composition of this product. The melting point was 52.0-52.5°C and was comparable to that of 51.5°C reported elsewhere (U.S. Patent, 1954). Thin-layer

chromatography showed one trace impurity which remained at the origin. Vapor phase chromatography gave one homogeneous peak. The infrared and nuclear magnetic resonance spectra were consistent with the spectra given in the literature for this compound.

B. Dosage Preparation

Solutions of thio-TEPA in phosphate-buffered saline were prepared on the day that they were used by blending for 20 seconds in a 10-ml Potter-Elvehjem tissue grinder with a Teflon pestle; unused solutions of the drug were discarded. Concentrations of thio-TEPA ranged from 0.028% to 0.112% for the chronic studies using rats and from 0.012% to 0.023% for the chronic studies using mice. Volumes of solutions used for injection were 0.25 ml/100 g body weight for the rats and 1.0 ml/100 g body weight for the mice.

C. Animals

For the subchronic studies, male Sprague-Dawley rats and male Swiss mice were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. On arrival at the laboratory, they were 30 days of age. The rats were quarantined for 5 days and the mice for 20 days prior to being placed on study.

In the chronic studies, Sprague-Dawley rats and B6C3F1 mice of each sex were obtained from Charles River Breeding Laboratories under a contract with the Division of Cancer Treatment, National Cancer Institute. Male rats were received at 29 days of age, female rats at 36 days of age, and male and female mice at 32 days of age. All animals were quarantined for periods of 6 days for rats and 10 days for mice. After these periods, animals with no visible signs of disease were assigned to control or dosed groups and earmarked for individual identification. Additional groups of male and female Sprague-Dawley rats for the chronic study were received at 30 days of age from Charles River Breeding Laboratories and quarantined for 28 days weeks prior to being placed on study.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 20-24°C, and the relative humidity was maintained at 40-60%. The air was changed 15 times per hour and passed through both intake and exhaust fiberglass roughing filters. In addition to natural light, illumination was provided by fluorescent light for 9 hours per day. Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) and water were supplied daily and were available ad libitum.

Rats were housed five per cage and mice seven per cage in solid-bottom stainless steel cages (Hahn Roofing and Sheet Metal Co., Birmingham, Ala.). Rat cages were provided with Iso-Dri® hardwood chip bedding (Carworth, Edison, N.J.); mouse cages were provided with Sterolit® clay bedding (Englehard Mineral and Chemical Co., New York, N.Y.). For initial studies with rats, cage tops were covered with disposable filter bonnets beginning at week 24; for later studies with rats, cage tops were covered with filter bonnets for the entire test. Filter bonnets were not used for the mouse cages. Bedding was replaced once per week; cages, water bottles, and feeders were sanitized at 82°C once per week; and racks were cleaned once per week.

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

RATS

Gavage Studies

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

Intraperitoneal Injection Studies

4′-(9-acridinylamino)methansulfon-m-aniside monohydrochloride (MAAM) (NSC 141549)

acronycine (CAS 7008-42-6)
5-azacytidine (CAS 320-67-2)
beta-2′-deoxy-6-thioguanosine monohydrate (beta-TGdR)
(CAS 789-61-7)
1,4-butanediol dimethanesulfonate (busulfan) (CAS 55-98-1)
emetine dihydrochloride tetrahydrate (CAS 316-42-7)
3,3′-iminobis-1-propanol dimethanesulfonate (ester)
hydrochloride [IPD] (CAS 3458-22-8)
(±)-4,4′-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione
(ICRF-159) (CAS 21416-87-5)
N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-
amine-2-oxide (isophosphamide) (CAS 3778-73-2)
N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzylamine
hydrochloride (phenoxybenzamine) (CAS 63-92-3)
N-(1-methylethyl)-4-((2-methylhydrazino)methyl)benzamide
monohydrochloride (procarbazine) (CAS 366-70-1)
2,4,6-tris(dimethylamino)-s-triazine (CAS 645-05-6)
adriamycin (CAS 23214-92-8)

MICE

Feed Studies

4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide
(acetohexamide) (CAS 968-81-0)
anthranilic acid (CAS 118-92-3)
1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide) (CAS 64-77-7)
4-chloro-N-((propylamino)carbonyl)benzenesulfonamide
(chlorpropamide) (CAS 94-20-2)
5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine
(pyrimethamine) (CAS 58-14-0)
2,6-diamino-3-(phenylazo)pyridine hydrochloride
(phenazopyridine hydrochloride) (CAS 136-40-3)
L-tryptophan (CAS 73-22-3)
N-9H-fluoren-2-ylacetamide (CAS 53-96-3)
N-(p-toluenesulfonyl)-N′-hexamethyleniminourea
(tolazamide) (CAS 1156-19-0)
1-phenethylbiguanide hydrochloride (phenformin) (CAS 114-86-3)
pyrazinecarboxamide (pyrazinamide) (CAS 98-96-4)
4,4′-sulfonyldianiline (dapsone) (CAS 80-08-0)
4,4′-thiodianiline (CAS 139-65-1)
ethionamide (CAS 536-33-4)

Gavage Studies

cholesterol (p-(bis(2-chloroethyl)amino)phenyl)acetate
(phenesterin) (CAS 3546-10-9)

estradiol bis((p-(bis(2-chloroethyl)amino)phenyl)acetate)
(estradiol mustard) (CAS 22966-79-6)

Intraperitoneal Injection Studies

4′-(9-acridinylamino)methansulfon-m-aniside monohydrochloride
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3,3′-iminobis-1-propanol dimethanesulfonate (ester)
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N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-
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hydrochloride (phenoxybenzamine) (CAS 63-92-3)
N-(1-methylethyl)-4-((2-methylhydrazino)methyl)benzamide
monohydrochloride (procarbazine) (CAS 366-70-1)

E. Subchronic Studies

Subchronic studies were conducted using male Sprague-Dawley rats and male Swiss mice to estimate the maximum tolerated doses of thio-TEPA, on the basis of which two concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration in the chronic studies. Rats were administered the drug at doses of 0.14, 0.35, 0.7, 1.4, or 2.8 mg/kg, and mice at doses of 0.23, 0.58, 1.15, 2.3, or 4.6 mg/kg. Dosed animals were injected intraperitoneally with thio-TEPA three times per week for 45 days and then observed for an additional 45 days. Five animals of each species were administered the chemical at

each dose, 10 animals of each species were maintained as vehicle controls, and 10 animals of each species were maintained as untreated controls.

There were no deaths in the rats at any dose tested. Mean body weight gains at 45 days in animals at 0.14, 0.35, or 0.7 mg/kg were unaffected in comparison with those of the vehicle controls; at 1.4 mg/kg the mean body weights were 79% of those of the controls, and at 2.8 mg/kg they were 70% of those of the controls. After 90 days, mean body weight gains were comparable to those of the controls in all groups except those at 1.4 mg/kg and 2.8 mg/kg, where they were approximately 85% of those of the controls. The vehicle controls gained slightly less weight than the untreated controls. The low and high doses for the chronic studies using rats were set at 1.4 and 2.8 mg/kg.

In mice, 3/5 animals died at 4.6 mg/kg and 1/5 died at 0.58 mg/kg. At 45 days, mean body weight gains in dosed animals were not greatly affected, except for slight losses in the group at 4.6 mg/kg. The low and high doses for the chronic studies using mice were set at 1.15 and 2.3 mg/kg.

F. Designs of the Chronic Studies

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

Table 1. Design of Chronic Studies of Thio-TEPA in Rats

Sex and Test Group	Initial No. of Animals[a]	Thio-TEPA Dose[b] (mg/kg)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Male				
Low-Dose Untreated-Control[c]	10	0		83
Low-Dose Vehicle-Control[c]	10	0[d]	52	30
Low-Dose[c]	39	0.7	52	30
Mid- and High-Dose Untreated-Control	10	0		87
Mid- and High-Dose Vehicle-Control	10	0[d]	34[e]	52
Mid-Dose	35	1.4	34[e]	44[f]
High-Dose	35	2.8	19[g]	
Female				
Low-Dose Untreated-Control[c]	10	0		82
Low-Dose Vehicle-Control[c]	10	0[d]	52	30
Low-Dose[c]	31	0.7	52	30
Mid- and High-Dose Untreated-Control	10	0		87
Mid- and High-Dose Vehicle-Control	10	0[d]	34[e]	53
Mid-Dose	35	1.4	34[e]	47
High-Dose	35	2.8	21[g]	

[a]Ages of rats when placed on study: mid- and high-dose males, 35 days; mid- and high-dose females, 42 days; low-dose males and females, 58 days.

[b]Thio-TEPA was administered intraperitoneally in phosphate-buffered saline three times per week at a volume of 0.25 ml/100 g body weight; doses were based on individual weights.

Table 1. Design of Chronic Studies of Thio-TEPA in Rats

(continued)

[c]Because of deaths in the high- and mid-dose groups, new dosed and control groups were started 69 weeks after the start of the original study.

[d]Vehicle controls received phosphate-buffered saline at the same volume as the dosed animals.

[e]Administration of the chemical to mid-dose males and females and to mid- and high-dose vehicle controls terminated at week 34, due to toxicity in the dosed groups.

[f]Observation of mid-dose males terminated at week 78, due to death of all animals.

[g]Administration of the chemical to high-dose males and females terminated at times indicated, due to death of all animals.

Table 2. Design of Chronic Studies of Thio-TEPA in Mice

Sex and Test Group	Initial No. of Animals[a]	Thio-TEPA Dose[b] (mg/kg)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Male				
Untreated-Control	15	0		87
Vehicle-Control	15	0[c]	52	35
Low-Dose	35	1.15	52	34
High-Dose	35	2.3	52	4[d]
Female				
Untreated-Control	15	0		87
Vehicle-Control	15	0[c]	52	35
Low-Dose	35	1.15	52	34
High-Dose	35	2.3	43[e]	

[a]All animals were 42 days of age when placed on study.

[b]Thio-TEPA was administered intraperitoneally in phosphate-buffered saline three times per week at a volume of 1.0 ml/100 g body weight based on the mean weight of the animals in each cage.

[c]Vehicle controls received only phosphate-buffered saline solution, at the same volume as dosed mice.

[d]Observation of high-dose males terminated at week 56, due to death of all animals.

[e]Administration of the chemical to high-dose females terminated at week 43, due to death of all animals.

Since the numbers of rats and mice in the control groups were small, pooled-control groups also were used for statistical comparisons. Pooled-control groups for the low-dose rats consisted of vehicle-control groups of 10 animals of each sex from the bioassay of thio-TEPA, combined with corresponding vehicle-control groups of 10 animals of each sex from similar bioassays of beta-2′-deoxy-6-thioguanosine monohydrate (β-TGDR) and 3,3′-iminobis-1-propanol dimethanesulfonate (ester) [IPD]; pooled-control groups for the mid-dose rats consisted of vehicle-control groups of 10 animals of each sex from the bioassay of thio-TEPA, combined with corresponding vehicle-control groups of 10 animals of each sex from similar bioassays of procarbazine and IPD. The total number of animals was 30 in both the low-dose pooled-control group and the mid-dose pooled-control group. For the mice, pooled-control groups consisted of vehicle-control groups of 15 animals of each sex from the bioassay of thio-TEPA, combined with corresponding vehicle-control groups of 15 animals of each sex from a similar bioassay of IPD, to give a total of 30 animals per group. The bioassays of the chemicals other than thio-TEPA were also conducted at Southern Research Institute and were started no more than 3 months apart from those for thio-TEPA. The vehicle-control groups of rats and mice used in the pooled-control groups were of the same strain, obtained from the same supplier, and examined by the same pathologists as in the

respective dosed groups; further, the same vehicle was used for the different vehicle-control groups.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, and animals that were moribund were killed and necropsied, except for those dying prior to day 100, due, presumably, to toxicity of the test chemical. Rats (mid- and high-dose) and mice were weighed individually each week for 8 weeks and every 2 weeks thereafter; low-dose rats were weighed once every 2 weeks for the period of administration of the chemical and once per month thereafter. Palpation for masses was carried out at each weighing.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, muscle, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder and bile duct (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, brain, and sensory organs. Peripheral blood smears were prepared from each animal whenever possible. Occasionally, additional

tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

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

tables were generated for verification of data transcription and for statistical review.

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances,

the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope

of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups;

Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the dosed group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a

control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of all dosed male rats, particularly those of the mid- and high-dose groups, were depressed throughout the study, when compared with either matched or vehicle controls; those of the dosed females were less markedly depressed (figures 1 and 2). Fluctuations in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to wide variation.

There was clinical evidence of respiratory disease in the high- and mid-dose groups of rats and their untreated and vehicle controls. To control the respiratory disease, these animals received oxytetracycline in drinking water at a dose of 0.6 mg/ml during weeks 24-30 and 0.3 mg/ml during weeks 30-35. No other signs of toxicity were reported for the rats.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for the male and female rats administered thio-TEPA at the doses of this bioassay, together with those of the controls, are shown in figures 3 and 4.

For each sex, the results of the Tarone test were significant

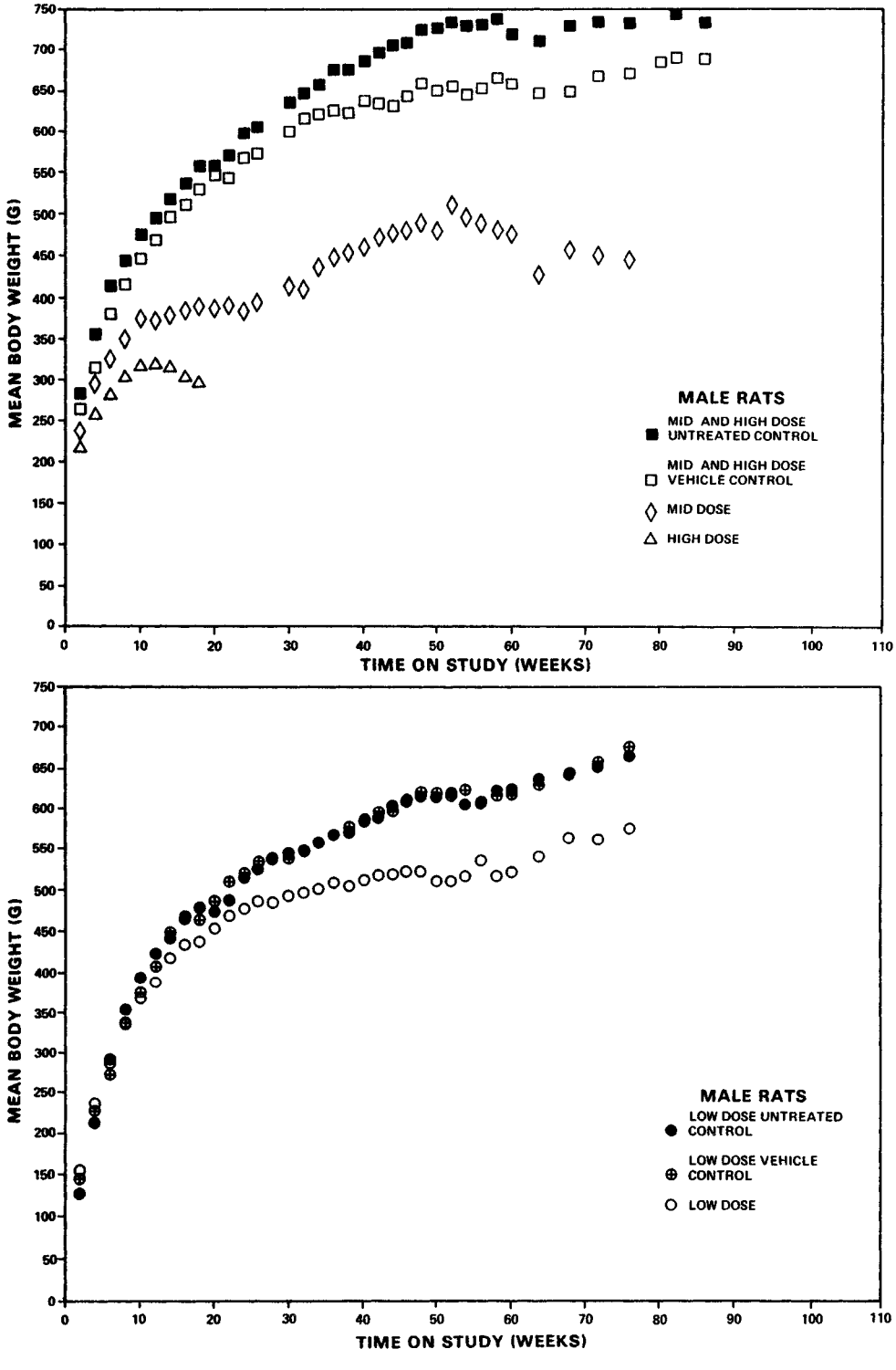


Figure 1. Growth Curves for Male Rats Treated with Thio-TEPA

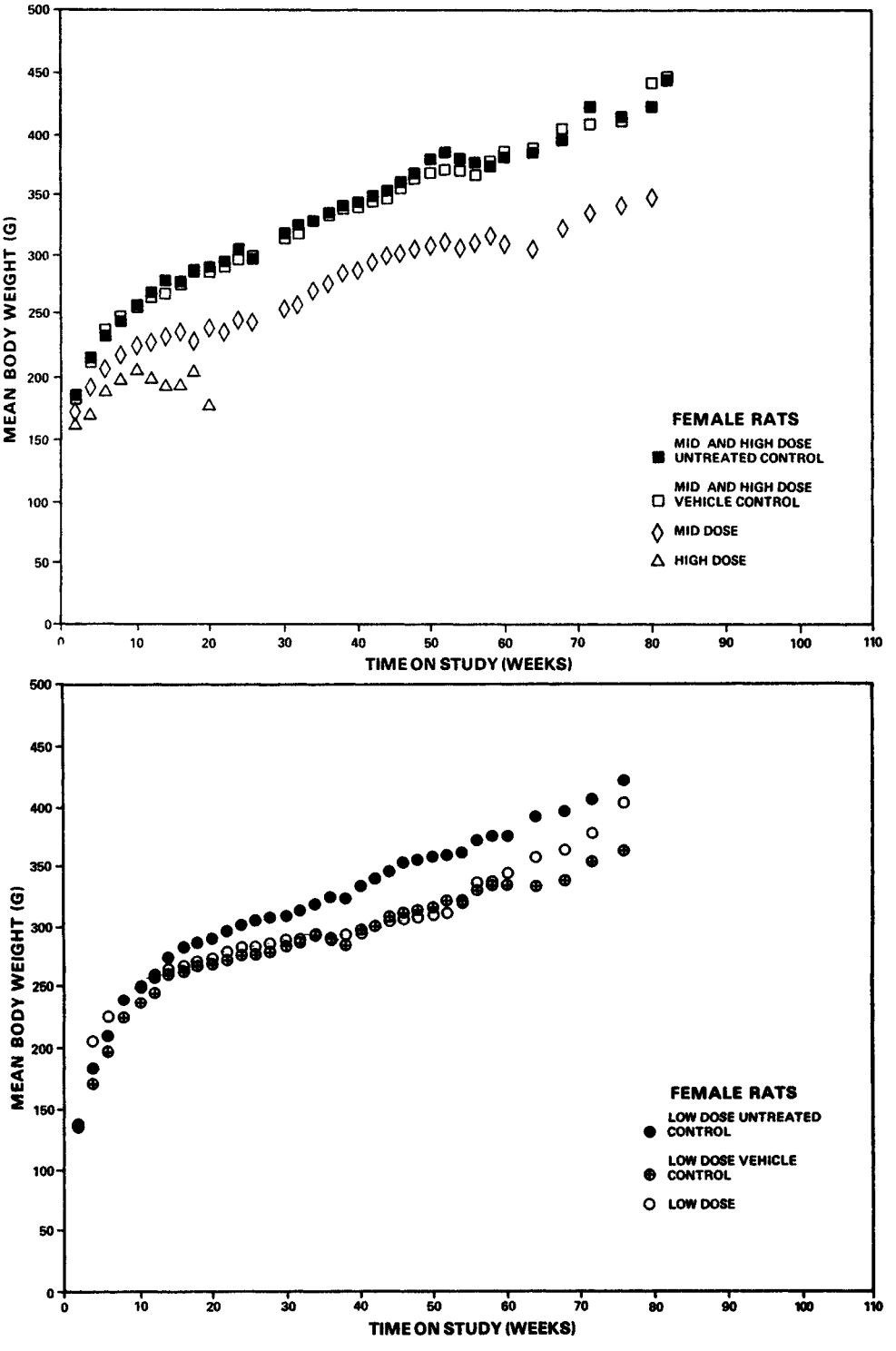


Figure 2. Growth Curves for Female Rats Treated with Thio-TEPA

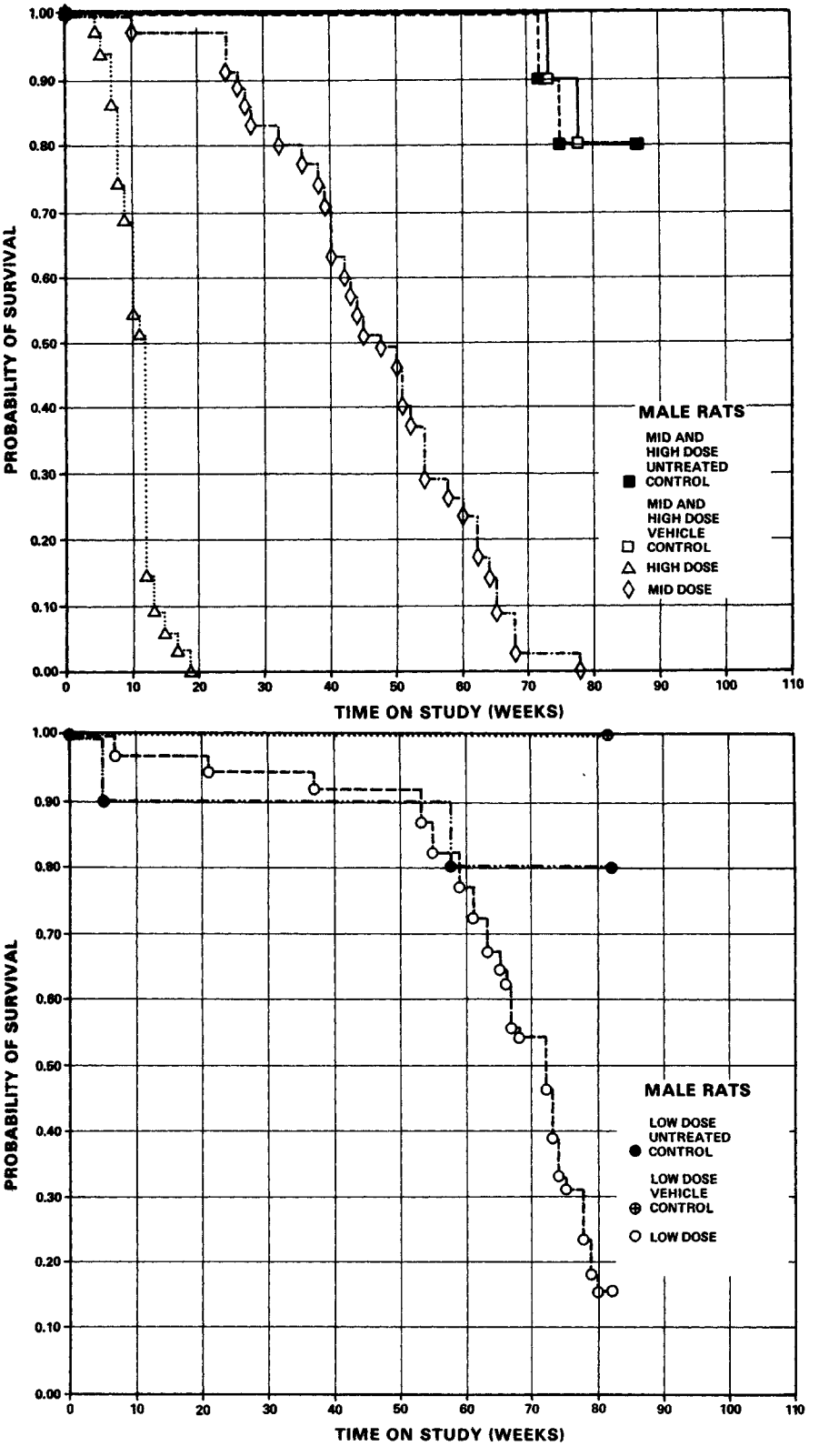


Figure 3. Survival Curves for Male Rats Treated with Thio-TEPA

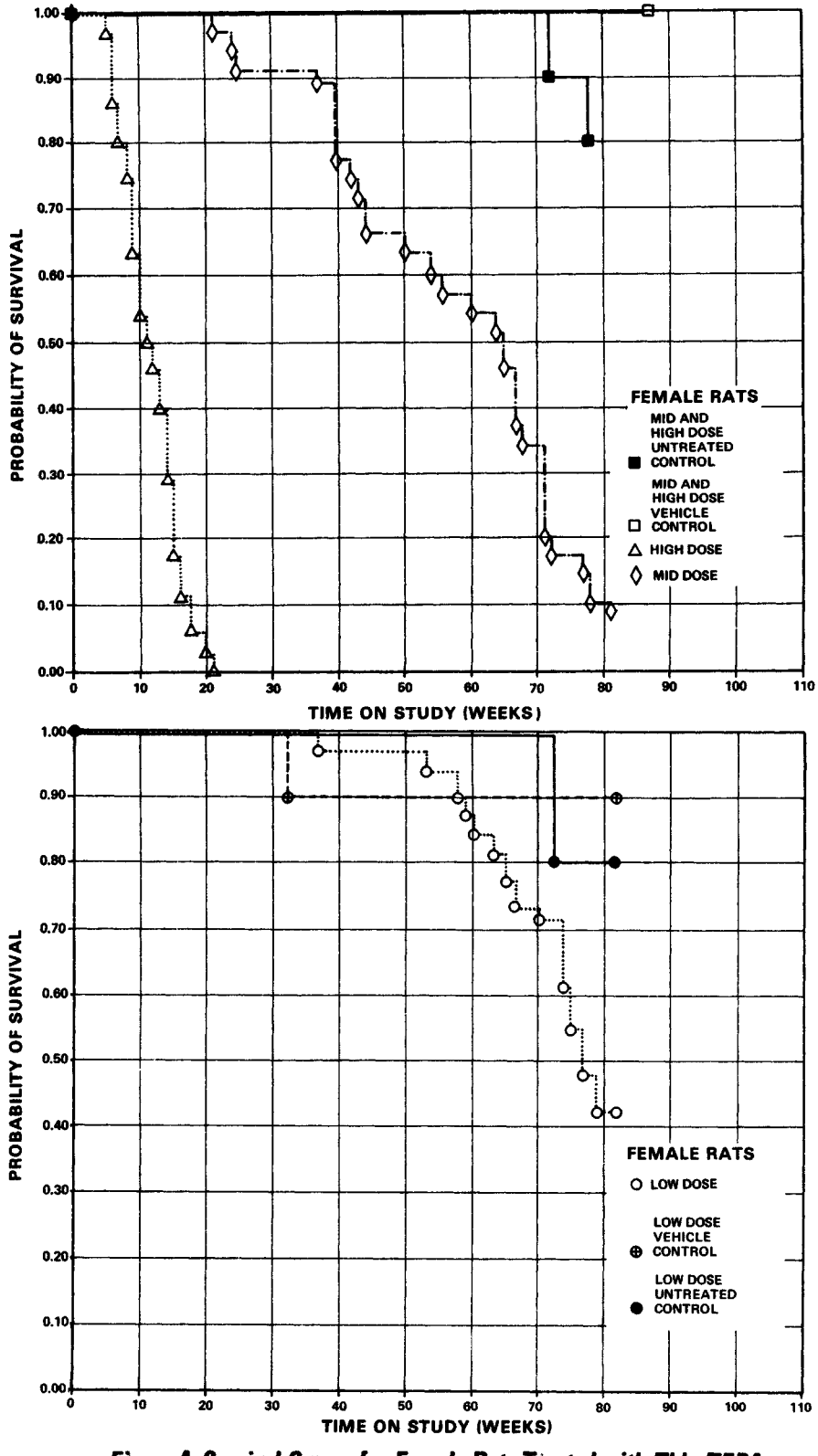


Figure 4. Survival Curves for Female Rats Treated with Thio-TEPA

($P < 0.001$), indicating that the administration of thio-TEPA decreased survival in a dose-related manner. At the high dose, all animals were dead at week 19 (males) or week 21 (females). Survival at the mid dose was also low, with all males dead by week 78, and with only 3/35 (8.6%) females surviving to termination, while 6/39 (15.4%) low-dose males and 13/31 (42%) low-dose females survived to the end of the study. Among the male vehicle controls, 8/10 (80%) of the mid- and high-dose controls and 10/10 (100%) of the low-dose vehicle controls survived to week 82; corresponding values for females were 7/10 (70%) and 9/10 (90%). Even using time-adjusted analyses, eliminating those rats dying before week 52 on study, in some dosed groups, insufficient numbers of animals 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-A4; findings on nonneoplastic lesions are summarized in Appendix C, tables C1-C4.

A variety of neoplasms were observed in the untreated controls, vehicle controls (phosphate-buffered saline), and dosed groups. Some types of neoplasms occurred only, or with a greater frequency, in rats of dosed groups as compared with controls.

Most of these lesions, however, are not uncommon in this strain of rat independent of the administration of any chemical. The incidence of several tumors was higher in the dosed groups. These tumors involved the skin, connective tissues, ear canal, nasal cavity and brain, hematopoietic tissues, lymphoreticular tissues, and uterus. The incidences of these tumors were as follows:

MALES	Combined[a] Untreated Controls	Combined[a] Vehicle Controls	Low Dose	Mid Dose
Number of rats necropsied	(19)	(20)	(37)	(30)
Integument				
Squamous-cell papilloma	0	1	1	0
Squamous-cell carcinoma	0	0	5	3
Trichoepithelioma	0	0	1	0
Basal-cell carcinoma	0	0	0	1
Sarcoma, NOS[b]	0	0	5	0
Fibroma	0	2	2	0
Fibrosarcoma	0	0	1	0

[a]Mid- and high-dose control group and low-dose group control were combined.
[b]Not otherwise specified

	Combined Untreated Controls	Combined Vehicle Controls	Low Dose	Mid Dose
Number of rats necropsied	(19)	(20)	(37)	(30)
Ear Canal				
Squamous-cell papilloma	0	0	1	0
Squamous-cell carcinoma	0	0	3	1
Nasal Cavity				
Carcinoma, NOS	0	0	1	0
Hematopoietic and Lymphoreticular Tissues				
Malignant lymphoma, histiocytic type	0	0	1	0
Leukemia, lymphocytic	0	0	3	5
Leukemia, granulocytic	0	0	2	1
Brain[c]	(18)	(20)	(36)	(28)
Sarcoma, NOS	0	0	0	1
Astrocytoma	0	0	1	0
Neuroepithelioma (Neuroblastoma)	0	0	2	0
Other Sites	(19)	(20)	(37)	(30)
Sarcoma, NOS	0	0	4	1
FEMALES				
Number of rats necropsied	(20)	(20)	(30)	(33)
Integument				
Squamous-cell papilloma	0	0	0	1
Squamous-cell carcinoma	0	0	0	3
Sarcoma, NOS	0	0	1	0
Fibroma	1	0	1	0
Fibrosarcoma	0	0	1	0

[c]Number of rats with tissue examined microscopically

	Combined Untreated Controls	Combined Vehicle Controls	Low Dose	Mid Dose
Number of rats necropsied	(20)	(20)	(30)	(33)
Ear Canal				
Squamous-cell papilloma	0	0	0	1
Squamous-cell carcinoma	0	0	2	5
Nasal Cavity				
Carcinoma, NOS	0	0	0	1
Brain[c]	(20)	(19)	(30)	(32)
Neuroepithelioma (Neuroblastoma)	0	0	2	1
Sarcoma, NOS	0	0	0	1
Uterus[c]	(20)	(20)	(30)	(32)
Adenocarcinoma, NOS	0	0	2	7
Squamous-cell carcinoma	0	0	1	0
Sarcoma, NOS	0	0	2	1
Stromal polyp	0	0	4	1
Other Sites[c]	(20)	(20)	(30)	(33)
Sarcoma, NOS	0	0	0	1

[c]Number of rats with tissue examined microscopically

The skin tumors were differentiated epithelial tumors with the majority being keratinizing squamous-cell carcinomas located in various regions of the head and neck. The squamous-cell tumors varied from benign acanthotic, hyperkeratotic, and papillary growths (papillomas) to less differentiated carcinomas that invaded the dermis. These latter tumors contained nests of

squamous cells forming whorls of keratin and cords or small groups of darkly staining anaplastic epithelial cells. The predominant cells were stratified and polygonal-shaped, had ample eosinophilic cytoplasm, and had large vesicular nuclei with prominent nucleoli. Two tumors appeared to arise from the basal cells of hair follicles, sebaceous glands, or other adnexal structures. The basal-cell tumors were composed of closely packed, small polygonal cells with scanty cytoplasm and darkly staining purple or blue round to oval nuclei. The cells had a tendency to form palisades. Various degrees of keratinization and hair-follicle formation were present. These tumors were classified as a trichoepithelioma, and a basal-cell carcinoma.

Several subcutaneous connective tissue tumors were observed in both dosed and untreated groups. These were spindle-cell tumors that varied from well-differentiated fibromas with extensive collagenous formation to less differentiated fibrosarcomas with less collagen and poorly differentiated sarcomas (sarcomas, NOS) with little or no collagen and irregular cystic or vascular spaces. The sarcomas occurred frequently around the head and neck as well as other subcutaneous and visceral sites.

Squamous-cell tumors, both benign and malignant, were observed in the ear canals (Zymbal's Gland). These tumors were similar in morphology to the squamous-cell tumors observed in the skin.

Ten tumors involved the brain and nasal cavity. Seven of the tumors were types which occur very rarely in untreated Sprague-Dawley rats. These tumors were neuroepitheliomas (neuroblastomas) and nasal carcinomas, NOS.

Lymphocytic leukemias that involved multiple organs including various lymph nodes, spleen, liver, lungs, ovaries, uterus, kidneys, and bone marrow were the primary hematopoietic tumors seen. A smaller number of animals had granulocytic leukemias.

Uterine adenocarcinomas were characterized by neoplastic epithelial cells having large vesicular nuclei, prominent eosinophilic nucleoli, and ample cytoplasm that were arranged into glands. The glands were usually separated by fibrovascular stroma. The neoplastic glandular tissue arose in the endometrium and both projected into the uterine lumen and infiltrated the underlying muscle layers. Frequently the neoplastic cells penetrated the serosal surface of the uterus with transplantation on the mesentery throughout the abdominal cavity. Pulmonary metastases were also frequent. One low-dose female had a cervical uterine squamous-cell carcinoma. A few animals had poorly differentiated spindle-cell uterine sarcomas (sarcomas, NOS) and endometrial stromal polyps.

In addition to the neoplastic lesions, a number of degenerative,

proliferative, and inflammatory changes were encountered also in animals of the dosed and control groups (Appendix C). Most of these nonneoplastic lesions are commonly seen in aged Sprague-Dawley rats.

None of the high-dose male or female rats were processed for microscopic evaluation because of the short life spans, and thereby, the lack of time for tumor development. These deaths which occurred at less than 150 days were assumed to be the result of chemical toxicity. Many mid-dose males had reduced life spans that were associated with moderate to severe suppurative bronchopneumonia and bone-marrow atrophy. The lower incidence of tumors in this group may have resulted in part from the reduced life span. The female groups had fewer early deaths associated with bone-marrow atrophy and bronchopneumonias. The effects in the females of reduced life spans from toxicity were not considered important. Chronic and interstitial nephritis occurred frequently, but did not appear to be chemical related.

Administration of thio-TEPA resulted in an increase of epithelial tumors in the skin, ear canal, nasal cavity, and uterus; of hematopoietic tumors, primarily lymphocytic leukemias; of spindle-cell sarcomas in the subcutis and various other locations; and of neuroepithelial brain tumors.

Based on the histopathologic examination, thio-TEPA given intraperitoneally to Sprague-Dawley rats at doses of 0.7 and 1.4 mg/kg appeared to be carcinogenic under the conditions of this bioassay. The dose of 2.8 mg/kg proved to be too toxic for an evaluation of carcinogenic activity.

D. Statistical Analyses of Results (Rats)

Tables E1-E8 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more than one group. Analyses of the incidences in the high-dose groups are not included in the tables, because, as a result of the low survival, animals in these groups were not examined histopathologically. The untreated controls also are not included in the tables and in the analyses because the test conditions of the vehicle controls more closely resemble those of the dosed rats. Since the low-dose and mid-dose vehicle controls were started at different dates, the low-dose and mid-dose groups are analyzed separately with their respective controls. Due to the low survivals of animals in the dosed groups, time-adjusted analyses were performed, eliminating animals that died before week 52 on study, 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. The statistical narrative in the following paragraphs is based on time-adjusted data only.

In rats of each sex, when the vehicle controls are used, there is no significant positive result in either the low-dose or mid-dose groups when the Bonferroni probability value of 0.025 is used as a significance level.

In male rats, when the pooled controls are used, a significant incidence of squamous-cell carcinoma in either the skin or ear canal is observed in both the low-dose and mid-dose groups ($P = 0.009$, low-dose; $P = 0.023$, mid-dose). In female rats, a significant incidence of squamous-cell carcinoma in either the skin or ear canal is observed in the mid-dose group ($P < 0.001$); however, the incidence was not significant in the low-dose group. While the vehicle-control groups were too small for effective analyses, the significant incidence of this tumor observed in both male and female rats, using pooled controls, suggests a dose association with the administration of thio-TEPA.

Leukemias were reported at a significant incidence ($P = 0.001$) in mid-dose male rats when compared with the pooled controls. When the incidences of leukemia or lymphoma are combined for analyses, a significant incidence ($P = 0.020$) is present in the low-dose

male group when compared with that in the pooled controls. The combination of leukemia or lymphoma did not appear at a significant incidence in the female groups. These results are based on the use of the pooled controls and appeared in significant incidences in males only; therefore, while suggestive of a dose relationship, the statistical evidence is not as clear as for squamous-cell carcinoma.

In female rats, adenocarcinoma was seen in a significant incidence in the mammary gland ($P = 0.006$) and in the uterus ($P = 0.001$) when the incidences in the mid-dose group were compared with those in the pooled controls. The incidence of mammary adenocarcinoma in the low-dose group also was higher than that in the pooled controls ($P = 0.033$), while the incidence of uterine carcinoma in the low-dose group was not significant. These data suggest a positive association between the administration of the test chemical and the formation of these tumors.

Significant results in the negative direction occurred in the incidences of pituitary tumors in the low-dose and mid-dose groups of female rats, and in the low-dose group of male rats.

In summary, the results of the statistical tests show that the incidences of squamous-cell carcinoma in the skin or ear canal in each sex, hematopoietic tumors in male rats, adenocarcinoma of

the mammary gland in female rats, and adenocarcinoma of the uterus in female rats are associated with the administration of thio-TEPA.

IV. RESULTS - MICE

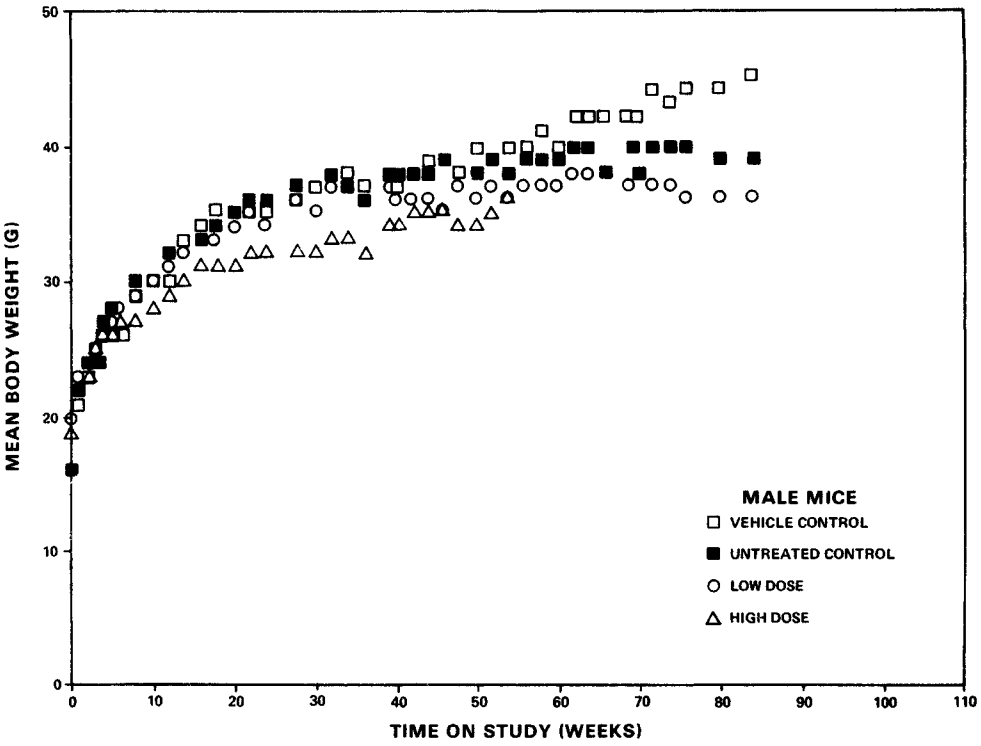
A. Body Weights and Clinical Signs (Mice)

Mean body weights of low-dose male and female mice were only slightly lower than those of the controls throughout much of the study (figure 5). Those of the high-dose animals, particularly those of the females, were lower throughout their period of survival. Fluctuations in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to wide variation. No other signs of toxicity were recorded.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered thio-TEPA at the doses of this bioassay, together with those of the controls, are shown in figure 6.

For each sex, the Tarone test result is significant ($P < 0.001$), indicating that thio-TEPA decreased survival in a dose-related manner. At the high-dose, none of the males survived past week 56 and none of the females past week 43. At the low-dose, 15/35 (44%) of the males and 17/35 (49%) of the females survived to termination of the study. Survival was 7/15 (47%) among vehicle-



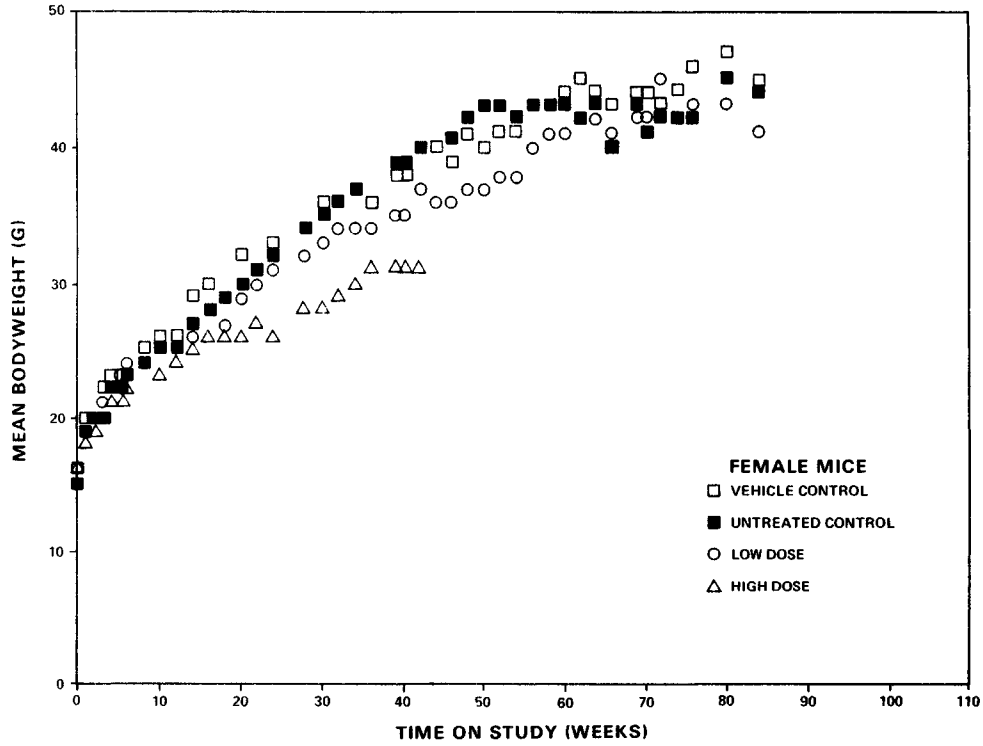


Figure 5. Growth Curves for Mice Treated with Thio-TEPA

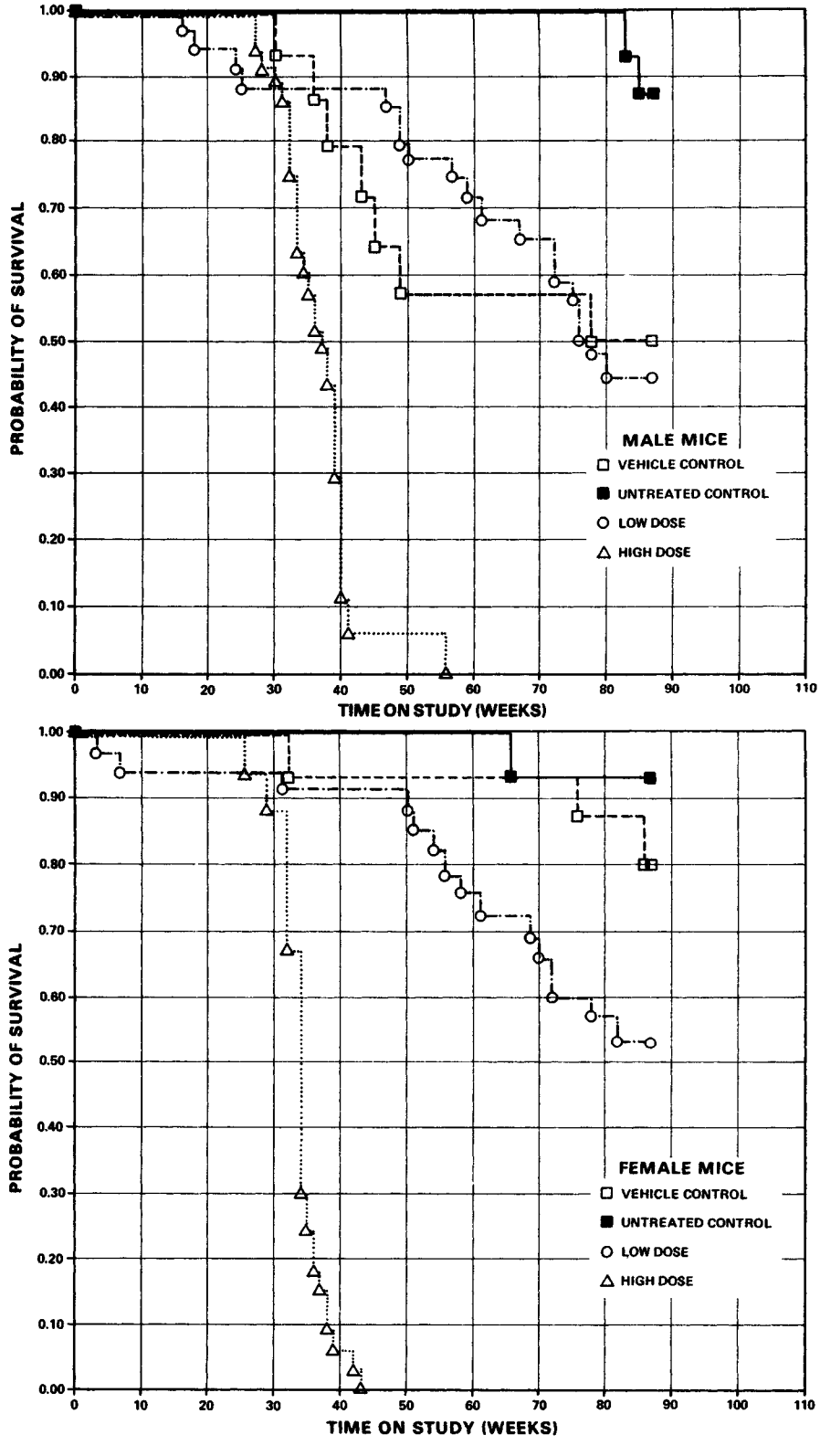


Figure 6. Survival Curves for Mice Treated with Thio-TEPA

control males and 12/15 (80%) among vehicle-control females in the bioassay. Statistical analyses were time-adjusted, eliminating those mice dying before week 52; however, in some groups, insufficient numbers of mice 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.

Excluding the lymphoreticular and epithelial tumors, the neoplasms listed in Appendix B occurred with approximately equal, or greater, frequency in the control mice than in the dosed mice, or occurred in insufficient numbers for accurate evaluation. These lesions are not uncommon in the B6C3F1 strain of mouse independent of the administration of any chemical.

Administration of thio-TEPA increased the frequency of skin tumors and lymphoreticular tumors. The distribution of these tumors was as follows:

MALE	Vehicle Control	Untreated Control	Low Dose	High Dose
Number of Mice Necropsied	(14)	(15)	(30)	(34)
Skin (including preputial glands and subcutaneous tissues)				
Squamous-cell or adnexal carcinoma	0	0	14	1
Basal-cell carcinoma	1	0	0	0
Carcinoma, NOS	0	0	1	0
Multiple Organs, Lymphoreticular				
Malignant lymphoma	0	1	2	16
Leukemia, lymphocytic	1	0	0	10
Leukemia, granulocytic	0	0	1	0
FEMALE				
Number of Mice Necropsied	(15)	(15)	(30)	(32)
Multiple Organs, Lymphoreticular				
Malignant lymphoma	0	1	2	20
Leukemia, lymphocytic	0	0	3	12

The morphology of the skin tumors was similar to that described previously for the rats. The majority of the squamous-cell tumors were malignant, occurred in the groin or pelvic area, and were associated with preputial glands. Two squamous-cell carcinomas metastasized to the lungs. One mouse had a poorly differentiated spindle-cell carcinoma.

The malignant lymphomas were classified as lymphocytic, histiocytic, or mixed types and were usually solid tumors

involving multiple organs including the spleen, lymph nodes, and liver.

In addition to the malignant lymphomas, many female mice had lymphocytic leukemias. These leukemias were composed of neoplastic lymphocytes similar in appearance to those seen in the malignant lymphomas, but they had a more generalized distribution with sinusoidal involvement of the liver. One mouse had a granulocytic leukemia that was composed of well-differentiated neutrophils.

In addition to the neoplastic lesions, a number of degenerative, proliferative, and inflammatory changes were encountered also in animals of the dosed and control groups (Appendix D). These nonneoplastic lesions are commonly seen in aged B6C3F1 mice. The high-dose male and female mice had reduced life spans which were associated with the high incidence of lymphoreticular neoplasms.

Based on the histopathologic examination, thio-TEPA given intraperitoneally to B6C3F1 mice was carcinogenic under conditions of this bioassay. The tumors induced were malignant lymphomas and lymphocytic leukemias in males and females and squamous-cell carcinomas of the skin in males.

D. Statistical Analyses of Results (Mice)

Tables F1-F4 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more than one group. The untreated controls are not included in the tables and analyses, because the test conditions of the vehicle controls more closely resemble those of the dosed mice. Due to the low survival of the high-dose mice, time-adjusted analyses were performed, eliminating animals that died before week 52 on study, 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. The statistical narrative in the following paragraphs is based on time-adjusted data only.

In male mice, the results of the Cochran-Armitage test for dose-related trend in the incidence of squamous-cell carcinoma at all sites are significant ($P = 0.018$), and the Fisher exact test shows that the incidence in the low-dose group is significantly higher ($P = 0.004$) than that in the matched controls. There were only two animals at risk in the high-dose group, and the squamous-cell carcinoma occurred in one of these two animals. This tumor was not present in significant incidences in female

mice; however, the statistical analysis suggests a positive dose association in male mice.

The results of the Cochran-Armitage test for positive dose-related trend in the combined incidence of lymphoma or leukemia in both male and female mice are significant ($P < 0.001$). In the female high-dose group, the incidence is 32/32 (100%) and in the male high-dose group it is 26/28 (93%). The results of the Fisher exact show that the incidences in the high-dose groups are significantly higher ($P < 0.001$) than those in either type of control groups. The statistical conclusion is that the incidences of these hematopoietic tumors in mice are dose associated.

In summary, the results of the statistical tests show that the incidences of squamous-cell carcinoma at all sites in male mice and of the hematopoietic tumors in each sex are associated with the administration of thio-TEPA.

V. DISCUSSION

Under the conditions of this bioassay, thio-TEPA was toxic to both rats and mice, as evidenced by reduced mean body weights and by high mortality. Mean body weights of high-, mid-, and low-dose male rats, high- and mid-dose female rats, and high-dose male and female mice were all markedly lower than those of corresponding controls. All high-dose male rats died by week 19, all high-dose females by week 21, all mid-dose males by week 78, 91% of the mid-dose females by termination week 81, and 85% of the low-dose males and 51% of the low-dose females by termination week 82. Histopathologic evaluation of tissues was performed only on the low- and mid-dose groups of rats, since all high-dose males and females died before the occurrence of tumors could be expected. All of the high-dose male mice died by week 56, all of the high-dose females by week 43, and 77% of the low-dose males and 51% of the low-dose females by termination week 86. Because of this high mortality, time-adjusted analyses were performed on incidences of tumors in each species and each sex.

In rats, the incidence of combined neoplasms of the hematopoietic system (lymphoma, lymphocytic leukemia, or granulocytic leukemia) was significant in the males in both the low-dose ($P = 0.020$) and mid-dose ($P = 0.001$) groups, using pooled controls (pooled

controls 0/29, low-dose 6/34; pooled controls 0/30, mid-dose 6/16).

Squamous-cell carcinoma of the skin or ear canal occurred at a significant incidence in the male rats in both the low-dose ($P = 0.009$) and mid-dose ($P = 0.023$) groups, using pooled controls (pooled controls 0/29, low-dose 7/33; pooled controls 0/30, mid-dose 3/13) and in the mid-dose females ($P < 0.001$), using pooled controls (pooled controls 0/28, mid-dose 8/21); in addition, two low-dose females had such tumors, with none occurring in the corresponding low-dose controls.

The incidence of adenocarcinoma of the uterus was significant in the mid-dose female rats ($P = 0.001$), using pooled controls (pooled controls 0/28, mid-dose 7/21); in addition, two low-dose females had adenocarcinoma of the uterus, with no such tumor occurring in the corresponding low-dose controls. Adenocarcinoma of the mammary gland occurred at a significant incidence in the mid-dose female rats ($P = 0.006$), using pooled controls (pooled controls 1/28, mid-dose 8/24). In addition, seven low-dose females had these tumors, but they were not significant, since one of the low-dose pooled-control females had the tumor; and 3/10 low-dose untreated-control females had the tumor. Thus, the occurrence of mammary adenocarcinoma in the female rats cannot be clearly related to administration of the test chemical.

Also in rats, neuroepitheliomas or nasal carcinomas occurred in three low-dose males, two low-dose females, and two mid-dose females. Although these are not statistically significant incidences, these tumors did not occur among control animals and no such tumors have occurred in 380 or more Sprague-Dawley control rats of each sex in other bioassays at the same laboratory. Thus, they may be associated with administration of the chemical.

In the high-dose groups of both male and female mice, but not in the low-dose groups, the incidences of lymphoma or lymphocytic leukemia were significantly higher ($P < 0.001$) for each sex than those of either the vehicle or pooled controls (males: vehicle controls 1/8, pooled controls 1/18, low-dose 2/24, high-dose 26/28; females: vehicle controls 0/14, pooled controls 0/29, low-dose 5/26, high-dose 32/32). These tumors were observed even though all of the high-dose males died as early as week 56 and all of the high-dose females as early as week 43. In addition, granulocytic leukemia occurred in one low-dose male mouse.

In the low-dose male mice, squamous-cell carcinoma was found in the skin of seven animals, in the preputial glands of six animals, and in the ear canal of two animals. A carcinoma of the preputial gland was also found in a high-dose male. When the incidences of the tumors at the different sites were combined,

the incidence in the low-dose group, but not in the high-dose group was statistically significant using either the vehicle ($P = 0.004$) or the pooled ($P < 0.001$) controls (vehicle controls 0/8, pooled controls 0/18, low-dose 14/24, high-dose 1/2).

In previous tests of thio-TEPA for carcinogenicity, Schmähl and Osswald (1970) observed a variety of tumors in male rats of the BR 46 strain that had been injected intravenously with 1 mg/kg body weight weekly for 52 weeks. Shimkin et al. (1966), using a pulmonary tumor test system, reported the induction of lung tumors in A/J strain mice given intraperitoneal injections of thio-TEPA three times per week for 4 weeks and observed for 39 weeks after the first injection. Stoner et al. (1973), using the same test system, reported the induction of lung tumors in mice of the A/He strain given total dosages of the chemical of 4.7 or 9.4 mg/kg by intraperitoneal injection three times per week for 4 weeks and observed 24 weeks after the first injection.

It is concluded that under the conditions of this bioassay, thio-TEPA was carcinogenic in both Sprague-Dawley rats and B6C3F1 mice. In the rats, the chemical induced squamous-cell carcinoma of the skin or ear canal in both males and females, and hematopoietic neoplasms in the males; in the mice, it induced lymphoma or lymphocytic leukemia in both sexes and squamous-cell carcinoma in the skin and associated glands of males.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (CONTROL GROUPS)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE, UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	10	10	10	10
ANIMALS NECROPSIED	10	9	10	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	9	10	10
INTEGUMENTARY SYSTEM				
*SKIN	(10)	(9)	(10)	(10)
SQUAMOUS CELL PAPILLOMA				1 (10%)
FIBROMA			1 (10%)	
*SUBCUT TISSUE	(10)	(9)	(10)	(10)
FIBROMA			1 (10%)	
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
NONE				
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
*PITUITARY	(10)	(7)	(10)	(9)
CHROMOPHOBE ADENOMA		1 (14%)		3 (33%)

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

TABLE A1. MALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
CHROMOPHOBE CARCINOMA				1 (11%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(9)	(10)	(10)
FIBROADENOMA	2 (20%)		1 (10%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	10	10
NATURAL DEATH@	2	2	1	
MORIBUND SACRIFICE			1	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	8	8	8	10
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	1	3	5
TOTAL PRIMARY TUMORS	2	1	3	5
TOTAL ANIMALS WITH BENIGN TUMORS	2	1	3	4
TOTAL BENIGN TUMORS	2	1	3	4
TOTAL ANIMALS WITH MALIGNANT TUMORS				1
TOTAL MALIGNANT TUMORS				1
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	39	35	35
ANIMALS NECROPSIED	37	30	32
ANIMALS EXAMINED HISTOPATHOLOGICALLY	37	29	0
INTEGUMENTARY SYSTEM			
*SKIN	(37)	(30)	(32)
SQUAMOUS CELL PAPILLOMA	1 (3%)		
SQUAMOUS CELL CARCINOMA	5 (14%)	3 (10%)	
BASAL-CELL CARCINOMA		1 (3%)	
TRICHOEPITHELIOMA	1 (3%)		
*SUBCUT TISSUE	(37)	(30)	(32)
SARCOMA, NOS	5 (14%)		
FIBROMA	2 (5%)		
FIBROSARCOMA	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(37)	(30)	(32)
CARCINOMA,NOS	1 (3%)		
#LUNG	(36)	(29)	
SQUAMOUS CELL CARCINOMA, METASTA		1 (3%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (3%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(37)	(30)	(32)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)		
LYMPHOCYTIC LEUKEMIA	3 (8%)	5 (17%)	
GRANULOCYTIC LEUKEMIA	2 (5%)	1 (3%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. MALE RATS (TREATED GROUPS): NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(37)	(29)	
CARCINOMA,NOS		1 (3%)	
URINARY SYSTEM			
#KIDNEY	(37)	(29)	
HAMARTOMA	1 (3%)		
ENDOCRINE SYSTEM			
#PITUITARY	(28)	(24)	
CHROMOPHOBE ADENOMA	1 (4%)	1 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(37)	(30)	(32)
ADENOCARCINOMA, NOS	1 (3%)		
NERVOUS SYSTEM			
#BRAIN	(36)	(28)	
SARCOMA, NOS		1 (4%)	
ASTROCYTOMA	1 (3%)		
NEUROBLASTOMA	1 (3%)		
OLFACTORY NEUROBLASTOMA	1 (3%)		
SPECIAL SENSE ORGANS			
*EAR CANAL	(37)	(30)	(32)
SQUAMOUS CELL PAPILLOMA	1 (3%)		
SQUAMOUS CELL CARCINOMA	3 (8%)	1 (3%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A2. MALE RATS (TREATED GROUPS): NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES			
*MEDIASTINUM	(37)	(30)	(32)
SARCOMA, NOS	1 (3%)		
*ABDOMINAL CAVITY	(37)	(30)	(32)
SARCOMA, NOS		1 (3%)	
*MESENTERY	(37)	(30)	(32)
SARCOMA, NOS	2 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(37)	(30)	(32)
SQUAMOUS CELL CARCINOMA, METASTA		1 (3%)	
CRANIAL CAVITY			
SARCOMA, NOS	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	39	35	35
NATURAL DEATH@	7	13	26
MORIBUND SACRIFICE	26	22	9
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	6		
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. MALE RATS (TREATED GROUPS): NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	27	14	
TOTAL PRIMARY TUMORS	36	16	
TOTAL ANIMALS WITH BENIGN TUMORS	6	2	
TOTAL BENIGN TUMORS	7	2	
TOTAL ANIMALS WITH MALIGNANT TUMORS	26	12	
TOTAL MALIGNANT TUMORS	29	14	
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	
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 A3.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (CONTROL GROUPS)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	10	10	10	10
ANIMALS NECROPSIED	10	10	10	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	10	10
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(10)	(10)	(10)	(10)
FIBROMA	1 (10%)			
RESPIRATORY SYSTEM				
NONE				
HEMATOPOIETIC SYSTEM				
NONE				
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
NONE				
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(10)	(10)	(10)	(8)
CHROMOPHOBE ADENOMA	5 (50%)	6 (60%)	2 (20%)	1 (13%)

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

TABLE A3. FEMALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
CHROMOPHOBE CARCINOMA		1 (10%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(10)	(10)	(10)
ADENOCARCINOMA, NOS		3 (30%)	1 (10%)	
FIBROADENOMA	2 (20%)	6 (60%)	5 (50%)	2 (20%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	10	10
NATURAL DEATH@	2			1
MORIBUND SACRIFICE		2		
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED		1		
TERMINAL SACRIFICE	8	7	10	9
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A3. FEMALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	9	5	3
TOTAL PRIMARY TUMORS	8	16	8	3
TOTAL ANIMALS WITH BENIGN TUMORS	7	9	5	3
TOTAL BENIGN TUMORS	8	12	7	3
TOTAL ANIMALS WITH MALIGNANT TUMORS		4	1	
TOTAL MALIGNANT TUMORS		4	1	
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A4.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	31	35	35
ANIMALS NECROPSIED	30	33	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	30	33	0
INTEGUMENTARY SYSTEM			
*SKIN	(30)	(33)	(34)
SQUAMOUS CELL PAPILLOMA		1 (3%)	
SQUAMOUS CELL CARCINOMA		3 (9%)	
*SUBCUT TISSUE	(30)	(33)	(34)
SARCOMA, NOS	1 (3%)		
FIBROMA	1 (3%)		
FIBROSARCOMA	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(30)	(33)	(34)
CARCINOMA,NOS		1 (3%)	
#LUNG	(30)	(33)	
ADENOCARCINOMA, NOS, METASTATIC	2 (7%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(30)	(33)	(34)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
LYMPHOCYTIC LEUKEMIA		1 (3%)	
GRANULOCYTIC LEUKEMIA	1 (3%)		
#MANDIBULAR L. NODE	(28)	(1)	
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (4%)		
#THYMUS	(30)	(33)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE A4. FEMALE RATS (TREATED GROUPS): NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(24)		
SARCOMA, NOS	1 (4%)		
URINARY SYSTEM			
#KIDNEY	(30)	(33)	
HAMARTOMA	1 (3%)		
ENDOCRINE SYSTEM			
#PITUITARY	(29)	(32)	
CHROMOPHOBE ADENOMA	4 (14%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(30)	(33)	(34)
ADENOMA, NOS		3 (9%)	
ADENOCARCINOMA, NOS	7 (23%)	8 (24%)	
FIBROADENOMA	8 (27%)	4 (12%)	
#UTERUS	(30)	(32)	
ADENOCARCINOMA, NOS	2 (7%)	7 (22%)	
SARCOMA, NOS	2 (7%)	1 (3%)	
ENDOMETRIAL STROMAL POLYP	4 (13%)	1 (3%)	
#CERVIX UTERI	(30)	(32)	
SQUAMOUS CELL CARCINOMA	1 (3%)		
#OVARY	(30)	(32)	
LUTEOMA		1 (3%)	
SARCOMA, NOS		1 (3%)	
NERVOUS SYSTEM			
#BRAIN	(30)	(32)	
SARCOMA, NOS		1 (3%)	
OLFACTORY NEUROBLASTOMA	2 (7%)	1 (3%)	

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

TABLE A4. FEMALE RATS (TREATED GROUPS): NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EAR CANAL	(30)	(33)	(34)
SQUAMOUS CELL PAPILLOMA		1 (3%)	
SQUAMOUS CELL CARCINOMA	2 (7%)	5 (15%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(30)	(33)	(34)
ADENOCARCINOMA, NOS, METASTATIC	1 (3%)	1 (3%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(30)	(33)	(34)
ADENOCARCINOMA, NOS		1 (3%)	
ADENOCARCINOMA, NOS, METASTATIC		4 (12%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	31	35	35
NATURAL DEATH@	9	10	15
MORIBUND SACRIFICE	9	22	20
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	3	
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A4. FEMALE RATS (TREATED GROUPS): NEOPLASMS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	26	
TOTAL PRIMARY TUMORS	39	43	
TOTAL ANIMALS WITH BENIGN TUMORS	14	9	
TOTAL BENIGN TUMORS	18	11	
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	22	
TOTAL MALIGNANT TUMORS	21	32	
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	5	
TOTAL SECONDARY TUMORS	3	5	
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 GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	@34	35
ANIMALS NECROPSIED	14	15	30	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	14	15	30	33
INTEGUMENTARY SYSTEM				
*SKIN	(14)	(15)	(30)	(34)
CARCINOMA,NOS			1 (3%)	
SQUAMOUS CELL CARCINOMA			7 (23%)	
BASAL-CELL CARCINOMA	1 (7%)			
*SUBCUT TISSUE	(14)	(15)	(30)	(34)
SQUAMOUS CELL CARCINOMA			1 (3%)	
SARCOMA, NOS			1 (3%)	
RESPIRATORY SYSTEM				
#LUNG	(14)	(15)	(30)	(33)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	1 (3%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (7%)	4 (27%)	5 (17%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(14)	(15)	(30)	(34)
MALIGNANT LYMPHOMA, NOS				2 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				14 (41%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)	
MALIGNANT LYMPHOMA, MIXED TYPE			1 (3%)	
LYMPHOCYTIC LEUKEMIA	1 (7%)			10 (29%)
GRANULOCYTIC LEUKEMIA			1 (3%)	
#MESENTERIC L. NODE	(2)	(5)	(1)	(15)
MALIGNANT LYMPHOMA, NOS		1 (20%)		
CIRCULATORY SYSTEM				
#MYOCARDIUM	(14)	(15)	(30)	(32)
HEMANGIOMA			1 (3%)	

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

@NOTE: 35 ANIMALS WERE INITIALLY IN STUDY BUT ONE WAS FOUND TO BE A FEMALE IN A MALE GROUP AND WAS DELETED.

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(14)	(15)	(30)	(33)
HEPATOCELLULAR ADENOMA	1 (7%)	2 (13%)	3 (10%)	
HEPATOCELLULAR CARCINOMA	1 (7%)		1 (3%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(14)	(15)	(30)	(34)
SQUAMOUS CELL CARCINOMA			6 (20%)	1 (3%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR CANAL	(14)	(15)	(30)	(34)
SQUAMOUS CELL PAPILLOMA			1 (3%)	
SQUAMOUS CELL CARCINOMA			2 (7%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	15	15	35	35
NATURAL DEATH@	7	2	13	13
MORIBUND SACRIFICE			6	22
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	1			
TERMINAL SACRIFICE	7	13	15	
ANIMAL MISSING				
ANIMAL DELETED (WRONG SEX)			1	
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	19	27
TOTAL PRIMARY TUMORS	5	7	32	27
TOTAL ANIMALS WITH BENIGN TUMORS	2	5	8	
TOTAL BENIGN TUMORS	2	6	10	
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	1	18	27
TOTAL MALIGNANT TUMORS	3	1	22	27
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				

@ INCLUDES AUTOLYZED ANIMALS

* 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 GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	35	35
ANIMALS MISSING			1	2
ANIMALS NECROPSIED	15	15	30	32
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	15	30	32
INTEGUMENTARY SYSTEM				
*SKIN	(15)	(15)	(30)	(32)
SQUAMOUS CELL PAPILLOMA			1 (3%)	
RESPIRATORY SYSTEM				
#LUNG	(15)	(15)	(29)	(32)
ADENOCARCINOMA, NOS, METASTATIC			1 (3%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			5 (17%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(15)	(15)	(30)	(32)
MALIGNANT LYMPHOMA, NOS				1 (3%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			2 (7%)	19 (59%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (7%)		
LYMPHOCYTIC LEUKEMIA			3 (10%)	12 (38%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(15)	(15)	(30)	(32)
HEPATOCELLULAR ADENOMA			2 (7%)	
URINARY SYSTEM				
NONE				

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#ADRENAL	(15)	(15)	(28)	(32)
CORTICAL CARCINOMA			1 (4%)	
PHEOCHROMOCYTOMA			1 (4%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(15)	(15)	(30)	(32)
ADENOCARCINOMA, NOS			1 (3%)	
#OVARY	(15)	(15)	(29)	(31)
CARCINOMA,NOS			3 (10%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR CANAL	(15)	(15)	(30)	(32)
SQUAMOUS CELL PAPILLOMA			1 (3%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	15	15	35	35
NATURAL DEATH@	2	1	11	16
MORIBUND SACRIFICE	1		4	17
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED			2	
TERMINAL SACRIFICE	12	14	17	
ANIMAL MISSING			1	2
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*		1	17	32
TOTAL PRIMARY TUMORS		1	20	32
TOTAL ANIMALS WITH BENIGN TUMORS			10	
TOTAL BENIGN TUMORS			10	
TOTAL ANIMALS WITH MALIGNANT TUMORS		1	9	32
TOTAL MALIGNANT TUMORS		1	10	32
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	
TOTAL SECONDARY TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (CONTROL GROUPS)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	10	10	10	10
ANIMALS NECROPSIED	10	9	10	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	9	10	10
INTEGUMENTARY SYSTEM				
*SKIN	(10)	(9)	(10)	(10)
ULCER, CHRONIC				1 (10%)
RESPIRATORY SYSTEM				
#TRACHEA	(10)	(9)	(10)	(10)
INFLAMMATION, NOS	1 (10%)			
INFLAMMATION, ACUTE/CHRONIC			1 (10%)	
INFLAMMATION, CHRONIC		1 (11%)		
INFLAMMATION, CHRONIC SUPPURATIV				1 (10%)
#LUNG/BRONCHUS	(10)	(9)	(10)	(10)
BRONCHIECTASIS		1 (11%)		
#LUNG/BRONCHIOLE	(10)	(9)	(10)	(10)
HYPERPLASIA, LYMPHOID	1 (10%)		1 (10%)	
#LUNG	(10)	(9)	(10)	(10)
BRONCHOPNEUMONIA SUPPURATIVE			1 (10%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(10)	(9)	(10)	(10)
ATROPHY, NOS	2 (20%)	4 (44%)	5 (50%)	7 (70%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(10)	(9)	(10)	(10)
HYPERPLASIA, NODULAR		1 (11%)		

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
*BILE DUCT	(10)	(9)	(10)	(10)
HYPERPLASIA, NOS	1 (10%)			
URINARY SYSTEM				
*KIDNEY	(10)	(9)	(10)	(10)
INFLAMMATION, INTERSTITIAL	6 (60%)		4 (40%)	
INFLAMMATION, SUPPURATIVE	1 (10%)			
INFLAMMATION, CHRONIC		6 (67%)		8 (80%)
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(9)	(10)	(10)
CYST, NOS				1 (10%)
#PROSTATE	(10)	(9)	(10)	(10)
INFLAMMATION, CHRONIC SUPPURATIV		1 (11%)		1 (10%)
#TESTIS	(9)	(9)	(10)	(10)
ATROPHY, NOS		1 (11%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		2	2	
NO NECROPSY PERFORMED		1		

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	39	35	35
ANIMALS NECROPSIED	37	30	32
ANIMALS EXAMINED HISTOPATHOLOGICALLY	37	29	0
INTEGUMENTARY SYSTEM			
*SKIN	(37)	(30)	(32)
EPIDERMAL INCLUSION CYST	2 (5%)		
DERMAL INCLUSION CYST		1 (3%)	
INFLAMMATION, SUPPURATIVE	1 (3%)		
ABSCESS, CHRONIC	1 (3%)		
HYPERKERATOSIS	1 (3%)		
KERATIN-PEARL FORMATION	1 (3%)	1 (3%)	
RESPIRATORY SYSTEM			
#TRACHEA	(37)	(28)	
INFLAMMATION, CHRONIC	2 (5%)		
#LUNG/BRONCHIOLE	(36)	(29)	
HYPERPLASIA, PLASMA CELL		2 (7%)	
#LUNG	(36)	(29)	
HEMORRHAGE	1 (3%)		
INFLAMMATION, SUPPURATIVE	1 (3%)		
BRONCHOPNEUMONIA SUPPURATIVE	2 (6%)	10 (34%)	
BRONCHOPNEUMONIA CHRONIC SUPPURA	3 (8%)	5 (17%)	
ABSCESS, CHRONIC		1 (3%)	
METAPLASIA, SQUAMOUS	1 (3%)	2 (7%)	
HYPERPLASIA, PLASMA CELL		1 (3%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(35)	(29)	
ATROPHY, NOS	17 (49%)	10 (34%)	
#SPLEEN	(37)	(28)	
INFLAMMATION, NECROTIZING	1 (3%)		

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

TABLE C2. MALE RATS (TREATED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
ATROPHY, NOS	1 (3%)		
ANGIECTASIS	1 (3%)		
HEMATOPOIESIS	4 (11%)	1 (4%)	
#MANDIBULAR L. NODE	(31)	(6)	
CONGESTION, NOS	1 (3%)		
HYPERPLASIA, RETICULUM CELL	1 (3%)		
#MESENTERIC L. NODE	(31)	(6)	
CONGESTION, NOS	1 (3%)		
INFLAMMATION, GRANULOMATOUS	1 (3%)		
CYTOMEGALY	1 (3%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(37)	(28)	
INFLAMMATION, INTERSTITIAL	1 (3%)		
CALCIFICATION, METASTATIC	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(37)	(29)	
HEMORRHAGE	1 (3%)		
ANGIECTASIS		1 (3%)	
#PANCREAS	(37)	(29)	
NECROSIS, FAT	1 (3%)		
#ESOPHAGUS	(36)	(27)	
ULCER, NOS	1 (3%)		
INFLAMMATION, SUPPURATIVE	1 (3%)		
#GASTRIC MUCOSA	(37)	(29)	
CALCIFICATION, METASTATIC	1 (3%)		
#COLON	(36)	(29)	
HEMORRHAGE	1 (3%)		
#CECUM	(36)	(29)	
THROMBOSIS, NOS		1 (3%)	
URINARY SYSTEM			
#KIDNEY	(37)	(29)	
CALCULUS, NOS		1 (3%)	

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

TABLE C2. MALE RATS (TREATED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, INTERSTITIAL		7 (24%)	
INFLAMMATION, CHRONIC	26 (70%)		
CALCIFICATION, METASTATIC	1 (3%)		
ENDOCRINE SYSTEM			
#ADRENAL	(37)	(29)	
ANGIECTASIS	1 (3%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(36)	(27)	
ATROPHY, NOS	15 (42%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(37)	(30)	(32)
HEMORRHAGE	1 (3%)		
INFLAMMATION, SUPPURATIVE	1 (3%)		
*EYE/CORNEA	(37)	(30)	(32)
ULCER, CHRONIC	1 (3%)		
*EYE/CONJUNCTIVA	(37)	(30)	(32)
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	
*MIDDLE EAR	(37)	(30)	(32)
INFLAMMATION, SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (3%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(37)	(30)	(32)
INFLAMMATION, CHRONIC	1 (3%)		

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

TABLE C2. MALE RATS (TREATED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
*PLEURA	(37)	(30)	(32)
INFLAMMATION, SUPPURATIVE	1 (3%)		
*MESENTERY	(37)	(30)	(32)
NECROSIS, FAT	1 (3%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
NECROPSY PERF/NO HISTO PERFORMED		1	31
NO NECROPSY PERFORMED	1		
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY	1	5	3

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

TABLE C3.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (CONTROL GROUPS)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
ANIMALS INITIALLY IN STUDY	10	10	10	10
ANIMALS NECROPSIED	10	10	10	10
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	10	10
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#TRACHEA	(10)	(10)	(10)	(10)
INFLAMMATION, NOS	1 (10%)			
INFLAMMATION, CHRONIC				1 (10%)
#LUNG	(10)	(10)	(10)	(10)
PNEUMONIA, LIPID		1 (10%)		
PNEUMONIA INTERSTITIAL CHRONIC		1 (10%)		
BRONCHOPNEUMONIA CHRONIC SUPPURA		1 (10%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(10)	(10)	(10)	(9)
ATROPHY, NOS	4 (40%)	7 (70%)	7 (70%)	7 (78%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER/PERIPORTAL	(10)	(10)	(10)	(10)
FIBROSIS	1 (10%)			
#PANCREATIC ACINUS	(10)	(10)	(10)	(10)
ATROPHY, NOS	1 (10%)			

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(10)	(10)
INFLAMMATION, INTERSTITIAL			1 (10%)	
INFLAMMATION, CHRONIC		3 (30%)		1 (10%)
GLOMERULONEPHRITIS, CHRONIC	1 (10%)			
ENDOCRINE SYSTEM				
#ADRENAL	(10)	(10)	(10)	(10)
ANGIECTASIS	2 (20%)	1 (10%)	1 (10%)	3 (30%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(10)	(10)	(10)
CYST, NOS	2 (20%)	1 (10%)	5 (50%)	1 (10%)
HEMORRHAGIC CYST		1 (10%)		
#UTERUS	(10)	(10)	(10)	(10)
INFLAMMATION, SUPPURATIVE			1 (10%)	
#UTERUS/ENDOMETRIUM	(10)	(10)	(10)	(10)
INFLAMMATION, SUPPURATIVE	5 (50%)	1 (10%)		
#OVARY	(10)	(10)	(9)	(10)
CYST, NOS		1 (10%)		6 (60%)
INFLAMMATION, HEMORRHAGIC		1 (10%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (10%)		
NERVOUS SYSTEM				
#BRAIN	(10)	(10)	(10)	(9)
HYDROCEPHALUS, NOS			1 (10%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	MID AND HIGH DOSE UNTREATED CONTROL	LOW DOSE UNTREATED CONTROL	MID AND HIGH DOSE VEHICLE CONTROL	LOW DOSE VEHICLE CONTROL
BODY CAVITIES				
*MESENTERY	(10)	(10)	(10)	(10)
STEATITIS				1 (10%)
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, FOCAL GRANULOMATOU		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1		2	

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

TABLE C4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA (TREATED GROUPS)

	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	31	35	35
ANIMALS NECROPSIED	30	33	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	30	33	0
INTEGUMENTARY SYSTEM			
*SKIN	(30)	(33)	(34)
INFLAMMATION, SUPPURATIVE		1 (3%)	
HYPERKERATOSIS		1 (3%)	
PARAKERATOSIS		1 (3%)	
RESPIRATORY SYSTEM			
#TRACHEA	(30)	(33)	
INFLAMMATION, NOS		2 (6%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (3%)	
INFLAMMATION, CHRONIC	3 (10%)		
#LUNG/BRONCHIOLE	(30)	(33)	
METAPLASIA, SQUAMOUS		1 (3%)	
#LUNG	(30)	(33)	
EDEMA, NOS	1 (3%)		
HEMORRHAGE	1 (3%)		
BRONCHOPNEUMONIA SUPPURATIVE	1 (3%)	4 (12%)	
ABSCESS, NOS		2 (6%)	
BRONCHOPNEUMONIA CHRONIC SUPPURA	1 (3%)	4 (12%)	
INFLAMMATION, GRANULOMATOUS	3 (10%)		
CYTOMEGALY	2 (7%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(29)	(33)	
ATROPHY, NOS	13 (45%)	8 (24%)	
#SPLEEN	(30)	(33)	
HEMORRHAGE	1 (3%)		

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

TABLE C4. FEMALE RATS (TREATED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
ANGIECTASIS	1 (3%)		
HEMATOPOIESIS	5 (17%)	7 (21%)	
#MESENTERIC L. NODE	(28)	(1)	
CONGESTION, NOS	2 (7%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(30)	(33)	
HEMORRHAGE	2 (7%)		
INFLAMMATION, CHRONIC NECROTIZIN	1 (3%)		
INFLAMMATION, GRANULOMATOUS	1 (3%)		
INFLAMMATION, NECRO GRAN	1 (3%)		
NECROSIS, FOCAL	1 (3%)		
CYTOPLASMIC VACUOLIZATION	1 (3%)		
HEPATOCYTOMEGALY	2 (7%)		
HEMATOPOIESIS	1 (3%)		
#LIVER/CENTRILOBULAR	(30)	(33)	
NECROSIS, NOS		1 (3%)	
NECROSIS, COAGULATIVE	1 (3%)		
#PANCREAS	(30)	(33)	
ATROPHY, NOS		1 (3%)	
#COLON	(29)	(30)	
ULCER, NOS	1 (3%)		
*RECTUM	(30)	(33)	(34)
HEMATOMA, NOS		1 (3%)	
URINARY SYSTEM			
#KIDNEY	(30)	(33)	
HYDRONEPHROSIS	1 (3%)		
INFLAMMATION, INTERSTITIAL		1 (3%)	
GLOMERULONEPHRITIS, MEMBRANOUS		1 (3%)	
INFLAMMATION, CHRONIC	10 (33%)		

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

TABLE C4. FEMALE RATS (TREATED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ADRENAL	(30)	(33)	
ANGIECTASIS	11 (37%)	4 (12%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(30)	(33)	(34)
CYST, NOS	13 (43%)	3 (9%)	
INFLAMMATION, VESICULAR		1 (3%)	
*VAGINA	(30)	(33)	(34)
EPIDERMAL INCLUSION CYST	1 (3%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (3%)		
#UTERUS	(30)	(32)	
HEMORRHAGE	1 (3%)		
ANGIECTASIS	1 (3%)		
METAPLASIA, SQUAMOUS	1 (3%)		
#UTERUS/ENDOMETRIUM	(30)	(32)	
INFLAMMATION, SUPPURATIVE	4 (13%)	4 (13%)	
ULCER, CHRONIC	1 (3%)		
INFLAMMATION, CHRONIC SUPPURATIV	6 (20%)	2 (6%)	
HYPERPLASIA, CYSTIC	2 (7%)		
#OVARY	(30)	(32)	
CYST, NOS	14 (47%)		
INFLAMMATION, SUPPURATIVE		1 (3%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (3%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EAR CANAL	(30)	(33)	(34)
KERATIN-PEARL FORMATION		1 (3%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C4. FEMALE RATS (TREATED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
NECROPSY PERF/NO HISTO PERFORMED			34
AUTOLYSIS/NO NECROPSY	1	2	1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	@34	35
ANIMALS NECROPSIED	14	15	30	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	14	15	30	33
INTEGUMENTARY SYSTEM				
*SKIN	(14)	(15)	(30)	(34)
EPIDERMAL INCLUSION CYST			1 (3%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)		1 (3%)	
*SUBCUT TISSUE	(14)	(15)	(30)	(34)
EDEMA, NOS				2 (6%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (7%)		
METAPLASIA, SQUAMOUS			1 (3%)	
RESPIRATORY SYSTEM				
#LUNG	(14)	(15)	(30)	(33)
INFLAMMATION, INTERSTITIAL				1 (3%)
BRONCHOPNEUMONIA SUPPURATIVE		1 (7%)		
PERIARTERITIS			1 (3%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(13)	(14)	(29)	(32)
ATROPHY, NOS				4 (13%)
HYPERPLASIA, GRANULOCYTIC			1 (3%)	
#SPLEEN	(14)	(15)	(30)	(31)
HYPERPLASIA, GRANULOCYTIC				1 (3%)
HYPERPLASIA, LYMPHOID			2 (7%)	
HEMATOPOIESIS	1 (7%)	2 (13%)	18 (60%)	10 (32%)
#MESENTERIC L. NODE	(2)	(5)	(1)	(15)
CONGESTION, NOS		4 (80%)		
HYPERPLASIA, LYMPHOID	1 (50%)			

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

@NOTE: 35 ANIMALS WERE INITIALLY IN STUDY BUT ONE WAS FOUND TO BE A FEMALE IN A MALE GROUP AND WAS DELETED.

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
#MYOCARDIUM	(14)	(15)	(30)	(32)
INFLAMMATION, INTERSTITIAL			1 (3%)	
INFLAMMATION, CHRONIC			1 (3%)	
DIGESTIVE SYSTEM				
#LIVER	(14)	(15)	(30)	(33)
MINERALIZATION			1 (3%)	
CONGESTION, NOS		1 (7%)		
NECROSIS, NOS			1 (3%)	
NECROSIS, FOCAL				1 (3%)
HYPERPLASIA, NODULAR		3 (20%)		
#LIVER/CENTRILOBULAR	(14)	(15)	(30)	(33)
NECROSIS, NOS			1 (3%)	
#LIVER/PERIPORTAL	(14)	(15)	(30)	(33)
FIBROSIS			1 (3%)	
URINARY SYSTEM				
#KIDNEY	(14)	(15)	(30)	(33)
HYDRONEPHROSIS			1 (3%)	
INFLAMMATION, SUPPURATIVE				1 (3%)
PYELONEPHRITIS SUPPURATIVE	1 (7%)			
INFLAMMATION, CHRONIC			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#URINARY BLADDER	(14)	(15)	(30)	(33)
INFLAMMATION, ACUTE/CHRONIC	1 (7%)			
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)			
ENDOCRINE SYSTEM				
#ADRENAL	(14)	(15)	(30)	(33)
ANGIECTASIS			1 (3%)	
REPRODUCTIVE SYSTEM				
#PROSTATE	(14)	(15)	(30)	(33)
INFLAMMATION, SUPPURATIVE			2 (7%)	1 (3%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS			1 (3%)	
#TESTIS	(14)	(15)	(30)	(33)
ATROPHY, NOS				1 (3%)
#TUNICA ALBUGINEA	(14)	(15)	(30)	(33)
MINERALIZATION			1 (3%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR CANAL	(14)	(15)	(30)	(34)
KERATIN-PEARL FORMATION			1 (3%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(14)	(15)	(30)	(34)
HYPERPLASIA, LYMPHOID			1 (3%)	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	7	5	6	1
NECROPSY PERF/NO HISTO PERFORMED				1
AUTOLYSIS/NO NECROPSY	1		4	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	35	35
ANIMALS MISSING			1	2
ANIMALS NECROPSIED	15	15	30	32
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	15	30	32
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(15)	(15)	(30)	(32)
EDEMA, NOS				5 (16%)
RESPIRATORY SYSTEM				
#LUNG/BRONCHIOLE	(15)	(15)	(29)	(32)
HYPERPLASIA, LYMPHOID	1 (7%)	1 (7%)	1 (3%)	
#LUNG	(15)	(15)	(29)	(32)
INFLAMMATION, INTERSTITIAL			2 (7%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (3%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(15)	(15)	(29)	(32)
ATROPHY, NOS	1 (7%)		4 (14%)	
#SPLEEN	(15)	(15)	(30)	(32)
ANGIECTASIS			1 (3%)	
HEMATOPOIESIS	3 (20%)		5 (17%)	2 (6%)
#MESENTERIC L. NODE	(2)	(1)	(4)	(24)
HYPERPLASIA, GRANULOCYTIC	1 (50%)			
HYPERPLASIA, RETICULUM CELL			1 (25%)	
HYPERPLASIA, LYMPHOID	1 (50%)		1 (25%)	
#INGUINAL LYMPH NODE	(2)	(1)	(4)	(24)
CONGESTION, NOS	1 (50%)			
ATROPHY, NOS	1 (50%)			
CIRCULATORY SYSTEM				
#MYOCARDIUM	(15)	(15)	(29)	(32)
INFLAMMATION, INTERSTITIAL			1 (3%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(15)	(15)	(30)	(32)
FIBROSIS, DIFFUSE			1 (3%)	
NECROSIS, FOCAL		1 (7%)		
INFARCT, NOS		1 (7%)		
HYPERPLASIA, NODULAR			1 (3%)	
ANGIECTASIS			1 (3%)	
HEMATOPOIESIS			1 (3%)	
#PANCREAS	(15)	(15)	(28)	(32)
ATROPHY, NOS	1 (7%)			
URINARY SYSTEM				
#KIDNEY	(15)	(15)	(30)	(32)
HYDRONEPHROSIS	1 (7%)			
INFLAMMATION, INTERSTITIAL	1 (7%)			
AMYLOIDOSIS			1 (3%)	
HYPERPLASIA, LYMPHOID	1 (7%)			
#URINARY BLADDER	(15)	(15)	(29)	(32)
INFLAMMATION, CHRONIC SUPPURATIV	1 (7%)			
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
#UTERUS	(15)	(15)	(29)	(31)
EDEMA, NOS	1 (7%)			
#UTERUS/ENDOMETRIUM	(15)	(15)	(29)	(31)
INFLAMMATION, CHRONIC SUPPURATIV		1 (7%)		
HYPERPLASIA, CYSTIC	10 (67%)	10 (67%)	9 (31%)	
#OVARY	(15)	(15)	(29)	(31)
CYST, NOS			2 (7%)	1 (3%)
HEMORRHAGE			1 (3%)	
ATROPHY, NOS			1 (3%)	
NERVOUS SYSTEM				
NONE				

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
*EAR CANAL	(15)	(15)	(30)	(32)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(15)	(15)	(30)	(32)
INFLAMMATION, NOS	1 (7%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(15)	(15)	(30)	(32)
PERIARTERITIS		1 (7%)		
HYPERPLASIA, LYMPHOID			1 (3%)	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	4	3	6	
ANIMAL MISSING/NO NECROPSY			1	2
AUTO/NECROPSY/HISTO PERF			1	
AUTOLYSIS/NO NECROPSY			4	1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

Table E1. Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Skin: Squamous-cell Carcinoma[b]	0/30 (0)	0/10 (0)	5/37 (14)
P Values[c,d]			P = 0.045**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.044
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.381
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	53
Subcutaneous Tissue: Sarcoma, NOS[b]	0/30 (0)	0/10 (0)	5/37 (14)
P Values[c,d]			P = 0.045**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.044
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.381
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	61

Table E1. Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Subcutaneous Tissue: Sarcoma or Fibrosarcoma[b]	1/30 (3)	0/10 (0)	6/37 (16)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			4.865
Lower Limit			0.642
Upper Limit			216.767
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.484
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	61
Subcutaneous Tissue: Fibroma[b]	0/30 (0)	0/10 (0)	2/37 (5)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.244
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.088
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	74

Table E1. Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Hematopoietic System: Granulocytic Leukemia[b]	0/30 (0)	0/10 (0)	2/37 (5)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.244
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.088
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	55
Hematopoietic System: Lymphoma or Lymphocytic Leukemia[b]	0/30 (0)	0/10 (0)	4/37 (11)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.767
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.279
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	37

Table E1. Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Hematopoietic System:			
Leukemia or Lymphoma[b]	0/30 (0)	0/10 (0)	6/37 (16)
P Values[c,d]			P = 0.023**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.325
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.484
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	37
Pituitary: Chromophobe Adenoma[b]	7/26 (27)	3/9 (33)	1/28 (4)
P Values[c,d]			P = 0.038*(N) P = 0.019**(N)
Relative Risk (Pooled Control)[e]			0.133
Lower Limit			0.003
Upper Limit			0.931
Relative Risk (Vehicle Control)[e]			0.107
Lower Limit			0.002
Upper Limit			1.186
Weeks to First Observed Tumor	--	82	78

Table E1. Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Ear Canal: Squamous-cell Carcinoma[b]	0/30 (0)	0/10 (0)	3/37 (8)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.497
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.181
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	74
Skin and Ear Canal: Squamous-cell Carcinoma[b]	0/30 (0)	0/10 (0)	7/37 (19)
P Values[c,d]			P = 0.011**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.608
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.587
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	53

Table E1. Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Mesentery: Sarcoma, NOS[b]	0/30 (0)	0/10 (0)	2/37 (5)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.244
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.088
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	66

[a]Treated group received dose of 0.7 mg/kg.

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

[c]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Mid-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Skin: Squamous-cell Carcinoma[b]	0/30 (0)	0/10 (0)	3/30 (10)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.614
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.223
Upper Limit			Infinite
Weeks to First Observed Tumor		--	44
Hematopoietic System:			
Lymphocytic Leukemia[b]	0/30 (0)	0/10 (0)	5/30 (17)
P Values[c,d]			P = 0.026**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.291
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.471
Upper Limit			Infinite
Weeks to First Observed Tumor		--	40

Table E2. Analyses of the Incidence of Primary Tumors in Mid-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Hematopoietic System: All Leukemia[b]	0/30 (0)	0/10 (0)	6/30 (20)
P Values[c,d]			P = 0.012**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.638
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.598
Upper Limit			Infinite
Weeks to First Observed Tumor		--	40
Pituitary: Chromophobe Adenoma[b]	2/29 (7)	0/10 (0)	1/24 (4)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			0.604
Lowe Limit			0.011
Upper Limit			10.830
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.024
Upper Limit			Infinite
Weeks to First Observed Tumor		--	54

Table E2. Analyses of the Incidence of Primary Tumors in Mid-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Skin and Ear Canal:			
Squamous-cell Carcinoma[b]	0/30 (0)	0/10 (0)	3/30 (10)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.614
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.223
Upper Limit			Infinite
Weeks to First Observed Tumor		--	44

[a]Treated group received dose of 1.4 mg/kg.

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

[c]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E3. Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Subcutaneous Tissue: Sarcoma, NOS, or Fibrosarcoma[b]	0/30 (0)	0/10 (0)	2/30 (7)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.301
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.109
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	79
Hematopoietic System: Leukemia or Lymphoma[b]	1/30 (3)	0/10 (0)	2/30 (7)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			2.000
Lower Limit			0.110
Upper Limit			113.910
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.109
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	63

Table E3. Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Pituitary: Chromophobe Adenoma[b]	14/28 (50)	1/8 (13)	4/29 (14)
P Values[c,d]			P = 0.004**(N)
Relative Risk (Pooled Control)[e]			0.276
Lower Limit			0.078
Upper Limit			0.752
Relative Risk (Vehicle Control)[e]			1.103
Lower Limit			0.142
Upper Limit			52.317
Weeks to First Observed Tumor	--	82	75
Ear Canal: Squamous-cell Carcinoma[b]	0/30 (0)	0/10 (0)	2/30 (7)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.301
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.109
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	74

Table E3. Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Brain: Olfactory Neuroblastoma[b]	0/30 (0)	0/10 (0)	2/30 (7)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.301
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.109
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	59
Mammary Gland: Adenocarcinoma, NOS[b]	1/30 (3)	0/10 (0)	7/30 (23)
P Values[c,d]			P = 0.026**
Relative Risk (Pooled Control)[e]			7.000
Lower Limit			0.987
Upper Limit			302.176
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.726
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	37

Table E3. Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Mammary Gland: Fibroadenoma[b]	6/30 (20)	2/10 (20)	8/30 (27)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			1.333
Lower Limit			0.464
Upper Limit			4.085
Relative Risk (Vehicle Control)[e]			1.333
Lower Limit			0.348
Upper Limit			11.664
Weeks to First Observed Tumor	--	82	66
Uterus: Adenocarcinoma, NOS[b]	0/30 (0)	0/10 (0)	2/30 (7)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.301
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.109
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	70

Table E3. Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Uterus: Sarcoma, NOS[b]	0/30 (0)	0/10 (0)	2/30 (7)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.301
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.109
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	82
Uterus: Endometrial Stromal Polyp[b]	1/30 (3)	0/10 (0)	4/30 (13)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			4.000
Lower Limit			0.428
Upper Limit			189.625
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.345
Upper Limit			Infinite
Weeks to First Observed Tumor	--	--	63

Table E3. Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated group received dose of 0.7 mg/kg.

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

[c]Beneath the incidence of tumors in a treated groups is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E4. Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Skin: Squamous-cell Carcinoma[b]	0/28 (0)	0/10 (0)	3/33 (9)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.522
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.203
Upper Limit			Infinite
Weeks to First Observed Tumor		--	64
Hematopoietic System: Leukemia or Lymphoma[b]	0/28 (0)	0/10 (0)	3/33 (9)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.522
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.203
Upper Limit			Infinite
Weeks to First Observed Tumor		--	25

Table E4. Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Pituitary: Chromophobe Adenoma[b]	8/28 (29)	2/10 (20)	0/32 (0)
P Values[c,d]			P = 0.001**(N)
Relative Risk (Pooled Control)[e]			0.000
Lower Limit			0.000
Upper Limit			0.374
Relative Risk (Vehicle Control)[e]			0.000
Lower Limit			0.000
Upper Limit			1.028
Weeks to First Observed Tumor		87	--
Mammary Gland: Adenoma, NOS[b]	0/28 (0)	0/10 (0)	3/33 (9)
P Values[c,d]			N.S.
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			0.522
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.203
Upper Limit			Infinite
Weeks to First Observed Tumor		--	43

Table E4. Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Mammary Gland: Adenocarcinoma, NOS[b]	1/28 (4)	1/10 (10)	8/33 (24)
P Values[c,d]			P = 0.025**
Relative Risk (Pooled Control)[e]			6.788
Lower Limit			1.004
Upper Limit			289.508
Relative Risk (Vehicle Control)[e]			2.424
Lower Limit			0.409
Upper Limit			103.495
Weeks to First Observed Tumor		87	40
Mammary Gland: Fibroadenoma[b]	10/28 (36)	5/10 (50)	4/33 (12)
P Values[c,d]			P = 0.020*(N) P = 0.030**(N)
Relative Risk (Pooled Control)[e]			0.339
Lower Limit			0.088
Upper Limit			1.036
Relative Risk (Vehicle Control)[e]			0.242
Lower Limit			0.071
Upper Limit			0.948
Weeks to First Observed Tumor		87	56

Table E4. Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Uterus: Adenocarcinoma, NOS[b]	0/28 (0)	0/10 (0)	7/32 (22)
P Values[c,d]			P = 0.009**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.745
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.680
Upper Limit			Infinite
Weeks to First Observed Tumor		--	50
Ear Canal: Squamous-cell Carcinoma[b]	0/28 (0)	0/10 (0)	5/33 (15)
P Values[c,d]			P = 0.040**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.097
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.427
Upper Limit			Infinite
Weeks to First Observed Tumor		--	71

Table E4. Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Skin and Ear Canal:			
Squamous-cell Carcinoma[b]	0/28 (0)	0/10 (0)	8/33 (24)
P Values[c,d]			P = 0.005**
Relative Risk (Pooled Control)[e]			Infinite
Lower Limit			1.991
Upper Limit			Infinite
Relative Risk (Vehicle Control)[e]			Infinite
Lower Limit			0.776
Upper Limit			Infinite
Weeks to First Observed Tumor		--	64

[a]Treated group received dose of 1.4 mg/kg.

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

[c]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E5. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Skin: Squamous-cell Carcinoma[c]	0/29 (0)	0/10 (0)	5/33 (15)
P Values[d,e]			P = 0.036**
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			1.134
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.427
Upper Limit			Infinite
Weeks to First Observed Tumor		--	53
Subcutaneous Tissue: Sarcoma, NOS[c]	0/29 (0)	0/10 (0)	5/33 (15)
P Values[d,e]			P = 0.036**
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			1.134
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.427
Upper Limit			Infinite
Weeks to First Observed Tumor		--	61

Table E5. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Subcutaneous Tissue: Sarcoma or Fibrosarcoma[c]	1/30 (3)	0/10 (0)	6/33 (18)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			5.455
Lower Limit			0.722
Upper Limit			241.878
Relative Risk (Vehicle Control)[f]			Infinte
Lower Limit			0.543
Upper Limit			Infinite
Weeks to First Observed Tumor		--	61
Subcutaneous Tissue: Fibroma[c]	0/29 (0)	0/10 (0)	2/33 (6)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.265
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.099
Upper Limit			Infinite
Weeks to First Observed Tumor		--	74

Table E5. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Hematopoietic System: Granulocytic Leukemia[c]	0/29 (0)	0/10 (0)	2/34 (6)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.257
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.096
Upper Limit			Infinite
Weeks to First Observed Tumor		--	55
Hematopoietic System: Lymphoma or Lymphocytic Leukemia[b]	0/29 (0)	0/10 (0)	4/34 (12)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.088
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.304
Upper Limit			Infinite
Weeks to First Observed Tumor		--	37

Table E5. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Hematopoietic System: Leukemia or Lymphoma[b]	0/29 (0)	0/10 (0)	6/34 (18)
P Values[d,e]			P = 0.020**
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			1.397
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.527
Upper Limit			Infinite
Weeks to First Observed Tumor		--	37
Pituitary: Chromophobe Adenoma[c]	7/25 (28)	3/9 (33)	1/27 (4)
P Values[d,e]			P = 0.041*(N) P = 0.019**(N)
Relative Risk (Pooled Control)[f]			0.132
Lower Limit			0.003
Upper Limit			0.925
Relative Risk (Vehicle Control)[f]			0.111
Lower Limit			0.003
Upper Limit			1.227
Weeks to First Observed Tumor		82	78

Table E5. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Ear Canal: Squamous-cell Carcinoma[c]	0/29 (0)	0/10 (0)	3/33 (9)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.540
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.203
Upper Limit			Infinite
Weeks to First Observed Tumor		--	74
Skin or Ear Canal: Squamous-cell Carcinoma[c]	0/29 (0)	0/10 (0)	7/33 (21)
P Values[d,e]			P = 0.009**
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			1.748
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.659
Upper Limit			Infinite
Weeks to First Observed Tumor		--	53

Table E5. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Mesentery: Sarcoma, NOS[c]	0/29 (0)	0/10 (0)	2/33 (6)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.265
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.099
Upper Limit			Infinite
Weeks to First Observed Tumor		--	66

[a]Ireated group received dose of 0.7 mg/kg.

[b]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 37 weeks of the study.

[c]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 52 weeks of the study.

[d]Beneath the incidence of tumors in a treated goup is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when P < 0.05; otherwise, not significant (N.S.) is indicated.

[e]A negative value (N) indicates a lower incidence in a treated group than in a control group.

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

Table E6. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Hematopoietic System:			
Lymphocytic Leukemia[b]	0/30 (0)	0/10 (0)	5/16 (31)
P Values[e,f]			P = 0.003**
Relative Risk (Pooled Control)[g]			Infinite
Lower Limit			2.453
Upper Limit			Infinite
Relative Risk (Vehicle Control)[g]			Infinite
Lower Limit			0.892
Upper Limit			Infinite
Weeks to First Observed Tumor		--	40
Hematopoietic System: All Leukemia[b]	0/30 (0)	0/10 (0)	6/16 (38)
P Values[e,f]			P = 0.035* P = 0.001**
Relative Risk (Pooled Control)[g]			Infinite
Lower Limit			3.123
Upper Limit			Infinite
Relative Risk (Vehicle Control)[g]			Infinite
Lower Limit			1.135
Upper Limit			Infinite
Weeks to First Observed Tumor		--	40

Table E6. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Pituitary: Chromophobe Adenoma[d]	2/29 (7)	0/10 (0)	1/6 (17)
P Values[e,f]			N.S.
Relative Risk (Pooled Control)[g]			2.417
Lower Limit			0.042
Upper Limit			34.031
Relative Risk (Vehicle Control)[g]			Infinite
Lower Limit			0.096
Upper Limit			Infinite
Weeks to First Observed Tumor		--	54
Skin or Ear Canal: Squamous-cell Carcinoma[c]	0/30 (0)	0/10 (0)	3/13 (23)
P Values[e,f]			P = 0.023**
Relative Risk (Pooled Control)[g]			Infinite
Lower Limit			1.435
Upper Limit			Infinite
Relative Risk (Vehicle Control)[g]			Infinite
Lower Limit			0.521
Upper Limit			Infinite
Weeks to First Observed Tumor		--	44

Table E6. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Male Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated group received dose of 1.4 mg/kg.

[b]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 40 weeks of the study.

[c]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 44 weeks of the study.

[d]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 52 weeks of the study.

[e]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[f]A negative value (N) indicates a lower incidence in a treated group than in a control group.

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

Table E7. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Subcutaneous Tissue: Sarcoma, NOS, or Fibrosarcoma[c]	0/28 (0)	0/9 (0)	2/29 (7)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.292
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.103
Upper Limit			Infinite
Weeks to First Observed Tumor		--	79
Hematopoietic System: Leukemia or Lymphoma[c]	1/28 (4)	0/9 (0)	2/29 (7)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			1.931
Lower Limit			0.107
Upper Limit			109.859
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.103
Upper Limit			Infinite
Weeks to First Observed Tumor		--	63

Table E7. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Pituitary: Chromophobe Adenoma[c]	14/28 (50)	1/8 (13)	4/28 (14)
P Values[d,e]			P = 0.005**(N)
Relative Risk (Pooled Control)[f]			0.286
Lower Limit			0.087
Upper Limit			0.777
Relative Risk (Vehicle Control)[f]			1.143
Lower Limit			0.147
Upper Limit			54.086
Weeks to First Observed Tumor		82	75
Ear Canal: Squamous-cell Carcinoma[c]	0/28 (0)	0/9 (0)	2/29 (7)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.292
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.103
Upper Limit			Infinite
Weeks to First Observed Tumor		--	74

Table E7. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Brain: Olfactory Neuroblastoma[c]	0/28 (0)	0/9 (0)	2/29 (7)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.292
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.103
Upper Limit			Infinite
Weeks to First Observed Tumor		--	59
Mammary Gland: Adenocarcinoma, NOS[b]	1/28 (4)	0/9 (0)	7/30 (23)
P Values[d,e]			P = 0.033**
Relative Risk (Pooled Control)[f]			6.533
Lower Limit			0.926
Upper Limit			282.066
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.663
Upper Limit			Infinite
Weeks to First Observed Tumor		--	37

Table E7. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Mammary Gland: Fibroadenoma[c]	6/28 (21)	2/9 (22)	8/29 (28)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			1.287
Lower Limit			0.452
Upper Limit			3.917
Relative Risk (Vehicle Control)[f]			1.241
Lower Limit			0.335
Upper Limit			10.781
Weeks to First Observed Tumor		82	66
Uterus: Adenocarcinoma, NOS[c]	0/28 (0)	0/9 (0)	2/29 (7)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.292
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.103
Upper Limit			Infinite
Weeks to First Observed Tumor		--	70

Table E7. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Low-Dose Vehicle Control	Low Dose
Uterus: Sarcoma, NOS[c]	0/28 (0)	0/9 (0)	2/29 (7)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			Infinite
Lower Limit			0.292
Upper Limit			Infinite
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.103
Upper Limit			Infinite
Weeks to First Observed Tumor		--	82
Uterus: Endometrial Stromal Polyp[c]	1/28 (4)	0/9 (0)	4/29 (14)
P Values[d,e]			N.S.
Relative Risk (Pooled Control)[f]			3.862
Lower Limit			0.416
Upper Limit			182.833
Relative Risk (Vehicle Control)[f]			Infinite
Lower Limit			0.326
Upper Limit			Infinite
Weeks to First Observed Tumor		--	63

Table E7. Time-adjusted Analyses of the Incidence of Primary Tumors in Low-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated group received dose of 0.7 mg/kg.

[b]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 37 weeks of the study.

[c]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 52 weeks of the study.

[d]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[e]A negative value (N) indicates a lower incidence in a treated group than in a control group.

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

Table E8. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Skin: Squamous-cell Carcinoma[f]	0/28 (0)	0/10 (0)	3/21 (14)
P Values[g,h]			N.S.
Relative Risk (Pooled Control)[i]			Infinite
Lower Limit			0.824
Upper Limit			Infinite
Relative Risk (Vehicle Control)[i]			Infinite
Lower Limit			0.320
Upper Limit			Infinite
Weeks to First Observed Tumor		--	64
Hematopoietic System: Lymphocytic Leukemia or Lymphoma[b]	0/28 (0)	0/10 (0)	3/22 (14)
P Values[g,h]			N.S.
Relative Risk (Pooled Control)[i]			Infinite
Lower Limit			0.786
Upper Limit			Infinite
Relative Risk (Vehicle Control)[i]			Infinite
Lower Limit			0.305
Upper Limit			Infinite
Weeks to First Observed Tumor		--	25

Table E8. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Pituitary: Chromophobe Adenoma[f]	8/28 (29)	2/10 (20)	0/20 (0)
P Values[g,h]			P = 0.008**(N)
Relative Risk (Pooled Control)[i]			0.000
Lower Limit			0.000
Upper Limit			0.583
Relative Risk (Vehicle Control)[i]			0.000
Lower Limit			0.000
Upper Limit			1.609
Weeks to First Observed Tumor		87	--
Mammary Gland: Adenoma[d]	0/28 (0)	0/10 (0)	3/22 (14)
P Values[g,h]			N.S.
Relative Risk (Pooled Control)[i]			Infinite
Lower Limit			0.786
Upper Limit			Infinite
Relative Risk (Vehicle Control)[i]			Infinite
Lower Limit			0.305
Upper Limit			Infinite
Weeks to First Observed Tumor		--	43

Table E8. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Mammary Gland: Adenocarcinoma, NOS[c]	1/28 (4)	1/10 (10)	8/24 (33)
P Values[g,h]			P = 0.006**
Relative Risk (Pooled Control)[i]			9.333
Lower Limit			1.398
Upper Limit			388.857
Relative Risk (Vehicle Control)[i]			3.333
Lower Limit			0.567
Upper Limit			139.059
Weeks to First Observed Tumor		87	40
Mammary Gland: Fibroadenoma[f]	10/28 (36)	5/10 (50)	4/21 (19)
P Values[g,h]			N.S.
Relative Risk (Pooled Control)[i]			0.533
Lower Limit			0.141
Upper Limit			1.555
Relative Risk (Vehicle Control)[i]			0.381
Lower Limit			0.113
Upper Limit			1.434
Weeks to First Observed Tumor		87	56

Table E8. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Uterus: Adenocarcinoma, NOS[e]	0/28 (0)	0/10 (0)	7/21 (33)
P Values[g,h]			P = 0.044* P = 0.001**
Relative Risk (Pooled Control)[i]			Infinite
Lower Limit			2.684
Upper Limit			Infinite
Relative Risk (Vehicle Control)[i]			Infinite
Lower Limit			1.044
Upper Limit			Infinite
Weeks to First Observed Tumor		--	50
Ear Canal: Squamous-cell Carcinoma[f]	0/28 (0)	0/10 (0)	5/21 (24)
P Values[g,h]			P = 0.011**
Relative Risk (Pooled Control)[i]			Infinite
Lower Limit			1.737
Upper Limit			Infinite
Relative Risk (Vehicle Control)[i]			Infinite
Lower Limit			0.676
Upper Limit			Infinite
Weeks to First Observed Tumor		--	71

Table E8. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Mid-Dose Vehicle Control	Mid Dose
Skin and Ear Canal:			
Squamous-cell Carcinoma[f]	0/28 (0)	0/10 (0)	8/21 (38)
P Values[g,h]			P = 0.026* P < 0.001**
Relative Risk (Pooled Control)[i]			Infinite
Lower Limit			3.164
Upper Limit			Infinite
Relative Risk (Vehicle Control)[i]			Infinite
Lower Limit			1.230
Upper Limit			Infinite
Weeks to First Observed Tumor		--	64

[a]Treated group received dose of 1.4 mg/kg.

[b]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 25 weeks of the study.

[c]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 40 weeks of the study.

[d]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 43 weeks of the study.

Table E8. Time-adjusted Analyses of the Incidence of Primary Tumors in Mid-Dose Female Rats Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[e]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 50 weeks of the study.

[f]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 52 weeks of the study.

[g]Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the vehicle-control group (*) or with the pooled-control group (**) when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[h]A negative value (N) indicates a lower incidence in a treated group than in a control group.

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE GIVEN INTRAPERITONEAL INJECTIONS OF THIO-TEPA

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Skin: Squamous-cell Carcinoma[b]	0/28 (0)	0/14 (0)	7/30 (23)	0/34 (0)
P Values[c,d]	N.S.	N.S.	P = 0.007**	N.S.
Departure from Linear Trend[e]	P < 0.001	P < 0.001		
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			1.863	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.978	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	67	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	1/28 (4)	1/14 (7)	5/30 (17)	0/33 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.007	P = 0.043		
Relative Risk (Pooled Control)[f]			4.667	0.000
Lower Limit			0.571	0.000
Upper Limit			212.161	15.686
Relative Risk (Vehicle Control)[f]			2.333	0.000
Lower Limit			0.306	0.000
Upper Limit			106.152	7.858
Weeks to First Observed Tumor	--	87	83	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Lymphocytic Leukemia[b]	1/28 (4)	1/14 (7)	2/30 (7)	26/34 (76)
P Values[c,d]	P < 0.001	P < 0.001	N.S.	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P = 0.001	P = 0.003		
Relative Risk (Pooled Control)[f]			1.867	21.412
Lower Limit			0.103	4.109
Upper Limit			106.333	770.826
Relative Risk (Vehicle Control)[f]			0.933	10.706
Lower Limit			0.055	2.187
Upper Limit			53.204	385.659
Weeks to First Observed Tumor	--	78	61	26

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Hematopoietic System:				
Leukemia or Lymphoma[b]	1/28 (4)	1/14 (7)	3/30 (10)	26/34 (76)
P Values[c,d]	P < 0.001	P < 0.001	N.S.	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P = 0.003	P = 0.006		
Relative Risk (Pooled Control)[f]			2.800	21.412
Lower Limit			0.242	4.109
Upper Limit			141.729	770.721
Relative Risk (Vehicle Control)[f]			1.400	10.706
Lower Limit			0.129	2.187
Upper Limit			70.914	385.659
Weeks to First Observed Tumor	--	78	61	26

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma[b]	1/28 (4)	1/14 (7)	4/30 (13)	0/33 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.023			
Relative Risk (Pooled Control)[f]			3.733	0.000
Lower Limit			0.401	0.000
Upper Limit			177.009	15.686
Relative Risk (Vehicle Control)[f]			1.867	0.000
Lower Limit			0.215	0.000
Upper Limit			88.558	7.858
Weeks to First Observed Tumor	--	87	67	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Ear Canal: Squamous-cell Carcinoma[b]	0/28 (0)	0/14 (0)	2/30 (7)	0/34 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.040			
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.282	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.147	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	83	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Preputial Gland: Squamous-cell Carcinoma[b]	0/28 (0)	0/14 (0)	6/30 (20)	1/34 (3)
P Values[c,d]	N.S.	N.S.	P = 0.014**	N.S.
Departure from Linear Trend[e]	P = 0.002	P = 0.007		
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			1.534	0.045
Upper Limit			Infinite	Infinite
Relative Risk (Vehicle Control)[f]			Infinite	Infinite
Lower Limit			0.805	0.023
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	72	56

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
All Sites: Squamous-cell Carcinoma[b]	0/28 (0)	0/14 (0)	14/30 (47)	1/34 (3)
P Values[c,d]	N.S.	N.S.	P < 0.001** P = 0.001*	N.S.
Departure from Linear Trend[e]	P < 0.001	P < 0.001		
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			4.211	0.045
Upper Limit			Infinite	Infinite
Relative Risk (Vehicle Control)[f]			Infinite	Infinite
Lower Limit			2.209	0.023
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	67	56

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated groups received doses of 1.15 or 2.3 mg/kg.

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

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

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

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

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	0/30 (0)	0/15 (0)	5/29 (17)	0/32 (0)
P Values[c,d]	N.S.	N.S.	P = 0.024**	N.S.
Departure from Linear Trend[e]	P = 0.001	P = 0.005		
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			1.336	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.698	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	86	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Hematopoietic System: Lymphocytic Leukemia or Lymphoma[b]	1/30 (3)	0/15 (0)	5/30 (17)	32/32 (100)
P Values[c,d]	P < 0.001	P < 0.001	N.S.	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P = 0.001	P = 0.038		
Relative Risk (Pooled Control)[f]			5.000	30.030
Lower Limit			0.609	8.208
Upper Limit			227.307	Infinite
Relative Risk (Vehicle Control)[f]			Infinite	Infinite
Lower Limit			0.675	6.468
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	31	26

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma[b]	0/30 (0)	0/15 (0)	2/30 (7)	0/32 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.040			
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.301	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.157	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	86	--
Ovary: Carcinoma, NOS[b]	0/29 (0)	0/15 (0)	3/29 (10)	0/31 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.011	P = 0.030		
Relative Risk (Pooled Control)[f]			Infinite	--
Lower Limit			0.615	--
Upper Limit			Infinite	--
Relative Risk (Vehicle Control)[f]			Infinite	--
Lower Limit			0.332	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	78	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated groups received doses of 1.15 or 2.3 mg/kg.

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

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

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

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

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

Table F3. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Skin: Squamous-cell Carcinoma[d]	0/18 (0)	0/8 (0)	7/24 (29)	0/2 (0)
P Values[e,f]	N.S.	N.S.	P = 0.013**	N.S.
Relative Risk (Pooled Control)[h]			Infinite	--
Lower Limit			1.544	--
Upper Limit			Infinite	--
Relative Risk (Matched Control)[h]			Infinite	--
Lower Limit			0.754	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	67	--
Lung: Alveolar/Bronchiolar Adenoma[d]	1/18 (6)	1/8 (13)	5/24 (21)	0/2 (0)
P Values[e,f]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[h]			3.750	0.000
Lower Limit			0.479	0.000
Upper Limit			168.323	93.466
Relative Risk (Matched Control)[h]			1.667	0.000
Lower Limit			0.246	0.000
Upper Limit			74.916	41.780
Weeks to First Observed Tumor		87	83	--

Table F3. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Lymphocytic Leukemia[b]	1/18 (6)	1/8 (13)	2/24 (8)	26/28 (93)
P Values[e,f]	P < 0.001	P < 0.001	N.S.	P < 0.001* P < 0.001**
Departure from Linear Trend[g]	P < 0.001	P = 0.002		
Relative Risk (Pooled Control)[h]			1.500	16.714
Lower Limit			0.086	3.601
Upper Limit			84.637	358.473
Relative Risk (Matched Control)[h]			0.667	7.429
Lower Limit			0.043	1.771
Upper Limit			37.663	159.766
Weeks to First Observed Tumor		78	61	26

Table F3. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Hematopoietic System: Leukemia or Lymphoma[b]	1/18 (6)	1/8 (13)	3/24 (13)	26/28 (93)
P Values[e,f]	P < 0.001	P < 0.001	N.S.	P < 0.001* P < 0.001**
Departure from Linear Trend[g]	P = 0.003	P = 0.004		
Relative Risk (Pooled Control)[h]			2.250	16.714
Lower Limit			0.202	3.601
Upper Limit			112.716	358.473
Relative Risk (Matched Control)[h]			1.000	7.429
Lower Limit			0.103	1.771
Upper Limit			50.152	159.766
Weeks to First Observed Tumor		78	61	26

Table F3. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma[d]	1/18 (6)	1/8 (13)	4/24 (17)	0/2 (0)
P Values[e,f]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[h]			3.000	0.000
Lower Limit			0.336	0.000
Upper Limit			140.603	93.466
Relative Risk (Matched Control)[h]			1.333	0.000
Lower Limit			0.173	0.000
Upper Limit			62.559	41.780
Weeks to First Observed Tumor		87	67	--
Ear Canal: Squamous-cell Carcinoma[d]	0/18 (0)	0/8 (0)	2/24 (8)	0/2 (0)
P Values[e,f]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[h]			Infinite	--
Lower Limit			0.232	--
Upper Limit			Infinite	--
Relative Risk (Matched Control)[h]			Infinite	--
Lower Limit			0.113	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	83	--

Table F3. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Preputial Gland: Squamous-cell Carcinoma[d]	0/18 (0)	0/8 (0)	6/24 (25)	1/2 (50)
P Values[e,f]	P = 0.014	N.S.	P = 0.026**	N.S.
Relative Risk (Pooled Control)[h]			Infinite	Infinite
Lower Limit			1.271	1.487
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[h]			Infinite	Infinite
Lower Limit			0.620	0.232
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	72	56
All Sites: Squamous-cell Carcinoma[d]	0/18 (0)	0/8 (0)	14/24 (58)	1/2 (50)
P Values[e,f]	P = 0.001	P = 0.018	P = 0.004* P < 0.001**	N.S.
Relative Risk (Pooled Control)[h]			Infinite	Infinite
Lower Limit			3.513	0.487
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[h]			Infinite	Infinite
Lower Limit			1.709	0.232
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	67	56

Table F3. Time-adjusted Analyses of the Incidence of Primary Tumors in Male Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated groups received doses of 1.15 or 2.3 mg/kg.

[b]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 26 weeks of the study.

[c]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 32 weeks of the study.

[d]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 52 weeks of the study.

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

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

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

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

Table F4. Time-adjusted Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[d]	0/29 (0)	0/14 (0)	5/24 (21)	0/0 (-)
P Values[e,f]	P = 0.034	N.S.	P = 0.015**	N.S.
Relative Risk (Pooled Control)[h]			Infinite	--
Lower Limit			1.567	--
Upper Limit			Infinite	--
Relative Risk (Matched Control)[h]			Infinite	--
Lower Limit			0.795	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	86	--
Hematopoietic System: Lymphoma or Lymphocytic Leukemia[b]	0/29 (0)	0/14 (0)	5/26 (19)	32/32 (100)
P Values[e,f]	P < 0.001	P < 0.001	P = 0.019**	P < 0.001* P < 0.001**
Departure from Linear Trend[g]	P = 0.006	P = 0.011		
Relative Risk (Pooled Control)[h]			Infinite	Infinite
Lower Limit			1.445	12.195
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[h]			Infinite	Infinite
Lower Limit			0.733	6.060
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	31	26

Table F4. Time-adjusted Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

Topography: Morphology	Pooled Control	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma[d]	0/29 (0)	0/14 (0)	2/25 (8)	0/0 (-)
P Values[e,f]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[h]			Infinite	--
Lower Limit			0.350	--
Upper Limit			Infinite	--
Relative Risk (Matched Control)[h]			Infinite	--
Lower Limit			0.177	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	86	--
Ovary: Carcinoma, NOS[d]	0/28 (0)	0/14 (0)	3/24 (13)	0/0 (-)
P Values[e,f]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[h]			Infinite	--
Lower Limit			0.720	--
Upper Limit			Infinite	--
Relative Risk (Matched Control)[h]			Infinite	--
Lower Limit			0.377	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	78	--

Table F4. Time-adjusted Analyses of the Incidence of Primary Tumors in Female Mice Given Intraperitoneal Injections of Thio-TEPA[a]

(continued)

[a]Treated groups received doses of 1.15 or 2.3 mg/kg.

[b]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 26 weeks of the study.

[c]Number of tumor-bearing animals/number of animals examined at site (percent) wich survived at least 31 weeks of the study.

[d]Number of tumor-bearing animals/number of animals examined at site (percent) which survived at least 52 weeks of the study.

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

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

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

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

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

April 26, 1978

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

The primary reviewer said that, under the conditions of test, Thio-TEPA induced squamous-cell carcinomas of the skin and ear canal in both sexes of treated rats and hematopoetic neoplasms in the males. Lymphomas or lymphocytic leukemia were induced in both sexes of mice and squamous-cell carcinomas in the skin and associated glands of males. After a brief description of the experimental design and conditions of test, he noted the following points in his critique: the poor survival among the high dose treated animals resulting from excessive toxicity; the higher percentage of bone marrow atrophy reported in control animals than in treated ones; the high mortality among control animals necessitated the use of pooled controls for statistical analysis; the large number of other chemicals tested in the same room and at the same time; and the negative trend for pituitary tumors in treated animals as compared to controls. Despite the experimental shortcomings, the primary reviewer said that the conclusion on the carcinogenicity of Thio-TEPA was still valid. He added that Thio-TEPA would appear to pose a carcinogenic risk to man.

The secondary reviewer agreed with the primary reviewer's critique of the bioassay of Thio-TEPA.

It was moved that the report on the bioassay of Thio-TEPA be accepted as written. The motion was seconded and approved unanimously.

Members present were:

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

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

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