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

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REPORT ON THE BIOASSAY OF N,N'-DIETHYLTHIOUREA
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of N,N'-diethylthiourea 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 significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because 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 a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of N,N'-diethylthiourea was conducted by Litton Bionetics, Inc., Bethesda, Maryland, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. N. P. Page (1,2), Dr. E. K. Weisburger (1) and Dr. J. H. Weisburger (1,3). The principal investigators for the contract were Dr. F. M. Garner (4,5) and Dr. B. M. Ulland (4,5). Mr. S. Johnson (4) was the coprincipal investigator for the contract. Animal treatment and observation were supervised by Mr. R. Cypher (4), Mr. D. S. Howard (4) and Mr. H. D. Thornett (4); Mr. H. Paulin (4) analyzed dosed feed mixtures. Ms. J. Blalock (4) was responsible for data collection and assembly. Chemical analysis was performed by Midwest Research Institute (6) and the analytical results were reviewed by Dr. N. Zimmerman (7).

Histopathologic examinations were performed by Dr. N. J. Wosu (4) at Litton Bionetics, Inc., the pathology narratives were written by Dr. N. J. Wosu (4), and the diagnoses included in this report represent the interpretation of this pathologist. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (8).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (9); the statistical analysis was performed by Mr. W. W. Belew (7,10) and Mr. R. M. Helfand (7), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (11).

This report was prepared at METREK, a Division of The MITRE Corporation (7) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (7), task leader Ms. P. Walker (7), senior biologist Mr. M. Morse (7), biochemist Mr. S. C. Drill (7), and technical editor Ms. P. A. Miller (7). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,12), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,13), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay for the possible carcinogenicity of N,N'-diethylthiourea was conducted using Fischer 344 rats and B6C3F1 mice. N,N'-Diethylthiourea was administered in the feed, at either of two concentrations, to groups of 50 males and 50 females of each species. Twenty animals of each sex and species, except for 19 male mice, were placed on test as controls. The high and low dietary concentrations of N,N'-diethylthiourea were, respectively, 250 and 125 ppm for rats and 500 and 250 ppm for mice. The compound was administered in the diet for 103 weeks, followed by an observation period of 1 week for all dosed groups.

There were no significant positive associations between the dosages of N,N'-diethylthiourea administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Compound-related mean body weight depression was apparent among dosed male and female mice when compared to their respective controls, indicating that the concentrations of N,N'-diethylthiourea administered to mice may have approximated the maximum tolerated dosages.

There were statistically significant elevated incidences of follicular-cell carcinomas of the thyroid in high dose male rats. In addition, there were statistically significant elevated incidences of a combination of thyroid follicular-cell carcinomas and follicular-cell adenomas in high dose male and female rats.

Under the conditions of this bioassay, N,N'-diethylthiourea was carcinogenic to Fischer 344 rats, causing follicular-cell carcinomas of the thyroid in males and follicular-cell neoplasms of the thyroid in females. There was no evidence for the carcinogenicity of the compound in B6C3F1 mice.

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I. INTRODUCTION

N,N'-Diethylthiourea (Figure 1) (NCI No. C03816), a corrosion inhibitor and accelerator in elastomer manufacture, was selected for bioassay by the National Cancer Institute because of the structural similarity of this compound to ethylene thiourea, a tumorigen in hybrid mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR) (Innes et al., 1969).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is N,N'-diethylthiourea.* It is also called 1,3-diethyl-2-thiourea, and 1,3-diethylthiourea.

N,N'-Diethylthiourea is used as a corrosion inhibitor in solutions of hydrochloric acid or sulfuric acid for the pickling of iron or steel, and for reducing the corrosion of ferrous metals and aluminum alloys in brine (Hawley, 1971; Rose and Rose, 1966). N,N'-Diethylthiourea is also used as a vulcanization accelerator in the manufacture of elastomers (Hawley, 1971).

Specific production data for N,N'-diethylthiourea are not available; however, this compound is produced annually in quantities greater than 1000 pounds or $1000 in value by two U.S. companies (Stanford Research Institute, 1977).

The potential for exposure to N,N'-diethylthiourea is greatest for workers involved in the production of this compound and the formulation and use of corrosion inhibitive solutions containing N,N'-diethylthiourea, and those in the elastomer manufacturing industry.

*The CAS registry number is 105-55-5.

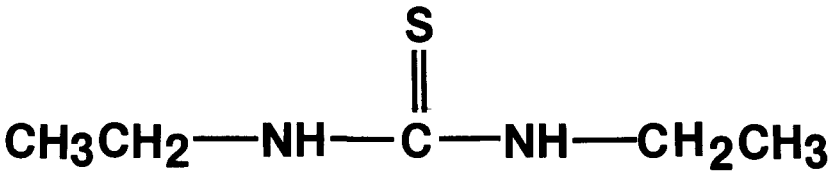


FIGURE 1
CHEMICAL STRUCTURE OF N, N'-DIETHYLTHIOUREA

II. MATERIALS AND METHODS

A. Chemicals

Practical-grade* N,N'-diethylthiourea was purchased from Pfaltz and Bauer Chemical Company, Stamford, Connecticut. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The experimentally determined range in melting point, 74° to 76°C, was close to that reported in the literature (77°C [Beilstein's Handbuch der Organischen Chemie, 1973]). Thin-layer chromatography (TLC) was performed utilizing two solvent systems (i.e., ethyl acetate and acetone:chloroform) and visualized by ultraviolet light, dichromate and heat. The plate developed with ethyl acetate revealed the presence of two spots, one of which was an impurity, remaining at the origin. Development with the second solvent system resulted in detection of no impurities. Elemental analysis was within the acceptable limits (5 percent) of experimental variation expected for $C_5H_{12}N_2S$, the molecular formula for N,N'-diethylthiourea. Titration of the thiourea function provided results greater than 99 percent of theoretical. High pressure liquid chromatography indicated the presence of two impurities. The results of infrared (IR) and nuclear magnetic resonance (NMR) analyses were consistent with those reported in the literature (Sadtler Standard Spectra). Ultraviolet/visible (UV/VIS) analysis revealed λ_{max} at 252 nm with a molar extinction coefficient

*Similar to technical-grade (i.e., may contain minor impurities).

(ϵ) of 13.8 x 10^3. The reported literature λ_{max} was at 250 nm and ϵ was 15.8 x 10^3 (Gosaier and Rao, 1967).

A second batch of the compound was purchased nine months later from the same supplier. The experimentally determined range in melting point for this batch was 76° to 78°C. Elemental analysis was, as previously, within acceptable limits (5 percent) of experimental variation. TLC, performed as for the first batch, indicated no impurities. Titration of the thiourea function again provided results greater than 99 percent of theoretical. High speed liquid chromotography showed the presence of one impurity (0.1 percent of the total) of high motility. IR and NMR analyses were consistent with those reported in the literature (Sadtler Standard Spectra). UV/VIS analysis revealed λ_{max} at 215 and 240 nm with ϵ of 11 x 10^3 and 14 x 10^3, respectively.

Throughout this report the term N,N'-diethylthiourea is used to represent these batches of this practical-grade chemical.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). N,N'-Diethylthiourea was administered to the dosed animals as a component of the diet.

The chemical was removed from its container and a proper amount was blended with an aliquot of the ground feed using a mortar and pestle. Once visual homogeneity was attained, the mixture was placed in a 6 kg capacity Patterson-Kelley standard model twin-shell

stainless steel V-blender along with the remainder of the feed to be prepared. After 20 minutes of blending, the mixtures were placed in double plastic bags and stored in the dark at 4°C. The mixture was prepared once weekly.

Dosed feed preparations containing 250 and 500 ppm of N,N'-diethylthiourea were analyzed spectrophotometrically. The mean result immediately after preparation was 73.6 percent of theoretical (ranging from 62.8 to 83.2 percent) including correction for the analytical method of recovery used.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. All rats were supplied by the Frederick Cancer Research Center, Frederick, Maryland. All mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts.

Rats and mice were approximately 4 weeks old when received. Upon receipt, animals were examined for visible signs of disease or parasites. Obviously ill or runted animals were culled. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals which did not manifest clinical signs of disease were placed on test at this time. Animals were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given species and sex.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 22° to 26°C and the relative humidity was maintained between 45 and 55 percent. Incoming air was filtered through HEPA filters (Flanders Filters, McLean, Virginia) at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided 8 hours per day (9:00 a.m. to 5:00 p.m.).

All rats were housed four per cage by sex and all mice were housed five per cage by sex. Throughout the study dosed and control animals of both species were housed in polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) suspended from aluminum racks. Racks were fitted with a continuous piece of stainless steel mesh over which a sheet of filter paper was firmly secured. Filter paper was changed at 2-week intervals, when the racks were sanitized. Clean cages and bedding were provided twice weekly. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used in polycarbonate cages for the entire bioassay.

Acidulated water (pH 2.5) was supplied to animals in water bottles filled by an automated metering device that was checked daily for diluting accuracy. Water bottles were changed and washed twice weekly, and sipper tubes were washed at weekly intervals. During the period of chemical administration, dosed and control animals received treated or untreated Wayne Lab-Blox® meal as appropriate. The feed

was supplied in hanging stainless steel hoppers which were refilled three times per week and sanitized weekly. Food and water were available ad libitum for both species.

All dosed and control rats were housed in a room with other rats receiving diets containing* 4-nitro-o-phenylenediamine (99-56-9); and 1-phenyl-3-methyl-5-pyrazolone (89-25-8); and other rats intubated with 3-(chloromethyl)pyridine hydrochloride (3099-31-8).

All dosed and control mice were housed in a room with mice receiving diets containing EDTA trisodium salt (150-38-9); 3,3'-dimethoxybenzidine-4,4'-diisocyanate (91-93-0); triphenyltin hydroxide (76-87-9); diaminozide (1596-84-5); carbromal (75-65-6); p-quinone dioxime (105-11-3); 4-amino-2-nitrophenol (119-34-6); other mice intubated with lithocholic acid (434-13-9); and other mice receiving I.P. injections of methiodol sodium (126-31-8).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of N,N'-diethylthiourea for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Rats were distributed among five groups, each consisting of five males and five females. N,N'-Diethylthiourea was incorporated into the basal laboratory diet and supplied ad libitum to four of the five rat groups in concentrations of 147, 215, 316 and

*CAS registry numbers are given in parentheses.

464 ppm. The remaining rat group served as a control group, receiving only the basal laboratory diet.

Mice were distributed among six groups, each consisting of five males and five females. N,N'-Diethylthiourea was incorporated into the basal laboratory diet and supplied ad libitum to five of the six mouse groups in concentrations of 680, 1000, 1470, 2160 and 3150 ppm. The sixth mouse group served as a control group, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 7 weeks, followed by a 1-week observation period during which all animals were fed the basal laboratory diet. Individual body weights and food consumption data were recorded twice weekly throughout the study. Upon termination of the study all survivors were sacrificed and necropsied.

At the end of the subchronic test, mean body weight gain among male rats dosed with 316 ppm was 3 percent greater than the mean body weight gain of their controls, while female rats receiving the same concentration had a mean body weight gain 11 percent less than that of their controls. Mean body weight gain among male rats dosed with 215 ppm was 10 percent less than the mean body weight gain of their controls, while female rats receiving the same concentration had a mean body weight gain 1 percent less than that of their controls. One female rat receiving a concentration of 316 ppm died while

another had an arched back and rough coat. The high concentration selected for administration to dosed rats in the chronic bioassay was 250 ppm.

At the end of the subchronic test, mean body weight gain among male mice dosed with 680 ppm was 10 percent less than the mean body weight gain of their controls, while female mice receiving the same concentration had a mean body weight gain 8 percent less than that of their controls. The high concentration selected for administration to dosed mice in the chronic bioassay was 500 ppm.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, concentrations administered, and duration of treated and untreated observation periods) are summarized in Tables 1 and 2.

All rats were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The dietary concentrations of N,N'-diethylthiourea utilized were 250 and 125 ppm. Throughout this report those rats receiving the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to as the low dose groups. Dosed rats were supplied with feed containing N,N'-diethylthiourea for 103 weeks followed by a 1-week observation period.

All mice were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The dietary

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
N,N'-DIETHYLTHIOUREA FEEDING EXPERIMENT

	INITIAL GROUP SIZE	N,N'-DIETHYL-THIOUREA CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	104
LOW DOSE	50	125	103	
		0		1
HIGH DOSE	50	250	103	
		0		1
FEMALE				
CONTROL	20	0	0	104
LOW DOSE	50	125	103	
		0		1
HIGH DOSE	50	250	103	
		0		1

[a]Concentrations given in parts per million.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
N,N'-DIETHYLTHIOUREA FEEDING EXPERIMENT

	INITIAL GROUP SIZE	N,N'-DIETHYL-THIOUREA CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
CONTROL	19	0	0	104
LOW DOSE	50	250	103	
		0		1
HIGH DOSE	50	500	103	
		0		1
FEMALE				
CONTROL	20	0	0	104
LOW DOSE	50	250	103	
		0		1
HIGH DOSE	50	500	103	
		0		1

[a]Concentrations given in parts per million.

concentrations of N,N'-diethylthiourea utilized were 500 and 250 ppm. Throughout this report those mice receiving the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to as the low dose groups. Dosed mice were supplied with feed containing N,N'-diethylthiourea for 103 weeks followed by a 1-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice daily for mortality. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group. Body weights of rats were recorded once monthly throughout the bioassay. Body weights of mice were recorded once a week for the first 5 weeks and at monthly intervals thereafter.

All moribund animals or animals that developed large, palpable masses that jeopardized their health were sacrificed. A necropsy was performed on each animal regardless of whether it died, was sacrificed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide asphyxiation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of all major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in a 10 percent neutral buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, tunica vaginalis, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were recorded in each group at the time that the test was initiated.

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) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing 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 was 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, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) 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, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined 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 was 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 animals died naturally or were 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 to its control was calculated from

the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ 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. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

No evidence of mean body weight depression was associated with compound administration in either male or female rats (Figure 2).

No abnormal clinical signs were recorded.

B. Survival

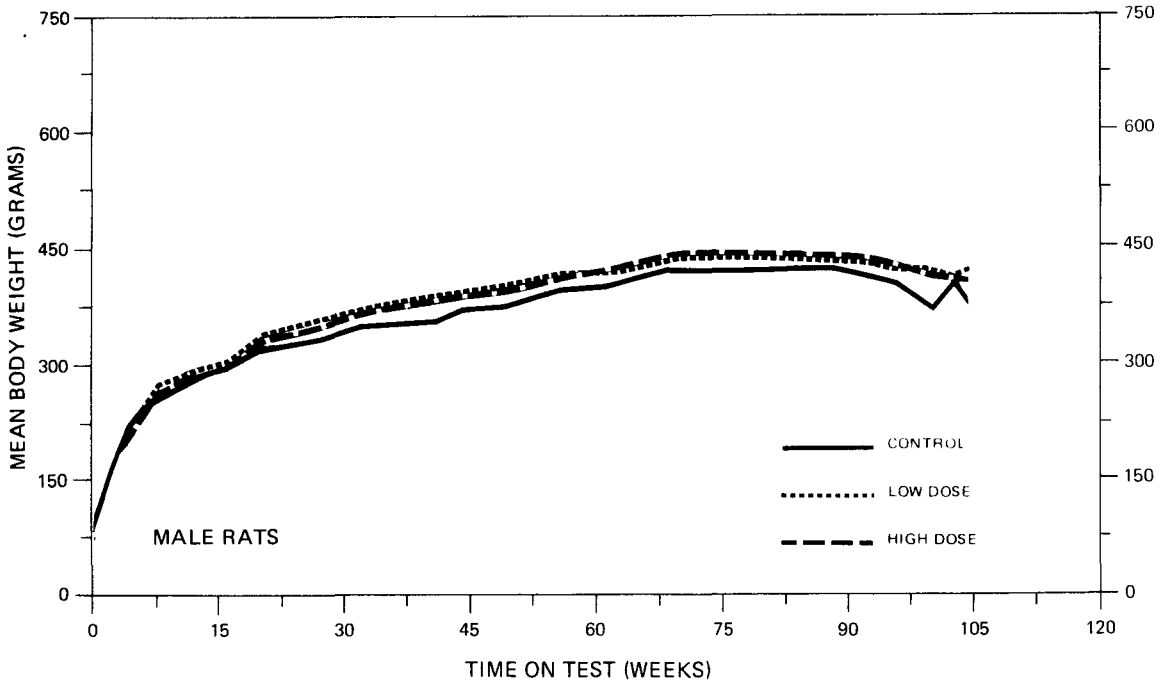
The estimated probabilities of survival for male and female rats in the control and N,N'-diethylthiourea-dosed groups are shown in Figure 3. The Tarone test for association between increased dosage and mortality was not significant for either males or females.

There were adequate numbers of male rats at risk from late-developing tumors as 82 percent (41/50) of the high dose, 82 percent (41/50) of the low dose, and 80 percent (16/20) of the controls survived on test until the termination of the study.

For females 84 percent (42/50) of the high dose, 88 percent (44/50) of the low dose, and 90 percent (18/20) of the controls survived on test until the termination of the study. Thus, there were adequate numbers of female rats at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2).



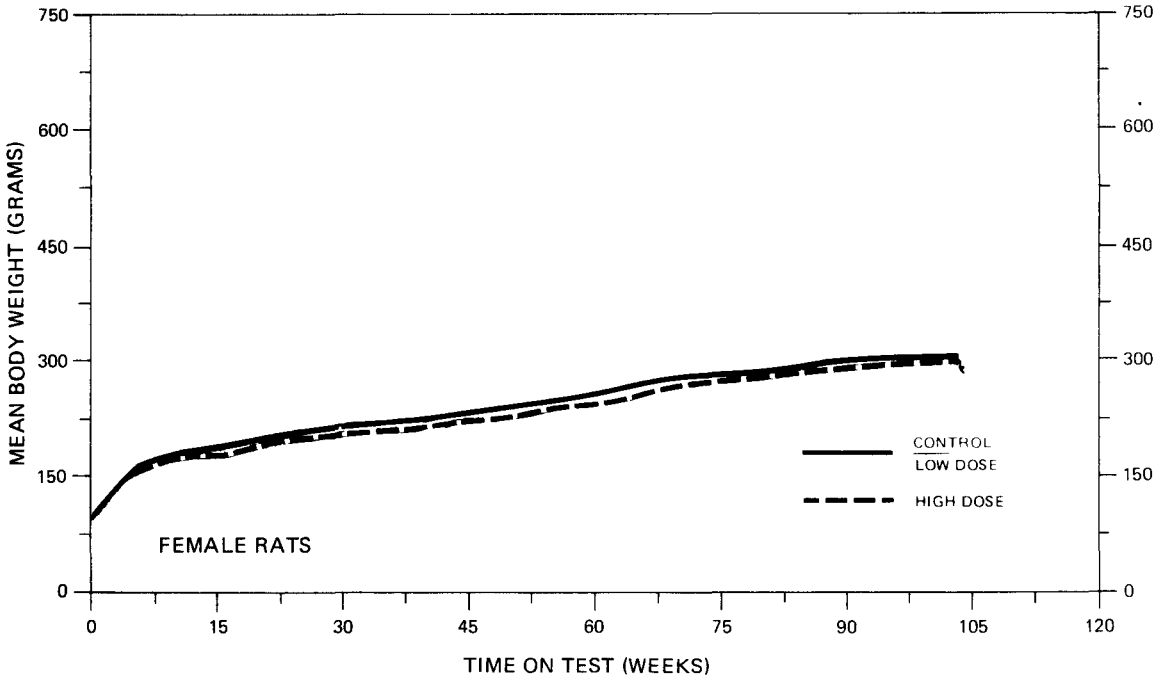
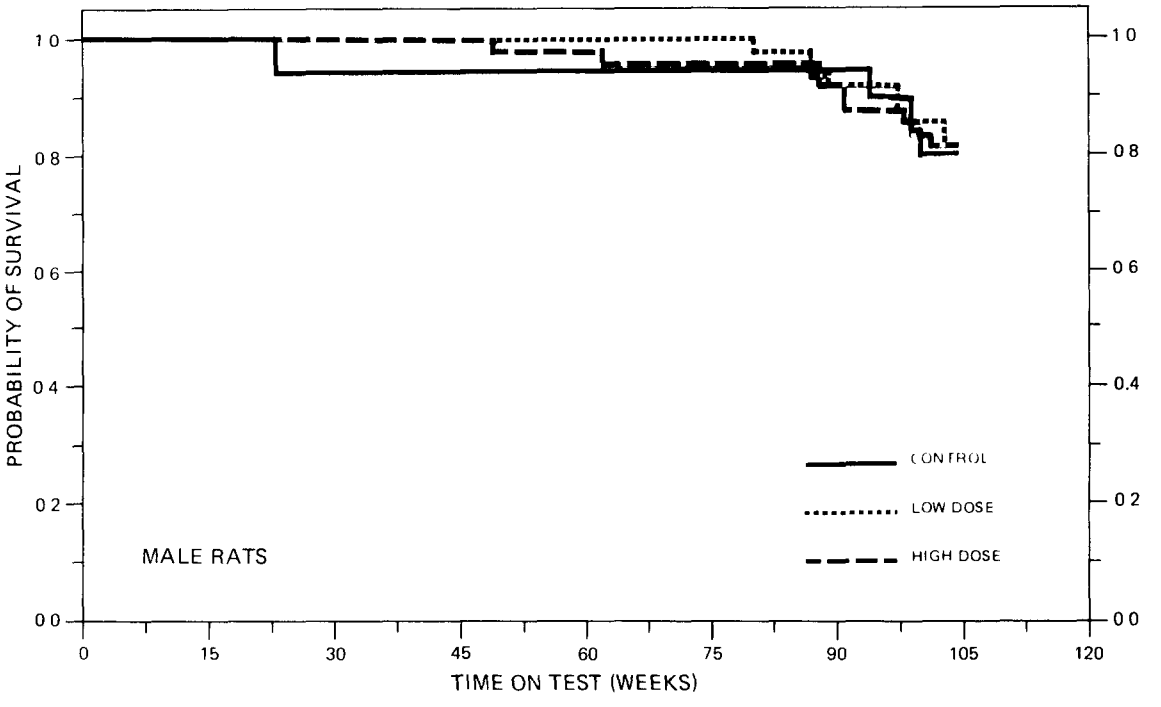


FIGURE 2
GROWTH CURVES FOR N,N'-DIETHYLTHIOUREA CHRONIC STUDY RATS



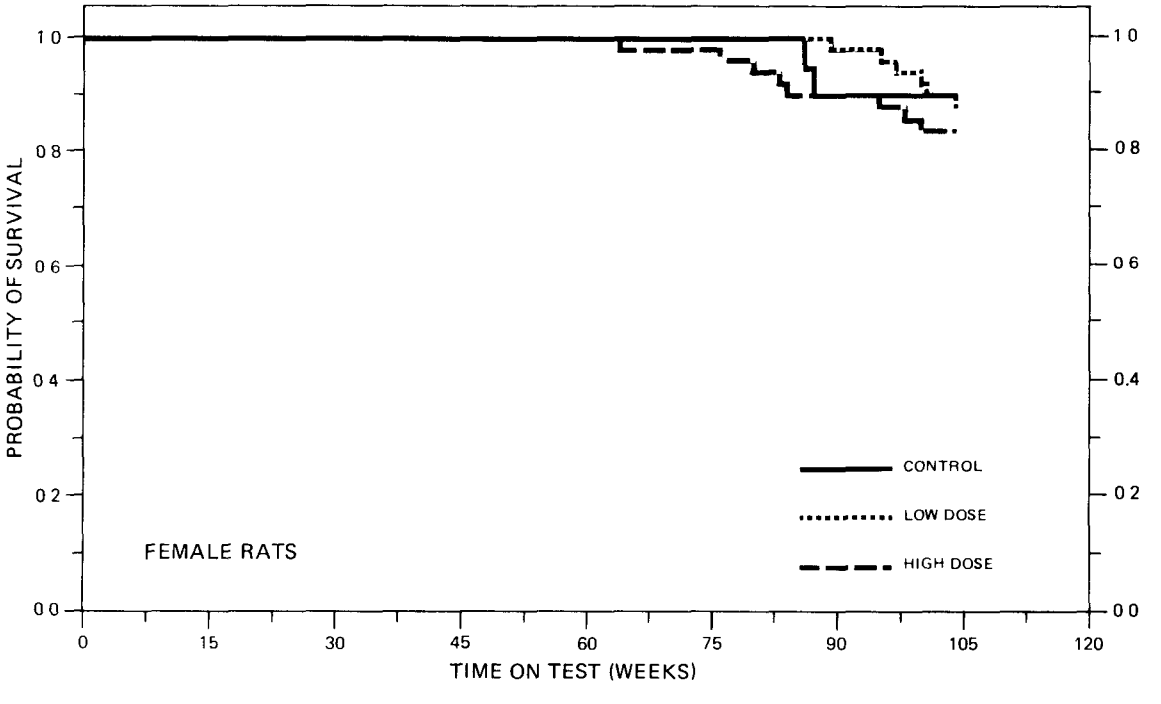


FIGURE 3
SURVIVAL COMPARISONS OF N,N'-DIETHYLTHIOUREA CHRONIC STUDY RATS

A relatively high incidence of thyroid tumors was observed and appeared to be related to the dietary administration of N,N'-diethylthiourea. The summary of thyroid tumor incidence is as follow:

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Thyroid Number of Animals with Tissues Examined Histopathologically	(18)	(45)	(48)	(18)	(46)	(46)
C-Cell Adenoma	0	0	2	0	1	1
C-Cell Carcinoma	1	0	1	0	0	1
Follicular-Cell Adenoma (All Types)	0	0	6	0	4	9
Follicular-Cell Carcinoma (All types)	0	1	11	0	1	8

Nearly all of these neoplasms were recognized and described during gross examination. Microscopically they were of follicular-cell as well as C-cell origin and included benign-appearing as well as malignant types. C-cell adenomas were discrete, well-delineated and generally consisted of a solid arrangement of monomorphous well-differentiated cells. The malignant C-cell neoplasms were more pleomorphic and showed a less organized cellular arrangement, but remained well-differentiated and had moderate to low mitotic activity. Although generally less well-delineated than the adenomas, there was no extra glandular invasion or metastasis. The follicular adenomas were generally nodular, well-differentiated and in many cases cystic. They were

mostly papillary in arrangement. The malignant follicular-cell neoplasms were generally large and showed variable histologic appearance even within the same neoplasm. Follicular, solid and papillary patterns, as well as combinations of these were recognized. Most of these were markedly cystic as well. The degree of differentiation was variable. Many of these destroyed adjacent parenchyma by invasion as well as by comparison. Three of these tumors invaded local tissue, the most frequent sites being the trachea and lungs. None was observed to metastasize to distant sites. Occasionally the same animal had more than one type of thyroid tumor (e.g., C-cell and follicular-cell types within the same lobe or benign and malignant tumors within contralateral lobes). Such neoplasms were listed individually. Thus, the number of neoplasms may be found to exceed the number of animals bearing them.

There were a few neoplasms found in other organs. These were similar in type, incidence, and distribution in dosed and control groups and were, therefore, not considered to be associated with compound administration.

Thyroid hyperplasia (cystic and follicular-cell) was commonly recognized and appeared to be related to dietary administration and dosage of the compound. Other nonneoplastic lesions were of the frequency and severity expected in aged Fischer 344 rats.

It was concluded from this pathologic examination that under the conditions of this bioassay N,N'-diethylthiourea was

carcinogenic in Fischer 344 rats, inducing thyroid neoplasms and hyperplasia.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or N,N'-diethylthiourea-dosed groups and where such tumors were observed in at least 5 percent of the group.

For male rats, the incidence of follicular-cell carcinomas of the thyroid was significant ($P = 0.001$) using the Cochran-Armitage test when comparing the dosed groups to the control. The Cochran-Armitage test was supported by a significant ($P = 0.021$) Fisher exact test comparing the high dose group to the control. Furthermore, the combined incidences of follicular-cell carcinomas or follicular-cell adenomas of the thyroid in male rats resulted in a significant ($P < 0.001$) Cochran-Armitage test and a significant ($P = 0.004$) high dose Fisher exact test.

For female rats, the Cochran-Armitage test indicated a significant ($P < 0.001$) positive association between dose and the combined incidence of follicular-cell carcinomas or follicular-cell adenomas of the thyroid. This result was supported by a significant ($P = 0.001$) high dose Fisher exact test comparison.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH N,N'-DIETHYLTHIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	0/20(0.00)	3/50(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.250	0.022
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	87	104
Skin and Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma[b]	0/20(0.00)	3/50(0.06)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.250	0.123
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	87	104
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/20(0.10)	8/50(0.16)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.600	0.400
Lower Limit	---	0.364	0.032
Upper Limit	---	14.699	5.277
Weeks to First Observed Tumor	99	89	88

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma or Chromophobe Carcinoma[b]	0/17(0.00)	6/46(0.13)	6/48(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.624	0.598
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	87	101
Adrenal: Pheochromocytoma[b]	1/18(0.06)	4/50(0.08)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.440	1.080
Lower Limit	---	0.159	0.096
Upper Limit	---	69.469	55.565
Weeks to First Observed Tumor	104	104	104
Thyroid: Follicular-Cell Carcinoma[b]	0/18(0.00)	1/45(0.02)	11/48(0.23)
P Values[c]	P = 0.001	N.S.	P = 0.021
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.022	1.309
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	91

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma or Follicular-Cell Adenoma[b]	0/18(0.00)	1/45(0.02)	15/48(0.31)
P Values[c]	P < 0.001	N.S.	P = 0.004
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.022	1.857
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	91
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/18(0.06)	0/45(0.00)	3/48(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	1.125
Lower Limit	---	0.000	0.100
Upper Limit	---	7.461	57.811
Weeks to First Observed Tumor	104	---	104
Testis: Interstitial-Cell Tumor[b]	14/20(0.70)	37/49(0.76)	36/50(0.72)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.079	1.029
Lower Limit	---	0.793	0.753
Upper Limit	---	1.629	1.579
Weeks to First Observed Tumor	94	88	88

TABLE 3 (CONCLUDED)

[a]Treated groups received doses of 125 or 250 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH N,N'-DIETHYLTHIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/20(0.15)	7/50(0.14)	4/49(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.933	0.544
Lower Limit	---	0.245	0.104
Upper Limit	---	5.215	3.477
Weeks to First Observed Tumor	104	89	83
Pituitary: Chromophobe Adenoma or Chromophobe Carcinoma[b]	5/18(0.28)	18/47(0.38)	22/45(0.49)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.379	1.760
Lower Limit	---	0.607	0.806
Upper Limit	---	4.166	5.126
Weeks to First Observed Tumor	87	95	64
Thyroid: Follicular-Cell Carcinoma[b]	0/18(0.00)	1/46(0.02)	8/46(0.17)
P Values[c]	P = 0.006	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.022	0.939
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	100

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma or Follicular-Cell Adenoma[b]	0/18(0.00)	4/46(0.09)	17/46(0.37)
P Values[c]	P < 0.001	N.S.	P = 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.380	2.227
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	80
Mammary Gland: Fibroadenoma[b]	0/20(0.00)	6/50(0.12)	6/49(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.667	0.680
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	101	84
Uterus: Endometrial Stromal Polyp[b]	4/19(0.21)	6/49(0.12)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.582	0.396
Lower Limit	---	0.161	0.085
Upper Limit	---	2.569	1.955
Weeks to First Observed Tumor	86	104	76

TABLE 4 (CONCLUDED)

[a]Treated groups received doses of 125 or 250 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

There were no other significant positive associations between administration of the compound and an increased incidence of tumors at any site in either male or female rats.

Based upon these statistical results, the administration of N,N'-diethylthiourea was associated with the increased incidence of follicular-cell carcinomas of the thyroid in male and follicular-cell neoplasms of the thyroid in female Fischer 344 rats.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Dose-related mean body weight depression was apparent in both male and female mice after week 30 (Figure 4).

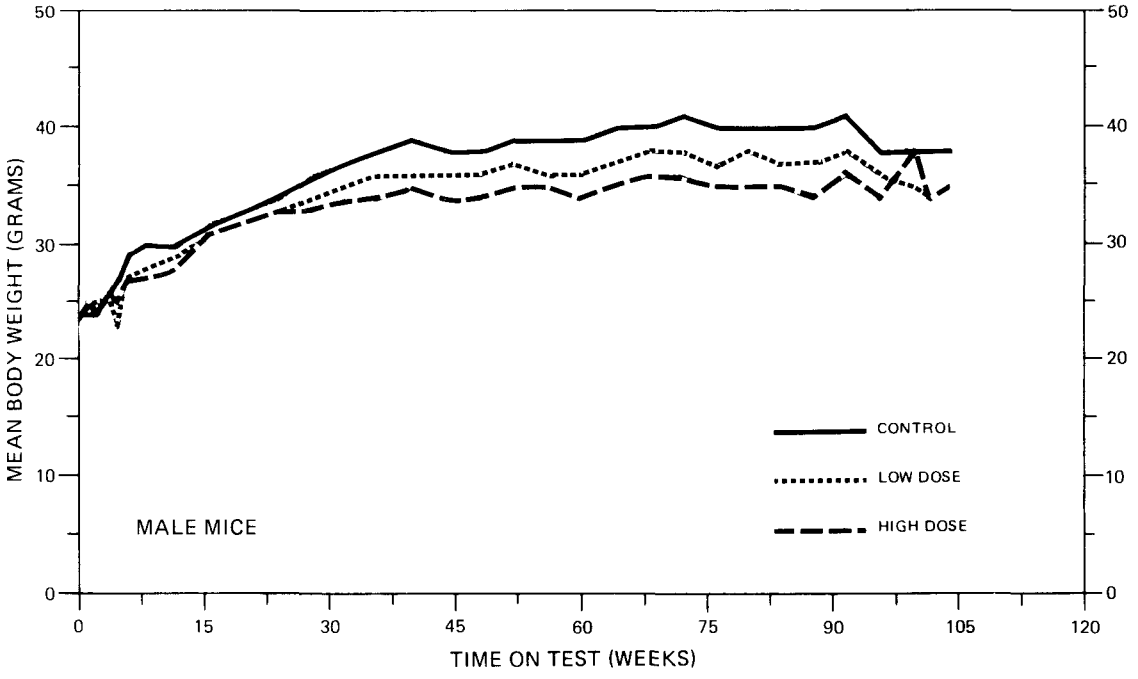
No abnormal clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female mice in the control and N,N'-diethylthiourea-dosed groups are shown in Figure 5. The Tarone test for association between dosage and mortality was not significant for either male or female mice.

The actual percentage of male and female mice surviving on test in the dosed and control groups are shown in Figure 6. There were adequate numbers of male mice at risk from late-developing tumors. Despite 2 low dose and 4 control males missing by week 18, 94 percent (47/50) of the high dose, 94 percent (47/50) of the low dose and 79 percent (15/19) of the controls survived on test for at least 80 weeks.

Eight females from the high dose group, 2 from the low dose group and 1 control were missing by week 22. There were, however, adequate numbers of female mice at risk from late-developing tumors as 60 percent (30/50) of the high dose, 66 percent (33/50) of the low dose and 70 percent (14/20) of the controls survived on test until the termination of the study.



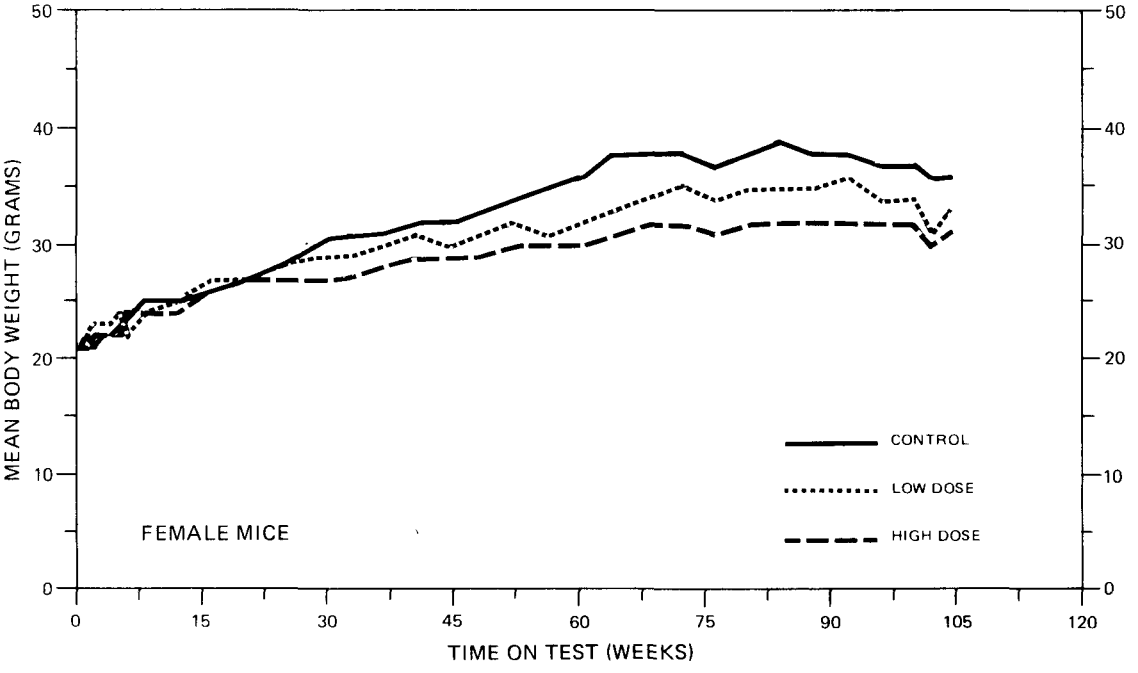


FIGURE 4
GROWTH CURVES FOR N,N'-DIETHYLTHIOUREA CHRONIC STUDY MICE

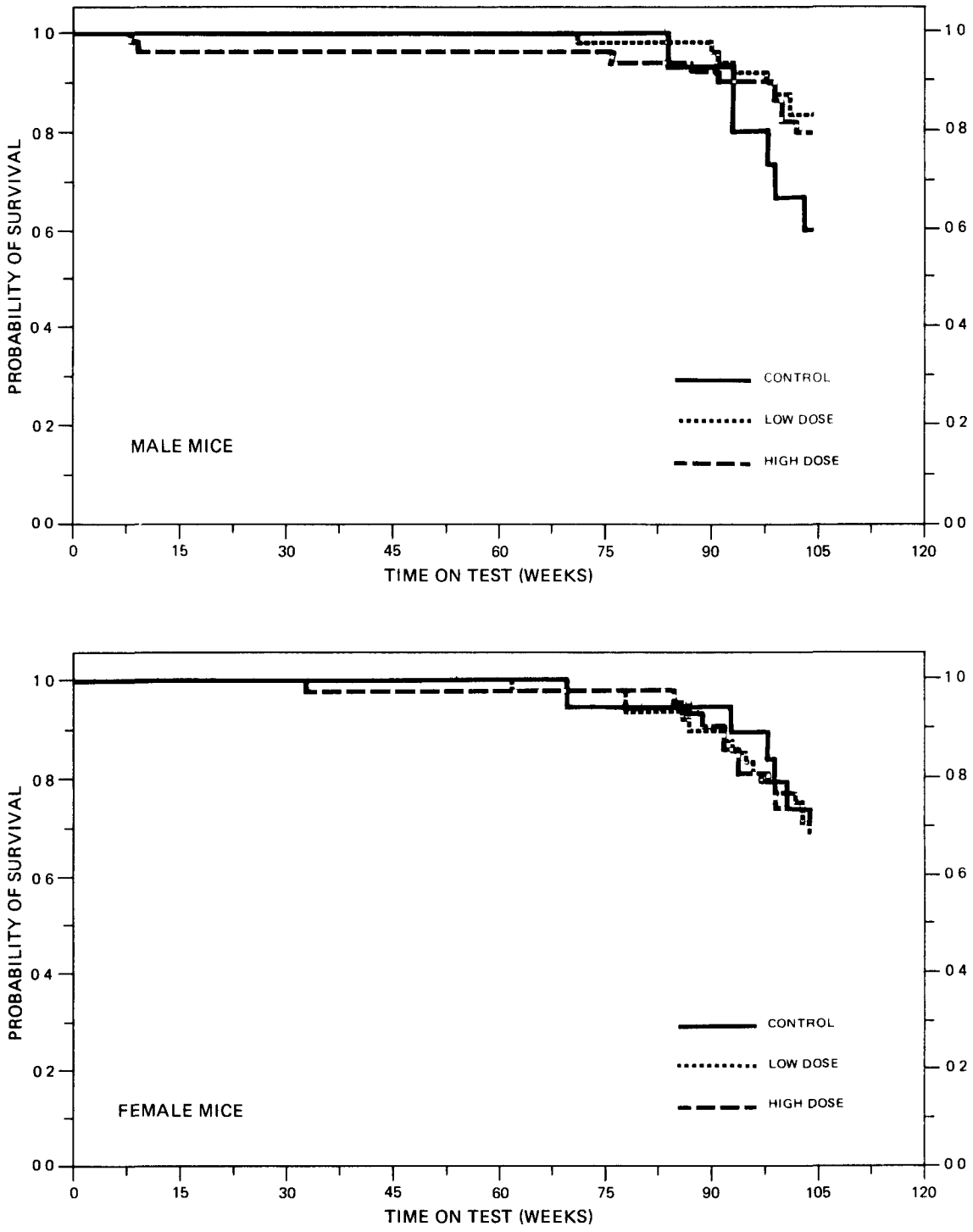
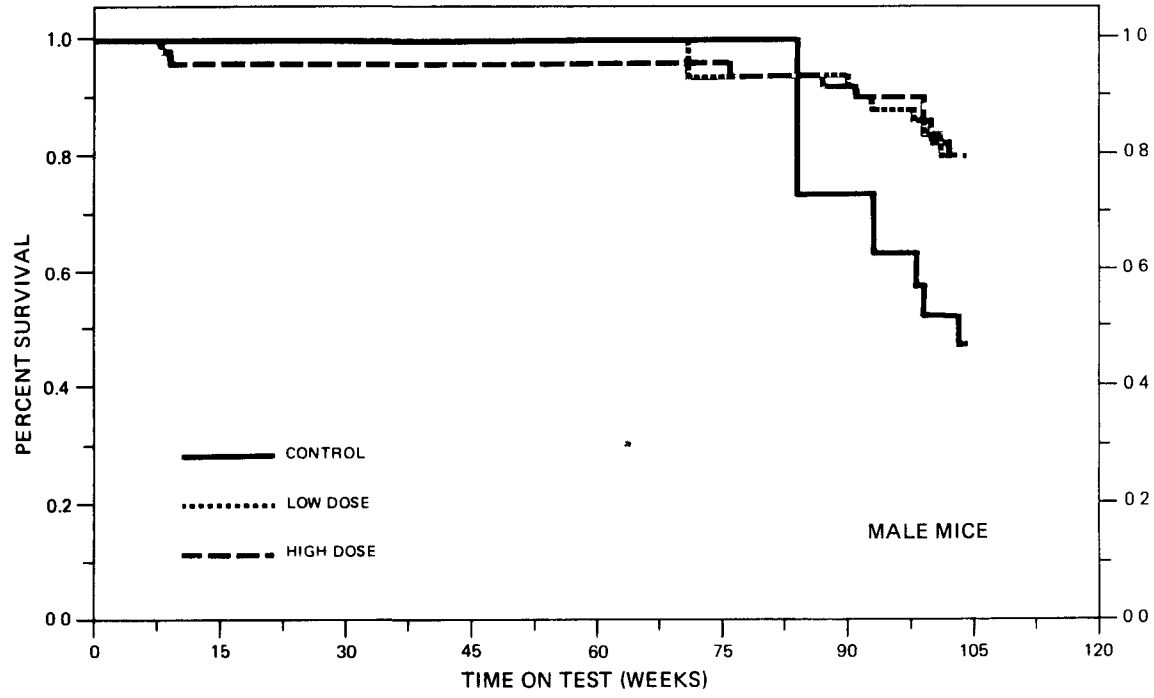


FIGURE 5
SURVIVAL PROBABILITY COMPARISONS OF N,N'-DIETHYLTHIOUREA CHRONIC STUDY MICE



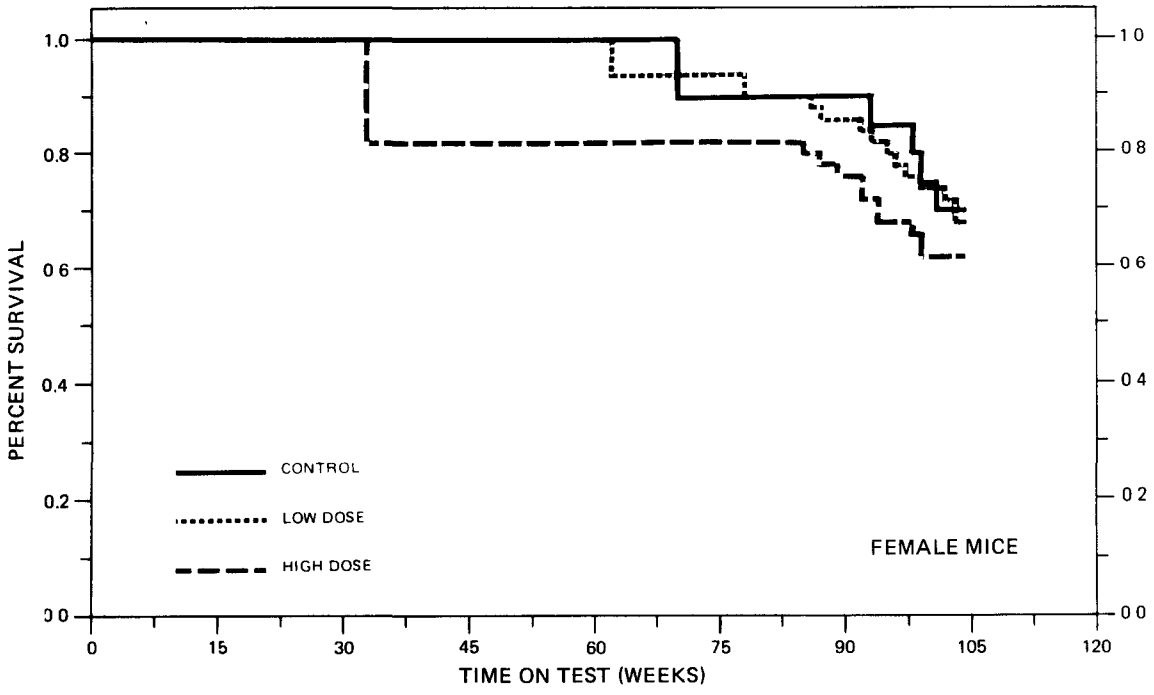


FIGURE 6
PERCENT SURVIVAL OF N,N'-DIETHYLTHIOUREA CHRONIC STUDY MICE

C. Pathology

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).

In both sexes, the neoplasms observed were similar in type and distribution in dosed and control mice, and were well within the incidence expected to occur spontaneously in aged B6C3F1 mice. The severity and incidence of nonneoplastic lesions were also not unusual.

Based on the results of this pathologic examination, N,N'-diethylthiourea was not carcinogenic in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or N,N'-diethylthiourea-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site in mice of either sex indicated a positive association between the administration of N,N'-diethylthiourea and an increased tumor incidence. Thus, under the conditions of this bioassay, there was no statistical evidence that N,N'-diethylthiourea was a carcinogen in B6C3F1 mice.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH N,N'-DIETHYLTHIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	2/13(0.15)	4/46(0.09)	6/46(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.565	0.848
Lower Limit	---	0.096	0.183
Upper Limit	---	5.886	8.071
Weeks to First Observed Tumor	99	104	99
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/15(0.20)	11/48(0.23)	12/49(0.24)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.146	1.224
Lower Limit	---	0.369	0.404
Upper Limit	---	5.853	6.185
Weeks to First Observed Tumor	93	90	76
Circulatory System: Hemangioma or Hemangiosarcoma[b]	1/15(0.07)	1/48(0.02)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.313	0.918
Lower Limit	---	0.004	0.083
Upper Limit	---	24.060	47.229
Weeks to First Observed Tumor	104	104	99

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	2/14(0.14)	5/48(0.10)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.729	0.286
Lower Limit	---	0.141	0.023
Upper Limit	---	7.229	3.739
Weeks to First Observed Tumor	104	71	104
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	5/14(0.36)	7/48(0.15)	3/49(0.06)
P Values[c]	P = 0.006(N)	N.S.	P = 0.010(N)
Relative Risk (Control)[d]	---	0.408	0.171
Lower Limit	---	0.143	0.033
Upper Limit	---	1.439	0.788
Weeks to First Observed Tumor	93	71	104

[a]Treated groups received doses of 250 or 500 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH N,N'-DIETHYLTHIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	8/19(0.42)	15/48(0.31)	9/41(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.742	0.521
Lower Limit	---	0.374	0.224
Upper Limit	---	1.732	1.336
Weeks to First Observed Tumor	93	78	92
Uterus: Endometrial Stromal Polyp[b]	0/17(0.00)	3/45(0.07)	2/38(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.239	0.139
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	62	104

[a]Treated groups received doses of 250 or 500 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

In male mice a possible negative association between dose and the combined incidence of hepatocellular carcinomas or hepatocellular adenomas was noted.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by N,N'-diethylthiourea that could not be established under the conditions of this test.

V. DISCUSSION

There were no significant positive associations between the dosages of N,N'-diethylthiourea administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Compound-related mean body weight depression was apparent among dosed male and female mice when compared to their respective controls, indicating that the concentrations of N,N'-diethylthiourea administered to mice may have approximated the maximum tolerated dosages.

Neoplasms and hyperplasia of the thyroid were observed with greater frequency among dosed rats than among controls. When the incidences of follicular-cell carcinomas of the thyroid in male rats (i.e., 0/18, 1/45 [2 percent], and 11/48 [23 percent] in the control, low dose, and high dose, respectively) were analyzed, there was a statistically significant positive association between dosage and increased incidence. This finding was supported by the high dose to control Fisher exact comparison. In both sexes of rats, statistical analysis of the incidences of a combination of follicular-cell carcinomas and follicular-cell adenomas of the thyroid resulted in significant positive Cochran-Armitage tests. For males and females, the high dose to control Fisher exact comparisons were also significant.

For mice, none of the statistical tests for any site revealed a significant positive association between administration of the compound and increased tumor incidence.

Under the conditions of this bioassay, N,N'-diethylthiourea was carcinogenic to Fischer 344 rats, causing follicular-cell carcinomas of the thyroid in males and follicular-cell neoplasms of the thyroid in females. There was no evidence for the carcinogenicity of the compound in B6C3F1 mice.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, Chapter 14. J. Wiley & Sons, New York, 1971.

Beilstein's Handbuch der Organischen Chemie, 4th edition. Springer Verlag, Berlin, p. 118, 1973.

Berenblum, I., editor, Carcinogenicity Testing. International Union Against Cancer, Technical Report Series, Vol. 2. International Union Against Cancer, Geneva, 1969.

Chemical Abstracts Service, The Chemical Abstracts Service (CAS) Ninth Collective Index, Volumes 76-85, 1972-1976. American Chemical Society, Washington, D.C., 1977.

Cox, D.R., Analysis of Binary Data, Chapters 4 and 5. Methuen and Co., Ltd., London, 1970.

Cox, D.R., "Regression Models and Life-Tables." Journal of the Royal Statistical Society, Series "B" 34:187-220, 1972.

Gart, J.J., "The Comparison of Proportions: A Review of Significance Tests, Confidence Limits, and Adjustments for Stratification." International Statistical Institute Review 39:148-169, 1971.

Gosaier, R.K. and C.N.R. Rao, "Electronic Absorption Spectra of Thiourea Derivatives." Can. J. Chem. 45(16):1897, 1967.

Hawley, G.G., editor, The Condensed Chemical Dictionary, 8th edition. Van Nostrand Reinhold Company, New York, 1971.

Innes, J.R.M., B.M. Ulland, M.G. Valerio, L. Petrucelli, L. Fishbein, E.R. Hart, A.J. Pallotta, R.R. Bates, H.L. Falk, J.J. Gart, M. Klein, I. Mitchell, and J. Peters, "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note." Journal of the National Cancer Institute 42(6):1101-1114, 1969.

Kaplan, E.L., and P. Meier, "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53:457-481, 1958.

Linhart, M.S., J.A. Cooper, R.L. Martin, N.P. Page, and J.A. Peters, "Carcinogenesis Bioassay Data System." Computers and Biomedical Research 7:230-248, 1974.

Miller, R.G., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York, 1966.

Rose, A. and E. Rose, editors, The Condensed Chemical Dictionary, 7th edition. Van Nostrand Reinhold Company, New York, 1966.

Sadtler Standard Spectra. Sadtler Research Laboratories, Philadelphia, Pennsylvania, NMR No. 190, IR No. 11236.

Saffiotti, U., R. Montesano, A.R. Sellakumar, F. Cefis, and D.G. Kaufman, "Respiratory Tract Carcinogenesis in Hamsters Induced by Different Numbers of Administration of Benzo (a) Pyrene and Ferric Oxide." Cancer Research 32:1073-1079, 1972.

Stanford Research Institute, 1977 Directory of Chemical Producers, U.S.A. Menlo Park, California, 1977.

Tarone, R.E., "Tests for Trend in Life-Table Analysis." Biometrika 62:679-682, 1975.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH N,N'-DIETHYLTHIOUREA

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
NEUROFIBROSARCOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROSARCOMA		3 (6%)	1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(44)	(46)
FOLLICULAR-CELL CARCINOMA, INVAS			1 (2%)
#LUNG	(20)	(48)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
FOLLICULAR-CELL CARCINOMA, INVAS			2 (4%)
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMIA,NOS		4 (8%)	
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
LYMPHOCYTIC LEUKEMIA	1 (5%)		
GRANULOCYTIC LEUKEMIA	1 (5%)	2 (4%)	1 (2%)
MONOCYTIC LEUKEMIA		1 (2%)	1 (2%)
#MESENTERIC L. NODE	(17)	(49)	(44)
OSTEOSARCOMA		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(19)	(47)	(49)
FOLLICULAR-CELL CARCINOMA, INVAS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
DIGESTIVE SYSTEM			
#SMALL INTESTINE	(19)	(49)	(48)
NEOPLASM, NOS			1 (2%)
ADENOCARCINOMA, NOS		1 (2%)	
#SMALL INTESTINAL SER	(19)	(49)	(48)
OSTEOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
LIPOSARCOMA		1 (2%)	
OSTEOSARCOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(46)	(48)
CHROMOPHOBE ADENOMA		6 (13%)	5 (10%)
CHROMOPHOBE CARCINOMA			1 (2%)
#ADRENAL	(18)	(50)	(50)
PHEOCHROMOCYTOMA	1 (6%)	4 (8%)	3 (6%)
HEMANGIOMA	1 (6%)		
OSTEOSARCOMA		1 (2%)	
#THYROID	(18)	(45)	(48)
FOLLICULAR-CELL ADENOMA			6 (13%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	11 (23%)
C-CELL ADENOMA			2 (4%)
C-CELL CARCINOMA	1 (6%)		1 (2%)
#PARATHYROID	(13)	(29)	(21)
ADENOMA, NOS		1 (3%)	
#PANCREATIC ISLETS	(19)	(49)	(48)
ISLET-CELL ADENOMA		2 (4%)	
ISLET-CELL CARCINOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(20)	(50)	(50)
CARCINOMA, NOS			1 (2%)

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

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
ADENOMA, NOS			1 (2%)
#TESTIS	(20)	(49)	(50)
INTERSTITIAL-CELL TUMOR	14 (70%)	37 (76%)	36 (72%)
NERVOUS SYSTEM			
#BRAIN	(19)	(49)	(49)
OSTEOSARCOMA, METASTATIC		1 (2%)	
GLIOMA, NOS			1 (2%)
EPENDYMOMA	1 (5%)		
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(20)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF THORAX	(20)	(50)	(50)
FOLLICULAR-CELL CARCINOMA, INVAS			1 (2%)
BODY CAVITIES			
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
MESOTHELIOMA, MALIGNANT			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	6	6
MORIBUND SACRIFICE	1	3	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	41	41
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL(UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	48	47
TOTAL PRIMARY TUMORS	21	70	77
TOTAL ANIMALS WITH BENIGN TUMORS	15	42	43
TOTAL BENIGN TUMORS	16	50	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	16	19
TOTAL MALIGNANT TUMORS	5	19	21
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	3
TOTAL SECONDARY TUMORS		2	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(49)
LEUKEMIA,NOS	1 (5%)	4 (8%)	3 (6%)
GRANULOCYTIC LEUKEMIA	1 (5%)	1 (2%)	1 (2%)
MONOCYTIC LEUKEMIA	1 (5%)	1 (2%)	
#SPLEEN	(20)	(49)	(48)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(20)	(49)	(49)
GRANULOCYTIC LEUKEMIA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#PAROTID GLAND	(19)	(49)	(46)
CYSTADENOMA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
#LIVER	(20)	(49)	(49)
HEMANGIOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(47)	(45)
CHROMOPHOBE ADENOMA	5 (28%)	17 (36%)	20 (44%)
CHROMOPHOBE CARCINOMA		1 (2%)	2 (4%)
#ADRENAL	(20)	(49)	(48)
ADENOMA, NOS		1 (2%)	
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	1 (5%)	1 (2%)	2 (4%)
#THYROID	(18)	(46)	(46)
FOLLICULAR-CELL ADENOMA		4 (9%)	9 (20%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	8 (17%)
C-CELL ADENOMA		1 (2%)	1 (2%)
C-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)	
PAPILLARY ADENOCARCINOMA	1 (5%)		1 (2%)
CYSTADENOMA, NOS			1 (2%)
FIBROADENOMA		6 (12%)	6 (12%)
#UTERUS	(19)	(49)	(48)
ADENOCARCINOMA, NOS	1 (5%)		
ENDOMETRIAL STROMAL POLYP	4 (21%)	6 (12%)	4 (8%)
#UTERUS/ENDOMETRIUM	(19)	(49)	(48)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(48)
NEOPLASM, NOS, METASTATIC			1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
CHROMOPHOBE CARCINOMA, INVASIVE			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(49)
LIPOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	5	4
MORIBUND SACRIFICE		1	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	44	41
ANIMAL MISSING			1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	13	33	41
TOTAL PRIMARY TUMORS	15	49	66
TOTAL ANIMALS WITH BENIGN TUMORS	10	28	31
TOTAL BENIGN TUMORS	10	38	47
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	11	17
TOTAL MALIGNANT TUMORS	5	11	19
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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH N,N'-DIETHYLTHIOUREA

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL(UNTR) 22-2365	LOW DOSE 22-2363	HIGH DOSE 22-2361
ANIMALS INITIALLY IN STUDY	@20	50	50
ANIMALS MISSING	4	2	
ANIMALS NECROPSIED	15	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	48	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(15)	(48)	(49)
FIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(13)	(46)	(46)
NEOPLASM, NOS, METASTATIC		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (15%)	4 (9%)	5 (11%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
SARCOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(15)	(48)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	4 (8%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (13%)	2 (4%)	6 (12%)
LEUKEMIA,NOS	1 (7%)	2 (4%)	1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(14)	(48)	(43)
SARCOMA, NOS		1 (2%)	
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (7%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	1 (2%)
#LYMPH NODE	(14)	(45)	(42)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
#LIVER	(14)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
@ 20 ANIMALS INITIALLY IN STUDY BUT ONE ANIMAL WAS FOUND TO BE FEMALE IN A MALE GROUP
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2365	LOW DOSE 22-2363	HIGH DOSE 22-2361
DIGESTIVE SYSTEM			
#LIVER	(14)	(48)	(49)
HEPATOCELLULAR ADENOMA	3 (21%)	2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA	2 (14%)	5 (10%)	2 (4%)
SARCOMA, NOS			1 (2%)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (7%)		1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(10)	(42)	(35)
PHEOCHROMOCYTOMA			1 (3%)
#THYROID	(7)	(30)	(34)
FOLLICULAR-CELL ADENOMA	1 (14%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(15)	(47)	(44)
INTERSTITIAL-CELL TUMOR			1 (2%)
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 B1 (CONCLUDED)

	CONTROL(UNTR) 22-2365	LOW DOSE 22-2363	HIGH DOSE 22-2361
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	7	10
MORIBUND SACRIFICE		1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	40	40
ANIMAL MISSING	4	2	
ANIMAL DELETED (WRONG SEX)	1		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	20	23
TOTAL PRIMARY TUMORS	13	24	29
TOTAL ANIMALS WITH BENIGN TUMORS	5	6	8
TOTAL BENIGN TUMORS	6	6	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	16	18
TOTAL MALIGNANT TUMORS	7	18	19
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	2	8
ANIMALS NECROPSIED	19	48	41
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	47	41
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(48)	(41)
MYXOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
*NOSE	(19)	(48)	(41)
FIBROSARCOMA		1 (2%)	
#LUNG	(18)	(45)	(41)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (6%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(48)	(41)
MALIGNANT LYMPHOMA, NOS	1 (5%)	3 (6%)	3 (7%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (16%)	7 (15%)	2 (5%)
LEUKEMIA,NOS	1 (5%)	1 (2%)	1 (2%)
PLASMACYTIC LEUKEMIA		1 (2%)	
ERYTHROCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(18)	(46)	(40)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			2 (5%)
#MESENTERIC L. NODE	(17)	(46)	(40)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (6%)		
#KIDNEY	(18)	(46)	(40)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL(UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*LIP	(19)	(48)	(41)
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROSARCOMA		1 (2%)	
*LIVER	(19)	(46)	(40)
HEPATOCELLULAR ADENOMA			2 (5%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(20)	(23)
CHROMOPHOBE CARCINOMA		1 (5%)	
BASOPHIL ADENOMA		1 (5%)	
#THYROID	(12)	(31)	(25)
FOLLICULAR-CELL ADENOMA	1 (8%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(48)	(41)
CARCINOMA,NOS	1 (5%)		
#UTERUS	(17)	(45)	(38)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP		3 (7%)	2 (5%)
#OVARY	(16)	(43)	(35)
PAPILLARY CYSTADENOMA, NOS	1 (6%)		
GRANULOSA-CELL TUMOR			1 (3%)
NERVOUS SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL(UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(19)	(48)	(41)
FIBROSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	12	6
MORIBUND SACRIFICE	1	3	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	33	30
ANIMAL MISSING	1	2	8

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL(UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	23	15
TOTAL PRIMARY TUMORS	12	28	15
TOTAL ANIMALS WITH BENIGN TUMORS	3	6	4
TOTAL BENIGN TUMORS	3	6	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	19	10
TOTAL MALIGNANT TUMORS	9	22	10
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* 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 TREATED WITH N,N'-DIETHYLTHIOUREA

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH N, N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(44)	(46)
INFLAMMATION, CHRONIC SUPPURATIV	1 (5%)		
#LUNG	(20)	(48)	(49)
MINERALIZATION			1 (2%)
ATELECTASIS		5 (10%)	3 (6%)
CONGESTION, NOS	2 (10%)	8 (17%)	5 (10%)
HEMORRHAGE	3 (15%)	7 (15%)	2 (4%)
BRONCHOPNEUMONIA, ACUTE		1 (2%)	
PNEUMONIA, CHRONIC MURINE	4 (20%)	7 (15%)	10 (20%)
GRANULOMA, FOREIGN BODY			1 (2%)
PERIVASCULAR CUFFING		1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (5%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(50)	(48)
HEMOSIDEROSIS			2 (4%)
HEMATOPOIESIS	1 (5%)		1 (2%)
MYELOPOIESIS	1 (5%)		
#MANDIBULAR L. NODE	(17)	(49)	(44)
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(17)	(49)	(44)
INFLAMMATION, CHRONIC		1 (2%)	
DEPLETION		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
HYPERPLASIA, LYMPHOID	1 (6%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(19)	(47)	(49)
THROMBUS, MURAL		1 (2%)	
#MYOCARDIUM	(19)	(47)	(49)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	6 (32%)	8 (17%)	7 (14%)
FIBROSIS	4 (21%)	12 (26%)	11 (22%)
FIBROSIS, FOCAL		1 (2%)	
*CORONARY ARTERY	(20)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, FOCAL	1 (5%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
CHOLANGIOFIBROSIS		1 (2%)	
DEGENERATION, NOS		1 (2%)	2 (4%)
DEGENERATION, GRANULAR			1 (2%)
DEGENERATION, HYDROPIC		1 (2%)	
NECROSIS, NOS			1 (2%)
METAMORPHOSIS FATTY	1 (5%)	3 (6%)	2 (4%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
CLEAR-CELL CHANGE			1 (2%)
ANGIECTASIS			1 (2%)
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	6 (30%)	7 (14%)	24 (48%)
#PANCREAS	(19)	(49)	(48)
ATROPHY, NOS	1 (5%)		
ATROPHY, FOCAL	1 (5%)	1 (2%)	
#PANCREATIC ACINUS	(19)	(49)	(48)
ATROPHY, NOS	2 (11%)	1 (2%)	
#SMALL INTESTINE	(19)	(49)	(48)
INFLAMMATION, NOS	1 (5%)		

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
#PEYERS PATCH	(19)	(49)	(48)
HYPERPLASIA, LYMPHOID	1 (5%)		1 (2%)
#COLON	(20)	(48)	(49)
PARASITISM		7 (15%)	12 (24%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS			1 (2%)
CONGESTION, ACUTE	1 (5%)		
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC	2 (10%)	8 (16%)	15 (30%)
NEPHROPATHY			1 (2%)
NEPHROPATHY, TOXIC	4 (20%)	9 (18%)	3 (6%)
HYPERPLASIA, TUBULAR CELL		1 (2%)	1 (2%)
#KIDNEY/CORTEX	(20)	(50)	(50)
CYST, NOS		1 (2%)	
#URINARY BLADDER	(18)	(41)	(40)
CALCULUS, NOS	1 (6%)		
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(46)	(48)
CONGESTION, NOS		2 (4%)	
HEMORRHAGIC CYST			1 (2%)
#ADRENAL	(18)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	
CYTOPLASMIC VACUOLIZATION			2 (4%)
#ADRENAL CORTEX	(18)	(50)	(50)
METAMORPHOSIS FATTY		1 (2%)	
#THYROID	(18)	(45)	(48)
FOLLICULAR CYST, NOS		1 (2%)	4 (8%)
ATROPHY, NOS			1 (2%)
HYPERPLASIA, C-CELL		2 (4%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
#THYROID FOLLICLE	(18)	(45)	(48)
ATROPHY, NOS		6 (13%)	6 (13%)
HYPERPLASIA, CYSTIC		1 (2%)	5 (10%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(17)	(44)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
#TESTIS	(20)	(49)	(50)
ATROPHY, NOS	2 (10%)		7 (14%)
NERVOUS SYSTEM			
#BRAIN	(19)	(49)	(49)
HEMATOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS	1		

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

TABLE C1 (CONCLUDED)

	CONTROL(UNTR) 11-1365	LOW DOSE 11-1363	HIGH DOSE 11-1361
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2		

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(49)
DERMAL INCLUSION CYST			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(45)	(46)
INFLAMMATION, NOS	3 (16%)	1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	1 (2%)
#LUNG	(20)	(49)	(49)
ATELECTASIS	3 (15%)	4 (8%)	2 (4%)
THROMBOSIS, NOS		1 (2%)	
CONGESTION, NOS	5 (25%)	6 (12%)	1 (2%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE	2 (10%)	3 (6%)	1 (2%)
BRONCHOPNEUMONIA, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
PNEUMONIA, CHRONIC MURINE	6 (30%)	7 (14%)	13 (27%)
BRONCHOPNEUMONIA, CHRONIC			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (5%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(48)
PIGMENTATION, NOS			1 (2%)
HEMOSIDEROSIS	2 (10%)	5 (10%)	4 (8%)
HEMATOPOIESIS	3 (15%)	4 (8%)	2 (4%)
#MESENTERIC L. NODE	(18)	(50)	(47)
HYPERPLASIA, DIFFUSE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
HYPERPLASIA, RETICULUM CELL			2 (4%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(18)	(46)	(48)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		7 (15%)	5 (10%)
FIBROSIS	3 (17%)	3 (7%)	8 (17%)
SCLEROSIS			1 (2%)
FIBROSIS, FOCAL		1 (2%)	
*AORTA	(20)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(19)	(49)	(46)
ATROPHY, FOCAL		1 (2%)	
#LIVER	(20)	(49)	(49)
INFLAMMATION, ACUTE FOCAL			1 (2%)
GRANULOMA, NOS		1 (2%)	
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
METAMORPHOSIS FATTY			1 (2%)
BASOPHILIC CYTO CHANGE	1 (5%)	4 (8%)	1 (2%)
HYPERPLASIA, FOCAL	3 (15%)	2 (4%)	12 (24%)
LYMPHOCYTOSIS			1 (2%)
HEMATOPOIESIS		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(49)	(49)
NECROSIS, NOS		2 (4%)	
*BILE DUCT	(20)	(50)	(49)
HYPERPLASIA, NOS	1 (5%)	4 (8%)	9 (18%)
#PANCREAS	(20)	(47)	(48)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS, DIFFUSE			1 (2%)
ATROPHY, FOCAL		1 (2%)	2 (4%)
#PANCREATIC ACINUS	(20)	(47)	(48)
CYTOPLASMIC VACUOLIZATION		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
#PEYERS PATCH	(19)	(49)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#ILEUM	(19)	(49)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#COLON	(19)	(49)	(47)
PARASITISM	5 (26%)	4 (8%)	5 (11%)
HYPERPLASIA, LYMPHOID			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(49)
INFLAMMATION, CHRONIC	5 (25%)	5 (10%)	17 (35%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
NEPHROPATHY, TOXIC		4 (8%)	3 (6%)
NEPHROSIS, CHOLEMIC			1 (2%)
INFARCT, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(47)	(45)
CYST, NOS	3 (17%)	1 (2%)	
HEMORRHAGIC CYST	1 (6%)	1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL		1 (2%)	1 (2%)
#ADRENAL	(20)	(49)	(48)
HEMORRHAGIC CYST	1 (5%)		
LIPOIDOSIS	1 (5%)	2 (4%)	2 (4%)
CYTOPLASMIC VACUOLIZATION		4 (8%)	
ANGIECTASIS		2 (4%)	
#ADRENAL CORTEX	(20)	(49)	(48)
METAMORPHOSIS FATTY		1 (2%)	
#THYROID	(18)	(46)	(46)
FOLLICULAR CYST, NOS		3 (7%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (6%)		
ATROPHY, NOS			1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	1 (6%)	2 (4%)	6 (13%)

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

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
#THYROID FOLLICLE	(18)	(46)	(46)
ATROPHY, NOS		3 (7%)	11 (24%)
HYPERPLASIA, CYSTIC		1 (2%)	4 (9%)
HYPERPLASIA, ADENOMATOUS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(49)
DILATATION/DUCTS		1 (2%)	
CYSTIC DUCTS		2 (4%)	
HYPERPLASIA, NOS		1 (2%)	
*MAMMARY DUCT	(20)	(50)	(49)
DILATATION, NOS		1 (2%)	
#UTERUS	(19)	(49)	(48)
DILATATION, NOS			1 (2%)
HEMORRHAGE		2 (4%)	
HEMATOMA, NOS	1 (5%)		1 (2%)
INFLAMMATION, NOS	1 (5%)		
NECROSIS, NOS	1 (5%)		
POLYPOID HYPERPLASIA	1 (5%)		
#UTERUS/ENDOMETRIUM	(19)	(49)	(48)
INFLAMMATION, NOS	2 (11%)	2 (4%)	
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, SUPPURATIVE	3 (16%)		1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	2 (11%)		
FIBROSIS, DIFFUSE		1 (2%)	
HYPERPLASIA, NOS	1 (5%)		2 (4%)
HYPERPLASIA, CYSTIC	2 (11%)		
#UTERUS/MYOMETRIUM	(19)	(49)	(48)
ABSCESS, NOS	1 (5%)		1 (2%)
#OVARY	(19)	(49)	(47)
CYST, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE C2 (CONCLUDED)

	CONTROL(UNTR) 11-1366	LOW DOSE 11-1364	HIGH DOSE 11-1362
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	9	2
ANIMAL MISSING/NO NECROPSY			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH N,N'-DIETHYLTHIOUREA

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 22-2365	LOW DOSE 22-2363	HIGH DOSE 22-2361
ANIMALS INITIALLY IN STUDY	@20	50	50
ANIMALS MISSING	4	2	
ANIMALS NECROPSIED	15	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	15	48	49
INTEGUMENTARY SYSTEM			
*SKIN	(15)	(48)	(49)
INFLAMMATION, GRANULOMATOUS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(13)	(46)	(46)
ATELECTASIS			1 (2%)
EDEMA, NOS			1 (2%)
PNEUMONIA, ASPIRATION		1 (2%)	
PNEUMONIA, CHRONIC MURINE			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(14)	(48)	(43)
HEMORRHAGE		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (7%)	2 (4%)	1 (2%)
#MANDIBULAR L. NODE	(14)	(45)	(42)
HYPERPLASIA, NOS		1 (2%)	
#MESENTERIC L. NODE	(14)	(45)	(42)
CONGESTION, CHRONIC			1 (2%)
HEMORRHAGIC CYST		1 (2%)	
INFLAMMATION, HEMORRHAGIC			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (7%)	2 (4%)	2 (5%)
HYPERPLASIA, DIFFUSE			1 (2%)
HYPERPLASIA, PLASMA CELL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (7%)	2 (4%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 20 ANIMALS INITIALLY IN STUDY BUT ONE ANIMAL WAS FOUND TO BE FEMALE IN A MALE GROUP

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2365	LOW DOSE 22-2363	HIGH DOSE 22-2361
DIGESTIVE SYSTEM			
#LIVER	(14)	(48)	(49)
CYST, NOS		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
DEGENERATION, GRANULAR		1 (2%)	1 (2%)
DEGENERATION, HYDROPIC		1 (2%)	
INFARCT, NOS	1 (7%)		
AMYLOIDOSIS			1 (2%)
METAMORPHOSIS FATTY			2 (4%)
NUCLEAR ENLARGEMENT			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, DIFFUSE			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#LIVER/HEPATOCYTES	(14)	(48)	(49)
BASOPHILIC CYTO CHANGE			1 (2%)
HYPERPLASIA, DIFFUSE			2 (4%)
#DUODENUM	(15)	(46)	(47)
AMYLOIDOSIS		1 (2%)	
#ILEUM	(15)	(46)	(47)
FIBROSIS			1 (2%)
#COLON	(15)	(47)	(46)
NEMATODIASIS	4 (27%)	3 (6%)	
URINARY SYSTEM			
#KIDNEY	(14)	(48)	(47)
HYDRONEPHROSIS		1 (2%)	1 (2%)
PYELONEPHRITIS, CHRONIC		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL(UNTR) 22-2365	LOW DOSE 22-2363	HIGH DOSE 22-2361
NERVOUS SYSTEM			
#BRAIN	(15)	(47)	(46)
CYTOPLASMIC VACUOLIZATION			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*LARYNGEAL MUSCLE	(15)	(48)	(49)
PARASITISM		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(15)	(48)	(49)
AMYLOIDOSIS	1 (7%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	15	15
ANIMAL MISSING/NO NECROPSY	4	2	
AUTO/NECROPSY/HISTO PERF		1	1
AUTOLYSIS/NO NECROPSY			1

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH N,N'-DIETHYLTHIOUREA

	CONTROL (UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	2	8
ANIMALS NECROPSIED	19	48	41
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	47	41
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(18)	(45)	(41)
ATELECTASIS		2 (4%)	2 (5%)
CONGESTION, NOS		1 (2%)	2 (5%)
PNEUMONIA, CHRONIC MURINE	2 (11%)	2 (4%)	2 (5%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS		2 (4%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(44)	(39)
HYPERPLASIA, GRANULOCYTIC			2 (5%)
#SPLEEN	(18)	(46)	(40)
CONGESTION, CHRONIC			1 (3%)
INFARCT, NOS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL	1 (6%)	1 (2%)	
HYPERPLASIA, LYMPHOID	1 (6%)	2 (4%)	3 (8%)
HEMATOPOIESIS	1 (6%)	1 (2%)	
#SPLENIC FOLLICLES	(18)	(46)	(40)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#MANDIBULAR L. NODE	(17)	(46)	(40)
HYPERPLASIA, RETICULUM CELL	1 (6%)		
HYPERPLASIA, LYMPHOID		3 (7%)	
#MESENTERIC L. NODE	(17)	(46)	(40)
CONGESTION, CHRONIC			1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
INFLAMMATION, CHRONIC			1 (3%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	1 (3%)
PIGMENTATION, NOS			1 (3%)
HYPERPLASIA, RETICULUM CELL	2 (12%)		1 (3%)
HYPERPLASIA, LYMPHOID		1 (2%)	2 (5%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(46)	(40)
INFLAMMATION, DIFFUSE		1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (3%)
FIBROSIS, FOCAL			1 (3%)
DEGENERATION, GRANULAR	1 (5%)		
DEGENERATION, HYDROPIC	1 (5%)	1 (2%)	1 (3%)
METAMORPHOSIS FATTY		2 (4%)	1 (3%)
HYPERPLASIA, DIFFUSE			1 (3%)
#LIVER/PERIPORTAL	(19)	(46)	(40)
INFLAMMATION, GRANULOMATOUS			1 (3%)
FIBROSIS	1 (5%)		
#LIVER/HEPATOCYTES	(19)	(46)	(40)
HYPERPLASIA, NOS		2 (4%)	
#PANCREAS	(18)	(44)	(40)
ATROPHY, NOS	1 (6%)		
#SMALL INTESTINE	(17)	(43)	(39)
HYPERPLASIA, LYMPHOID		1 (2%)	
#PEYERS PATCH	(17)	(43)	(39)
HYPERPLASIA, RETICULUM CELL	1 (6%)		
#COLON	(18)	(42)	(39)
NEMATODIASIS		1 (2%)	1 (3%)
PARASITISM		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(18)	(46)	(40)
INFLAMMATION, CHRONIC		1 (2%)	1 (3%)

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

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
PERIVASCULAR CUFFING			2 (5%)
#URINARY BLADDER	(15)	(34)	(28)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(20)	(23)
HEMORRHAGIC CYST			1 (4%)
HYPERPLASIA, CHROMOPHOBE-CELL		1 (5%)	
#THYROID	(12)	(31)	(25)
CYST, NOS			1 (4%)
FOLLICULAR CYST, NOS		1 (3%)	
DEGENERATION, NOS			2 (8%)
HYPERPLASIA, FOCAL		1 (3%)	
#PANCREATIC ISLETS	(18)	(44)	(40)
HYPERTROPHY, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(17)	(45)	(38)
HYDROMETRA	1 (6%)	6 (13%)	6 (16%)
FIBROSIS, DIFFUSE			1 (3%)
HYPERPLASIA, STROMAL			1 (3%)
#UTERUS/ENDOMETRIUM	(17)	(45)	(38)
CYST, NOS	1 (6%)		
HYPERPLASIA, CYSTIC	2 (12%)	5 (11%)	8 (21%)
#UTERUS/MYOMETRIUM	(17)	(45)	(38)
ABSCESS, NOS		1 (2%)	
AMYLOIDOSIS			1 (3%)
#OVARY/OVIDUCT	(17)	(45)	(38)
CYST, NOS	1 (6%)		
#OVARY	(16)	(43)	(35)
CYST, NOS	3 (19%)	5 (12%)	4 (11%)
PAROVARIAN CYST		1 (2%)	
ABSCESS, NOS		1 (2%)	

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

TABLE D2 (CONCLUDED)

	CONTROL(UNTR) 22-2366	LOW DOSE 22-2364	HIGH DOSE 22-2362
NERVOUS SYSTEM			
#BRAIN	(19)	(44)	(38)
CORPORA AMYLACEA	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(19)	(48)	(41)
STEATITIS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	5	5
ANIMAL MISSING/NO NECROPSY	1	2	8
AUTO/NECROPSY/HISTO PERF	1	1	1
AUTO/NECROPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY			1

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

Review of the Bioassay of N,N'-Diethylthiourea* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

August 31, 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 N,N'-Diethylthiourea for carcinogenicity.

The primary reviewer agreed with the conclusion in the report that N,N'-Diethylthiourea was carcinogenic in both sexes of treated rats. After a brief description of the experimental design, she noted as shortcomings of the study: 1) the small number of matched controls; 2) the fact that other chemicals were under test in the same room in which this study was conducted; and 3) the treated animals may not have received a maximum tolerated dose, since a noticeable weight effect was not observed. Despite the shortcomings, she said that the study was still valid, although she questioned if the thyroid effect was sufficient evidence to regard N,N'-Diethylthiourea to be a carcinogen. The primary reviewer felt no statement could be made concerning the human risk posed by N,N'-Diethylthiourea.

A Program staff pathologist commented that C-cell tumors are the most common type of thyroid neoplasms in Fischer rats, occurring about three or four times more frequently than follicular-cell tumors.

A motion was approved unanimously that the report on the bioassay of N,N'-Diethylthiourea be accepted as written.

Members present were:

Arnold Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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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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