National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 148
1978

BIOASSAY OF 1-PHENYL-2-THIOUREA FOR POSSIBLE CARCINOGENICITY

CAS No. 103-85-5

NCI-CG-TR-148

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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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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DHEW Publication No. (NIH) 78-1704

REPORT ON THE BIOASSAY OF 1-PHENYL-2-THIOUREA
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 1-phenyl-2-thiourea 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 1-phenyl-2-thiourea was conducted by Litton Bionetics, Inc., Bethesda, Maryland, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., 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. S. 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. J. F. Hardisty (4) at Litton Bionetics, Inc., the pathology narratives were written by Dr. J. F. Hardisty (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).

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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 of 1-phenyl-2-thiourea for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 1-Phenyl-2-thiourea was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low concentrations of 1-phenyl-2-thiourea utilized in the chronic bioassay were, respectively, 120 and 60 ppm for rats and 300 and 150 ppm for mice. Twenty animals of each species and sex were placed on test as controls. A 78-week period of chemical administration was followed by an additional observation period of 26 weeks for rats and 13 weeks for mice.

Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related depression of mean body weight gain was observed in male and female mice when compared with their controls, but growth retardation was not observed in any dosed rat group. In addition, since no significant accelerated mortality or other toxic effects were associated with the dietary administration of 1-phenyl-2-thiourea to rats, it is possible that the compound was not administered to these animals at the maximum tolerated concentrations.

There were no tumors in either sex of rats or mice for which a significant positive association could be established between chemical administration and tumor incidence.

Under the conditions of this bioassay, 1-phenyl-2-thiourea was not carcinogenic to Fischer 344 rats or B6C3F1 mice.

TABLE OF CONTENTS

		Page
I.	INTRODUCTION	1
II.	MATERIALS AND METHODS	4
	A. Chemicals	4
	B. Dietary Preparation	4
	C. Animals	5
	D. Animal Maintenance	6
	E. Selection of Initial Concentrations	7
	F. Experimental Design	9
	G. Clinical and Histopathologic Examinations	12
	H. Data Recording and Statistical Analyses	14
III.	CHRONIC TESTING RESULTS: RATS	19
	A. Body Weights and Clinical Observations	19
	B. Survival	19
	C. Pathology	19
	D. Statistical Analyses of Results	22
IV.	CHRONIC TESTING RESULTS: MICE	30
	A. Body Weights and Clinical Observations	30
	B. Survival	30
	C. Pathology	33
	D. Statistical Analyses of Results	33
V.	DISCUSSION	39
VI.	BIBLIOGRAPHY	40
APPENDIX A	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1-PHENYL-2-THIOUREA	A-1
APPENDIX B	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1-PHENYL-2-THIOUREA	B-1
APPENDIX C	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1-PHENYL-2-THIOUREA	C-1
APPENDIX D	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 1-PHENYL-2-THIOUREA	D-1

LIST OF ILLUSTRATIONS

Figure Number		Page
1	CHEMICAL STRUCTURE OF 1-PHENYL-2-THIOUREA	2
2	GROWTH CURVES FOR 1-PHENYL-2-THIOUREA CHRONIC STUDY RATS	20
3	SURVIVAL COMPARISONS OF 1-PHENYL-2-THIOUREA CHRONIC STUDY RATS	21
4	GROWTH CURVES FOR 1-PHENYL-2-THIOUREA CHRONIC STUDY MICE	31
5	SURVIVAL COMPARISONS OF 1-PHENYL-2-THIOUREA CHRONIC STUDY MICE	32

LIST OF TABLES

Table Number		Page
1	DESIGN SUMMARY FOR FISCHER 344 RATS--1-PHENYL-2-THIOUREA FEEDING EXPERIMENT	10
2	DESIGN SUMMARY FOR B6C3F1 MICE--1-PHENYL-2-THIOUREA FEEDING EXPERIMENT	11
3	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH 1-PHENYL-2-THIOUREA	23
4	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH 1-PHENYL-2-THIOUREA	26
5	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH 1-PHENYL-2-THIOUREA	34
6	ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH 1-PHENYL-2-THIOUREA	36
A1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 1-PHENYL-2-THIOUREA	A-3

LIST OF TABLES (Concluded)

Table Number		Page
A2	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 1-PHENYL-2-THIOUREA	A-7
B1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 1-PHENYL-2-THIOUREA	B-3
B2	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH 1-PHENYL-2-THIOUREA	B-6
C1	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH 1-PHENYL-2-THIOUREA	C-3
C2	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH 1-PHENYL-2-THIOUREA	C-8
D1	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH 1-PHENYL-2-THIOUREA	D-3
D2	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH 1-PHENYL-2-THIOUREA	D-7

I. INTRODUCTION

1-Phenyl-2-thiourea (Figure 1) (NCI No. C02017) 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), and the widespread oral exposure to this compound.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is phenylthiourea.* It is also called phenylthiocarbamide; 1-phenylthiourea; N-phenylthiourea; and PTU.

The ability to perceive the bitter taste of 1-phenyl-2-thiourea is genetically determined; consequently, this compound has been used extensively as a test substance in genetics research and in demonstrations of genetic polymorphism (Gosselin et al., 1976; Winchester, 1966). The gene responsible for 1-phenyl-2-thiourea tasting ability is dominant and is present in about 70 percent of the U.S. population (Winchester, 1966).

1-Phenyl-2-thiourea is also used occasionally as a rodenticide but its effectiveness in this application is limited by the compound's bitter taste (Gosselin et al., 1976).

Specific production data for 1-phenyl-2-thiourea are not available; however, this compound is produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by two U.S. companies (Stanford Research Institute, 1977).

*The CAS registry number is 103-85-5.

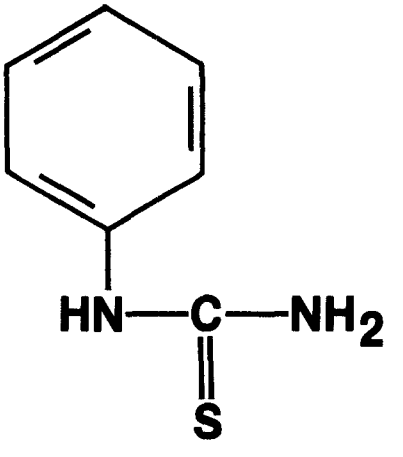


FIGURE 1
CHEMICAL STRUCTURE OF 1-PHENYL-2-THIOUREA

As 1-phenyl-2-thiourea is frequently used in classroom demonstrations of genetic polymorphism in taste, a substantial number of people are exposed to small amounts of this compound via ingestion (Wheatcroft and Thornburn, 1972). Chronic intake of 1-phenyl-2-thiourea is thought to lead to enlargement of the thyroid gland (goiter) and other glandular problems in humans (Wheatcroft and Thornburn, 1972).

II. MATERIALS AND METHODS

A. Chemicals

1-Phenyl-2-thiourea was purchased from Eastman Chemical Company, Rochester, New York. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. Although the melting point (149° to 150°C) was somewhat different than that reported in the literature (154°C [Weast, 1977]), the narrow range close to the reported value suggested a compound of high purity. Thin-layer chromatography was performed utilizing two solvent systems (chloroform:dichloromethane:ethyl acetate:formic acid and chloroform:acetone). Each plate showed only one spot. Infrared analysis was consistent with the structure of the compound and nuclear magnetic resonance analysis was consistent with that reported in the literature (Sadtler Standard Spectra,a). Ultraviolet analysis yielded a λ_{max} of 265 nm with a molar extinction coefficient of 1.45×10^4. This value agrees quite well with the value reported in the literature (1.39×10^4) (Sadtler Standard Spectra,b). The data suggest that the compound was of extremely high purity. Stability studies performed by thin-layer chromatography at six-month intervals indicated no degradation, as detectable by the method employed.

Throughout this report, the term 1-phenyl-2-thiourea is used to represent this material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois).

1-Phenyl-2-thiourea 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.

The stability of 1-phenyl-2-thiourea in feed was determined spectrophotometrically. Ten days after preparation of diets containing 60 and 120 ppm concentrations of 1-phenyl-2-thiourea, 93 $\pm$ 6 percent of the initial concentrations were recovered from the feed.

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 and 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 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 stainless steel mesh lid 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 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* dibutyltin diacetate (1067-33-0); amitrole (61-82-5); zinc acetate (57-34-6); and copper acetate (80-12-5).

All dosed and control mice were housed in a room with other mice receiving diets containing Michler's ketone (90-94-8); 4,4'-methylenebis(N,N-dimethyl)-benzenamine (101-61-1); trimethylthiourea (2489-77-2); p-chloroaniline (106-47-8); dibutyltin diacetate (1067-33-0); 2-nitro-p-phenylenediamine (5307-14-2); 3-chloro-p-toluidine (95-74-9); 5-chloro-o-toluidine (95-79-4); and N-phenyl-p-phenylenediamine hydrochloride (2198-59-6).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 1-phenyl-2-thiourea for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Rats were distributed among six groups, each

*CAS registry numbers are given in parentheses.

consisting of five males and five females. 1-Phenyl-2-thiourea was incorporated into the basal laboratory diet and supplied ad libitum to five of the six rat groups in concentrations of 45, 70, 100, 145, and 215 ppm. The sixth rat group served as a control group, receiving only the basal laboratory diet.

Mice were distributed among ten groups, each consisting of five males and five females. 1-Phenyl-2-thiourea was incorporated into the basal laboratory diet and supplied ad libitum to eight of the ten mouse groups in concentrations of 25, 37, 55, 80, 120, 375, 680, and 810 ppm. The two remaining groups served as the control groups, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 4 weeks, followed by a 2-week observation period during which all animals were fed the basal diet. Individual body weights and food consumption data were recorded twice weekly throughout the study. Upon termination of the observation period, all survivors were sacrificed and necropsied.

At the end of the subchronic test, mean body weight gains among male rats dosed with 215, 145, 100, 70 and 45 ppm were, respectively, 73, 72, 1, 29, and 2 percent less than the mean body weight gain of their controls, while female rats receiving the same concentrations displayed respective mean body weight gains of 19, 20, 2, 11 and 8 percent less than that of their controls. The high concentration

selected for administration to dosed rats in the chronic bioassay was 120 ppm.

At a dietary concentration of 810 ppm, 2 male and 2 female mice died. At the end of the subchronic test, mean body weight gains among male mice dosed with 810, 650, 375, and 120 ppm were, respectively, 3 percent less than, 3 percent more than, 3 percent more than, and 6 percent less than the mean body weight gain of their controls, while female mice receiving the same concentrations displayed respective mean body weight gains of 10 percent less than, 9 percent more than, 1 percent more than, and 5 percent less than that of their controls. Mean body weight gains among male mice dosed with 80, 55, 37 and 25 ppm were, respectively, 5, 7, 4, and 1 percent greater than the mean body weight gain of their controls, while female mice receiving the same concentrations displayed respective mean body weight gains of 1, 2, 3, and 2 percent less than that of their controls. The high concentration selected for administration to dosed mice in the chronic bioassay was 300 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

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
1-PHENYL-2-THIOUREA FEEDING EXPERIMENT

	INITIAL GROUP SIZE	1-PHENYL-2-THIOUREA CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	103
LOW DOSE	50	60	78	
		0		26
HIGH DOSE	50	120	78	
		0		26
FEMALE				
CONTROL	20	0	0	104
LOW DOSE	50	60	78	
		0		26
HIGH DOSE	50	120	78	
		0		26

[a]Concentrations given in parts per million.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1-PHENYL-2-THIOUREA FEEDING EXPERIMENT

	INITIAL GROUP SIZE	1-PHENYL-2-THIOUREA CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	91
LOW DOSE	50	150	78	
		0		13
HIGH DOSE	50	300	78	
		0		13
FEMALE				
CONTROL	20	0	0	91
LOW DOSE	50	150	78	
		0		13
HIGH DOSE	50	300	78	
		0		13

[a]Concentrations given in parts per million.

concentrations of 1-phenyl-2-thiourea utilized were 120 and 60 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 1-phenyl-2-thiourea for 78 weeks, followed by an additional observation period of 26 weeks.

All mice were approximately 6 weeks old at the time the test was initiated, and were placed on test simultaneously. The dietary concentrations of 1-phenyl-2-thiourea utilized were 300 and 150 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 1-phenyl-2-thiourea for 78 weeks, followed by an additional observation period of 13 weeks.

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 a week for the first 6 weeks, every 2 weeks for the next 12 weeks, and at monthly intervals thereafter. Body weights of mice were recorded at monthly intervals throughout the bioassay.

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, 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 compound-related mean body weight depression was apparent 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 1-phenyl-2-thiourea-dosed groups are shown in Figure 3. For both males and females, the Tarone test for positive association between dosage and mortality was not significant.

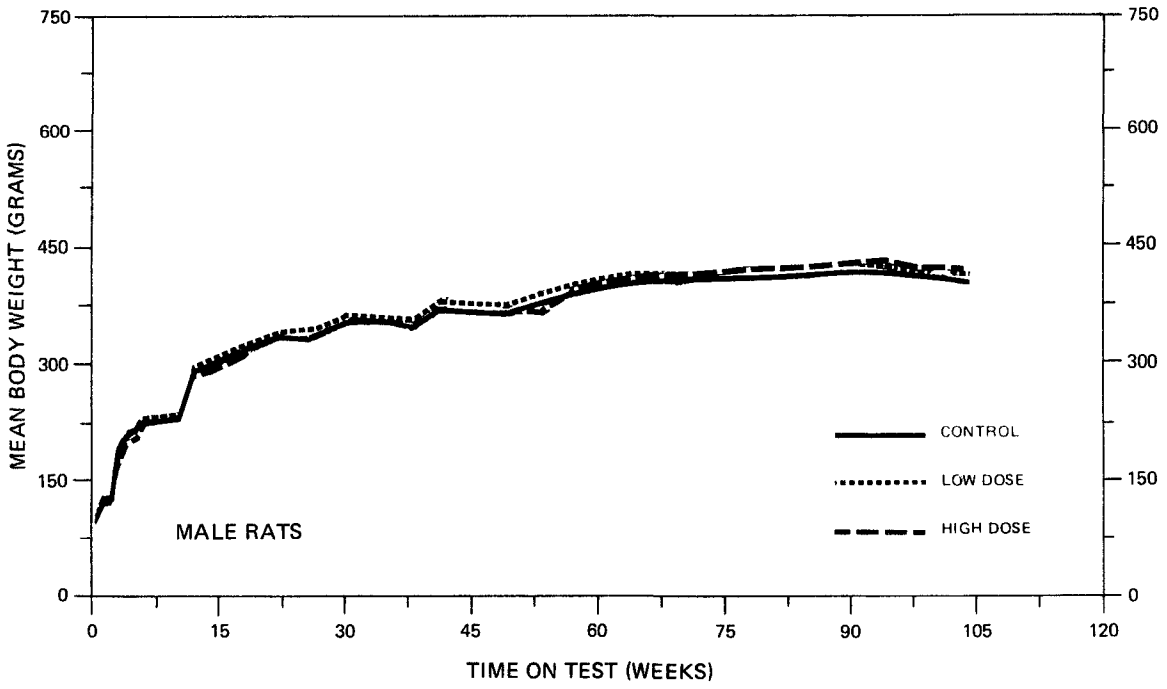
Adequate numbers of male rats were at risk from late-developing tumors, as 86 percent (43/50) of the high dose, 82 percent (41/50) of the low dose and 90 percent (18/20) of the control group survived on test until the termination of the study.

For female rats, 78 percent (39/50) of the high dose, 74 percent (37/50) of the low dose, and 80 percent (16/20) of the control group survived on test until the termination of the study, thus providing adequate numbers 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).

A variety of neoplastic lesions was seen with approximately equal frequency in the control and dosed rats. The most frequently



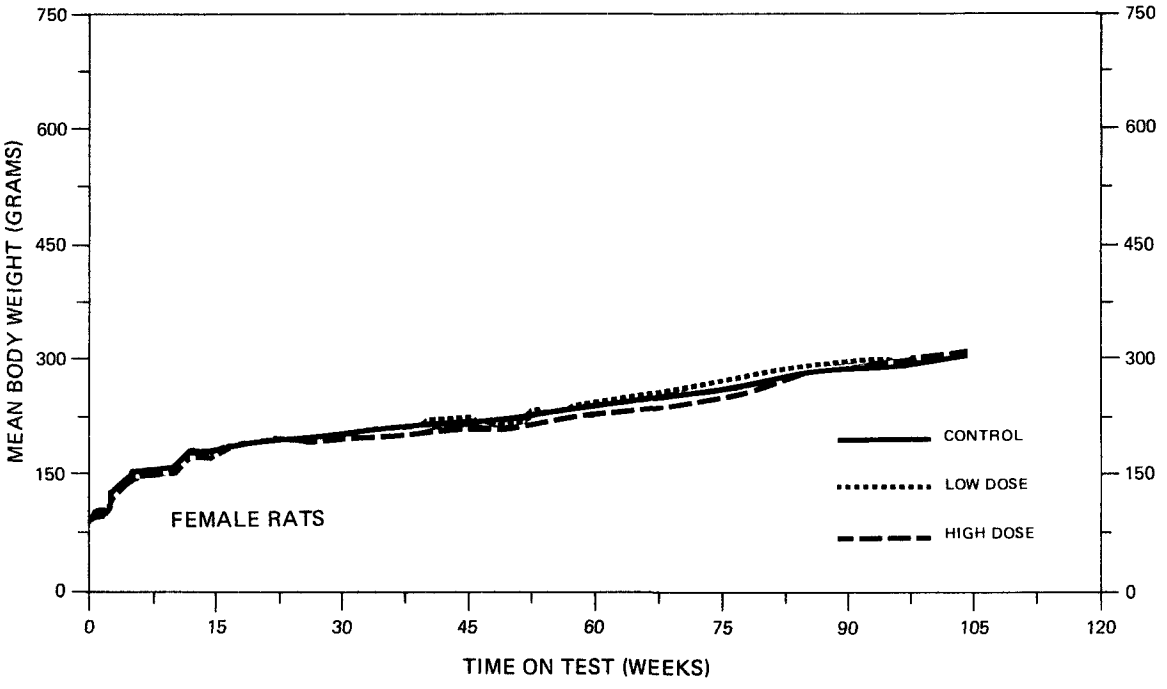
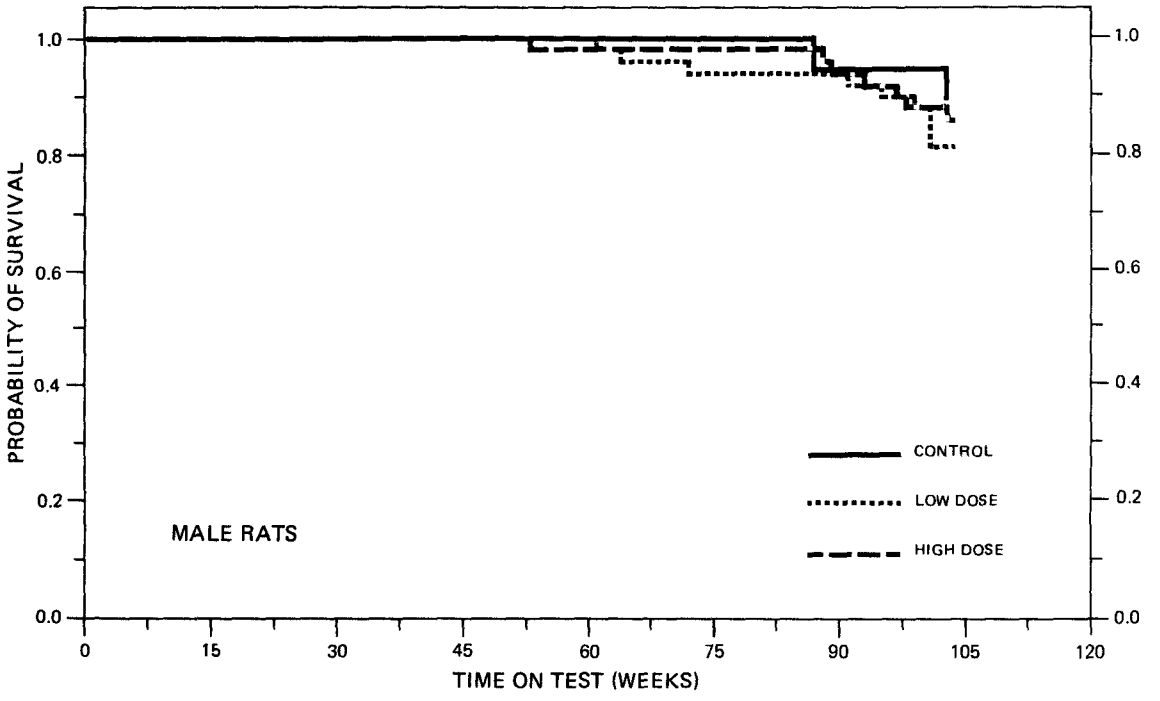


FIGURE 2
GROWTH CURVES FOR 1-PHENYL-2-THIOUREA CHRONIC STUDY RATS



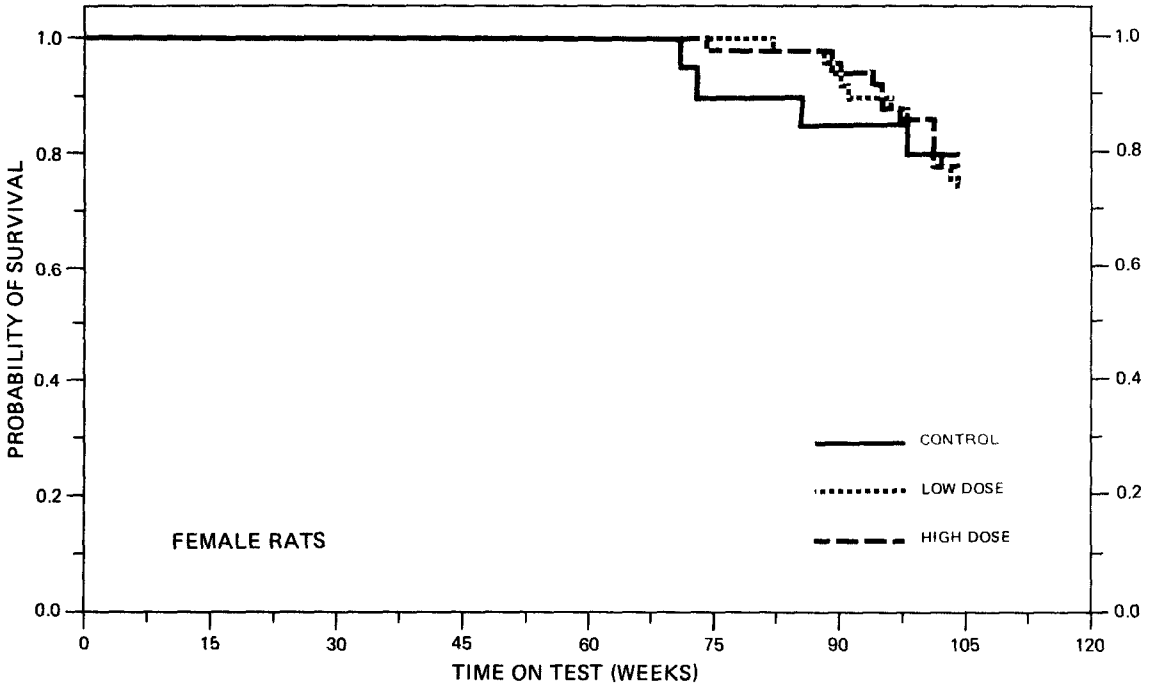


FIGURE 3
SURVIVAL COMPARISONS OF 1-PHENYL-2-THIOUREA CHRONIC STUDY RATS

observed neoplasm in male rats was interstitial-cell tumors of the testis. A high incidence of this neoplasm is characteristic of aged male Fischer 344 rats. Chromophobe adenomas of the pituitary and fibroadenomas of the mammary gland were the most frequently observed neoplasms in the female rats.

A variety of inflammatory, degenerative and proliferative lesions commonly seen in aged Fischer 344 rats was seen with approximately equal frequency in dosed and control animals.

The results of this pathologic examination indicate that 1-phenyl-2-thiourea was not carcinogenic to male or female Fischer 344 rats under the conditions of this bioassay.

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 1-phenyl-2-thiourea-dosed groups and where such tumors were observed in at least 5 percent of the group.

For female rats the Fisher exact test indicated a significantly ($P = 0.030$) higher incidence of pituitary chromophobe adenomas in the low dose group than in the control group. This result was not supported by the Cochran-Armitage test or the high dose Fisher exact test and is above the $P = 0.025$ probability required by the Bonferroni inequality.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 1-PHENYL-2-THIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	2/20(0.10)	0/49(0.00)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.800
Lower Limit	---	0.000	0.128
Upper Limit	---	1.372	8.436
Weeks to First Observed Tumor	103	---	104
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/20(0.05)	5/50(0.10)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.000	2.400
Lower Limit	---	0.249	0.325
Upper Limit	---	92.596	108.021
Weeks to First Observed Tumor	87	91	93
Pituitary: Chromophobe Adenoma[b]	2/19(0.11)	4/44(0.09)	5/47(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.864	1.011
Lower Limit	---	0.139	0.187
Upper Limit	---	9.058	10.082
Weeks to First Observed Tumor	103	104	104

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	1/20(0.05)	6/48(0.13)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.500	0.816
Lower Limit	---	0.339	0.046
Upper Limit	---	112.370	47.195
Weeks to First Observed Tumor	103	104	104
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	0/20(0.00)	2/46(0.04)	3/46(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.133	0.272
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	104
Testis: Interstitial-Cell Tumor[b]	18/20(0.90)	43/48(0.90)	39/49(0.80)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.995	0.884
Lower Limit	---	0.872	0.771
Upper Limit	---	1.255	1.186
Weeks to First Observed Tumor	103	91	89

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	2/19(0.11)	3/45(0.07)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.633	0.432
Lower Limit	---	0.081	0.034
Upper Limit	---	7.210	5.669
Weeks to First Observed Tumor	103	104	104

[a]Treated groups received doses of 60 or 120 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 1-PHENYL-2-THIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/20(0.05)	4/50(0.08)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.600	1.600
Lower Limit	---	0.175	0.175
Upper Limit	---	77.169	77.169
Weeks to First Observed Tumor	73	101	101
Pituitary: Chromophobe Adenoma[b]	5/19(0.26)	26/47(0.55)	18/50(0.36)
P Values[c]	N.S.	P = 0.030	N.S.
Departure from Linear Trend[e]	P = 0.014	---	---
Relative Risk (Control)[d]	---	2.102	1.368
Lower Limit	---	0.978	0.595
Upper Limit	---	6.009	4.173
Weeks to First Observed Tumor	98	82	94
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	3/17(0.18)	1/45(0.02)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.126	0.340
Lower Limit	---	0.003	0.052
Upper Limit	---	1.468	2.369
Weeks to First Observed Tumor	103	104	89

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/20(0.05)	1/45(0.02)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.444	1.702
Lower Limit	---	0.006	0.186
Upper Limit	---	34.140	81.978
Weeks to First Observed Tumor	103	104	101
Mammary Gland: Fibroadenoma[b]	3/20(0.15)	15/50(0.30)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.022	---	---
Relative Risk (Control)[d]	---	2.000	0.667
Lower Limit	---	0.662	0.147
Upper Limit	---	9.943	4.014
Weeks to First Observed Tumor	103	101	94
Uterus: Endometrial Stromal Polyp[b]	0/18(0.00)	1/48(0.02)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.021	0.227
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	104

TABLE 4 (CONCLUDED)

[a]Treated groups received doses of 60 or 120 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.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

No other tests for any site in either male or female rats were significant. Thus, based upon these statistical results, there was no conclusive evidence that 1-phenyl-2-thiourea was a carcinogen in Fischer 344 rats under the conditions of this bioassay.

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 3 and 4, 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 rats by 1-phenyl-2-thiourea that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

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

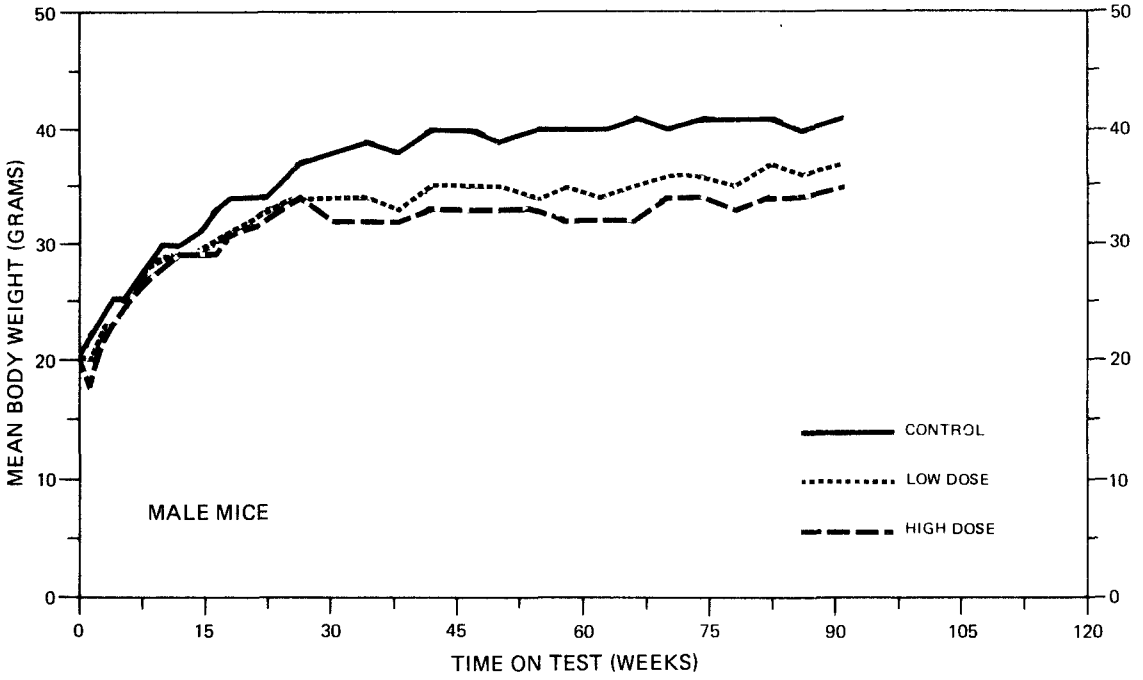
No abnormal clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 1-phenyl-2-thiourea-dosed groups are shown in Figure 5. For both male and female mice, the Tarone test for positive association between dosage and mortality was not significant.

Adequate numbers of male mice were at risk from late-developing tumors, as 92 percent (46/50) of the high dose, 92 percent (46/50) of the low dose and 85 percent (17/20) of the control group survived on test until the termination of the study. One male mouse was missing from the low dose group in week 12 and one was missing from the control group in week 65.

For female mice, 88 percent (44/50) of the high dose, 74 percent (37/50) of the low dose, and 95 percent (19/20) of the control group survived on test until the termination of the study, thus providing adequate numbers at risk from late-developing tumors. Five low dose females were missing in week 38 with three additional low dose females missing in week 58.



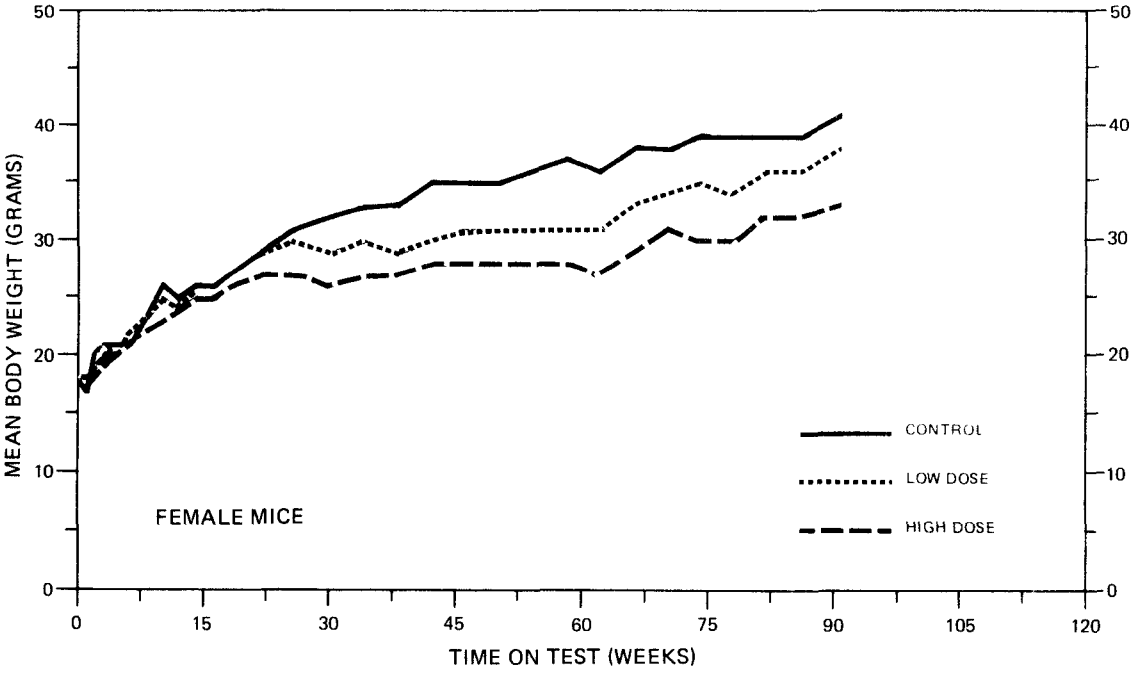
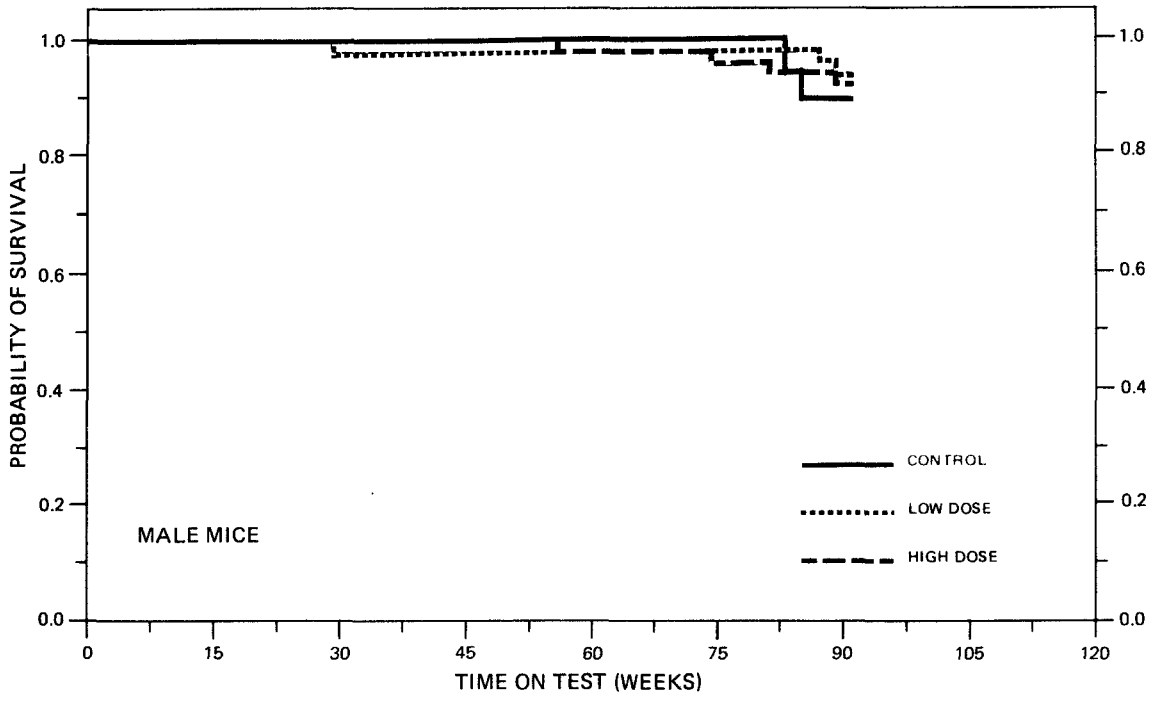


FIGURE 4
GROWTH CURVES FOR 1-PHENYL-2-THIOUREA CHRONIC STUDY MICE



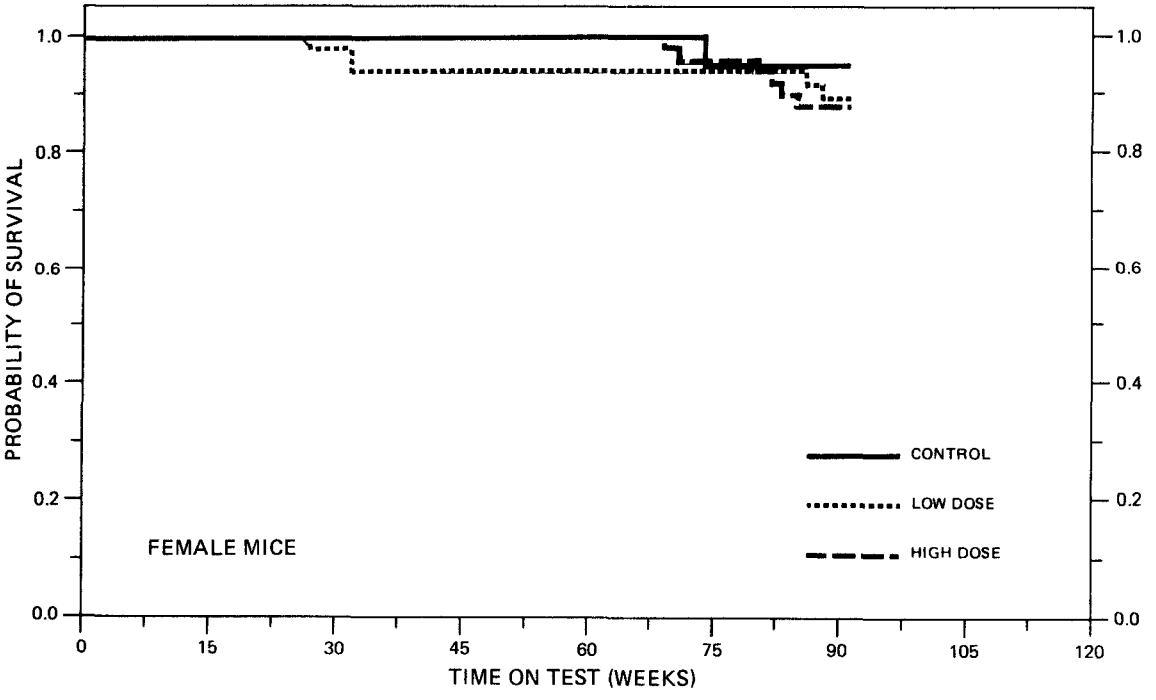


FIGURE 5
SURVIVAL COMPARISONS OF 1-PHENYL-2-THIOUREA CHRONIC STUDY MICE

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).

A variety of neoplastic lesions was present in the dosed and control groups. There were instances in this study where neoplastic lesions occurred only, or with increased frequency, in dosed mice as compared with controls. These lesions were all of types which are known to occur spontaneously in B6C3F1 mice at incidences similar to those observed in this study.

A variety of inflammatory and proliferative lesions commonly seen in B6C3F1 mice occurred with approximately equal frequency in dosed and control mice.

The results of this pathologic examination indicate that under the conditions of this study, dietary administration of 1-phenyl-2-thiourea was not carcinogenic to B6C3F1 mice of either sex.

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 1-phenyl-2-thiourea-dosed groups and where such tumors were observed in at least 5 percent of the group.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 1-PHENYL-2-THIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	3/19(0.16)	6/49(0.12)	6/49(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.776	0.776
Lower Limit	---	0.191	0.191
Upper Limit	---	4.463	4.463
Weeks to First Observed Tumor	91	91	91
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/19(0.05)	5/49(0.10)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.939	0.760
Lower Limit	---	0.243	0.043
Upper Limit	---	89.722	43.961
Weeks to First Observed Tumor	91	87	91
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	1/19(0.05)	7/48(0.15)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.771	1.163
Lower Limit	---	0.401	0.103
Upper Limit	---	121.980	59.809
Weeks to First Observed Tumor	83	91	91

TABLE 5 (CONCLUDED)

[a]Treated groups received doses of 150 or 300 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 1-PHENYL-2-THIOUREA[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/19(0.00)	0/40(0.00)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.243
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	85
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/19(0.00)	3/40(0.07)	5/49(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.298	0.511
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	85
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/20(0.15)	6/42(0.14)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.952	0.667
Lower Limit	---	0.233	0.147
Upper Limit	---	5.450	4.014
Weeks to First Observed Tumor	74	88	71

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	0/19(0.00)	0/39(0.00)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.383
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	91

[a]Treated groups received doses of 150 or 300 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.

None of the statistical tests for any site in mice of either sex indicated a significant positive association between the administration of 1-phenyl-2-thiourea and an increased tumor incidence. Thus, at the dose levels used in this experiment, there was no evidence that 1-phenyl-2-thiourea was a carcinogen in B6C3F1 mice.

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 1-phenyl-2-thiourea that could not be established under the conditions of this test.

V. DISCUSSION

Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Distinct dose-related depression of mean body weight gain was observed in male and female mice when compared with their controls, but growth retardation was not observed in any dosed rat group. In addition, since no significant accelerated mortality or other toxic effects were associated with the dietary administration of 1-phenyl-2-thiourea to rats, it is possible that the compound was not administered to these animals at the maximum tolerated concentrations.

No neoplasms in either sex of either species occurred for which a significant positive association between chemical administration and tumor incidence could be established. All observed neoplasms were of types and incidences known to occur spontaneously in Fischer 344 rats or B6C3F1 mice.

Under the conditions of this bioassay, 1-phenyl-2-thiourea was not carcinogenic to Fischer 344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1-PHENYL-2-THIOUREA

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
SARCOMA, NOS	1 (5%)		
FIBROMA	1 (5%)		1 (2%)
FIBROSARCOMA		1 (2%)	1 (2%)
LIPOMA	1 (5%)		
FIBROADENOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			2 (4%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
LEUKEMIA,NOS		3 (6%)	3 (6%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
ERYTHROCYTIC LEUKEMIA		1 (2%)	1 (2%)
#SPLEEN	(20)	(47)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
#LIVER	(20)	(48)	(50)
LEUKEMIA,NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(50)
HEPATOCELLULAR ADENOMA		1 (2%)	1 (2%)
NEOPLASTIC NODULE		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(44)	(47)
CHROMOPHOBE ADENOMA	2 (11%)	4 (9%)	5 (11%)
#ADRENAL	(20)	(48)	(49)
PHEOCHROMOCYTOMA	1 (5%)	5 (10%)	2 (4%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(19)	(45)	(44)
C-CELL ADENOMA	1 (5%)	2 (4%)	1 (2%)
C-CELL CARCINOMA	1 (5%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(20)	(46)	(46)
ISLET-CELL ADENOMA		2 (4%)	2 (4%)
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA	1 (5%)		1 (2%)
#TESTIS	(20)	(48)	(49)
INTERSTITIAL-CELL TUMOR	18 (90%)	43 (90%)	39 (80%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
FIBROSARCOMA		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	6	4
MORIBUND SACRIFICE	1	3	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	41	43
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	47	45
TOTAL PRIMARY TUMORS	30	68	67
TOTAL ANIMALS WITH BENIGN TUMORS	18	45	42
TOTAL BENIGN TUMORS	27	58	54
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	9	11
TOTAL MALIGNANT TUMORS	3	9	11
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1
TOTAL SECONDARY TUMORS		2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
CYSTADENOMA, NOS		1 (2%)	
SARCOMA, NOS		2 (4%)	
FIBROMA		2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(50)
CARCINOMA, NOS, METASTATIC	1 (5%)		1 (2%)
C-CELL CARCINOMA, METASTATIC			1 (2%)
PHEOCHROMOCYTOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
LEUKEMIA,NOS		2 (4%)	1 (2%)
#MEDIASTINAL L.NODE	(17)	(41)	(41)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#LIVER	(20)	(48)	(49)
LEUKEMIA,NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
DIGESTIVE SYSTEM			
#SMALL INTESTINE	(20)	(45)	(49)
ADENOCARCINOMA, NOS		1 (2%)	
JRINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(47)	(50)
CHROMOPHOBE ADENOMA	5 (26%)	26 (55%)	18 (36%)
#ADRENAL	(17)	(45)	(50)
ADENOMA, NOS		1 (2%)	
PHEOCHROMOCYTOMA	2 (12%)	1 (2%)	3 (6%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (6%)		
#THYROID	(20)	(45)	(47)
C-CELL ADENOMA	1 (5%)	1 (2%)	2 (4%)
C-CELL CARCINOMA	1 (5%)		2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA	3 (15%)	15 (30%)	5 (10%)
HEMANGIOMA		1 (2%)	
*CLITORAL GLAND	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
SEBACEOUS ADENOMA			1 (2%)
#UTERUS	(18)	(48)	(50)
SARCOMA, NOS			2 (4%)
ENDOMETRIAL STROMAL POLYP		1 (2%)	3 (6%)
#OVARY	(18)	(45)	(47)
SERTOLI-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			

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

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(20)	(50)	(50)
EPITHELIAL TUMOR, NOS, BENIGN	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LIPOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	5	4
MOPIBUND SACRIFICE	2	8	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	37	39
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	37	30
TOTAL PRIMARY TUMORS	15	59	42
TOTAL ANIMALS WITH BENIGN TUMORS	10	34	26
TOTAL BENIGN TUMORS	12	50	34
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	9	8
TOTAL MALIGNANT TUMORS	3	9	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		2
TOTAL SECONDARY TUMORS	2		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1-PHENYL-2-THIOUREA

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	1	
ANIMALS NECROPSIED	19	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(49)	(50)
SARCOMA, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (16%)	5 (10%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(49)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)	1 (2%)
LEUKEMIA,NOS		1 (2%)	
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
#LYMPH NODE	(13)	(34)	(32)
MALIGNANT LYMPHOMA, NOS	1 (8%)	1 (3%)	
#MESENTERIC L. NODE	(13)	(34)	(32)
MALIGNANT LYMPHOMA, NOS			1 (3%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(48)	(49)
HEPATOCELLULAR ADENOMA	1 (5%)	6 (13%)	3 (6%)

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

TABLE B1 (CONTINUED)

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
HEPATOCELLULAR CARCINOMA		1 (2%)	
HEMANGIOMA		1 (2%)	1 (2%)
#SMALL INTESTINE	(19)	(23)	(48)
ADENOMA, NOS	1 (5%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	2	3
MORIBUND SACRIFICE		1	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	46	46
ANIMAL MISSING	1	1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	16	12
TOTAL PRIMARY TUMORS	6	20	12
TOTAL ANIMALS WITH BENIGN TUMORS	5	11	9
TOTAL BENIGN TUMORS	5	12	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	8	3
TOTAL MALIGNANT TUMORS	1	8	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		8	
ANIMALS NECROPSIED	20	42	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	41	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(40)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(42)	(50)
MALIGNANT LYMPHOMA, NOS	2 (10%)	4 (10%)	2 (4%)
LEUKEMIA,NOS	1 (5%)	1 (2%)	3 (6%)
#SPLEEN	(18)	(40)	(46)
HEMANGIOMA	1 (6%)		
#LIVER	(19)	(39)	(48)
MALIGNANT LYMPHOMA, NOS		2 (5%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(39)	(48)
HEPATOCELLULAR ADENOMA			3 (6%)
HEPATOCELLULAR CARCINOMA			1 (2%)

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

TABLE B2 (CONTINUED)

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
URINARY SYSTEM			
#URINARY BLADDER	(19)	(41)	(47)
LIPOMA	1 (5%)		
HEMANGIOSARCOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(31)	(30)
CHROMOPHOBE ADENOMA			1 (3%)
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(41)	(50)
LEIOMYOMA		1 (2%)	
#OVARY	(16)	(33)	(45)
TERATOMA, NOS		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(42)	(50)
LIPOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2 (CONCLUDED)

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	5	3
MORIBUND SACRIFICE			3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	19	37	44
ANIMAL MISSING		8	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	11	15
TOTAL PRIMARY TUMORS	5	14	15
TOTAL ANIMALS WITH BENIGN TUMORS	2	4	6
TOTAL BENIGN TUMORS	2	5	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	6	9
TOTAL MALIGNANT TUMORS	3	8	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1-PHENYL-2-THIOUREA

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
EDEMA, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL		2 (4%)	
PNEUMONIA, LIPID			1 (2%)
PNEUMONIA, CHRONIC MURINE	1 (5%)	11 (22%)	12 (24%)
PNEUMONIA INTERSTITIAL CHRONIC			2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (5%)	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(44)	(48)
MYELOSCLEROSIS	1 (5%)		
#SPLEEN	(20)	(47)	(49)
CONGESTION, NOS		1 (2%)	1 (2%)
HEMOSIDEROSIS	5 (25%)	8 (17%)	5 (10%)
HEMATOPOIESIS	4 (20%)	3 (6%)	5 (10%)
#SPLENIC RED PULP	(20)	(47)	(49)
DEPLETION		1 (2%)	
#MESENTERIC L. NODE	(18)	(45)	(40)
HYPERPLASIA, LYMPHOID			1 (3%)
CIRCULATORY SYSTEM			
#HEART	(20)	(49)	(49)
PERIARTERITIS		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
#MYOCARDIUM	(20)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS		3 (6%)	1 (2%)
FIBROSIS, FOCAL			1 (2%)
DEGENERATION, NOS	5 (25%)	11 (22%)	12 (24%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(50)
CYST, NOS	1 (5%)		
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY	2 (10%)	1 (2%)	1 (2%)
BASOPHILIC CYTO CHANGE	1 (5%)	5 (10%)	1 (2%)
CLEAR-CELL CHANGE		1 (2%)	1 (2%)
HEPATOCYTOMEGALY		1 (2%)	2 (4%)
#LIVER/CENTRILOBULAR	(20)	(48)	(50)
CONGESTION, NOS		1 (2%)	
#LIVER/PERIPORTAL	(20)	(48)	(50)
FIBROSIS			1 (2%)
#BILE DUCT	(20)	(48)	(50)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, NOS	2 (10%)	10 (21%)	7 (14%)
#PANCREAS	(20)	(46)	(46)
FIBROSIS			1 (2%)
FIBROSIS, DIFFUSE		1 (2%)	1 (2%)
NECROSIS, FAT		1 (2%)	
ATROPHY, FOCAL			1 (2%)
#STOMACH	(20)	(47)	(50)
HYPERPLASIA, ADENOMATOUS			1 (2%)
#SMALL INTESTINE	(20)	(46)	(49)
HYPERPLASIA, LYMPHOID			2 (4%)
#LARGE INTESTINE	(20)	(47)	(49)
NEMATODIASIS	2 (10%)	12 (26%)	7 (14%)

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
INFLAMMATION, NOS	1 (5%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	12 (60%)	29 (59%)	21 (42%)
CALCINOSIS, NOS			1 (2%)
PIGMENTATION, NOS	1 (5%)	3 (6%)	4 (8%)
LIPOMATOSIS		1 (2%)	
#KIDNEY/TUBULE	(20)	(49)	(50)
BASOPHILIC CYTO CHANGE			2 (4%)
#KIDNEY/PELVIS	(20)	(49)	(50)
HYPERPLASIA, EPITHELIAL	1 (5%)		
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(44)	(47)
CYST, NOS	1 (5%)		
#PITUITARY/BASOPHIL	(19)	(44)	(47)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
#ADRENAL	(20)	(48)	(49)
HEMORRHAGIC CYST	1 (5%)		
METAMORPHOSIS FATTY		1 (2%)	
CYTOLOGIC DEGENERATION		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
#ADRENAL CORTEX	(20)	(48)	(49)
HYPERPLASIA, NOS			1 (2%)
#ADRENAL MEDULLA	(20)	(48)	(49)
HYPERPLASIA, NOS	5 (25%)	7 (15%)	7 (14%)
#THYROID	(19)	(45)	(44)
PIGMENTATION, NOS	1 (5%)	4 (9%)	4 (9%)
GOITER COLLOID			1 (2%)
HYPERPLASIA, C-CELL		5 (11%)	2 (5%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
#PANCREATIC ISLETS	(20)	(46)	(46)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ABSCESS, NOS		1 (2%)	
#PROSTATE	(20)	(44)	(47)
HYPERPLASIA, EPITHELIAL	1 (5%)		
#TESTIS	(20)	(48)	(49)
ATROPHY, NOS	2 (10%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(47)	(50)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
STEATITIS		1 (2%)	
*PERITONEUM	(20)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
*PLEURA	(20)	(50)	(50)
FOAM-CELL			1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
NECROSIS, FAT			1

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

	CONTROL(UNTR) 11-1035	LOW DOSE 11-1033	HIGH DOSE 11-1031
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			2
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO		1	

\# 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 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
INFLAMMATION, INTERSTITIAL			1 (2%)
PNEUMONIA, LIPID			1 (2%)
PNEUMONIA, CHRONIC MURINE	1 (5%)	9 (18%)	14 (28%)
PNEUMONIA INTERSTITIAL CHRONIC	2 (11%)		
GRANULOMA, NOS			1 (2%)
LIPOGRANULOMA			2 (4%)
GRANULOMA, FOREIGN BODY			1 (2%)
FOAM-CELL		1 (2%)	1 (2%)
HYPERPLASIA, ADENOMATOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(17)	(43)	(45)
OSTEOSCLEROSIS			1 (2%)
#SPLEEN	(20)	(47)	(48)
CONGESTION, NOS			2 (4%)
HEMOSIDEROSIS	6 (30%)	10 (21%)	7 (15%)
ERYTHROPHAGOCYTOSIS			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
HEMATOPOIESIS	6 (30%)	10 (21%)	4 (8%)
#CERVICAL LYMPH NODE	(17)	(41)	(41)
HYPERPLASIA, PLASMA CELL		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(47)	(49)
FIBROSIS			1 (2%)
FIBROSIS, FOCAL			1 (2%)
DEGENERATION, NOS	1 (5%)	10 (21%)	15 (31%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(17)	(44)	(48)
INFLAMMATION, NOS			1 (2%)
#LIVER	(20)	(48)	(49)
HEMORRHAGE			1 (2%)
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL	1 (5%)	1 (2%)	
METAMORPHOSIS FATTY	2 (10%)	3 (6%)	3 (6%)
BASOPHILIC CYTO CHANGE	5 (25%)	13 (27%)	15 (31%)
EOSINOPHILIC CYTO CHANGE			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#HEPATIC CAPSULE	(20)	(48)	(49)
HEMORRHAGIC CYST	1 (5%)		
#LIVER/PERIPORTAL	(20)	(48)	(49)
INFLAMMATION, CHRONIC			1 (2%)
#BILE DUCT	(20)	(48)	(49)
DILATATION, NOS		1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (5%)	2 (4%)	4 (8%)
#PANCREAS	(19)	(47)	(48)
FIBROSIS	1 (5%)		1 (2%)
ATROPHY, FOCAL	1 (5%)		
#SMALL INTESTINE	(20)	(45)	(49)
PARASITISM			1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
#LARGE INTESTINE	(20)	(46)	(44)
NEMATODIASIS	4 (20%)	9 (20%)	9 (20%)
#COLON	(20)	(46)	(44)
HYPERPLASIA, LYMPHOID		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
URINARY SYSTEM			
#KIDNEY	(18)	(47)	(50)
GLOMERULONEPHRITIS, NOS		1 (2%)	
GLOMERULONEPHRITIS, MEMBRANOUS		1 (2%)	
INFLAMMATION, CHRONIC	4 (22%)	18 (38%)	28 (56%)
NEPHROSIS, NOS		2 (4%)	
PIGMENTATION, NOS	2 (11%)	6 (13%)	2 (4%)
#URINARY BLADDER	(15)	(40)	(40)
HYPERTROPHY, NOS		1 (3%)	
HYPERPLASIA, EPITHELIAL		1 (3%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(47)	(50)
RETENTION FLUID		1 (2%)	
CYST, NOS	1 (5%)	5 (11%)	5 (10%)
#ADRENAL	(17)	(45)	(50)
CYST, NOS		1 (2%)	
LIPOIDOSIS		2 (4%)	
#ADRENAL CORTEX	(17)	(45)	(50)
CYST, NOS			1 (2%)
HEMORRHAGIC CYST	1 (6%)	1 (2%)	
HYPERPLASIA, NODULAR		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(17)	(45)	(50)
HYPERPLASIA, NOS	3 (18%)	4 (9%)	4 (8%)
#THYROID	(20)	(45)	(47)
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (5%)		
HYPERPLASIA, C-CELL	2 (10%)	6 (13%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS	2 (10%)	2 (4%)	1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
ADENOSIS	1 (5%)	2 (4%)	
LACTATION			1 (2%)
#UTERUS	(18)	(48)	(50)
HYDROMETRA			1 (2%)
ABSCESS, NOS		1 (2%)	
#CERVIX UTERI	(18)	(48)	(50)
ABSCESS, NOS			1 (2%)
DEGENERATION, MUCOID	1 (6%)		
#UTERUS/ENDOMETRIUM	(18)	(48)	(50)
CYST, NOS			1 (2%)
INFLAMMATION, NOS	1 (6%)		
ABSCESS, NOS		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, CYSTIC		1 (2%)	2 (4%)
#OVARY	(18)	(45)	(47)
CYST, NOS	1 (6%)	1 (2%)	
FOLLICULAR CYST, NOS		1 (2%)	
PAROVARIAN CYST		1 (2%)	2 (4%)
CONGESTION, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(49)
HYDROCEPHALUS, NOS	1 (5%)		1 (2%)
HEMORRHAGE			1 (2%)
ATROPHY, NOS		1 (2%)	
ATROPHY, PRESSURE	1 (5%)	1 (2%)	2 (4%)
SPECIAL SENSE ORGANS			
*EAR	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(20)	(50)	(50)
FOAM-CELL		2 (4%)	4 (8%)

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

TABLE C2 (CONCLUDED)

	CONTROL(UNTR) 11-1036	LOW DOSE 11-1034	HIGH DOSE 11-1032
*MESENTERY	(20)	(50)	(50)
NECROSIS, FAT	1 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
PIGMENTATION, NOS	1 (5%)	2 (4%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	2	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 1-PHENYL-2-THIOUREA

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	1	
ANIMALS NECROPSIED	19	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(49)	(50)
CYST, NOS			1 (2%)
*SUBCUT TISSUE	(19)	(49)	(50)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(19)	(49)	(49)
HYPERPLASIA, EPITHELIAL	1 (5%)		
#LUNG/BRONCHIOLE	(19)	(49)	(49)
INFLAMMATION, NOS	1 (5%)		
INFLAMMATION, ACUTE	1 (5%)		
#LUNG	(19)	(49)	(49)
THROMBUS, ORGANIZED		1 (2%)	
EDEMA, NOS	1 (5%)	1 (2%)	2 (4%)
HEMORRHAGE		1 (2%)	
PNEUMONIA, ASPIRATION			1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	2 (4%)
PERIVASCULAR CUFFING		1 (2%)	3 (6%)
FOAM-CELL		1 (2%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)	
EPITHELIALIZATION		1 (2%)	
HEMATOPOIETIC SYSTEM			
*SPLEEN	(19)	(47)	(46)
HYPERPLASIA, LYMPHOID		1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(48)	(49)
DEGENERATION, NOS		1 (2%)	2 (4%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(17)	(45)	(44)
PERIVASCULAR CUFFING	1 (6%)	3 (7%)	2 (5%)
#LIVER	(19)	(48)	(49)
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, ACUTE FOCAL	2 (11%)	4 (8%)	1 (2%)
PERIVASCULAR CUFFING		1 (2%)	2 (4%)
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
BASOPHILIC CYTO CHANGE	1 (5%)	1 (2%)	
#STOMACH	(19)	(45)	(47)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
#SMALL INTESTINE	(19)	(23)	(48)
HYPERPLASIA, LYMPHOID		1 (4%)	
#LARGE INTESTINE	(19)	(43)	(48)
NEMATODIASIS	4 (21%)	5 (12%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(48)	(49)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, NOS			1 (2%)
INFLAMMATION, CHRONIC	3 (16%)	8 (17%)	3 (6%)
PERIVASCULAR CUFFING	2 (11%)	14 (29%)	4 (8%)
#KIDNEY/PELVIS	(19)	(48)	(49)
HEMORRHAGE		1 (2%)	
ENDOCRINE SYSTEM			
NONE			

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

TABLE D1 (CONTINUED)

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
REPRODUCTIVE SYSTEM			
#PROSTATE	(19)	(46)	(44)
HYPERPLASIA, CYSTIC	4 (21%)	4 (9%)	3 (7%)
*SEMINAL VESICLE	(19)	(49)	(50)
DEGENERATION, NOS		1 (2%)	
#TESTIS	(19)	(48)	(48)
DEGENERATION, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(18)	(47)	(46)
COPPORA AMYLACEA	9 (50%)	9 (19%)	11 (24%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(19)	(49)	(50)
FOAM-CELL		1 (2%)	
*MESENTERY	(19)	(49)	(50)
STEATITIS		1 (2%)	
PERIARTERITIS			1 (2%)
NECROSIS, FAT	1 (5%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(19)	(49)	(50)
PERIVASCULAR CUFFING	3 (16%)	9 (18%)	4 (8%)

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

TABLE D1 (CONCLUDED)

	CONTROL(UNTR) 22-2035	LOW DOSE 22-2033	HIGH DOSE 22-2031
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	8	17
ANIMAL MISSING/NO NECROPSY	1	1	
AUTO/NECROPSY/HISTO PERF			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 1-PHENYL-2-THIOUREA

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		8	
ANIMALS NECROPSIED	20	42	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	41	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(40)	(49)
INFLAMMATION, INTERSTITIAL		1 (3%)	
PNEUMONIA, CHRONIC MURINE		1 (3%)	5 (10%)
PERIVASCULAR CUFFING			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(40)	(46)
HYPERPLASIA, LYMPHOID			2 (4%)
HEMATOPOIESIS		1 (3%)	
#LYMPH NODE	(16)	(36)	(42)
HEMORRHAGE	1 (6%)		
#MESENTERIC L. NODE	(16)	(36)	(42)
HYPERPLASIA, LYMPHOID			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(40)	(47)
INFLAMMATION, NOS			1 (2%)
*PULMONARY ARTERY	(20)	(42)	(50)
HYPERTROPHY, NOS	1 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(19)	(39)	(48)
INFLAMMATION, FOCAL	3 (16%)		

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

TABLE D2 (CONTINUED)

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
INFLAMMATION, ACUTE FOCAL	1 (5%)	7 (18%)	5 (10%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
PERIVASCULAR CUFFING	1 (5%)	3 (8%)	
NECROSIS, FOCAL			2 (4%)
PIGMENTATION, NOS		1 (3%)	
GLYCOGENIC CELL			2 (4%)
ANGIECTASIS			1 (2%)
#PANCREAS	(19)	(39)	(46)
CYSTIC DUCTS	1 (5%)		
#STOMACH	(18)	(39)	(48)
INFLAMMATION, SUPPURATIVE			1 (2%)
#SMALL INTESTINE	(19)	(40)	(49)
HYPERPLASIA, LYMPHOID	1 (5%)		2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(40)	(48)
HYDRONEPHROSIS	1 (5%)	1 (3%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC	3 (15%)	6 (15%)	2 (4%)
PERIVASCULAR CUFFING	1 (5%)	3 (8%)	3 (6%)
NEPHROSIS, CHOLEMIC			1 (2%)
#URINARY BLADDER	(19)	(41)	(47)
HYPERPLASIA, LYMPHOID			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(19)	(38)	(45)
METAMORPHOSIS FATTY	1 (5%)		
#THYROID	(16)	(32)	(43)
GOITER COLLOID		1 (3%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(41)	(50)
HYDROMETRA		1 (2%)	
CYST, NOS	1 (5%)	2 (5%)	1 (2%)

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

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
PYOMETRA	1 (5%)	2 (5%)	3 (6%)
DECIDUA		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(41)	(50)
CYST, NOS	6 (30%)	11 (27%)	1 (2%)
INFLAMMATION, NOS	1 (5%)	1 (2%)	3 (6%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE	2 (10%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	1 (5%)		17 (34%)
#UTERUS/MYOMETRIUM	(20)	(41)	(50)
INFLAMMATION, NOS			1 (2%)
#OVARY/OVIDUCT	(20)	(41)	(50)
INFLAMMATION, NOS		1 (2%)	
#OVARY	(16)	(33)	(45)
CYST, NOS	5 (31%)	4 (12%)	3 (7%)
FOLLICULAR CYST, NOS	1 (6%)		1 (2%)
PAROVARIAN CYST	1 (6%)	3 (9%)	
INFLAMMATION, NOS		1 (3%)	
PIGMENTATION, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(40)	(49)
INFLAMMATION, NOS	1 (5%)		
#BRAIN	(20)	(40)	(49)
CORPORA AMYLACEA	4 (20%)	11 (28%)	7 (14%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(20)	(42)	(50)
INFLAMMATION, NOS			1 (2%)

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

TABLE D2 (CONCLUDED)

	CONTROL(UNTR) 22-2036	LOW DOSE 22-2034	HIGH DOSE 22-2032
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(42)	(50)
PERIVASCULAR CUFFING	3 (15%)	4 (10%)	9 (18%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		6	2
ANIMAL MISSING/NO NECROPSY		8	
AUTO/NECROPSY/NO HISTO		1	

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

Review of the Bioassay of 1-Phenyl-2-Thiourea* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

June 29, 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 1-Phenyl-2-Thiourea for carcinogenicity.

The reviewer agreed with the conclusion in the report that 1-Phenyl-2-Thiourea was not carcinogenic under the conditions of test. After a brief description of the experimental design, he commented on the studies' deficiencies. Among those noted were the inadequate control group size, the lack of analytical data on the dietary concentration of the test substance, the conduct of the study in a room in which other chemicals were under test, and an improperly run subchronic study. Despite the shortcomings, the reviewer said the study was still adequate enough to form a conclusion on the carcinogenicity of

1-Phenyl-2-Thiourea. He moved that the report on the bioassay of 1-Phenyl-2-Thiourea be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. 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.

☆U.S. GOVERNMENT PRINTING OFFICE: 1978-260-899/3190

NIH Publication No. 78-1704