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BIOASSAY OF

N, N' - DICYCLOHEXYLTHIOUREA

FOR POSSIBLE CARCINOGENICITY

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

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FOREWORD: This report presents the results of the bioassay of N,N′-dicyclohexylthiourea 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 environmental chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that the test chmeical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of N,N′-dicyclohexylthiourea was conducted by The Dow Chemical Company, Indianapolis, Indiana, 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 and doses were determined by Drs. J. L. Emerson[1] and E. K. Weisburger[2]. Dr. C. G. Gerbig[1] supervised the preparation of the feed mixtures and was responsible for animal care. Histopathologic examinations were performed by Dr. J. L. Emerson, and the diagnoses included in this report represent his interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[3]. The statistical analyses were performed by Dr. J. R. Joiner[4], using methods selected for the bioassay program by Dr. J. J. Gart[5]. Chemicals used in this bioassay were analyzed under the direction of Dr. E. Murrill[6], and the analytical results were reviewed by Dr. C. W. Jameson[4].

This report was prepared at Tracor Jitco[4] under the direction of Dr. Marshall Steinberg, Director of the Bioassay Program; Dr. L. A. Campbell, Deputy Director for Science; Drs. J. F. Robens and R. W. Fogleman, toxicologists; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Waitz, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of NCI[5]: Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh M. Pettigrew, and Dr. Robert E. Tarone.

The following other scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings:

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SUMMARY

A bioassay of N,N′-dicyclohexylthiourea for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were administered N,N′-dicyclohexylthiourea at one of two doses, either 25,000 or 50,000 ppm, for 109 weeks for rats or 104 weeks for mice. Matched controls consisted of 50 untreated rats or 50 untreated mice of each sex.

Mean body weights of male rats and male mice were unaffected by the compound, whereas mean body weights of the females of each species showed mild dose-related retardation over the bioassay period, when compared with the matched controls. Survival was sufficient to termination of the study in all groups of both rats and mice for the development of late-appearing tumors.

In male rats there was an increased incidence of hyperplasia of the follicular cells of the thyroid (males: controls 3/43, low-dose 16/49, high-dose 15/49; females: controls 1/48, low-dose 7/48, high-dose 5/49). The incidences of tumors of the follicular cells of the thyroid, although increased among the dosed male rats, were not statistically significant in either sex.

In mice, a variety of neoplasms of the type usually encountered in the B6C3F1 strain were observed in both dosed and control animals. None of the tumors occurred at statistically significant incidences. Follicular-cell hyperplasia of the thyroid was observed at an increased incidence in both the dosed males and females (males: controls 3/39, low-dose 12/46, high-dose 9/45; females: controls 8/38, low-dose 22/46, high-dose 21/46).

An increase in proliferative lesions of the follicular cells of

the thyroid was associated with the administration of N,N′-dicyclohexylthiourea in both Fischer 344 rats and B6C3F1 mice. However, because statistical significance was not achieved and because thyroid tumors are not rare spontaneous lesions in these strains of animals and occur with a variable incidence, it is concluded that under the conditions of this bioassay N,N′-dicyclohexylthiourea was not demonstrated to be carcinogenic in either species.

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I. INTRODUCTION

N,N′-Dicyclohexylthiourea (CAS 1212-29-9; NCI C04524) is a chemical intermediate used in the production of dicyclohexylcarbodiimide, a reagent used in the synthesis of peptide and phosphodiester internucleotide bonds (Lehninger, 1970). Dicyclohexylcarbodiimide has been found to inhibit ATPase, the enzyme that catalyzes the active transport of Na^+ and K^+ through cellular membranes. This compound also inhibits energy transfer required for the phosphorylation of ADP to ATP (Schoner et al., 1972). N,N′-dicyclohexylthiourea was tested because it was the closest structural analogue of dicyclohexylcarbodiimide that was available in the quantities needed for a 2-year study. Dicyclohexylcarbodiimide was of interest because its use in the laboratory results in occupational exposure.

II. MATERIALS AND METHODS

A. Chemical

The N,N′-dicyclohexylthiourea used in the chronic study was obtained in a single batch (Lot No. A5633) from Pfaltz and Bauer, Inc., Stamford, Connecticut. The identity and purity of this batch was confirmed in analyses at Midwest Research Institute. Thiourea titration indicated 99.0 $\pm$ 0.5% purity. Both thin-layer and high-pressure liquid chromatography indicated one homogeneous component. The melting point was 181.6-183°C (literature: 181-183°C). Elemental analyses (C, H, N, S) were correct for $C_{13}H_{24}N_2S$, the molecular formula of N,N′-dicyclohexylthiourea. The identity was confirmed by nuclear magnetic resonance, infrared, and ultraviolet spectra, which were in agreement with the structure.

The chemical was stored in plastic-lined fiber drums at room temperature.

B. Dietary Preparation

Test diets were prepared by combining N,N′-dicyclohexylthiourea with Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) to make a 10% premix. This premix was placed in a Patterson-Kelly Twin Shell Blender with the appropriate amount of

animal meal to obtain the required concentrations, and blended for 20 minutes. All dietary preparations were stored in plastic-lined fiber drums and refrigerated at 4°C for no longer than 14-17 days.

The stability of the treated feed mixtures was checked at the Midwest Research Institute by determining the concentration of N,N′-dicyclohexylthiourea in formulated diets stored at 4°C for a 2-week period. The results of these analyses indicated that N,N′-dicyclohexylthiourea mixed with animal meal is stable for 2 weeks at 4°C.

C. Animals

Fischer 344 rats were obtained from two sources, A. R. Schmidt/Sprague-Dawley, Madison, Wisconsin, and Harlan Industries, Cumberland, Indiana. Hybrid B6C3F1 mice were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Animal suppliers were under contract with the Division of Cancer Treatment, NCI, to provide the animals used for testing. On arrival at the laboratory, all animals were approximately 28 days of age and were quarantined for 1-2 weeks for an acclimation period. They were then assigned to control and treatment groups, and individually identified. The rats were ear-clipped and the mice were

toe-clipped. Rats that were received from multiple suppliers were distributed proportionately throughout each treatment and control group, so that 3/4 of the rats in each group were from A. R. Schmidt and 1/4 were from Harlan Industries.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature was maintained at 23°C with a range from 22-25°C, and the relative humidity was maintained at 45-55%. The room air was changed 15 times per hour. All rooms were equipped with automatic timers which controlled lighting and provided illumination 14 hours per day. Food and deionized, chlorinated well water were available ad libitum.

Rats in the chronic study were housed individually in suspended cages made of stainless-steel wire mesh (Ford Fence Co., Indianapolis, Ind.). At week 45, rats were housed three per cage in suspended polycarbonate filtered cages (Maryland Plastics, Federalsburg, Md.) and an automatic watering system and provided with autoclaved Absorb-Dri® bedding (Lab Products, Inc., Garfield, N.J.). The cages were changed, washed, and sanitized at 82°C twice per week. The feeders were changed, washed, and sterilized once per week, and the filters were changed every 2 weeks.

Mice were housed five per cage in prebedded filtered cages made of disposable polypropylene (Lab Products, Inc., Garfield, N.J.). The cages were changed twice per week and the used cages were incinerated. Feeders, water bottles, and cage lids also were changed twice per week, and filters were changed once per week. Feeders and sipper tubes were washed and sterilized prior to use. Water bottles and cage lids were sanitized at 82°C.

Rats and mice were housed in separate rooms. The animal racks were rotated within the rooms once per week; the cages were kept in fixed positions on the racks. The rats treated with N,N′-dicyclohexylthiourea were housed in the same room as rats being fed 1,3-dichloro-5,5-dimethylhydantoin (CAS 118-52-5), proflavine hydrochloride (CAS 952-23-8), and the positive control, N-2-fluorenylacetamide (CAS 53-96-3). The mice treated with N,N′-dicyclohexylthiourea were housed in the same room as mice being fed 2-amino-5-nitrothiazole (CAS 121-66-4), 1,3-dichloro-5,5-dimethylhydantoin, proflavine hydrochloride, and N-2-fluorenylacetamide. Mice administered 3-nitropropionic acid (CAS 504-88-1) by gavage were also in the same room. Untreated controls were housed in the same room with respective treated animals.

E. Subchronic Studies

Subchronic studies were conducted with rats and mice to estimate the maximum tolerated doses of N,N′-dicyclohexylthiourea, on the basis of which low and high concentrations (hereinafter referred to as "low doses" and "high doses"), were determined for administration in the chronic studies. All animals were treated for 6 weeks and observed for an additional 2 weeks. The parameters assessed were body weight changes, gross pathology, and mortality.

Rats were treated with concentrations of 2,500, 5,000, 10,000, 25,000, or 50,000 ppm. Mean body weight gain was slightly lower (91% of controls) at 50,000 ppm in males, and slightly lower (87-96% of controls), but not dose related, in all female treated groups.

Mice were administered the same concentrations as rats. Mean body weight gain was slightly depressed in females at concentrations of 10,000 ppm and higher, although decreases in mean weight gain were not dose related. These same concentrations had no effect on growth in males. No mortality, clinical signs of toxicity, or compound-related pathology were observed in mice.

Because no appreciable toxicity was observed with any concentration used, and because there was an upper limit of 50,000 ppm

for the chronic studies, 25,000 and 50,000 ppm were used as the low and high doses for the chronic studies for males and females of both species.

F. Designs of Chronic Studies

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

G. Clinical and Pathologic Examinations

All animals were observed twice per day for signs of toxicity, and those that were moribund were killed and necropsied. Some moribund animals were isolated from their cage-mates for a few days prior to being killed. The animals were weighed every 14 days during the first 3 months and every 28 days thereafter. Clinical observations were recorded once per week.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and animals found dead. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, colon, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, testis or ovary, prostate or uterus, brain, and eyes. Occasional-

Table 1. Design of N,N′-Dicyclohexylthiourea Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	N,N′-Dicyclohexylthiourea in Diet[b] (ppm)	Time on Study (weeks)
Males			
Matched-Control	50	0	109
Low-Dose	50	25,000	109
High-Dose	50	50,000	109
Females			
Matched-Control	50	0	109
Low-Dose	50	25,000	109
High-Dose	50	50,000	109

[a]Rats were approximately 47 days of age when placed on study.

[b]Diets containing N,N′-dicyclohexylthiourea were administered 7 days per week.

Table 2. Design of N,N′-Dicyclohexylthiourea
Chronic Feeding Studies in Mice

Sex and Treatment Group	Initial No. of Animals[a]	N,N′-Dicyclohexylthiourea in Diet[b] (ppm)	Time on Study (weeks)
Males			
Matched-Control	50	0	104
Low-Dose	50	25,000	104
High-Dose	50	50,000	104
Females			
Matched-Control	50	0	104
Low-Dose	50	25,000	104
High-Dose	50	50,000	104

[a]Mice were approximately 44 days of age when placed on study.

[b]Diets containing N,N′-dicyclohexylthiourea were administered 7 days per week.

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

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

H. Data Recording and Statistical Analyses

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

These data were analyzed using the statistical techniques

described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

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

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

appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of 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) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

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

ship. This method also provides a two-tailed test of departure from linear trend.

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

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

noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated 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% 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 ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

The mean body weights of treated male rats were comparable to those of controls throughout the study. Treated females had appreciably decreased mean body weights, after approximately 10 weeks on study, which appeared to be dose related (figure 1). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variation. The treated rats were generally comparable to the controls in appearance and behavior throughout the 2 years of the study. Unilateral, and occasionally bilateral, cataracts were observed at the end of the first year and throughout the second year of the study in both control and treated rats.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed N,N′-dicyclohexylthiourea at the doses of this experiment, together with those of the matched controls, are shown in figure 2.

The results of the Tarone test for positive dose-related trend in mortality are not significant at the 0.05 level in either sex. In the males 34/50 (68%) of the high-dose group, 39/50 (78%) of

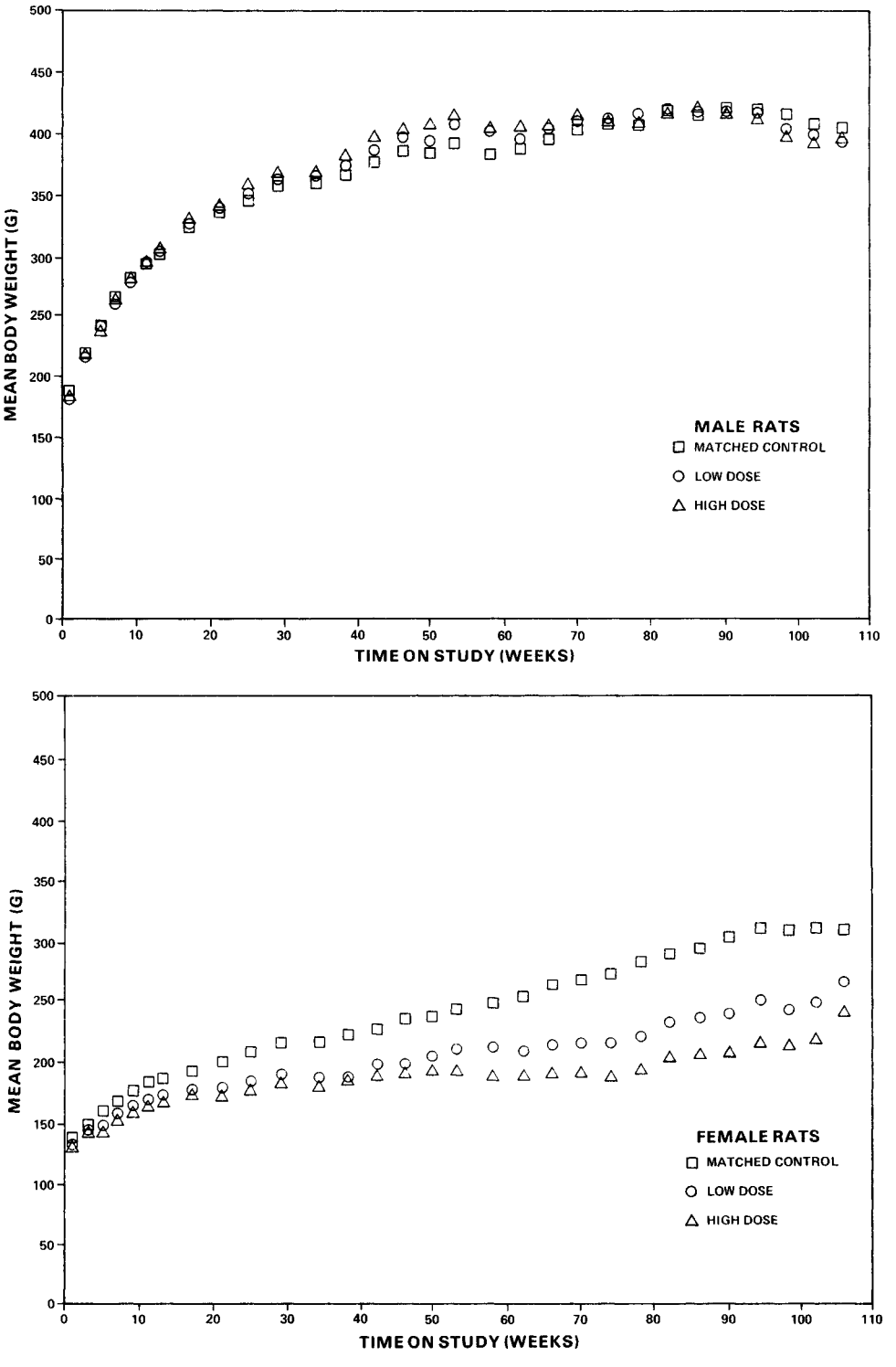

Figure 1. Growth Curves For Rats Fed N, N'-Dicyclohexylthiourea In The Diet

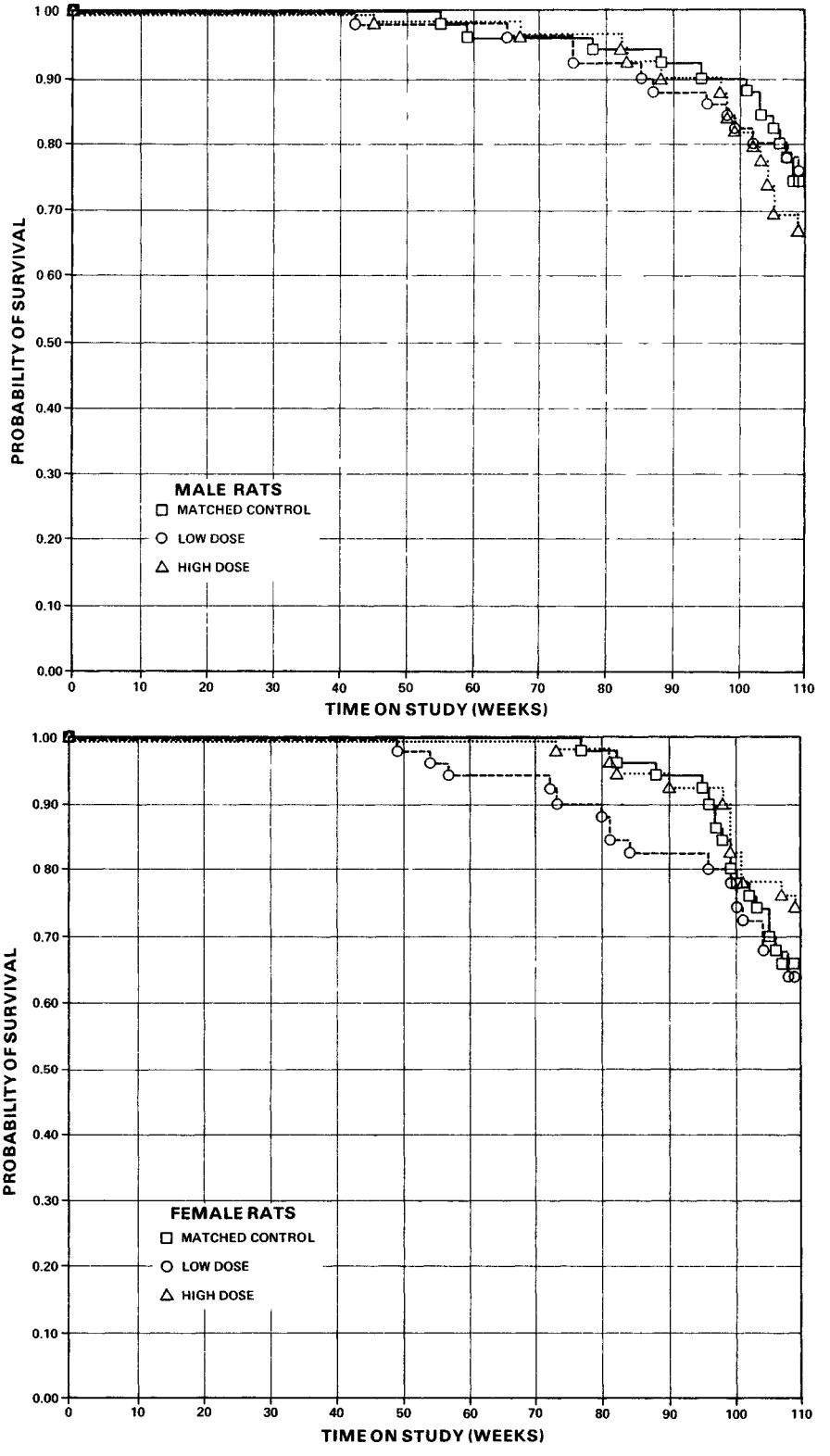

Figure 2. Survival Curves For Rats Fed N, N'-Dicyclohexylthiourea In The Diet

the low-dose group, and 37/50 (74%) of the matched controls lived to the end of the study. In the females, 38/50 (76%) of the high-dose group, 32/50 (64%) of the low-dose group, and 33/50 (66%) of the controls survived to termination of the study. Survival was sufficient in all groups for the development of late-appearing tumors.

C. Pathology (Rats)

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

A variety of tumors occurred in both the control and treated groups. Each type of neoplasm represented in the tables has been encountered previously as a spontaneous lesion in the rat. Some types of neoplasms occurred only, or with a greater frequency, in rats of treated groups as compared with the controls, and the converse was also true.

The incidence of proliferative lesions and neoplasms of the thyroid was as follows:

MALE	Matched Control	Low Dose	High Dose
Number of animals with tissues examined microscopically	43	49	49
Thyroid			
Cystic follicles	2 (5%)	10 (20%)	3 (6%)
Hyperplasia, C-cell	30 (70%)	19 (39%)	30 (61%)
C-cell adenoma	4 (9%)	9 (18%)	12 (24%)
Hyperplasia, follicular-cell	3 (7%)	16 (33%)	15 (31%)
Follicular-cell adenoma	0 (0%)	0 (0%)	1 (2%)
Follicular-cell carcinoma	1 (2%)	7 (14%)	5 (10%)
FEMALE			
Number of animals with tissues examined microscopically	48	48	49
Thyroid			
Cystic follicles	0 (0%)	4 (8%)	2 (4%)
Hyperplasia, C-cell	32 (67%)	38 (79%)	35 (71%)
C-cell adenoma	8 (17%)	4 (8%)	9 (18%)
Hyperplasia, follicular-cell	1 (2%)	7 (15%)	5 (10%)
Follicular-cell adenoma	1 (2%)	0 (0%)	0 (0%)
Follicular-cell carcinoma	1 (2%)	0 (0%)	3 (6%)

The incidence of follicular-cell hyperplasia was markedly increased in the male and female treated groups. This was associated with an increase in the incidence of follicular-cell carcinoma of both of the treated male groups, but not of the female groups.

At the time of necropsy, most thyroid tumors were apparent and were characterized by unilateral enlargement of the gland and/or cystic appearance. Microscopically, follicular-cell hyperplasia was characterized by focal papillary infolding of simple cuboidal or columnar epithelium into a normal-sized or distended follicular lumen. The follicular epithelium was hyperbasophilic, and there was an increase in the number of cells per unit area. Discrete circumscribed lesions of this type which compressed the surrounding parenchyma were classified as adenomas. Proliferative lesions were classified as follicular-cell carcinoma, based on the presence of cellular anaplasia, increased mitosis, and altered histologic architecture by disorderly arrangement of cellular nests and/or sheets.

Hyperplasia and adenoma of the C-cells were considered to be spontaneous and not treatment related.

The nonneoplastic lesions consisted of degenerative, proliferative, and inflammatory changes which are commonly observed in aging rats. These conditions did not appear to be treatment related, other than the thyroid follicular-cell hyperplasia, which was associated with an increased incidence of follicular-cell carcinoma.

The histopathologic results of this study indicate that N,N′-dicy-

clohexylthiourea induced follicular-cell hyperplasia and follicular-cell carcinoma in Fischer 344 rats, when administered in the diet under conditions of this study. This effect was more pronounced in males than in females.

D. Statistical Analyses of Results (Rats)

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

In male rats, the Cochran-Armitage test result for positive dose-related trend in the incidence of C-cell adenoma of the thyroid is significant (P = 0.040), and the Fisher exact test shows that the incidence in the high-dose group is higher (P = 0.049) than that in the matched controls, but the value of 0.049 is higher than the 0.025 value needed for statistical significance when the multiple comparison criterion is considered.

The result of the Cochran-Armitage test for positive dose-related trend in proportions is significant (P = 0.038) in the incidence of basal-cell carcinoma of the skin in male rats, but the Fisher exact test results are not significant. The Fisher exact test shows that the incidence of follicular-cell carcinoma of the thyroid and the combined incidence of follicular-cell adenoma and

carcinoma of the thyroid in the low-dose male rats are higher (P = 0.045) than that of the corresponding matched-control group; however, this probability level is above the 0.025 level required for significance when the Bonferroni inequality criterion for multiple comparison is considered. The Cochran-Armitage test results on these two incidences are not significant. In females, none of the specific incidences of tumors are statistically significant in the positive direction. In each sex, there are several indications of results in a negative direction, where the incidence in the control group exceeds the incidence in the treated groups. This type of result cannot be attributed to differences in survival of the groups, since survival was comparable in all groups.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Among the treated male mice, the mean body weights were comparable to those of the controls throughout the study; among the females, however, there was a dose-related reduction in mean body weight gains from about week 20 to the end of the bioassay (figure 3). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variation. The treated mice were generally comparable to the controls in appearance and behavior during the first year of the study.

Focal alopecia, focal dermatitis, and small palpable nodules in the perineal area were observed in increasing numbers of male mice after 7 months on study. These lesions were associated with fighting among male animals.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed N,N′-dicyclohexylthiourea at the doses of this experiment, together with those of the matched controls, are shown in figure 4.

The results of the Tarone test for positive dose-related trend in

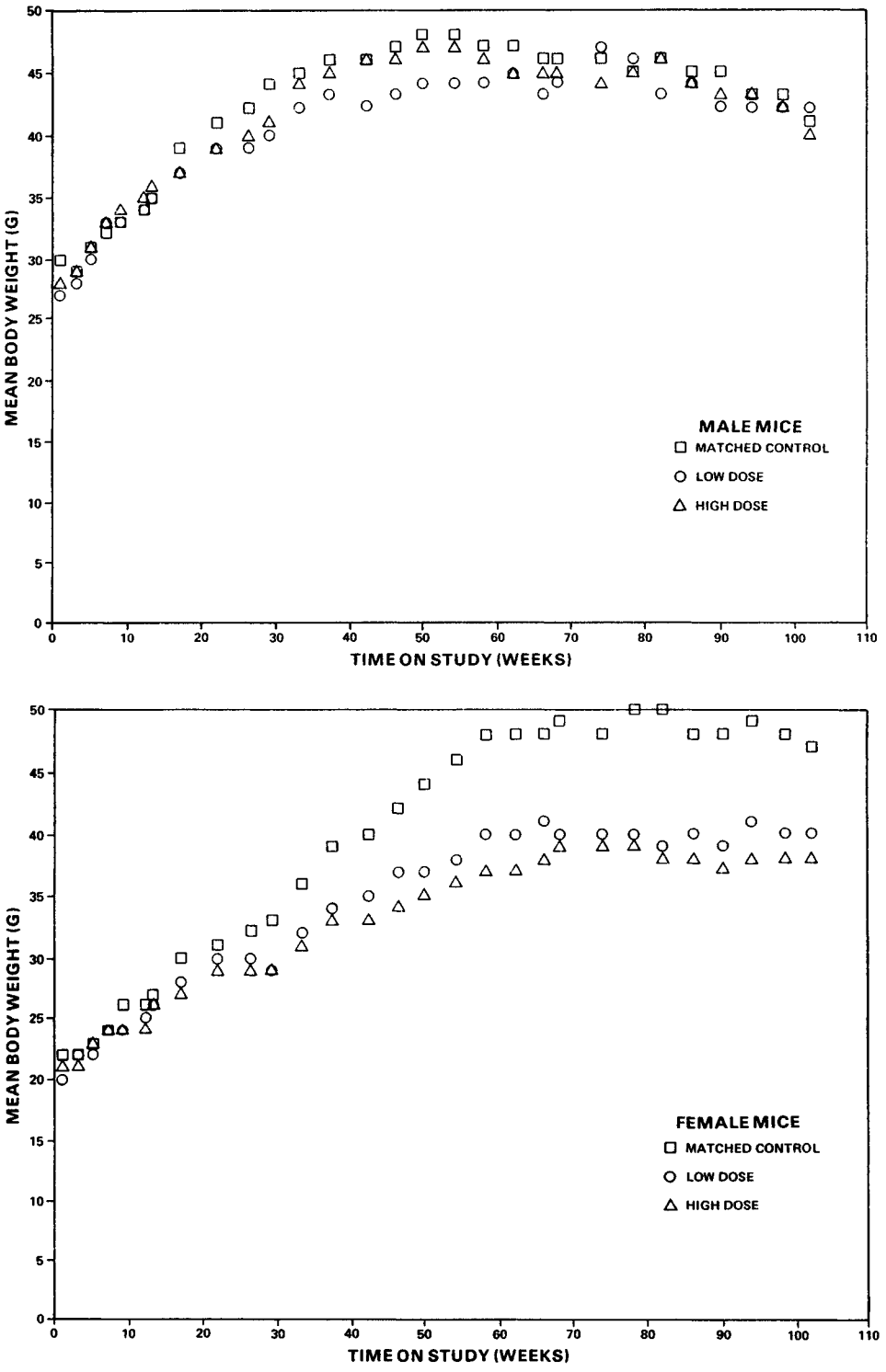

Figure 3. Growth Curves For Mice Fed N, N'-Dicyclohexylthiourea In The Diet

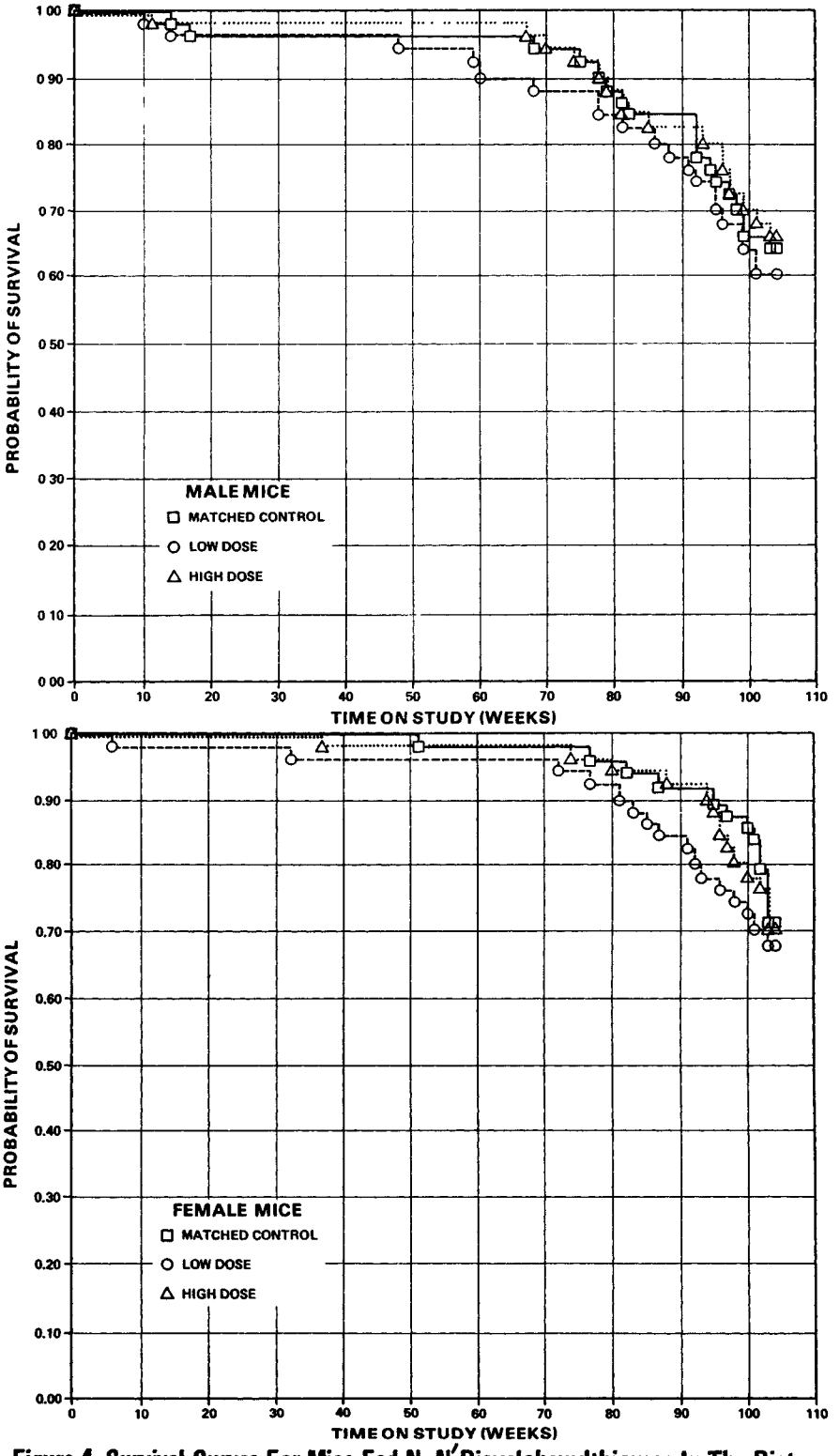

Figure 4. Survival Curves For Mice Fed N, N'-Dicyclohexylthiourea In The Diet

mortality are not significant at the 0.05 level in either sex. In the males, 33/50 (66%) of the high-dose group, 30/50 (60%) of the low-dose group, and 32/50 (64%) of the controls lived to the end of the study. In the females, 35/50 (70%) of the high-dose group, 32/50 (64%) of the low-dose group, and 34/49 (69%) of the controls survived to termination of the study. Survival was sufficient in all groups for the development of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

A variety of tumors occurred in both the control and treated groups. Each type of neoplasm represented in the tables has been encountered previously as a spontaneous lesion in the mouse. Some types of neoplasms occurred only, or with a greater frequency, in mice of treated groups as compared with controls; the converse was also true.

The incidence of proliferative lesions and neoplasms of the thyroid was as follows:

	Matched Control	Low Dose	High Dose
MALE			
Number of animals with tissues examined microscopically	39	46	45
Thyroid			
Cystic follicles	2 (5%)	2 (4%)	3 (7%)
Hyperplasia, follicular-cell	3 (8%)	12 (26%)	9 (20%)
Follicular-cell adenoma	1 (3%)	0 (0%)	0 (0%)
Follicular-cell carcinoma	1 (3%)	0 (0%)	0 (0%)
FEMALE			
Number of animals with tissues examined microscopically	38	46	46
Thyroid			
Cystic follicles*	2 (6%)	0 (0%)	5 (11%)
Hyperplasia, follicular-cell	8 (21%)	22 (48%)	21 (46%)
Follicular-cell adenoma	1 (3%)	0 (0%)	1 (2%)
Follicular-cell carcinoma	0 (0%)	0 (0%)	0 (0%)

*Includes cyst, NOS (not otherwise specified), follicular cyst, NOS, and cystic follicles.

The increased incidence of follicular-cell hyperplasia in treated male and female groups was considered to be related to treatment. Grossly, many of these lesions appeared to be cystic, and there was unilateral enlargement of the gland. Histologically, the lesion was composed of cystic dilitation of follicles with

follicular-cell hyperplasia. The follicular-cell hyperplasia was characterized by papillary infoldings with hyperbasophilic epithelium.

Several chronic inflammatory, degenerative, and proliferative conditions were observed in all groups. These conditions were considered to be of common occurrence, spontaneous, and not related to treatment, with the exception of thyroid follicular cell hyperplasia, which was attributed to treatment.

The histopathologic results of this study indicate that N,N'-dicyclohexylthiourea was not carcinogenic when administered to B6C3F1 mice for 2 years under the conditions of this study; however, follicular-cell hyperplasia of the thyroid was associated with treatment.

D. Statistical Analyses of Results (Mice)

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

In each sex, there is no incidence of tumors having significantly higher incidences in the treated groups than in the controls. In female mice, a negative trend is observed in the incidence of

hepatocellular carcinoma and in the incidence of granulocytic sarcoma of the hematopoietic system, where the incidence in the control group exceeds the incidences in the treated groups; however, comparisons between the treated groups and the controls are not significant.

In each of the 95% confidence intervals of relative risk, snown in the tables, the value of one is included; this indicates the absence of positive significant results. It should also be noted that each of the intervals has an upper limit greater than une, indicating the theoretical possibility of the induction oi tumors by N,N'-dicyclohexylthiourea, which could not be detected under the conditions of this test.

V. DISCUSSION

The administration of N,N′-dicyclohexylthiourea in feed at the doses used in this study resulted in decreased mean body weights in female rats and female mice. Weights of male rats and male mice were not affected. Survival was adequate in all groups of both species for the development of late-appearing tumors.

In male rats, there was increased incidence both of tumors and of hyperplasia of the follicular cells of the thyroid, as follows:

	Matched Control	Low Dose	High Dose
Male Rats			
Hyperplasia	3/43 (7%)	16/49 (32%)	15/49 (30%)
Adenoma and carcinoma	1/43 (2%)	7/49 (14%)	6/49 (12%)
Female Rats			
Hyperplasia	1/48 (2%)	7/48 (15%)	5/49 (10%)
Adenoma and carcinoma	2/48 (4%)	0/48	3/49 (6%)

The incidence of follicular-cell carcinoma of the thyroid in low-dose male rats was higher ($P = 0.045$) than that in controls; however, this is above the level required for significance by the multiple comparison criterion. The incidences in female rats were not significant.

In addition, in male rats there was a significant (P = 0.040) dose-related trend in the incidence of C-cell adenoma of the thyroid, and the incidence in the high-dose group was higher (P = 0.049) than that in the controls (controls 4/43, low-dose 9/49, high-dose 12/49). However, this is above the level required for significance by the multiple comparison criterion.

In mice, a variety of neoplasms of the type usually encountered in the B6C3F1 strain were observed in both treated and control animals. None of the tumors occurred at statistically significant incidences. Follicular-cell hyperplasia of the thyroid was observed at an increased incidence in both the treated males and females (males: controls 3/39, low-dose 12/46, high-dose 9/45; females: controls 8/38, low-dose 22/46; high-dose 21/46).

An increase in proliferative lesions of the follicular cells of the thyroid was associated with the administration of N,N′-dicyclohexylthiourea in both Fischer 344 rats and B6C3F1 mice. However, because statistical significance was not achieved and because thyroid tumors are not rare spontaneous lesions in these strains of animals and occur with a variable incidence, it is concluded that under the conditions of this bioassay N,N′-dicyclohexylthiourea was not demonstrated to be carcinogenic in either species.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED N,N′-DICYCLOHEXYLTHIOUREA IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		2 (4%)	2 (4%)
SQUAMOUS CELL CARCINOMA	2 (4%)		
BASAL-CELL CARCINOMA			3 (6%)
KERATOACANTHOMA		2 (4%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	1 (2%)		2 (4%)
LIPOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	4 (8%)	2 (4%)
LIPOSARCOMA, METASTATIC			1 (2%)
MESOTHELIOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	13 (26%)	7 (14%)	9 (18%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		4 (8%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
GRANULOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(49)	(46)	(48)
MALIG.LYMPHOMA, UNDIFFER-TYPE	2 (4%)	1 (2%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(38)	(30)	(37)
LIPOSARCOMA			1 (3%)
CIRCULATORY SYSTEM			
#HEART	(46)	(49)	(50)
LIPOSARCOMA, METASTATIC			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(48)	(49)
ADENOCARCINOMA, NOS			1 (2%)
#LIVER	(49)	(49)	(50)
NEOPLASTIC NODULE		3 (6%)	2 (4%)
#SMALL INTESTINE	(42)	(50)	(49)
ADENOMA, NOS		1 (2%)	
MUCINOUS ADENOCARCINOMA			2 (4%)
#ILEUM	(42)	(50)	(49)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
LIPOSARCOMA			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA	1 (2%)		
#URINARY BLADDER	(47)	(48)	(48)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(45)	(49)
CHROMOPHOBE ADENOMA	13 (27%)	8 (18%)	4 (8%)
#ADRENAL	(50)	(50)	(50)
PHEOCHROMOCYTOMA	5 (10%)	5 (10%)	2 (4%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(43)	(49)	(49)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	7 (14%)	5 (10%)
C-CELL ADENOMA	4 (9%)	9 (18%)	12 (24%)
#PARATHYROID	(25)	(26)	(25)
ADENOMA, NOS	1 (4%)		
#PANCREATIC ISLETS	(48)	(47)	(47)
ISLET-CELL ADENOMA	3 (6%)	3 (6%)	6 (13%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROMA		1 (2%)	3 (6%)
FIBROADENOMA	2 (4%)	1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	5 (10%)		
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	46 (92%)	44 (88%)	42 (84%)
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(49)
MENINGIOMA			1 (2%)
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
BASAL-CELL CARCINOMA			1 (2%)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
LIPOSARCOMA, METASTATIC			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	1 (2%)
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT	1 (2%)	3 (6%)	2 (4%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	7	6
MORIBUND SACRIFICE	9	5	10
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	37	38	33
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	46	48
TOTAL PRIMARY TUMORS	104	108	119
TOTAL ANIMALS WITH BENIGN TUMORS	47	45	46
TOTAL BENIGN TUMORS	82	77	81
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	24	28
TOTAL MALIGNANT TUMORS	22	27	34
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	2
TOTAL SECONDARY TUMORS	1	1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		4	4
TOTAL UNCERTAIN TUMORS		4	4
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 FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL CARCINOMA			1 (2%)
FIBROSARCOMA			2 (4%)<-
LIPOMA		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(49)	(48)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		
#LUNG	(50)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, UNDIFFER-TYPE	12 (24%)		2 (4%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
UNDIFFERENTIATED LEUKEMIA			1 (2%)
#SPLEEN	(50)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE		3 (6%)	4 (8%)
#MEDIASTINAL L.NODE	(38)	(38)	(41)
FIBROSARCOMA, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
<- MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN TISSUES IS COUNTED ONCE ONLY

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)	1 (2%)	1 (2%)
#SMALL INTESTINE	(46)	(48)	(48)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY/PELVIS	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA	1 (2%)		
#URINARY BLADDER	(42)	(49)	(48)
TRANSITIONAL-CELL CARCINOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(48)	(49)
CHROMOPHOBE ADENOMA	26 (52%)	21 (44%)	29 (59%)
#ADRENAL	(50)	(50)	(50)
PHEOCHROMOCYTOMA	1 (2%)		1 (2%)
GANGLIONEUROMA		1 (2%)	
#THYROID	(48)	(48)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)		
FOLLICULAR-CELL CARCINOMA	1 (2%)		3 (6%)
C-CELL ADENOMA	8 (17%)	4 (8%)	9 (18%)
#PANCREATIC ISLETS	(50)	(47)	(50)
ISLET-CELL ADENOMA	3 (6%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	2 (4%)		
FIBROMA	1 (2%)		
FIBROADENOMA	10 (20%)	6 (12%)	2 (4%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	4 (8%)		
#UTERUS	(50)	(49)	(49)
ADENOCARCINOMA, NOS	2 (4%)		
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	9 (18%)	5 (10%)	11 (22%)
#OVARY	(49)	(49)	(48)
SERTOLI-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
#MIDBRAIN	(49)	(49)	(50)
ASTROCYTOMA			1 (2%)
*SPINAL CORD	(50)	(50)	(50)
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	10	7	6
MORIBUND SACRIFICE	7	11	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	33	32	37
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	31	43
TOTAL PRIMARY TUMORS	88	47	74
TOTAL ANIMALS WITH BENIGN TUMORS	44	26	37
TOTAL BENIGN TUMORS	65	38	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	8	13
TOTAL MALIGNANT TUMORS	22	8	18
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	1
TOTAL UNCERTAIN TUMORS	1	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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN

MICE FED N,N′-DICYCLOHEXYLTHIOUREA IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA			2 (4%)
HEMANGIOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	5 (10%)	2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	1 (2%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	4 (8%)	4 (8%)	5 (10%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	2 (4%)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	3 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		3 (6%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)	4 (8%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	4 (8%)	2 (4%)
GRANULOCYTIC SARCOMA	1 (2%)		
#SPLEEN	(49)	(49)	(49)
HEMANGIOMA	1 (2%)	1 (2%)	
HEMANGIOSARCOMA	2 (4%)	1 (2%)	2 (4%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#BRONCHIAL LYMPH NODE	(42)	(32)	(34)
HEPATOCELLULAR CARCINOMA, METAST			1 (3%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(42)	(32)	(34)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (3%)	
#PEYERS PATCH	(46)	(45)	(47)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)		1 (2%)
#ILEUM	(46)	(45)	(47)
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(48)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(49)
HEPATOCELLULAR ADENOMA	9 (18%)	7 (14%)	12 (24%)
HEPATOCELLULAR CARCINOMA	17 (35%)	12 (24%)	15 (31%)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA		2 (4%)	3 (6%)
ANGIOSARCOMA	1 (2%)	1 (2%)	
*BILE DUCT	(50)	(50)	(50)
BILE DUCT ADENOMA		1 (2%)	
#COLON	(39)	(35)	(32)
ADENOCARCINOMA, NOS		1 (3%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(47)	(45)	(48)
CORTICAL ADENOMA		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PHEOCHROMOCYTOMA	2 (4%)	1 (2%)	3 (6%)
#THYROID	(39)	(46)	(45)
FOLLICULAR-CELL ADENOMA	1 (3%)		
FOLLICULAR-CELL CARCINOMA	1 (3%)		
#PANCREATIC ISLETS	(48)	(46)	(45)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	15	13
MORIBUND SACRIFICE	4	5	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	30	33
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	39	37	39
TOTAL PRIMARY TUMORS	60	51	61
TOTAL ANIMALS WITH BENIGN TUMORS	18	10	17
TOTAL BENIGN TUMORS	22	12	23
TOTAL ANIMALS WITH MALIGNANT TUMORS	29	29	29
TOTAL MALIGNANT TUMORS	38	39	38
TOTAL ANIMALS WITH SECONDARY TUMORS#	6	3	3
TOTAL SECONDARY TUMORS	7	6	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	@50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	2 (4%)	4 (8%)
MYXOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	3 (6%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		5 (10%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	6 (12%)	1 (2%)	6 (12%)
MALIGNANT LYMPHOMA, MIXED TYPE	9 (18%)	5 (10%)	10 (20%)
MONOCYTIC LEUKEMIA			1 (2%)
GRANULOCYTIC SARCOMA	3 (6%)		
#SPLEEN	(49)	(48)	(49)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (2%)	3 (6%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	3 (6%)
#MESENTERIC L. NODE	(42)	(34)	(39)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		1 (3%)
#RENAL LYMPH NODE	(42)	(34)	(39)
MALIGNANT LYMPHOMA, NOS		1 (3%)	

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

@ 50 ANIMALS WERE INITIALLY IN THE SYUDY, BUT ONE ANIMAL WAS FOUND TO BE A MALE IN A FEMALE GROUP.

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(49)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SMALL INTESTINE	(44)	(49)	(46)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#PEYERS PATCH	(44)	(49)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	2 (4%)
#UTERUS	(47)	(45)	(47)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)		
#OVARY	(45)	(42)	(44)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)		
#THYMUS	(18)	(29)	(25)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
#LIVER	(49)	(49)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	1 (2%)	3 (6%)
HEPATOCELLULAR CARCINOMA	4 (8%)	1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(34)	(40)	(40)
CHROMOPHOBE ADENOMA	5 (15%)	10 (25%)	7 (18%)
#ADRENAL	(48)	(48)	(50)
PHEOCHROMOCYTOMA		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MYXOSARCOMA		1 (2%)	
#THYROID	(38)	(46)	(46)
FOLLICULAR-CELL ADENOMA	1 (3%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOCA/SQUAMOUS METAPLASIA			1 (2%)
#UTERUS	(47)	(45)	(47)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA			1 (2%)
#OVARY	(45)	(42)	(44)
PAPILLARY CYSTADENOMA, NOS		2 (5%)	
MUCINOUS CYSTADENOMA			1 (2%)
GRANULOSA-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(49)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS	2 (4%)		
*HARDERIAN GLAND	(49)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(49)	(50)	(50)
MYXOSARCOMA		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
FIBROSARCOMA		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	9	13	10
MORIBUND SACRIFICE	5	3	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	34	34	35
ANIMAL MISSING			
ANIMAL DELETED(WRONG SEX)	1		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	36	37	37
TOTAL PRIMARY TUMORS	46	48	49
TOTAL ANIMALS WITH BENIGN TUMORS	13	15	12
TOTAL BENIGN TUMORS	13	15	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	28	29	31
TOTAL MALIGNANT TUMORS	33	32	35
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		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 FED N,N'-DICYCLOHEXYLTHIOUREA IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(44)	(47)	(48)
INFLAMMATION, NOS	1 (2%)	27 (57%)	20 (42%)
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, CHRONIC	15 (34%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	6 (14%)		
#TRACHEAL SUBMUCOSA	(44)	(47)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#LUNG/BRONCHUS	(49)	(49)	(50)
BRONCHIECTASIS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	2 (4%)	1 (2%)	
METAPLASIA, SQUAMOUS		1 (2%)	
HYPERPLASIA, LYMPHOID	38 (78%)	38 (78%)	31 (62%)
#LUNG/BRONCHIOLE	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LUNG	(49)	(49)	(50)
ATELECTASIS		1 (2%)	
HEMORRHAGE	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (2%)		
ABSCESS, NOS	1 (2%)		
PNEUMONIA, CHRONIC MURINE		2 (4%)	6 (12%)
GRANULOMA, NOS			1 (2%)
CALCIFICATION, FOCAL	1 (2%)		
ALVEOLAR MACROPHAGES	3 (6%)	1 (2%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
#LUNG/ALVEOLI	(49)	(49)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)
HEMORRHAGE	2 (4%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC	12 (24%)	11 (22%)	10 (20%)
HYPERPLASIA, ERYTHROID	1 (2%)	3 (6%)	4 (8%)
HYPERPLASIA, GRANULOCYTIC			2 (4%)
#SPLEEN	(49)	(46)	(48)
RUPTURE			1 (2%)
FIBROSIS, FOCAL	1 (2%)	1 (2%)	
HEMOSIDEROSIS	32 (65%)	31 (67%)	32 (67%)
HEMATOPOIESIS	35 (71%)	30 (65%)	33 (69%)
ERYTHROPOIESIS		2 (4%)	1 (2%)
GRANULOPOIESIS		2 (4%)	1 (2%)
#MEDIASTINAL L.NODE	(41)	(43)	(43)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(46)	(49)	(50)
GRANULOMA, NOS			1 (2%)
PERIARTERITIS			1 (2%)
#MYOCARDIUM	(46)	(49)	(50)
INFLAMMATION, FOCAL	2 (4%)		
INFLAMMATION, INTERSTITIAL	2 (4%)	7 (14%)	2 (4%)
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL	22 (48%)	7 (14%)	20 (40%)
NECROSIS, FOCAL			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PULMONARY ARTERY	(50)	(50)	(50)
MEDIAL CALCIFICATION	21 (42%)		2 (4%)
#HEPATIC SINUSOID	(49)	(49)	(50)
CONGESTION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(48)	(49)
FIBROSIS, FOCAL			1 (2%)
#LIVER	(49)	(49)	(50)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, FOCAL	1 (2%)		
GRANULOMA, NOS			1 (2%)
NECROSIS, FOCAL		1 (2%)	
NECROSIS, DIFFUSE			1 (2%)
METAMORPHOSIS FATTY	7 (14%)	2 (4%)	6 (12%)
BASOPHILIC CYTO CHANGE		1 (2%)	
FOCAL CELLULAR CHANGE	5 (10%)	3 (6%)	4 (8%)
HEMATOPOIESIS	1 (2%)		
#LIVER/CENTRILOBULAR	(49)	(49)	(50)
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY			1 (2%)
*BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	4 (8%)		
HYPERPLASIA, FOCAL	39 (78%)	36 (72%)	42 (84%)
#PANCREAS	(48)	(47)	(47)
PERIARTERITIS	2 (4%)		
#PANCREATIC DUCT	(48)	(47)	(47)
FIBROSIS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	13 (27%)	12 (26%)	10 (21%)
#PANCREATIC ACINUS	(48)	(47)	(47)
ATROPHY, NOS	1 (2%)		
#GASTRIC MUCOSA	(50)	(50)	(50)
EROSION	1 (2%)		1 (2%)
#CARDIAC STOMACH	(50)	(50)	(50)
EDEMA, NOS	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, FOCAL	1 (2%)		
ULCER, FOCAL	1 (2%)	1 (2%)	1 (2%)
#PEYERS PATCH	(42)	(50)	(49)
HYPERPLASIA, LYMPHOID	3 (7%)		7 (14%)
#COLON	(44)	(45)	(40)
NEMATODIASIS	8 (18%)	2 (4%)	1 (3%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)		1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	14 (28%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	30 (60%)	30 (60%)	30 (60%)
NEPHROPATHY			1 (2%)
CALCIFICATION, FOCAL			2 (4%)
HEMOSIDEROSIS	1 (2%)		
#KIDNEY/CAPSULE	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)
PIGMENTATION, NOS		6 (12%)	8 (16%)
#KIDNEY/MEDULLA	(50)	(50)	(50)
CAST, NOS			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
CAST, NOS			2 (4%)
DEGENERATION, HYALINE		1 (2%)	
PIGMENTATION, NOS		1 (2%)	
#CONVOLUTED TUBULES	(50)	(50)	(50)
PIGMENTATION, NOS	2 (4%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
CALCIFICATION, FOCAL	3 (6%)		1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#URINARY BLADDER	(47)	(48)	(48)
CONGESTION, NOS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(45)	(49)
HEMOSIDEROSIS		2 (4%)	1 (2%)
ANGIECTASIS	5 (10%)	7 (16%)	3 (6%)
#ADRENAL	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
ANGIECTASIS	11 (22%)	9 (18%)	15 (30%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYTOLOGIC DEGENERATION		1 (2%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	4 (8%)	2 (4%)
#THYROID	(43)	(49)	(49)
ULTIMOBRANCHIAL CYST			1 (2%)
CYSTIC FOLLICLES	2 (5%)	10 (20%)	3 (6%)
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, C-CELL	30 (70%)	19 (39%)	30 (61%)
HYPERPLASIA, FOLLICULAR-CELL	3 (7%)	16 (33%)	15 (31%)
#THYROID FOLLICLE	(43)	(49)	(49)
PIGMENTATION, NOS	9 (21%)	1 (2%)	1 (2%)
#PARATHYROID	(25)	(26)	(25)
HYPERPLASIA, NOS	2 (8%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, SUPPURATIVE	2 (4%)		1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	2 (4%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS			3 (6%)
#PROSTATE	(44)	(47)	(47)
CYST, NOS			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	6 (13%)
INFLAMMATION, SUPPURATIVE	5 (11%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#TESTIS	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
CALCIFICATION, NOS	1 (2%)		
CALCIFICATION, FOCAL	1 (2%)		
ATROPHY, NOS	44 (88%)	39 (78%)	39 (78%)
ATROPHY, FOCAL	2 (4%)		1 (2%)
ASPERMATOGENESIS	1 (2%)		1 (2%)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	
#TESTIS/TUBULE	(50)	(50)	(50)
CALCIFICATION, FOCAL	6 (12%)		1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
FIBROSIS		1 (2%)	2 (4%)
NECROSIS, NOS			1 (2%)
*DUCT OF EPIDIDYMIS	(50)	(50)	(50)
DISTENTION			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(49)
HEMORRHAGE	1 (2%)		
#CEREBELLUM	(50)	(48)	(49)
HEMORRHAGE		1 (2%)	
NECROSIS, ISCHEMIC		1 (2%)	
*SPINAL CORD	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE	2 (4%)	1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PUS			1 (2%)
CATARACT	16 (32%)	15 (30%)	21 (42%)
CALCIFICATION, NOS	2 (4%)		
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ULCER, NOS	1 (2%)	1 (2%)	
*EAR	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
HEMOPERITONEUM			1 (2%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL			1 (2%)
FIBROSIS		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
PERIARTERITIS	1 (2%)		
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
MULTIPLE SITES			
CONGESTION, NOS			1
*MULTIPLE ORGANS	(50)	(50)	(50)
JAUNDICE, NOS	2 (4%)		
DIAPHRAGM			
HERNIA, NOS		1	1
ADIPOSE TISSUE			
INFLAMMATION, NOS			1

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS			1

SPECIAL MORPHOLOGY SUMMARY

AUTO/NECROPSY/HISTO PERF		1	

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, FOCAL	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#TRACHEA	(49)	(48)	(48)
INFLAMMATION, NOS		25 (52%)	24 (50%)
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	16 (33%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	4 (8%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
METAPLASIA, SQUAMOUS		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
#TRACHEAL SUBMUCOSA	(49)	(48)	(48)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
#LUNG/BRONCHUS	(50)	(49)	(49)
BRONCHIECTASIS	1 (2%)		
HYPERPLASIA, FOCAL			1 (2%)
HYPERPLASIA, LYMPHOID	42 (84%)	38 (78%)	42 (86%)
#LUNG	(50)	(49)	(49)
EDEMA, NOS	1 (2%)		1 (2%)
BRONCHOPNEUMONIA, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	2 (4%)
BRONCHOPNEUMONIA SUPPURATIVE		3 (6%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PNEUMONIA, CHRONIC MURINE	1 (2%)	7 (14%)	3 (6%)
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
CYTOMEGALY		1 (2%)	
ALVEOLAR MACROPHAGES	13 (26%)	3 (6%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
#LUNG/ALVEOLI	(50)	(49)	(49)
EDEMA, NOS		1 (2%)	
HEMATOPOIETIC SYSTEM			
*BLOOD	(50)	(50)	(50)
ANEMIA, NOS		1 (2%)	
#BONE MARROW	(50)	(50)	(50)
HYPERPLASIA, HEMATOPOIETIC	10 (20%)	3 (6%)	7 (14%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)	1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(49)
FIBROSIS	1 (2%)		
HEMOSIDEROSIS	32 (64%)	43 (86%)	43 (88%)
LYMPHOID DEPLETION		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
LEUKEMOID REACTION		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
HEMATOPOIESIS	36 (72%)	43 (86%)	40 (82%)
ERYTHROPOIESIS	2 (4%)	1 (2%)	4 (8%)
GRANULOPOIESIS	4 (8%)	2 (4%)	5 (10%)
#MEDIASTINAL L.NODE	(38)	(38)	(41)
CONGESTION, NOS	1 (3%)		
HEMOSIDEROSIS	2 (5%)		
#THYMUS	(36)	(40)	(40)
CONGESTION, NOS		1 (3%)	
HEMOSIDEROSIS		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(49)
ENDOCARDITIS, BACTERIAL	1 (2%)		
#HEART/ATRIUM	(50)	(50)	(49)
THROMBOSIS, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, FOCAL		1 (2%)	
#MYOCARDIUM	(50)	(50)	(49)
INFLAMMATION, FOCAL	2 (4%)		
INFLAMMATION, INTERSTITIAL	3 (6%)	6 (12%)	4 (8%)
INFLAMMATION, SUPPURATIVE			1 (2%)
FIBROSIS, FOCAL	17 (34%)	1 (2%)	9 (18%)
*PULMONARY ARTERY	(50)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)		
MEDIAL CALCIFICATION	12 (24%)		5 (10%)
CALCIFICATION, FOCAL	1 (2%)		
#HEPATIC SINUSOID	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS		1 (2%)	
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL		2 (4%)	
METAMORPHOSIS FATTY	10 (20%)	1 (2%)	2 (4%)
PIGMENTATION, NOS	1 (2%)		
CYTOPLASMIC CHANGE, NOS	1 (2%)		
BASOPHILIC CYTO CHANGE			2 (4%)
FOCAL CELLULAR CHANGE			2 (4%)
ANGIECTASIS		2 (4%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
HEMATOPOIESIS			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
NECROSIS, NOS	1 (2%)		
NECROSIS, DIFFUSE	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(50)
NODULE			1 (2%)
DEGENERATION, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*BILE DUCT	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	21 (42%)	23 (46%)	26 (52%)
HYPERPLASIA, CYSTIC			1 (2%)
#PANCREAS	(50)	(47)	(50)
ECTOPIA	1 (2%)		
EDEMA, NOS	1 (2%)		
#PANCREATIC DUCT	(50)	(47)	(50)
HYPERPLASIA, FOCAL	9 (18%)	2 (4%)	8 (16%)
#CARDIAC STOMACH	(49)	(50)	(50)
ULCER, FOCAL		1 (2%)	1 (2%)
NECROSIS, FOCAL		1 (2%)	
#PEYERS PATCH	(46)	(48)	(48)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID	2 (4%)	3 (6%)	7 (15%)
#JEJUNUM	(46)	(48)	(48)
ULCER, NOS	1 (2%)		
#COLON	(47)	(40)	(42)
NEMATODIASIS	2 (4%)	1 (3%)	1 (2%)
*RECTUM	(50)	(50)	(50)
PROLAPSE			1 (2%)
INFLAMMATION, NOS			1 (2%)
ULCER, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		
INFLAMMATION, CHRONIC	3 (6%)		
GLOMERULONEPHRITIS, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	27 (54%)	8 (16%)	3 (6%)
NEPHROPATHY			1 (2%)
CALCIFICATION, FOCAL		1 (2%)	1 (2%)
PIGMENTATION, NOS	1 (2%)		
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PIGMENTATION, NOS		31 (62%)	42 (84%)
#RENAL PAPILLA	(50)	(50)	(50)
CALCIUM DEPOSIT		1 (2%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
CAST, NOS		2 (4%)	1 (2%)
PIGMENTATION, NOS	1 (2%)	1 (2%)	
#CONVOLUTED TUBULES	(50)	(50)	(50)
DEGENERATION, HYALINE	1 (2%)		
PIGMENTATION, NOS	13 (26%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
CALCIFICATION, FOCAL	4 (8%)	1 (2%)	22 (44%)
HYPERPLASIA, FOCAL	1 (2%)		
#U. BLADDER/MUCOSA	(42)	(49)	(48)
HEMORRHAGE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(48)	(49)
CYST, NOS	1 (2%)		
CONGESTION, NOS	1 (2%)		
HEMORRHAGE	5 (10%)		
HEMORRHAGIC CYST	1 (2%)		
HEMOSIDEROSIS	2 (4%)	1 (2%)	
ANGIECTASIS	26 (52%)	21 (44%)	25 (51%)
#ADRENAL	(50)	(50)	(50)
CONGESTION, NOS	4 (8%)		
HEMORRHAGE	3 (6%)		1 (2%)
NECROSIS, FOCAL	1 (2%)		
PIGMENTATION, NOS	1 (2%)		
ANGIECTASIS	6 (12%)	18 (36%)	13 (26%)
#ADRENAL CORTEX	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)		
CYTOLOGIC DEGENERATION		1 (2%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(48)	(48)	(49)
ULTIMOBRANCHIAL CYST		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CYSTIC FOLLICLES		4 (8%)	2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
FIBROSIS	1 (2%)		
SCLEROSIS	1 (2%)		
HYPERPLASIA, C-CELL	32 (67%)	38 (79%)	35 (71%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	7 (15%)	5 (10%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	7 (14%)	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		
ADENOSIS		1 (2%)	
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
CYST, NOS	2 (4%)		
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	
NECROSIS, NOS	3 (6%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
METAPLASIA, SQUAMOUS	1 (2%)		
#UTERUS	(50)	(49)	(49)
HYDROMETRA	2 (4%)		
INFLAMMATION, NOS			6 (12%)
INFLAMMATION, SUPPURATIVE		1 (2%)	2 (4%)
PYOMETRA	1 (2%)		
HEMOSIDEROSIS	1 (2%)		
#CERVIX UTERI	(50)	(49)	(49)
HYPERPLASIA, STROMAL		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(49)	(49)
CYST, NOS	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL			1 (2%)
INFLAMMATION, SUPPURATIVE	23 (46%)	9 (18%)	10 (20%)
NECROSIS, NOS			1 (2%)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	7 (14%)		3 (6%)
#UTERUS/MYOMETRIUM	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY/OVIDUCT	(50)	(49)	(49)
INFLAMMATION, NOS			2 (4%)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, SUPPURATIVE	18 (36%)	12 (24%)	10 (20%)
#OVARY	(49)	(49)	(48)
CYST, NOS	2 (4%)	8 (16%)	8 (17%)
FOLLICULAR CYST, NOS	1 (2%)	1 (2%)	
PAROVARIAN CYST	15 (31%)		
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(49)	(50)
LYMPHOCYTOSIS		1 (2%)	
#BRAIN	(49)	(49)	(50)
DILATATION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
#MIDBRAIN	(49)	(49)	(50)
COMPRESSION	2 (4%)	7 (14%)	5 (10%)
#CEREBELLUM	(49)	(49)	(50)
GLIOSIS		1 (2%)	
*SPINAL CORD	(50)	(50)	(50)
CYST, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
CATARACT	11 (22%)	28 (56%)	27 (54%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL		1 (2%)	
*LENS CAPSULE	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
*EAR	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	3 (6%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*EAR CANAL	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
FIBROSIS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE HIP/THIGH	(50)	(50)	(50)
ATROPHY, NOS		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, FOCAL	1 (2%)		
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, FOCAL	1 (2%)		1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS	5 (10%)		1 (2%)
JAUNDICE, NOS	3 (6%)		
DIAPHRAGM			
HERNIA, NOS	2	1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED N,N'-DICYCLOHEXYLTHIOUREA IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED N,N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
ULCER, NOS		1 (2%)	1 (2%)
INFLAMMATION, FOCAL	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(49)
INFLAMMATION, FOCAL		1 (2%)	
HYPERPLASIA, LYMPHOID	28 (56%)	28 (56%)	27 (55%)
#LUNG/BRONCHIOLE	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
HYPERPLASIA, PAPILLARY	1 (2%)		
#LUNG	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFARCT HEMORRHAGIC			1 (2%)
ALVEOLAR MACROPHAGES	4 (8%)	3 (6%)	3 (6%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	1 (2%)
#LUNG/ALVEOLI	(50)	(50)	(49)
CONGESTION, NOS			1 (2%)
HEMORRHAGE			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(48)	(49)
HYPERPLASIA, HEMATOPOIETIC	35 (73%)	33 (69%)	36 (73%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, ERYTHROID			1 (2%)
HYPERPLASIA, GRANULOCYTIC		4 (8%)	2 (4%)
#SPLEEN	(49)	(49)	(49)
AMYLOIDOSIS	2 (4%)		
HEMOSIDEROSIS	2 (4%)	2 (4%)	
HYPERPLASIA, LYMPHOID	8 (16%)	3 (6%)	15 (31%)
HEMATOPOIESIS	21 (43%)	23 (47%)	22 (45%)
ERYTHROPOIESIS	1 (2%)	6 (12%)	1 (2%)
GRANULOPOIESIS		6 (12%)	2 (4%)
#LYMPH NODE	(42)	(32)	(34)
ERYTHROPHAGOCYTOSIS		1 (3%)	
#MANDIBULAR L. NODE	(42)	(32)	(34)
HEMOSIDEROSIS	1 (2%)		
#MESENTERIC L. NODE	(42)	(32)	(34)
CONGESTION, NOS		1 (3%)	2 (6%)
HYPERPLASIA, EOSINOPHILIC			1 (3%)
CIRCULATORY SYSTEM			
#HEART	(48)	(50)	(50)
PERIARTERITIS		1 (2%)	
#MYOCARDIUM	(48)	(50)	(50)
INFLAMMATION, INTERSTITIAL	3 (6%)	1 (2%)	1 (2%)
#ENDOCARDIUM	(48)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(49)
HEMORRHAGE	1 (2%)		
FIBROSIS, FOCAL	2 (4%)		
CIRRHOSIS, NOS		1 (2%)	
PELIOSIS HEPATIS	1 (2%)		
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	3 (6%)	3 (6%)	2 (4%)
NECROSIS, COAGULATIVE	3 (6%)		
INFARCT, NOS	1 (2%)		
METAMORPHOSIS FATTY	3 (6%)	1 (2%)	1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CALCIFICATION, NOS			1 (2%)
CALCIFICATION, FOCAL	1 (2%)		
FOCAL CELLULAR CHANGE	1 (2%)	2 (4%)	2 (4%)
CLEAR-CELL CHANGE	2 (4%)		1 (2%)
ANGIECTASIS	6 (12%)	1 (2%)	1 (2%)
LEUKEMOID REACTION			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
GRANULOPOIESIS		1 (2%)	
#HEPATIC CAPSULE	(49)	(50)	(49)
FIBROSIS, FOCAL	1 (2%)	1 (2%)	
#LIVER/KUPFFER CELL	(49)	(50)	(49)
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, NOS			2 (4%)
HYPERPLASIA, FOCAL	3 (6%)	1 (2%)	
#LIVER/HEPATOCYTES	(49)	(50)	(49)
DEGENERATION, NOS	1 (2%)		
NECROSIS, FOCAL			2 (4%)
FOCAL CELLULAR CHANGE		1 (2%)	
*BILE DUCT	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
HYPERPLASIA, FOCAL	8 (16%)	2 (4%)	2 (4%)
HYPERPLASIA, LYMPHOID		3 (6%)	
#PANCREAS	(48)	(46)	(45)
CYSTIC DUCTS	1 (2%)		
#PANCREATIC DUCT	(48)	(46)	(45)
DISTENTION		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	
#GASTRIC MUCOSA	(47)	(43)	(43)
AMYLOIDOSIS	1 (2%)		
CALCIFICATION, FOCAL			1 (2%)
METAPLASIA, SQUAMOUS			1 (2%)
#CARDIAC STOMACH	(47)	(43)	(43)
INFLAMMATION, FOCAL	1 (2%)	1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERKERATOSIS	1 (2%)		
#PEYERS PATCH	(46)	(45)	(47)
HYPERPLASIA, LYMPHOID	9 (20%)	2 (4%)	6 (13%)
#JEJUNUM	(46)	(45)	(47)
INFLAMMATION, SUPPURATIVE		1 (2%)	
NECROSIS, NOS		1 (2%)	
#ILEUM	(46)	(45)	(47)
ULCER, NOS	1 (2%)		
AMYLOIDOSIS	1 (2%)		
#COLON	(39)	(35)	(32)
NEMATODIASIS	1 (3%)		
*RECTUM	(50)	(50)	(50)
PROLAPSE		1 (2%)	1 (2%)
*ANUS	(50)	(50)	(50)
PROLAPSE		1 (2%)	
CYST, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MULTIPLE CYSTS	1 (2%)		
PYELONEPHRITIS, NOS	1 (2%)	2 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC FOCAL	6 (12%)		1 (2%)
SCLEROSIS			1 (2%)
GLOMERULOSCLEROSIS, NOS		1 (2%)	
AMYLOIDOSIS	2 (4%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
HYPERPLASIA, LYMPHOID	33 (66%)	23 (46%)	35 (70%)
#KIDNEY/CORTEX	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
SCAR			1 (2%)
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
#KIDNEY/GLOMERULUS	(50)	(50)	(50)
EMBOLISM, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, DIFFUSE			1 (2%)
#CONVOLUTED TUBULES	(50)	(50)	(50)
DEGENERATION, HYALINE	1 (2%)		
#URINARY BLADDER	(43)	(44)	(46)
DISTENTION	2 (5%)		
INFLAMMATION, SUPPURATIVE	1 (2%)		1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#U.BLADDER/SUBMUCOSA	(43)	(44)	(46)
EOSINOPHILIC INFILTRATE		1 (2%)	
PERIARTERITIS			1 (2%)
HYPERPLASIA, LYMPHOID	15 (35%)	1 (2%)	9 (20%)
*URETHRA	(50)	(50)	(50)
CALCULUS, NOS	1 (2%)	1 (2%)	
OBSTRUCTION, NOS	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(47)	(45)	(48)
AMYLOIDOSIS	2 (4%)		
ANGIECTASIS		1 (2%)	
#ADRENAL/CAPSULE	(47)	(45)	(48)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	30 (64%)	32 (71%)	35 (73%)
#ADRENAL CORTEX	(47)	(45)	(48)
CYST, NOS			1 (2%)
#THYROID	(39)	(46)	(45)
CYSTIC FOLLICLES	2 (5%)	2 (4%)	3 (7%)
AMYLOIDOSIS	1 (3%)		
HYPERPLASIA, C-CELL			2 (4%)
HYPERPLASIA, FOLLICULAR-CELL	3 (8%)	12 (26%)	9 (20%)
#PANCREATIC ISLETS	(48)	(46)	(45)
HYPERPLASIA, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
PROLAPSE	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*PREPUCE	(50)	(50)	(50)
HYPERKERATOSIS	1 (2%)	1 (2%)	
ACANTHOSIS	1 (2%)	1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
NECROSIS, NOS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
METAPLASIA, SQUAMOUS		1 (2%)	
#PROSTATE	(44)	(43)	(39)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	1 (3%)
*SEMINAL VESICLE	(50)	(50)	(50)
DISTENTION		3 (6%)	
*COAGULATING GLAND	(50)	(50)	(50)
NECROSIS, COAGULATIVE		1 (2%)	
INFARCT, NOS		1 (2%)	
#TESTIS	(50)	(49)	(50)
ATROPHY, NOS	5 (10%)	1 (2%)	1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#BRAIN	(50)	(49)	(50)
CORPORA AMYLACEA	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
NECROSIS, FAT	2 (4%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
ADIPOSE TISSUE			
LYMPHOCYTIC INFLAMMATORY INFILTR			1
INFLAMMATION, CHRONIC SUPPURATIV	1		
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF		1	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED N, N'-DICYCLOHEXYLTHIOUREA IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(39)	(46)	(47)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
#LUNG/BRONCHUS	(48)	(50)	(49)
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	32 (67%)	33 (66%)	37 (76%)
#LUNG	(48)	(50)	(49)
CONGESTION, NOS		1 (2%)	
ALVEOLAR MACROPHAGES	4 (8%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LUNG/ALVEOLI	(48)	(50)	(49)
CONGESTION, NOS			4 (8%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(47)	(49)
HYPERPLASIA, NOS			1 (2%)
MYELOFIBROSIS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC	37 (76%)	39 (83%)	40 (82%)
HYPERPLASIA, ERYTHROID			2 (4%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)	2 (4%)	4 (8%)
#SPLEEN	(49)	(48)	(49)
HEMOSIDEROSIS	1 (2%)	3 (6%)	1 (2%)

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

@ 50 ANIMALS WERE INITIALLY IN THE SYUDY, BUT ONE ANIMAL WAS FOUND TO BE A MALE IN A FEMALE GROUP.

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, PAPILLARY			1 (2%)
HYPERPLASIA, LYMPHOID	16 (33%)	12 (25%)	10 (20%)
HEMATOPOIESIS	36 (73%)	25 (52%)	25 (51%)
ERYTHROPOIESIS		2 (4%)	
GRANULOPOIESIS		2 (4%)	
#LYMPH NODE	(42)	(34)	(39)
INFLAMMATION, SUPPURATIVE	1 (2%)		
NECROSIS, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID			1 (3%)
#MANDIBULAR L. NODE	(42)	(34)	(39)
HYPERPLASIA, HEMATOPOIETIC		1 (3%)	
#BRONCHIAL LYMPH NODE	(42)	(34)	(39)
HYPERPLASIA, NOS		1 (3%)	
#MEDIASTINAL L.NODE	(42)	(34)	(39)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC L. NODE	(42)	(34)	(39)
CONGESTION, NOS	1 (2%)		1 (3%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
NECROSIS, FOCAL		1 (3%)	
#THYMUS	(18)	(29)	(25)
HYPERPLASIA, LYMPHOID	1 (6%)		
CIRCULATORY SYSTEM			
#HEART	(48)	(50)	(48)
PERIARTERITIS	1 (2%)		
#MYOCARDIUM	(48)	(50)	(48)
DEGENERATION, NOS		1 (2%)	
CALCIFICATION, FOCAL	1 (2%)		1 (2%)
#ENDOCARDIUM	(48)	(50)	(48)
INFLAMMATION, FOCAL	1 (2%)		
#HEPATIC SINUSOID	(49)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(50)
THROMBOSIS, NOS	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CONGESTION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)		
DEGENERATION, NOS	1 (2%)		
NECROSIS, FOCAL	3 (6%)		2 (4%)
NECROSIS, COAGULATIVE		5 (10%)	
METAMORPHOSIS FATTY	3 (6%)	3 (6%)	
FOCAL CELLULAR CHANGE		1 (2%)	
ANGIECTASIS	4 (8%)		1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (2%)	2 (4%)	1 (2%)
HYPERPLASIA, LYMPHOID		4 (8%)	1 (2%)
HEMATOPOIESIS		2 (4%)	2 (4%)
#HEPATIC CAPSULE	(49)	(49)	(50)
FRACTURE, NOS			1 (2%)
#LIVER/KUPFFER CELL	(49)	(49)	(50)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#LIVER/HEPATOCYTES	(49)	(49)	(50)
DEGENERATION, NOS	3 (6%)		
NECROSIS, FOCAL			1 (2%)
*BILE DUCT	(49)	(50)	(50)
DISTENTION			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)		7 (14%)
HYPERPLASIA, LYMPHOID		3 (6%)	6 (12%)
#PANCREAS	(43)	(49)	(49)
ECTOPIA	1 (2%)		
CYSTIC DUCTS	2 (5%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
NECROSIS, FAT	1 (2%)		
#PANCREATIC DUCT	(43)	(49)	(49)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREATIC ACINUS	(43)	(49)	(49)
ATROPHY, NOS	2 (5%)		
#STOMACH	(45)	(49)	(47)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#CARDIAC STOMACH	(45)	(49)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
#SMALL INTESTINE	(44)	(49)	(46)
AMYLOIDOSIS		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PEYERS PATCH	(44)	(49)	(46)
HYPERPLASIA, LYMPHOID	5 (11%)	3 (6%)	3 (7%)
*RECTUM	(49)	(50)	(50)
PROLAPSE		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(49)
HYDRONEPHROSIS			1 (2%)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	3 (6%)		
NECROSIS, FAT	1 (2%)		
ATROPHY, NOS			1 (2%)
HYPERPLASIA, LYMPHOID	34 (69%)	31 (63%)	34 (69%)
#KIDNEY/CORTEX	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID		2 (4%)	
#KIDNEY/TUBULE		(49)	(49)
CYST, NOS			1 (2%)
#CONVOLUTED TUBULES	(49)	(49)	(49)
DEGENERATION, HYALINE	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#KIDNEY/PELVIS	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#URINARY BLADDER	(40)	(41)	(46)
HYPERPLASIA, LYMPHOID			3 (7%)
#U.BLADDER/SUBMUCOSA	(40)	(41)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
HYPERPLASIA, FOCAL	1 (3%)		
HYPERPLASIA, LYMPHOID	26 (65%)	11 (27%)	32 (70%)
HEMATOPOIESIS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(34)	(40)	(40)
CYST, NOS			1 (3%)
ANGIECTASIS	2 (6%)	11 (28%)	10 (25%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL	(48)	(48)	(50)
NECROSIS, FOCAL			1 (2%)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
#ADRENAL/CAPSULE	(48)	(48)	(50)
HYPERPLASIA, NOS		3 (6%)	
HYPERPLASIA, FOCAL	43 (90%)	39 (81%)	46 (92%)
#ADRENAL CORTEX	(48)	(48)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(38)	(46)	(46)
CYST, NOS			2 (4%)
CYSTIC FOLLICLES	1 (3%)		3 (7%)
FOLLICULAR CYST, NOS	1 (3%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	2 (4%)
INVOLUTION, NOS			1 (2%)
HYPERPLASIA, C-CELL		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL	8 (21%)	22 (48%)	21 (46%)
#THYROID FOLLICLE	(38)	(46)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
PIGMENTATION, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
NECROSIS, DIFFUSE			1 (2%)
METAPLASIA, SQUAMOUS			1 (2%)
*VAGINA	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
#UTERUS	(47)	(45)	(47)
HYDROMETRA	1 (2%)		
INFLAMMATION, SUPPURATIVE	4 (9%)		
METAPLASIA, SQUAMOUS		2 (4%)	3 (6%)
#UTERUS/ENDOMETRIUM	(47)	(45)	(47)
INFLAMMATION, SUPPURATIVE	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, VESICULAR		1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)
HYPERPLASIA, CYSTIC	37 (79%)	35 (78%)	40 (85%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY/OVIDUCT	(47)	(45)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	1 (2%)
#OVARY	(45)	(42)	(44)
CYST, NOS	1 (2%)	12 (29%)	12 (27%)
FOLLICULAR CYST, NOS			3 (7%)
PAROVARIAN CYST	12 (27%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
NECROSIS, FOCAL		1 (2%)	
NECROSIS, FAT	1 (2%)		
HYPERPLASIA, LYMPHOID		2 (5%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
PERIVASCULAR CUFFING		1 (2%)	
#MIDBRAIN	(49)	(50)	(50)
COMPRESSION		1 (2%)	
MALACIA		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(49)	(50)	(50)
INFLAMMATION, INTERSTITIAL	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
BODY CAVITIES			
*PERITONEUM	(49)	(50)	(50)
HEMOPERITONEUM			2 (4%)
*MESENTERY	(49)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS		1 (2%)	
NECROSIS, FOCAL		1 (2%)	1 (2%)
NECROSIS, FAT	2 (4%)		2 (4%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
CONGESTION, NOS		1 (2%)	
AMYLOIDOSIS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	
AUTO/NECROPSY/HISTO PERF		1	

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED N,N′-DICYCLOHEXYLTHIOUREA IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Skin: Basal-cell Carcinoma[b]	0/50 (0)	0/50 (0)	3/50 (6)
P Values[c,d]	P = 0.038	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	Infinite
Lower Limit		--	0.601
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	109
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/49 (2)	4/49 (8)	2/50 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		4.000	1.960
Lower Limit		0.415	0.106
Upper Limit		192.765	113.310
Weeks to First Observed Tumor	109	109	67

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	2/49 (4)	4/49 (8)	5/50 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.000	2.450
Lower Limit		0.302	0.424
Upper Limit		21.298	24.777
Weeks to First Observed Tumor	109	109	67
Hematopoietic System: Lymphoma[b]	15/50 (30)	12/50 (24)	14/50 (28)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.800	0.933
Lower Limit		0.382	0.468
Upper Limit		1.637	1.842
Weeks to First Observed Tumor	94	75	45

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia[b]	15/50 (30)	12/50 (24)	15/50 (30)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.800	1.000
Lower Limit		0.382	0.513
Upper Limit		1.637	1.949
Weeks to First Observed Tumor	94	75	45
Liver: Neoplastic Nodule[b]	0/49 (0)	3/49 (6)	2/50 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	Infinite
Lower Limit		0.602	0.290
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	109	109

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	13/49 (27)	8/45 (18)	4/49 (8)
P Values[c,d]	P = 0.012 (N)	N.S.	P = 0.015 (N)
Relative Risk (Matched Control)[f]		0.670	0.308
Lower Limit		0.266	0.078
Upper Limit		1.571	0.915
Weeks to First Observed Tumor	103	109	98
Adrenal: Pheochromocytoma[b]	5/50 (10)	5/50 (10)	2/50 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	0.400
Lower Limit		0.246	0.039
Upper Limit		4.082	2.313
Weeks to First Observed Tumor	109	109	98

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma[b]	1/43 (2)	7/49 (14)	5/49 (10)
P Values[c,d]	N.S.	P = 0.045	N.S.
Relative Risk (Matched Control)[f]		6.143	4.388
Lower Limit		0.840	0.520
Upper Limit		270.462	202.926
Weeks to First Observed Tumor	109	109	109
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	1/43 (2)	7/49 (14)	6/49 (12)
P Values[c,d]	N.S.	P = 0.045	N.S.
Relative Risk (Matched Control)[f]		6.143	5.265
Lower Limit		0.840	0.678
Upper Limit		270.462	236.684
Weeks to First Observed Tumor		109	83

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma[b]	4/43 (9)	9/49 (18)	12/49 (24)
P Values[c,d]	P = 0.040	N.S.	P = 0.049
Relative Risk (Matched Control)[f]		1.975	2.633
Lower Limit		0.599	0.873
Upper Limit		8.212	10.434
Weeks to First Observed Tumor	109	109	102
Pancreatic Islets: Islet-cell Adenoma[b]	3/48 (6)	3/47 (6)	6/47 (13)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.021	2.043
Lower Limit		0.144	0.466
Upper Limit		7.264	11.972
Weeks to First Observed Tumor	108	109	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroma[b]	0/50 (0)	1/50 (2)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	Infinite
Lower Limit		0.054	0.601
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	109	83
Testis: Interstitial-cell Tumor[b]	46/50 (92)	44/50 (88)	42/50 (84)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.957	0.913
Lower Limit		0.847	0.806
Upper Limit		1.105	1.076
Weeks to First Observed Tumor	88	85	97

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Multiple Organs: Mesothelioma, Malignant[b]	1/50 (2)	3/50 (6)	2/50 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		3.000	2.000
Lower Limit		0.251	0.109
Upper Limit		154.270	115.621
Weeks to First Observed Tumor	107	109	109

[a]Treated groups received doses of 25,000 or 50,000 ppm in feed.

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

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

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

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

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

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma[b]	13/50 (26)	4/50 (8)	6/50 (12)
P Values[c,d]	P = 0.036 (N)	P = 0.016 (N)	N.S.
Relative Risk (Matched Control)[f]		0.308	0.462
Lower Limit		0.079	0.156
Upper Limit		0.918	1.188
Weeks to First Observed Tumor	97	108	101
Hematopoietic System: Lymphoma or Leukemia[b]	13/50 (26)	4/50 (8)	7/50 (14)
P Values[c,d]	N.S.	P = 0.016 (N)	N.S.
Relative Risk (Matched Control)[f]		0.308	0.538
Lower Limit		0.079	0.198
Upper Limit		0.918	1.320
Weeks to First Observed Tumor	97	108	101

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	26/50 (52)	21/48 (44)	29/49 (59)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.841	1.138
Lower Limit		0.532	0.773
Upper Limit		1.325	1.668
Weeks to First Observed Tumor	96	81	73
Thyroid: Follicular-cell Carcinoma[b]	1/48 (2)	0/48 (0)	3/49 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	2.939
Lower Limit		0.000	0.245
Upper Limit		18.644	151.056
Weeks to First Observed Tumor	109	--	109

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Adenoma or Carcinoma[b]	2/48 (4)	0/48 (0)	3/49 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	1.469
Lower Limit		0.000	0.175
Upper Limit		3.377	16.960
Weeks to First Observed Tumor	82	--	109
Thyroid: C-cell Adenoma[b]	8/48 (17)	4/48 (8)	9/49 (18)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.500	1.102
Lower Limit		0.117	0.413
Upper Limit		1.731	3.001
Weeks to First Observed Tumor	99	109	98

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	3/50 (6)	0/47 (0)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	0.333
Lower Limit		0.000	0.006
Upper Limit		1.766	3.983
Weeks to First Observed Tumor	109	--	109
Mammary Gland: Fibroadenoma[b]	10/50 (20)	6/50 (12)	2/50 (4)
P Values[c,d]	P = 0.011 (N)	N.S.	P = 0.014 (N)
Relative Risk (Matched Control)[f]		0.600	0.200
Lower Limit		0.194	0.022
Upper Limit		1.673	0.879
Weeks to First Observed Tumor	97	109	109

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	9/50 (18)	5/49 (10)	11/49 (22)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.567	1.247
Lower Limit		0.160	0.517
Upper Limit		1.741	3.099
Weeks to First Observed Tumor	88	100	82

[a]Treated groups received doses of 25,000 or 50,000 ppm in feed.

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

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

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

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

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

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED N,N′-DICYCLOHEXYLTHIOUREA IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	4/50 (8)	4/50 (8)	5/49 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	1.276
Lower Limit		0.197	0.292
Upper Limit		5.083	6.070
Weeks to First Observed Tumor	92	81	101
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	9/50 (19)	5/50 (10)	9/49 (18)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.556	1.020
Lower Limit		0.157	0.392
Upper Limit		1.708	2.653
Weeks to First Observed Tumor	75	59	101

Table F1. Analyses of the Incidence if Primary Tumors in Male Mice Fed N,N'-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma[b]	11/50 (22)	17/50 (34)	13/50 (26)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.546	1.182
Lower Limit		0.765	0.542
Upper Limit		3.257	2.626
Weeks to First Observed Tumor	82	81	74
Liver: Hepatocellular Carcinoma[b]	17/49 (35)	12/50 (24)	15/49 (31)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.692	0.882
Lower Limit		0.340	0.466
Upper Limit		1.367	1.655
Weeks to First Observed Tumor	78	92	96

Table F1. Analyses of the Incidence if Primary Tumors in Male Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma[b]	26/49 (53)	18/50 (36)	25/49 (51)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.679	0.962
Lower Limit		0.413	0.635
Upper Limit		1.106	1.457
Weeks to First Observed Tumor	78	92	67
Adrenal: Pheochromocytoma[b]	2/47 (4)	1/45 (2)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.522	1.469
Lower Limit		0.009	0.176
Upper Limit		9.670	16.939
Weeks to First Observed Tumor	78	103	67

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma[b]	2/50 (4)	2/50 (4)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.000	2.000
Lower Limit		0.075	0.301
Upper Limit		13.326	21.316
Weeks to First Observed Tumor	103	99	97
All Sites: Hemangioma or Hemangiosarcoma[b]	4/50 (8)	3/50 (6)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.750	1.000
Lower Limit		0.116	0.198
Upper Limit		4.204	5.083
Weeks to First Observed Tumor	92	99	97

[a]Treated groups received doses of 25,000 or 50,000 ppm in feed.

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

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

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

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

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

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

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed N,N'-Dicyclohexylthiourea in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/48 (2)	2/50 (4)	4/49 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.920	3.918
Lower Limit		0.103	0.405
Upper Limit		110.994	188.793
Weeks to First Observed Tumor	103	104	102
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	4/48 (8)	2/50 (4)	4/49 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.480	0.980
Lower Limit		0.045	0.192
Upper Limit		3.183	4.972
Weeks to First Observed Tumor	77	104	104

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed N,N'-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma[b]	20/49 (41)	23/50 (46)	27/50 (54)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.127	1.323
Lower Limit		0.689	0.838
Upper Limit		1.855	2.103
Weeks to First Observed Tumor	51	91	74
Hematopoietic System: Granulocytic Sarcoma[b]	3/49 (6)	0/50 (0)	0/50 (0)
P Values[c,d]	P = 0.036 (N)	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.629	1.629
Weeks to First Observed Tumor	100	--	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: All Neoplasms	23/49 (47)	23/50 (46)	28/50 (56)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.980	1.193
Lower Limit		0.617	0.785
Upper Limit		1.559	1.817
Weeks to First Observed Tumor	51	91	74
Liver: Hepatocellular Carcinoma[b]	4/49 (8)	1/49 (2)	0/50 (0)
P Values[c,d]	P = 0.025 (N)	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.250	0.000
Lower Limit		0.005	0.000
Upper Limit		2.409	1.057
Weeks to First Observed Tumor	103	104	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma[b]	5/49 (10)	2/49 (4)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.400	0.588
Lower Limit		0.040	0.096
Upper Limit		2.310	2.851
Weeks to First Observed Tumor	103	104	103
Pituitary: Chromophobe Adenoma[b]	5/34 (15)	10/40 (25)	7/40 (18)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.700	1.190
Lower Limit		0.594	0.362
Upper Limit		5.751	4.349
Weeks to First Observed Tumor	103	72	103

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Ovary: Papillary Cystadenoma, NOS[b]	0/45 (0)	2/42 (5)	0/44 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.038		
Relative Risk (Matched Control)[f]		Infinite	--
Lower Limit		0.318	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	104	--
All Sites: Hemangiosarcoma[b]	1/49 (2)	3/50 (6)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.940	0.980
Lower Limit		0.246	0.013
Upper Limit		151.180	75.404
Weeks to First Observed Tumor	103	87	104

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed N,N′-Dicyclohexylthiourea in the Diet[a]

(continued)

All Sites: Hemangioma or Hemangiosarcoma[b]	1/49 (2)	3/50 (6)	2/50 (4)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.940	1.960
Lower Limit		0.246	0.105
Upper Limit		151.180	113.312
Weeks to First Observed Tumor	103	87	104

[a]Treated groups received doses of 25,000 or 50,000 ppm in feed.

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

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

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

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

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

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

January 18, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, 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 organic chemistry, biostatistics, biochemistry, 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 NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which N,N'-Dicyclohexylthiourea was reviewed.

The primary reviewer agreed with the staff's conclusion that N,N'-Dicyclohexylthiourea was not carcinogenic in either species, under the conditions of test. After briefly describing the experimental design, he commented that the study was well conducted and survival was adequate. He felt that the slight increase in the incidence of follicular cell lesions of the thyroid, in both species, was not significant. The primary reviewer indicated that N,N'-Dicyclohexylthiourea probably did not pose a carcinogenic risk to humans.

The secondary reviewer noted the increased incidence in tracheal inflammation found in the treated rats. He opined that it may have been due to a local irritant effect caused by the diet. He objected to the practice of housing animals from different studies together in the same room. He suggested that dietary concentrations of test chemicals be given as mg/kg body wt./day rather than on a parts/million

basis. In conclusion, the secondary reviewer said that N,N'-Dicyclohexylthiourea was not representative of the class of dicyclohexylcarbodiimide, although it was originally selected as a model compound.

A Subgroup member noted the unusually high incidence of liver tumors in the control male mice and lymphomas in the control female mice. He questioned the meaningfulness of these tumor types induced by N,N'-Dicyclohexylthiourea and other compounds, given the high spontaneous incidence. A discussion ensued as to the use of pooled controls in evaluating the variability of spontaneous tumor incidences.

It was moved that the report be accepted as written. It was further moved that N,N'-Dicyclohexylthiourea did not appear to present a carcinogenic risk to humans. The motion was seconded. A Subgroup member put forth an amendment stating that any conclusion drawn on the bioassay should consider the unusually high incidences of hepatocellular carcinomas in control male mice and lymphomas in the control female mice. Those in favor of the amendment were Mr. Garfinkel, Dr. Kensler, and Dr. Rowe. Opposed to the amendment were Dr. Strong, Dr. Wolfe, Dr. Highland, and Mr. Samuels. A vote on the motion was passed unanimously.

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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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