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BIOASSAY OF 1-NITRONAPHTHALENE FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Technical Report

BIOASSAY OF

1-NITRONAPHTHALENE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

REPORT ON BIOASSAY OF 1-NITRONAPHTHALENE FOR POSSIBLE CARCINOGENICITY

Availability

1-Nitronaphthalene (CAS 86-57-7) has been tested for cancer-causing activity with rats and mice in the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute. A report is available to the public.

Summary: A bioassay of technical-grade 1-nitronaphthalene for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 1-Nitronaphthalene was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low time-weighted average concentrations used in the chronic study were, respectively, 0.18 and 0.06 percent for rats and 0.12 and 0.06 percent for mice. After a 78-week period of chemical administration, the rats were observed for an additional period of up to 31 weeks and the mice for an additional period of up to 20 weeks. For rats 50 animals of each sex were placed on test as controls for the low dose groups and 25 of each sex for the high dose groups. For mice 50 animals of each sex were placed on test as controls for each dosed group.

In both species adequate numbers of animals in all groups survived sufficiently long for the development of late-appearing tumors; however, no compound-related increase in the incidence of neoplasms, nonneoplastic lesions, or other toxic effects was evident.

Under the conditions of this bioassay 1-nitronaphthalene was not demonstrated to be carcinogenic in Fischer 344 rats or B6C3F1 mice.

Single copies of the report are available from the Office of Cancer Communications, National Cancer Institute, Building 31, Room 10A21, National Institutes of Health, Bethesda, Maryland 20014.

Dated: June 16, 1978

Director
National Institutes of Health

(Catalogue of Federal Domestic Assistance Program Number 13.393, Cancer Cause and Prevention Research)

REPORT ON THE BIOASSAY OF 1-NITRONAPHTHALENE
FOR POSSIBLE CARCINOGENICITY

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

FOREWORD: This report presents the results of the bioassay of 1-nitronaphthalene 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 the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of 1-nitronaphthalene was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3).

Histopathologic examinations were performed by Dr. R. W. Fleischman (3), Dr. D. W. Hayden (3), Dr. A. S. Krishna Murthy (3), Dr. A. Russfield (3), and Dr. Yoon (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (4).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (5); the statistical analysis was performed by Mr. W. W. Belew (6), and Dr. A. Chu (5) using methods selected for the Bioassay Program by Dr. J. J. Gart (7).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for

this report at METREK are the project coordinator, Dr. L. W. Thomas (6), the task leader, Dr. M. R. Kornreich (6), the senior biologist, Ms. P. Walker (6), the chemist, Dr. N. Zimmerman (6), and the technical editor, Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (7), Mr. J. Nam (7), Dr. H. M. Pettigrew (7), and Dr. R. E. Tarone (7).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,8), and Dr. J. M. Ward (1).

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SUMMARY

A bioassay of technical-grade 1-nitronaphthalene for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. 1-Nitronaphthalene was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low time-weighted average concentrations used in the chronic study were, respectively, 0.18 and 0.06 percent for rats and 0.12 and 0.06 percent for mice. After a 78-week period of chemical administration, the rats were observed for an additional period of up to 31 weeks and the mice for an additional period of up to 20 weeks. For rats 50 animals of each sex were placed on test as controls for the low dose groups and 25 of each sex for the high dose groups. For mice 50 animals of each sex were placed on test as controls for each dosed group.

In both species adequate numbers of animals in all groups survived sufficiently long for the development of late-appearing tumors; however, no compound-related increase in the incidence of neoplasms, nonneoplastic lesions, or other toxic effects was evident.

Under the conditions of this bioassay 1-nitronaphthalene was not demonstrated to be carcinogenic in Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

1-Nitronaphthalene (NCI No. C01956), a monosubstituted naphthalene derivative with a variety of commercial uses, was selected for bioassay by the National Cancer Institute because of its structural analogy to the suspected carcinogen 1-naphthylamine (International Agency for Research on Cancer [IARC], 1974), and its similarity to both the tumorigenic agent 2-nitronaphthylene (Conzelman et al., 1970) and the human bladder carcinogen 2-naphthylamine (IARC, 1974).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 1-nitro-naphthalene.* It is also known as alpha-nitronaphthalene or simply as nitronaphthalene.

Most of the 1-nitronaphthalene produced appears to be used as an intermediate for the preparation of 1-naphthylamine, which is used in the manufacture of numerous dyes and intermediates, and in the production of rodenticides (Treibl, 1967). 1-Nitronaphthalene is also sulfonated to produce 1-nitronaphthalene-5-sulfonic acid, a dye intermediate (Hawley, 1971). 1,5- and 1,8-Dinitronaphthalenes, produced by further nitration of 1-nitronaphthalene, have had limited use in the dye industry (Treibl, 1967).

1-Nitronaphthalene is also used as a deblooming agent for petroleum and oils (in concentrations of 2-3 parts/1000 parts oil) (Treibl, 1967), and as a modifier to decrease the burning rate of explosives (Bureau of Explosives, 1977).

*The CAS registry number is 86-57-7.

Specific production statistics for 1-nitronaphthalene are not available; however, one U.S. company reported production or sales in excess of 1000 lbs or $1000 in value in 1975 (U.S. International Trade Commission, 1977).

A risk of exposure to 1-nitronaphthalene exists for all workers involved in the manufacture and handling of the compound and the production of its derivatives. Workers who produce or handle petroleum, oils, or explosives which contain 1-nitronaphthalene may also be exposed to the compound. The general population may experience exposure as a result of industrial discharge of 1-nitronaphthalene into rivers and streams. 1-Nitronaphthalene has been detected in the Rhine River (Gusten et al., 1974), and an unspecified isomer of nitronaphthalene has been detected in the Waal River in the Netherlands (Meijers, 1973; as cited in Urso, 1977).

1-Nitronaphthalene is a moderate local irritant (Sax, 1975) and its vapors are poisonous and lacrimatory (Treibl, 1967).

II. MATERIALS AND METHODS

A. Chemicals

1-Nitronaphthalene was purchased from Aldrich Chemical Company, Madison, Wisconsin, and chemical analysis was performed by Mason Research Institute, Worcester, Massachusetts. Although the narrow range of the experimentally observed melting point (50° to 53°C) suggested a compound of fairly high purity, the deviation from the literature value of 61.5°C indicated the presence of impurities. Thin-layer chromatography, visualized with ultraviolet light, revealed a single major spot with an R_f of 0.67 and one other spot of uncharacterized identity. The observed λ_{max} of 335 nm was close to the reported value of 330 nm. The extraneous peak at 220 nm indicated the presence of a significant impurity or impurities.

Throughout this report the term 1-nitronaphthalene is used to represent this material.

B. Dietary Preparation

The basal laboratory diet for both treated and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 1-Nitronaphthalene was administered to the treated animals as a component of the diet.

The chemical was removed from its container and proper amounts were ground to a powder in a Quaker City crystal mill, sifted and weighed out under an exhaust hood. The compound was hand blended in an aluminum bowl with an aliquot of the ground feed. Once visual

homogeneity was attained, the mixture was placed in a 6 kg capacity Patterson-Kelley standard model twin-shell stainless steel V-blender along with the remainder of the feed to be prepared. After 20 minutes of blending, the mixtures were placed in double plastic bags, and stored in the dark at 4°C. The mixture was prepared once weekly.

C. Animals

Two animals species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. All rats and mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts except for the high dose control rats, which were supplied by Laboratory Supply Company, Inc., Indianapolis, Indiana. Treated and control animals for both species were received in separate shipments.

Upon arrival, a sample of animals was examined for parasites and other signs of disease. The remaining animals were quarantined by species for 2 weeks prior to initiation of the test. Animals were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given species and sex.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C and a range in relative humidity of 5 to 90 percent. Incoming air was filtered through Tri-Dek® 15/40 denier

Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. During quarantine and for the first 11 months of study, high dose treated and control rats were housed in wire-mesh cages (Fenco Cage Products, Boston, Massachusetts) suspended over newpapers. Low dose treated and control rats were held in wire-mesh cages for the first 13 months of study. Newspapers under cages were replaced daily and cages and racks washed weekly. For the remainder of the study, all rats were held in suspended polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) equipped with disposable nonwoven fiber filter sheets. Clean cages and bedding were provided twice weekly. SAN-I-CEL® corncob bedding (Paxton Processing Company, Paxton, Illinois) was used in polycarbonate cages for low dose treated and control rats for the duration of the study and for high dose treated and control rats until the last 2 months of the study. Hardwood chip bedding (Aspen bedding, American Excelsior Company, Baltimore, Maryland) was used for high dose treated and control rats for the final 2 months of study. Stainless steel cage racks (Fenco Cage Products) were cleaned once every 2 weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate cages fitted with perforated stainless steel lids or wire bar lids (both from Lab Products, Inc.). Nonwoven fiber filter bonnets were used over cage lids. Mice

were initially housed ten per cage. High dose treated and control mice and low dose treated and control mice were housed five per cage after 13, 14, 18, and 18 months on test, respectively. Clean cages, lids, and bedding were provided three times per week when cage populations were ten, and twice per week when cage populations were reduced to five.

Hardwood chip bedding (Ab-sorb-dri®, Wilner Wood Products Company, Norway, Maine) was used for the first 2 months for high dose treated mice, for the first 4 months for high dose control mice, and for the first 8 months for low dose treated and low dose control mice. Corncob bedding (SAN-I-CEL®) was used for the next 12 months. A second type of corncob bedding (Bed-o-Cobs®, The Andersons Cob Division, Maumee, Ohio) was then used for the remainder of the study.

Water was available ad libitum for both species from 250 ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced twice weekly and, for rats only, water was supplied as needed between changes.

During quarantine low dose treated and control rats and mice received pelleted Wayne Lab-Blox®. Other groups received Wayne Lab-Blox® meal during quarantine. During the period of chemical administration, treated and control animals received treated or untreated Wayne Lab-Blox® meal as appropriate. The food, replenished daily, was supplied in Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) for the first 14 months of study

for high dose treated and control rats and for the entire study for all other rat and mouse groups. All groups received feed, whether treated or untreated, ad libitum. High dose treated and control rats were fed from stainless steel gangstyle hoppers (Scientific Cages, Inc., Bryan, Texas) after the first 14 months of study. During the untreated observation period, rats were fed pellets on the cage floor and mice were fed pellets from the food hopper incorporated into the wire bar cage lids.

All treated and control rats were housed in a room with other rats receiving diets treated with* 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 2-aminoanthraquinone (117-79-3); 3-amino-9-ethylcarbazole hydrochloride; 6-nitrobenzimidazole (94-52-0); 2,4-diaminoanisole sulfate (615-05-4); and APC (8003-03-0).

High dose mice were in a room with other mice receiving diets treated with 2,5-toluenediamine sulfate (6369-59-1); 5-nitro-o-toluidine (99-55-8); hydrazobenzene (530-50-7); 6-nitrobenzimidazole (94-52-0); 3-amino-9-ethylcarbazole hydrochloride; 5-nitro-o-anisidine (99-59-2); and 2,4-diaminoanisole sulfate (615-05-4). High dose control mice were in a room in which other mice were receiving diets treated with 2-methyl-1-nitroanthraquinone (129-15-7); acetylaminofluorene (53-96-3); p-cresidine (120-71-8); 4-chloro-m-phenylenediamine (5131-60-2); and fenaminosulf (140-56-7). Low dose treated and control male mice were in a room in which other mice were receiving

*CAS registry numbers are given in parentheses.

diets treated with amitrole (61-82-5); N,N-dimethyl-p-nitrosoaniline (138-89-6); 2,5-toluenediamine sulfate (6369-59-1); 2,4-dinitrotoluene (121-14-2); 2-aminoanthraquinone (117-79-3); 3-amino-4-ethoxyacetanilide (17026-81-2); 3-amino-9-ethylcarbazole hydrochloride; 1-amino-2-methylanthraquinone (82-28-0); 5-nitro-o-anisidine (99-59-2); 4-nitroanthranilic acid (619-17-0); 5-nitroacenaphthene (602-87-9); 3-nitro-p-acetophenetide (1777-84-0); 2,4-diaminoanisole sulfate (615-05-4); and APC (8003-03-0). Low dose treated and control female mice were in a room with other mice receiving diets treated with diarylanilide yellow (6358-85-6).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 1-nitronaphthalene for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among four groups, each consisting of five males and five females. 1-Nitronaphthalene was incorporated into the basal laboratory diet and supplied ad libitum to three of the four groups of each species in concentrations of 0.05, 0.10, and 0.15 percent. The fourth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for a period of 4 weeks, followed by a 2-week observation period during which all animals were fed the untreated basal diet. Individual body weights were recorded weekly throughout the study. Daily food consumption

per cage was monitored during the test. At the end of the observation period, all survivors were sacrificed and necropsied.

The highest concentration causing no deaths, no compound-related gross abnormalities, and no mean body weight depression in excess of 19 percent relative to controls during the 6-week subchronic test was to be selected as the high concentration utilized for the rat and mouse chronic bioassays.

A single death occurred among the female rat group receiving a dietary concentration of 0.05 percent. This death and all gross abnormalities observed were attributed to the development of chronic murine pneumonia. The initial high concentration selected for administration to rats and mice in the chronic bioassay was 0.06 percent. However, when the chronic bioassay was begun, concentrations of 0.05 and 0.06 percent were utilized for rats and mice, respectively.

F. Experimental Design

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

The high dose, low dose, and control rats were all approximately 6 weeks old at the time they were placed on test. The initial high and low concentrations of 1-nitronaphthalene in diets were 0.05 and 0.03 percent, respectively. The low dose rat group (0.03 percent) was sacrificed after 5 months and no histopathologic examinations

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
1-NITRONAPHTHALENE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	1-NITRO-NAPHTHALENE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[a]
MALE					
LOW DOSE CONTROL	50	0	0	107	0
HIGH DOSE CONTROL	25	0	0	109	0
LOW DOSE	50	0.05 0.06 0	12 66	 29	0.06
HIGH DOSE	50	0.18 0	78	 31	0.18
FEMALE					
LOW DOSE CONTROL	50	0	0	108	0
HIGH DOSE CONTROL	25	0	0	109	0
LOW DOSE	50	0.05 0.06	12 66	 29	0.06
HIGH DOSE	50	0.18 0	78	 31	0.18

[a] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1-NITRONAPHTHALENE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	1-NITRONAPHTHALENE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	96
HIGH DOSE CONTROL	50	0	0	98
LOW DOSE	50	0.06 0	78	18
HIGH DOSE	50	0.12 0	78	20
FEMALE				
LOW DOSE CONTROL	50	0	0	97
HIGH DOSE CONTROL	50	0	0	98
LOW DOSE	50	0.06 0	78	19
HIGH DOSE	50	0.12 0	78	20

were performed because the dose was considered, on the basis of weight depression, to be too low. At that time, a new high dose rat group, receiving a dietary concentration of 0.18 percent, was started. The initial high dose treated and high dose control groups which had been on test for 3 months became the low dose treated and low dose control groups. At this time, the dosage for the new low dose group was increased from 0.05 to 0.06 percent. Treated rats were supplied with dosed feed for a total of 78 weeks followed by a 29- to 31-week observation period.

The high dose, low dose, and control mice were all approximately 6 weeks old at the time they were placed on test. The initial high and low concentrations of 1-nitronaphthalene in diets administered to males and females were 0.06 and 0.03 percent, respectively. The low dose mice (0.03 percent) were sacrificed after 5 months and no histopathologic examinations were performed because the dose was considered, on the basis of weight depression, to be too low. At that time, a new high dose mouse group, receiving a dietary concentration of 0.12 percent was started. The initial high dose group became the low dose group. Treated mice were supplied with dosed feed for a total of 78 weeks followed by an 18- to 20-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice daily for mortality. Body weights were recorded twice weekly for the first

12 weeks of the study and at monthly intervals thereafter. Food consumption, for two cages from each group, was monitored for seven consecutive days once a month for the first nine months of the bioassay and for three consecutive days each month thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide inhalation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

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

Tissues for which slides were prepared were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An

occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment 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 used Tarone's (1975) extensions of Cox's methods for testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control

group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

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

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

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

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

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it

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

III. CHRONIC TESTING RESULTS: RATS

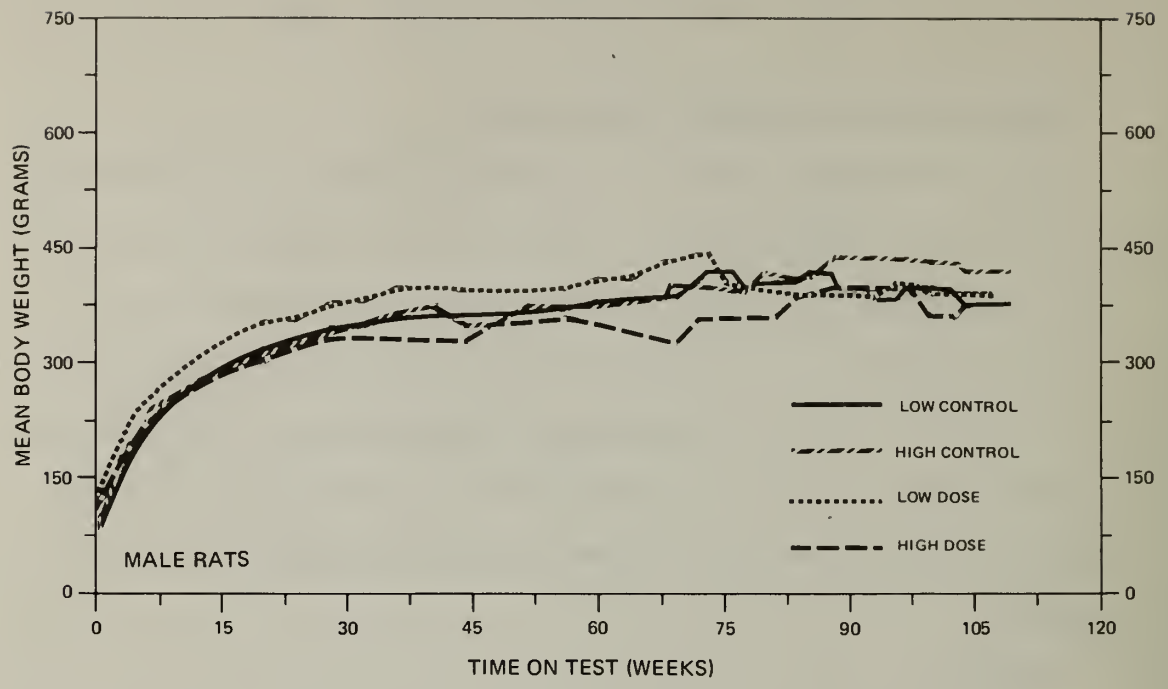
A. Body Weights and Clinical Observations

Mean body weight depression was observed in male and female high dose rats. The difference from controls was more apparent in females than males (Figure 1). Large palpable masses were observed in two low dose females. One low dose male had a growth on the posterior ventral surface, a crusted cutaneous lesion developed on the dorsolateral surface of a low dose control male, and one high dose female exhibited rectal bleeding. No other clinical abnormalities were reported.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 1-nitronaphthalene-treated groups are shown in Figure 2.

For male rats the Cox test for positive association between increased dosage and accelerated mortality was not significant. Five animals were terminated from each of the groups in week 78. Additionally, 10 rats were terminated from the low dose control group in week 29. In the low dose group, 5 rats were reported moribund in week 41; no common cause of death could be ascertained. Thirty-six out of 50 of the high dose, 29/50 of the low dose, 13/25 of the high dose control, and 27/50 of the low dose control male rats survived until termination of the experiment. The survival of male rats was, therefore, adequate to permit meaningful statistical analyses.



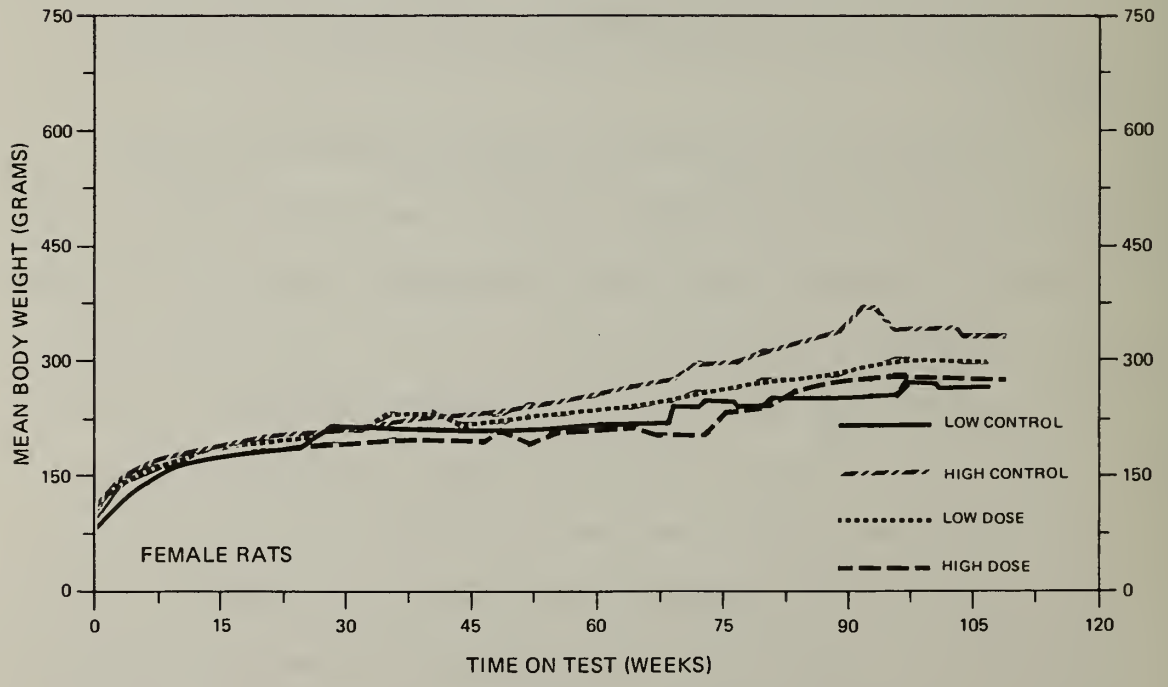
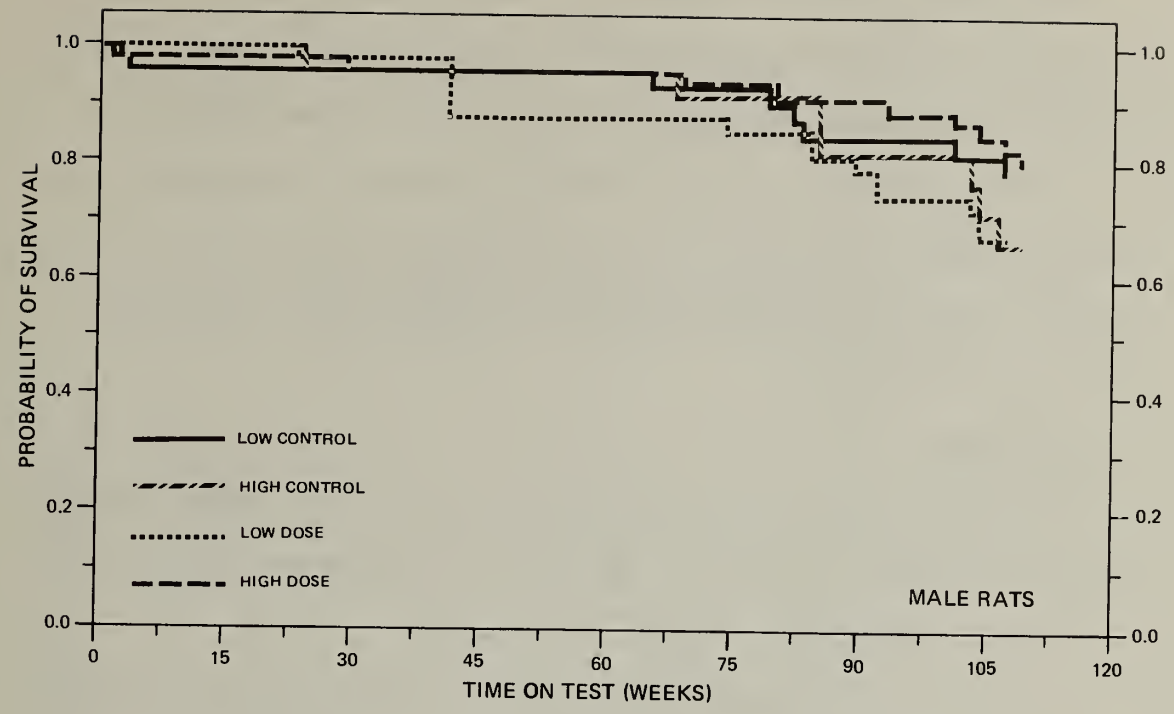


FIGURE 1
GROWTH CURVES FOR 1-NITRONAPHTHALENE CHRONIC STUDY RATS



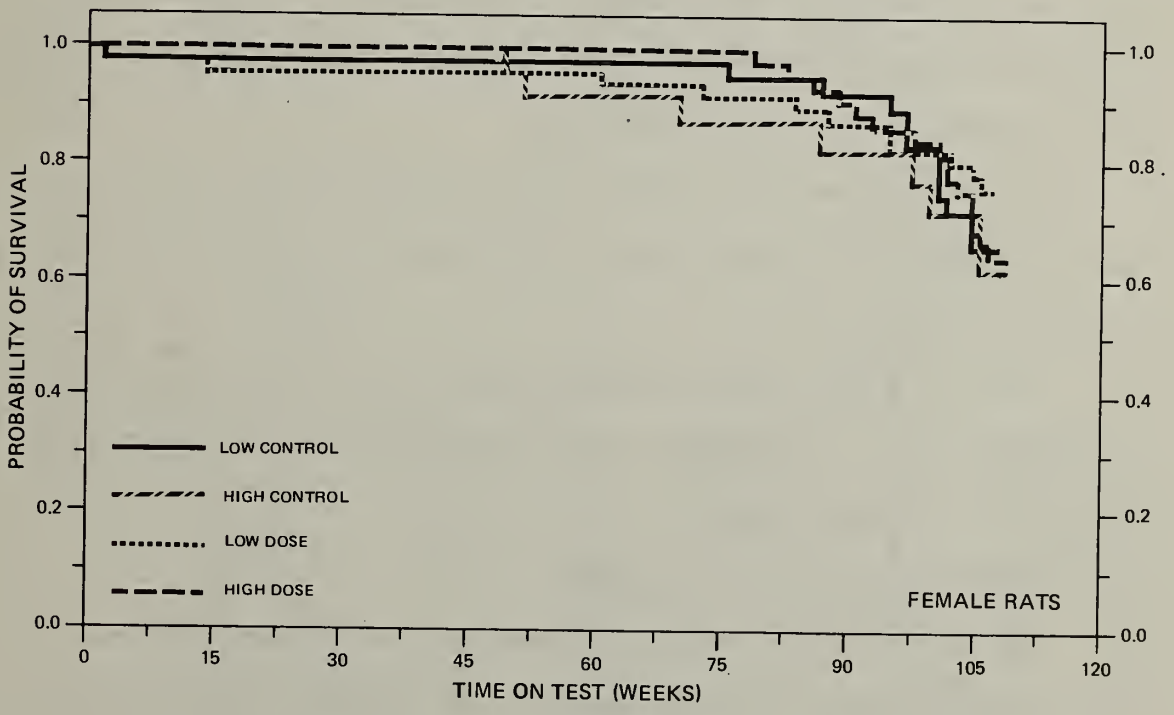


FIGURE 2
SURVIVAL COMPARISONS OF 1-NITRONAPHTHALENE CHRONIC STUDY RATS

For female rats the Cox test was also not significant. As with the males, 5 animals from each of the groups were sacrificed in week 78 and 10 additional rats from the low dose control were sacrificed in week 29. Survival of female rats was adequate for meaningful statistical analyses with 38/50 of the high dose, 37/50 of the low dose, 15/25 of the high dose, and 29/50 of the control group surviving at week 100 of the study.

C. Pathology

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

A variety of neoplasms were observed in rats fed 1-nitronaphthalene. These neoplasms were similar in number and type to neoplasms observed in control animals and the occurrence of the neoplasms was not considered to be compound-related.

Inflammatory and degenerative lesions which commonly occur in aging Fischer 344 rats were seen and they were not considered to be compound-related.

Based upon this histopathologic examination it is the conclusion that there was no carcinogenic effect attributable to feeding Fischer 344 rats 1-nitronaphthalene.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/46(0.00)	3/25(0.12)	1/48(0.02)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	0.510
Lower Limit	---	---	0.051	0.074
Upper Limit	---	---	Infinite	3.594
Weeks to First Observed Tumor	---	78	103	93
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/46(0.04)	4/25(0.16)	3/48(0.06)	1/50(0.02)
P Values[c]	---	---	N.S.	P = 0.040(N)
Relative Risk (Control)[d]	---	---	1.438	0.125
Lower Limit	---	---	0.173	0.003
Upper Limit	---	---	16.575	1.189
Weeks to First Observed Tumor	79	85	104	109
Pituitary: Adenoma NOS, Basophil Adenoma or Chromophobe Adenoma[b]	12/41(0.29)	3/21(0.14)	2/45(0.04)	3/43(0.07)
P Values[c]	---	---	P = 0.002(N)	N.S.
Relative Risk (Control)[d]	---	---	0.152	0.488
Lower Limit	---	---	0.018	0.073
Upper Limit	---	---	0.628	3.406
Weeks to First Observed Tumor	101	78	92	107

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	6/43(0.14)	4/25(0.16)	1/48(0.02)	3/48(0.06)
P Values[c]	---	---	P = 0.040(N)	N.S.
Relative Risk (Control)[d]	---	---	0.149	0.391
Lower Limit	---	---	0.003	0.063
Upper Limit	---	---	1.162	2.153
Weeks to First Observed Tumor	107	68	107	109
Thyroid: Adenocarcinoma NOS or Follicular-Cell Carcinoma[b]	2/45(0.04)	0/23(0.00)	1/43(0.02)	3/45(0.07)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.523	Infinite
Lower Limit	---	---	0.009	0.317
Upper Limit	---	---	9.671	Infinite
Weeks to First Observed Tumor	107	---	107	109
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/45(0.02)	0/23(0.00)	3/43(0.07)	0/45(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	3.140	---
Lower Limit	---	---	0.264	---
Upper Limit	---	---	160.819	---
Weeks to First Observed Tumor	107	---	92	---

TABLE 3 (Concluded)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islets: Islet-Cell Adenoma[b]	2/42(0.05)	2/25(0.08)	1/48(0.02)	1/47(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.438	0.266
Lower Limit	---	---	0.008	0.005
Upper Limit	---	---	8.110	4.902
Weeks to First Observed Tumor	107	109	107	109
Testis: Interstitial-Cell Tumor[b]	33/45(0.73)	19/24(0.79)	41/48(0.85)	46/49(0.94)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.165	1.186
Lower Limit	---	---	0.924	0.963
Upper Limit	---	---	1.426	1.411
Weeks to First Observed Tumor	78	78	78	78

[a]Treated groups received time-weighted average concentrations of 0.06 or 0.18 percent in feed.

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

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

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

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH 1-NITRONAPHTHALENE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia[b]	2/49(0.04)	2/23(0.09)	3/48(0.06)	1/50(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.531	0.230
Lower Limit	---	---	0.183	0.004
Upper Limit	---	---	17.665	4.242
Weeks to First Observed Tumor	101	106	73	86
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/49(0.08)	2/23(0.09)	3/48(0.06)	2/50(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.766	0.460
Lower Limit	---	---	0.118	0.036
Upper Limit	---	---	4.285	6.082
Weeks to First Observed Tumor	101	106	73	86
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	2/49(0.04)	2/23(0.09)	0/47(0.00)	2/49(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.469
Lower Limit	---	---	0.000	0.037
Upper Limit	---	---	3.519	6.202
Weeks to First Observed Tumor	97	106	---	107

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Carcinoma NOS or Adenocarcinoma NOS[b]	2/43(0.05)	0/21(0.00)	1/43(0.02)	1/41(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.500	Infinite
Lower Limit	---	---	0.009	0.028
Upper Limit	---	---	9.239	Infinite
Weeks to First Observed Tumor	107	---	84	107
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	18/43(0.42)	8/21(0.38)	9/43(0.21)	11/41(0.27)
P Values[c]	---	---	P = 0.031(N)	N.S.
Relative Risk (Control)[d]	---	---	0.500	0.704
Lower Limit	---	---	0.226	0.318
Upper Limit	---	---	1.030	1.740
Weeks to First Observed Tumor	76	78	84	98
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	2/46(0.04)	3/23(0.13)	1/47(0.02)	2/47(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.489	0.326
Lower Limit	---	---	0.008	0.029
Upper Limit	---	---	9.071	2.683
Weeks to First Observed Tumor	108	109	78	109

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/47(0.02)	3/21(0.14)	1/45(0.02)	1/42(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.044	0.167
Lower Limit	---	---	0.014	0.003
Upper Limit	---	---	80.198	1.951
Weeks to First Observed Tumor	107	109	107	109
Mammary: Adenoma NOS or Adenocarcinoma NOS[b]	1/49(0.02)	2/23(0.09)	4/48(0.08)	0/50(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	4.083	0.000
Lower Limit	---	---	0.424	0.000
Upper Limit	---	---	196.654	1.549
Weeks to First Observed Tumor	101	98	95	---
Mammary: Fibroadenoma[b]	4/49(0.08)	4/23(0.17)	8/48(0.17)	6/50(0.12)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.042	0.690
Lower Limit	---	---	0.589	0.186
Upper Limit	---	---	8.695	3.075
Weeks to First Observed Tumor	101	109	95	98

TABLE 4 (Concluded)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	10/48(0.21)	6/23(0.26)	9/46(0.20)	10/49(0.20)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.939	0.782
Lower Limit	---	---	0.372	0.302
Upper Limit	---	---	2.330	2.352
Weeks to First Observed Tumor	78	87	84	91

[a]Treated groups received time-weighted average concentrations of 0.06 or 0.18 percent in feed.

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

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

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

every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or 1-nitronaphthalene-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between the administration of 1-nitronaphthalene and tumor incidence. Additional time-adjusted analyses also indicated no significant positive associations. Thus, at the dose levels used in this experiment there was no convincing evidence that 1-nitronaphthalene was a carcinogen in Fischer 344 rats.

When low dose female rats having pituitary adenomas were grouped with those having pituitary chromophobe adenomas and the resulting incidence of females with tumors was compared to the controls, the Fisher exact tests showed a negative association. This trend was not significant, however, under the Bonferroni criterion.

Similarly, in male rats the combined incidences of pituitary adenomas, chromophobe adenomas, or basophil adenomas was significantly ($P = 0.002$) higher in the low dose control than in the low dose group. However, the incidence in the low dose control of 12/41 (29 percent) appeared unexpectedly high when compared to the historical control incidence of 21/594 (3 percent) in male Fischer 344 rats observed at Mason Research Institute during the NCI Bioassay Program.

The Fisher exact comparison of the incidence of adrenal pheochromocytomas in the low dose treated male rats with the low dose control male rats gave a value of P = 0.040. This value was not significant under the Bonferroni criterion. Similarly, the value of P = 0.040 for the Fisher exact test comparing the incidences of leukemia or malignant lymphomas in the high dose males with that in the high dose control males was not significant under the Bonferroni criterion.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of a significantly increased rate of tumor incidence induced in rats by 1-nitronaphthalene that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

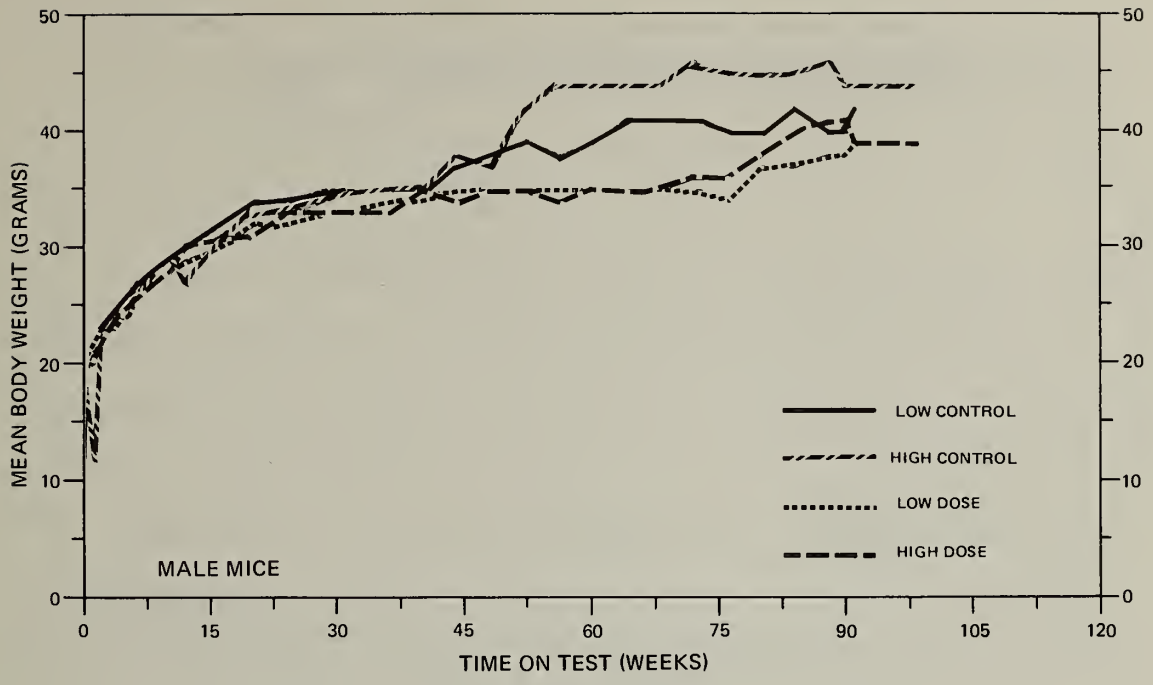
Mean body weight depression was apparent in both male and female treated mice (Figure 3). No clinical abnormalities were observed in treated or control males or females.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 1-nitronaphthalene-treated groups are shown in Figure 4.

For male mice the Cox test for positive association between increased dosage and accelerated mortality was not significant. Five animals were sacrificed from the high dose group and from each of the control groups in week 78. Adequate numbers of male mice were available for meaningful statistical analyses of the incidence of late-developing tumors, with 42/50 of the high dose, 45/50 of the low dose, 37/50 of the high dose control, and 42/50 of the low dose control surviving to the termination of the study.

For female mice the Cox test for a positive dose-related trend in mortality was also not significant. As with the males, 5 animals were terminated in week 78 from the high dose and each control group. Survival was relatively good with 35/50 of the high dose, 44/50 of the low dose, 35/50 of the high dose control, and 37/50 of the low dose control surviving until termination of the study. The survival of female mice was adequate for meaningful statistical analyses.



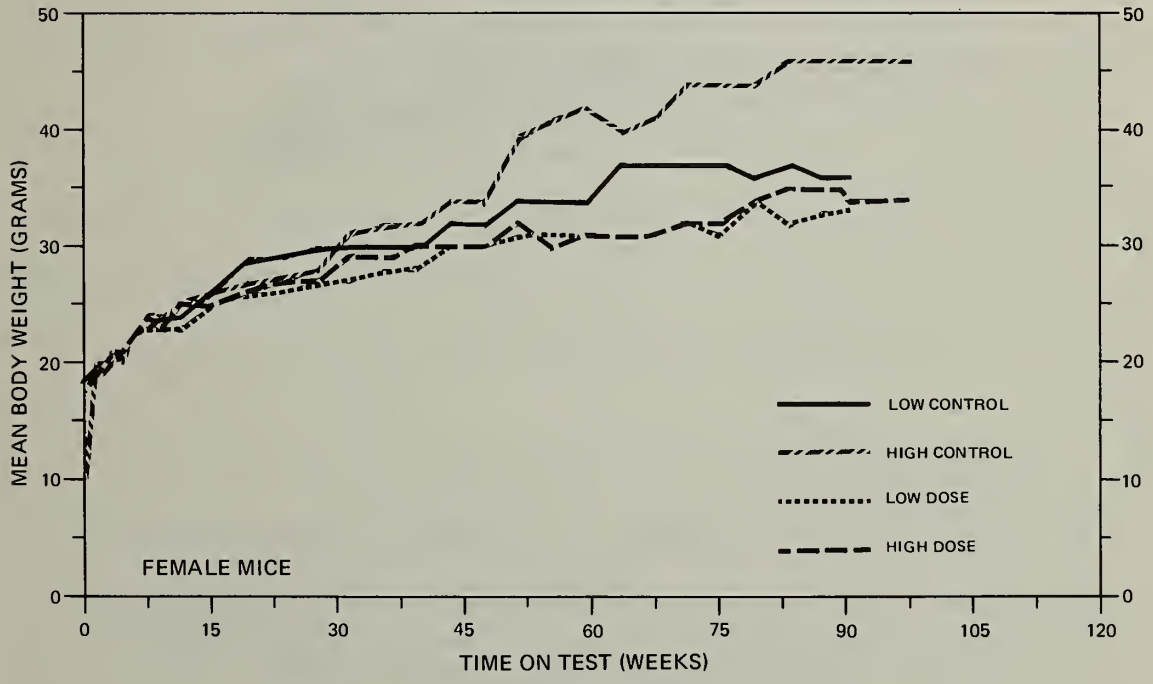
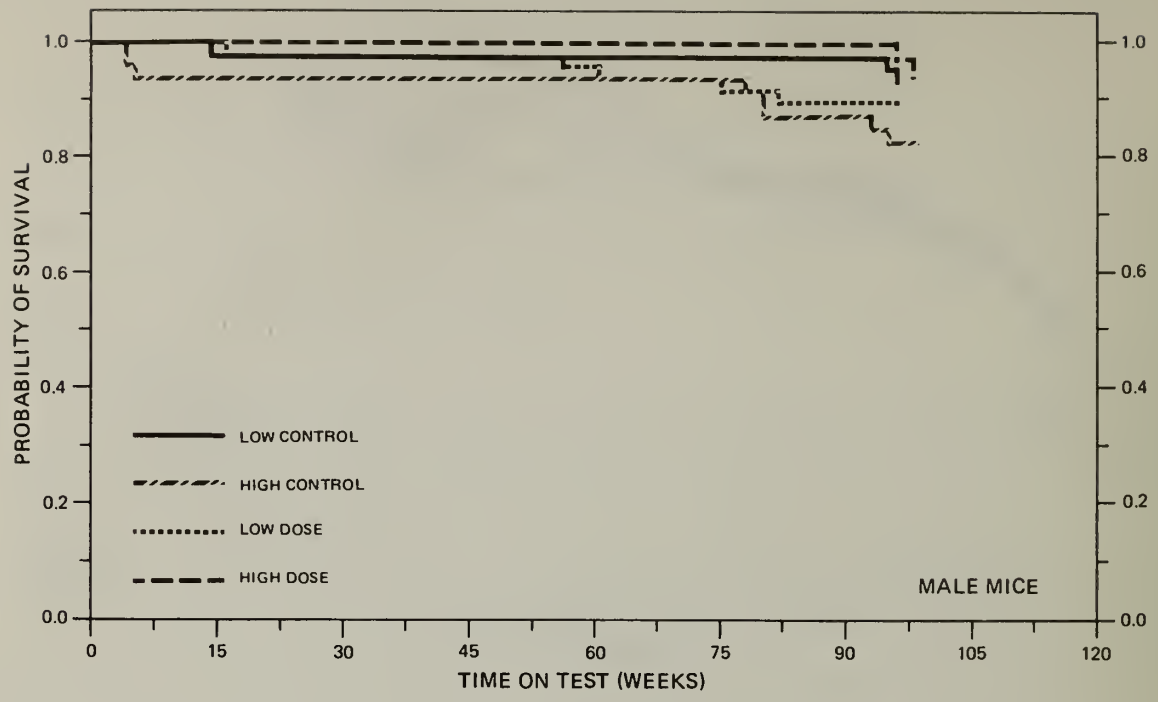


FIGURE 3
GROWTH CURVES FOR 1-NITRONAPHTHALENE CHRONIC STUDY MICE



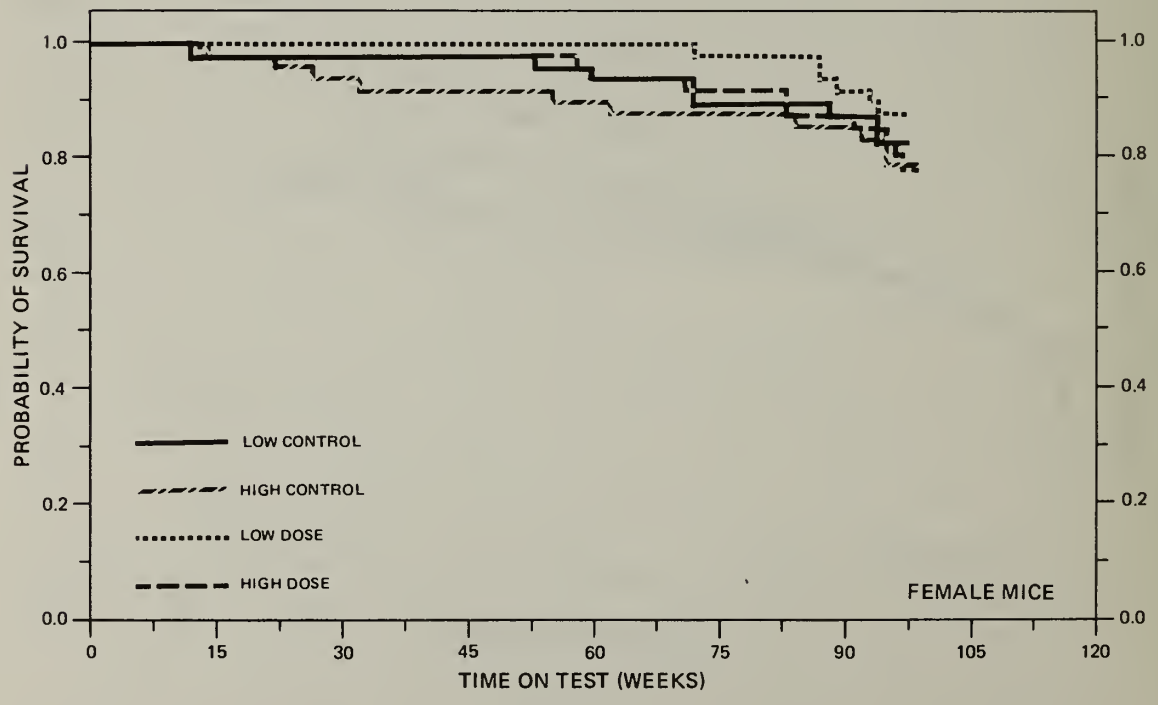


FIGURE 4
SURVIVAL COMPARISONS OF 1-NITRONAPHTHALENE CHRONIC STUDY MICE

C. Pathology

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

A variety of neoplasms were observed in the treated mice. These neoplasms appeared to be randomly and spontaneously distributed and were judged to be unrelated to the administration of 1-nitronaphthalene.

Nonneoplastic lesions which commonly occur in aging B6C3F1 mice were seen. These lesions were not considered to be compound-related.

On the basis of the histopathologic examinations, the conclusion is that 1-nitronaphthalene was not carcinogenic to B6C3F1 mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or 1-nitronaphthalene-dosed groups and where such tumors were observed in at least 5 percent of the group.

When considered separately, the Fisher exact comparisons for the incidences of alveolar/bronchiolar adenomas or alveolar/bronchiolar carcinomas in treated female mice were not significant. When animals with either of these tumors were pooled and the resulting combined incidences analyzed, the value of P = 0.031 obtained for the Fisher

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	6/48(0.13)	4/45(0.09)	0/47(0.00)	1/49(0.02)
P Values[c]	---	---	P = 0.014(N)	P = 0.049(N)
Relative Risk (Control)[d]	---	---	0.000	0.230
Lower Limit	---	---	0.000	0.005
Upper Limit	---	---	0.637	2.209
Weeks to First Observed Tumor	96	97	---	98
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	6/48(0.13)	11/45(0.24)	8/47(0.17)	9/49(0.18)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.362	0.751
Lower Limit	---	---	0.450	0.305
Upper Limit	---	---	4.403	1.806
Weeks to First Observed Tumor	96	78	96	78
Hematopoietic System: Malignant Lymphoma[b]	4/48(0.08)	2/45(0.04)	4/49(0.08)	2/49(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.837	0.918
Lower Limit	---	---	0.278	0.069
Upper Limit	---	---	19.547	12.222
Weeks to First Observed Tumor	96	97	75	78

TABLE 5 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma or Leukemia[b]	4/48(0.08)	2/45(0.06)	4/49(0.08)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.837	1.378
Lower Limit	---	---	0.278	0.166
Upper Limit	---	---	19.547	15.892
Weeks to First Observed Tumor	96	97	75	78
Circulatory System: Hemangiosarcoma or Hemangioma[b]	2/48(0.04)	0/45(0.00)	0/49(0.00)	1/49(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	Infinite
Lower Limit	---	---	0.000	0.049
Upper Limit	---	---	3.309	Infinite
Weeks to First Observed Tumor	96	---	---	98
Liver: Hepatocellular Carcinoma[b]	7/48(0.15)	10/45(0.22)	8/49(0.16)	8/49(0.16)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.119	0.735
Lower Limit	---	---	0.386	0.277
Upper Limit	---	---	3.346	1.882
Weeks to First Observed Tumor	78	93	96	98

TABLE 5 (Concluded)

[a]Treated groups received time-weighted average concentrations of 0.06 or 0.12 percent in feed.

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

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

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

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH 1-NITRONAPHTHALENE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	4/46(0.09)	1/45(0.02)	4/44(0.09)	7/46(0.15)
P Values[c]	---	---	N.S.	P = 0.031
Relative Risk (Control)[d]	---	---	1.046	6.848
Lower Limit	---	---	0.207	0.935
Upper Limit	---	---	5.276	301.000
Weeks to First Observed Tumor	96	98	96	97
Hematopoietic System: Malignant Lymphoma[b]	5/48(0.10)	11/46(0.24)	4/46(0.09)	7/49(0.14)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.364	0.597
Lower Limit	---	---	0.091	0.215
Upper Limit	---	---	1.126	1.538
Weeks to First Observed Tumor	96	95	93	60
Hematopoietic System: Malignant Lymphoma or Leukemia[b]	5/48(0.10)	12/46(0.26)	4/46(0.09)	7/49(0.14)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.835	0.548
Lower Limit	---	---	0.176	0.201
Upper Limit	---	---	3.634	1.371
Weeks to First Observed Tumor	96	95	93	60

TABLE 6 (Continued)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	1/47(0.02)	4/45(0.09)	0/46(0.00)	1/48(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.234
Lower Limit	---	---	0.000	0.005
Upper Limit	---	---	19.040	2.254
Weeks to First Observed Tumor	96	78	---	98
Stomach: Squamous-Cell Papilloma or Squamous-Cell Carcinoma[b]	1/44(0.02)	3/42(0.07)	0/46(0.00)	1/48(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.292
Lower Limit	---	---	0.000	0.006
Upper Limit	---	---	17.820	3.474
Weeks to First Observed Tumor	96	98	---	98
Pituitary: Adenoma NOS[b]	2/42(0.05)	6/37(0.16)	0/37(0.00)	2/44(0.05)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	0.280
Lower Limit	---	---	0.000	0.029
Upper Limit	---	---	3.803	1.461
Weeks to First Observed Tumor	97	98	---	91

TABLE 6 (Concluded)

[a]Treated groups received time-weighted average concentrations of 0.06 or 0.12 percent in feed.

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

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

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

exact comparison of the high dose to the high dose control was not significant under the Bonferroni criterion.

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

In male mice, the Fisher exact test indicated a negative association ($P = 0.049$) when the incidence of alveolar/bronchiolar carcinoma in the high dose mice was compared to that in the high dose controls. This result, however, was not significant using the Bonferroni criterion. The Fisher exact test comparing the incidences of this same tumor in low dose mice also showed a negative association ($P = 0.014$). When the incidences of alveolar/bronchiolar adenomas were combined with those of alveolar/bronchiolar carcinomas no significant results were observed.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of a significantly

increased rate of tumor incidence induced in mice by 1-nitronaphthalene that could not be established under the conditions of this test.

V. DISCUSSION

Under the conditions of this bioassay, adequate numbers of 1-nitronaphthalene-treated rats and mice survived sufficiently long for the development of late-appearing tumors. However, exposure to the compound did not result in a positive association between dietary concentration and the incidence of any tumor in either species. In rats and mice, no compound-related increase in the incidence of neoplasms, nonneoplastic lesions, or other toxic effects was evident. In both species and sexes there was at least slight compound-related mean body weight depression.

Under the conditions of this bioassay 1-nitronaphthalene was not demonstrated to be carcinogenic in Fischer 344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1-NITRONAPHTHALENE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 1-NITRONAPHTHALENE

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	46	25	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	25	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(25)	(49)	(50)
SQUAMOUS CELL PAPILLOMA				1 (2%)
BASAL-CELL CARCINOMA			1 (2%)	
SEBACEOUS ADENOCARCINOMA			1 (2%)	
HEMANGIOSARCOMA			1 (2%)	
*SUBCUT TISSUE	(46)	(25)	(49)	(50)
FIBROMA			2 (4%)	1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(45)	(11)	(47)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)	
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
#LUNG	(46)	(25)	(48)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (8%)		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (4%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, METASTATIC		1 (4%)		
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(25)	(49)	(50)
UNDIFFERENTIATED LEUKEMIA	1 (2%)	2 (8%)		
MYELOMONOCYTIC LEUKEMIA			2 (4%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		2 (8%)		
MONOCYTIC LEUKEMIA	1 (2%)			
#BONE MARROW	(44)	(25)	(48)	(47)
OSTEOSARCOMA, METASTATIC			1 (2%)	

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
#SPLEEN	(46)	(25)	(48)	(48)
HEMANGIOMA			1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)	
MYELOMONOCYTIC LEUKEMIA			1 (2%)	
#LYMPH NODE	(38)	(24)	(41)	(47)
ADENOCARCINOMA, NOS, METASTATIC	1 (3%)			
#MANDIBULAR L. NODE	(38)	(24)	(41)	(47)
GLIOMA,METASTATIC				1 (2%)
#MEDIASTINAL L.NODE	(38)	(24)	(41)	(47)
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (2%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(38)	(24)	(48)	(47)
LYMPHANGIOSARCOMA			1 (2%)	
#LIVER	(46)	(25)	(48)	(49)
NEOPLASTIC NODULE				2 (4%)
HEPATOCELLULAR CARCINOMA			2 (4%)	
PHEOCHROMOCYTOMA, INVASIVE				1 (2%)
#STOMACH	(45)	(24)	(48)	(47)
SQUAMOUS CELL PAPILLOMA		1 (4%)		
BASAL-CELL CARCINOMA		1 (4%)		
URINARY SYSTEM				
#URINARY BLADDER	(42)	(23)	(47)	(48)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
TRANSITIONAL-CELL CARCINOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(21)	(45)	(43)
CARCINOMA,NOS			2 (4%)	

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
ADENOMA, NOS	2 (5%)	1 (5%)	2 (4%)	3 (7%)
CHROMOPHOBE ADENOMA	10 (24%)			
BASOPHIL ADENOMA		2 (10%)		
#ADRENAL	(43)	(25)	(48)	(48)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
PHEOCHROMOCYTOMA	6 (14%)	2 (8%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT		2 (8%)		2 (4%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
#THYROID	(45)	(23)	(43)	(45)
ADENOMA, NOS	1 (2%)			
ADENOCARCINOMA, NOS	2 (4%)			
FOLLICULAR-CELL CARCINOMA			1 (2%)	3 (7%)
C-CELL ADENOMA	1 (2%)		2 (5%)	
C-CELL CARCINOMA			1 (2%)	
#PARATHYROID	(32)	(15)	(22)	(29)
ADENOMA, NOS				1 (3%)
#PANCREATIC ISLETS	(42)	(25)	(48)	(47)
ISLET-CELL ADENOMA	2 (5%)	2 (8%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(25)	(49)	(50)
FIBROADENOMA		1 (4%)	1 (2%)	
*PREPUTIAL GLAND	(46)	(25)	(49)	(50)
CARCINOMA,NOS		1 (4%)		
ADENOMA, NOS		1 (4%)		
#PROSTATE	(45)	(23)	(47)	(49)
PARAGANGLIOMA, NOS	1 (2%)			
#TESTIS	(45)	(24)	(48)	(49)
INTERSTITIAL-CELL TUMOR	33 (73%)	19 (79%)	41 (85%)	46 (94%)
NERVOUS SYSTEM				
#BRAIN	(44)	(25)	(48)	(49)
GLIOMA, NOS				1 (2%)
ASTROCYTOMA	1 (2%)			

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
SPECIAL SENSE ORGANS				
*EAR CANAL	(46)	(25)	(49)	(50)
SQUAMOUS CELL CARCINOMA		1 (4%)		1 (2%)
MUSCULOSKELETAL SYSTEM				
*LUMBAR VERTEBRA	(46)	(25)	(49)	(50)
OSTEOSARCOMA			1 (2%)	
BODY CAVITIES				
*BODY CAVITIES	(46)	(25)	(49)	(50)
MESOTHELIOMA, NOS			2 (4%)	1 (2%)
*MEDIASTINUM	(46)	(25)	(49)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (4%)		
*PLEURA	(46)	(25)	(49)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (4%)		
ALL OTHER SYSTEMS				
SITE UNKNOWN				
CARCINOMA,NOS			1	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	6	3	5	4
MORIBUND SACRIFICE	2	4	10	5
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED			1	
TERMINAL SACRIFICE	27	13	29	36
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	22	43	47
TOTAL PRIMARY TUMORS	61	41	71	69
TOTAL ANIMALS WITH BENIGN TUMORS	33	20	41	46
TOTAL BENIGN TUMORS	55	31	51	57
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	9	15	8
TOTAL MALIGNANT TUMORS	5	10	18	9
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	1	3
TOTAL SECONDARY TUMORS	4	3	4	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		2	3
TOTAL UNCERTAIN TUMORS	1		2	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 1-NITRONAPHTHALENE

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	49	23	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	23	47	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(23)	(48)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)	
BASAL-CELL TUMOR				1 (2%)
TRICHOEPITHELIOMA				1 (2%)
SEBACEOUS ADENOCARCINOMA		1 (4%)		
LIPOMA			1 (2%)	
*SUBCUT TISSUE	(49)	(23)	(48)	(50)
SQUAMOUS CELL CARCINOMA				1 (2%)
FIBROMA			1 (2%)	1 (2%)
LEIOMYOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(49)	(23)	(47)	(50)
CARCINOMA, NOS, METASTATIC				1 (2%)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (4%)	2 (4%)	1 (2%)
FOLLICULAR-CELL CARCINOMA, METAS				1 (2%)
SARCOMA, NOS				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(23)	(48)	(50)
MALIGNANT LYMPHOMA, NOS				1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)			
UNDIFFERENTIATED LEUKEMIA		2 (9%)		
MYELOMONOCYTIC LEUKEMIA			3 (6%)	1 (2%)
MONOCYTIC LEUKEMIA	2 (4%)			
*SPLENIC CAPSULE	(49)	(23)	(46)	(49)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
#MEDIASTINAL L.NODE	(41)	(21)	(41)	(48)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
#MESENTERIC L. NODE	(41)	(21)	(41)	(48)
CARCINOMA, NOS, METASTATIC				1 (2%)
#RENAL LYMPH NODE	(41)	(21)	(41)	(48)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(49)	(23)	(47)	(49)
CARCINOMA, NOS, METASTATIC				1 (2%)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
NEOPLASTIC NODULE		2 (9%)		2 (4%)
HEPATOCELLULAR CARCINOMA	2 (4%)			
#HEPATIC CAPSULE	(49)	(23)	(47)	(49)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
#PANCREAS	(46)	(22)	(43)	(48)
CARCINOMA, NOS, METASTATIC				1 (2%)
#ESOPHAGUS	(48)	(22)	(47)	(46)
SQUAMOUS CELL PAPILLOMA				1 (2%)
URINARY SYSTEM				
#KIDNEY	(49)	(23)	(47)	(49)
TUBULAR-CELL ADENOCARCINOMA				1 (2%)
#KIDNEY/CAPSULE	(49)	(23)	(47)	(49)
CARCINOMA, NOS, METASTATIC				1 (2%)
#URINARY BLADDER	(41)	(22)	(44)	(47)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)	

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(21)	(43)	(41)
CARCINOMA,NOS			1 (2%)	1 (2%)
ADENOMA, NOS	3 (7%)	1 (5%)	9 (21%)	11 (27%)
ADENOCARCINOMA, NOS	2 (5%)			
CHROMOPHOBE ADENOMA	15 (35%)	7 (33%)		
#ADRENAL	(46)	(23)	(47)	(47)
CORTICAL ADENOMA			1 (2%)	1 (2%)
PHEOCHROMOCYTOMA	2 (4%)	2 (9%)	1 (2%)	2 (4%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (4%)		
#THYROID	(47)	(21)	(45)	(42)
ADENOMA, NOS	1 (2%)			
ADENOCARCINOMA, NOS	2 (4%)			
FOLLICULAR-CELL CARCINOMA				1 (2%)
C-CELL ADENOMA	1 (2%)	2 (10%)		1 (2%)
C-CELL CARCINOMA		1 (5%)	1 (2%)	
#THYROID FOLLICLE	(47)	(21)	(45)	(42)
PAPILLARY CYSTADENOCARCINOMA,NOS		1 (5%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(23)	(48)	(50)
ADENOMA, NOS	1 (2%)		4 (8%)	
ADENOCARCINOMA, NOS	1 (2%)	2 (9%)		
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (2%)			
INFILTRATING DUCT CARCINOMA		1 (4%)		
FIBROADENOMA	4 (8%)	4 (17%)	8 (17%)	6 (12%)
*PREPUTIAL GLAND	(49)	(23)	(48)	(50)
SQUAMOUS CELL CARCINOMA				1 (2%)
#UTERUS	(48)	(23)	(46)	(49)
ADENOCARCINOMA, NOS	4 (8%)		1 (2%)	
ENDOMETRIAL STROMAL POLYP	10 (21%)	6 (26%)	9 (20%)	10 (20%)
#UTERUS/ENDOMETRIUM	(48)	(23)	(46)	(49)
UNDIFFERENTIATED CARCINOMA				1 (2%)
#OVARY	(47)	(22)	(45)	(49)
CARCINOMA,NOS				1 (2%)

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

TABLE A2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
ADENOCARCINOMA, NOS				1 (2%)
GRANULOSA-CELL TUMOR			1 (2%)	1 (2%)
NERVOUS SYSTEM				
#BRAIN	(49)	(23)	(47)	(50)
ASTROCYTOMA				1 (2%)
SPECIAL SENSE ORGANS				
*EAR CANAL	(49)	(23)	(48)	(50)
FIBROMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(49)	(23)	(48)	(50)
MESOTHELIOMA, MALIGNANT	1 (2%)			
*MEDIASTINUM	(49)	(23)	(48)	(50)
SARCOMA, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	25	50	50
NATURAL DEATH@	5	3	7	9
MORIBUND SACRIFICE	7	5	4	7
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	23	12	34	29
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	19	32	34
TOTAL PRIMARY TUMORS	56	34	46	52
TOTAL ANIMALS WITH BENIGN TUMORS	27	18	27	26
TOTAL BENIGN TUMORS	39	23	37	36
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	8	8	12
TOTAL MALIGNANT TUMORS	17	9	8	13
TOTAL ANIMALS WITH SECONDARY TUMORS#	2			3
TOTAL SECONDARY TUMORS	4			10
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	1	3
TOTAL UNCERTAIN TUMORS		2	1	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1-NITRONAPHTHALENE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 1-NITRONAPHTHALENE

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	46	48	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	45	48	49	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(49)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(45)	(48)	(47)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		2 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	7 (16%)		8 (17%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	4 (9%)	6 (13%)		1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(48)	(49)	(49)
MALIGNANT LYMPHOMA, NOS		2 (4%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	1 (2%)	
LEUKEMIA,NOS				1 (2%)
#SPLEEN	(45)	(47)	(47)	(47)
HEMANGIOMA		1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#MANDIBULAR L. NODE	(35)	(44)	(37)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)			
#MESENTERIC L. NODE	(35)	(44)	(37)	(47)
MALIGNANT LYMPHOMA, NOS			1 (3%)	1 (2%)
#RENAL LYMPH NODE	(35)	(44)	(37)	(47)
MALIGNANT LYMPHOMA, NOS				1 (2%)
#LIVER	(45)	(48)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	

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

TABLE B1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
#PEYERS PATCH	(43)	(48)	(47)	(48)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(45)	(48)	(49)	(49)
HEPATOCELLULAR CARCINOMA	10 (22%)	7 (15%)	8 (16%)	8 (16%)
HEMANGIOMA		1 (2%)		
HEMANGIOSARCOMA				1 (2%)
#PANCREAS	(44)	(48)	(45)	(46)
SEMINOMA/DYSGERMINOMA, METASTATI				1 (2%)
#STOMACH	(42)	(47)	(48)	(48)
SQUAMOUS CELL PAPILLOMA	1 (2%)			
SQUAMOUS CELL CARCINOMA		1 (2%)		
#SMALL INTESTINE	(43)	(48)	(47)	(48)
SEMINOMA/DYSGERMINOMA, METASTATI				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#THYROID	(40)	(47)	(38)	(43)
FOLLICULAR-CELL ADENOMA		1 (2%)		
REPRODUCTIVE SYSTEM				
#TESTIS	(45)	(47)	(48)	(47)
INTERSTITIAL-CELL TUMOR			1 (2%)	
SEMINOMA/DYSGERMINOMA				1 (2%)
NERVOUS SYSTEM				
NONE				

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

TABLE B1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
SPECIAL SENSE ORGANS				
*EAR CANAL	(46)	(48)	(49)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(46)	(48)	(49)	(49)
SEMINOMA/DYSGERMINOMA, METASTATI				1 (2%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	7	3	4	2
MORIBUND SACRIFICE	1		1	
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	37	42	45	42
ANIMAL MISSING				1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	17	19	21
TOTAL PRIMARY TUMORS	25	21	22	22
TOTAL ANIMALS WITH BENIGN TUMORS	8	2	9	8
TOTAL BENIGN TUMORS	8	3	9	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	15	13	14
TOTAL MALIGNANT TUMORS	17	18	13	14
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		2	1
TOTAL SECONDARY TUMORS	1		2	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 TREATED WITH 1-NITRONAPHTHALENE

	HIGH DOSE CONTROL(UNTR) 06-0077	LOW DOSE CONTROL(UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	46	48	46	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	47	46	48
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(46)	(49)
FIBROSARCOMA	2 (4%)			
*SUBCUT TISSUE	(46)	(48)	(46)	(49)
FIBROSARCOMA				1 (2%)
LEIOMYOSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(45)	(46)	(44)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	3 (7%)	3 (7%)	5 (11%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(48)	(46)	(49)
MALIGNANT LYMPHOMA, NOS	3 (7%)	1 (2%)	3 (7%)	6 (12%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	6 (13%)	2 (4%)	1 (2%)	
LYMPHOCYTIC LEUKEMIA	1 (2%)			
#SPLEEN	(43)	(46)	(46)	(48)
HEMANGIOSARCOMA		1 (2%)		1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#PEYERS PATCH	(43)	(44)	(46)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#KIDNEY	(43)	(46)	(46)	(48)
MALIGNANT LYMPHOMA, NOS				1 (2%)
#THYMUS	(27)	(31)	(25)	(38)
MALIGNANT LYMPHOMA, NOS		1 (3%)		

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(45)	(47)	(46)	(48)
HEPATOCELLULAR CARCINOMA	4 (9%)	1 (2%)		1 (2%)
FIBROSARCOMA		1 (2%)		
#STOMACH	(42)	(44)	(46)	(48)
SQUAMOUS CELL PAPILLOMA	3 (7%)	1 (2%)		
SQUAMOUS CELL CARCINOMA				1 (2%)
#COLON	(41)	(40)	(42)	(47)
LEIOMYOSARCOMA		1 (3%)		
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(37)	(42)	(37)	(44)
CARCINOMA, NOS		1 (2%)		
ADENOMA, NOS	6 (16%)	2 (5%)		2 (5%)
#ADRENAL	(43)	(45)	(45)	(46)
CORTICAL ADENOMA	1 (2%)			
PHEOCHROMOCYTOMA		1 (2%)		
#THYROID	(30)	(43)	(31)	(43)
FOLLICULAR-CELL ADENOMA			1 (3%)	
#PANCREATIC ISLETS	(41)	(44)	(43)	(47)
ISLET-CELL ADENOMA	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(48)	(46)	(49)
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)	

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

TABLE B2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
#UTERUS	(43)	(45)	(44)	(48)
LEIOMYOSARCOMA		1 (2%)		
ENDOMETRIAL STROMAL POLYP		3 (7%)		
HEMANGIOMA			1 (2%)	
#OVARY	(41)	(45)	(45)	(47)
LUTEOMA	1 (2%)			
TUBULAR ADENOMA		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(46)	(48)	(46)	(49)
CARCINOMA,NOS				1 (2%)
PAPILLARY ADENOMA				1 (2%)
PAPILLARY CYSTADENOMA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(46)	(48)	(46)	(49)
LEIOMYOSARCOMA			1 (2%)	
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	8	6	5	5
MORIBUND SACRIFICE	2	2	1	5
SCHEDULED SACRIFICE	5	5		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	35	37	44	35
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	20	12	20
TOTAL PRIMARY TUMORS	32	24	12	23
TOTAL ANIMALS WITH BENIGN TUMORS	12	11	5	7
TOTAL BENIGN TUMORS	13	11	5	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	11	7	14
TOTAL MALIGNANT TUMORS	19	13	7	14
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1-NITRONAPHTHALENE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MALE RATS TREATED WITH 1-NITRONAPHTHALENE

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	46	25	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	25	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(25)	(49)	(50)
EPIDERMAL INCLUSION CYST				1 (2%)
NECROSIS, NOS		1 (4%)		
*SUBCUT TISSUE	(46)	(25)	(49)	(50)
ABSCESS, NOS			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
*LARYNX	(46)	(25)	(49)	(50)
INFLAMMATION ACUTE AND CHRONIC		1 (4%)		
INFLAMMATION, CHRONIC		7 (28%)		
#TRACHEA	(45)	(11)	(47)	(48)
INFLAMMATION, NOS	9 (20%)	1 (9%)		
INFLAMMATION, ACUTE/CHRONIC			32 (68%)	
INFLAMMATION, CHRONIC	10 (22%)		1 (2%)	43 (90%)
#TRACHEAL SUBMUCOSA	(45)	(11)	(47)	(48)
HYPERPLASIA, NOS			1 (2%)	
#LUNG/BRONCHUS	(46)	(25)	(48)	(49)
BRONCHIECTASIS		2 (8%)		8 (16%)
INFLAMMATION, FOCAL		1 (4%)		
ABSCESS, NOS				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC	8 (17%)			
PERIVASCULAR CUFFING			2 (4%)	
#BRONCHIAL MUCOUS GLA	(46)	(25)	(48)	(49)
ABSCESS, NOS	1 (2%)			
NECROSIS, NOS	1 (2%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
HYPERPLASIA, ADENOMATOUS	1 (2%)			
#LUNG/BRONCHIOLE	(46)	(25)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)			
#LUNG	(46)	(25)	(48)	(49)
ATELECTASIS	1 (2%)			
CONGESTION, NOS	1 (2%)			
EDEMA, NOS	1 (2%)			
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	3 (7%)			
INFLAMMATION, INTERSTITIAL	1 (2%)	2 (8%)		
INFLAMMATION, SUPPURATIVE	1 (2%)			
BRONCHOPNEUMONIA, ACUTE		1 (4%)	1 (2%)	1 (2%)
ABSCESS, NOS		1 (4%)		
PNEUMONIA, CHRONIC MURINE	1 (2%)	11 (44%)		9 (18%)
INFLAMMATION, CHRONIC	1 (2%)			
GRANULOMA, NOS		1 (4%)		
PERIVASCULITIS	5 (11%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)	
#LUNG/ALVEOLI	(46)	(25)	(48)	(49)
HEMORRHAGE			2 (4%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(44)	(25)	(48)	(47)
HYPERPLASIA, HEMATOPOIETIC		2 (8%)		
HYPOPLASIA, HEMATOPOIETIC			2 (4%)	
#SPLEEN	(46)	(25)	(48)	(48)
THROMBOSIS, NOS	1 (2%)			
CONGESTION, NOS			2 (4%)	
FIBROSIS	1 (2%)			
INFARCT, HEALED	1 (2%)			
HEMOSIDEROSIS		1 (4%)		
RETICULOCYTOSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC		1 (4%)		
HYPERPLASIA, ERYTHROID	12 (26%)	1 (4%)		
HYPERPLASIA, RETICULUM CELL	8 (17%)		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)	
HEMATOPOIESIS			1 (2%)	
#LYMPH NODE	(38)	(24)	(41)	(47)
INFLAMMATION, NOS	1 (3%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
HYPERPLASIA, NOS	1 (3%)			
PLASMACYTOSIS		1 (4%)		
HYPERPLASIA, RETICULUM CELL	3 (8%)			
#MANDIBULAR L. NODE	(38)	(24)	(41)	(47)
HYPERPLASIA, PLASMA CELL				1 (2%)
#MEDIASTINAL L.NODE	(38)	(24)	(41)	(47)
PLASMACYTOSIS	1 (3%)			
HYPERPLASIA, PLASMA CELL				1 (2%)
#MESENTERIC L. NODE	(38)	(24)	(41)	(47)
HEMATOPOIESIS			1 (2%)	
#RENAL LYMPH NODE	(38)	(24)	(41)	(47)
HYPERPLASIA, NOS				1 (2%)
CIRCULATORY SYSTEM				
*LYMPHATIC VESSELS	(46)	(25)	(49)	(50)
INFLAMMATION, NOS	1 (2%)			
#HEART	(46)	(25)	(48)	(49)
PERIARTERITIS		1 (4%)		
#HEART/ATRIUM	(46)	(25)	(48)	(49)
INFLAMMATION PROLIFERATIVE			1 (2%)	
#MYOCARDIUM	(46)	(25)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, INTERSTITIAL	22 (48%)		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	3 (7%)			
FIBROSIS	7 (15%)			1 (2%)
FIBROSIS, FOCAL		1 (4%)	2 (4%)	
FIBROSIS, DIFFUSE			11 (23%)	
DEGENERATION, NOS		10 (40%)		
*AORTA	(46)	(25)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
MEDIAL CALCIFICATION				1 (2%)
CALCIFICATION, FOCAL		1 (4%)		
*PULMONARY ARTERY	(46)	(25)	(49)	(50)
HYPERTROPHY, NOS	1 (2%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
*TESTICULAR ARTERY	(46)	(25)	(49)	(50)
CALCIFICATION, NOS			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(46)	(25)	(48)	(49)
CONGESTION, NOS			1 (2%)	
CONGESTION, CHRONIC PASSIVE		1 (4%)		
HEMORRHAGE			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
CHOLANGIOFIBROSIS		1 (4%)		
DEGENERATION, HYALINE			1 (2%)	
NECROSIS, FOCAL	3 (7%)	1 (4%)	1 (2%)	
NECROSIS, COAGULATIVE	1 (2%)			
METAMORPHOSIS FATTY	1 (2%)	4 (16%)	1 (2%)	
HYPERPLASIA, NODULAR			3 (6%)	
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	23 (50%)		9 (19%)	
ANGIECTASIS			1 (2%)	
#LIVER/CENTRILOBULAR	(46)	(25)	(48)	(49)
NECROSIS, NOS				1 (2%)
#LIVER/PERIPORTAL	(46)	(25)	(48)	(49)
FIBROSIS	1 (2%)			
*BILE DUCT	(46)	(25)	(49)	(50)
INFLAMMATION, NOS	6 (13%)			
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
HYPERPLASIA, NOS	32 (70%)	6 (24%)		
HYPERPLASIA, FOCAL	1 (2%)		3 (6%)	
#PANCREAS	(42)	(25)	(48)	(47)
INFLAMMATION, NOS	10 (24%)	1 (4%)		
INFLAMMATION, INTERSTITIAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			14 (29%)	
HYPERPLASIA, INTRADUCTAL	1 (2%)			
#PANCREATIC DUCT	(42)	(25)	(48)	(47)
HYPERPLASIA, NOS		1 (4%)		
#PANCREATIC ACINUS	(42)	(25)	(48)	(47)
ATROPHY, NOS	4 (10%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
#STOMACH	(45)	(24)	(48)	(47)
EPIDERMAL INCLUSION CYST	1 (2%)	1 (4%)		
ULCER, NOS	2 (4%)			
PERIARTERITIS			1 (2%)	
HYPERPLASIA, NOS	6 (13%)			
HYPERKERATOSIS	1 (2%)			
ACANTHOSIS	1 (2%)			
#PEYERS PATCH	(43)	(24)	(48)	(48)
HYPERPLASIA, NOS	7 (16%)	2 (8%)		
#ILEUM	(43)	(24)	(48)	(48)
HYPERPLASIA, LYMPHOID			2 (4%)	
#COLON	(43)	(24)	(47)	(46)
NEMATODIASIS	3 (7%)		3 (6%)	
URINARY SYSTEM				
#KIDNEY	(46)	(24)	(48)	(48)
CONGESTION, NOS			1 (2%)	
GLOMERULONEPHRITIS, NOS	33 (72%)	5 (21%)	1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)		2 (4%)	
GLOMERULONEPHRITIS, SUBACUTE			35 (73%)	
NEPHROPATHY		1 (4%)		
NEPHROSIS, NOS		16 (67%)		45 (94%)
GLOMERULOSCLEROSIS, NOS			1 (2%)	
#URINARY BLADDER	(42)	(23)	(47)	(48)
CALCULUS, NOS		3 (13%)		
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, EPITHELIAL	3 (7%)			
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(21)	(45)	(43)
HYPERPLASIA, NOS	3 (7%)			
HYPERPLASIA, FOCAL			3 (7%)	
HYPERPLASIA, CHROMOPHOBE-CELL	2 (5%)			
#PITUITARY/BASOPHIL	(41)	(21)	(45)	(43)
NODULE		1 (5%)		

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL(UNTR) 01-0037	HIGH DOSE CONTROL(UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
#ADRENAL CORTEX	(43)	(25)	(48)	(48)
METAMORPHOSIS FATTY			3 (6%)	
HYPERTROPHY, FOCAL	1 (2%)	1 (4%)		
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL			4 (8%)	
#ZONA FASCICULATA	(43)	(25)	(48)	(48)
CONGESTION, NOS				1 (2%)
#ADRENAL MEDULLA	(43)	(25)	(48)	(48)
NECROSIS, NOS	1 (2%)			
CALCIFICATION, NOS	1 (2%)			
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASIA, NOS	6 (14%)		1 (2%)	
HYPERPLASIA, FOCAL			3 (6%)	
#THYROID	(45)	(23)	(43)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, C-CELL	1 (2%)			
#PANCREATIC ISLETS	(42)	(25)	(48)	(47)
CONGESTION, NOS			1 (2%)	
HYPERPLASIA, NOS	2 (5%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(25)	(49)	(50)
GALACTOCELE			1 (2%)	
HYPERPLASIA, NOS	5 (11%)	3 (12%)	1 (2%)	
LACTATION		7 (28%)		
*PREPUTIAL GLAND	(46)	(25)	(49)	(50)
ABSCESS, NOS	1 (2%)			
HYPERPLASIA, NOS	1 (2%)			
#PROSTATE	(45)	(23)	(47)	(49)
INFLAMMATION, NOS	21 (47%)	1 (4%)		
INFLAMMATION, FOCAL	3 (7%)			
INFLAMMATION, ACUTE			2 (4%)	
INFLAMMATION, ACUTE FOCAL			6 (13%)	
INFLAMMATION, ACUTE/CHRONIC			5 (11%)	

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
ATROPHY, NOS		4 (17%)		
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, FOCAL	5 (11%)			
HYPERPLASIA, PAPILLARY	2 (4%)			
METAPLASIA, SQUAMOUS	5 (11%)			
*SEMINAL VESICLE	(46)	(25)	(49)	(50)
ATROPHY, NOS		1 (4%)		
#TESTIS	(45)	(24)	(48)	(49)
HEMORRHAGE			1 (2%)	
DEGENERATION, NOS			36 (75%)	
CALCIFICATION, FOCAL		4 (17%)		
ATROPHY, NOS	2 (4%)	12 (50%)		6 (12%)
ASPERMATOGENESIS	1 (2%)			
HYPERPLASIA, INTERSTITIAL CELL	19 (42%)	2 (8%)	3 (6%)	
#TESTIS/TUBULE	(45)	(24)	(48)	(49)
DEGENERATION, NOS	6 (13%)			1 (2%)
*EPIDIDYMIS	(46)	(25)	(49)	(50)
STEATITIS				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(44)	(25)	(48)	(49)
HEMORRHAGE		2 (8%)	1 (2%)	
CALCIFICATION, FOCAL		1 (4%)		
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(46)	(25)	(49)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
*EYE/RETINA	(46)	(25)	(49)	(50)
DEGENERATION, NOS			1 (2%)	
*EYE/CRYSTALLINE LENS	(46)	(25)	(49)	(50)
CATARACT			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(46)	(25)	(49)	(50)
CALCIFICATION, FOCAL		1 (4%)		

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

TABLE C1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0084	LOW DOSE 01-0036	HIGH DOSE 01-0106
*CARTILAGE, NOS	(46)	(25)	(49)	(50)
CYST, NOS	1 (2%)			
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			2	1
AUTO/NECROPSY/HISTO PERF	1			
AUTO/NECROPSY/NO HISTO			1	1
AUTOLYSIS/NO NECROPSY	4		1	

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

TABLE C2

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH 1-NITRONAPHTHALENE

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
ANIMALS INITIALLY IN STUDY	50	25	50	50
ANIMALS NECROPSIED	49	23	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	23	47	50
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
*LARYNX	(49)	(23)	(48)	(50)
INFLAMMATION ACUTE AND CHRONIC		1 (4%)		
INFLAMMATION, CHRONIC		3 (13%)		
#TRACHEA	(48)	(5)	(47)	(46)
INFLAMMATION, NOS	9 (19%)			
INFLAMMATION, ACUTE/CHRONIC			25 (53%)	
INFLAMMATION, CHRONIC	10 (21%)		1 (2%)	22 (48%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
POLYP, INFLAMMATORY	1 (2%)		2 (4%)	
#LUNG/BRONCHUS	(49)	(23)	(47)	(50)
BRONCHIECTASIS	1 (2%)			1 (2%)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, CHRONIC	9 (18%)			
#LUNG/BRONCHIOLE	(49)	(23)	(47)	(50)
INFLAMMATION, NOS	1 (2%)			
#LUNG	(49)	(23)	(47)	(50)
HEMORRHAGE			2 (4%)	
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	7 (14%)		1 (2%)	
INFLAMMATION, INTERSTITIAL	2 (4%)	3 (13%)		
BRONCHOPNEUMONIA NECROTIZING				1 (2%)
PNEUMONIA, CHRONIC MURINE		8 (35%)		1 (2%)
GRANULOMA, FOREIGN BODY		1 (4%)		
PERIVASCULITIS	6 (12%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
CALCIFICATION, FOCAL		1 (4%)		
HYPERPLASIA, EPITHELIAL		1 (4%)		
#LUNG/ALVEOLI	(49)	(23)	(47)	(50)
HEMORRHAGE				1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(22)	(46)	(48)
HYPERPLASIA, HEMATOPOIETIC		1 (5%)		
#SPLEEN	(49)	(23)	(46)	(49)
HEMATOMA, NOS		1 (4%)		
HEMOSIDEROSIS		2 (9%)		1 (2%)
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC	3 (6%)	3 (13%)		
HYPERPLASIA, ERYTHROID	17 (35%)	4 (17%)		
HYPERPLASIA, PLASMA CELL	1 (2%)			
HYPERPLASIA, RETICULUM CELL	11 (22%)			
HEMATOPOIESIS		3 (13%)		
ERYTHROPOIESIS				2 (4%)
#LYMPH NODE	(41)	(21)	(41)	(48)
INFLAMMATION, NOS	3 (7%)			
HYPERPLASIA, NOS	2 (5%)			
PLASMACYTOSIS	3 (7%)			
HYPERPLASIA, PLASMA CELL	1 (2%)			
#MANDIBULAR L. NODE	(41)	(21)	(41)	(48)
HYPERPLASIA, PLASMA CELL				1 (2%)
#MEDIASTINAL L.NODE	(41)	(21)	(41)	(48)
HEMORRHAGE			1 (2%)	
CIRCULATORY SYSTEM				
#HEART	(49)	(23)	(47)	(49)
NECROSIS, FOCAL			1 (2%)	
#APEX OF HEART	(49)	(23)	(47)	(49)
SCAR				1 (2%)
#MYOCARDIUM	(49)	(23)	(47)	(49)
INFLAMMATION, NOS	1 (2%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
INFLAMMATION, INTERSTITIAL	24 (49%)	1 (4%)		
INFLAMMATION, ACUTE/CHRONIC			2 (4%)	
FIBROSIS	5 (10%)			
FIBROSIS, FOCAL			4 (9%)	
FIBROSIS, DIFFUSE			7 (15%)	
DEGENERATION, NOS		4 (17%)		
*CORONARY ARTERY	(49)	(23)	(48)	(50)
INFLAMMATION, ACUTE			1 (2%)	
*PORTAL VEIN	(49)	(23)	(48)	(50)
THROMBUS, MURAL	1 (2%)			
DIGESTIVE SYSTEM				
#PAROTID GLAND	(44)	(22)	(46)	(48)
INFLAMMATION, CHRONIC				1 (2%)
#LIVER	(49)	(23)	(47)	(49)
CONGESTION, CHRONIC PASSIVE		1 (4%)		
FIBROSIS	1 (2%)			
CHOLANGIOFIBROSIS		1 (4%)		
PERIVASCULITIS	1 (2%)			
NECROSIS, FOCAL	4 (8%)		1 (2%)	
NECROSIS, COAGULATIVE	2 (4%)			
NECROSIS, HEMORRHAGIC			1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	2 (9%)	3 (6%)	2 (4%)
BASOPHILIC CYTO CHANGE		4 (17%)		1 (2%)
HYPERPLASIA, NODULAR	1 (2%)		1 (2%)	
HYPERPLASIA, FOCAL	22 (45%)	3 (13%)	24 (51%)	
ANGIECTASIS	1 (2%)			1 (2%)
#LIVER/CENTRILOBULAR	(49)	(23)	(47)	(49)
CONGESTION, PASSIVE				1 (2%)
NECROSIS, NOS				1 (2%)
*BILE DUCT	(49)	(23)	(48)	(50)
INFLAMMATION, NOS	5 (10%)			
HYPERPLASIA, NOS	27 (55%)	2 (9%)	7 (15%)	
HYPERPLASIA, FOCAL			6 (13%)	
#PANCREAS	(46)	(22)	(43)	(48)
INFLAMMATION, NOS	7 (15%)			
INFLAMMATION, ACUTE/CHRONIC			9 (21%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
#PANCREATIC DUCT	(46)	(22)	(43)	(48)
HYPERPLASIA, NOS	1 (2%)			
#PANCREATIC ACINUS	(46)	(22)	(43)	(48)
ATROPHY, NOS	2 (4%)			
#STOMACH	(48)	(23)	(44)	(47)
INFLAMMATION, NOS	2 (4%)			
INFLAMMATION, FOCAL	2 (4%)			
HYPERPLASIA, EPITHELIAL	1 (2%)			
#GASTRIC MUCOSA	(48)	(23)	(44)	(47)
NECROSIS, FOCAL			1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
#PEYERS PATCH	(47)	(23)	(44)	(47)
HYPERPLASIA, NOS	6 (13%)	4 (17%)		
#ILEUM	(47)	(23)	(44)	(47)
HYPERPLASIA, LYMPHOID			1 (2%)	
#COLON	(43)	(22)	(44)	(47)
NEMATODIASIS	3 (7%)		4 (9%)	
PARASITISM		2 (9%)		
URINARY SYSTEM				
#KIDNEY	(49)	(23)	(47)	(49)
HYDRONEPHROSIS	1 (2%)			1 (2%)
GLOMERULONEPHRITIS, NOS	33 (67%)	4 (17%)		
INFLAMMATION, INTERSTITIAL	1 (2%)			
GLOMERULONEPHRITIS, MEMBRANOUS	1 (2%)			
PYELONEPHRITIS, ACUTE		1 (4%)		
GLOMERULONEPHRITIS, SUBACUTE			30 (64%)	
INFLAMMATION, CHRONIC	1 (2%)			
PYELONEPHRITIS, CHRONIC		1 (4%)		
NEPHROSIS, NOS		10 (43%)		32 (65%)
NECROSIS, FOCAL			1 (2%)	
CALCIFICATION, FOCAL		1 (4%)		
#KIDNEY/TUBULE	(49)	(23)	(47)	(49)
NECROSIS, NOS		1 (4%)		
#URINARY BLADDER	(41)	(22)	(44)	(47)
INFLAMMATION, NOS	1 (2%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
HYPERPLASIA, EPITHELIAL			1 (2%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(21)	(43)	(41)
HEMORRHAGIC CYST		1 (5%)	1 (2%)	
HYPERPLASIA, NOS	2 (5%)			
HYPERPLASIA, FOCAL		1 (5%)	1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)			
#ADRENAL CORTEX	(46)	(23)	(47)	(47)
NODULE	1 (2%)			
METAMORPHOSIS FATTY			5 (11%)	
HYPERPLASIA, NODULAR			3 (6%)	
HYPERPLASIA, NOS	7 (15%)		2 (4%)	
HYPERPLASIA, FOCAL			4 (9%)	
#ADRENAL MEDULLA	(46)	(23)	(47)	(47)
HYPERPLASIA, NOS	4 (9%)			
HYPERPLASIA, FOCAL			1 (2%)	
#THYROID	(47)	(21)	(45)	(42)
HYPERPLASIA, C-CELL		3 (14%)		3 (7%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			
#PANCREATIC ISLETS	(46)	(22)	(43)	(48)
HYPERPLASIA, NOS	1 (2%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(23)	(48)	(50)
DILATATION/DUCTS			1 (2%)	
GALACTOCELE	5 (10%)	1 (4%)	7 (15%)	
HYPERPLASIA, NOS	17 (35%)	1 (4%)	14 (29%)	
HYPERPLASIA, PAPILLARY	1 (2%)			
LACTATION		9 (39%)		
*MAMMARY DUCT	(49)	(23)	(48)	(50)
HYPERPLASIA, NOS			1 (2%)	
#UTERUS	(48)	(23)	(46)	(49)
HYDROMETRA	3 (6%)		3 (7%)	
INFLAMMATION, SUPPURATIVE	1 (2%)			

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
PYOMETRA		3 (13%)		
ABSCESS, NOS	2 (4%)		1 (2%)	
HYPERPLASIA, ADENOMATOUS	5 (10%)		1 (2%)	
HYPERPLASIA, STROMAL			1 (2%)	
#CERVIX UTERI	(48)	(23)	(46)	(49)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
FIBROSIS			1 (2%)	
#UTERUS/ENDOMETRIUM	(48)	(23)	(46)	(49)
HEMORRHAGE			1 (2%)	
INFLAMMATION, NOS	14 (29%)	1 (4%)		
INFLAMMATION, FOCAL	1 (2%)		1 (2%)	
INFLAMMATION, SUPPURATIVE	2 (4%)			7 (14%)
INFLAMMATION, ACUTE			15 (33%)	
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
ABSCESS, NOS			2 (4%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC		1 (4%)		
HYPERPLASIA, NOS	1 (2%)	1 (4%)	3 (7%)	1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
HYPERPLASIA, CYSTIC	2 (4%)	1 (4%)	11 (24%)	2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
#OVARY/OVIDUCT	(48)	(23)	(46)	(49)
RETENTION FLUID			1 (2%)	
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE		1 (4%)	5 (11%)	
ABSCESS, NOS		1 (4%)	1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
#OVARY	(47)	(22)	(45)	(49)
CYST, NOS	4 (9%)	3 (14%)	4 (9%)	6 (12%)
INFLAMMATION, SUPPURATIVE				2 (4%)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
ABSCESS, NOS			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			
FIBROSIS, FOCAL			1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)			
NERVOUS SYSTEM				
#BRAIN	(49)	(23)	(47)	(50)
HYDROCEPHALUS, NOS		1 (4%)		

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

TABLE C2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0084	LOW DOSE 02-0036	HIGH DOSE 02-0106
HEMORRHAGE		1 (4%)		
CALCIFICATION, FOCAL		1 (4%)		
#CEREBELLUM	(49)	(23)	(47)	(50)
INFARCT HEMORRHAGIC			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKULL	(49)	(23)	(48)	(50)
OSTEOPETROSIS			1 (2%)	
*STERNUM	(49)	(23)	(48)	(50)
OSTEOPETROSIS			1 (2%)	
BODY CAVITIES				
*ABDOMINAL CAVITY	(49)	(23)	(48)	(50)
STEATITIS				1 (2%)
*PLEURA	(49)	(23)	(48)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FOCAL			2	
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF				2
AUTO/NECROPSY/NO HISTO			1	
AUTOLYSIS/NO NECROPSY	1	2	2	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 1-NITRONAPHTHALENE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 1-NITRONAPHTHALENE

	HIGH DOSE CONTROL(UNTR) 05-0077	LOW DOSE CONTROL(UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	46	48	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	45	48	49	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(49)	(49)
FIBROSIS		1 (2%)		
ALOPECIA		1 (2%)		
HYPERKERATOSIS			1 (2%)	
ACANTHOSIS			1 (2%)	
*SUBCUT TISSUE	(46)	(48)	(49)	(49)
ABSCESS, NOS			1 (2%)	
NECROSIS, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(45)	(48)	(47)	(49)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, FOCAL		1 (2%)		
#LUNG	(45)	(48)	(47)	(49)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, INTERSTITIAL		14 (29%)		
ARTERIOSCLEROSIS, NOS	1 (2%)			
HYPERPLASIA, EPITHELIAL		2 (4%)		
#LUNG/ALVEOLI	(45)	(48)	(47)	(49)
INFLAMMATION, FOCAL		2 (4%)		
FIBROSIS, FOCAL		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(45)	(47)	(45)	(46)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	1 (2%)
#SPLEEN	(45)	(47)	(47)	(47)
CONGESTION, NOS			1 (2%)	

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
INFLAMMATION, NOS		1 (2%)		
FIBROSIS	1 (2%)			
HYPERPLASIA, NOS		2 (4%)		
HYPERPLASIA, HEMATOPOIETIC		2 (4%)		
HYPERPLASIA, ERYTHROID		2 (4%)		
HYPERPLASIA, RETICULUM CELL	3 (7%)			
HYPERPLASIA, LYMPHOID		2 (4%)		
HEMATOPOIESIS	1 (2%)		2 (4%)	1 (2%)
ERYTHROPOIESIS				1 (2%)
#LYMPH NODE	(35)	(44)	(37)	(47)
HEMORRHAGIC CYST		1 (2%)		
INFLAMMATION, NOS		13 (30%)		
DEGENERATION, CYSTIC		1 (2%)		
HYPERPLASIA, NOS		2 (5%)		
HYPERPLASIA, HEMATOPOIETIC		1 (2%)		
HYPERPLASIA, LYMPHOID		2 (5%)		
MYELOID METAPLASIA		2 (5%)		
#PAROTID LYMPH NODE	(35)	(44)	(37)	(47)
HYPERPLASIA, LYMPHOID				1 (2%)
#MEDIASTINAL L.NODE	(35)	(44)	(37)	(47)
NECROSIS, NOS		1 (2%)		
#PANCREATIC L.NODE	(35)	(44)	(37)	(47)
INFLAMMATION, NOS		1 (2%)		
HYPERPLASIA, NOS				1 (2%)
#LUMBAR LYMPH NODE	(35)	(44)	(37)	(47)
HYPERPLASIA, PLASMA CELL				1 (2%)
#MESENTERIC L. NODE	(35)	(44)	(37)	(47)
HEMORRHAGE		1 (2%)		
INFLAMMATION, NOS		9 (20%)		
HYPERPLASIA, NOS			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	2 (4%)
#THYMUS	(19)	(34)	(32)	(34)
NECROSIS, NOS		1 (3%)		
CIRCULATORY SYSTEM				
#HEART/VENTRICLE	(44)	(48)	(48)	(49)
MELANIN		2 (4%)		

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
#MYOCARDIUM	(44)	(48)	(48)	(49)
INFLAMMATION, INTERSTITIAL		2 (4%)		
FIBROSIS		5 (10%)		
*BLOOD VESSEL	(46)	(48)	(49)	(49)
INFLAMMATION, NOS		2 (4%)		
*PULMONARY ARTERY	(46)	(48)	(49)	(49)
MINERALIZATION		2 (4%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(43)	(47)	(46)	(48)
INFLAMMATION, NOS		2 (4%)		
PERIVASCULAR CUFFING		1 (2%)		
#LIVER	(45)	(48)	(49)	(49)
INFLAMMATION, FOCAL	2 (4%)			
DEGENERATION, NOS	1 (2%)			
NECROSIS, NOS			1 (2%)	
NECROSIS, FOCAL		13 (27%)		
METAMORPHOSIS FATTY	3 (7%)	3 (6%)		
BASOPHILIC CYTO CHANGE				1 (2%)
MEGALOCYTOSIS				1 (2%)
HYPERPLASIA, NODULAR		2 (4%)		
HYPERPLASTIC NODULE			2 (4%)	2 (4%)
HYPERPLASIA, FOCAL		1 (2%)		
ANGIECTASIS		1 (2%)		
MYELOID METAPLASIA		1 (2%)		
#LIVER/PERIPORTAL	(45)	(48)	(49)	(49)
INFLAMMATION, NOS	1 (2%)			
#LIVER/HEPATOCYTES	(45)	(48)	(49)	(49)
DEGENERATION, NOS		1 (2%)		
*GALLBLADDER	(46)	(48)	(49)	(49)
INFLAMMATION, FOCAL		1 (2%)		
*BILE DUCT	(46)	(48)	(49)	(49)
INFLAMMATION, NOS	1 (2%)			
#PANCREAS	(44)	(48)	(45)	(46)
CYSTIC DUCTS				1 (2%)

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
INFLAMMATION, NOS		7 (15%)		
INFLAMMATION, FOCAL		1 (2%)		
DEGENERATION, CYSTIC		1 (2%)		
METAMORPHOSIS FATTY		1 (2%)		
#PANCREATIC DUCT	(44)	(48)	(45)	(46)
HYPERPLASIA, NOS		1 (2%)		
#PANCREATIC ACINUS	(44)	(48)	(45)	(46)
ATROPHY, NOS				1 (2%)
HYPERTROPHY, FOCAL		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)		
#STOMACH	(42)	(47)	(48)	(48)
INFLAMMATION, NOS		13 (28%)		
ULCER, NOS		1 (2%)		
INFLAMMATION, FOCAL		1 (2%)		
INFLAMMATION, INTERSTITIAL		1 (2%)		
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)	
HYPERKERATOSIS		3 (6%)		
ACANTHOSIS		3 (6%)		
#GASTRIC MUCOSA	(42)	(47)	(48)	(48)
HYPERPLASIA, FOCAL		1 (2%)		
#PEYERS PATCH	(43)	(48)	(47)	(48)
HYPERPLASIA, NOS		2 (4%)		
#ILEUM	(43)	(48)	(47)	(48)
HEMORRHAGE		1 (2%)		
INFLAMMATION, NOS		2 (4%)		
#COLON	(38)	(45)	(47)	(47)
PARASITISM		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(45)	(47)	(48)	(49)
CALCULUS, NOS	20 (44%)			
HYDRONEPHROSIS			1 (2%)	
GLOMERULONEPHRITIS, NOS		6 (13%)		

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, INTERSTITIAL	5 (11%)	23 (49%)		
INFLAMMATION, CHRONIC	1 (2%)			
PERIVASCULITIS	2 (4%)			
ARTERIOSCLEROSIS, NOS	1 (2%)			
NEPHROSIS, NOS	1 (2%)			
GLOMERULOSCLEROSIS, NOS				1 (2%)
HYPERPLASIA, TUBULAR CELL	2 (4%)			
#KIDNEY/TUBULE	(45)	(47)	(48)	(49)
DEGENERATION, NOS	1 (2%)			
NECROSIS, FOCAL		1 (2%)		
METAMORPHOSIS FATTY	9 (20%)			
#URINARY BLADDER	(44)	(48)	(48)	(48)
INFLAMMATION, NOS		4 (8%)		
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	
HYPERPLASIA, EPITHELIAL		9 (19%)		
ENDOCRINE SYSTEM				
#PITUITARY	(36)	(42)	(34)	(40)
HYPERPLASIA, NOS		3 (7%)		
HYPERPLASIA, FOCAL		3 (7%)		
#ADRENAL CORTEX	(43)	(45)	(46)	(45)
NODULE		1 (2%)		
HYPERTROPHY, FOCAL		1 (2%)		
HYPERPLASIA, NOS		1 (2%)		
#ADRENAL MEDULLA	(43)	(45)	(46)	(45)
DEGENERATION, NOS		1 (2%)		
#THYROID	(40)	(47)	(38)	(43)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
HYPERPLASIA, FOCAL			1 (3%)	
HYPERPLASIA, PAPILLARY		1 (2%)		
HYPERPLASIA, C-CELL			1 (3%)	
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)		
#PANCREATIC ISLETS	(44)	(48)	(45)	(46)
HYPERPLASIA, NOS		2 (4%)		
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(46)	(48)	(49)	(49)
DILATATION/DUCTS				1 (2%)

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

TABLE D1 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
ABSCESS, NOS		2 (4%)		
#PROSTATE	(44)	(48)	(47)	(47)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	
#TESTIS/TUBULE	(45)	(47)	(48)	(47)
DEGENERATION, NOS	2 (4%)	4 (9%)		
*SCROTUM	(46)	(48)	(49)	(49)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	
NERVOUS SYSTEM				
#CEREBRAL CORTEX	(45)	(48)	(48)	(48)
MINERALIZATION		3 (6%)		
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(46)	(48)	(49)	(49)
STEATITIS	1 (2%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	8		22	20
ANIMAL MISSING/NO NECROPSY				1

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

TABLE D1 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 05-0077	LOW DOSE CONTROL (UNTR) 05-0037	LOW DOSE 05-0036	HIGH DOSE 05-0105
AUTO/NECROPSY/HISTO PERF			1	
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY	4	2	1	

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 1-NITRONAPHTHALENE

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	46	48	46	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	47	46	48
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(46)	(49)
INFLAMMATION ACUTE AND CHRONIC				1 (2%)
FIBROSIS	1 (2%)			
FIBROSIS, FOCAL	1 (2%)			
*SUBCUT TISSUE	(46)	(48)	(46)	(49)
MINERALIZATION		1 (2%)		
INFLAMMATION ACUTE AND CHRONIC				1 (2%)
FIBROSIS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(45)	(46)	(44)	(46)
INFLAMMATION, FOCAL		1 (2%)		
#LUNG	(45)	(46)	(44)	(46)
INFLAMMATION, INTERSTITIAL	2 (4%)	10 (22%)		
PERIARTERITIS	1 (2%)			
HYPERPLASIA, EPITHELIAL		3 (7%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(44)	(45)	(43)	(47)
MYELOFIBROSIS		1 (2%)		
#SPLEEN	(43)	(46)	(46)	(48)
HYPERPLASIA, HEMATOPOIETIC		16 (35%)		
HYPERPLASIA, ERYTHROID		6 (13%)		
HYPERPLASIA, RETICULUM CELL	2 (5%)			
HYPERPLASIA, LYMPHOID	4 (9%)	10 (22%)	2 (4%)	
HEMATOPOIESIS	1 (2%)	1 (2%)	2 (4%)	

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
ERYTHROPOIESIS			2 (4%)	2 (4%)
MYELOPOIESIS		1 (2%)		
#SPLENIC CAPSULE	(43)	(46)	(46)	(48)
ABSCESS, NOS			1 (2%)	
#LYMPH NODE	(41)	(39)	(30)	(36)
CYST, NOS		1 (3%)		
INFLAMMATION, NOS		15 (38%)		
HYPERPLASIA, NOS		1 (3%)		
RETICULOCYTOSIS		1 (3%)		
HYPERPLASIA, HEMATOPOIETIC		2 (5%)		
MYELOID METAPLASIA		1 (3%)		
#LUMBAR LYMPH NODE	(41)	(39)	(30)	(36)
HYPERPLASIA, PLASMA CELL				2 (6%)
HYPERPLASIA, LYMPHOID				1 (3%)
#THYMUS	(27)	(31)	(25)	(38)
ECTOPIA			1 (4%)	
CIRCULATORY SYSTEM				
#HEART/VENTRICLE	(45)	(46)	(43)	(47)
MELANIN		4 (9%)		
#MYOCARDIUM	(45)	(46)	(43)	(47)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
CALCIFICATION, FOCAL	1 (2%)			
*CORONARY ARTERY	(46)	(48)	(46)	(49)
INFLAMMATION, ACUTE				1 (2%)
*PULMONARY ARTERY	(46)	(48)	(46)	(49)
HYPERPLASIA, NOS	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(43)	(45)	(42)	(48)
INFLAMMATION, NOS		2 (4%)		
PERIVASCULAR CUFFING		4 (9%)		
#LIVER	(45)	(47)	(46)	(48)
INFLAMMATION, NOS		1 (2%)		

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, GRANULOMATOUS				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)	
NECROSIS, FOCAL		22 (47%)	1 (2%)	
CYTOPLASMIC CHANGE, NOS	1 (2%)			
MEGALOCYTOSIS			1 (2%)	
HYPERPLASTIC NODULE		1 (2%)		2 (4%)
HYPERPLASIA, FOCAL				1 (2%)
HYPERPLASIA, DIFFUSE	1 (2%)			
ANGIECTASIS		1 (2%)	1 (2%)	1 (2%)
HEMATOPOIESIS		3 (6%)		
#LIVER/PERIPORTAL	(45)	(47)	(46)	(48)
INFLAMMATION, NOS	1 (2%)			
*GALLBLADDER	(46)	(48)	(46)	(49)
INFLAMMATION, NOS		3 (6%)		
*BILE DUCT	(46)	(48)	(46)	(49)
INFLAMMATION, NOS	1 (2%)	1 (2%)		
INFLAMMATION, CHRONIC				1 (2%)
#PANCREAS	(41)	(44)	(43)	(47)
INFLAMMATION, NOS		5 (11%)		
INFLAMMATION, CHRONIC FOCAL				1 (2%)
PERIARTERITIS		1 (2%)		
METAMORPHOSIS FATTY			2 (5%)	
ATROPHY, FOCAL			1 (2%)	
#PANCREATIC DUCT	(41)	(44)	(43)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
#PANCREATIC ACINUS	(41)	(44)	(43)	(47)
ATROPHY, NOS			1 (2%)	
#STOMACH	(42)	(44)	(46)	(48)
INFLAMMATION, NOS		7 (16%)		
ULCER, NOS		1 (2%)		
INFLAMMATION, FOCAL		1 (2%)		
ULCER, FOCAL			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC			2 (4%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)	
HYPERPLASIA, NOS		1 (2%)		

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, ADENOMATOUS		1 (2%)		
HYPERKERATOSIS		1 (2%)		
ACANTHOSIS		1 (2%)		
#GASTRIC MUCOSA	(42)	(44)	(46)	(48)
ULCER, ACUTE				1 (2%)
HYPERPLASIA, FOCAL		1 (2%)		
#PEYERS PATCH	(43)	(44)	(46)	(48)
HYPERPLASIA, NOS		1 (2%)	1 (2%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(43)	(46)	(46)	(48)
GLOMERULONEPHRITIS, NOS		14 (30%)		
INFLAMMATION, INTERSTITIAL	3 (7%)	16 (35%)		
GLOMERULONEPHRITIS, CHRONIC				1 (2%)
PERIVASCULITIS	4 (9%)			
GLOMERULOSCLEROSIS, NOS			1 (2%)	
#KIDNEY/CORTEX	(43)	(46)	(46)	(48)
SCAR				1 (2%)
#KIDNEY/GLOMERULUS	(43)	(46)	(46)	(48)
AMYLOIDOSIS	1 (2%)			
#KIDNEY/PELVIS	(43)	(46)	(46)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#URINARY BLADDER	(41)	(46)	(46)	(47)
INFLAMMATION, NOS		4 (9%)		
HYPERPLASIA, EPITHELIAL		10 (22%)		
ENDOCRINE SYSTEM				
#PITUITARY	(37)	(42)	(37)	(44)
HYPERPLASIA, FOCAL		6 (14%)		
#ADRENAL CORTEX	(43)	(45)	(45)	(46)
NODULE		3 (7%)		
#THYROID	(30)	(43)	(31)	(43)
FOLLICULAR CYST, NOS		1 (2%)		

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

TABLE D2 (CONTINUED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
INFLAMMATION, NOS		1 (2%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(48)	(46)	(49)
GALACTOCELE		1 (2%)		
HYPERPLASIA, NOS		4 (8%)		
#UTERUS	(43)	(45)	(44)	(48)
HYDROMETRA	4 (9%)	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE			1 (2%)	
ABSCESS, NOS		3 (7%)		
FIBROSIS		1 (2%)		
#UTERUS/ENDOMETRIUM	(43)	(45)	(44)	(48)
CYST, NOS	2 (5%)			
INFLAMMATION, NOS		10 (22%)		1 (2%)
INFLAMMATION, SUPPURATIVE		4 (9%)	11 (25%)	6 (13%)
HYPERPLASIA, NOS	1 (2%)	4 (9%)		
HYPERPLASIA, CYSTIC	35 (81%)	18 (40%)	29 (66%)	33 (69%)
HYPERPLASIA, ADENOMATOUS		1 (2%)		
#OVARY/OVIDUCT	(43)	(45)	(44)	(48)
INFLAMMATION, NOS		5 (11%)		
#OVARY	(41)	(45)	(45)	(47)
CYST, NOS	1 (2%)	3 (7%)	4 (9%)	4 (9%)
HEMORRHAGIC CYST			1 (2%)	1 (2%)
INFLAMMATION, NOS		4 (9%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
INFLAMMATION, SUPPURATIVE		10 (22%)	6 (13%)	2 (4%)
ABSCESS, NOS		4 (9%)		
INFLAMMATION ACUTE AND CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC			3 (7%)	
FIBROSIS				1 (2%)
DEGENERATION, CYSTIC		1 (2%)		
CALCIFICATION, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(43)	(44)	(44)	(46)
PERIARTERITIS				1 (2%)

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

TABLE D2 (CONCLUDED)

	HIGH DOSE CONTROL (UNTR) 06-0077	LOW DOSE CONTROL (UNTR) 06-0037	LOW DOSE 06-0036	HIGH DOSE 06-0105
NECROSIS, FIBRINOID				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(46)	(48)	(46)	(49)
RESORPTION		3 (6%)		
*VERTEBRA	(46)	(48)	(46)	(49)
OSTEOSCLEROSIS	1 (2%)			
*SKELETAL MUSCLE	(46)	(48)	(46)	(49)
ABSCESS, NOS			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
CMENTUM				
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1	2	6
AUTO/NECROPSY/HISTO PERF	2	2		
AUTO/NECROPSY/NO HISTO		1		1
AUTOLYSIS/NO NECROPSY	4	2	4	1

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

Review of the Bioassay of 1-Nitronaphthalene* 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 1-Nitronaphthalene was reviewed.

After a brief description of the conditions of test, the primary reviewer said that the study appeared to be adequate for evaluative purposes. He agreed with the staff's conclusion that 1-Nitronaphthalene was not carcinogenic in treated rats or mice, under the conditions of test.

The secondary reviewer also agreed with the staff's conclusion that 1-Nitronaphthalene was not carcinogenic in either test species. He pointed out the chronic inflammation of the trachea found in the treated animals. He also noted that the major impurity in the 1-Nitronaphthalene was not identified. The secondary reviewer recommended that dietary concentrations be given in mg/kg body wt./day rather than in parts/million. In conclusion, he commented on the undesirable practice of housing more than one study in the same room at the same time.

It was moved that the report be accepted as written. The motion was seconded and approved unanimously.

Members Present Were:

Arnold Brown (Acting Chairman), Mayo Clinic
Lawrence Garfinkel, American Cancer Society
Joseph Highland, Environmental Defense Fund
Charles Kensler, Arthur D. Little Company
Verald K. Rowe, Dow Chemical, U.S.A.
Sheldon Samuels, Industrial Union Department, AFL-CIO
Louise Strong, University of Texas Health Sciences Center
Sidney Wolfe, Health Research Group

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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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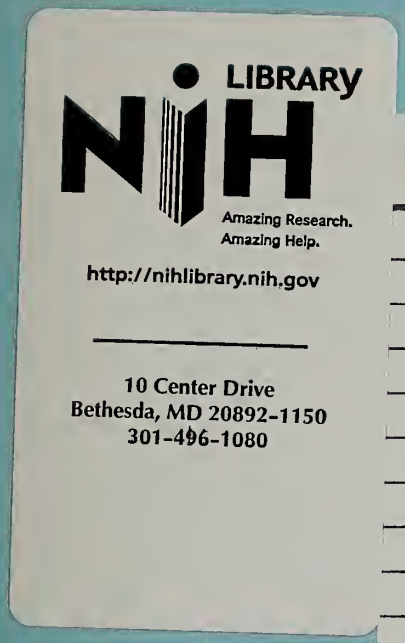

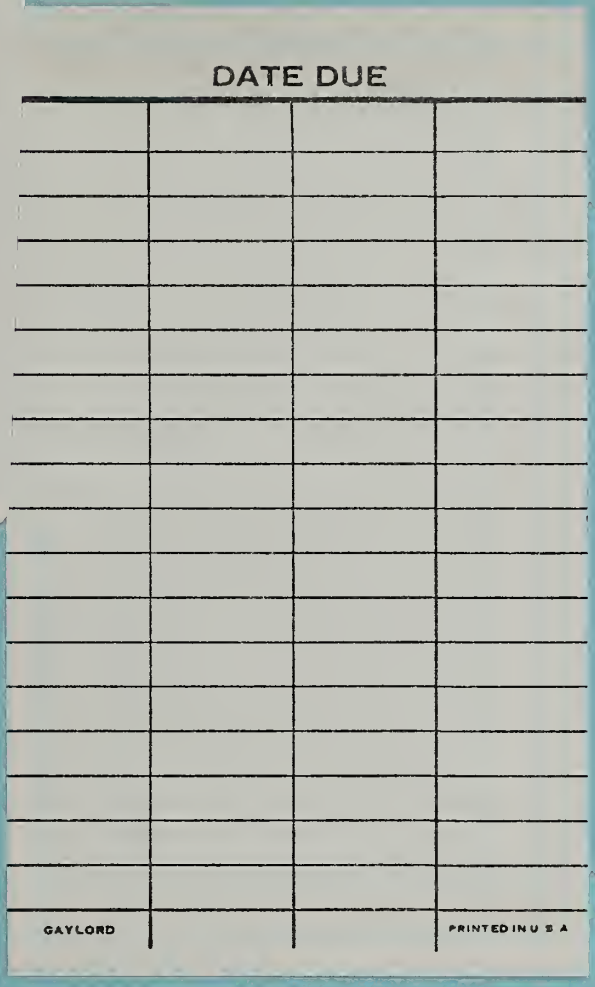

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