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

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REPORT ON THE BIOASSAY OF 6-NITROBENZIMIDAZOLE
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 6-nitrobenzimidazole conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of 6-nitrobenzimidazole 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. A. S. Krishna Murthy (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 (6,7), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (8).

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), task leader Dr. M. R. Kornreich (6,9), senior biologist Ms. P. Walker (6), biochemist Mr. S. C. Drill (6), chemist Dr. N. Zimmerman (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,9), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Mason Research Institute, 57 Union Street, Worcester, Massachusetts.

4. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

5. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

6. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

7. Now with the Solar Energy Research Institute, Cole Boulevard, Golden, Colorado.

8. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

9. Now with Clement Associates, Inc., 1010 Wisconsin Avenue, N.W., Washington, D.C.

10. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay for possible carcinogenicity of 6-nitrobenzimidazole was conducted using Fischer 344 rats and B6C3F1 mice. 6-Nitrobenzimidazole was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The dietary concentrations used in the chronic bioassay were 0.5 and 0.12 percent for the high and low dose rats, respectively, and 0.24 and 0.12 percent for the high and low dose mice, respectively. After a 78-week period of compound administration, observation of the rats continued for up to an additional 29 weeks and observation of the mice continued for an additional 18 weeks. For each species and each dosed group, 49 or 50 animals of each sex were placed on test as controls.

There were no significant positive associations between the administered dietary concentrations of 6-nitrobenzimidazole and mortality in either sex of rats or mice. In all groups adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors.

Among both male and female mice, the incidences of hepatocellular carcinomas in high dose groups were statistically significant relative to controls.

Among rats of both sexes, nonneoplastic lesions of the eyes and of the Harderian glands appeared to be associated with administration of 6-nitrobenzimidazole. No neoplasms, however, were attributed to compound administration.

Under the conditions of this bioassay, dietary administration of 6-nitrobenzimidazole was not carcinogenic to Fischer 344 rats; however, the compound was carcinogenic to B6C3F1 mice, causing hepatocellular carcinomas in both sexes.

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I. INTRODUCTION

6-Nitrobenzimidazole (Figure 1) (NCI No. C01912), a heterocyclic aromatic compound used in photographic developers, was selected for bioassay by the National Cancer Institute because of the suspect status of aromatic nitro- compounds.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 5-nitro-1H-benzimidazole.*

The sole commercial use of 6-nitrobenzimidazole appears to be as an antifogging agent in photographic developing solutions (Hawley, 1971; Kosar, 1965). This compound has been found to be effective against the intestinal nematode Nippostrongyliasis brasiliensis in mice (Denisova et al., 1975) but it does not appear to have been used commercially as an anthelmintic.

Specific production statistics for 6-nitrobenzimidazole are not available; however, the inclusion of this compound in the 1977 Directory of Chemical Producers, U.S.A. (Stanford Research Institute, 1977) implies that it is produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually).

The potential for exposure to 6-nitrobenzimidazole is greatest for workers in the chemical industry and for persons handling photographic chemicals containing this compound.

6-Nitrobenzimidazole is a local irritant but does not appear to penetrate the intact skin (Raleigh, 1977).

*The CAS registry number is 94-52-0.

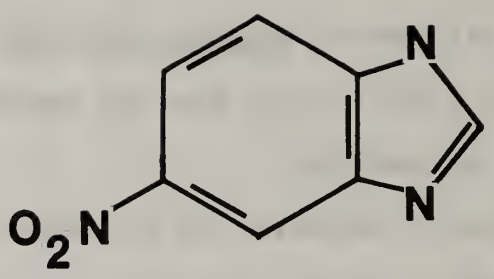


FIGURE 1
CHEMICAL STRUCTURE OF 6-NITROBENZIMIDAZOLE

II. MATERIALS AND METHODS

A. Chemicals

A commercially available grade of 6-nitrobenzimidazole was purchased from Carroll Products, Wood River Junction, Rhode Island. Melting point analysis was performed by Mason Research Institute, Worcester, Massachusetts. The experimentally determined melting point range of 205° to 208°C conformed favorably to the literature value of 209° to 210°C (Grasselli and Ritchey, 1975).

Throughout this report, the term 6-nitrobenzimidazole is used in referring to this compound.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois). 6-Nitrobenzimidazole was administered to the dosed animals as a component of the diet.

Proper amounts of the chemical were removed from the stock bottle under an exhaust hood. The compound was blended in an aluminum bowl with an aliquot of the feed. Once visual homogeneity was attained, the mixture was placed into a 6 kg capacity Patterson-Kelley twin-shell stainless-steel V-blender along with the remainder of the meal. The blender was sealed and operated for 20 minutes. The mixtures were placed in double plastic bags and stored in the dark at 4°C. Mixtures were prepared weekly, and the unused portion was discarded 2 weeks after formulation.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. High dose rats and their controls and all mice were received from Charles River Breeding Laboratories, Wilmington, Massachusetts. Low dose rats and their controls were obtained from Laboratory Supply Company, Indianapolis, Indiana. Dosed 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 test. Animals were assigned to groups and distributed among cages so that average body weight per cage was approximately equal for a given sex and species.

D. Animal Maintenance

All animals were housed by species in rooms maintained at 20° to 30°C. 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 13 months of study, all rats were kept in galvanized- or stainless-steel wire-mesh cages (Fenco Cage Products, Boston, Massachusetts) suspended above newspapers. 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 nonwoven fiber filter sheets. Clean bedding and cages were provided twice weekly. SAN-I-CEL® corncob bedding (Paxton Processing Company, Paxton, Illinois) was used for low dose rats and their controls for the first 7 and 8 months, respectively, that they were housed in polycarbonate cages. Aspen hardwood chip bedding (American Excelsior Company, Baltimore, Maryland) was used for the remainder of the study. Stainless steel cage racks were cleaned once every 2 weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate cages (Lab Products, Inc.). During quarantine and dosing periods, cages were fitted with perforated stainless steel lids. During the final observation period, stainless steel wire bar lids were used. Both types of lids were from Lab Products, Inc. Nonwoven fiber filter bonnets were used over cage lids. Low dose mice and their controls were housed ten per cage for the first 17 months of study and five per cage thereafter. The number of high dose and high dose control mice per cage was reduced to five after 12 and 10 months, respectively. 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. Ab-sorb-dri® hardwood chips (Wilner Wood Products Company, Norway, Maine) were used for the first 7 months for low dose mice and their

controls and for the first 2 months for high dose mice and their controls. SAN-I-CEL® was used during the next 12 months. A second source of corncob bedding (Bed-o-cobs®, The Andersons Cob Division, Maumee, Ohio) was used for the remainder of the study. Reusable filter bonnets and pipe cage racks were sanitized every 2 weeks throughout the study.

Water was available 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. Food and water were available ad libitum.

Pelleted Wayne Lab Blox® was supplied to low dose rats and their controls during quarantine and to all rats and mice during the final observation period. During the dosing period, all animals were supplied with Wayne Lab-Blox® meal containing the appropriate concentration of 6-nitrobenzimidazole. Control animals had untreated meal available. Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) containing stainless steel baffles were used to distribute powdered feed to mice and to low dose rats and their controls throughout the study. High dose rats and their controls were fed from Alpine® feed cups during quarantine and for the first 11 months of study. For the remainder of the study, these rats were fed from stainless steel gangstyle food hoppers (Scientific Cages, Inc., Bryan, Texas). During the final observation period, mice were fed pellets from wire bar hoppers incorporated into the

cage lids, and rats were fed pellets on the cage floor. Food hoppers were changed on the same schedule as were cages. Food was replenished daily in Alpine® feed cups.

All dosed rats and low dose control rats were housed in a room with other rats receiving diets containing* hydrazobenzene (530-50-7); 5-nitro-o-toluidine (99-55-8); 3-amino-9-ethylcarbazole hydrochloride; 2-aminoanthraquinone (117-79-3); 2,4-diaminoanisole sulfate (615-05-4); 1-nitronaphthalene (86-57-7); and APC (8003-03-0). High dose control rats were housed in a room with other rats receiving diets containing amitrole (61-82-5) and 3-nitro-p-acetophenetide (1777-84-0).

All dosed mice were housed in a room with other mice receiving diets containing 2,5-toluenediamine sulfate (6369-59-1); 1-nitronaphthalene (86-57-7); 5-nitro-o-toluidine (99-55-8); 5-nitro-o-anisidine (99-59-2); hydrazobenzene (530-50-7); 3-amino-9-ethylcarbazole hydrochloride; and 2,4-diaminoanisole sulfate (615-05-4). Control mice were housed in a room with other mice receiving diets containing 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); 5-nitroacenaphthene (602-87-9); 3-amino-9-ethylcarbazole hydrochloride; 1-amino-2-methylanthraquinone (82-28-0); 2,4-diaminoanisole sulfate (615-05-4); 5-nitro-o-anisidine (99-59-2); 4-nitroanthranilic acid (619-17-0);

*CAS registry numbers are given in parentheses.

1-nitronaphthalene (86-57-7); 3-nitro-p-acetophenetide (1777-84-0); amitrole (61-82-5); and APC (8003-03-0).

E. Selection of Initial Concentrations

In order to establish the high dose of 6-nitrobenzimidazole for administration to dosed 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. 6-Nitrobenzimidazole was incorporated into the basal laboratory diet and supplied ad libitum to three of the four groups of each species in concentrations of 0.08, 0.12, and 0.16 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 4 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet.

Two male rats receiving a dietary concentration of 0.08 percent died with chronic murine pneumonia. All other animals survived until the end of the study.

A dietary concentration of 0.08 percent produced mean weight depressions of 15.7 and 14 percent for male and female rats, respectively. A concentration of 0.12 percent produced mean weight depressions of 12 and 7.4 percent for male and female rats, respectively, while a level of 0.16 percent produced mean weight depressions of 5.0 and 4.1 percent for male and female rats, respectively.

Mean weight depressions in male and female mice, respectively, were 5.1 and 15.8 percent at a dietary concentration of 0.08 percent; 8.4 and 12.2 percent at a dietary concentration of 0.12 percent; and 3.2 and 16.4 percent at a dietary concentration of 0.16 percent.

The high concentration selected for administration to rats and mice in the chronic bioassay was 0.12 percent.

F. Experimental Design

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

Rats to receive a higher dietary concentration of 6-nitrobenzimidazole and all control rats were approximately 6 weeks old, while rats to receive a lower dietary concentration of 6-nitrobenzimidazole were approximately 7 weeks old at the time the test was initiated. The initial dietary concentrations of 6-nitrobenzimidazole were 0.12 and 0.06 percent. The rat group receiving a dietary concentration of 0.06 percent was sacrificed after 40 weeks and no histopathologic examinations were performed because the dose level was considered, on the basis of weight depression, to be too low. A new rat group, receiving 0.5 percent, and a corresponding control group, were started approximately 10 months after the initiation of the chronic study. The initial 0.12 percent group and its controls became the low dose and low dose control groups, respectively. Throughout this

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
6-NITROBENZIMIDAZOLE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	6-NITROBEN-ZIMIDAZOLE CONCENTRATION (PERCENT)	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	107
HIGH DOSE CONTROL	49	0	0	109
LOW DOSE	50	0.12 0	78	27
HIGH DOSE	50	0.50 0	78	29
FEMALE				
LOW DOSE CONTROL	50	0	0	108
HIGH DOSE CONTROL	50	0	0	110
LOW DOSE	50	0.12 0	78	27
HIGH DOSE	50	0.50 0	78	29

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
6-NITROBENZIMIDAZOLE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	6-NITROBENZIMIDAZOLE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
LOW DOSE CONTROL	50	0	0	96
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.12 0	78	18
HIGH DOSE	50	0.24 0	78	18
FEMALE				
LOW DOSE CONTROL	50	0	0	96
HIGH DOSE CONTROL	50	0	0	96
LOW DOSE	50	0.12 0	78	18
HIGH DOSE	50	0.24 0	78	18

report those rats receiving a dietary concentration of 0.50 percent are referred to as the high dose group and those receiving a concentration of 0.12 percent are referred to as the low dose group. Dosed rats were supplied with feed containing 6-nitrobenzimidazole for a total of 78 weeks. At the end of the period of compound administration, five males and five females from the high dose, high dose control, and low dose groups were sacrificed and necroposied according to protocol. The remaining rats were observed for up to an additional 29 weeks.

The dosed and control mice were all approximately 6 weeks old at the time they were placed on test. The initial dietary concentrations of 6-nitrobenzimidazole were 0.12 and 0.06 percent. The mouse groups receiving 0.06 percent were sacrificed after 6 months and no histopathologic examinations were performed because the dose level was considered, on the basis of weight depression, to be too low. New mouse groups, receiving 0.24 percent, and corresponding control groups, were started approximately 5 months after the initiation of the chronic study. Throughout this report those mice receiving a dietary concentration of 0.24 percent are referred to as the high dose groups and those receiving 0.12 percent are referred to as the low dose groups. Dosed rats were supplied with feed containing 6-nitrobenzimidazole for a total of 78 weeks. At the end of the period of compound administration, five males and five females from the high dose, high dose control, low dose, and low dose control

groups were sacrificed and necropsied, according to protocol. The remaining mice were observed for an additional 18-week period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment and body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. All animals were inspected twice daily. 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 killed at the end of the bioassay. The animals were euthanized by carbon dioxide inhalation, and were immediately necropsied. Gross and microscopic examinations were performed on all major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues 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.

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

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

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

lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was not used because, for both species, the high and low dose groups were started several months apart and were not considered to be directly comparable.

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

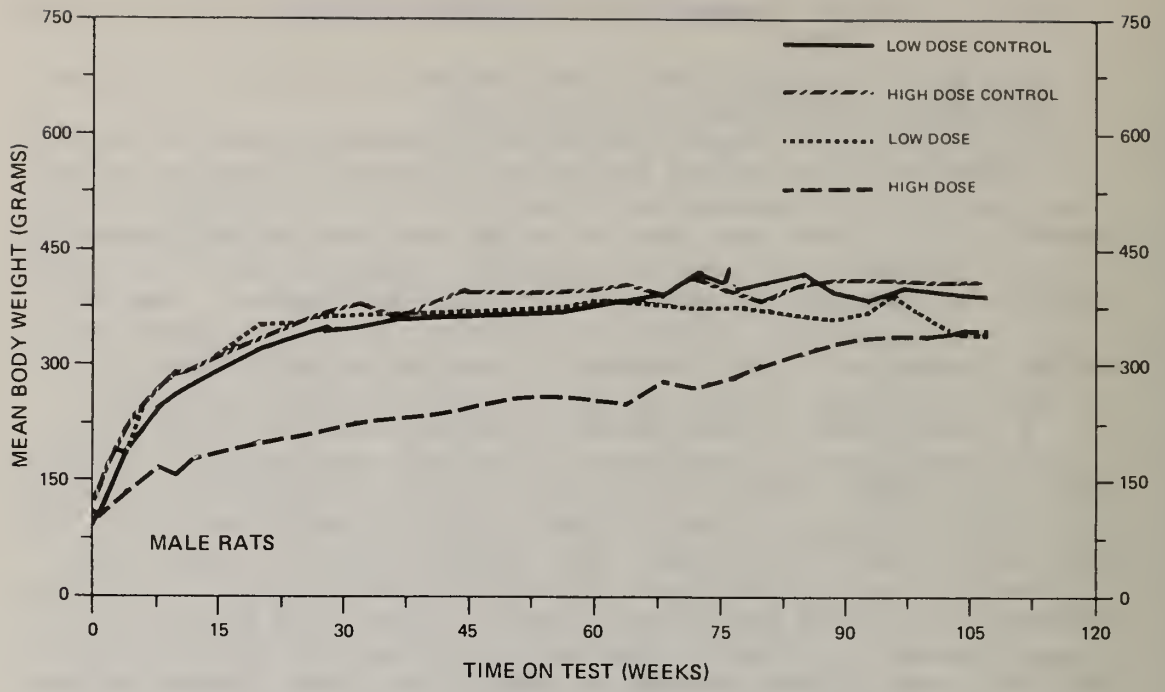
Marked mean body weight depression relative to controls was observed for high dose male rats and slight mean body weight depression relative to controls was observed for high dose females. Mean body weight depression was not apparent in low dose groups (Figure 2).

A dorsolateral crusted cutaneous lesion was reported in a low dose control male. Firm subcutaneous masses were reported in 2 high dose control males and 10 high dose control females. Alopecia was observed in one high dose control female. Eyes of 49 dosed rats of both sexes were either enlarged or opaque. No other clinical abnormalities were observed.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 6-nitrobenzimidazole-dosed groups are shown in Figure 3. For male and female rats the Cox tests did not indicate significant associations between dosage and mortality.

For males ten low dose control rats were sacrificed in week 29; additionally, five rats were sacrificed from each group in week 78. Adequate numbers of males were at risk from late-developing tumors as 68 percent (34/50) of the high dose, 82 percent (41/50) of the low dose, 61 percent (30/49) of the high dose control, and 54 percent (27/50) of the low dose control survived on test until the end of the study.



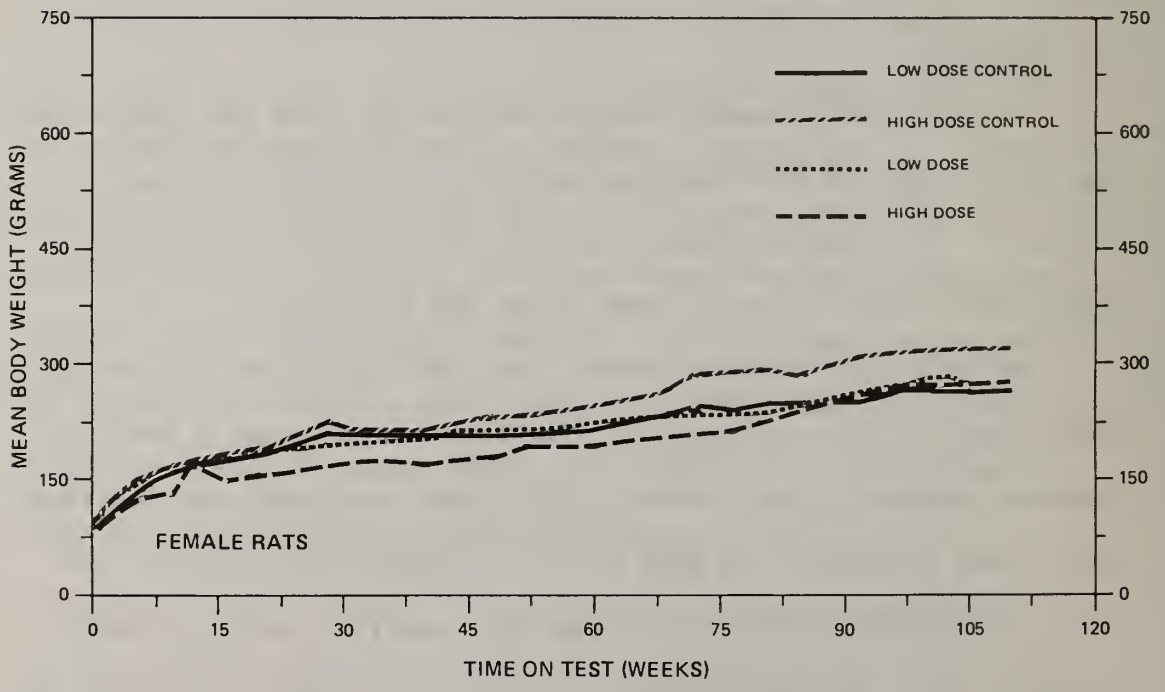
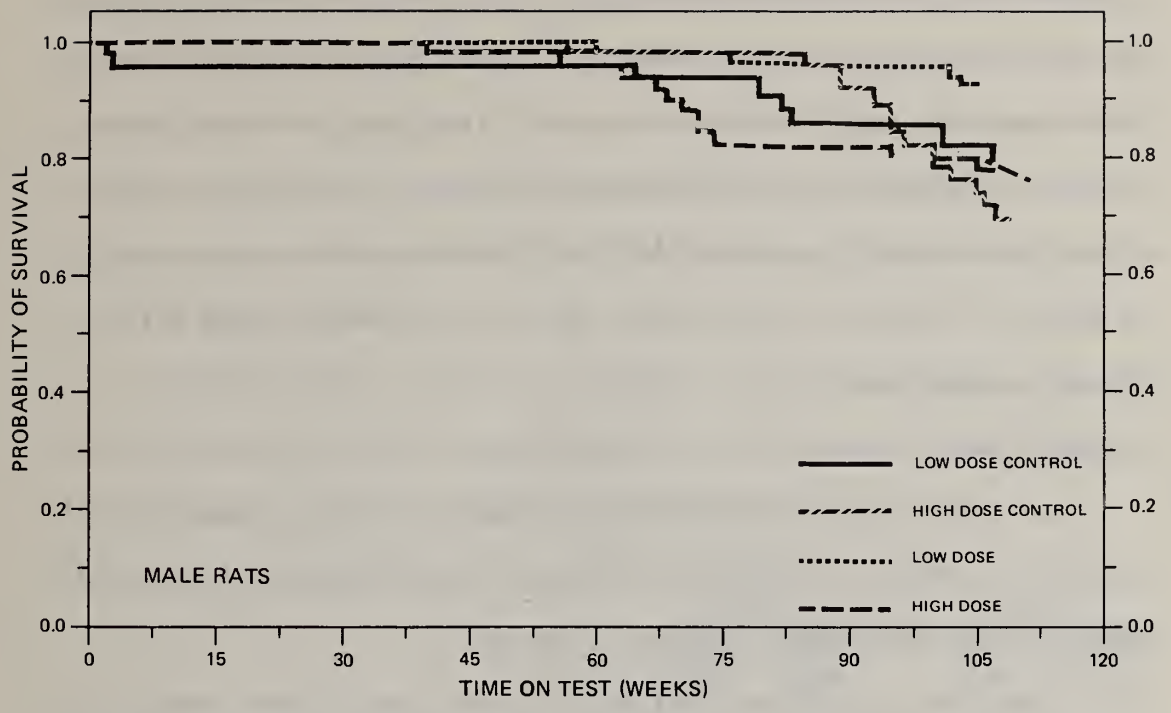


FIGURE 2
GROWTH CURVES FOR 6-NITROBENZIMIDAZOLE CHRONIC STUDY RATS



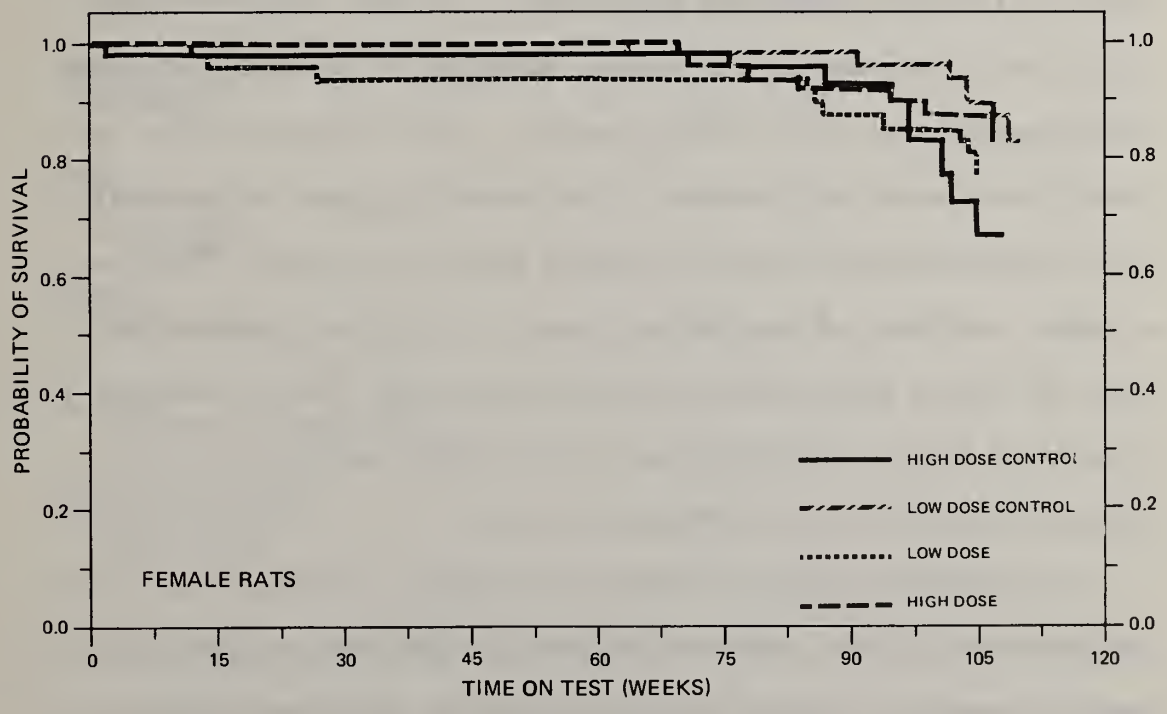


FIGURE 3
SURVIVAL COMPARISONS OF 6-NITROBENZIMIDAZOLE CHRONIC STUDY RATS

For females ten low dose control rats were sacrificed in week 29; additionally, five rats were sacrificed from each group in week 78. Adequate numbers of females were at risk from late-developing tumors, as 74 percent (37/50) of the high dose, 68 percent (34/50) of the low dose, 74 percent (37/50) of the high dose control, and 46 percent (23/50) of the low dose control survived on test until the end 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 was seen in both control and dosed rats. The most frequently observed neoplasms in the male rats were interstitial-cell adenomas of the testes, adenomas of the pituitary, and pheochromocytomas of the adrenal medulla. The neoplasms of the reproductive system and adenomas of the pituitary gland occurred with approximately equal frequency in dosed and control rats. There was a higher incidence of pheochromocytoma of the adrenal gland in both male and female dosed rats, but this neoplasm may not be compound-related because pheochromocytoma of the adrenal medulla frequently occurs in untreated, aged Fischer 344 rats.

The compound-related nonneoplastic changes involved the eye and the Harderian gland. Eyes of both control and dosed rats were examined at necropsy. Eyes of 49 dosed rats were either enlarged or

opaque and were, therefore, histologically evaluated. There appeared to be a dose-related increase in the incidence of retinal atrophy and cataract in the dosed rats. The eyes of control rats appeared normal at gross examination and were therefore not histologically evaluated. Inflammation and/or hyperplasia of the Harderian gland occurred only in a few high dose rats.

Retinal atrophy, cataract, and other associated changes, together with inflammation and/or hyperplasia of the Harderian gland occurring in these rats, are summarized in the following table.

	MALE		FEMALE	
	Low Dose	High Dose	Low Dose	High Dose
Number of Animals with Enlarged or Opaque Eyes	(3)	(23)	(2)	(21)
Retina				
Atrophy	3	21	1	18
Lens				
Cataract	2	13	2	14
Synechiae	0	7	0	7
Cornea				
Inflammation	0	6	0	2
Globe				
Intraocular Hemorrhage	0	4	0	2
Harderian Gland				
Inflammation	0	6	0	12
Hyperplasia	0	12	0	5

Retinal atrophy was more severe around the optic nerve than in the anterior portion. A few cells of the internal nuclear layer and

some ganglion cells persisted. Rods and cones were not recognizable. A fibrinous exudate and/or red blood cells were in the vitreous humor. Cataracts were found in eyes of all animals in which the lens was not lost during histologic processing. Lenticular changes varied from focal swelling to liquefaction. Mineral deposits were present in areas. The lens capsule was preserved except in advanced stages. The lens in some animals was the site of synechiae, probably due to iriditis. Inflammatory cells were present in the cornea of some animals. Red blood cells, inflammatory cells, and exudate were in the anterior chamber of some eyes. Canals of Schlemm, where recognizable, contained no inflammatory cells.

Clusters of mononuclear cells and/or pigment were found in Harderian glands of 18 high dose rats. Some of these glands were hyperplastic as evidenced by increased cellularity, basophilic cytoplasm, and occasional mitotic figures.

Although the lesions in the eyes and Harderian glands were only found in dosed rats and appeared dose-related, caution should be used in ascribing these effects to 6-nitrobenzimidazole because control rats were not examined microscopically for these lesions and because similar lesions occur sporadically in groups of untreated, aged Fischer 344 rats.

Based upon the findings of this pathology examination, the administration of 6-nitrobenzimidazole did not induce neoplastic

lesions in male or female Fischer 344 rats. This chemical, however, appeared to be toxic for the eyes.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or 6-nitrobenzimidazole-dosed groups and where such tumors were observed in at least 5 percent of the group.

For male rats the Fisher exact test indicated a significantly ($P = 0.012$) lower incidence of leukemia or malignant lymphoma in the high dose than in the high dose control. For female rats the high dose comparison had a probability level of $P = 0.028$ in the negative direction, a marginal result which was not significant under the Bonferroni criterion.

For females the Fisher exact test indicated a significantly ($P = 0.010$) lower incidence of pituitary adenomas in the high dose than in its control. For males the high dose comparison had a probability level of $P = 0.035$ in the negative direction, a marginal result which was not significant under the Bonferroni criterion.

The possibility of a negative association between dosage and incidence was noted in females for mammary fibroadenomas; the Fisher exact test indicated a significantly ($P < 0.001$) lower incidence in the high dose group than in the high dose control.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH 6-NITROBENZIMIDAZOLE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/46(0.00)	3/48(0.06)	1/48(0.02)	1/49(0.02)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite	0.327
Lower Limit	---	---	0.051	0.006
Upper Limit	---	---	Infinite	3.898
Weeks to First Observed Tumor	---	95	105	107
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/46(0.04)	6/48(0.13)	0/48(0.00)	0/49(0.00)
P Values[c]	---	---	---	P = 0.012(N)
Relative Risk (Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	3.236	0.612
Weeks to First Observed Tumor	79	93	---	---
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	12/41(0.29)	9/38(0.24)	8/44(0.18)	3/43(0.07)
P Values[c]	---	---	N.S.	P = 0.035(N)
Relative Risk (Control)[d]	---	---	0.621	0.295
Lower Limit	---	---	0.247	0.055
Upper Limit	---	---	1.479	1.082
Weeks to First Observed Tumor	101	85	105	107

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma[b]	6/43(0.14)	7/47(0.15)	9/47(0.19)	14/49(0.29)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.372	1.918
Lower Limit	---	---	0.478	0.801
Upper Limit	---	---	4.311	5.112
Weeks to First Observed Tumor	107	107	105	56
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	6/43(0.14)	8/47(0.17)	10/47(0.21)	14/49(0.29)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.525	1.679
Lower Limit	---	---	0.552	0.729
Upper Limit	---	---	4.687	4.183
Weeks to First Observed Tumor	107	107	60	56
Pancreatic Islets: Islet-Cell Adenoma[b]	2/42(0.05)	0/46(0.00)	3/47(0.06)	0/48(0.00)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.340	---
Lower Limit	---	---	0.162	---
Upper Limit	---	---	15.435	---
Weeks to First Observed Tumor	107	---	105	---

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	33/45(0.73)	42/47(0.89)	43/47(0.91)	10/48(0.21)
P Values[c]	---	---	P = 0.021	P < 0.001(N)
Relative Risk (Control)[d]	---	---	1.248	0.233
Lower Limit	---	---	1.008	0.154
Upper Limit	---	---	1.448	0.381
Weeks to First Observed Tumor	78	78	78	107

[a]Treated groups received doses of 0.12 or 0.5 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 its 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 on the relative risk of the treated group to the control group.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH 6-NITROBENZIMIDAZOLE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/49(0.08)	5/50(0.10)	0/48(0.00)	0/50(0.00)
P Values[c]	---	---	N.S.	P = 0.028(N)
Relative Risk (Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	1.100	0.793
Weeks to First Observed Tumor	101	104	---	---
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	18/43(0.42)	17/40(0.43)	21/45(0.47)	8/46(0.17)
P Values[c]	---	---	N.S.	P = 0.010(N)
Relative Risk (Control)[d]	---	---	1.115	0.409
Lower Limit	---	---	0.666	0.175
Upper Limit	---	---	1.881	0.885
Weeks to First Observed Tumor	76	78	78	107
Adrenal: Pheochromocytoma[b]	2/46(0.04)	3/49(0.06)	1/47(0.02)	8/49(0.16)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.489	2.667
Lower Limit	---	---	0.008	0.686
Upper Limit	---	---	9.071	14.798
Weeks to First Observed Tumor	108	109	105	95

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)	2/45(0.04)	3/45(0.07)	3/47(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	3.133	1.436
Lower Limit	---	---	0.263	0.173
Upper Limit	---	---	160.702	16.546
Weeks to First Observed Tumor	107	110	105	107
Mammary Gland: Fibroadenoma[b]	4/49(0.08)	19/50(0.38)	3/48(0.06)	1/50(0.02)
P Values[c]	---	---	N.S.	P < 0.001(N)
Relative Risk (Control)[d]	---	---	0.766	0.053
Lower Limit	---	---	0.118	0.001
Upper Limit	---	---	4.285	0.308
Weeks to First Observed Tumor	101	107	104	99
Uterus: Adenocarcinoma NOS[b]	4/48(0.08)	1/50(0.02)	0/46(0.00)	2/49(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	0.000	2.041
Lower Limit	---	---	0.000	0.110
Upper Limit	---	---	1.123	117.931
Weeks to First Observed Tumor	95	109	---	107

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	10/48(0.21)	10/50(0.20)	9/46(0.20)	3/49(0.06)
P Values[c]	---	---	N.S.	P = 0.039(N)
Relative Risk (Control)[d]	---	---	0.939	0.306
Lower Limit	---	---	0.372	0.057
Upper Limit	---	---	2.330	1.105
Weeks to First Observed Tumor	78	78	87	107

[a]Treated groups received doses of 0.12 or 0.5 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 its 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 on the relative risk of the treated group to the control group.

For males the Fisher exact tests indicated a significantly ($P = 0.021$) higher incidence of interstitial-cell tumors of the testes in the low dose group than in the low dose control, but that the high dose group had a significantly ($P < 0.001$) lower incidence than the high dose control. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, 251/334 (75 percent) of the untreated Fischer 344 males had one of these tumors--compared to the 33/45 (73 percent), 42/47 (89 percent), 43/47 (91 percent), and 10/48 (21 percent) observed in the low dose control, high dose control, low dose, and high dose groups, respectively, in this bioassay.

None of the other statistical tests for any site in rats of either sex was significant under the Bonferroni criterion. Based upon these statistical results there was no convincing evidence that 6-nitrobenzimidazole was a carcinogen in rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by 6-nitrobenzimidazole that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Significant mean body weight depression was observed only in the female high dose group when compared to the high dose controls after week 30 (Figure 4).

No clinical abnormalities were noted in mice of any group.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 6-nitrobenzimidazole-dosed groups are shown in Figure 5. For both male and female mice the Cox tests did not detect any significant association between dosage and mortality.

From each sex five high dose control mice were sacrificed in week 49, with five mice each from each of the high dose, high dose control, and low dose control groups sacrificed in week 78 or 79. Adequate numbers of males were at risk from late-developing tumors, as 86 percent (43/50) of the high dose, 94 percent (47/50) of the low dose, 78 percent (39/50) of the high dose control, and 86 percent (43/50) of the low dose control survived on test until the end of the study. Survival of the females was also adequate as 76 percent (38/50) of the high dose, 80 percent (40/50) of the low dose, 76 percent (38/50) of the high dose control, and 72 percent (36/50) of the low dose control survived on test until the end of the study.

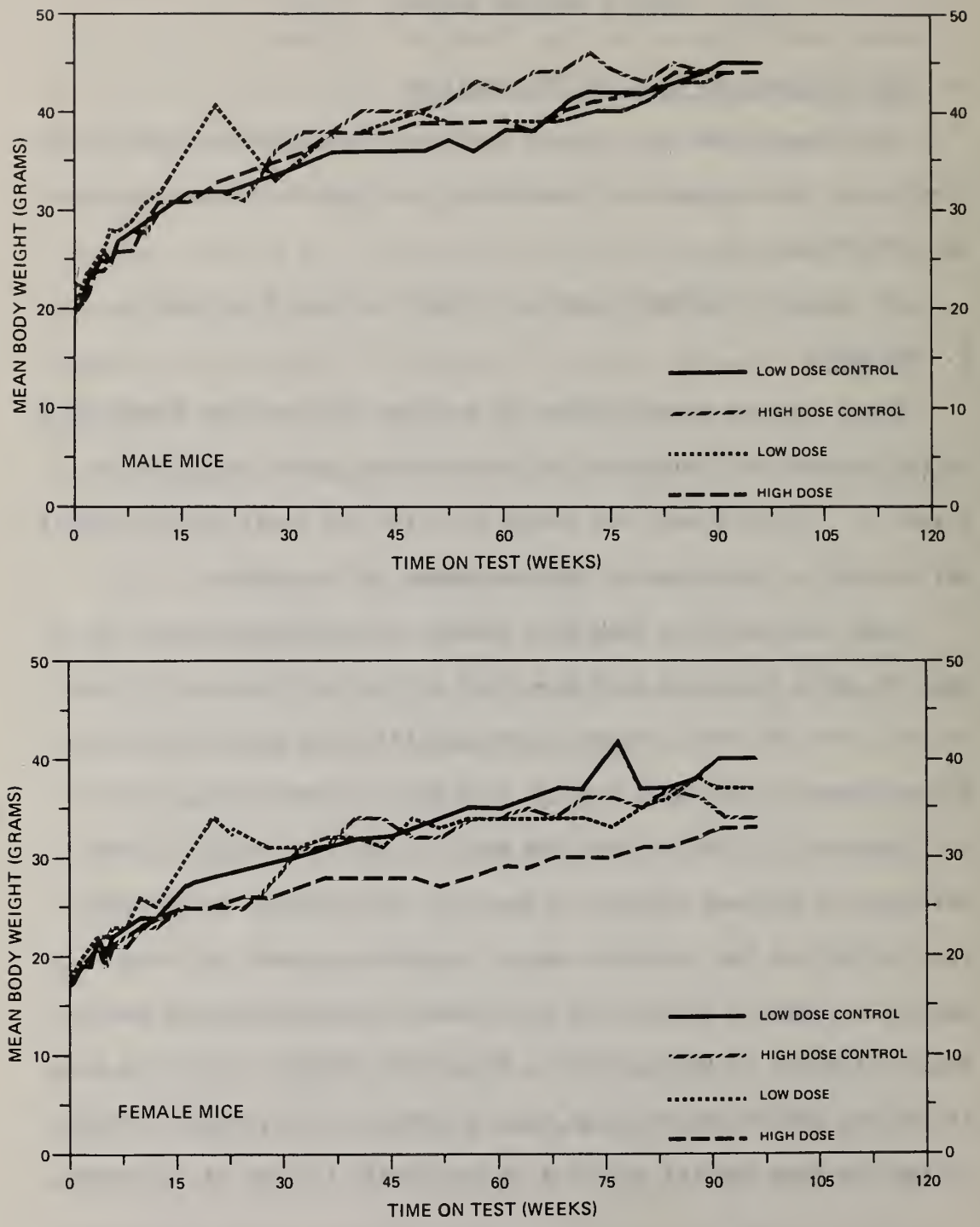


FIGURE 4
GROWTH CURVES FOR 6-NITROBENZIMIDAZOLE CHRONIC STUDY MICE

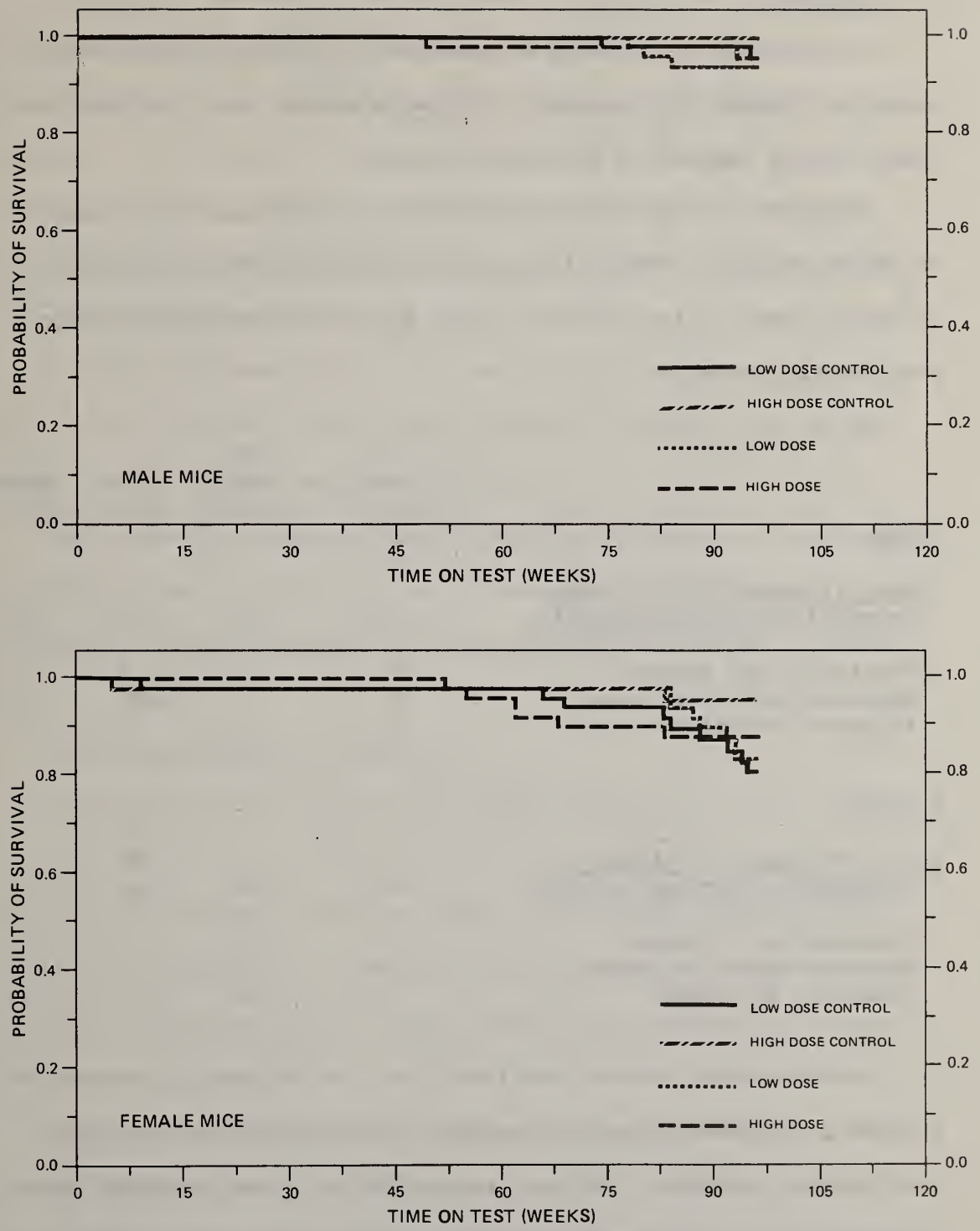


FIGURE 5
SURVIVAL COMPARISONS OF 6-NITROBENZIMIDAZOLE CHRONIC STUDY MICE

C. Pathology

Histopathologic findings of 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).

There was an increased incidence of hepatocellular carcinomas in the dosed mice. The following table summarizes the occurrence of these tumors in the different mouse groups and the number with pulmonary metastases:

	Low Dose Control	High Dose Control	Low Dose	High Dose
MALES				
Number of animals with livers examined histopathologically	(50)	(48)	(50)	(50)
Hepatocellular Adenoma	0	2	3	1
Hepatocellular Carcinoma	12	6	16	21
Pulmonary Metastases	1	1	1	3
FEMALES				
Number of animals with livers examined histopathologically	(47)	(50)	(44)	(47)
Hepatocellular Adenoma	0	0	2	9
Hepatocellular Carcinoma	2	1	2	11
Pulmonary Metastases	1	0	0	0

Hepatocellular adenoma involved a few lobules and in areas compressed the adjacent normal parenchyma. Hepatocytes were large with eosinophilic cytoplasm; in some, vacuolated cytoplasm suggested fatty metamorphosis. Nuclei were vesicular and there was an occasional

mitotic figure. Hepatocellular carcinoma involved a part or an entire lobe of the liver, and lobular architecture was distorted. A pleomorphism in the size of transformed hepatocytes was evident. Cytoplasm of the tumor cell was acidophilic or vacuolated. Nuclei were hyperchromatic, and some contained inclusion bodies. Mitotic figures were numerous. There were areas of necrosis and hemorrhage in some of the large tumors.

A variety of nonneoplastic lesions was observed with approximately equal frequency in both dosed and control mice. None of the lesions appeared to be compound-related.

Based upon the findings of this pathology examination, 6-nitrobenzimidazole was considered to be carcinogenic to B6C3F1 mice, causing an increased incidence of hepatocellular carcinomas in both males and females.

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 6-nitrobenzimidazole-dosed groups and where such tumors were observed in at least 5 percent of the group.

A high incidence of hepatocelluar carcinomas or hepatocellular adenomas was observed in the dosed groups of both male and female mice. For both males and females the Fisher exact test indicated a

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 6-NITROBENZIMIDAZOLE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	5/50(0.10)	5/49(0.10)	3/50(0.06)	0/50(0.00)
P Values[c]	---	---	N.S.	P = 0.027(N)
Relative Risk (Control)[d]	---	---	0.600	0.000
Lower Limit	---	---	0.098	0.000
Upper Limit	---	---	2.910	0.777
Weeks to First Observed Tumor	95	96	84	---
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	5/50(0.10)	10/49(0.20)	8/50(0.16)	4/50(0.08)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.600	0.392
Lower Limit	---	---	0.497	0.096
Upper Limit	---	---	5.808	1.258
Weeks to First Observed Tumor	95	96	84	96
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	5/50(0.10)	5/49(0.10)	6/50(0.12)	3/50(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.200	0.588
Lower Limit	---	---	0.326	0.096
Upper Limit	---	---	4.660	2.851
Weeks to First Observed Tumor	74	96	78	96

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	12/50(0.24)	6/48(0.13)	16/50(0.32)	21/50(0.42)
P Values[c]	---	---	N.S.	P = 0.001
Relative Risk (Control)[d]	---	---	1.333	3.360
Lower Limit	---	---	0.663	1.460
Upper Limit	---	---	2.754	9.189
Weeks to First Observed Tumor	95	78	80	79
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	12/50(0.24)	8/48(0.17)	19/50(0.38)	22/50(0.44)
P Values[c]	---	---	N.S.	P = 0.003
Relative Risk (Control)[d]	---	---	1.583	2.640
Lower Limit	---	---	0.823	1.272
Upper Limit	---	---	3.164	6.100
Weeks to First Observed Tumor	95	78	80	79

[a]Treated groups received doses of 0.12 or 0.24 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 its 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 on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 6-NITROBENZIMIDAZOLE[a]

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	2/46(0.04)	3/50(0.06)	4/43(0.09)	2/49(0.04)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	2.140	0.680
Lower Limit	---	---	0.324	0.059
Upper Limit	---	---	22.665	5.680
Weeks to First Observed Tumor	96	78	96	96
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	7/48(0.15)	2/50(0.04)	7/44(0.16)	3/49(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	1.091	1.531
Lower Limit	---	---	0.354	0.183
Upper Limit	---	---	3.347	17.671
Weeks to First Observed Tumor	83	96	93	83
Thyroid: Follicular-Cell Adenoma[b]	0/41(0.00)	0/44(0.00)	0/42(0.00)	2/33(0.06)
P Values[c]	---	---	N.S.	N.S.
Relative Risk (Control)[d]	---	---	---	Infinite
Lower Limit	---	---	---	0.396
Upper Limit	---	---	---	Infinite
Weeks to First Observed Tumor	---	---	---	95

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS or Chromophobe Adenoma[b]	5/43(0.12)	3/42(0.07)	12/39(0.31)	0/33(0.00)
P Values[c]	---	---	P = 0.031	N.S.
Relative Risk (Control)[d]	---	---	2.646	0.000
Lower Limit	---	---	0.963	0.000
Upper Limit	---	---	8.681	2.086
Weeks to First Observed Tumor	95	96	96	96
Liver: Hepatocellular Carcinoma[b]	2/47(0.04)	1/50(0.02)	2/44(0.05)	11/47(0.23)
P Values[c]	---	---	N.S.	P < 0.001
Relative Risk (Control)[d]	---	---	1.068	11.702
Lower Limit	---	---	0.080	1.812
Upper Limit	---	---	14.171	490.029
Weeks to First Observed Tumor	94	96	96	78
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	2/47(0.04)	1/50(0.02)	4/44(0.09)	20/47(0.43)
P Values[c]	---	---	N.S.	P < 0.001
Relative Risk (Control)[d]	---	---	2.136	21.277
Lower Limit	---	---	0.323	3.667
Upper Limit	---	---	22.656	849.969
Weeks to First Observed Tumor	94	96	96	78

TABLE 6 (CONCLUDED)

[a]Treated groups received doses of 0.12 or 0.24 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 its 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 on the relative risk of the treated group to the control group.

significantly ($P \leq 0.001$) higher incidence of hepatocellular carcinomas in the high dose groups than in the high dose controls. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, it was found that 49/350 (14 percent) of the untreated male B6C3F1 mice and 13/350 (3.7 percent) of the untreated female B6C3F1 mice had heptocellular carcinomas. The incidences of these neoplasms in the high dose control mouse groups in this bioassay (i.e., 6/48 [13 percent] in males and 1/50 [2 percent] in females) closely parallel the historical control data. Based upon these results, the administration of 6-nitrobenzimidazole was associated with the increased incidence of hepatocellular carcinomas in both male and female mice.

No other statistical tests at any sites in either male or female mice (including the lung in males and the pituitary in females) were 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 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by 6-nitrobenzimidazole that could not be established under the conditions of this test.

V. DISCUSSION

There were no significant positive associations between the administered dietary concentrations of 6-nitrobenzimidazole and mortality in either sex of rats or mice. In all groups adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors.

Several deficiencies in the conduct of this set of experiments made interpretation difficult. The starting of high and low dose groups of rats and mice several months apart prevented direct evaluation of dose-related effects.

The greatly lower body weights in the high dose male rats suggests that the maximum tolerated dose may have been exceeded in this group. It is interesting that the lower body weights in this group were associated with lower incidences than expected for leukemia and testicular tumors. On the other hand, in female dosed rats where body weights were not affected, lower than expected incidences of pituitary and mammary tumors were observed.

No neoplasm occurred at a significantly higher incidence in dosed rats when compared with the appropriate control group, except interstitial-cell tumors of the testes in low dose males. The incidence of these neoplasms was within the range commonly seen in Fischer 344 rats.

The significance of the nonneoplastic ocular lesions in rats is not clear because the control rats were not adequately examined.

These lesions appear to be related to administration of 6-nitrobenzimidazole because grossly visible lesions were restricted to dosed rats, the incidences were high, and the incidences appeared to be dose-related. Because such lesions occur sporadically in groups of aged Fischer 344 rats, however, it is necessary that additional experiments be conducted to confirm these findings.

In mice, hepatocellular carcinomas occurred generally at greater incidences in the dosed groups than in their controls (i.e., 12/50, 16/50, 6/48, and 21/50 in the low dose control, low dose, high dose control and high dose males, respectively, and 2/47, 2/44, 1/50, and 11/47 in the low dose control, low dose, high dose control, and high dose females). For both male and female mice, the Fisher exact comparison of the high dose group to the high dose control group indicated that the incidences for the dosed group were significantly higher than those for the controls. In addition, comparison of the incidences of these neoplasms in the high dose control male and female mice in this bioassay with the historical control data for hepatocellular carcinomas in untreated male and female B6C3F1 mice indicates that the incidences observed in the high dose controls in this bioassay closely approximated the historical incidence. No other neoplasms occurred in mice at increased incidences which were statistically significant under the Bonferroni criterion.

Under the conditions of this bioassay, dietary administration of 6-nitrobenzimidazole was not carcinogenic to Fischer 344 rats;

however, the compound was carcinogenic to B6C3F1 mice, causing hepatocellular carcinomas in both sexes.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 6-NITROBENZIMIDAZOLE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
ANIMALS INITIALLY IN STUDY	50	@50	50	50
ANIMALS NECROPSIED	46	48	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	48	48	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(46)	(48)	(48)	(49)
SARCOMA, NOS		1 (2%)		
FIBROMA		3 (6%)	1 (2%)	1 (2%)
FIBROSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(45)	(48)	(47)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
#LUNG	(46)	(48)	(48)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(46)	(48)	(48)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)		
LEUKEMIA,NOS		1 (2%)		
UNDIFFERENTIATED LEUKEMIA	1 (2%)			
MYELOMONOCYTIC LEUKEMIA		4 (8%)		
MONOCYTIC LEUKEMIA	1 (2%)			
#LYMPH NODE	(38)	(44)	(37)	(45)
ADENOCARCINOMA, NOS, METASTATIC	1 (3%)			
CIRCULATORY SYSTEM				
NONE				

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** EXCLUDES PARTIALLY AUTOLYZED ANIMALS
@ 50 ANIMALS WERE INITIALLY IN THE STUDY, BUT ONE ANIMAL WAS FOUND TO BE A FEMALE IN A MALE GROUP.

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(38)	(47)	(36)	(49)
ADENOCARCINOMA, NOS		1 (2%)		
SARCOMA, NOS		1 (2%)		
#LIVER	(46)	(48)	(48)	(49)
NEOPLASTIC NODULE				1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)		
#PANCREAS	(42)	(46)	(47)	(48)
ACINAR-CELL ADENOMA			1 (2%)	
#ILEUM	(43)	(46)	(47)	(49)
SARCOMA, NOS		1 (2%)		
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(38)	(44)	(43)
ADENOMA, NOS	2 (5%)	9 (24%)	3 (7%)	3 (7%)
CHROMOPHOBE ADENOMA	10 (24%)		5 (11%)	
#ADRENAL	(43)	(47)	(47)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
PHEOCHROMOCYTOMA	6 (14%)	7 (15%)	9 (19%)	14 (29%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	1 (2%)	
#THYROID	(45)	(48)	(38)	(45)
ADENOMA, NOS	1 (2%)			
ADENOCARCINOMA, NOS	2 (4%)			
FOLLICULAR-CELL ADENOMA				1 (2%)
C-CELL ADENOMA	1 (2%)		1 (3%)	
C-CELL CARCINOMA		1 (2%)		
#PARATHYROID	(32)	(28)	(20)	(22)
ADENOMA, NOS		1 (4%)		
#PANCREATIC ISLETS	(42)	(46)	(47)	(48)
ISLET-CELL ADENOMA	2 (5%)		3 (6%)	

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

TABLE A1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
REPRODUCTIVE SYSTEM				
#PROSTATE	(45)	(44)	(47)	(49)
PARAGANGLIOMA, NOS	1 (2%)			
#TESTIS	(45)	(47)	(47)	(48)
INTERSTITIAL-CELL TUMOR	33 (73%)	42 (89%)	43 (91%)	10 (21%)
NERVOUS SYSTEM				
#BRAIN	(44)	(48)	(47)	(49)
GLIOMA, NOS		1 (2%)		
ASTROCYTOMA	1 (2%)			1 (2%)
OLFACTORY NEUROBLASTOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*ZYMBAL'S GLAND	(46)	(48)	(48)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)	
SEBACEOUS ADENOCARCINOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(46)	(48)	(48)	(49)
MESOTHELIOMA, MALIGNANT		2 (4%)		
ALL OTHER SYSTEMS				
NONE				

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

TABLE A1 (CONCLUDED)

	LOW DOSE CONTROL(UNTR) 01-0037	HIGH DOSE CONTROL(UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	6	4	4
MORIBUND SACRIFICE	2	8		7
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	27	30	41	34
ANIMAL MISSING				
ANIMAL DELETED(WRONG SEX)		1		
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	44	45	25
TOTAL PRIMARY TUMORS	61	80	70	33
TOTAL ANIMALS WITH BENIGN TUMORS	33	43	44	23
TOTAL BENIGN TUMORS	55	62	67	30
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	17	3	2
TOTAL MALIGNANT TUMORS	5	18	3	2
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		
TOTAL SECONDARY TUMORS	4	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1			1
TOTAL UNCERTAIN TUMORS	1			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	50	48	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(48)	(50)
BASAL-CELL CARCINOMA		1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(48)	(50)
FIBROMA		1 (2%)		
FIBROSARCOMA		1 (2%)		
LEIOMYOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)		
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(48)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)			
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
MYELOMONOCYTIC LEUKEMIA		3 (6%)		
MONOCYTIC LEUKEMIA	2 (4%)			
#SPLEEN	(49)	(48)	(47)	(50)
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
#RENAL LYMPH NODE	(41)	(47)	(38)	(46)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
CIRCULATORY SYSTEM				
NONE				

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) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(47)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)			
HEPATOCELLULAR CARCINOMA	2 (4%)			
#ILEUM	(47)	(48)	(47)	(49)
LEIOMYOSARCOMA		1 (2%)		
URINARY SYSTEM				
#URINARY BLADDER	(41)	(46)	(47)	(48)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(40)	(45)	(46)
ADENOMA, NOS	3 (7%)	17 (43%)	1 (2%)	8 (17%)
ADENOCARCINOMA, NOS	2 (5%)			
CHROMOPHOBE ADENOMA	15 (35%)		20 (44%)	
#ADRENAL	(46)	(49)	(47)	(49)
CORTICAL ADENOMA		1 (2%)		
PHEOCHROMOCYTOMA	2 (4%)	3 (6%)	1 (2%)	8 (16%)
#ADRENAL MEDULLA	(46)	(49)	(47)	(49)
GANGLIONEUROMA		1 (2%)		
#THYROID	(47)	(45)	(45)	(47)
ADENOMA, NOS	1 (2%)			
ADENOCARCINOMA, NOS	2 (4%)			
FOLLICULAR-CELL CARCINOMA		1 (2%)		1 (2%)
C-CELL ADENOMA	1 (2%)	1 (2%)	1 (2%)	3 (6%)
C-CELL CARCINOMA		1 (2%)	2 (4%)	
#PANCREATIC ISLETS	(46)	(48)	(45)	(48)
ISLET-CELL ADENOMA		2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(48)	(50)
ADENOMA, 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) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)	
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (2%)			
FIBROADENOMA	4 (8%)	19 (38%)	3 (6%)	1 (2%)
*CLITORAL GLAND	(49)	(50)	(48)	(50)
CARCINOMA,NOS				1 (2%)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
ADENOMA, NOS		2 (4%)		
#UTERUS	(48)	(50)	(46)	(49)
ADENOCARCINOMA, NOS	4 (8%)	1 (2%)		2 (4%)
LEIOMYOSARCOMA			1 (2%)	
ENDOMETRIAL STROMAL POLYP	10 (21%)	10 (20%)	9 (20%)	3 (6%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	1 (2%)	
#OVARY	(47)	(49)	(47)	(49)
GRANULOSA-CELL TUMOR		1 (2%)		1 (2%)
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(47)	(50)
ASTROCYTOMA			1 (2%)	
OLIGODENDROGLIOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*EAR CANAL	(49)	(50)	(48)	(50)
FIBROMA	1 (2%)			
*ZYMBAL'S GLAND	(49)	(50)	(48)	(50)
SEBACEOUS ADENOCARCINOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*BODY CAVITIES	(49)	(50)	(48)	(50)
MESOTHELIOMA, MALIGNANT	1 (2%)			
ALL OTHER SYSTEMS				
SITE UNKNOWN				
SQUAMOUS CELL CARCINOMA		1		

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

TABLE A2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	5	5	4	4
MORIBUND SACRIFICE	7	3	7	4
SCHEDULED SACRIFICE	15	5	5	5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	23	37	34	37
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	38	31	26
TOTAL PRIMARY TUMORS	56	73	44	30
TOTAL ANIMALS WITH BENIGN TUMORS	27	35	28	21
TOTAL BENIGN TUMORS	39	59	36	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	12	8	5
TOTAL MALIGNANT TUMORS	17	13	8	5
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1		
TOTAL SECONDARY TUMORS	4	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1		1
TOTAL UNCERTAIN TUMORS		1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 6-NITROBENZIMIDAZOLE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	49	50	50
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA		5 (10%)	5 (10%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	5 (10%)	3 (6%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	3 (6%)	4 (8%)	2 (4%)
#SPLEEN	(50)	(49)	(50)	(49)
HEMANGIOMA				1 (2%)
HEMANGIOSARCOMA		1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#LYMPH NODE	(45)	(42)	(44)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	1 (2%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(50)	(48)	(50)	(50)
HEPATOCELLULAR ADENOMA		2 (4%)	3 (6%)	1 (2%)

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

TABLE B1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
HEPATOCELLULAR CARCINOMA	12 (24%)	6 (13%)	16 (32%)	21 (42%)
HEMANGIOMA	1 (2%)			
HEMANGIOSARCOMA, UNC PRIM OR MET		1 (2%)		
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#ADRENAL	(49)	(44)	(48)	(47)
PHEOCHROMOCYTOMA		1 (2%)		
#THYROID	(40)	(45)	(46)	(38)
ADENOCARCINOMA, NOS	1 (3%)			
FOLLICULAR-CELL ADENOMA			2 (4%)	1 (3%)
#PANCREATIC ISLETS	(46)	(47)	(48)	(49)
ISLET-CELL ADENOMA	1 (2%)			
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(49)	(50)	(50)
ADENOMA, NOS	1 (2%)			
PAPILLARY ADENOMA			2 (4%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				

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

TABLE B1 (CONCLUDED)

	LOW DOSE CONTROL(UNTR) 05-0070	HIGH DOSE CONTROL(UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(49)	(50)	(50)
NEUROFIBROSARCOMA	1 (2%)			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	2		1	1
MORIBUND SACRIFICE			2	1
SCHEDULED SACRIFICE	5	10		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	43	39	47	43
ANIMAL MISSING		1		
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	22	29	25
TOTAL PRIMARY TUMORS	27	26	37	31
TOTAL ANIMALS WITH BENIGN TUMORS	3	8	12	7
TOTAL BENIGN TUMORS	3	8	12	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	15	22	21
TOTAL MALIGNANT TUMORS	24	17	25	24
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1	3
TOTAL SECONDARY TUMORS	1	1	1	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		1		
TOTAL UNCERTAIN TUMORS		1		

* 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 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			2	1
ANIMALS NECROPSIED	48	50	44	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	44	49
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(46)	(50)	(43)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)			
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	4 (9%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)		
OSTEOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(50)	(44)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			4 (9%)	2 (4%)
LYMPHOCYTIC LEUKEMIA	1 (2%)			
ERYTHROCYTIC LEUKEMIA	1 (2%)			
#SPLEEN	(47)	(49)	(44)	(45)
HEMANGIOSARCOMA	1 (2%)			
MALIGNANT LYMPHOMA, NOS	1 (2%)			
#LYMPH NODE	(36)	(44)	(37)	(41)
MALIGNANT LYMPHOMA, NOS			1 (3%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)	1 (2%)
#MESENTERIC L. NODE	(36)	(44)	(37)	(41)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (3%)			
#PEYERS PATCH	(45)	(48)	(43)	(42)
MALIGNANT LYMPHOMA, NOS	1 (2%)			
CIRCULATORY SYSTEM				
NONE				

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

TABLE B2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
DIGESTIVE SYSTEM				
#LIVER	(47)	(50)	(44)	(47)
HEPATOCELLULAR ADENOMA			2 (5%)	9 (19%
HEPATOCELLULAR CARCINOMA	2 (4%)	1 (2%)	2 (5%)	11 (23%
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(42)	(39)	(33)
ADENOMA, NOS	5 (12%)	1 (2%)	12 (31%)	
CHROMOPHOBE ADENOMA		2 (5%)		
#ADRENAL	(47)	(48)	(44)	(40)
CORTICAL ADENOMA	1 (2%)			
#THYROID	(41)	(44)	(42)	(33)
FOLLICULAR-CELL ADENOMA				2 (6%)
REPRODUCTIVE SYSTEM				
#UTERUS	(43)	(47)	(43)	(45)
LEIOMYOMA	1 (2%)			
LEIOMYOSARCOMA				1 (2%)
HEMANGIOSARCOMA				1 (2%)
#UTERUS/ENDOMETRIUM	(43)	(47)	(43)	(45)
CARCINOMA, NOS			1 (2%)	
#OVARY/OVIDUCT	(43)	(47)	(43)	(45)
PAPILLARY ADENOMA	1 (2%)	1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(48)	(50)	(44)	(49)
ADENOMA, NOS	1 (2%)			1 (2%)

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

TABLE B2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
PAPILLARY ADENOMA		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
OMENTUM				
HEMANGIOSARCOMA	1			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	6	2	7	6
MORIBUND SACRIFICE	3		1	
SCHEDULED SACRIFICE	5	10		5
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	36	38	40	38
ANIMAL MISSING			2	1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	LOW DOSE CONTROL(UNTR) 06-0070	HIGH DOSE CONTROL(UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	18	10	22	25
TOTAL PRIMARY TUMORS	22	11	28	30
TOTAL ANIMALS WITH BENIGN TUMORS	8	7	16	11
TOTAL BENIGN TUMORS	9	7	18	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	4	9	15
TOTAL MALIGNANT TUMORS	13	4	10	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	2			
TOTAL SECONDARY TUMORS	2			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 6-NITROBENZIMIDAZOLE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
ANIMALS INITIALLY IN STUDY	50	@50	50	50
ANIMALS NECROPSIED	46	48	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	46	48	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(46)	(48)	(48)	(49)
EPIDERMAL INCLUSION CYST			1 (2%)	
EDEMA, NOS				1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
*SUBCUT TISSUE	(46)	(48)	(48)	(49)
NECROSIS, NOS				1 (2%)
METAPLASIA, OSSEOUS		1 (2%)		
RESPIRATORY SYSTEM				
*OLFACTORY GLAND	(46)	(48)	(48)	(49)
INFLAMMATION, NOS			1 (2%)	
#TRACHEA	(45)	(48)	(47)	(49)
INFLAMMATION, NOS	9 (20%)	2 (4%)	23 (49%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)	
INFLAMMATION, CHRONIC	10 (22%)			
#LUNG/BRONCHUS	(46)	(48)	(48)	(49)
BRONCHIECTASIS		1 (2%)	1 (2%)	3 (6%)
INFLAMMATION, NOS		7 (15%)		4 (8%)
INFLAMMATION, FOCAL				3 (6%)
INFLAMMATION, SUPPURATIVE				2 (4%)
INFLAMMATION, CHRONIC	8 (17%)			
HYPERPLASIA, EPITHELIAL				2 (4%)
POLYP			1 (2%)	
METAPLASIA, SQUAMOUS				1 (2%)
#BRONCHIAL MUCOUS GLA	(46)	(48)	(48)	(49)
ABSCESS, NOS	1 (2%)			

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
NECROSIS, NOS	1 (2%)			
HYPERPLASIA, ADENOMATOUS	1 (2%)			
#LUNG/BRONCHIOLE	(46)	(48)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	1 (2%)			
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, PAPILLARY				1 (2%)
#LUNG	(46)	(48)	(48)	(49)
ATELECTASIS	1 (2%)			
CONGESTION, NOS	1 (2%)			
EDEMA, NOS	1 (2%)			
HEMORRHAGE			1 (2%)	
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL	3 (7%)		7 (15%)	
INFLAMMATION, INTERSTITIAL	1 (2%)	4 (8%)		14 (29%)
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, NECROTIZING		1 (2%)		3 (6%)
ABSCESS, NOS				3 (6%)
PNEUMONIA, CHRONIC MURINE	1 (2%)	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)			
PERIVASCULITIS	5 (11%)			
HYPERPLASIA, EPITHELIAL		1 (2%)		
METAPLASIA, SQUAMOUS				1 (2%)
#LUNG/ALVEOLI	(46)	(48)	(48)	(49)
INFLAMMATION, NOS			2 (4%)	
INFLAMMATION, FOCAL			1 (2%)	
FIBROSIS, FOCAL			1 (2%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(46)	(48)	(48)	(48)
THROMBOSIS, NOS	1 (2%)			
FIBROSIS	1 (2%)	1 (2%)		
INFARCT, HEALED	1 (2%)			
HEMOSIDEROSIS		1 (2%)		25 (52%)
RETICULOCYTOSIS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC		9 (19%)	1 (2%)	10 (21%)
HYPERPLASIA, ERYTHROID	12 (26%)	10 (21%)	17 (35%)	9 (19%)
HYPERPLASIA, RETICULUM CELL	8 (17%)		4 (8%)	
HEMATOPOIESIS				6 (13%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
ERYTHROPOIESIS			7 (15%)	
MYELOPOIESIS			7 (15%)	
#SPLENIC CAPSULE	(46)	(48)	(48)	(48)
CYST, NOS				1 (2%)
#LYMPH NODE	(38)	(44)	(37)	(45)
HEMORRHAGE		1 (2%)		
INFLAMMATION, NOS	1 (3%)		3 (8%)	1 (2%)
HYPERPLASIA, NOS	1 (3%)		2 (5%)	3 (7%)
HISTIOCYTOSIS			1 (3%)	
RETICULOCYTOSIS				1 (2%)
LYMPHOCYTOSIS				1 (2%)
PLASMACYTOSIS		1 (2%)		4 (9%)
HYPERPLASIA, RETICULUM CELL	3 (8%)			
HYPERPLASIA, LYMPHOID		3 (7%)	2 (5%)	1 (2%)
#LYMPH NODE OF THORAX	(38)	(44)	(37)	(45)
EDEMA, NOS			1 (3%)	
DEGENERATION, NOS			1 (3%)	
PLASMACYTOSIS			1 (3%)	
#MEDIASTINAL L.NODE	(38)	(44)	(37)	(45)
PLASMACYTOSIS	1 (3%)			
HYPERPLASIA, RETICULUM CELL			1 (3%)	
CIRCULATORY SYSTEM				
*LYMPHATIC VESSELS	(46)	(48)	(48)	(49)
INFLAMMATION, NOS	1 (2%)			
#MYOCARDIUM	(46)	(48)	(48)	(49)
INFLAMMATION, NOS	1 (2%)		2 (4%)	
INFLAMMATION, INTERSTITIAL	22 (48%)	23 (48%)	31 (65%)	4 (8%)
INFLAMMATION, CHRONIC FOCAL	3 (7%)			
FIBROSIS	7 (15%)	12 (25%)	14 (29%)	29 (59%)
*ARTERY	(46)	(48)	(48)	(49)
INFLAMMATION, NOS			1 (2%)	
*AORTA	(46)	(48)	(48)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
*PULMONARY ARTERY	(46)	(48)	(48)	(49)
MINERALIZATION			4 (8%)	

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
HYPERTROPHY, NOS	1 (2%)			
*MESENTERIC ARTERY	(46)	(48)	(48)	(49)
ARTERIOSCLEROSIS, NOS			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(46)	(48)	(48)	(49)
FIBROSIS				1 (2%)
FIBROSIS SEPTAL LIVER		2 (4%)		
NECROSIS, FOCAL	3 (7%)	2 (4%)	2 (4%)	1 (2%)
NECROSIS, COAGULATIVE	1 (2%)			
METAMORPHOSIS FATTY	1 (2%)		6 (13%)	12 (24%)
HYPERPLASIA, FOCAL	23 (50%)	15 (31%)	4 (8%)	
ANGIECTASIS		1 (2%)		
#LIVER/CENTRILOBULAR	(46)	(48)	(48)	(49)
NECROSIS, NOS		1 (2%)		
#LIVER/PERIPORTAL	(46)	(48)	(48)	(49)
FIBROSIS	1 (2%)			
*BILE DUCT	(46)	(48)	(48)	(49)
INFLAMMATION, NOS	6 (13%)	3 (6%)	1 (2%)	
HYPERPLASIA, NOS	32 (70%)	43 (90%)	26 (54%)	27 (55%)
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(42)	(46)	(47)	(48)
INFLAMMATION, NOS	10 (24%)	17 (37%)	17 (36%)	8 (17%)
PERIARTERITIS				2 (4%)
DEGENERATION, CYSTIC			1 (2%)	1 (2%)
HYPERPLASIA, INTRADUCTAL	1 (2%)			
#PANCREATIC DUCT	(42)	(46)	(47)	(48)
HYPERPLASIA, NOS			6 (13%)	
#PANCREATIC ACINUS	(42)	(46)	(47)	(48)
ATROPHY, NOS	4 (10%)			
HYPERPLASIA, FOCAL		1 (2%)		
#ESOPHAGUS	(46)	(45)	(45)	(46)
DYSPLASIA, NOS		1 (2%)		
#STOMACH	(45)	(48)	(47)	(49)
EPIDERMAL INCLUSION CYST	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) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
INFLAMMATION, NOS		1 (2%)	1 (2%)	2 (4%)
ULCER, NOS	2 (4%)			
INFLAMMATION, FOCAL			2 (4%)	1 (2%)
HYPERPLASIA, NOS	6 (13%)			
HYPERPLASIA, EPITHELIAL			3 (6%)	
HYPERPLASIA, FOCAL			3 (6%)	1 (2%)
HYPERPLASIA, BASAL CELL		1 (2%)		
HYPERKERATOSIS	1 (2%)	2 (4%)	2 (4%)	2 (4%)
ACANTHOSIS	1 (2%)	2 (4%)	3 (6%)	4 (8%)
#PEYERS PATCH	(43)	(46)	(47)	(49)
HYPERPLASIA, NOS	7 (16%)	12 (26%)	4 (9%)	10 (20%)
#JEJUNUM	(43)	(46)	(47)	(49)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#ILEUM	(43)	(46)	(47)	(49)
INFLAMMATION, NOS		2 (4%)		
#COLON	(43)	(46)	(44)	(45)
NEMATODIASIS	3 (7%)			
PARASITISM		3 (7%)	4 (9%)	2 (4%)
URINARY SYSTEM				
#KIDNEY	(46)	(48)	(48)	(49)
GLOMERULONEPHRITIS, NOS	33 (72%)	47 (98%)	46 (96%)	46 (94%)
INFLAMMATION, INTERSTITIAL	1 (2%)			
ABSCESS, NOS				1 (2%)
FIBROSIS, DIFFUSE		6 (13%)		
HYPERPLASIA, EPITHELIAL				7 (14%)
#KIDNEY/MEDULLA	(46)	(48)	(48)	(49)
MINERALIZATION				5 (10%)
#URINARY BLADDER	(42)	(43)	(46)	(44)
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, EPITHELIAL	3 (7%)	1 (2%)	3 (7%)	
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(38)	(44)	(43)
HYPERPLASIA, NOS	3 (7%)	1 (3%)	2 (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) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
HYPERPLASIA, FOCAL		2 (5%)		15 (35%)
HYPERPLASIA, CHROMOPHOBE-CELL	2 (5%)		3 (7%)	
#ADRENAL CORTEX	(43)	(47)	(47)	(49)
HYPERTROPHY, FOCAL	1 (2%)		1 (2%)	
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL MEDULLA	(43)	(47)	(47)	(49)
NECROSIS, NOS	1 (2%)			
CALCIFICATION, NOS	1 (2%)			
HYPERPLASIA, NODULAR	1 (2%)	1 (2%)	1 (2%)	5 (10%)
HYPERPLASIA, NOS	6 (14%)		2 (4%)	
HYPERPLASIA, FOCAL		4 (9%)	2 (4%)	4 (8%)
#THYROID	(45)	(48)	(38)	(45)
FOLLICULAR CYST, NOS				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (3%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)			
HYPERPLASIA, C-CELL	1 (2%)	3 (6%)	1 (3%)	1 (2%)
#THYROID FOLLICLE	(45)	(48)	(38)	(45)
PIGMENTATION, NOS				4 (9%)
#PARATHYROID	(32)	(28)	(20)	(22)
HYPERPLASIA, NOS		1 (4%)		
HYPERPLASIA, FOCAL			1 (5%)	
#PANCREATIC ISLETS	(42)	(46)	(47)	(48)
HYPERPLASIA, NOS	2 (5%)	1 (2%)	6 (13%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(46)	(48)	(48)	(49)
GALACTOCELE		2 (4%)		
HYPERPLASIA, NOS	5 (11%)	4 (8%)	1 (2%)	2 (4%)
*PREPUTIAL GLAND	(46)	(48)	(48)	(49)
ABSCESS, NOS	1 (2%)			
HYPERPLASIA, NOS	1 (2%)			
#PROSTATE	(45)	(44)	(47)	(49)
INFLAMMATION, NOS	21 (47%)	17 (39%)	25 (53%)	25 (51%)

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

TABLE C1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 01-0037	HIGH DOSE CONTROL (UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
INFLAMMATION, FOCAL	3 (7%)			
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL	5 (11%)			
HYPERPLASIA, PAPILLARY	2 (4%)			
METAPLASIA, SQUAMOUS	5 (11%)		4 (9%)	
#TESTIS	(45)	(47)	(47)	(48)
MINERALIZATION		1 (2%)		1 (2%)
INFLAMMATION, NOS			1 (2%)	
PERIARTERITIS				1 (2%)
ATROPHY, NOS	2 (4%)	6 (13%)	19 (40%)	23 (48%)
ATROPHY, FOCAL				4 (8%)
ASPERMATOGENESIS	1 (2%)			
HYPERPLASIA, INTERSTITIAL CELL	19 (42%)	3 (6%)	26 (55%)	4 (8%)
#TESTIS/TUBULE	(45)	(47)	(47)	(48)
MINERALIZATION			15 (32%)	21 (44%)
DEGENERATION, NOS	6 (13%)		1 (2%)	
*EPIDIDYMIS	(46)	(48)	(48)	(49)
INFLAMMATION, NOS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(46)	(48)	(48)	(49)
MINERALIZATION				1 (2%)
HEMORRHAGE				3 (6%)
SYNECHIA, NOS				2 (4%)
SYNECHIA, POSTERIOR				5 (10%)
CATARACT			2 (4%)	13 (27%)
*EYE ANTERIOR CHAMBER	(46)	(48)	(48)	(49)
HEMORRHAGE				1 (2%)
*EYE/CORNEA	(46)	(48)	(48)	(49)
INFLAMMATION, NOS				3 (6%)
ULCER, NOS				1 (2%)
INFLAMMATION, ACUTE				1 (2%)

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

TABLE C1 (CONCLUDED)

	LOW DOSE CONTROL(UNTR) 01-0037	HIGH DOSE CONTROL(UNTR) 01-0118	LOW DOSE 01-0043	HIGH DOSE 01-0099
INFLAMMATION PROLIFERATIVE				2 (4%)
*EYE/RETINA	(46)	(48)	(48)	(49)
ATROPHY, NOS			3 (6%)	21 (43%
*HARDERIAN GLAND	(46)	(48)	(48)	(49)
INFLAMMATION, CHRONIC				6 (12%
NECROSIS, FOCAL				1 (2%)
HYPERPLASIA, NOS				10 (20%
HYPERPLASIA, DIFFUSE				2 (4%)
MUSCULOSKELETAL SYSTEM				
*CARTILAGE,NOS	(46)	(48)	(48)	(49)
CYST, NOS	1 (2%)			
BODY CAVITIES				
*PERITONEUM	(46)	(48)	(48)	(49)
INFLAMMATION, NOS				1 (2%)
*PLEURA	(46)	(48)	(48)	(49)
GRANULOMA, NOS				2 (4%)
*PERICARDIUM	(46)	(48)	(48)	(49)
INFLAMMATION, NECROTIZING				1 (2%)
INFLAMMATION WITH FIBROSIS				1 (2%)
ALL OTHER SYSTEMS				
OMENTUM				
NECROSIS, FAT		2		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED				1
AUTO/NECROPSY/HISTO PERF	1		1	
AUTOLYSIS/NO NECROPSY	4	1	2	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 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	49	50	48	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(48)	(50)
INFLAMMATION, NOS		1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(48)	(50)
MINERALIZATION		1 (2%)		
ABSCESS, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(48)	(49)	(48)	(49)
INFLAMMATION, NOS	9 (19%)		19 (40%)	
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC	10 (21%)		3 (6%)	
POLYP, INFLAMMATORY	1 (2%)			
#LUNG/BRONCHUS	(49)	(50)	(48)	(50)
BRONCHIECTASIS	1 (2%)		1 (2%)	2 (4%)
INFLAMMATION, NOS	1 (2%)	3 (6%)		6 (12%)
INFLAMMATION, FOCAL			1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	9 (18%)		1 (2%)	
#LUNG/BRONCHIOLE	(49)	(50)	(48)	(50)
INFLAMMATION, NOS	1 (2%)		1 (2%)	
HYPERPLASIA, NOS				2 (4%)
#LUNG	(49)	(50)	(48)	(50)
EDEMA, NOS			2 (4%)	
INFLAMMATION, NOS	1 (2%)			1 (2%)
INFLAMMATION, FOCAL	7 (14%)		6 (13%)	
INFLAMMATION, INTERSTITIAL	2 (4%)	6 (12%)	15 (31%)	7 (14%)
INFLAMMATION, NECROTIZING				1 (2%)

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) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
ABSCESS, NOS				2 (4%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
PNEUMONIA, CHRONIC MURINE			2 (4%)	
INFLAMMATION, GRANULOMATOUS				2 (4%)
PERIVASCULITIS	6 (12%)		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		2 (4%)
#LUNG/ALVEOLI	(49)	(50)	(48)	(50)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, FOCAL			1 (2%)	
FIBROSIS, FOCAL			4 (8%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(46)	(47)	(46)
OSTEOSCLEROSIS		1 (2%)		
#SPLEEN	(49)	(48)	(47)	(50)
INFLAMMATION, NOS			11 (23%)	
INFLAMMATION, ACUTE			1 (2%)	
HEMOSIDEROSIS		12 (25%)	1 (2%)	30 (60%)
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, HEMATOPOIETIC	3 (6%)	25 (52%)	10 (21%)	7 (14%)
HYPERPLASIA, ERYTHROID	17 (35%)	19 (40%)	16 (34%)	7 (14%)
HYPERPLASIA, PLASMA CELL	1 (2%)			
HYPERPLASIA, RETICULUM CELL	11 (22%)		6 (13%)	
HEMATOPOIESIS				30 (60%)
ERYTHROPOIESIS			12 (26%)	
MYELOPOIESIS			12 (26%)	
#SPLENIC CAPSULE	(49)	(48)	(47)	(50)
HEMORRHAGIC CYST		1 (2%)		
#LYMPH NODE	(41)	(47)	(38)	(46)
INFLAMMATION, NOS	3 (7%)		9 (24%)	
HYPERPLASIA, NOS	2 (5%)		1 (3%)	1 (2%)
RETICULOCYTOSIS				2 (4%)
LYMPHOCYTOSIS				2 (4%)
PLASMACYTOSIS	3 (7%)	1 (2%)	1 (3%)	
HYPERPLASIA, PLASMA CELL	1 (2%)			
HYPERPLASIA, LYMPHOID		4 (9%)	1 (3%)	
#PANCREATIC L.NODE	(41)	(47)	(38)	(46)
PLASMACYTOSIS			1 (3%)	

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL(UNTR) 02-0037	HIGH DOSE CONTROL(UNTR) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
HYPERPLASIA, LYMPHOID			1 (3%)	
#THYMUS	(42)	(34)	(40)	(31)
CYST, NOS				1 (3%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(49)	(50)	(47)	(50)
INFLAMMATION, NOS	1 (2%)	1 (2%)		
INFLAMMATION, INTERSTITIAL	24 (49%)	23 (46%)	30 (64%)	4 (8%)
FIBROSIS	5 (10%)	15 (30%)	17 (36%)	26 (52%
#ENDOCARDIUM	(49)	(50)	(47)	(50)
INFLAMMATION, NOS		1 (2%)		
*ARTERY	(49)	(50)	(48)	(50)
INFLAMMATION, NOS			2 (4%)	1 (2%)
*PULMONARY ARTERY	(49)	(50)	(48)	(50)
MINERALIZATION			4 (8%)	
*PORTAL VEIN	(49)	(50)	(48)	(50)
THROMBUS, MURAL	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(44)	(50)	(40)	(50)
INFLAMMATION, NOS				1 (2%)
#LIVER	(49)	(50)	(47)	(50)
FIBROSIS	1 (2%)			1 (2%)
PERIVASCULITIS	1 (2%)			
NECROSIS, FOCAL	4 (8%)	2 (4%)	7 (15%)	
NECROSIS, COAGULATIVE	2 (4%)			1 (2%)
METAMORPHOSIS FATTY	1 (2%)	6 (12%)	14 (30%)	1 (2%)
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASTIC NODULE				1 (2%)
HYPERPLASIA, FOCAL	22 (45%)	38 (76%)	16 (34%)	
ANGIECTASIS	1 (2%)		1 (2%)	1 (2%)
HYPERPLASIA, ERYTHROID		1 (2%)		
HEMATOPOIESIS		2 (4%)		
*BILE DUCT	(49)	(50)	(48)	(50)
INFLAMMATION, NOS	5 (10%)	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) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
HYPERPLASIA, NOS	27 (55%)	32 (64%)	22 (46%)	30 (60%)
HYPERPLASIA, FOCAL		1 (2%)		
#PANCREAS	(46)	(48)	(45)	(48)
INFLAMMATION, NOS	7 (15%)	6 (13%)	12 (27%)	13 (27%)
DEGENERATION, CYSTIC			1 (2%)	2 (4%)
#PANCREATIC DUCT	(46)	(48)	(45)	(48)
HYPERPLASIA, NOS	1 (2%)		1 (2%)	1 (2%)
#PANCREATIC ACINUS	(46)	(48)	(45)	(48)
MINERALIZATION			1 (2%)	
NECROSIS, FOCAL			1 (2%)	
ATROPHY, NOS	2 (4%)			
HYPERTROPHY, FOCAL				1 (2%)
#STOMACH	(48)	(48)	(47)	(50)
INFLAMMATION, NOS	2 (4%)	1 (2%)	2 (4%)	
INFLAMMATION, FOCAL	2 (4%)		1 (2%)	
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)	
HYPERPLASIA, FOCAL				1 (2%)
ACANTHOSIS		2 (4%)		2 (4%)
#GASTRIC MUCOSA	(48)	(48)	(47)	(50)
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
#PEYERS PATCH	(47)	(48)	(47)	(49)
HYPERPLASIA, NOS	6 (13%)	15 (31%)		12 (24%
#COLON	(43)	(46)	(44)	(43)
NEMATODIASIS	3 (7%)			
PARASITISM		2 (4%)	7 (16%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(47)	(50)
MINERALIZATION				2 (4%)
HYDRONEPHROSIS	1 (2%)			
GLOMERULONEPHRITIS, NOS	33 (67%)	43 (86%)	41 (87%)	45 (90%
INFLAMMATION, INTERSTITIAL	1 (2%)		2 (4%)	
GLOMERULONEPHRITIS, MEMBRANOUS	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) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
INFLAMMATION, CHRONIC	1 (2%)			
FIBROSIS, DIFFUSE		1 (2%)		
DEGENERATION, CYSTIC				1 (2%)
NECROSIS, FOCAL			1 (2%)	
CALCIFICATION, NOS			1 (2%)	
HYPERPLASIA, TUBULAR CELL				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
#URINARY BLADDER	(41)	(46)	(47)	(48)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	
HYPERPLASIA, EPITHELIAL			2 (4%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(40)	(45)	(46)
CYST, NOS				1 (2%)
PERIVASCULITIS		1 (3%)		
HYPERPLASIA, NOS	2 (5%)			
HYPERPLASIA, FOCAL		3 (8%)		1 (2%)
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)		1 (2%)	
#ADRENAL	(46)	(49)	(47)	(49)
METAMORPHOSIS FATTY		1 (2%)		
HYPERPLASIA, FOCAL				1 (2%)
#ADRENAL CORTEX	(46)	(49)	(47)	(49)
HEMORRHAGE				1 (2%)
NODULE	1 (2%)		1 (2%)	
HYPERTROPHY, NOS			1 (2%)	
HYPERTROPHY, FOCAL				2 (4%)
HYPERPLASIA, NODULAR			1 (2%)	
HYPERPLASIA, NOS	7 (15%)			
HYPERPLASIA, FOCAL			3 (6%)	1 (2%)
#ADRENAL MEDULLA	(46)	(49)	(47)	(49)
HYPERPLASIA, NODULAR		3 (6%)		3 (6%)
HYPERPLASIA, NOS	4 (9%)			
HYPERPLASIA, FOCAL		3 (6%)	2 (4%)	5 (10%)
#THYROID	(47)	(45)	(45)	(47)
CYSTIC FOLLICLES		1 (2%)		
FOLLICULAR CYST, NOS				2 (4%)

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

TABLE C2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
HYPERPLASIA, C-CELL		1 (2%)	5 (11%)	
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			
#PANCREATIC ISLETS	(46)	(48)	(45)	(48)
HYPERPLASIA, NOS	1 (2%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(48)	(50)
GALACTOCELE	5 (10%)	16 (32%)	3 (6%)	
HYPERPLASIA, NOS	17 (35%)	8 (16%)	6 (13%)	4 (8%)
HYPERPLASIA, PAPILLARY	1 (2%)			
#UTERUS	(48)	(50)	(46)	(49)
HYDROMETRA	3 (6%)		3 (7%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)			
PYOMETRA			1 (2%)	1 (2%)
ABSCESS, NOS	2 (4%)			1 (2%)
HYPERPLASIA, ADENOMATOUS	5 (10%)	1 (2%)	1 (2%)	
#UTERUS/ENDOMETRIUM	(48)	(50)	(46)	(49)
INFLAMMATION, NOS	14 (29%)	22 (44%)	15 (33%)	11 (22%)
INFLAMMATION, FOCAL	1 (2%)		2 (4%)	
INFLAMMATION, SUPPURATIVE	2 (4%)			
HYPERPLASIA, NOS	1 (2%)	6 (12%)	2 (4%)	4 (8%)
HYPERPLASIA, CYSTIC	2 (4%)		3 (7%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)	1 (2%)		
#OVARY/OVIDUCT	(48)	(50)	(46)	(49)
INFLAMMATION, NOS	1 (2%)	10 (20%)	5 (11%)	5 (10%
INFLAMMATION, SUPPURATIVE		2 (4%)		
ABSCESS, NOS			1 (2%)	1 (2%)
#OVARY	(47)	(49)	(47)	(49)
CYST, NOS	4 (9%)	8 (16%)	3 (6%)	4 (8%)
INFLAMMATION, NOS			2 (4%)	1 (2%)
ABSCESS, NOS				7 (14%
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			
DEGENERATION, NOS			1 (2%)	
DEGENERATION, CYSTIC				3 (6%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)			
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(47)	(50)
REACTION, FOREIGN BODY				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) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(48)	(50)
MINERALIZATION				1 (2%)
SYNECHIA, NOS				6 (12%
SYNECHIA, POSTERIOR				1 (2%)
CATARACT		1 (2%)	1 (2%)	14 (28%
*EYE POSTERIOR CHAMBER	(49)	(50)	(48)	(50)
HEMORRHAGE				2 (4%)
*EYE/CORNEA	(49)	(50)	(48)	(50)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
*EYE/RETINA	(49)	(50)	(48)	(50)
DEGENERATION, NOS			1 (2%)	
ATROPHY, NOS		1 (2%)	1 (2%)	18 (36%
*EYE/CRYSTALLINE LENS	(49)	(50)	(48)	(50)
CATARACT			1 (2%)	
*HARDERIAN GLAND	(49)	(50)	(48)	(50)
INFLAMMATION, CHRONIC				11 (22%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
DEGENERATION, NOS				2 (4%)
NECROSIS, FOCAL				1 (2%)
PIGMENTATION, NOS				1 (2%)
HYPERPLASIA, NOS		1 (2%)		5 (10%)
*EAR	(49)	(50)	(48)	(50)
HEMORRHAGE				1 (2%)
MUSCULOSKELETAL SYSTEM				
*BONE	(49)	(50)	(48)	(50)
RESORPTION			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
SITE UNKNOWN				
THROMBOSIS, NOS				1

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

TABLE C2 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 02-0037	HIGH DOSE CONTROL (UNTR) 02-0118	LOW DOSE 02-0043	HIGH DOSE 02-0099
HEMORRHAGE				1
OMENTUM				
NECROSIS, FAT		1		
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY	1		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 6-NITROBENZIMIDAZOLE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING		1		
ANIMALS NECROPSIED	50	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	49	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(49)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, FOCAL		3 (6%)		
INFLAMMATION, NECROTIZING		1 (2%)		
ABSCESS, NOS	2 (4%)			
INFLAMMATION, GRANULOMATOUS			1 (2%)	
ACARIASIS			3 (6%)	
*SUBCUT TISSUE	(50)	(49)	(50)	(50)
NECROSIS, FAT	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(50)	(49)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)		
#LUNG/BRONCHIOLE	(50)	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, FOCAL		1 (2%)		
PERIVASCULITIS	1 (2%)			
#LUNG	(50)	(49)	(50)	(50)
HEMORRHAGE	2 (4%)		1 (2%)	
INFLAMMATION, INTERSTITIAL		10 (20%)	7 (14%)	1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, ADENOMATOUS			1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(50)	(49)	(50)	(49)
PERIVASCULITIS			1 (2%)	

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
HYPERPLASIA, NOS		6 (12%)	7 (14%)	1 (2%)
RETICULOCYTOSIS		1 (2%)	1 (2%)	2 (4%)
LYMPHOCYTOSIS			1 (2%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC		5 (10%)	3 (6%)	2 (4%)
HYPERPLASIA, ERYTHROID			1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)		
#SPLENIC FOLLICLES	(50)	(49)	(50)	(49)
HYPERPLASIA, NOS	2 (4%)			
#HEMOLYMPH NODES	(50)	(49)	(50)	(49)
INFLAMMATION, NOS			2 (4%)	
#LYMPH NODE	(45)	(42)	(44)	(48)
INFLAMMATION, NOS		10 (24%)	9 (20%)	1 (2%)
PERIVASCULITIS			1 (2%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)	
RETICULOCYTOSIS		2 (5%)	4 (9%)	1 (2%)
LYMPHOCYTOSIS			4 (9%)	1 (2%)
PLASMACYTOSIS			1 (2%)	
HYPERPLASIA, HEMATOPOIETIC			2 (5%)	
HYPERPLASIA, PLASMA CELL			1 (2%)	
HYPERPLASIA, RETICULUM CELL				1 (2%)
HYPERPLASIA, LYMPHOID		3 (7%)	8 (18%)	2 (4%)
#MESENTERIC L. NODE	(45)	(42)	(44)	(48)
HYPERPLASIA, RETICULUM CELL	1 (2%)			
CIRCULATORY SYSTEM				
#HEART	(49)	(49)	(50)	(50)
MINERALIZATION		1 (2%)		
#HEART/VENTRICLE	(49)	(49)	(50)	(50)
MELANIN				6 (12%
#MYOCARDIUM	(49)	(49)	(50)	(50)
INFLAMMATION, FOCAL			1 (2%)	
#AORTIC VALVE	(49)	(49)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
*AORTA	(50)	(49)	(50)	(50)
INFLAMMATION, NOS			2 (4%)	

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(49)	(48)	(49)	(48)
PERIVASCULITIS	1 (2%)			
#LIVER	(50)	(48)	(50)	(50)
NECROSIS, FOCAL	1 (2%)	9 (19%)	4 (8%)	6 (12%)
NECROSIS, COAGULATIVE			1 (2%)	
METAMORPHOSIS FATTY	2 (4%)		1 (2%)	3 (6%)
HEPATOCYTOMEGALY	2 (4%)			
DEPLETION	1 (2%)			
HYPERPLASIA, NODULAR	2 (4%)			
HYPERPLASTIC NODULE		1 (2%)		
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL	1 (2%)			1 (2%)
HYPERPLASIA, DIFFUSE	1 (2%)			1 (2%)
HEMATOPOIESIS			1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(48)	(50)	(50)
NECROSIS, NOS	1 (2%)			
#LIVER/KUPFFER CELL	(50)	(48)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)			
*GALLBLADDER	(50)	(49)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
NECROSIS, NOS			1 (2%)	
#PANCREAS	(46)	(47)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, FOCAL	1 (2%)			
DEGENERATION, CYSTIC				2 (4%)
NECROSIS, NOS			1 (2%)	
#PANCREATIC ACINUS	(46)	(47)	(48)	(49)
DEGENERATION, NOS			1 (2%)	
METAMORPHOSIS FATTY			2 (4%)	
HYPERTROPHY, FOCAL			1 (2%)	
#STOMACH	(49)	(48)	(47)	(49)
INFLAMMATION, NOS			5 (11%)	2 (4%)
ULCER, NOS			1 (2%)	
INFLAMMATION, FOCAL		2 (4%)		

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
INFLAMMATION, NECROTIZING		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)		
HYPERKERATOSIS		1 (2%)	1 (2%)	
ACANTHOSIS		1 (2%)	1 (2%)	
#GASTRIC MUCOSA	(49)	(48)	(47)	(49)
INFLAMMATION, FOCAL	1 (2%)			
#PEYERS PATCH	(49)	(49)	(49)	(48)
HYPERPLASIA, NOS	1 (2%)	7 (14%)	5 (10%)	10 (21%
#COLON	(46)	(43)	(47)	(41)
GRANULOMA, NOS	1 (2%)			
PARASITISM		3 (7%)		
URINARY SYSTEM				
#KIDNEY	(49)	(49)	(50)	(50)
HYDRONEPHROSIS			1 (2%)	
GLOMERULONEPHRITIS, NOS		2 (4%)	4 (8%)	
INFLAMMATION, INTERSTITIAL	3 (6%)	16 (33%)	7 (14%)	7 (14%
#URINARY BLADDER	(47)	(48)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	4 (8%)	2 (4%)	
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(40)	(45)	(37)
HYPERPLASIA, FOCAL			1 (2%)	3 (8%)
#ADRENAL	(49)	(44)	(48)	(47)
HYPERPLASIA, NOS		3 (7%)		
#ADRENAL/CAPSULE	(49)	(44)	(48)	(47)
HYPERPLASIA, NOS		3 (7%)	4 (8%)	8 (17%
#ADRENAL CORTEX	(49)	(44)	(48)	(47)
HYPERTROPHY, FOCAL			2 (4%)	
#PARATHYROID	(26)	(24)	(21)	(19)
HYPERPLASIA, FOCAL				1 (5%)

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

TABLE D1 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
#PANCREATIC ISLETS	(46)	(47)	(48)	(49)
HYPERPLASIA, NOS			2 (4%)	
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(50)	(49)	(50)	(50)
ABSCESS, NOS		1 (2%)		
#TESTIS/TUBULE	(50)	(48)	(50)	(50)
MINERALIZATION			1 (2%)	
DEGENERATION, NOS			1 (2%)	
*EPIDIDYMIS	(50)	(49)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(50)	(49)	(50)	(50)
CATARACT				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION, ACUTE		1		
OMENTUM				
NECROSIS, NOS			1	

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

TABLE D1 (CONCLUDED)

	LOW DOSE CONTROL (UNTR) 05-0070	HIGH DOSE CONTROL (UNTR) 05-0118	LOW DOSE 05-0043	HIGH DOSE 05-0098
NECROSIS, FAT		1	1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	12	5	3	5
ANIMAL MISSING/NO NECROPSY		1		
AUTO/NECROPSY/HISTO PERF				1

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 6-NITROBENZIMIDAZOLE

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING			2	1
ANIMALS NECROPSIED	48	50	44	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	50	44	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(48)	(50)	(44)	(49)
ABSCESS, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(46)	(50)	(43)	(49)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, FOCAL		1 (2%)		
#LUNG/BRONCHIOLE	(46)	(50)	(43)	(49)
INFLAMMATION, NOS	1 (2%)			
HYPERPLASIA, NOS		1 (2%)		
#LUNG	(46)	(50)	(43)	(49)
HEMORRHAGE			1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)	14 (28%)	8 (19%)	1 (2%)
HYPERPLASIA, EPITHELIAL			2 (5%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(46)	(49)	(44)	(47)
MYELOFIBROSIS	1 (2%)			5 (11%)
#SPLEEN	(47)	(49)	(44)	(45)
HYPERPLASIA, NOS		9 (18%)	7 (16%)	
RETICULOCYTOSIS				1 (2%)
LYMPHOCYTOSIS				1 (2%)
HYPERPLASIA, HEMATOPOIETIC		6 (12%)	8 (18%)	
HYPERPLASIA, ERYTHROID			3 (7%)	
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)		

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL(UNTR) 06-0070	HIGH DOSE CONTROL(UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
#SPLENIC FOLLICLES	(47)	(49)	(44)	(45)
HYPERPLASIA, NOS	3 (6%)			
#HEMOLYMPH NODES	(47)	(49)	(44)	(45)
INFLAMMATION, NOS		2 (4%)		
HYPERPLASIA, NOS		1 (2%)		
#LYMPH NODE	(36)	(44)	(37)	(41)
INFLAMMATION, NOS	1 (3%)	9 (20%)		2 (5%)
AMYLOIDOSIS			1 (3%)	
HYPERPLASIA, NOS	1 (3%)	3 (7%)		
RETICULOCYTOSIS		1 (2%)		2 (5%)
LYMPHOCYTOSIS				2 (5%)
PLASMACYTOSIS			1 (3%)	
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	1 (3%)	
HYPERPLASIA, PLASMA CELL	1 (3%)			
HYPERPLASIA, LYMPHOID		4 (9%)		
#ABDOMINAL LYMPH NODE	(36)	(44)	(37)	(41)
PLASMACYTOSIS	1 (3%)			
CIRCULATORY SYSTEM				
#HEART/VENTRICLE	(44)	(50)	(44)	(49)
MELANIN				4 (8%)
#MYOCARDIUM	(44)	(50)	(44)	(49)
INFLAMMATION, FOCAL		1 (2%)		
FIBROSIS, FOCAL	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(45)	(48)	(42)	(46)
PERIVASCULITIS	3 (7%)			
PERIVASCULAR CUFFING	1 (2%)	3 (6%)		
#LIVER	(47)	(50)	(44)	(47)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
NECROSIS, FOCAL	2 (4%)	7 (14%)	10 (23%)	1 (2%)
NECROSIS, COAGULATIVE				1 (2%)

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	2 (4%)
HYPERPLASIA, DIFFUSE			1 (2%)	
HEMATOPOIESIS			5 (11%)	
*GALLBLADDER	(48)	(50)	(44)	(49)
INFLAMMATION, NOS			1 (2%)	
*BILE DUCT	(48)	(50)	(44)	(49)
INFLAMMATION, ACUTE/CHRONIC	4 (8%)			
#PANCREAS	(43)	(48)	(41)	(43)
INFLAMMATION, NOS	1 (2%)	2 (4%)	3 (7%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)			
PERIARTERITIS	1 (2%)			
#PANCREATIC ACINUS	(43)	(48)	(41)	(43)
ATROPHY, NOS	1 (2%)			
#STOMACH	(45)	(49)	(42)	(45)
INFLAMMATION, NOS		1 (2%)	1 (2%)	
INFLAMMATION, FOCAL		1 (2%)		
ULCER, FOCAL	1 (2%)			
HYPERPLASIA, NOS				1 (2%)
HYPERKERATOSIS			1 (2%)	
ACANTHOSIS		2 (4%)	1 (2%)	
#PEYERS PATCH	(45)	(48)	(43)	(42)
HYPERPLASIA, NOS	1 (2%)	7 (15%)	1 (2%)	3 (7%)
URINARY SYSTEM				
#KIDNEY	(45)	(50)	(44)	(47)
GLOMERULONEPHRITIS, NOS	3 (7%)	4 (8%)	9 (20%)	
GLOMERULONEPHRITIS, FOCAL	2 (4%)	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)	12 (24%)	7 (16%)	
GLOMERULONEPHRITIS, MEMBRANOUS	2 (4%)			
PYELONGPHRITIS, ACUTE/CHRONIC	1 (2%)			
GLOMERULONEPHRITIS, CHRONIC	1 (2%)			
GLOMERULOSCLEROSIS, NOS			1 (2%)	
AMYLOIDOSIS			1 (2%)	
#KIDNEY/TUBULE	(45)	(50)	(44)	(47)
MINERALIZATION		1 (2%)		

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
NECROSIS, FOCAL			1 (2%)	
#URINARY BLADDER	(45)	(48)	(42)	(44)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
PERIARTERITIS	1 (2%)			
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (5%)	
ENDOCRINE SYSTEM				
#PITUITARY	(43)	(42)	(39)	(33)
HYPERPLASIA, FOCAL				2 (6%)
#ADRENAL	(47)	(48)	(44)	(40)
NODULE				1 (3%)
AMYLOIDOSIS			1 (2%)	
HYPERPLASIA, HEMATOPOIETIC			1 (2%)	
#ADRENAL/CAPSULE	(47)	(48)	(44)	(40)
HYPERPLASIA, NOS		5 (10%)	5 (11%)	3 (8%)
#ADRENAL CORTEX	(47)	(48)	(44)	(40)
NODULE		1 (2%)	1 (2%)	
HYPERTROPHY, FOCAL				1 (3%)
HYPERPLASIA, NOS		1 (2%)		
#THYROID	(41)	(44)	(42)	(33)
INFLAMMATION, FOCAL		1 (2%)		
NECROSIS, FOCAL			1 (2%)	
HYPERPLASIA, PAPILLARY		2 (5%)		
HYPERPLASIA, ADENOMATOUS		1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)			
#PARATHYROID	(23)	(27)	(23)	(18)
AMYLOIDOSIS			1 (4%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(50)	(44)	(49)
GALACTOCELE			1 (2%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)	
#UTERUS	(43)	(47)	(43)	(45)
HYDROMETRA	3 (7%)	13 (28%)	6 (14%)	1 (2%)

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

TABLE D2 (CONTINUED)

	LOW DOSE CONTROL (UNTR) 06-0070	HIGH DOSE CONTROL (UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
ABSCESS, NOS	2 (5%)			
#UTERUS/ENDOMETRIUM	(43)	(47)	(43)	(45)
INFLAMMATION, NOS	2 (5%)	8 (17%)	5 (12%)	2 (4%)
INFLAMMATION, SUPPURATIVE	2 (5%)		2 (5%)	
INFLAMMATION, ACUTE	6 (14%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)			
ABSCESS, NOS				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	3 (7%)			
HYPERPLASIA, NOS	1 (2%)	8 (17%)	10 (23%)	5 (11%
HYPERPLASIA, CYSTIC	20 (47%)	6 (13%)	1 (2%)	6 (13%
METAPLASIA, SQUAMOUS	1 (2%)			
#OVARY/OVIDUCT	(43)	(47)	(43)	(45)
INFLAMMATION, NOS		4 (9%)	2 (5%)	
INFLAMMATION, SUPPURATIVE	4 (9%)		3 (7%)	
ABSCESS, NOS	1 (2%)	1 (2%)		
#OVARY	(45)	(48)	(43)	(42)
CYST, NOS		10 (21%)	2 (5%)	3 (7%)
INFLAMMATION, NOS		4 (8%)	2 (5%)	
INFLAMMATION, SUPPURATIVE	6 (13%)		3 (7%)	
INFLAMMATION, NECROTIZING			1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)			
ABSCESS, CHRONIC	1 (2%)			
PERIARTERITIS	1 (2%)	1 (2%)		
DEGENERATION, CYSTIC		3 (6%)	2 (5%)	2 (5%)
AMYLOIDOSIS			1 (2%)	
#OVARY/FOLLICLE	(45)	(48)	(43)	(42)
HEMORRHAGE			1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(46)	(48)	(43)	(46)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE D2 (CONCLUDED)

	LOW DOSE CONTROL(UNTR) 06-0070	HIGH DOSE CONTROL(UNTR) 06-0118	LOW DOSE 06-0043	HIGH DOSE 06-0098
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(48)	(50)	(44)	(49)
PERIVASCULITIS	1 (2%)			
OMENTUM				
MINERALIZATION			1	
NECROSIS, FAT			1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		3	2	4
ANIMAL MISSING/NO NECROPSY			2	1
AUTO/NECROPSY/HISTO PERF		1	1	4
AUTO/NECROPSY/NO HISTO	1			
AUTOLYSIS/NO NECROPSY	2		4	

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

Review of the Bioassay of 6-Nitrobenzimidazole* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

October 25, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 6-Nitrobenzimidazole for carcinogenicity.

The reviewer for the report on the bioassay of 6-Nitrobenzimidazole said that, under the conditions of test, the compound produced a statistically significant incidence of hepatocellular carcinomas in both sexes of treated mice. No significant incidences of neoplastic lesions were observed among treated rats. He noted, however, that occular changes, adrenal hyperplasia, and myocardial fibrosis were found in treated rats. After breifly describing the experimental design, the reviewer said that the study appeared to be adequate. Although the results of the bioassay by themself did not indicate that 6-Nitrobenzimidazole poses a significant human risk, the reviewer said that if the compound is shown to produce neoplasms in other species or is demonstrated to be mutagenic, its human risk should be reevaluated.

A Program staff pathologist noted that occular changes, adrenal hyperplasia, and myocardial fibrosis are relatively common findings in Fischer rats. Another Program staff pathologist added that cardiomyopathy increases in severity and incidence with age.

There was no objection to a recommendation that the report on the bioassay of 6-Nitrobenzimidazole be accepted as written.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Kenneth Wilcox, Michigan State Health Department

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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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