

National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 19
1979

**BIOASSAY OF
PROCARBAZINE
FOR POSSIBLE CARCINOGENICITY**

CAS No. 366-70-1

NCI-CG-TR-19

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



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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

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FOREWARD: This report presents the results of the bioassay of procarbazine conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected environmental chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of procarbazine was conducted by Southern Research Institute (1), Birmingham, Alabama, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design and doses were determined by Drs. D. P. Griswold (1), J. D. Prejean (1), E. K. Weisburger (2) and J. H. Weisburger (2,3). Ms. J. Belzer (1) and Mr. I. Brown (1) were responsible for the care of the laboratory animals and the administration of the test chemical. Data management and retrieval were performed by Ms. C. A. Dominick (1). Histopathologic examinations were performed by Drs. S. D. Kosanke (1) and J. C. Peckham (1), and the diagnoses included in this report represent their interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). Statistical analyses were performed by Dr. J. R. Joiner (5) and Ms. P. L. Yong (5), using methods selected for the bioassay program by Dr. J. J. Gart (6).

Chemicals used in this bioassay were analyzed under the direction of Mr. C. Hewitt (7), and Dr. P. Lim (8), and analytical results were reviewed by Dr. S. S. Olin (5).

This report was prepared at Tracor Jitco (5) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. G. L. Miller, Ms. L. A. Owen, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Dawn G. Goodman (9), Dr. Richard A. Griesemer, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire (10), and Dr. Jerrold M. Ward.

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SUMMARY

A bioassay of procarbazine for possible carcinogenicity was conducted by administering the test chemical by intraperitoneal injection to Sprague-Dawley rats and B6C3F1 mice.

Groups of 34 or 35 males and 35 or 36 females of both species were administered procarbazine at one of two doses, either 15 or 30 mg/kg for rats, and either 6 or 12 mg/kg for mice. Injections were made three times per week for 26 weeks for the rats and 52 weeks for the mice. Following the periods of injection, the dosed animals were observed for a maximum period of 60 weeks for rats and 33 weeks for mice, depending on survival. Vehicle controls, used for statistical evaluation, consisted of 10 rats and 15 mice of each sex, administered saline solution on the same schedule as the test solution; the same numbers of rats and mice served as untreated controls. Pooled controls consisted of the vehicle controls from this bioassay together with the vehicle controls from two other bioassays similarly performed at the same laboratory. The pooled-control groups consisted of 40 rats of each sex and 45 mice of each sex. Surviving rats were killed at 86 weeks and surviving mice were killed at 85 weeks.

Mean body weights of low- and high-dose rats and of high-dose female mice were lower than those of the vehicle controls. Survival rates of both rats and mice showed significant dose-related trends.

In rats, malignant lymphomas, adenocarcinomas of the mammary gland, and the combination of olfactory neuroblastomas, adenocarcinomas, or carcinomas of the brain, olfactory bulb, or cerebrum were induced in statistically significant numbers.

In mice, malignant lymphomas or leukemias, olfactory neuroblastomas or undifferentiated carcinomas, alveolar/bronchiolar adenomas, and adenocarcinomas of the uterus were induced in statistically significant numbers.

It is concluded that under the conditions of this bioassay, procarbazine was carcinogenic for both Sprague-Dawley rats and B6C3F1 mice, producing several types of tumors in both sexes of these two species.

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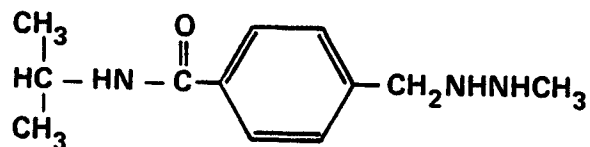
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I. INTRODUCTION



Procarbazine

Procarbazine (CAS 366-70-1; NCI C01810) is a methylhydrazine derivative which has been shown to have effective antineoplastic activity in advanced Hodgkin's disease and in oat-cell carcinoma of the lung (Oliverio, 1973; Carter and Slavik, 1974). It has also been shown to have carcinogenic activity in rats and mice (Kelly et al., 1968; Kelly et al., 1969). The mechanism of the cytotoxic action of this drug is not understood, although it is clear that it leads to the inhibition of protein, RNA, and DNA synthesis. Its oxidative metabolic products include formaldehyde, N-hydroxymethyl derivatives, and hydrogen peroxide, which are capable of carcinostatic effects, and azomethine, which has been shown to have carcinostatic and carcinogenic effects similar to those of procarbazine (Oliverio, 1973). Methylation of nucleic acids by the N-methyl group of procarbazine is also being

studied (Oliverio, 1973; Carter and Slavik, 1974). Procarbazine was selected for screening by the carcinogenesis bioassay program in an attempt to evaluate the carcinogenic effects of certain anticancer agents and other drugs which are used extensively and for prolonged periods in humans.

II. MATERIALS AND METHODS

A. Chemical

Procarbazine hydrochloride, which is the generic name for N-iso-propyl- α -(2-methylhydrazino)-p-toluamide hydrochloride, was purchased from Hoffman La Roche, Nutley, New Jersey, by the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute. Elemental analyses (C, H, N, Cl) of the single batch (Lot No. PP-9) gave a percentage composition equivalent to theoretical values. In paper chromatographic analysis, the sample showed two minor ultraviolet-absorbing impurities. No attempt was made to identify or quantitate these impurities. The infrared spectrum was comparable to spectra obtained from samples known to be pure. Nuclear magnetic resonance and ultraviolet spectra were as expected for procarbazine hydrochloride. The chemical was stored at -20°C .

B. Dosage Preparation

Concentrations of 0.60 and 1.2% (w/v) procarbazine for rats and 0.06 and 0.12% (w/v) for mice were prepared in buffered saline (pH 6.9) for intraperitoneal injection of the chemical. To

minimize decomposition of the drug, fresh solutions were prepared immediately before injection of the test animals.

C. Animals

Sprague-Dawley rats and B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts, through contracts with the Division of Cancer Treatment, National Cancer Institute. Upon arrival at the laboratory, the male rats were 28 days old, the females 35 days old, and the male and female mice 28 days old. All animals were housed within the test facility for 1 week. Animals with no clinical signs of disease were assigned to dosed or control groups and were earmarked for individual identification.

D. Animal Maintenance

All animals were housed in temperature-and humidity-controlled rooms. Air was maintained at 20 to 24^oC and 40 to 60% relative humidity. Fresh air was filtered through fiberglass roughing filters and was changed 15 times per hour. In addition to natural light, illumination was provided by fluorescent light for

9 hours per day. Wayne[®] Sterilizable Lab Blox (Allied Mills, Inc., Chicago, Ill.) and water were supplied daily and were available ad libitum.

Rats were housed five per cage and mice seven per cage in solid-bottom stainless steel cages (Hahn Roofing and Sheet Metal Co., Birmingham, Ala.). The bottoms of the rat cages were lined with Iso-Dri[®] hardwood chips (Carworth, Edison, N.J.), and cage tops were covered with disposable filter bonnets beginning at week 22; mouse cages were provided with Sterolit[®] clay bedding (Englehard Mineral and Chemical Co., New York, N.Y.). Bedding was replaced one time per week; cages, water bottles, and feeders were sanitized at 82°C one time per week; and racks were cleaned one time per week.

The rats and mice were housed in separate rooms. Dosed animals were housed in the same room as their respective control animals. Animals administered procarbazine were maintained in the same rooms as animals of the same species administered the following chemicals:

RATS

Feeding Studies

(CAS 136-40-3) 2,6-diamino-3-(phenylazo)pyridine hydrochloride

Gavage Studies

(CAS 3546-10-9) cholesterol (p-(bis(2-chloroethyl)amino)phenyl) acetate) (phenesterin)

(CAS 22966-79-6) estradiol bis((p-(bis(2-chloroethyl)amino)phenyl) acetate) (estradiol mustard)

Intraperitoneal Injection Studies

(CAS 3458-22-8) 3,3'-iminobis-1-propanol dimethanesulfonate (ester) hydrochloride (IPD)

(CAS 320-67-2) 5-azacytidine

(CAS 21416-87-5) (+)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione (ICRF-159)

(CAS 789-61-7) beta-2'-deoxy-6-thioguanosine (β -TGDR)

(CAS 55-98-1) 1,4-butanediol dimethanesulfonate (busulfon)

(CAS 7008-42-6) acronycine

(CAS 483-18-1) emetine dihydrochloride tetrahydrate

(CAS 3778-73-2) N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide (isophosphamide)

(CAS 52-24-4) tris(1-aziridiny)phosphine sulfide (thioTEPA)

(CAS 63-92-3) N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl) benzylamine hydrochloride (phenoxybenzamine hydrochloride)

(NSC 141549) 4'-(9-acridinylamino)methansulfon-m-aniside monohydrochloride (MAAM)

MICE

Feeding Studies

(CAS 118-92-3) anthranilic acid

(CAS 98-96-4) pyrazinocarboxamide

(CAS 73-22-3) L-tryptophan

(CAS 64-77-7) 1-butyl-3-(p-tolylsulfonyl)urea (tolbutamide)
 (CAS 80-08-0) 4,4'-sulfonyldianiline
 (CAS 139-65-1) 4,4'-thiodianiline
 (CAS 136-40-3) 2,6-diamino-3-(phenylazo)pyridine hydrochloride
 (CAS 536-33-4) 2-ethyl-4-pyridinecarbothioamide (ethionamide)
 (CAS 58-14-0) 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine
 (pyrimethamine)
 (CAS 94-20-2) 4-chloro-N-((propylamino)carbonyl)benzenesulfonamide (chlorpropamide)
 (CAS 53-96-3) N-9H-fluorenyl-2-acetamide
 (CAS 114-86-3) 1-phenethylbiguanide hydrochloride (phenformin)
 (CAS 968-81-0) 4-acetyl-N-((cyclohexylamino)carbonyl)benzenesulfonamide (acetohexamide)
 (CAS 1156-19-0) N-(p-toluenesulfonyl)-N'-hexamethyleniminourea (tolazamide)

Gavage Studies

(CAS 3546-10-9) cholesterol(p-(bis(2-chloroethyl)amino)phenyl)acetate (phenesterin)
 (CAS 22966-79-6) estradiol bis((p-bis(2-chloroethyl)amino)phenyl)-acetate (estradiol mustard)

Intraperitoneal Injection Studies

(CAS 3458-22-8) 3,3'-iminobis-1-propanol dimethanesulfonate (ester) hydrochloride (IPD)
 (CAS 320-67-2) 5-azacytidine
 (CAS 21416-87-5) (+)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione (ICRF-159)
 (CAS 789-61-7) beta-2'-dexy-6-thioguanosine (β -TGDR)
 (CAS 55-98-1) 1,4-butanediol dimethanesulfonate (busulfan)
 (CAS 7008-42-6) acronycine
 (CAS-483-18-1) emetine dihydrochloride tetrahydrate
 (CAS 3778-73-2) N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine-2-oxide (isophosphamide)
 (CAS 52-24-4) tris(1-aziridiny)phosphine sulfide (thio-TEPA)
 (CAS 63-92-3) N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzylamine hydrochloride (phenoxybenzamine hydrochloride)
 (NSC 141549) 4'-(9-acridinylamino)methanesulfon-m-aniside monohydrochloride (MAAM)
 (CAS 645-05-6) 2,4,6-tris(dimethylamino)-s-triazine

E. Chronic Studies

The test groups, doses administered, and durations of the chronic studies are shown in tables 1 and 2.

Since the numbers of animals in the vehicle-control groups were small, pooled-control groups also were used for statistical comparisons. The pooled-control groups consisted of the vehicle controls from the bioassay of procarbazine combined with the vehicle controls from the bioassays of 3,3'-iminobis-1-propanol dimethanesulfonate (ester) hydrochloride (CAS 3458-22-8) and isophosphamide (CAS 3778-73-2), to give groups of 40 male or 40 female rats and 45 male or 45 female mice. The bioassays of the two test chemicals other than procarbazine were also conducted at Southern Research Institute and overlapped the bioassay of procarbazine by at least 1 year using rats and at least 15 months using mice. The vehicle-control groups of rats and the vehicle-control groups of mice that were used in the respective pooled-control groups were each of the same strain, obtained from the same supplier, and their tissues were diagnosed by the same pathologist.

The doses for the chronic studies were established on the basis of results of an earlier study at Southern Research Institute in

Table 1. Procarbazine Chronic Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Procarbazine Dosage (b) (mg/kg)	Time on Study	
			Dosed (weeks)	Observed (weeks)
<u>Male</u>				
Untreated-Control	10	0		86
Vehicle-Control(c)	10	0	26	60
Low-Dose	34	15	26	34
High-Dose	35	30	26	17(d)
<u>Female</u>				
Untreated-Control	10	0		86
Vehicle-Control(c)	10	0	26	60(d)
Low-Dose	36	15	26	27(d)
High-Dose	35	30	26	5

- (a) The males were 35 days of age, and the females were 42 days of age when placed on study; however, all animals were placed on study at the same time.
- (b) Procarbazine was administered intraperitoneally three times per week in buffered saline at a volume of 0.25 ml/100 g body weight during the period of administration.
- (c) Vehicle controls were administered buffered saline (0.25 ml/100 g body weight).
- (d) Observation of high-dose males and of low- and high-dose females was terminated at the times indicated, due to the deaths of all animals.

Table 2. Procarbazine Chronic Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Procarbazine Dosage (b) (mg/kg)	Time on Study	
			Dosed (weeks)	Observed (weeks)
<u>Male</u>				
Untreated-Control	15	0		85
Vehicle-Control(c)	15	0	52	33
Low-Dose	35	6	52	33
High-Dose	35	12	52	15(d)
<u>Female</u>				
Untreated-Control	15	0		85
Vehicle-Control(c)	15	0	52	33
Low-Dose	35	6	52	33
High-Dose	35	12	52	15(d)

- (a) All animals were 35 days of age when placed on study; all animals were placed on study at the same time.
- (b) Procarbazine was administered intraperitoneally three times per week in buffered saline at a volume of 1.0 ml/100 g body weight during the period of administration.
- (c) Vehicle controls were administered buffered saline (1.0 ml/100 g body weight).
- (d) Observation of the high-dose group was terminated, at the times indicated, due to the deaths of all animals.

which procarbazine was administered three times per week for 6 months to Sprague-Dawley rats and Swiss Webster mice. The doses selected (referred to in this report as "high doses" and "low doses") were 30 and 15 mg/kg for the Sprague-Dawley rats and 12 and 6 mg/kg for the B6C3F1 mice used in the present bioassay.

F. Clinical and Pathologic Examinations

All animals were observed twice daily. Observations to identify sick, tumor-bearing, and moribund animals were made daily. Animals were weighed individually each week for the first 8 weeks and every 2 weeks thereafter, and palpated for masses at each weighing. Animals that were moribund at the time of daily examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated. The following tissues were examined microscopically: skin, muscle, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver,

gallbladder and bile duct (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, brain, and sensory organs. Occasionally, additional tissues were also examined microscopically.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

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

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

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals

in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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

The Cochran-Armitage test for linear trend in proportions, with

continuity correction (Armitage, 1971), is also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

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

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972).

The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 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 dosed 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 dosed 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 dosed group than in the control.

The lower and upper limits of the confidence interval of the

relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

The mean body weights of the high- and low-dose rats of each sex were lower than those of the corresponding vehicle and untreated controls from approximately week 10 on study to the end of the survival periods (figure 1). Fluctuation in the growth curves may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to wide variations. No records were kept of specific clinical signs; however, as a part of a colony treatment for control of an intercurrent respiratory disease, the animals in this study were administered oxytetracycline in the drinking water during weeks 23 to 29 (0.6 mg/ml) and weeks 29 to 34 (0.3 mg/ml).

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats receiving procarbazine at the doses used in this bioassay, together with those of the untreated and vehicle controls, are shown by the Kaplan and Meier curves in figure 2.

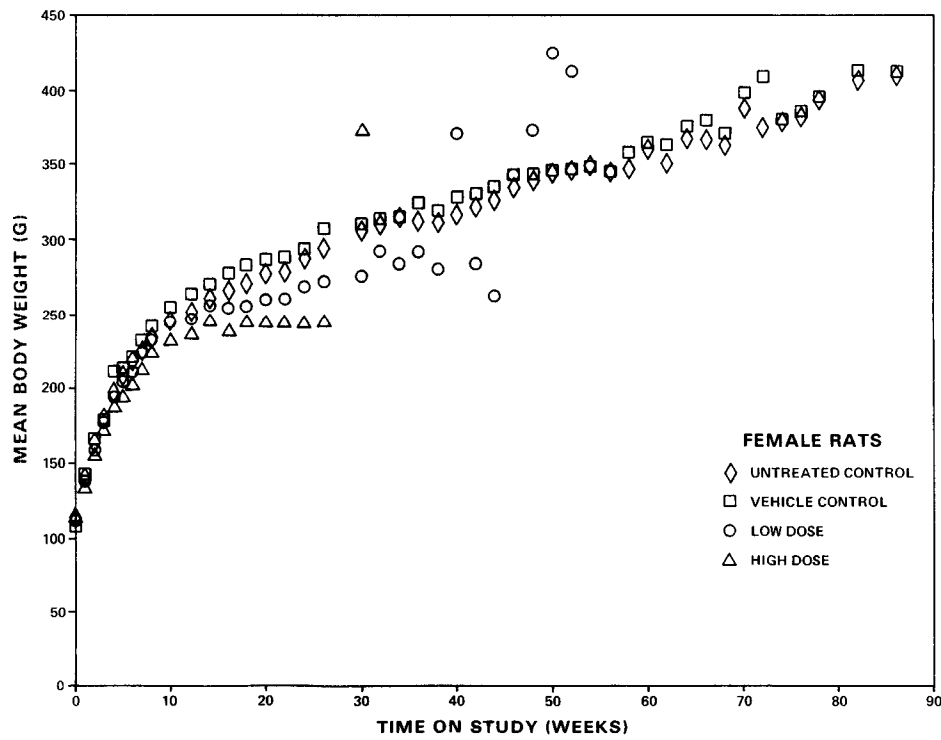
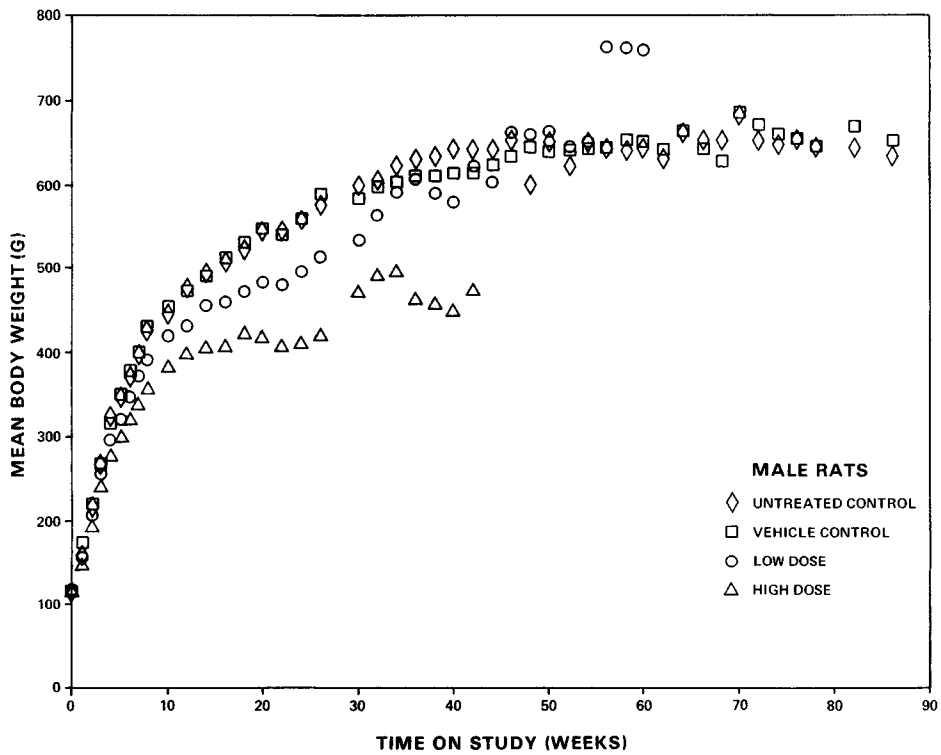


Figure 1. Growth Curves For Rats Treated With Procarbazine

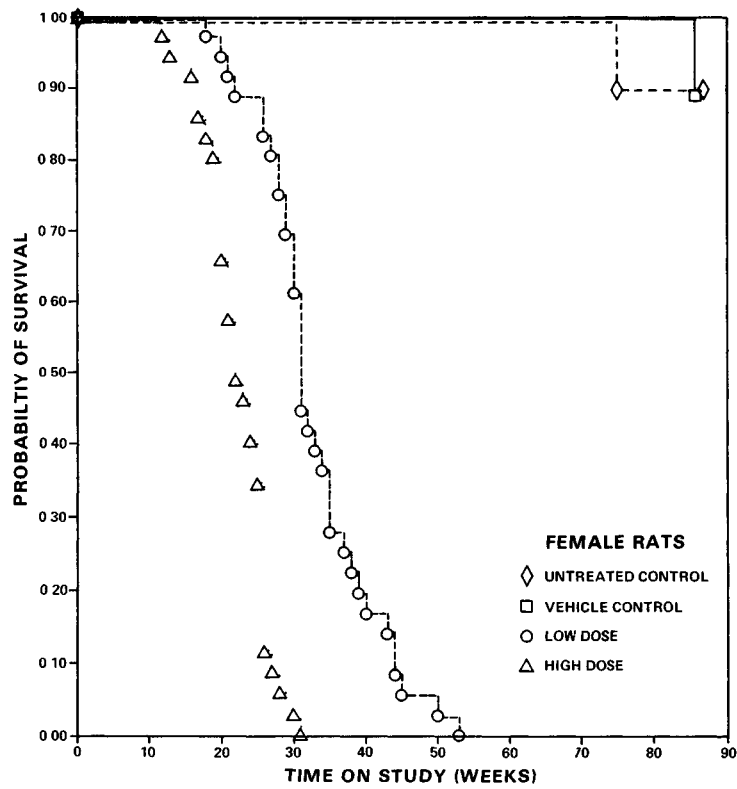
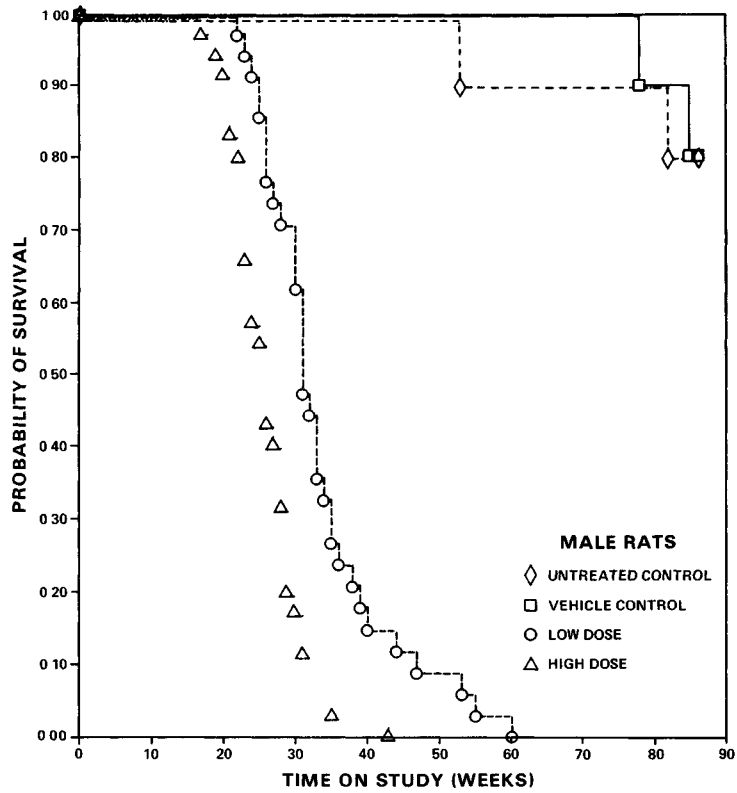


Figure 2. Survival Curves For Rats Treated With Procarbazine

In both sexes, the Tarone test results for positive dose-related trend in the proportions of dosed animals compared to vehicle controls surviving over the test period are significant (P less than 0.001).

In high-dose males, all of the animals died before week 44 of the study, with a median time on study at death of 26 weeks; 30/33 high-dose males that were necropsied were observed to have some kind of tumor. Mortality of the low-dose group was almost as high as that of the high-dose group. All of the low-dose males died before week 60, with a median time on study at death of 31 weeks; however, tumors were observed in 19/30 low-dose animals that were necropsied. Mortality was low among the vehicle-control males, with 80% of the animals living to the end of the study.

The dosed females also had poor survival, with no animal living to the end of the study. Tumors were observed in 27/30 low-dose females that were necropsied; the median time on study at death for this group was 31 weeks. In high-dose females, 30/31 animals that were necropsied had tumors, and the median time on study at death for this group was 22 weeks. Survival was high among the vehicle-control females, with 89% of the animals living to termination of the study.

C. Pathology (Rats)

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

The frequency of animals developing tumors and the mean numbers of tumors per animal increased in both the high- and low-dose groups of males and females.

The primary tissues affected were neuroepithelial, epithelial, and lymphoreticular or hematopoietic. The tumors observed included 45 olfactory and nasal neuroblastomas, adenocarcinomas, and carcinomas in 41 animals, 32 malignant lymphomas of lymphocytic type, and 52 adenocarcinomas or cystadenocarcinomas of the mammary gland. The neuroepithelial tumors, coded as "olfactory neuroblastomas" were unusual. They have also been termed "esthesioneuroepitheliomas" (Laskin et al., 1971) and "olfactory neuroepithelial tumors" (Herrold, 1964).

Histologic features which characterize the olfactory neuroblastomas (Obert et al., 1960) are:

- (1) plexiform intercellular fibrils;
- (2) poorly defined, almost nonexistent, cytoplasm;
- (3) round to oval, usually oval, nuclei;
- (4) chromatin usually distinct and sharply defined, but either coarse or fine;
- (5) compartmentation of sheets of neoplastic cells into lobules by slender vascular fibrous septa; and
- (6) true rosettes and pseudorosettes.

The tumors observed in this study met these criteria. In addition, some tumors had areas of adenocarcinomatous tissue which arose from the nasal epithelium and was mixed or associated with the neoplastic neural tissues. The tumors extended posteriorly into the adjacent brain. Lysis of the cranial bones was observed. Olfactory neuroblastomas have not been seen in untreated rats of this strain at Southern Research Institute.

The mammary glands of the dosed animals had an increased proportion of malignant tumors when compared with the control groups of this experiment and with untreated Sprague-Dawley rats previously observed at Southern Research Institute (Prejean et al., 1973). Malignant lymphoma, lymphocytic type (previously termed "disseminated lymphosarcoma" or "lymphocytic leukemia") and granulocytic leukemia occurred also in a greatly increased number of animals.

The majority of nonneoplastic proliferative lesions involved the lymphoreticular tissues and mammary glands of the dosed groups. The hyperplasias observed in the mammary glands of some animals not having tumors may have been associated with administration of the test chemical.

In addition, a variety of other neoplasms that have been encountered previously as spontaneous lesions in the rat occurred in both dosed and control (untreated and vehicle) groups.

The dosed animals had shorter life spans than those in the untreated- and vehicle-control groups. The high frequency of neoplasia suggests that the reduction in life span is directly related to carcinogenesis. However, many of the rats in both the low-dose and high-dose groups had respiratory disease that was believed to be chronic murine pneumonia.

Intraperitoneal administration of procarbazine to Sprague-Dawley rats resulted in the occurrence of tumors associated with administration of the test chemical. The principal tumors observed were olfactory neuroblastomas, adenocarcinomas of the mammary gland, and malignant lymphomas, lymphocytic type.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more dosed groups of either sex. The untreated controls are not included in the tables, since the test conditions of the vehicle controls were closer to those of the dosed animals.

In male rats, the Cochran-Armitage test results for positive dose-related trend in the incidence of lymphoma of the hematopoietic system are highly significant ($P = 0.002$) when the pooled-control group is used. The Fisher exact test shows that the incidence in the high-dose males is significantly higher than that in the pooled controls ($P = 0.003$). The lower limit of the 95% confidence interval of the relative risk shows a value greater than one. In females, the Cochran-Armitage test results are highly significant (P less than 0.001) when either the pooled-control group or the vehicle-control group is used. The departure from linear trend is highly significant (P less than 0.001) when the pooled-control group is used, and $P = 0.004$ when the vehicle-control group is used, since there is a steep rise in incidence in the high-dose animals. The Fisher exact test shows that the incidence in the high-dose females is significantly

higher (P less than 0.001) than that in either the pooled controls or the vehicle controls. This positive finding is also shown by the lower limits of the 95% confidence intervals of these relative risks, which have values greater than one. The statistical conclusion is that the incidence of lymphoma of the hematopoietic system in rats is associated with procarbazine for high-dose male and female rats in this experiment.

Leukemia was found exclusively in the high-dose males (3/33), and a significant Cochran-Armitage test result (P = 0.031) is observed when the pooled-control group is used; however, none of the Fisher exact test results is significant; therefore, it is inconclusive whether the incidence of leukemia in male rats is related to administration of the chemical. No such tumor was observed in females.

When these hematopoietic tumors (lymphoma and leukemia) are grouped for analyses in male rats, the significance of the Cochran-Armitage test becomes P less than 0.001 and P = 0.013 when the pooled controls and the vehicle controls are used, respectively. The incidence of the combination of lymphoma and leukemia in the high-dose groups compared with that in the pooled controls is statistically significant due to the high incidence of lymphoma.

In this study, adenocarcinomas, NOS (not otherwise specified), of the mammary gland were found only in the dosed animals. In male rats, the Cochran-Armitage test results are significant when the pooled controls ($P = 0.001$) and the vehicle controls ($P = 0.016$) are used. The Fisher exact test shows that the incidence in the high-dose males is significantly higher than that in the pooled controls ($P = 0.003$). This positive finding results in the value of the lower limit of the 95% confidence interval of the relative risk being greater than one. In females, the Cochran-Armitage test results are significant (P less than 0.001) when either the pooled-control group or the vehicle-control group is used. This positive finding is confirmed by the Fisher exact test, where the comparisons between the incidences in the dosed groups and the control groups are highly significant (probability levels 0.003 or less) and the lower limits of the 95% confidence intervals of these relative risks have values greater than one. The statistical conclusion is that the occurrence of adenocarcinomas, NOS, of the mammary gland in rats is related to administration of procarbazine. One adenoma of the mammary gland was found in the male high-dose group and another was observed in the female low-dose group. The analyses of the incidence of the grouped mammary gland tumors (adenomas and adenocarcinomas, NOS) show increased significance over that of the adenocarcinomas, NOS, alone.

There were three high-dose male rats with adenocarcinomas, NOS, of the olfactory bulb, and the results of the Cochran-Armitage test show in a probability level of 0.034 when the pooled-control group is used. None of the Fisher exact test results are significant. When the incidences of carcinomas, neuroblastomas and adeno- carcinomas of the brain and olfactory bulb are combined, the Cochran-Armitage test results are significant ($P = 0.003$) using the pooled-control group. Departures from linear trend are present ($P = 0.001$, pooled control; $P = 0.013$, matched control) because the incidences in the low-dose group exceeds that in the high-dose. The results of the Fisher exact test using the pooled controls are significant (P less than or equal to 0.001) in both dosed groups. It is concluded that the incidences of these tumors are related to administration of the chemical. In females, although the results of the Cochran-Armitage test on the incidence of olfactory neuroblastomas or mucinous adenocarcinomas of the brain or cerebrum are not significant, there is an indicated departure from linear trend (P less than 0.001), since the proportion is higher in the low-dose group than in the high-dose group. The Fisher exact test shows that the incidence in the low-dose females is significantly higher than that in either the vehicle- or pooled-control groups (P less than or equal to 0.007).

Brain, ear, and olfactory tumors were observed in both sexes as early as 21 weeks. When groupings of the types of tumors are made, as in adenomas and adenocarcinomas, NOS, of the mammary gland, the incidences of the individual components are not included in tables E1 and E2 unless the proportions are greater than 5% in any of the dosed groups. However, a list of the incidences of each type of tumor is provided in tables E1 and E2 of Appendix E. In summary, there are three types of tumors that appear to be associated with this chemical and four other types where the evidence is not statistically conclusive.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

The mean body weights of the dosed mice were not consistently different from those of the controls (figure 3). Those high-dose males still alive had low mean body weights starting at about week 40. Weights of high-dose and vehicle-control females were lower than those of low-dose and untreated-control females starting at approximately week 30 on study. Fluctuation in the growth curves may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to wide variation.

B. Survival (Mice)

Estimates of the probabilities of survival of male and female mice receiving procarbazine at the doses used in this bioassay, together with those of the untreated and vehicle controls, are shown by the Kaplan and Meier curves in figure 4.

In male mice, the Tarone test for positive dose-related trend in the proportions of dosed animals compared with vehicle controls surviving over the test period is highly significant (P less than

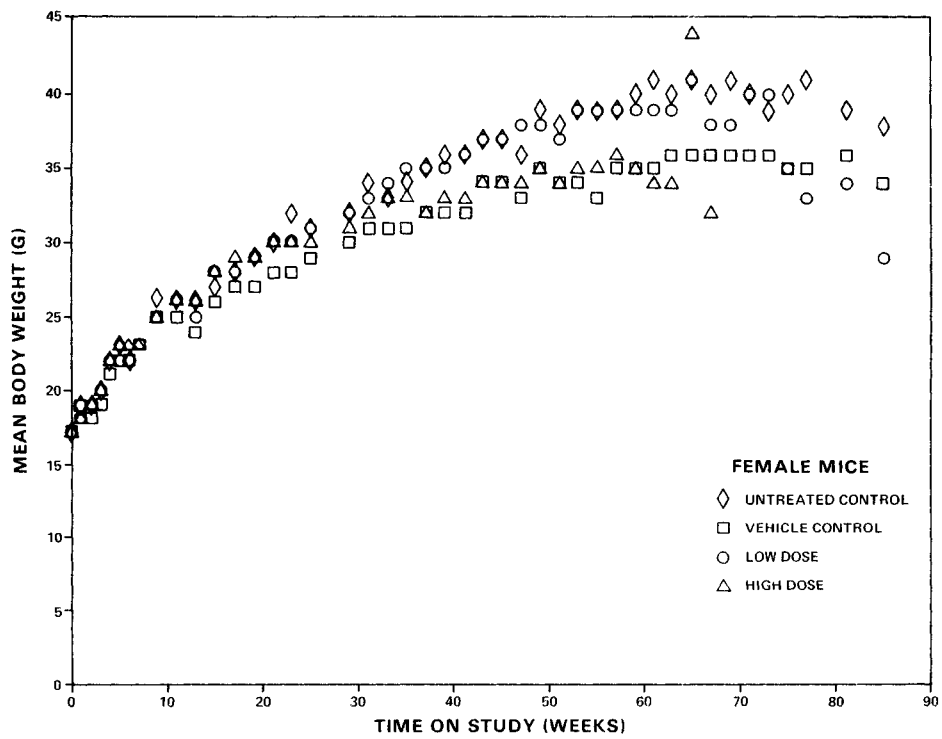
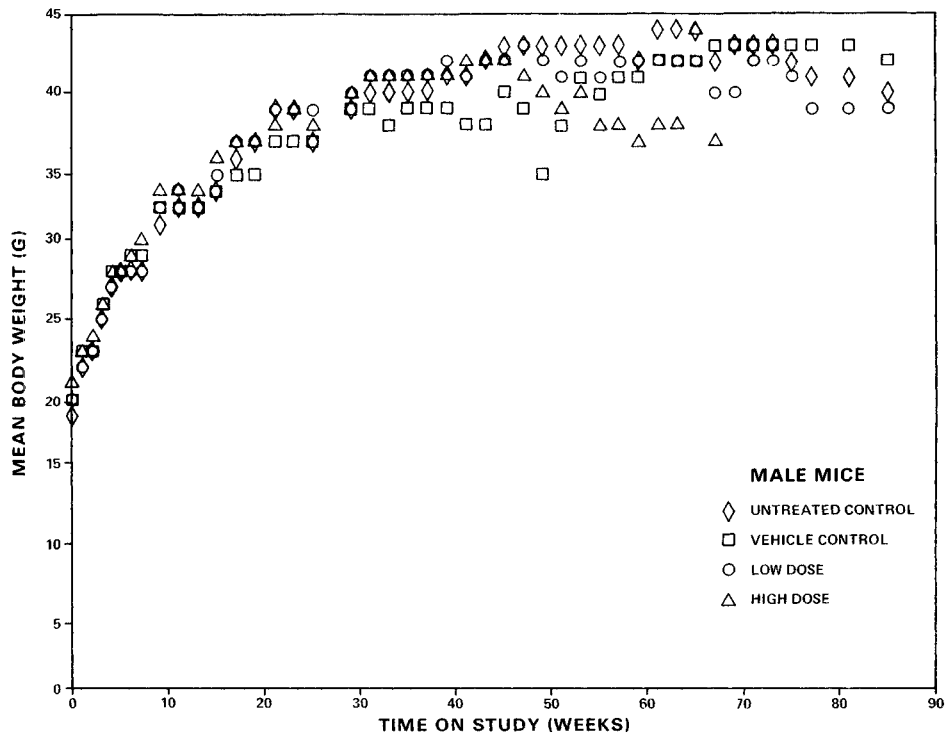


Figure 3. Growth Curves For Mice Treated With Procarbazine

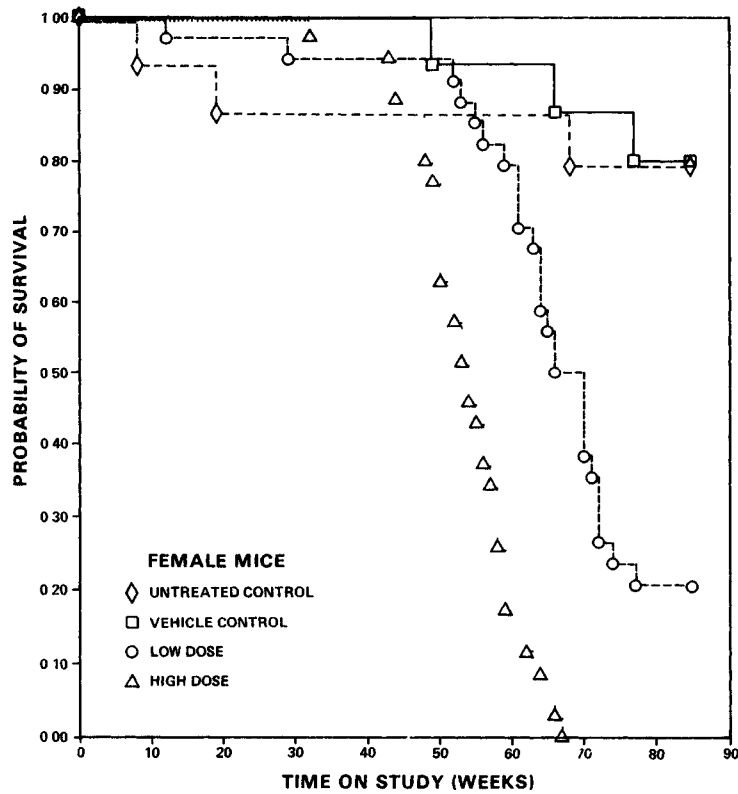
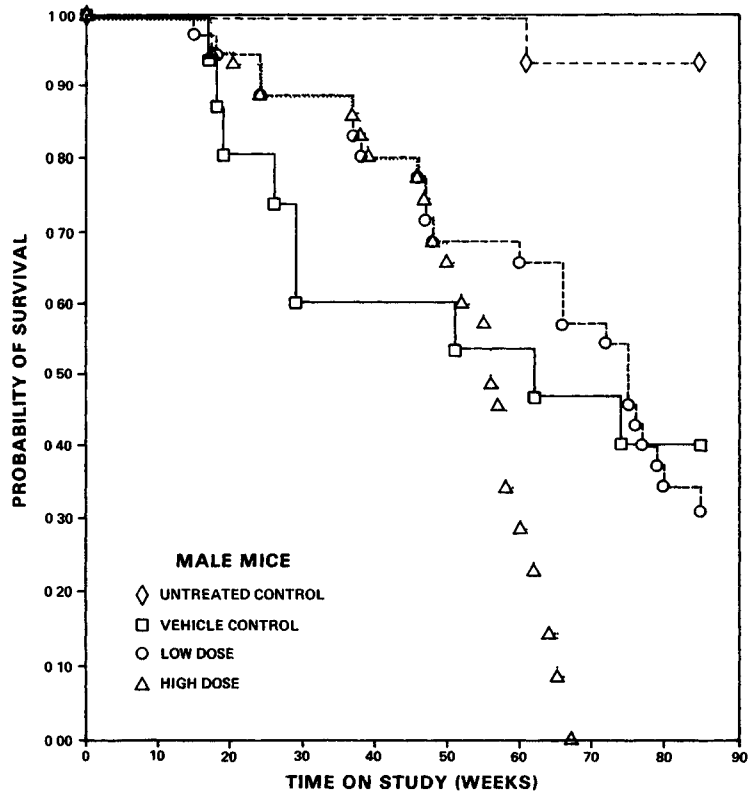


Figure 4. Survival Curves For Mice Treated With Procarbazine

0.001), and a departure from linear trend ($P = 0.012$) is observed, due to the sharp rise in mortality of the high-dose group. Forty percent of the vehicle controls and 31% of the low-dose group, but none of the high-dose group, lived to the end of the study; their respective median times on study at death were 62 weeks, 75 weeks, and 56 weeks. None of the vehicle controls developed tumors. In the low-dose male mice, 18/30 that were necropsied had developed tumors, and in the high-dose males, 20/31 animals that were necropsied had evidence of tumors; therefore, there is a possibility that the early deaths were associated with the administration of procarbazine.

In females, the Tarone test results are highly significant (P less than 0.001), and a departure from linear trend ($P = 0.049$) is observed, due to the steep increase in the mortality of the dosed groups. Eighty percent of the vehicle controls and 21% of the low-dose group, but none of the high-dose group, survived to termination of the study. The median times on study at death were 54 weeks and 66 weeks for the high-dose and low-dose animals, respectively. In the low-dose group, 19/23 animals necropsied had developed tumors, and in the high-dose group, 20/26 animals necropsied were observed to have tumors.

C. Pathology (Mice)

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

Malignant tumors of the olfactory bulbs and mucosa were observed in 23 high-dose male and female mice. The majority of these tumors were classified as olfactory neuroblastomas and resembled those observed in rats, as described previously. One of these olfactory neuroblastomas had invaded the adjacent cranial and facial bones. One mouse had a brain lesion which was classified as an undifferentiated carcinoma. One tumor of the brain, composed of reticulum cells or histiocytes, was coded as a sarcoma, NOS.

Another organ frequently affected by neoplasia was the uterus in both the high- and low-dose females. The most commonly observed uterine tumors were adenocarcinomas (14 in the low-dose group, 8 in the high-dose group, but none in the controls). These adenocarcinomas penetrated the serosa and invaded or proliferated into adjacent tissues of the abdomen. Metastatic uterine adenocarcinomas were observed in the lungs, heart, and liver.

Four dosed mice had uterine leiomyosarcomas and one had a malignant lymphoma of histiocytic type. One mouse had an undifferentiated spindle-cell sarcoma of the urinary bladder, coded as a sarcoma, NOS, which also involved the uterus, oviduct, ovaries, and mesenteric lymph nodes.

A variety of other neoplasms occurred in both dosed and control (untreated and vehicle) groups, which have been encountered previously as spontaneous lesions in the mouse. Nonneoplastic, proliferative lesions involved primarily the lymphoreticular tissues. A few mice had suppurative lesions suggestive of bacterial infections. These lesions were not associated with increased mortality or decreased life spans.

The high-dose groups had slightly reduced life spans; the median time of death was only slightly above a year. The high frequency of neoplasia and the extensive involvement of the brain and uterus could account for the majority of the deaths prior to termination of the study. The cause of the mortalities in the vehicle-control group could not be explained on the basis of postmortem examination of lesions.

The results of this study indicate that olfactory neuroblastomas in males and females and uterine adenocarcinomas in females were

related to administration of the chemical. Neither of these tumors was observed in the control groups.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that were observed in at least 5% of one or more dosed groups of either sex. The untreated controls are not included in the tables, since the test conditions of the vehicle controls were closer to those of the dosed groups.

Alveolar/bronchiolar adenomas of the lungs occurred exclusively in the dosed groups. For males, the Cochran-Armitage test for positive dose-related trend in proportions has a probability level of less than 0.001 when the pooled controls are used. The Fisher exact test shows that the incidences in the dosed groups are significantly higher than those in either the vehicle controls ($P = 0.020$) or the pooled controls (P less than 0.001); and this positive finding is accentuated by the values of the lower limits of the 95% confidence interval of the relative risks of the dosed group versus the control groups, which are greater than one. In females, the incidence of alveolar/bronchiolar

adenomas in the high-dose group is six times as high as that in the low-dose group; the Cochran-Armitage test results are significant when the vehicle controls ($P = 0.016$) and the pooled controls ($P = 0.001$) are used. Moreover, the Fisher exact test shows that the incidence in the high-dose females is significantly higher than that in the pooled controls ($P = 0.002$), and the lower limit of the 95% confidence interval of the relative risk shows a value greater than one. The statistical conclusion is that the occurrence of alveolar/bronchiolar adenomas of the lung in male and female mice is associated with procarbazine at the doses used in this experiment. In male mice, alveolar/bronchiolar carcinomas were observed in one animal of each dosed group and in one animal in the untreated-control group. Alveolar/bronchiolar carcinomas were not observed in female mice.

In females, since the incidence of lymphoma or leukemia of the hematopoietic system in the low-dose animals (8/23 (35%)) is over four times that in the high-dose animals (2/26 (8%)), the test for linear trend indicates a departure from linear trend when either the vehicle-control group ($P = 0.002$) or the pooled-control group (P less than 0.001) is used. The Fisher exact test shows that the incidence of lymphoma or leukemia in the low-dose females is significantly higher than that in either the vehicle controls ($P = 0.013$) or the pooled controls (P less than 0.001).

The lower limit of the 95% confidence interval of the relative risk of the low-dose group versus the pooled controls shows a value greater than one. The results of these statistical tests suggest that the incidence of lymphoma or leukemia in female mice may be related to administration of the test chemical.

The incidence of olfactory neuroblastomas or undifferentiated carcinomas of the brain is observed exclusively in the high-dose groups. In male mice, the Cochran-Armitage test results are highly significant when the vehicle controls ($P = 0.002$) and the pooled controls (P less than 0.001) are used. A significant departure from linear trend ($P = 0.020$) is observed when the pooled-control group is used, due to the sharp increase in the incidence of tumors in the high-dose group. This positive finding is confirmed by the Fisher exact test, which shows that the incidence in the high-dose animals is significantly higher than that in the pooled controls (P less than 0.001), and the lower limit of the 95% confidence interval of this relative risk shows a value greater than one. In females, the Cochran-Armitage test results are highly significant (P less than 0.001) when either of the control groups is used. An indicated departure from linear trend is observed when the pooled-control group ($P = 0.006$) or the vehicle-control group ($P = 0.030$) is used, due to

the steep increase in the incidence of tumors in the high-dose group. The Fisher exact test shows that the incidence in the high-dose females is significantly higher than that in either the vehicle controls (P = 0.003) or the pooled controls (P less than 0.001); because of this positive finding, values of the lower limits of the 95% confidence intervals are greater than one. The statistical conclusion is that the occurrence of olfactory neuroblastomas is related to administration of the test chemical.

The analyses of adenocarcinomas, NOS, of the uterus show that the Cochran-Armitage test is highly significant (P less than 0.001) when the pooled-control group is used. The departure from linear trend is also significant (P less than 0.001) when either the vehicle-control group or the pooled-control group is used, due to the sharp increase of the incidence of tumors in the dosed groups and the higher incidence of tumors in the low-dose group. The Fisher exact test results are all significant. The statistical conclusion is that the incidence of adenocarcinomas, NOS, of the uterus in female mice is related to administration of the test chemical.

Groupings of these types of tumors are made, as in fibromas and fibrosarcomas of the subcutaneous tissue in male mice; however, the incidences of the individual components are not listed in

tables F1 and F2 unless they are greater than 5% in any of the dosed groups. One adenocarcinoma, NOS, of the salivary gland was found a low-dose male mouse. Since this was the only tissue examined, the incidence of tumors in the low-dose group becomes 1/1(100%); however, it is not listed in table F1 because of the small sample size. A list of the incidences of each of tumor is provided in Appendix D, tables D1 and D2.

V. DISCUSSION

The doses of procarbazine used in the bioassay were toxic, as shown by the lowered body weights and/or rates of survival of the dosed animals. Mean body weights of all groups of rats administered procarbazine were lower than those of untreated- and vehicle-control groups. No consistent compound-related effect on weights occurred in mice. Survival of both rats and mice was markedly reduced and was dose related (P less than 0.001); however, high incidences of tumors were found in both rats and mice.

In rats, 21/60 dosed males and 20/59 dosed females, but no controls, had tumors involving epithelial and neuroepithelial tissue of the region of the nasal turbinates and nasal cavity, i.e., olfactory neuroblastomas, carcinomas NOS, adenocarcinomas NOS, and mucinous adenocarcinomas. The most frequent tumor, olfactory neuroblastoma, was present in a greater number of low-dose than high-dose animals of each sex. Direct comparisons of the combination of these tumors in the low-dose groups with both vehicle-control groups were significant. In the male, the incidence in the high-dose group was also significant, as was the dose-related trend, using pooled controls.

Malignant lymphoma in both male and female dosed rats was

statistically significant by direct comparison of the high-dose group with the pooled-control group. In female rats, direct comparison of the high-dose group with the vehicle-control group was also statistically significant. These lesions appeared as early as 12 weeks in female rats. Additionally, one eosinophilic leukemia and two granulocytic leukemias were found in high-dose males.

Adenocarcinomas of the mammary gland occurred in the dosed rats and were statistically significant for dose-related trend in both sexes and for direct comparisons of the high-dose group in males and both the high- and low-dose groups in females with vehicle controls. Several other neoplastic and nonneoplastic lesions were observed in the mammary glands of animals of each sex, including cystadenocarcinomas, adenomas, fibroadenomas, hyperplasias, and cysts.

Several types of squamous-cell tumors of the ear canal and Zymbal's gland were found in increased numbers among the dosed rats. These included keratocanthomas, squamous-cell papillomas, and squamous-cell carcinomas in two high-dose male rats, one low-dose, and one untreated-control male rat, and in four high-dose, three low-dose, but no control female rats. Although the incidence was low, tumors of the auditory canal were

previously reported in rats administered procarbazine by both Kelly et al. (1968) and Deckers et al. (1969).

In mice, tumors of the epithelium or neuroepithelium were also found in the olfactory bulbs and mucosa in 10 high-dose males and 11 high-dose females. Olfactory neuroblastomas, the tumor occurring with the highest incidences, were found only in high-dose males and high-dose females and were statistically significant by direct comparisons with both pooled-control groups. These tumors were also statistically significant by direct comparison in high-dose females with the vehicle-control group.

In mice, malignant lymphomas or leukemias were observed in four animals of each of the male dosed groups and in one untreated control, but were not found among vehicle controls of either sex. In females, the incidence in the low-dose group (6/23) was more than three times that in the high-dose group (2/26). The incidence of leukemia or lymphoma was significant in the low-dose group of females when compared with vehicle controls. In the high-dose female group, survival was markedly reduced, and none of the animals lived to the end of the study.

Alveolar/bronchiolar adenomas were found in significant proportions in low- and high-dose male and high-dose female mice.

In female mice, adenocarcinomas of the uterus were found only in dosed animals, and were significant in both dosed groups when compared with either vehicle-control group. However, the incidence was much higher in the low-dose group than in the high-dose group, and there was a significant departure from linear trend.

The findings of this bioassay confirm previous studies in Osborne-Mendel and Fischer 344 rats by Kelly et al. (1968), inbred R strain rats of Wistar origin by Deckers et al. (1974), random-bred Charles River CD strain rats by Grunberg and Prince (1969), (BALB/c x DBA/2)F1 mice by Kelly et al. (1969), and Swiss mice by Grunberg and Prince (1969). These previously reported studies described increased incidences of tumors of the lung, spleen, kidney, uterus, mammary glands, sebaceous glands, and the ear duct. The olfactory neuroblastomas observed in both rats and mice in the present bioassay were not previously described. Studies on metabolites and various degradation products of procarbazine in mice (Kelly et al., 1969) suggest that tumor-associated activity of the parent chemical is retained by the azo metabolite, N-isopropyl- α -(2-methylazo)-p-toluamide, and also by the hydrazone metabolite, N-isopropyl- α -(2-methylhydrazone)-p-toluamide, but not by the aldehyde oxidation product, N-isopropyl-p-formylbenzamide.

It is concluded that under the conditions of this bioassay,

procarbazine was carcinogenic for both Sprague-Dawley rats and B6C3F1 mice, producing several types of tumor in both sexes of these two species.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
RATS ADMINISTERED PROCARBAZINE
BY INTRAPERITONEAL INJECTION

TABLE A1.

**SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION**

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	34	35
ANIMALS NECROPSIED	9	10	31	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	10	28	33
INTEGUMENTARY SYSTEM				
*SKIN	(9)	(10)	(31)	(33)
BASAL-CELL CARCINOMA				1 (3%)
*SUBCUT TISSUE	(9)	(10)	(31)	(33)
CARCINOMA, NOS				1 (3%)
SARCOMA, NOS				1 (3%)
RESPIRATORY SYSTEM				
#LUNG	(9)	(10)	(28)	(33)
UNDIFFERENTIATED CARCINOMA METAS				1 (3%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(9)	(10)	(31)	(33)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			2 (6%)	9 (27%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		1 (10%)		
GRANULOCYTTIC LEUKEMIA				1 (3%)
EOSINOPHILIC LEUKEMIA				1 (3%)
#BONE MARROW	(9)	(10)	(28)	(29)
GRANULOCYTTIC LEUKEMIA				1 (3%)
#SMALL INTESTINE	(9)	(9)	(27)	(32)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			1 (4%)	
CIRCULATORY SYSTEM				
NONE				

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#PANCREAS ACINAR-CELL ADENOMA	(9)	(9)	(25)	(31) 1 (3%)
#SMALL INTESTINE CYSTADENOCARCINOMA, NOS	(9)	(9)	(27)	(32) 1 (3%)
#COLON ADENOCARCINOMA, NOS ADENOCARCINOMA IN ADENOMATOUS POLYP	(9)	(9)	(28) 1 (4%)	(31) 1 (3%)
URINARY SYSTEM				
#KIDNEY UNDIFFERENTIATED CARCINOMA	(9)	(10)	(28)	(32) 1 (3%)
ENDOCRINE SYSTEM				
#PITUITARY CHROMOPHOBE ADENOMA CHROMOPHOBE CARCINOMA	(8) 1 (13%)	(9) 2 (22%)	(26) 1 (4%)	(31) 1 (3%)
#ADRENAL CORTICAL ADENOMA	(9)	(9)	(28) 3 (11%)	(32) 2 (6%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND ADENOMA, NOS ADENOCARCINOMA, NOS CYSTADENOCARCINOMA, NOS FIBROADENOMA	(9) 3 (33%)	(10)	(31) 1 (3%)	(33) 1 (3%) 7 (21%) 2 (6%)
NERVOUS SYSTEM				
#CEREBRUM OLIGODENDROGLIOMA	(9)	(9)	(27)	(33) 1 (3%)
#BRAIN CARCINOMA, NOS	(9)	(9)	(27)	(33) 3 (9%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SARCOMA, NOS			1 (4%)	
ASTROCYTOMA	1 (11%)			
OLFACTORY NEUROBLASTOMA			12 (44%)	7 (21%)
#OLFACTORY BULB ADENOCARCINOMA, NOS	(9)	(9)	(27)	(33) 3 (9%)
SPECIAL SENSE ORGANS				
*EAR CANAL	(9)	(10)	(31)	(33)
SQUAMOUS CELL PAPILLOMA			1 (3%)	
SQUAMOUS CELL CARCINOMA	1 (11%)			
KERATOACANTHOMA				2 (6%)
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF HEAD	(9)	(10)	(31)	(33)
SARCOMA, NOS		1 (10%)		
BODY CAVITIES				
*PERITONEUM	(9)	(10)	(31)	(33)
FIBROSARCOMA				1 (3%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	34	35
NATURAL DEATH	2	2	17	15
MORBUND SACRIFICE			17	20
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	8	8		
ANIMAL MISSING				

② INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	4	19	30
TOTAL PRIMARY TUMORS	6	4	23	49
TOTAL ANIMALS WITH BENIGN TUMORS	4	2	4	6
TOTAL BENIGN TUMORS	4	2	5	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	2	18	30
TOTAL MALIGNANT TUMORS	2	2	18	43
TOTAL ANIMALS WITH SECONDARY TUMORS#				1
TOTAL SECONDARY TUMORS				1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	36	35
ANIMALS NECROPSIED	10	10	31	31
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	30	31
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE FIBROMA NEUROFIBROMA	(10)	(10)	(31) 1 (3%)	(31) 1 (3%)
RESPIRATORY SYSTEM				
#LUNG ADENOSQUAMOUS CARCINOMA	(10)	(10)	(29)	(31) 1 (3%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	(10)	(10)	(31)	(31) 20 (65%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#COLON ADENOMATOUS POLYP, NOS	(9)	(10)	(27)	(30) 1 (3%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY CHROMOPHOBE ADENOMA	(5) 3 (60%)	(10) 3 (30%)	(29) 1 (3%)	(29)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL CORTICAL ADENOMA	(10)	(10)	(30) 4 (13%)	(31) 2 (6%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND ADENOMA, NOS	(10)	(10)	(31) 1 (3%)	(31) 1 (3%)
ADENOCARCINOMA, NOS			16 (52%)	25 (81%)
CYSTADENOMA, NOS				1 (3%)
CYSTADENOCARCINOMA, NOS				1 (3%)
FIBROMA			1 (3%)	
FIBROADENOMA	2 (20%)	2 (20%)	4 (13%)	3 (10%)
#UTERUS LEIOMYOSARCOMA	(9)	(10)	(30) 1 (3%)	(30)
ENDOMETRIAL STROMAL POLYP	1 (11%)			1 (3%)
#UTERUS/ENDOMETRIUM ADENOMA, NOS	(9)	(10)	(30)	(30) 1 (3%)
NERVOUS SYSTEM				
#CEREBRUM **MUCINOUS ADENOCARCINOMA	(10)	(10)	(28)	(31) 1 (3%)
#BRAIN **OLFACTORY NEUROBLASTOMA	(10)	(10)	(28) 17 (61%)	(31) 2 (6%)
*CRANIAL NERVE NEUROFIBROMA	(10)	(10)	(31)	(31) 1 (3%)
SPECIAL SENSE ORGANS				
*EAR CANAL SQUAMOUS CELL PAPILLOMA	(10)	(10)	(31)	(31) 1 (3%)
SQUAMOUS CELL CARCINOMA			1 (3%)	
KERATOACANTHOMA			2 (6%)	3 (10%)
*ZYMBA'S GLAND KERATOACANTHOMA	(10)	(10)	(31)	(31) 1 (3%)
MUSCULOSKELETAL SYSTEM				
NONE				

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

** THESE TUMORS ARE OF NEUROEPITHELIAL ORIGIN

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*MESENTERY LIPOSARCOMA	(10)	(10)	(31)	(31) 1 (3%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	10	10	36	35
NATURAL DEATH ^a	1	1	15	14
MORIBUND SACRIFICE			21	21
SCHEDULED SACRIFICE		1		
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	9	8		
ANIMAL MISSING				
^a INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	4	27	30
TOTAL PRIMARY TUMORS	6	5	49	68
TOTAL ANIMALS WITH BENIGN TUMORS	4	4	11	13
TOTAL BENIGN TUMORS	6	5	14	17
TOTAL ANIMALS WITH MALIGNANT TUMORS			26	30
TOTAL MALIGNANT TUMORS			35	51
TOTAL ANIMALS WITH SECONDARY TUMORS#				
TOTAL SECONDARY TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
MICE ADMINISTERED PROCARBAZINE
BY INTRAPERITONEAL INJECTION

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	35	35
ANIMALS NECROPSIED	15	14	30	31
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	12	30	30
INTEGUMENTARY SYSTEM				
*SKIN	(15)	(14)	(30)	(31)
UNDIFFERENTIATED CARCINOMA				1 (3%)
*SUBCUT TISSUE	(15)	(14)	(30)	(31)
SPINDLE CELL MELANOMA			1 (3%)	
FIBROMA			1 (3%)	
FIBROSARCOMA			1 (3%)	1 (3%)
RESPIRATORY SYSTEM				
#LUNG	(15)	(12)	(30)	(30)
HEPATOCELLULAR CARCINOMA, METAST				1 (3%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (13%)		10 (33%)	10 (33%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (7%)		1 (3%)	1 (3%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(15)	(14)	(30)	(31)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	1 (7%)		1 (3%)	1 (3%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			2 (7%)	2 (6%)
GRANULOCYTIC LEUKEMIA			1 (3%)	1 (3%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#SALIVARY GLAND			(2)	
ADENOCARCINOMA, NOS			1 (50%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(15)	(11)	(30)	(29)
HEPATOCELLULAR ADENOMA	1 (7%)		3 (10%)	2 (7%)
HEPATOCELLULAR CARCINOMA				1 (3%)
HEMANGIOMA			1 (3%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
#BRAIN	(15)	(8)	(24)	(29)
**UNDIFFERENTIATED CARCINOMA				1 (3%)
**OLFACTORY NEUROBLASTOMA				9 (31%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

** THESE TUMORS ARE OF NEUROEPITHELIAL ORIGIN

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	15	15	35	35
NATURAL DEATH ^a		7	15	12
MORIBUND SACRIFICE	1	2	9	23
SCHEDULED SACRIFICE			2	
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	14	6	9	
ANIMAL MISSING				
a INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	5		18	20
TOTAL PRIMARY TUMORS	5		23	30
TOTAL ANIMALS WITH BENIGN TUMORS	3		13	10
TOTAL BENIGN TUMORS	3		15	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	2		8	16
TOTAL MALIGNANT TUMORS	2		8	18
TOTAL ANIMALS WITH SECONDARY TUMORS#				1
TOTAL SECONDARY TUMORS				1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS				
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN				

TABLE B2.

**SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION**

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	35	35
ANIMALS MISSING	1		1	
ANIMALS NECROPSIED	12	14	23	26
ANIMALS EXAMINED HISTOPATHOLOGICALLY	12	14	23	26
INTEGUMENTARY SYSTEM				
*SKIN	(12)	(14)	(23)	(26)
ADENOCARCINOMA, NOS				1 (4%)
*SUBCUT TISSUE	(12)	(14)	(23)	(26)
BASAL-CELL CARCINOMA			1 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(12)	(14)	(23)	(26)
ADENOCARCINOMA, NOS, METASTATIC			4 (17%)	4 (15%)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (4%)	6 (23%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(12)	(14)	(23)	(26)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			3 (13%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (4%)	1 (4%)
GRANULOCYTIC LEUKEMIA			2 (9%)	
#LYMPH NODE	(1)		(4)	(6)
ADENOCARCINOMA, NOS, METASTATIC				1 (17%)
#PULMONARY LYMPH NODE	(1)		(4)	(6)
ADENOCARCINOMA, NOS, METASTATIC			2 (50%)	
#MESENTERIC L. NODE	(1)		(4)	(6)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (25%)	1 (17%)
#UTERUS	(12)	(13)	(23)	(25)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (4%)	
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
#MYOCARDIUM ADENOCARCINOMA, NOS, METASTATIC	(12)	(14)	(22)	(23) 1 (4%)
DIGESTIVE SYSTEM				
#LIVER ADENOCARCINOMA, NOS, METASTATIC HEMANGIOMA	(12)	(14)	(23) 1 (4%)	(26) 1 (4%)
#SMALL INTESTINE ADENOCARCINOMA, NOS, METASTATIC	(12)	(14)	(22) 1 (5%)	(25)
URINARY SYSTEM				
#URINARY BLADDER SARCOMA, NOS	(12)	(13)	(18)	(26) 1 (4%)
ENDOCRINE SYSTEM				
#ADRENAL PHEOCHROMOCYTOMA	(12)	(14)	(22)	(26) 1 (4%)
#THYROID FOLLICULAR-CELL ADENOMA	(11)	(13)	(18) 1 (6%)	(19)
REPRODUCTIVE SYSTEM				
#UTERUS ADENOCARCINOMA, NOS LEIOMYOSARCOMA	(12)	(13)	(23) ^{-L} 14 (61%) 2 (9%)	(25) 8 (32%) 2 (8%)
NERVOUS SYSTEM				
#BRAIN SARCOMA, NOS **OLFACTORY NEUROBLASTOMA NEUROFIBROSARCOMA	(11)	(14)	(22)	(25) 1 (4%) 11 (44%) 1 (4%)
SPECIAL SENSE ORGANS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

** THESE TUMORS ARE OF NEUROEPITHELIAL ORIGIN

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*CRANIAL AND FACIAL B OLFACTORY NEUROBLASTOMA, INVASIV	(12)	(14)	(23)	(26) 1 (4%)
BODY CAVITIES				
*MESENTERY ADENOCARCINOMA, NOS, METASTATIC	(12)	(14)	(23) 3 (13%)	(26)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS SARCOMA, NOS	(12)	(14)	(23)	(26) 1 (4%)
SITE UNKNOWN ADENOMA, NOS				1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	15	15	35	35
NATURAL DEATH ^a	3	1	18	17
MORIBUND SACRIFICE		2	9	18
SCHEDULED SACRIFICE		1	6	
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	11	11	1	
ANIMAL MISSING	1		1	
^a INCLUDES AUTOLYZED ANIMALS				

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*			19	20
TOTAL PRIMARY TUMORS			27	37
TOTAL ANIMALS WITH BENIGN TUMORS			2	9
TOTAL BENIGN TUMORS			2	9
TOTAL ANIMALS WITH MALIGNANT TUMORS			19	20
TOTAL MALIGNANT TUMORS			25	28
TOTAL ANIMALS WITH SECONDARY TUMORS#			5	6
TOTAL SECONDARY TUMORS			11	7
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 ADMINISTERED PROCARBAZINE
BY INTRAPERITONEAL INJECTION**

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	34	35
ANIMALS NECROPSIED	9	10	31	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	10	28	33
INTEGUMENTARY SYSTEM				
*SKIN	(9)	(10)	(31)	(33)
EPIDERMAL INCLUSION CYST			1 (3%)	
INFLAMMATION, CHRONIC	1 (11%)			1 (3%)
FIBROSIS				
*SUBCUT TISSUE	(9)	(10)	(31)	(33)
INFLAMMATION, CHRONIC	1 (11%)			
RESPIRATORY SYSTEM				
#TRACHEA	(9)	(9)	(27)	(29)
CYST, NOS			2 (7%)	
INFLAMMATION, NOS				3 (10%)
LYMPHOCYTIC INFLAMMATORY INFILTR			3 (11%)	
INFLAMMATION, SUPPURATIVE			1 (4%)	5 (17%)
INFLAMMATION, ACUTE			1 (4%)	
INFLAMMATION, ACUTE SUPPURATIVE				1 (3%)
INFLAMMATION, ACUTE/CHRONIC			13 (48%)	5 (17%)
INFLAMMATION, CHRONIC	2 (22%)			1 (3%)
#LUNG/BRONCHUS	(9)	(10)	(28)	(33)
BRONCHIECTASIS				1 (3%)
INFLAMMATION, CHRONIC				1 (3%)
#LUNG/BRONCHIOLE	(9)	(10)	(28)	(33)
HYPERPLASIA, LYMPHOID	1 (11%)	3 (30%)		
#LUNG	(9)	(10)	(28)	(33)
EMBOLISM, NOS			1 (4%)	
CONGESTION, NOS			4 (14%)	
EDEMA, NOS			4 (14%)	1 (3%)
HEMORRHAGE			1 (4%)	1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BRONCHOPNEUMONIA, NOS				1 (3%)
INFLAMMATION, INTERSTITIAL				4 (12%)
BRONCHOPNEUMONIA SUPPURATIVE		3 (30%)	1 (4%)	5 (15%)
LEUKOCYTOSIS, NOS				1 (3%)
HYPERPLASIA, LYMPHOID				2 (6%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(9)	(10)	(28)	(29)
ATROPHY, NOS	2 (22%)	7 (70%)		5 (17%)
DEPLETION				1 (3%)
HYPERPLASIA, HEMATOPOIETIC			1 (4%)	4 (14%)
#SPLEEN	(9)	(9)	(26)	(33)
ATROPHY, NOS			18 (69%)	13 (39%)
HYPERPLASIA, NOS				3 (9%)
HYPERPLASIA, HEMATOPOIETIC			2 (8%)	2 (6%)
HYPERPLASIA, RETICULUM CELL				1 (3%)
HYPERPLASIA, LYMPHOID				1 (3%)
HEMATOPOIESIS		1 (11%)		3 (9%)
#LYMPH NODE			(20)	(21)
ATROPHY, NOS				5 (24%)
#MEDIASTINAL L.NODE			(20)	(21)
ATROPHY, NOS			18 (90%)	5 (24%)
HYPERPLASIA, NOS				1 (5%)
#PANCREATIC L.NODE			(20)	(21)
ATROPHY, NOS				1 (5%)
#MESENTERIC L. NODE			(20)	(21)
ATROPHY, NOS			1 (5%)	1 (5%)
HYPERPLASIA, NOS				1 (5%)
#THYMUS	(9)	(9)	(23)	(28)
HEMORRHAGE			3 (13%)	1 (4%)
ATROPHY, NOS			19 (83%)	20 (71%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(9)	(9)	(27)	(33)
INFLAMMATION, INTERSTITIAL			4 (15%)	1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ENDOCARDIUM FIBROSIS	(9)	(9)	(27) 2 (7%)	(33) 1 (3%)
DIGESTIVE SYSTEM				
#LIVER	(9)	(9)	(26)	(31)
HEMORRHAGE				1 (3%)
LYMPHOCYtic INFLAMMATORY INFILTR				1 (3%)
PERIARTERITIS				2 (6%)
NECROSIS, COAGULATIVE				1 (3%)
ANGIECTASIS			1 (4%)	
LEUKOCYTOSIS, NOS				1 (3%)
HEMATOPOIESIS				2 (6%)
#LIVER/CENTRIOLOBULAR DEGENERATION, NOS	(9)	(9)	(26) 1 (4%)	(31)
NECROSIS, NOS			2 (8%)	
#PANCREAS	(9)	(9)	(25)	(31)
INFLAMMATION, INTERSTITIAL				1 (3%)
GRANULOMA, NOS			2 (8%)	
NECROSIS, FAT			1 (4%)	
#PANCREATIC ACINUS HYPERPLASIA, NODULAR	(9)	(9)	(25)	(31)
				1 (3%)
#STOMACH	(9)	(9)	(28)	(32)
ULCER, NOS			2 (7%)	2 (6%)
ULCER, FOCAL				1 (3%)
PERIARTERITIS			2 (7%)	
URINARY SYSTEM				
#KIDNEY	(9)	(10)	(28)	(32)
LYMPHOCYtic INFLAMMATORY INFILTR				1 (3%)
INFLAMMATION, INTERSTITIAL	5 (56%)	5 (50%)	1 (4%)	2 (6%)
NEPHROPATHY			1 (4%)	
CALCIFICATION, NOS			1 (4%)	
HYPERPLASIA, TUBULAR CELL			5 (18%)	
LEUKOCYTOSIS, NOS				1 (3%)
#URINARY BLADDER INFLAMMATION, NOS	(9)	(9)	(25)	(33)
				1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, HEMORRHAGIC			1 (4%)	
ENDOCRINE SYSTEM				
#ADRENAL HEMATOPOIESIS	(9)	(9)	(28) 1 (4%)	(32)
#ADRENAL CORTEX DEGENERATION, NOS HYPERPLASIA, NODULAR	(9)	(9)	(28)	(32) 1 (3%) 3 (9%)
#THYROID ECTOPIA EPIDERMAL INCLUSION CYST HYPERPLASIA, CYSTIC	(9)	(9)	(20) 1 (5%)	(28) 1 (4%) 1 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND CYST, NOS HYPERPLASIA, NOS	(9)	(10) 1 (10%)	(31) 8 (26%)	(33) 4 (12%)
#PROSTATE HEMORRHAGE INFLAMMATION, SUPPURATIVE	(9)	(9)	(28) 1 (4%) 2 (7%)	(32)
*SEMINAL VESICLE HEMORRHAGE	(9)	(10)	(31) 1 (3%)	(33)
#TESTIS ADHESION, NOS ATROPHY, NOS	(9)	(9)	(25) 1 (4%) 6 (24%)	(32) 20 (63%)
*EPIDIDYMISS INFLAMMATION, FOCAL GRANULOMATOU	(9)	(10)	(31) 1 (3%)	(33)
NERVOUS SYSTEM				
#CEREBRUM HEMORRHAGE INFLAMMATION, NOS GLIOSIS	(9)	(9)	(27) 1 (4%) 1 (4%)	(33) 1 (3%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MALACIA			3 (11%)	
#OLFACTORY BULB HYPERPLASIA, NOS METAPLASIA, SQUAMOUS	(9)	(9)	(27)	(33) 1 (3%) 1 (3%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE INFLAMMATION, CHRONIC	(9)	(10)	(31)	(33) 1 (3%)
BODY CAVITIES				
*PERITONEUM FIBROSIS	(9)	(10)	(31)	(33) 1 (3%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1			
NECROPSY PERF/NO HISTO PERFORMED			1	
AUTO/NECROPSY/NO HISTO			2	
AUTOLYSIS/NO NECROPSY	1		3	2
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	10	36	35
ANIMALS NECROPSIED	10	10	31	31
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	10	30	31
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE INFLAMMATION, SUPPURATIVE	(10)	(10)	(31)	(31) 1 (3%)
RESPIRATORY SYSTEM				
#TRACHEA	(10)	(10)	(29)	(29)
LYMPHOCYtic INFLAMMATORY INFILTR	1 (10%)			
INFLAMMATION, SUPPURATIVE			2 (7%)	6 (21%)
INFLAMMATION, ACUTE/CHRONIC			9 (31%)	11 (38%)
#LUNG/BRONCHUS	(10)	(10)	(29)	(31)
BRONCHIECTASIS			2 (7%)	1 (3%)
INFLAMMATION, NOS				3 (10%)
INFLAMMATION, CHRONIC			2 (7%)	
#LUNG/BRONCHIOLE	(10)	(10)	(29)	(31)
HYPERPLASIA, LYMPHOID	1 (10%)	2 (20%)		
#LUNG	(10)	(10)	(29)	(31)
CONGESTION, NOS			1 (3%)	1 (3%)
EDEMA, NOS				1 (3%)
BRONCHOPNEUMONIA, NOS				3 (10%)
INFLAMMATION, FOCAL			1 (3%)	
BRONCHOPNEUMONIA DIFFUSE				1 (3%)
INFLAMMATION, INTERSTITIAL			1 (3%)	1 (3%)
BRONCHOPNEUMONIA SUPPURATIVE		1 (10%)	2 (7%)	
ABSCESS, NOS	2 (20%)	1 (10%)		
BRONCHOPNEUMONIA CHRONIC SUPPURA	2 (20%)		1 (3%)	
INFLAMMATION, FOCAL GRANULOMATOUS			1 (3%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(8)	(10)	(26)	(31)
ATROPHY, NOS	5 (63%)	5 (50%)		2 (6%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, HEMATOPOIETIC			4 (15%)	6 (19%)
#SPLEEN	(9)	(10)	(29)	(31)
ATROPHY, NOS			14 (48%)	8 (26%)
HYPERPLASIA, NOS			1 (3%)	
HYPERPLASIA, HEMATOPOIETIC			8 (28%)	2 (6%)
HEMATOPOIESIS			3 (10%)	
#LYMPH NODE			(26)	(27)
ATROPHY, NOS			1 (4%)	
HYPERPLASIA, PLASMA CELL			1 (4%)	
#MEDIASTINAL L.NODE			(26)	(27)
ATROPHY, NOS			20 (77%)	9 (33%)
HYPERPLASIA, NOS				1 (4%)
#THYMUS	(9)	(10)	(28)	(29)
CONGESTION, NOS				1 (3%)
HEMORRHAGE				1 (3%)
ATROPHY, NOS			23 (82%)	12 (41%)
HYPERPLASIA, NOS				2 (7%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(10)	(10)	(29)	(31)
INFLAMMATION, INTERSTITIAL				2 (6%)
DIGESTIVE SYSTEM				
#LIVER	(9)	(10)	(29)	(31)
HEMORRHAGE				1 (3%)
GRANULOMA, NOS			1 (3%)	
NECROSIS, NOS				1 (3%)
NECROSIS, FOCAL			1 (3%)	
HEMATOPOIESIS			2 (7%)	2 (6%)
#LIVER/CENTRILOBULAR	(9)	(10)	(29)	(31)
ATROPHY, NOS			1 (3%)	
#PANCREAS	(9)	(10)	(27)	(28)
INFLAMMATION, INTERSTITIAL				1 (4%)
#STOMACH	(9)	(10)	(27)	(30)
ULCER, NOS			2 (7%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(10)	(10)	(30)	(30)
PYELONEPHRITIS, NOS				1 (3%)
INFLAMMATION, INTERSTITIAL		2 (20%)		1 (3%)
NEPHROPATHY				1 (3%)
CALCIFICATION, FOCAL				1 (3%)
#KIDNEY/CORTEX	(10)	(10)	(30)	(30)
FIBROSIS				1 (3%)
INFARCT, HEALED			1 (3%)	
CALCIFICATION, NOS				1 (3%)
#KIDNEY/TUBULE	(10)	(10)	(30)	(30)
CALCIFICATION, NOS				1 (3%)
#KIDNEY/PELVIS	(10)	(10)	(30)	(30)
HYPERPLASIA, EPITHELIAL				1 (3%)
#URINARY BLADDER	(9)	(10)	(29)	(30)
INFLAMMATION, NOS				1 (3%)
ENDOCRINE SYSTEM				
#ADRENAL	(10)	(10)	(30)	(31)
THROMBOSIS, NOS				1 (3%)
INFLAMMATION, GRANULOMATOUS				1 (3%)
NECROSIS, FOCAL				1 (3%)
ANGIECTASIS	1 (10%)	2 (20%)		
#ADRENAL CORTEX	(10)	(10)	(30)	(31)
HYPERPLASIA, NODULAR			4 (13%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(10)	(10)	(31)	(31)
CYST, NOS	2 (20%)	3 (30%)		
HYPERPLASIA, NOS				2 (6%)
HYPERPLASIA, CYSTIC			1 (3%)	
#UTERUS	(9)	(10)	(30)	(30)
CYST, NOS				2 (7%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PYOMETRA			5 (17%)	1 (3%)
#UTERUS/ENDOMETRIUM	(9)	(10)	(30)	(30)
CYST, NOS				1 (3%)
INFLAMMATION, SUPPURATIVE	1 (11%)	2 (20%)		
FIBROSIS			27 (90%)	5 (17%)
ATROPHY, NOS			3 (10%)	1 (3%)
#OVARY/OVIDUCT	(9)	(10)	(30)	(30)
DILATATION, NOS			1 (3%)	
HYPERPLASIA, NOS			1 (3%)	
#OVARY	(9)	(10)	(25)	(23)
CYST, NOS			1 (4%)	
#OVARY/MEDULLA	(9)	(10)	(25)	(23)
HYPERPLASIA, NOS				1 (4%)
NERVOUS SYSTEM				
#CEREBRUM	(10)	(10)	(28)	(31)
DEGENERATION, CYSTIC			1 (4%)	
#BRAIN	(10)	(10)	(28)	(31)
HEMORRHAGE			1 (4%)	
MALACIA			1 (4%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(10)	(10)	(31)	(31)
HYPERPLASIA, NOS				1 (3%)
*BONE/PERIOSTEUM	(10)	(10)	(31)	(31)
HYPERPLASIA, NOS			1 (3%)	
*BONE/ENDOSTEUM	(10)	(10)	(31)	(31)
HYPERPLASIA, NOS			1 (3%)	
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*PERITONEUM	(10)	(10)	(31)	(31)
INFLAMMATION, NOS				2 (6%)
INFLAMMATION, SUPPURATIVE				1 (3%)
GRANULOMA, NOS			1 (3%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	1	1	
AUTO/NECROPSY/NO HISTO			1	
AUTOLYSIS/NO NECROPSY			5	4
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MICE ADMINISTERED PROCARBAZINE
BY INTRAPERITONEAL INJECTION

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	35	35
ANIMALS NECROPSIED	15	14	30	31
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	12	30	30
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(15)	(14)	(30)	(31)
EPIDERMAL INCLUSION CYST			1 (3%)	
INFLAMMATION, NECRO GRAN	1 (7%)			
RESPIRATORY SYSTEM				
#LUNG	(15)	(12)	(30)	(30)
INFLAMMATION, INTERSTITIAL				2 (7%)
BRONCHOPNEUMONIA SUPPURATIVE			1 (3%)	
BRONCHOPNEUMONIA, CHRONIC	1 (7%)			
HYPERPLASIA, LYMPHOID			1 (3%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(15)	(12)	(28)	(28)
HYPERPLASIA, HEMATOPOIETIC				1 (4%)
#SPLEEN	(15)	(12)	(30)	(28)
HYPERPLASIA, HEMATOPOIETIC				1 (4%)
HYPERPLASIA, RETICULUM CELL			1 (3%)	
HYPERPLASIA, LYMPHOID			2 (7%)	1 (4%)
HEMATOPOIESIS	2 (13%)	1 (8%)	2 (7%)	3 (11%)
#PULMONARY LYMPH NODE	(1)	(1)	(6)	(6)
HYPERPLASIA, LYMPHOID			1 (17%)	1 (17%)
#PANCREATIC L.NODE	(1)	(1)	(6)	(6)
HYPERPLASIA, LYMPHOID				1 (17%)
#MESENTERIC L. NODE	(1)	(1)	(6)	(6)
INFLAMMATION, HEMORRHAGIC			1 (17%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, PLASMA CELL	1 (100%)			
HYPERPLASIA, RETICULUM CELL			1 (17%)	
HYPERPLASIA, LYMPHOID			3 (50%)	4 (67%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(15)	(11)	(30)	(29)
CYST, NOS			1 (3%)	
FIBROSIS, DIFFUSE		1 (9%)		
HYPERPLASIA, NODULAR	1 (7%)			
ANGIECTASIS			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#PEYERS PATCH	(15)	(11)	(28)	(30)
HYPERPLASIA, RETICULUM CELL			1 (4%)	
URINARY SYSTEM				
#KIDNEY	(15)	(12)	(30)	(30)
INFLAMMATION, INTERSTITIAL		1 (8%)		
INFLAMMATION, SUPPURATIVE			2 (7%)	1 (3%)
PYELONEPHRITIS SUPPURATIVE				1 (3%)
INFARCT, NOS			1 (3%)	
#URINARY BLADDER	(15)	(12)	(30)	(30)
CALCULUS, NOS		1 (8%)		
INFLAMMATION, CHRONIC				1 (3%)
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
#PROSTATE	(15)	(12)	(30)	(30)
INFLAMMATION, SUPPURATIVE			2 (7%)	3 (10%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)	1 (3%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM INFLAMMATION, CHRONIC	(15)	(14)	(30)	(31) 1 (3%)
*MESENTERY HEMATOMA, ORGANIZED	(15)	(14)	(30) 1 (3%)	(31)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	6	9	6	8
NECROPSY PERF/NO HISTO PERFORMED		1		1
AUTO/NECROPSY/NO HISTO		1		
AUTOLYSIS/NO NECROPSY		1	5	4
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
ADMINISTERED PROCARBAZINE BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	15	15	35	35
ANIMALS MISSING	1		1	
ANIMALS NECROPSIED	12	14	23	26
ANIMALS EXAMINED HISTOPATHOLOGICALLY	12	14	23	26
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
*NASAL MUCOSA FIBROSIS	(12)	(14)	(23)	(26) 1 (4%)
#LUNG HYPERPLASIA, LYMPHOID	(12) 1 (8%)	(14)	(23)	(26)
HEMATOPOIETIC SYSTEM				
#SPLEEN HEMATOMA, NOS HYPERPLASIA, RETICULUM CELL HEMATOPOIESIS	(12) 1 (8%)	(14) 1 (7%)	(22) 2 (9%) 4 (18%)	(24) 1 (4%) 1 (4%) 4 (17%)
#MESENTERIC L. NODE HYPERPLASIA, RETICULUM CELL HYPERPLASIA, LYMPHOID	(1)		(4) 1 (25%)	(6) 1 (17%) 3 (50%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER HYPERPLASIA, NODULAR	(12) 1 (8%)	(14)	(23)	(26)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS		1 (7%)		1 (4%)
#PANCREAS INFLAMMATION, SUPPURATIVE	(11)	(14)	(21)	(23) 2 (9%)
#COLON INFLAMMATION, NOS INFLAMMATION, SUPPURATIVE	(12)	(14)	(21)	(24) 1 (4%) 1 (4%)
URINARY SYSTEM				
#KIDNEY INFLAMMATION, INTERSTITIAL GLOMERULONEPHRITIS, CHRONIC AMYLOIDOSIS	(12)	(14) 1 (7%)	(22) 2 (9%) 1 (5%)	(26)
ENDOCRINE SYSTEM				
NONE				
REPRODUCTIVE SYSTEM				
#UTERUS PYOMETRA FIBROSIS HYPERPLASIA, ADENOMATOUS	(12)	(13)	(23)	(25) 1 (4%) 1 (4%) 4 (16%)
#UTERUS/ENDOMETRIUM INFLAMMATION, SUPPURATIVE HYPERPLASIA, NOS HYPERPLASIA, CYSTIC	(12)	(13)	(23) 2 (9%) 2 (9%)	(25) 2 (8%) 1 (4%) 5 (20%)
#OVARY INFLAMMATION, CHRONIC SUPPURATIVE	(12)	(13)	(23) 1 (4%)	(25)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM INFLAMMATION, CHRONIC	(12)	(14)	(23)	(26) 1 (4%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	1	1	2
ANIMAL MISSING/NO NECROPSY	1		1	
AUTOLYSIS/NO NECROPSY	2	1	11	9
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY				
* NUMBER OF ANIMALS NECROPSIED				

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS
IN RATS ADMINISTERED PROCARBAZINE
BY INTRAPERITONEAL INJECTION

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Procarbazine by Intraperitoneal Injection (a)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Malignant Lymphoma (b)	1/39 (3)	1/10 (10)	3/31 (10)	9/33 (27)
P Values (c,d)	P = 0.002	N.S.	N.S.	P = 0.003**
Relative Risk (Pooled Vehicle Control)(f)			3.774	10.636
Lower Limit			0.321	1.599
Upper Limit			191.295	447.256
Relative Risk (Matched Vehicle Control)(f)			0.968	2.727
Lower Limit			0.094	0.475
Upper Limit			49.097	114.803
Weeks to First Observed Tumor		86	32	21
<hr/>				
Hematopoietic System: Leukemia (b)	0/39 (0)	0/10 (0)	0/31 (0)	3/33 (9)
P Values (c,d)	P = 0.031	N.S.	--	N.S.
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.718
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.203
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	20

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Leukemia or Malignant Lymphoma (b)	1/39 (3)	1/10 (10)	3/31 (10)	12/33 (36)
P Values (c,d)	P less than 0.001	P = 0.013	N.S.	P less than 0.001**
Relative Risk (Pooled Vehicle Control)(f)			3.774	14.182
Lower Limit			0.321	2.294
Upper Limit			191.295	578.099
Relative Risk (Matched Vehicle Control)(f)			0.968	3.636
Lower Limit			0.094	0.685
Upper Limit			49.097	148.380
Weeks to First Observed Tumor		86	32	20
Adrenal: Cortical Adenoma (b)	0/36 (0)	0/9 (0)	3/28 (11)	2/32 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.784	0.336
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.219	0.093
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	27	29

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Adenocarcinoma, NOS (b)	0/39 (0)	0/10 (0)	1/31 (3)	7/33 (21)
P Values (c,d)	P = 0.001	P = 0.016	N.S.	P = 0.003**
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.068	2.323
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.019	0.659
Upper Limit			Infinite	Infinite
95 Weeks to First Observed Tumor		--	28	17
Mammary Gland: Adenoma, NOS or Adenocarcinoma, NOS (b)	0/39 (0)	0/10 (0)	1/31 (3)	8/33 (24)
P Values (c,d)	P = 0.001	P = 0.009	N.S.	P = 0.001**
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.068	2.736
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.019	0.776
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	28	21

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Cystadenocarcinoma, NOS (b)	0/39 (0)	0/10 (0)	0/31 (0)	2/33 (6)
P Values (c,d)	N.S.	N.S.	--	N.S.
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.353
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.099
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	17
<hr/>				
Olfactory Bulb: Adenocarcinoma, NOS (b)	0/38 (0)	0/9 (0)	0/27 (0)	3/33 (9)
P Values (c,d)	P = 0.034	N.S.	--	N.S.
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.702
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.185
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	29

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Brain/Olfactory Bulb: Carcinoma, NOS, Neuroblastoma or Adenocarcinoma (b)	0/38 (0)	0/9 (0)	12/27 (44)	9/33 (27)
P Values (c,d)	P = 0.003	N.S.	P = 0.014*	P = 0.001**
Departure from Linear Trend	P = 0.001	P = 0.013	P less than 0.001**	
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			5.280	3.072
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			1.401	0.817
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	23	21
Ear Canal: Keratoacanthoma (b)	0/39 (0)	0/10 (0)	0/31 (0)	2/33 (6)
P Values (c,d)	N.S.	N.S.	--	N.S.
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.353
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.099
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	26

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

- (a) Dosed groups received doses of 15 or 30 mg/kg.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group (*) or with the pooled-control group (**) when P is less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
- (e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
- (f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Procarbazine by Intraperitoneal Injection (a)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Malignant Lymphoma (b)	0/40 (0)	0/10 (0)	0/31 (0)	20/31 (65)
P Values (c,d)	P less than 0.001	P less than 0.001	--	P less than 0.001* P less than 0.001**
Departure from Linear Trend (e)	P less than 0.001	P = 0.004		
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	8.567
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	2.363
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	12

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Adrenal: Cortical Adenoma (b)	1/38 (3)	0/10 (0)	4/30 (13)	2/31 (6)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)(f)			5.067	2.452
Lower Limit			0.536	0.134
Upper Limit			240.212	139.793
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.345	0.105
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	21	21

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Adenocarcinoma, NOS (b)	2/38 (5)	0/10 (0)	16/31 (52)	25/31 (81)
P Values (c,d)	P less than 0.001	P less than 0.001	P = 0.003* P less than 0.001**	P less than 0.001* P less than 0.001**
Relative Risk (Pooled Vehicle Control)(f)			9.806	15.323
Lower Limit			2.594	4.543
Upper Limit			79.193	102.409
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			1.842	3.051
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	22	16

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Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Adenoma, NOS Adenocarcinoma, NOS (b)	3/38 (8)	0/10 (0)	17/31 (55)	25/31 (81)
P Values (c,d)	P less than 0.001	P less than 0.001	P = 0.002* P less than 0.001**	P less than 0.001* P less than 0.001**
Relative Risk (Pooled Vehicle Control)(f)			6.946	10.215
Lower Limit			2.290	3.746
Upper Limit			32.191	38.520
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			1.971	3.051
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		—	21	16

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Cystadenocarcinoma, NOS (b)	0/38 (0)	0/10 (0)	0/31 (0)	1/31 (3)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.066
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.019
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	17
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Mammary Gland: Cystadenoma, NOS or Cystadenocarcinoma, NOS (b)	0/38 (0)	0/10 (0)	0/31 (0)	2/31 (6)
P Values (c,d)	N.S.	N.S.	--	N.S.
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.366
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.105
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	17

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Fibroadenoma (b)	10/38 (26)	2/10 (20)	4/31 (13)	3/31 (10)
P Values (c,d)	P = 0.044 (N)	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)(f)			0.490	0.368
Lower Limit			0.123	0.071
Upper Limit			1.511	1.279
Relative Risk (Matched Vehicle Control)(f)			0.645	0.484
Lower Limit			0.117	0.069
Upper Limit			6.542	5.328
Weeks to First Observed Tumor		84	26	20

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Brain: Olfactory Neuroblastoma (b)	0/38 (0)	0/10 (0)	17/28 (61)	2/31 (6)
P Values (c,d)	N.S.	N.S.	P = 0.001* P less than 0.001**	N.S.
Departure from Linear Trend(e)	P less than 0.001	P less than 0.001		
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			7.563	0.366
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			2.192	0.105
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	20	21

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography:</u> <u>Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Brain/Cerebrum: Olfactory Neuroblastoma or Mucinous Adenocarcinoma (b)	0/38 (0)	0/10 (0)	17/28 (61)	3/31 (10)
P Values (c,d)	N.S.	N.S.	P = 0.007* P less than 0.001**	N.S.
Departure from Linear Trend(e)	P less than 0.001	P less than 0.001		
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			7.564	0.746
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			1.598	0.216
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	20	21

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Ear Canal: Keratoacanthoma (b)	0/38 (0)	0/10 (0)	2/31 (6)	3/31 (10)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.366	0.746
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.105	0.216
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	27	22

(a) Dosed groups received doses of 15 or 30 mg/kg.

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

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group (*) or with the pooled-control group (**) when P is less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

- (d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
- (e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
- (f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN
MICE ADMINISTERED PROCARBAZINE
BY INTRAPERITONEAL INJECTION

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Procarbazine by Intraperitoneal Injection (a)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Subcutaneous Tissue: Fibroma or Fibrosarcoma (b)	0/42 (0)	0/14 (0)	2/30 (7)	1/31 (3)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.417	0.073
Upper Limit			Infinite	Infinite
Relative Risk (Matched-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.147	0.025
Upper Limit			Infinite	Infinite
Weeks to Observed Tumor		--	75	52
Lung: Alveolar/Bronchiolar Adenoma (b)	0/39 (0)	0/12 (0)	10/30 (33)	10/30 (33)
P Values (c,d)	P less than 0.001	N.S.	P = 0.020* P less than 0.001**	P = 0.020* P less than 0.001**
Relative Risk (Pooled-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			3.931	3.931
Upper Limit			Infinite	Infinite
Relative Risk (Matched-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			1.309	1.309
Upper Limit			Infinite	Infinite
Weeks to Observed Tumor		--	60	38

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Table F1. Analyses of the Incidence of Primary Tumors in Male Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	0/39 (0)	0/12 (0)	11/30 (37)	10/30 (33)
P Values (c,d)	P less than 0.001	N.S.	P = 0.013* P less than 0.001**	P = 0.020* P less than 0.001**
Departure from Linea Trend (e)	P = 0.024			
Relative Risk (Pooled-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			4.392	3.931
Upper Limit			Infinite	Infinite
Relative Risk (Matched-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			1.461	1.308
Upper Limit			Infinite	Infinite
Weeks to Observed Tumor			--	60
				38

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Lymphoma or Leukemia (b)	0/42 (0)	0/14 (0)	4/30 (13)	4/31 (13)
P Values (c,d)	P = 0.028	N.S.	P = 0.027*	P = 0.029*
Relative Risk (Pooled-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			1.310	1.268
Upper Limit			Infinite	Infinite
Relative Risk (Matched-Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.465	0.450
Upper Limit			Infinite	Infinite
Weeks to Observed Tumor		--	66	37
Liver: Hepatocellular Adenoma (b)	0/39 (0)	0/11 (0)	3/30 (10)	3/29 (10)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.790	0.818
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.243	0.123
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	75	56

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Malignant Lymphoma (b)	0/42 (0)	0/14 (0)	3/30 (10)	3/31 (10)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.849	0.822
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.301	0.291
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	66	37
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Liver: Hepatocellular Adenoma (b)	0/39 (0)	0/11 (0)	3/30 (10)	2/29 (7)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.790	0.401
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.243	0.123
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	75	56

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Liver: Hepatocellular Adenoma or Carcinoma (b)	0/39 (0)	0/11 (0)	3/30 (10)	3/29 (10)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.790	0.818
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.243	0.251
Upper Limit			Infinite	Infinite
Weeks to Observed Tumor		--	75	56
Brain: Olfactory Neuroblastoma (b)	0/36 (0)	0/8 (0)	0/24 (0)	9/29 (31)
P Values (c,d)	P less than 0.001	P = 0.003	N.S.	P less than 0.001**
Departure from Linear Trend (e)	P = 0.028			
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	3.327
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	0.844
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	47

Table Fl. Analyses of the Incidence of Primary Tumors in Male Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Brain: Olfactory Neuroblastoma or Undifferentiated Carcinoma (b)	0/36 (0)	0/8 (0)	0/24 (0)	10/29 (34)
P Values (c,d)	P less than 0.001	P = 0.002	--	P less than 0.001**
Departure from Linear Trend (e)	P = 0.020			
Relative Risk (Pooled Vehicle Control) (f)			--	Infinite
Lower Limit			--	3.768
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control) (f)			--	Infinite
Lower Limit			--	0.955
Upper Limit			--	Infinite
Weeks to Observed Tumor		--	--	47

(a) Dosed groups received doses of 6 or 12 mg/kg.

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

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group (*) or with the pooled-control group (**) when P is less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

- (d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
- (e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
- (f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Procarbazine by Intraperitoneal Injection (a)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Lung: Alveolar/Bronchiolar Adenoma (b)	0/43 (0)	0/14 (0)	1/23 (4)	6/26 (23)
P Values (c,d)	P = 0.001	P = 0.016	N.S.	P = 0.002**
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.100	2.681
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			0.034	0.931
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	77	50
Hematopoietic System:				
Malignant Lymphoma (b)	0/43 (0)	0/14 (0)	6/23 (26)	2/26 (8)
P Values (c,d)	N.S.	N.S.	P = 0.043*	N.S.
			P = 0.001**	
Departure from Linear Trend (e)	P = 0.002	P = 0.012		
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			3.038	0.493
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			1.054	0.170
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	55	53

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Lymphoma or Leukemia (b)	0/43 (0)	0/14 (0)	8/23 (35)	2/26 (8)
P Values (c,d)	N.S.	N.S.	P = 0.013* P less than 0.001**	N.S.
Departure from Linear Trend (e)	P less than 0.001	P = 0.002		
Relative Risk (Pooled Vehicle Control)(f)			Infinite	Infinite
Lower Limit			4.351	0.493
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control)(f)			Infinite	Infinite
Lower Limit			1.510	0.170
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	55	53

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Thyroid: Follicular-cell Adenoma (b)	0/42 (0)	0/13 (0)	1/18 (6)	0/19 (0)
P Values (c,d)	N.S.	N.S.	N.S.	--
Relative Risk (Pooled Vehicle Control)(f)			Infinite	--
Lower Limit			0.125	--
Upper Limit			Infinite	--
Relative Risk (Matched Vehicle Control)(f)			Infinite	--
Lower Limit			0.041	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor		--	81	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Uterus: Adenocarcinoma, NOS (b)	0/42 (0)	0/13 (0)	14/23 (61)	8/25 (32)
P Values (c,d)	P less than 0.001	N.S.	P less than 0.001* P less than 0.001**	P = 0.022* P less than 0.001**
Departure from Linear Trend (e)	P less than 0.001	P less than 0.001		
Relative Risk (Pooled Vehicle Control) (f)			Infinite	Infinite
Lower Limit			8.237	3.903
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control) (f)			Infinite	Infinite
Lower Limit			2.731	1.297
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	64	53

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Uterus: Leiomyosarcoma (b)	0/42 (0)	0/13 (0)	2/23 (9)	2/25 (8)
P Values (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.544	0.501
Upper Limit			Infinite	Infinite
Relative Risk (Matched Vehicle Control) (f)			Infinite	Infinite
Lower Limit			0.180	0.165
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor		--	55	44

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

<u>Topography: Morphology</u>	<u>Pooled Vehicle Control</u>	<u>Matched Vehicle Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Brain: Olfactory Neuroblastoma (b)	0/43 (0)	0/14 (0)	0/22 (0)	11/25 (44)
P Values (c,d)	P less than 0.001	P less than 0.001	--	P = 0.003* P less than 0.001**
Departure from Linear Trend (e)	P = 0.006	P = 0.030		
Relative Risk (Pooled Vehicle Control)(f)			--	Infinite
Lower Limit			--	5.829
Upper Limit			--	Infinite
Relative Risk (Matched Vehicle Control)(f)			--	Infinite
Lower Limit			--	2.023
Upper Limit			--	Infinite
Weeks to First Observed Tumor		--	--	44

(a) Dosed groups received doses of 6 or 12 mg/kg.

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

(c) Beneath the incidence of tumors in the vehicle-control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the vehicle-control group (*) or with the pooled-control group (**) when P is less than 0.05 for either control group; otherwise, not significant (N.S.) is indicated.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice
Administered Procarbazine by Intraperitoneal Injection (a)

(continued)

- (d) A negative trend (N) indicates a lower incidence in a dosed group than in the vehicle-control group.
- (e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
- (f) The 95% confidence interval of the relative risk between each dosed group and the specified control group.

