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p-CRESIDINE

FOR POSSIBLE CARCINOGENICITY

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

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REPORT ON THE BIOASSAY OF p-CRESIDINE
FOR POSSIBLE CARCINOGENICITY

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

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

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

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. D. W. Hayden (3), Dr. A. S. Krishna Murthy (3) and Dr. A. Russfield (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Mr. W. W. Belew (5,8) and Mr. R. M. Helfand (5), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (5) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (5), task leader Dr. M. R. Kornreich (5,10), senior biologist Ms. P. Walker (5), biochemist, Mr. S. C. Drill (5), and technical editor Ms. P. A. Miller (5). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,10), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,11), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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

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

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

4. Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri.

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

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

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

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

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

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

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

SUMMARY

A bioassay of p-cresidine for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. p-Cresidine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The dietary concentrations used in the chronic bioassay for low and high dose rats were 0.5 and 1.0 percent, respectively. The time-weighted average concentrations fed to low dose male, low dose female, high dose male and high dose female mice were 0.22, 0.22, 0.46, and 0.44 percent, respectively.

All dosed animals, except for high dose male mice, were administered p-cresidine in the diet for 104 weeks and observed for an additional period of up to 2 weeks. All high dose male mice were dead by the end of week 92. For each species, 50 animals of each sex were placed on test as controls and fed only the basal laboratory diet.

Mortality rates were dose-related for both sexes of both species. That incidences of certain tumors were higher in low dose than in high dose groups was probably due to accelerated mortality in the high dose groups.

In dosed rats of both sexes, statistically significant incidences of bladder carcinomas (combined incidences of papillary carcinomas, squamous-cell carcinomas, transitional-cell papillomas, transitional-cell carcinomas, and undifferentiated carcinomas) and olfactory neuroblastomas were observed. The combined incidence of neoplastic nodules of the liver, hepatocellular carcinomas, or mixed hepato/cholangio carcinomas was also significant in low dose male rats.

In both male and female dosed mice, the incidence of bladder carcinomas (combined incidence of carcinomas NOS, squamous-cell carcinomas, and transitional-cell carcinomas) was significant. The incidence of hepatocellular carcinomas was significant in dosed female mice.

Under the conditions of this bioassay, p-cresidine was carcinogenic to Fischer 344 rats, causing increased incidences of carcinomas and of papillomas of the urinary bladder in both sexes, increased incidences of olfactory neuroblastomas in both sexes, and of liver tumors in males. p-Cresidine was also carcinogenic in B6C3F1 mice, causing carcinomas of the urinary bladders in both sexes and hepatocellular carcinomas in females.

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I. INTRODUCTION

p-Cresidine (Figure 1) (NCI No. C02982), used in the production of various azo dyes, was selected for bioassay by the National Cancer Institute in response to the high incidence of bladder cancer observed among dye manufacturing industry workers (Anthony and Thomas, 1970; Wynder et al., 1963). Aromatic amines are one class of chemicals believed to contribute to the increased cancer risk in this industry (Wynder et al., 1963).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 2-methoxy-5-methylbenzenamine.* It is also known as 2-methoxy-5-methylaniline; 5-methyl-o-anisidine; m-amino-p-cresol methyl ether; MASO; and simply as cresidine.

p-Cresidine appears to be used solely as an intermediate for dyes and pigments. It is believed to be used in the preparation of eleven dyes which are produced commercially in the United States: C.I. (Colour Index) Direct Black 17, Direct Blue 67, Direct Blue 126, Direct Green 26, Direct Orange 34, Direct Orange 83, Direct Red 79, Direct Violet 9, Direct Violet 51, Direct Yellow 41, and Disperse Black 2 (Society of Dyers and Colourists, 1971; as cited in Urso, 1977).

Precise production figures for p-cresidine are not available; however, the Sherwin-Williams Company, which produces p-cresidine,

*The CAS registry number is 120-71-8.

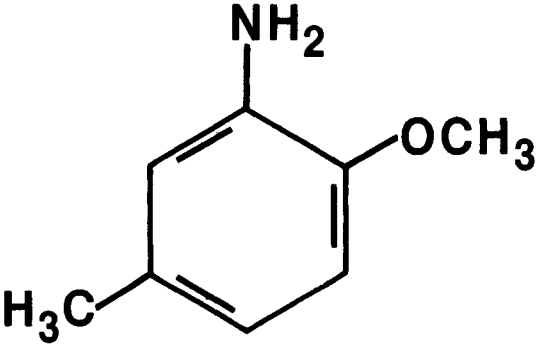


FIGURE 1
CHEMICAL STRUCTURE OF p-CRESIDINE

estimates that average use of the compound during the period 1971 to 1976 was about 590,000 pounds annually (Compton, 1977).

Since p-cresidine is used solely as an intermediate in dye manufacture, potential for exposure is primarily limited to workers in dye production facilities.

While adequate chronic toxicity data for p-cresidine are not available, a study of workmen involved in the manufacture and handling of the compound, conducted by the Sherwin-Williams Company, revealed no adverse health effects related to p-cresidine exposure (Compton, 1977).

II. MATERIALS AND METHODS

A. Chemicals

p-Cresidine was purchased from Carroll Products, Wood River Junction, Rhode Island by the NCI for Mason Research Institute, Worcester, Massachusetts and chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The experimentally determined melting point of 51.5° to 52.5°C, due to its narrow range and proximity to the literature value of 51° to 52°C (Pollock and Stevens, 1965), suggested a compound of high purity. Thin-layer chromatography using a benzene:ethyl acetate solvent system and visualized with ultraviolet light indicated the presence of three impurities, two less motile and one more motile than the major compound. Infrared analysis was consistent with the structure of the compound. Ultraviolet analysis indicated λ_{max} at 290 and 237 nm with respective molar extinction coefficients (ϵ) of 3312 and 6820. The literature values are λ_{max} = 290 and 236 nm with respective ϵ values of 3620 and 7120 (Mehta, 1978). Titration of the amine function with perchloric acid indicated a purity of 98.9 $\pm$ 0.1 percent.

Throughout this report the term p-cresidine is used to represent this technical-grade material.

B. Dietary Preparation

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

p-Cresidine was administered to the dosed animals as a component of the diet.

The brown amorphous chemical was removed from its shipping container and stored in an amber glass stock bottle inside a plastic bucket. The p-cresidine was weighed out in proper amounts from the stock bottle under an exhaust hood. The compound was dissolved with an appropriate amount of acetone (0.016 percent by volume of the final mix) with the help of a mortar and pestle. This liquid mixture was hand-blended in an aluminum bowl with an aliquot of the ground feed until all liquid was absorbed and visual homogeneity was attained. This premix was then placed into a 6 kg capacity Patterson-Kelley standard model twin-shell stainless steel V-blender along with the remainder of the diet. The blender was sealed and operated for 20 minutes. The mixture was then emptied into stainless steel trays and allowed to sit under the exhaust hood for 2 and 1/2 hours while being stirred with a glass rod every 1/2 hour, allowing evaporation of a large proportion of the acetone.

Prepared diets were placed in double clear plastic bags and stored in the dark at 4°C. Diets were prepared weekly and any unused portions were discarded after 2 weeks.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through

contracts of the Division of Cancer Treatment, National Cancer Institute from Charles River Breeding Laboratories, Wilmington, Massachusetts. Dosed and control animals for both species were received in separate shipments.

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

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex. During quarantine and for the first 12 months of study, dosed rats were housed in galvanized steel wire-mesh cages (Fenco Cage Products, Boston, Massachusetts) suspended over newspapers. Control rats were held in galvanized cages for the first 14 months of study. Newspapers under cages were replaced daily and cages and racks washed weekly. For the remainder of the study, all rats were housed in suspended polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) equipped with disposable

nonwoven fiber filter sheets. Clean bedding and cages were provided twice weekly. SAN-I-CEL® corncob bedding (Paxton Processing Company, Paxton, Illinois) was used during the first 6 months of polycarbonate caging. Aspen hardwood chip bedding (American Excelsior Company, Baltimore, Maryland) was used for the remainder of the study. Stainless steel cage racks (Fenco Cage Products) were cleaned once every 2 weeks, and disposable filters were replaced at that time.

Mice were housed by sex in polycarbonate cages fitted with perforated stainless steel lids (Lab Products, Inc.). Nonwoven fiber filter bonnets were used over cage lids. Dosed mice were housed ten per cage for the first 9 months and five per cage thereafter. Control mice were changed from ten per cage to five per cage after 11 months. Clean cages, lids, and bedding were provided three times per week when cage populations were ten and twice per week when cage populations were five. SAN-I-CEL® was used for the first 12 months for control mice, and for the first 10 months for dosed mice. Bed-o-Cobs® corncob bedding (The Andersons Cob Division, Maumee, Ohio) was used for 8 months subsequent to utilization of SAN-I-CEL®. Aspen bedding was then used until completion of the study for all groups of mice. Reusable filter bonnets and pipe racks were sanitized every 2 weeks throughout the study.

Water was available from 250 ml water bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced

twice weekly and, for rats only, water was supplied as needed between changes. Food and water were available ad libitum.

During the period of chemical administration, animals were supplied Wayne Lab-Blox® containing the appropriate concentrations of p-cresidine and acetone. The basal laboratory diet was supplied to control animals during the same period. Meal was distributed from Alpine® aluminum feed cups (Curtin Matheson Scientific, Inc., Woburn, Massachusetts) to rats while in galvanized-steel cages. While in polycarbonate cages, rats were fed from stainless steel gangstyle hoppers (Scientific Cages, Inc., Bryan, Texas). Mice were fed from Alpine® feed cups for the first 12 months (dosed groups) or 14 months (controls) of study. Stainless steel gangstyle feed hoppers were used for the remainder of the test. Food hoppers were changed on the same schedule as were cages. Food was replenished daily in Alpine® feed cups.

Dosed and control rats were housed in a room with other rats receiving diets containing* acetylaminofluorene (53-96-3); 2,3,5,6-tetrachloro-4-nitroanisole (2438-88-2); 4-chloro-o-phenylenediamine (95-83-0); 1H-benzotriazole (95-14-7); and 4-chloro-m-phenylenediamine (5131-60-2).

Dosed and control mice were housed in a room with other mice receiving diets containing 2-methyl-1-nitroanthraquinone (129-15-7); aniline hydrochloride (142-04-1); acetylaminofluorene (53-96-3); fenaminosulf (140-56-7); and 4-chloro-m-phenylenediamine (5131-60-2).

*CAS registry numbers are given in parentheses.

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of p-cresidine for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice.

Animals of each species were distributed among three groups, each consisting of five males and five females. p-Cresidine was administered to two of the three groups of each species at dietary concentrations of 1.0 and 3.0 percent for 8 weeks. The third group of each species served as a control group, receiving only the basal laboratory diet.

As deaths occurred among all groups except male rats receiving 3.0 percent p-cresidine in the feed, the high concentration chosen for the chronic study was 1.0 percent p-cresidine for both rats and mice.

F. Experimental Design

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

All animals were approximately 6 weeks old at the time they were placed on test. Dosed rats and mice shared the same median date of birth, while controls were born approximately 7 weeks earlier and placed on test 7 weeks before dosed animals.

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
p-CRESIDINE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	p-CRESIDINE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	50	0	0	106
LOW DOSE	50	0.5 0	104	1
HIGH DOSE	50	1.0 0	104	1
FEMALE				
CONTROL	50	0	0	106
LOW DOSE	50	0.5 0	104	2
HIGH DOSE	50	1.0 0	104	2

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
p-CRESIDINE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	p-CRESIDINE CONCENTRATION (PERCENT)	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[a]
MALE					
CONTROL	50	0	0	97	0
LOW DOSE	50	0.5 0.15 0	21 83	 2	0.22
HIGH DOSE[b]	50	1.0 0.3	21 71		0.46
FEMALE					
CONTROL	50	0	0	97	0
LOW DOSE	50	0.5 0.15 0	21 83	 2	0.22
HIGH DOSE	50	1.0 0.3 0	21 83	 2	0.44

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

[b] All animals in this group were dead by the end of week 92.

When it was noted that a trace acetone odor remained in the dosed feed, acetone controls were placed on test in addition to the untreated controls. However, these acetone controls were not entirely comparable to dosed animals because one set of acetone controls had an inadequate number of animals (only 10 animals of each sex and species) and were treated for parasites with piperazine adipate. A second set of acetone controls was not utilized in comparisons with dosed animals because they were obtained from a different supplier than the other groups.

The initial concentrations of p-cresidine used for both rats and mice were 1.0 and 0.5 percent. Throughout this report those animals initially receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. These concentrations were utilized throughout the study for rats; however, after 21 weeks, the concentrations administered to mice were decreased to 0.3 and 0.15 percent for the high and low dose groups, respectively. p-Cresidine was administered in the diet to dosed animals for a period of 104 weeks (except for high dose male mice which were all dead by week 92), followed by an observation period of up to 2 weeks.

For both species, control animals had the basal laboratory diet available ad libitum during the bioassay.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12

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

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

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

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

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

H. Data Recording and Statistical Analyses

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

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be

missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously

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

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

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

procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

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

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

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

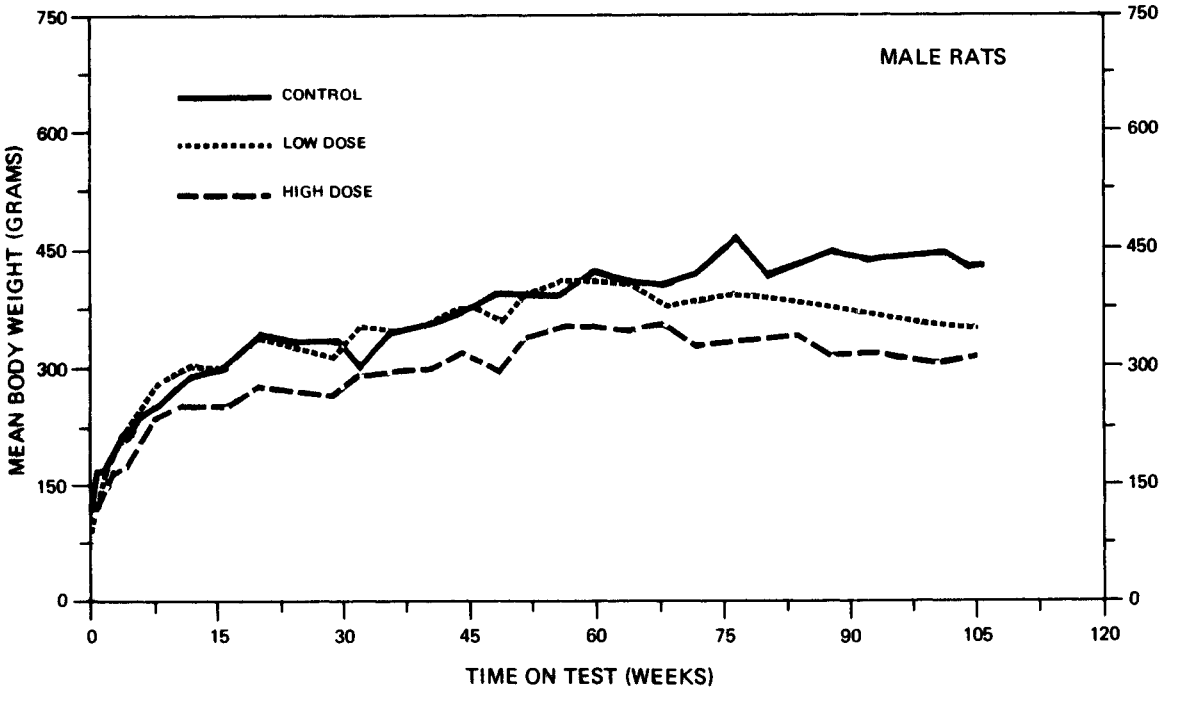
Male and female dosed rats had mean group body weights lower than those of their respective controls (Figure 2), especially the weights of the high dose male group which were markedly decreased throughout the study. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Subcutaneous masses on various parts of the body were observed in 2 control, 3 low dose, and 1 high dose males and in 3 control, 7 low dose, and 1 high dose females. Cutaneous masses or nodules were detected in 2 control and 3 low dose males and in 2 low dose and 1 high dose females. Skin lesions were observed in 1 control male. Other isolated clinical observations included penile swelling in 1 high dose male, swelling of a single nipple in 1 low dose female, and severe emaciation in 1 low dose male.

B. Survival

The estimated probabilities of survival for male and female rats in the control and p-cresidine-dosed groups are shown in Figure 3. For both male and female rats there were significant positive associations between dosage and mortality.

For males five rats from the control group were sacrificed in week 78. Sixty-two percent (31/50) of the high dose, 96 percent



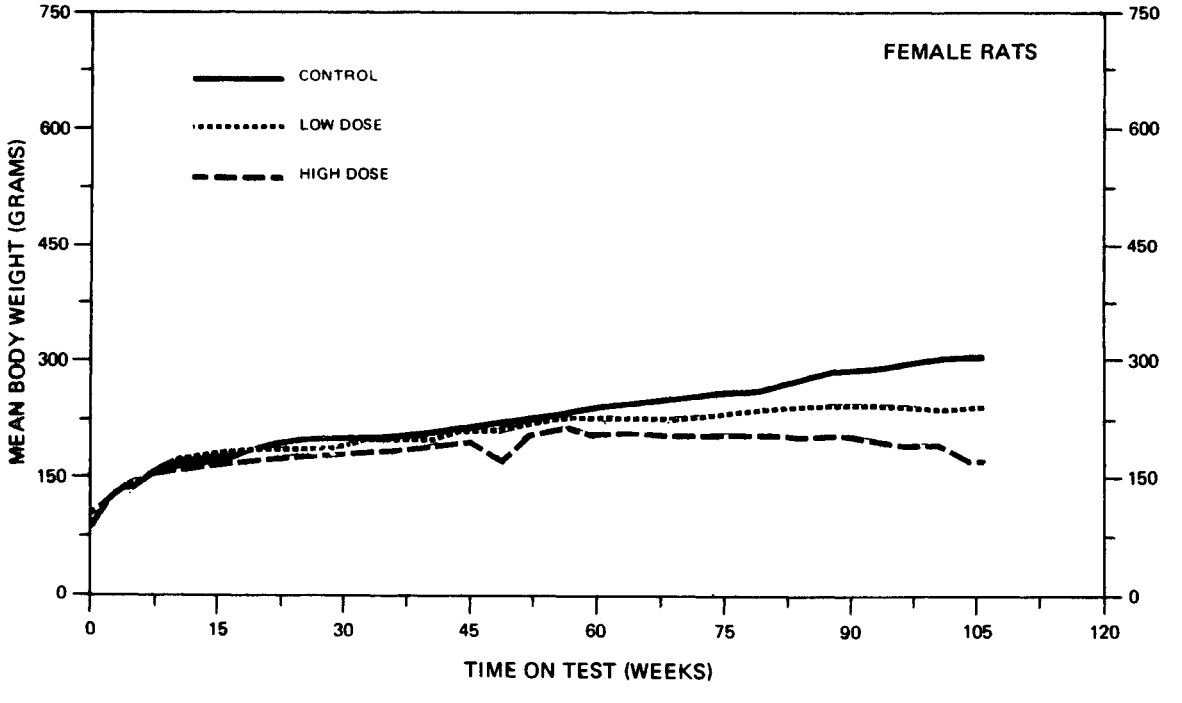
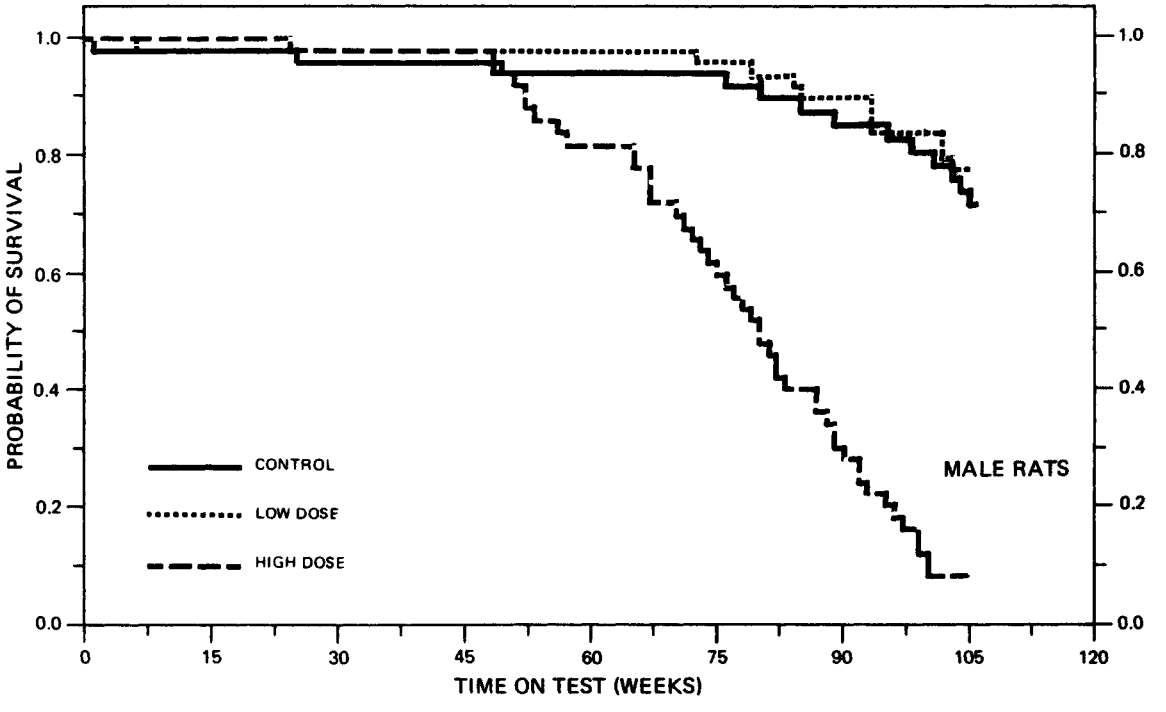


FIGURE 2
GROWTH CURVES FOR p-CRESIDINE CHRONIC STUDY RATS



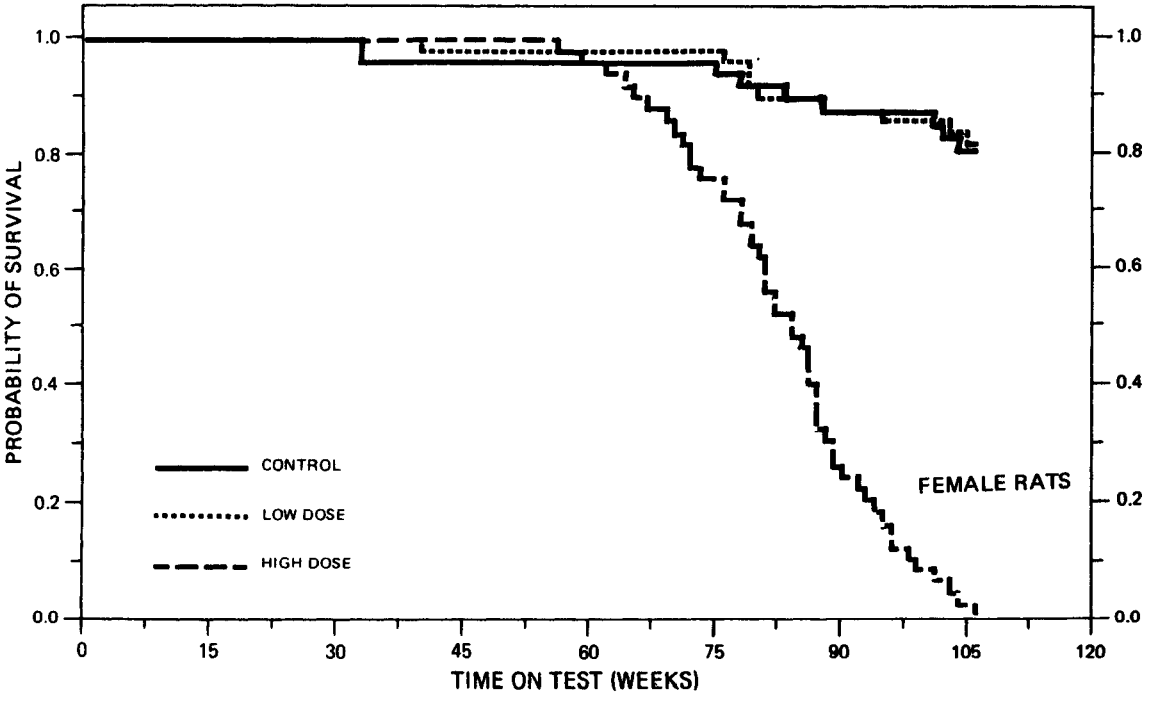


FIGURE 3
SURVIVAL COMPARISONS OF p-CRESIDINE CHRONIC STUDY RATS

(48/50) of the low dose, and 94 percent (47/50) of the control rats survived on test at least 75 weeks.

For female rats five of the controls were sacrificed in week 78. Seventy-six percent (38/50) of the high dose, 98 percent (49/50) of the low dose, and 96 percent (48/50) of the control rats survived on test at least 75 weeks.

C. Pathology

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

Both male and female rats fed p-cresidine showed compound-related effects in the urinary bladder and in the epithelium of the nasal cavity.

No neoplasms of the bladder were found in the control rats. In contrast, both male and female rats fed p-cresidine developed numerous dose-related neoplasms or hyperplasias in the bladder. The incidences of these lesions are tabulated in the table below:

MALE	Control	Low Dose	High Dose
Number of animals with tissues examined histopathologically	(48)	(48)	(47)
Urinary Bladder			
Hyperplasia	0	11(23%)	2(4%)
Undifferentiated Carcinoma	0	0	1(2%)
Papillary Carcinoma	0	0	4(9%)
Squamous-Cell Carcinoma	0	1(2%)	6(13%)
Transitional-Cell Papilloma	0	14(29%)	3(6%)
Transitional-Cell Carcinoma	0	15(31%)	31(66%)
Leiomyosarcoma	0	0	2(4%)
FEMALE			
Number of animals with tissues examined histopathologically	(47)	(49)	(46)
Urinary Bladder			
Hyperplasia	0	11(22%)	1(2%)
Neoplasm NOS	0	0	2(4%)
Papillary Carcinoma	0	0	1(2%)
Squamous-Cell Carcinoma	0	9(18%)	7(15%)
Transitional-Cell Papilloma	0	6(12%)	2(4%)
Transitional-Cell Carcinoma	0	22(45%)	33(72%)
Leiomyosarcoma	0	2(4%)	3(7%)

Hyperplasia was defined as the presence of more than three layers of epithelial cells lining the fully inflated bladder. Nuclei of these cells were histologically normal.

The neoplasms were classified as papillomas when they consisted of histologically benign, regularly arranged, transitional epithelium covering a papillary core composed of fibrovascular tissue. Tumors were diagnosed as transitional-cell carcinomas when nuclei of the transitional cells became pleomorphic and hyperchromatic and mitotic figures became frequent. They were classified as squamous-cell

carcinomas when, in addition to nuclear criteria of malignancy, the tumor cells showed cytoplasmic keratinization or developed intercellular bridges. There were no sharp boundary lines between these categories which formed a continuous spectrum of progressively malignant change. The carcinomas were invasive and a few of these tumors metastasized to distant organs. A few rats fed p-cresidine developed leiomyosarcomas of the bladder wall which tended to occur in association with malignant tumors of the bladder epithelium. There were neoplasms of the transitional-cell epithelium of the renal pelvis in 1/49 low dose female rats and in 2/49 low dose males. One high dose female developed an undifferentiated carcinoma of the renal parenchyma.

No nasopharyngeal neoplasms were found in the control groups. The incidence of neoplasms observed in the nasal cavity is summarized in the following table:

MALES	Control	Low Dose	High Dose
Number of animals necropsied	(48)	(50)	(47)
Nasal Cavity			
Neoplasm NOS, Malignant	0	0	1(2%)
Carcinoma NOS	0	0	1(2%)
Adenoma NOS	0	1(2%)	0
Neuroblastoma	0	0	1(2%)
Olfactory Neuroblastoma	0	1(2%)	20(43%)

FEMALES	Control	Low Dose	High Dose
Number of animals necropsied	(50)	(50)	(49)
Nasal Cavity			
Squamous-Cell Carcinoma	0	0	1(2%)
Squamous-Cell Carcinoma, Invasive	0	0	0
Adenocarcinoma NOS	0	0	1(2%)
Olfactory Neuroblastoma	0	0	11(22%)

The rats fed p-cresidine developed dose-related olfactory neuroblastomas. These tumors consisted of masses of cells having scant cytoplasm and large, ovoid nuclei with prominent chromatin. They were divided into lobules by very fine fibrovascular septae. In many tumors, rosettes, pseudorosettes, or palisade arrangement of cells suggested a neural origin. They frequently exhibited osteoclastic activity and local invasion, destroying the cribriform plate of the skull and invading the forebrain. Some tumors showed focal hemorrhagic necrosis. In addition, there was an adenoma, an adenocarcinoma, a squamous-cell carcinoma, and a polyp involving the nasal cavity of dosed rats. Males appeared to be more susceptible to nasal tumors than females.

p-Cresidine feeding had an equivocal effect on the liver of the rats. Males receiving the low dose of the compound developed several (10/49 [20 percent]) neoplastic nodules plus a few hepatic carcinomas. However, neoplastic nodules were seldom seen in high dose males (1/46 [2 percent]) and low dose females (4/48 [8 percent]) and were not seen at all in high dose females. Only a few carcinomas were observed in

dosed male rats. The criteria used for the diagnosis of these lesions were those of Squire and Levitt (1975).

No tumors of the preputial or clitoral glands were seen in controls; 3/50 (6 percent) occurred in low dose males, 3/50 (6 percent) in low dose females, and 2/47 (4 percent) in high dose males. There were gliomas in 2/48 (4 percent) low dose females, and in 3/43 (7 percent) high dose males. As the high dose of p-cresidine shortened the survival of both sexes by inducing massive bladder tumors, an effect on other organ systems may have been obscured.

Based on the results of this pathologic examination, p-cresidine was considered to be carcinogenic in Fischer 344 rats because it induced neoplasms of the urinary bladder and olfactory neuroblastomas of the nasal cavity. Neoplastic nodules of the liver may have been induced in the male rat.

D. Statistical Analyses of Results

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

In both male and female rats, the combined incidence of undifferentiated carcinomas, papillary carcinomas, squamous-cell carcinomas, transitional-cell papillomas, or transitional-cell carcinomas of the

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	3/48(0.06)	2/50(0.04)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.640	0.340
Lower Limit	---	0.055	0.007
Upper Limit	---	5.345	4.058
Weeks to First Observed Tumor	105	105	105
Nasal Cavity and Nasopharynx: Malignant Neoplasm NOS; Carcinoma NOS; or Adenocarcinoma NOS[b]	0/48(0.00)	0/50(0.00)	3/47(0.06)
P Values[c]	P = 0.035	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.615
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	67
Nasal Cavity: Olfactory Neuroblastoma or Neuroblastoma[b]	0/48(0.00)	1/50(0.02)	21/47(0.45)
P Values[c]	P < 0.001	N.S.	P < 0.001
Departure from Linear Trend[e]	P = 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.051	6.974
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	84	48

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Nasal Cavity: Neoplasm NOS, Malignant; Carcinoma NOS; Adenoma NOS; Neuroblastoma; or Olfactory Neuroblastoma[b]	0/48(0.00)	2/50(0.04)	23/47(0.49)
P Values[c]	P < 0.001	N.S.	P < 0.001
Departure from Linear Trend[e]	P = 0.002	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.284	7.699
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	84	48
Lung: Alveolar/Bronchiolar Adenoma[b]	3/48(0.06)	0/49(0.00)	0/45(0.00)
P Values[c]	P = 0.040(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.628	1.768
Weeks to First Observed Tumor	105	---	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	7/48(0.15)	1/50(0.02)	2/47(0.04)
P Values[c]	P = 0.037(N)	P = 0.026(N)	N.S.
Relative Risk (Control)[d]	---	0.137	0.292
Lower Limit	---	0.003	0.031
Upper Limit	---	1.009	1.436
Weeks to First Observed Tumor	80	105	72

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma, or Mixed Hepato/Cholangio Carcinoma[b]	0/48(0.00)	3/49(0.06)	1/46(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.590	0.056
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	78
Liver: Neoplastic Nodule, Hepatocellular Carcinoma, or Mixed Hepato/Cholangio Carcinoma[b]	0/48(0.00)	13/49(0.27)	2/46(0.04)
P Values[c]	N.S.	P < 0.001	N.S.
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	3.938	0.309
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	78

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Urinary Bladder: Undifferentiated Carcinoma, Papillary Carcinoma, Squamous-Cell Carcinoma, Transitional-Cell Papilloma, or Transitional-Cell Carcinoma[b]	0/48(0.00)	30/48(0.63)	44/47(0.94)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	10.044	16.426
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	93	51
Pituitary: Adenoma NOS, Chromophobe Adenoma, or Basophil Adenoma[b]	10/45(0.22)	9/48(0.19)	3/38(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.844	0.355
Lower Limit	---	0.335	0.067
Upper Limit	---	2.095	1.260
Weeks to First Observed Tumor	103	85	56
Adrenal: Cortical Adenoma[b]	0/46(0.00)	3/48(0.06)	0.44(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.578	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	102	---

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma[b]	4/46(0.09)	7/48(0.15)	3/44(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.677	0.784
Lower Limit	---	0.459	0.121
Upper Limit	---	7.336	4.367
Weeks to First Observed Tumor	78	102	80
Thyroid: C-Cell Carcinoma, or C-Cell Adenoma[b]	5/43(0.12)	2/41(0.05)	2/40(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.420	0.430
Lower Limit	---	0.042	0.043
Upper Limit	---	2.398	2.455
Weeks to First Observed Tumor	95	105	93
Pancreatic Islets: Islet-Cell Adenoma, or Islet-Cell Carcinoma[b]	0/44(0.00)	2/48(0.04)	2/40(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.272	0.327
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	97

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Preputial Gland: Adenoma NOS, or Carcinomas NOS[b]	0/48(0.00)	3/50(0.06)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.578	0.055
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	79	97
Testis: Interstitial-Cell Tumor[b]	37/48(0.77)	45/47(0.96)	23/46(0.50)
P Values[c]	P = 0.003(N)	P = 0.008	P = 0.006(N)
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	1.242	0.649
Lower Limit	---	1.038	0.471
Upper Limit	---	1.354	0.916
Weeks to First Observed Tumor	78	79	52
Brain and Brain Stem: Glioma NOS, or Oligodendroglioma[b]	0/46(0.00)	0/48(0.00)	3/43(0.07)
P Values[c]	P = 0.032	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.645
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	56

TABLE 3 (Concluded)

[a]Treated groups received doses of 0.5 or 1.0 percent in feed.

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

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

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

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

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Nasal Cavity: Olfactory Neuroblastoma[b]	0/50(0.00)	0/50(0.00)	11/49(0.22)
P Values[c]	P < 0.001	N.S.	P < 0.001
Departure from Linear Trend[e]	P = 0.013	---	---
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	3.389
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	62
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/50(0.08)	0/50(0.00)	0/49(0.00)
P Values[c]	P = 0.016(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.079	1.100
Weeks to First Observed Tumor	102	---	---
Liver: Neoplastic Nodule[b]	0/50(0.00)	4/48(0.08)	0/48(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.966	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	76	---

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Urinary Bladder: Leiomyosarcoma[b]	0/47(0.00)	2/49(0.04)	3/46(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.284	0.616
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	106	95
Urinary Bladder: Neoplasm NOS, Papillary Carcinoma, Squamous-Cell Carcinoma, or Transitional-Cell Carcinoma[b]	0/47(0.00)	31/49(0.63)	43/46(0.93)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P = 0.043	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	9.978	16.054
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	88	59

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS, or Chromophobe Adenoma[b]	17/40(0.43)	11/45(0.24)	7/40(0.18)
P Values[c]	P = 0.009(N)	N.S.	P = 0.013(N)
Relative Risk (Control)[d]	---	0.575	0.412
Lower Limit	---	0.282	0.165
Upper Limit	---	1.138	0.918
Weeks to First Observed Tumor	101	79	70
Adrenal: Cortical Adenoma[b]	0/48(0.00)	5/48(0.10)	1/44(0.02)
P Values[c]	N.S.	P = 0.028	N.S.
Departure from Linear Trend[e]	P = 0.010	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.263	0.059
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	79	86
Thyroid: Follicular-Cell Carcinoma[b]	0/43(0.00)	2/42(0.05)	0/40(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.304	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	106	---

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma[b]	0/43(0.00)	4/42(0.10)	0/40(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.954	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	103	---
Mammary Gland: Fibroadenoma[b]	6/50(0.12)	4/50(0.08)	1/49(0.02)
P Values[c]	P = 0.045(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.667	0.170
Lower Limit	---	0.147	0.004
Upper Limit	---	2.635	1.328
Weeks to First Observed Tumor	106	106	79
Uterus: Endometrial Stromal Polyp[b]	2/48(0.04)	8/47(0.17)	4/45(0.09)
P Values[c]	N.S.	P = 0.042	N.S.
Departure from Linear Trend[e]	P = 0.050	---	---
Relative Risk (Control)[d]	---	4.085	2.133
Lower Limit	---	0.872	0.322
Upper Limit	---	37.831	22.646
Weeks to First Observed Tumor	106	80	82

TABLE 4 (Concluded)

[a]Treated groups received doses of 0.5 or 1.0 in feed.

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

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

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

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

urinary bladder was increased in both dosed groups compared to the control group--appearing as early as week 51 in the males and week 59 in the females. For both sexes, the Cochran-Armitage test indicated a significant ($P < 0.001$) positive association between dose and incidence. For both sexes this was supported by significant ($P < 0.001$) Fisher exact test results for both dose levels compared to the control. Based on these results the administration of p-cresidine was associated with the increased incidence of carcinomas of the urinary bladder in both male and female rats.

Both the incidence of olfactory neuroblastomas in females and the combined incidence of neuroblastomas or olfactory neuroblastomas in males were increased in the high dose groups compared to the controls--appearing as early as week 48 in the males and week 62 in the females. For both sexes the Cochran-Armitage test indicated a significant ($P < 0.001$) positive association between dose and incidence. For both sexes these results were supported by significant ($P < 0.001$) Fisher exact tests comparing the high dose group to the control group. For males the combined incidence of nonspecific neoplasms, malignant carcinomas, or adenocarcinomas of the nasal cavity or nasopharynx was significant for the Cochran-Armitage test, but not for the Fisher exact tests. Based on these results, the administration of p-cresidine was associated with the increased incidence of neuroblastomas and olfactory neuroblastomas of the nasal cavity in both male and female rats.

In male rats the combined incidence of neoplastic nodules of the liver, hepatocellular carcinomas, or mixed hepato/cholangio carcinomas was increased in the low dose group compared to the control. The tumors were found after termination of the study in week 105. The Fisher exact test indicated a significantly ($P < 0.001$) higher incidence in the low dose group than in the control. The high dose Fisher exact comparison and the Cochran-Armitage test, however, were not significant, but these tests must be discounted due to the early deaths from cancer in the high dose group. Based on these results, the administration of p-cresidine was probably associated with the increased incidence of liver neoplasms in the male rats.

In male rats an increase in the combined incidence of gliomas and oligodendrogliomas of the brain or brain stem were observed in the high dose group. The Cochran-Armitage test indicated a significant ($P = 0.032$) positive association between dosage and incidence. This was not supported, however, by significant Fisher exact tests.

In males for lung neoplasms and for the incidence of leukemia or malignant lymphomas the Cochran-Armitage test was significant in the negative direction, but the Fisher exact tests were not significant under the Bonferroni criterion. Similarly, in the female rats the results did not impute any real importance to adrenal cortical adenomas, to mammary fibroadenomas, to endometrial stromal polyps, or to leukemias or malignant lymphomas.

The possibility of a negative association was observed between chemical administration and the incidence of pituitary adenomas in

female rats and the incidence of interstitial-cell tumors of the testis in males. This may have been due to the fact that survival was markedly better in the control and low dose groups than in the high dose group.

In summary, the administration of p-cresidine was associated with the incidences of carcinomas of the urinary bladder and of olfactory neuroblastomas in both males and females, and possibly with the incidence of liver neoplasms in males.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

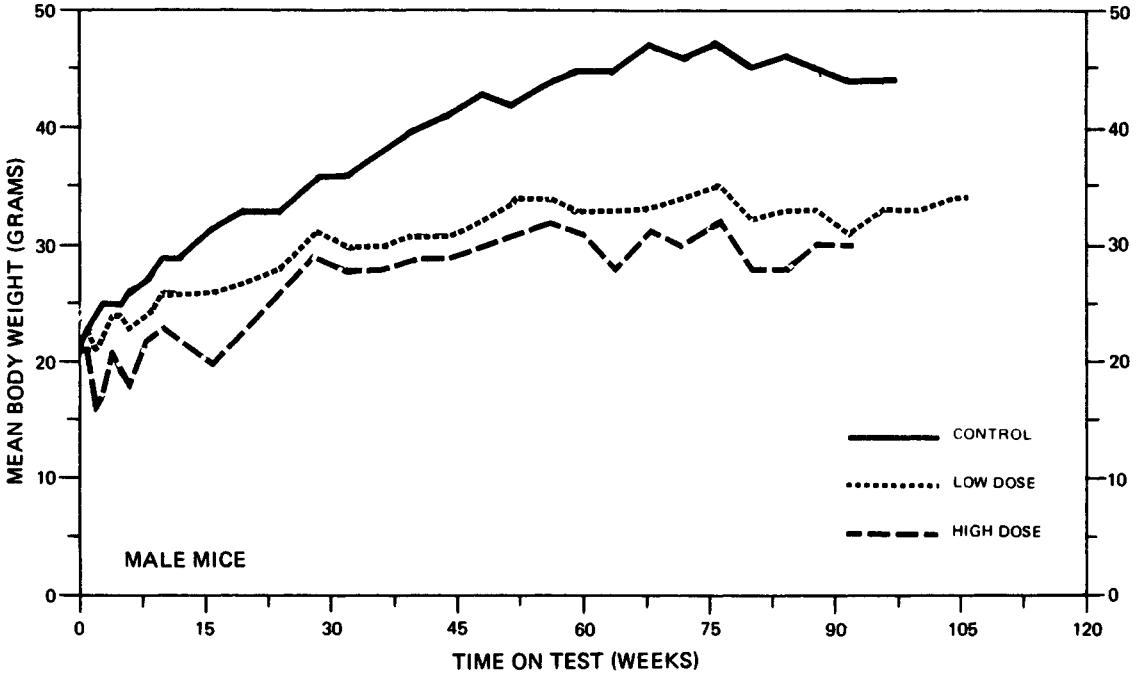
The mean body weights for dosed mice of both sexes were consistently lower than those for the control groups (Figure 4). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Only two dosed mice exhibited clinical signs. These were 1 low dose male with a hard mass in the abdominal cavity and 1 low dose female with a swollen, infected eye.

B. Survival

The estimated probabilities of survival for male and female mice in the control and p-cresidine-dosed groups are shown in Figure 5. For male mice and for female mice the Tarone tests showed significant positive associations between dosage and mortality.

For males five of the control mice were sacrificed in week 78. High early mortality was observed in the high dose group, with 50 percent (25/50) of the males dead by week 52 and 90 percent (45/50) dead by week 73. With 27 of these 45 mice observed to have a tumor of the urinary bladder, it seemed that mortality was associated with tumor incidence. Fifty percent (25/50) of the low dose and 98 percent (49/50) of the control mice survived on test for at least 75 weeks.



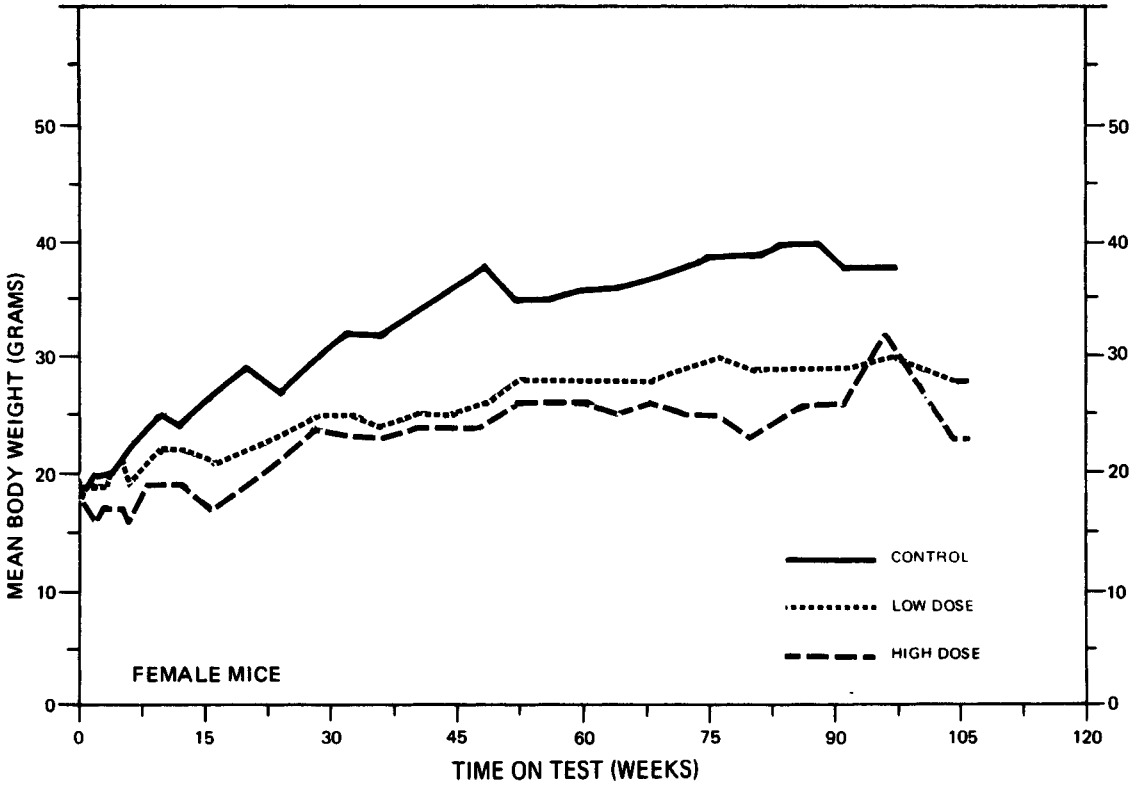
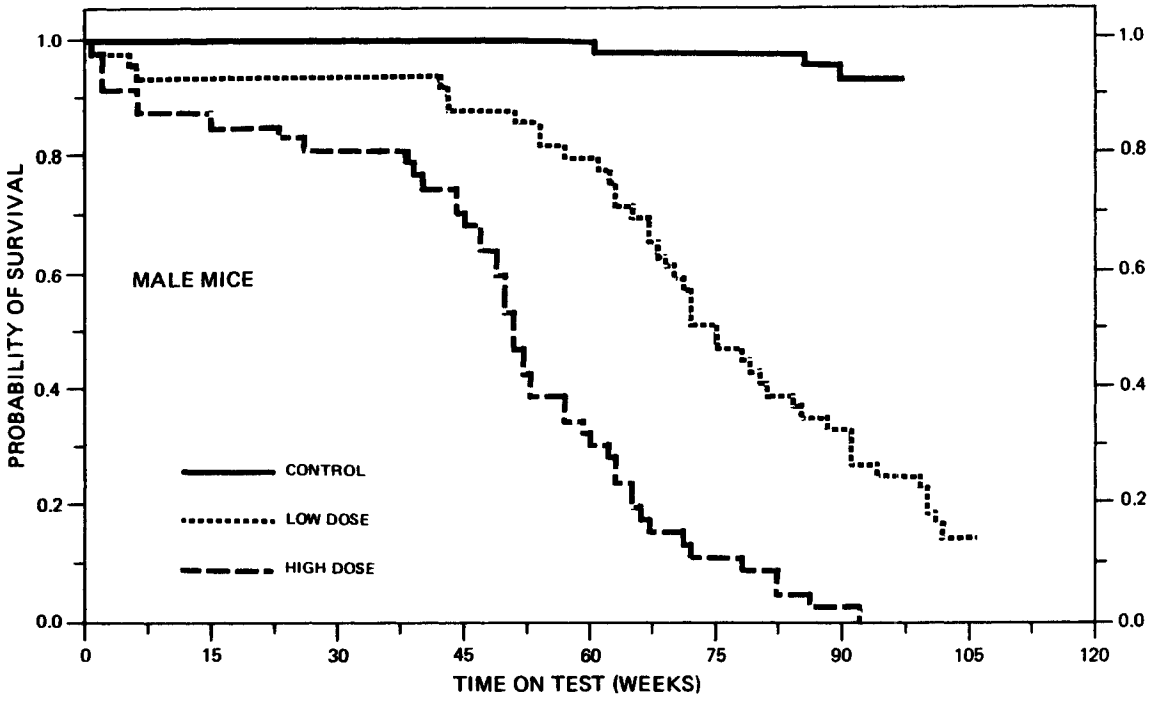


FIGURE 4
GROWTH CURVES FOR p-CRESIDINE CHRONIC STUDY MICE



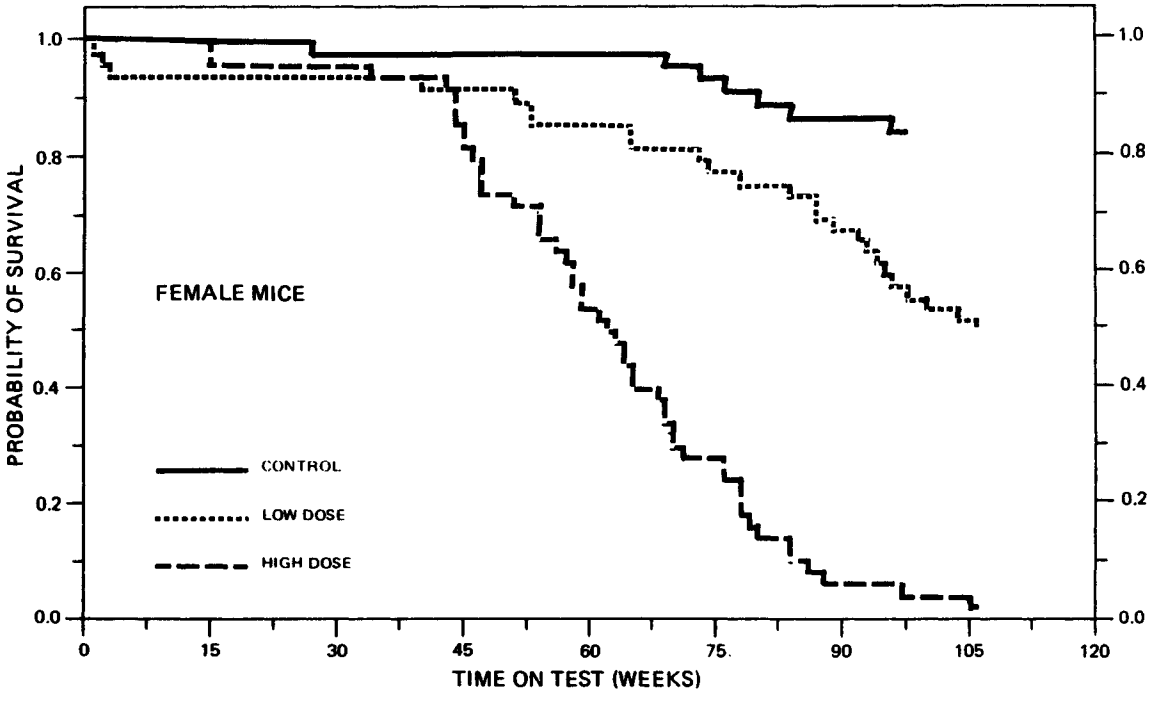


FIGURE 5
SURVIVAL COMPARISONS OF p-CRESIDINE CHRONIC STUDY MICE

For female mice five of the controls were sacrificed in week 78. Twenty-eight percent (14/50) of the high dose, 78 percent (39/50) of the low dose, and 90 percent (45/50) of the control mice survived on test for at least 75 weeks.

C. Pathology

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

p-Cresidine feeding produced a compound-related effect in the urinary bladder. No neoplasms of the urinary bladder occurred in the control mice. In the mice fed p-cresidine, there was a dose-related spectrum of bladder neoplasms which resembled rat bladder neoplasms previously described in this report. The hyperplasias and neoplasms of the urinary bladder in the mice are summarized in the table below:

MALE	Control	Low Dose	High Dose
Number of animals with tissues examined histopathologically	(50)	(42)	(35)
Urinary Bladder			
Hyperplasia	0	0	3(9%)
Dysplasia	0	0	1(3%)
Squamous-Cell Carcinoma	0	27(64%)	28(80%)
Transitional-Cell Carcinoma	0	13(31%)	3(9%)
Leiomyosarcoma	0	2(5%)	4(11%)

FEMALE

Number of animals with tissues examined histopathologically	(45)	(47)	(48)
Urinary Bladder			
Hyperplasia	0	2(4%)	0
Dysplasia	0	1(2%)	0
Neoplasm NOS	0	0	1(2%)
Neoplasm NOS, Malignant	0	1(2%)	0
Carcinoma NOS	0	0	1(2%)
Squamous-Cell Carcinoma	0	21(45%)	43(90%)
Transitional-Cell Carcinoma	0	20(43%)	0
Sarcoma NOS	0	0	1(2%)
Leiomyosarcoma	0	2(4%)	2(4%)

The bladders of those few mice that did not have bladder neoplasms showed epithelial hyperplasia such as that seen in rats or dysplasia which was characterized by nuclear hyperchromatism and irregularity. In contrast to those in the rats, the bladder tumors in the mice more frequently invaded adjacent structures or metastasized to distant organs and were more frequently squamous in type rather than transitional-cell. The mouse bladder tumors tended to be large, often filling the lumen of the organs and obstructing the ureters. In consequence, kidneys of the tumor-bearing animals had some degree of hydronephrosis. As in the rats, transitional-cell tumors occurred in the renal pelvis of two p-cresidine-dosed females.

There were no tumors of the nasal cavity in control mice. Of the mice fed p-cresidine two developed sarcomas, one an adenocarcinoma, and one a squamous-cell carcinoma of the nasal cavity. However, no olfactory neuroblastomas were observed.

The incidence of hepatocellular carcinomas in low dose female mice (13/45 [29 percent]), but not in the high dose female group (6/43 [14 percent]), was increased relative to controls (0/46). The incidence of liver tumors in dosed male mice was not increased. The early mortality resulting from fulminating tumors of the bladder in both sexes may have obscured a dose-related response of the liver.

Based upon this pathologic examination, p-cresidine was carcinogenic in B6C3F1 mice because it induced carcinomas of the urinary bladder in both sexes and hepatocellular carcinomas in female mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or p-cresidine-dosed groups and where such tumors were observed in at least 5 percent of the group. Because of the high mortality noted in mice of both sexes, these analyses were based on those mice surviving at least 52 weeks or at least until the development of the first tumor at the site of interest, whichever occurred first.

In both male and female mice the combined incidence of carcinomas NOS, squamous-cell carcinomas, or transitional-cell carcinomas of the urinary bladder was increased in the dosed groups compared to the control groups. These tumors were observed as early as week 44

TABLE 5

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH p-CRESIDINE[a,f]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma, or Alveolar/Bronchiolar Adenoma[b]	7/50(0.14)	2/39(0.05)	1/21(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.366	0.340
Lower Limit	---	0.039	0.008
Upper Limit	---	1.788	2.374
Weeks to First Observed Tumor	97	106	92
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/50(0.08)	0/42(0.00)	0/22(0.00)
P Values[c]	P = 0.047(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.278	2.370
Weeks to First Observed Tumor	97	---	---
Liver: Hepatocellular Carcinoma[b,f]	10/50(0.20)	11/41(0.27)	3/32(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.341	0.469
Lower Limit	---	0.574	0.088
Upper Limit	---	3.146	1.648
Weeks to First Observed Tumor	60	65	44

TABLE 5 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma, or Hepatocellular Adenoma[b,f]	15/50(0.30)	11/41(0.27)	3/32(0.09)
P Values[c]	P = 0.028(N)	N.S.	P = 0.024(N)
Relative Risk (Control)[d]	---	0.894	0.313
Lower Limit	---	0.418	0.062
Upper Limit	---	1.836	0.991
Weeks to First Observed Tumor	60	65	44
Urinary Bladder: Squamous-Cell Carcinoma of Transitional-Cell Carcinoma[b,f]	0/50(0.00)	40/42(0.95)	31/31(1.00)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	17.734	20.738
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	51	44

TABLE 5 (Concluded)

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[a]Treated groups received time-weighted average doses of 0.22 or 0.46 percent in feed.

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

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

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

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

[f]These analyses were based solely upon animals surviving at least 52 weeks, except for sites where the first tumor of interest was observed earlier than 52 weeks in any group of this sex and species, where the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

TABLE 6

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH p-CRESIDINE[a,f]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	3/45(0.07)	3/45(0.07)	0.34(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.000	0.000
Lower Limit	---	0.141	0.000
Upper Limit	---	7.095	2.173
Weeks to First Observed Tumor	97	106	---
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	4/45(0.09)	4/45(0.09)	1/34(0.03)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.000	0.331
Lower Limit	---	0.198	0.007
Upper Limit	---	5.051	3.135
Weeks to First Observed Tumor	97	106	70
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	6/46(0.13)	10/45(0.22)	1/36(0.03)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.024	---	---
Relative Risk (Control)[d]	---	1.704	0.213
Lower Limit	---	0.615	0.005
Upper Limit	---	5.229	1.638
Weeks to First Observed Tumor	69	87	54

TABLE 6 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b,f]	0/45(0.00)	13/44(0.30)	6/40(0.15)
P Values[c]	P = 0.028	P < 0.001	P = 0.009
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	4.126	1.809
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	53	44
Liver: Hepatocellular Carcinoma, or Hepatocellular Adenoma[b,f]	0/45(0.00)	14/44(0.32)	6/40(0.15)
P Values[c]	P = 0.030	P < 0.001	P = 0.009
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	4.484	1.809
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	53	44
Urinary Bladder: Carcinoma NOS, Squamous-Cell Carcinoma, or Transitional-Cell Carcinoma[b,f]	0/45(0.00)	41/46(0.89)	44/46(0.96)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	14.258	16.126
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	53	40

TABLE 6 (Continued)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Urinary Bladder: Transitional-Cell Carcinoma, Neoplasm NOS, Neoplasm NOS Malignant, Carcinoma NOS, or Squamous-Cell Carcinoma[b,f]	0/45(0.00)	42/46(0.91)	45/46(0.98)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	14.784	17.153
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	53	40
Thyroid: Follicular-Cell Adenoma[b]	1/28(0.04)	2/31(0.06)	0/30(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.806	0.000
Lower Limit	---	0.100	0.000
Upper Limit	---	103.026	17.204
Weeks to First Observed Tumor	97	94	---

TABLE 6 (Concluded)

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[a]Treated groups received time-weighted average doses of 0.22 or 0.44 percent in feed.

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

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

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

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

[f]These analyses were based solely upon animals surviving at least 52 weeks, except for sites where the first tumor of interest was observed earlier than 52 weeks in any group of this sex and species, where the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

in the males and week 40 in the females. For both sexes, the Cochran-Armitage test indicated a significant ($P < 0.001$) positive association between dose and incidence. These were supported by significant ($P < 0.001$) Fisher exact test results for both dose levels compared to the control.

In female mice an increased incidence of hepatocellular carcinomas was observed in the dosed groups compared to the control. The Cochran-Armitage test indicated a significant ($P = 0.028$) positive association between dose and incidence. This was supported by significant Fisher exact test results of both the high ($P = 0.009$) and low ($P < 0.001$) dose groups to the control. The departure from linear trend was also significant ($P = 0.001$) since tumor incidence was greater in the low dose group than in the high dose group. In historical control data compiled by this laboratory for the NCI Carcinogenesis Testing Program 19/275 (7 percent) of the female untreated control B6C3F1 mice had a hepatocellular carcinoma or a hepatocellular adenoma. For the male mice, however, the Cochran-Armitage test indicated a significant ($P = 0.028$) negative association between dose and the combined incidence of hepatocellular carcinomas and hepatocellular adenomas. The Fisher exact test comparing high dose to control also indicated a significant ($P = 0.024$) negative association. The historical control rate for untreated male B6C3F1 mice was 88/275 (32 percent) with these lesions. It was considered,

however, that the shorter survival in the high dose than in the control and low dose groups accounted for the apparently negative trend.

Based on these results the administration of p-cresidine was associated with the increased incidence of hepatocellular carcinoma in female mice and of carcinomas of the urinary bladder in both male and female mice.

V. DISCUSSION

Mortality rates were dose-related for both sexes of both species. Accelerated mortality of high dose animals during the latter half of the study was associated with bladder tumors. That incidences of certain tumors were higher in low dose than in high dose groups was probably due to this accelerated mortality.

Addition of p-cresidine to the diet was associated with increased incidences of neoplasms at several sites in rats. Male rats, having a higher incidence of neoplasms than females in the urinary bladder, nasal cavity, liver, and brain, appeared to be more sensitive to the tumorigenic effects of p-cresidine.

The urinary bladder was a target organ of p-cresidine carcinogenicity in rats. Bladder neoplasms were observed in dosed rats, but not in their controls. For both male and female rats the incidence of carcinomas (combined incidence of papillary carcinomas, squamous-cell carcinomas, transitional-cell papillomas, transitional-cell carcinomas and undifferentiated carcinomas) of the urinary bladder was dose-related and was significantly higher in each dosed group than in the corresponding control group. An elevated incidence of hyperplasia was also observed in urinary bladders of low dose rats of both sexes.

Dose-related increases in the incidence of neoplasms were also observed in nasal cavities of rats. The incidence of olfactory neuroblastomas in females and the combined incidence of neuroblastoma

and olfactory neuroblastoma of the nasal cavity in males were both significantly associated with p-cresidine dosage. The incidence of these neoplasms in high dose groups of both sexes was significantly higher than in controls. The combined incidences of carcinomas and adenocarcinomas of the nasal cavity or nasopharynx were significantly dose-related in male rats.

Among low dose male rats, the incidence of liver tumors (the combined incidence of neoplastic nodules, hepatocellular carcinomas, or mixed hepato/cholangio carcinomas) was significantly higher than in controls.

The urinary bladder was a target organ for carcinogenicity in mice as well as in rats. Although the spectrum of dose-related bladder neoplasms in mice was similar to that in rats, the bladder tumors in mice were more invasive and more frequently metastasized. In both male and female mice, the incidence of carcinomas (combined incidence of carcinomas NOS, squamous-cell carcinomas, and transitional-cell carcinomas) of the urinary bladder was significantly associated with p-cresidine dosage and was significantly greater in each dosed group than in controls. The bladders of those few mice without bladder neoplasms showed evidence of hyperplasia or dysplasia. No bladder neoplasms were found in control mice.

The incidence of hepatocellular carcinomas in each dosed female mouse group was significantly greater than in controls, and this

increased incidence was significantly associated with concentration of p-cresidine in the diet.

Under the conditions of this bioassay, p-cresidine was carcinogenic to Fischer 344 rats, causing increased incidences of carcinomas and of papillomas of the urinary bladder in both sexes, increased incidences of olfactory neuroblastomas in both sexes, and of liver tumors (hepatocellular carcinomas, hepato/cholangio carcinomas and neoplastic nodules) in males. p-Cresidine was also found to be carcinogenic in B6C3F1 mice, causing carcinomas of the urinary bladders in both sexes and hepatocellular carcinomas in females.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH p-CRESIDINE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	48	49	47
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(47)
TRICHOEPITHELIOMA		2 (4%)	
*SUBCUT TISSUE	(48)	(50)	(47)
FIBROMA	3 (6%)	2 (4%)	1 (2%)
FIBROSARCOMA	2 (4%)	2 (4%)	
LIPOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(48)	(50)	(47)
NEOPLASM, NOS, MALIGNANT			1 (2%)
CARCINOMA,NOS			1 (2%)
ADENOMA, NOS		1 (2%)	
NEUROBLASTOMA			1 (2%)
OLFACTORY NEUROBLASTOMA		1 (2%)	20 (43%)
*NASOPHARYNX	(48)	(50)	(47)
ADENOCARCINOMA, NOS			1 (2%)
#LUNG	(48)	(49)	(45)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
FIBROSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(47)
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (2%)
UNDIFFERENTIATED LEUKEMIA	2 (4%)	1 (2%)	
#SPLEEN	(48)	(49)	(45)
MYELOMONOCYTIC LEUKEMIA	4 (8%)		

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

TABLE A1
(CONTINUED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
#LYMPH NODE	(43)	(48)	(38)
MALIGNANT LYMPHOMA, NOS			1 (3%)
#SUBMANDIBULAR L.NODE	(43)	(48)	(38)
OLFACTORY NEUROBLASTOMA, METASTA			1 (3%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(45)	(48)	(43)
ACINAR-CELL ADENOMA		1 (2%)	
#PAROTID GLAND	(45)	(48)	(43)
OLFACTORY NEUROBLASTOMA, METASTA			1 (2%)
#LIVER	(48)	(49)	(46)
NEOPLASTIC NODULE		10 (20%)	1 (2%)
HEPATOCELLULAR CARCINOMA		2 (4%)	1 (2%)
MIXED HEPATO/CHOLANGIO CARCINOMA		1 (2%)	
#STOMACH	(48)	(49)	(46)
SQUAMOUS CELL PAPILLOMA		2 (4%)	
BASAL-CELL CARCINOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY/PELVIS	(48)	(49)	(46)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	
TRANSITIONAL-CELL CARCINOMA, INV		1 (2%)	
#URINARY BLADDER	(48)	(48)	(47)
UNDIFFERENTIATED CARCINOMA			1 (2%)
PAPILLARY CARCINOMA			4 (9%)
SQUAMOUS CELL CARCINOMA		1 (2%)	6 (13%)
TRANSITIONAL-CELL PAPILLOMA		14 (29%)	3 (6%)
TRANSITIONAL-CELL CARCINOMA		15 (31%)	31 (66%)
LEIOMYOSARCOMA			2 (4%)
*PROSTATIC URETHRA	(48)	(50)	(47)
UNDIFFERENTIATED CARCINOMA, INVA			1 (2%)

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

TABLE A1
(CONTINUED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(48)	(38)
ADENOMA, NOS	10 (22%)	1 (2%)	3 (8%)
CHROMOPHOBE ADENOMA		4 (8%)	
BASOPHIL ADENOMA		4 (8%)	
#ADRENAL	(46)	(48)	(44)
CORTICAL ADENOMA		3 (6%)	
PHEOCHROMOCYTOMA	4 (9%)	7 (15%)	3 (7%)
#THYROID	(43)	(41)	(40)
FOLLICULAR-CELL ADENOMA		1 (2%)	
C-CELL ADENOMA	3 (7%)	1 (2%)	1 (3%)
C-CELL CARCINOMA	2 (5%)	1 (2%)	1 (3%)
#PARATHYROID	(25)	(21)	(15)
ADENOMA, NOS	1 (4%)		
#PANCREATIC ISLETS	(44)	(48)	(40)
ISLET-CELL ADENOMA		1 (2%)	2 (5%)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(48)	(50)	(47)
CARCINOMA,NOS		2 (4%)	1 (2%)
PAPILLOMA, NOS			1 (2%)
ADENOMA, NOS		1 (2%)	
#PROSTATE	(45)	(48)	(46)
TRANSITIONAL-CELL CARCINOMA, INV		1 (2%)	
#TESTIS	(48)	(47)	(46)
INTERSTITIAL-CELL TUMOR	37 (77%)	45 (96%)	23 (50%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(46)	(48)	(43)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
#BRAIN	(46)	(48)	(43)
NEOPLASM, NOS, METASTATIC			1 (2%)

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

TABLE A1
(CONTINUED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
CARCINOMA, NOS, METASTATIC			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
GLIOMA, NOS			2 (5%)
OLFACTORY NEUROBLASTOMA, INVASIV			2 (5%)
OLFACTORY NEUROBLASTOMA, METASTA			5 (12%)
#BRAIN STEM	(46)	(48)	(43)
GLIOMA, NOS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKULL	(48)	(50)	(47)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*BODY CAVITIES	(48)	(50)	(47)
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(48)	(50)	(47)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	2	25
MORIBUND SACRIFICE	5	9	21
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	39	4
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1
(CONCLUDED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	42	49	46
TOTAL PRIMARY TUMORS	74	131	116
TOTAL ANIMALS WITH BENIGN TUMORS	40	48	28
TOTAL BENIGN TUMORS	61	91	37
TOTAL ANIMALS WITH MALIGNANT TUMORS	11	21	46
TOTAL MALIGNANT TUMORS	12	29	76
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	3	11
TOTAL SECONDARY TUMORS	2	3	14
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	11	2
TOTAL UNCERTAIN TUMORS	1	11	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
FIBROMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(49)
SARCOMA, NOS	1 (2%)	1 (2%)	
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
ADENOCARCINOMA, NOS			1 (2%)
OLFACTORY NEUROBLASTOMA			11 (22%)
#LUNG	(50)	(48)	(48)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
TRANSITIONAL-CELL CARCINOMA, MET		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	2 (4%)		
#SPLEEN	(50)	(49)	(47)
MYELOMONOCYTIC LEUKEMIA	2 (4%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2
(CONTINUED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
DIGESTIVE SYSTEM			
*MOUTH	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#SALIVARY GLAND	(46)	(48)	(43)
ACINAR-CELL ADENOMA		1 (2%)	
#LIVER	(50)	(48)	(48)
NEOPLASTIC NODULE		4 (8%)	
#PANCREAS	(46)	(49)	(43)
TRANSITIONAL-CELL CARCINOMA, MET			1 (2%)
#STOMACH	(49)	(48)	(46)
SQUAMOUS CELL CARCINOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(46)
UNDIFFERENTIATED CARCINOMA			1 (2%)
#KIDNEY/PELVIS	(49)	(49)	(46)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
#URINARY BLADDER	(47)	(49)	(46)
NEOPLASM, NOS			2 (4%)
PAPILLARY CARCINOMA			1 (2%)
SQUAMOUS CELL CARCINOMA		9 (18%)	7 (15%)
TRANSITIONAL-CELL PAPILLOMA		6 (12%)	2 (4%)
TRANSITIONAL-CELL CARCINOMA		22 (45%)	33 (72%)
LEIOMYOSARCOMA		2 (4%)	3 (7%)
*URETHRA	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(45)	(40)
ADENOMA, NOS	16 (40%)	2 (4%)	6 (15%)
CHROMOPHOBE ADENOMA	1 (3%)	9 (20%)	1 (3%)
#ADRENAL	(48)	(48)	(44)
CORTICAL ADENOMA		5 (10%)	1 (2%)

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

TABLE A2
(CONTINUED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
PHEOCHROMOCYTOMA	6 (13%)	1 (2%)	1 (2%)
#THYROID	(43)	(42)	(40)
FOLLICULAR-CELL CARCINOMA		2 (5%)	
C-CELL ADENOMA		4 (10%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOCARCINOMA, NOS	1 (2%)		
FIBROADENOMA	6 (12%)	4 (8%)	1 (2%)
*CLITORAL GLAND	(50)	(50)	(49)
CARCINOMA,NOS		2 (4%)	
ADENOMA, NOS		1 (2%)	
#UTERUS	(48)	(47)	(45)
ADENOCARCINOMA, NOS	1 (2%)		
FIBROMA	2 (4%)		
ENDOMETRIAL STROMAL POLYP	2 (4%)	8 (17%)	4 (9%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)		
CARCINOSARCOMA		1 (2%)	
#UTERUS/ENDOMETRIUM	(48)	(47)	(45)
ADENOCARCINOMA, NOS		1 (2%)	
ADENOCA/SQUAMOUS METAPLASIA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)
ADENOCARCINOMA, NOS, INVASIVE			1 (2%)
GLIOMA, NOS		1 (2%)	
OLIGODENDROGLIOMA		1 (2%)	
OLFACTORY NEUROBLASTOMA, INVASIV			1 (2%)
OLFACTORY NEUROBLASTOMA, METASTA			3 (7%)
#CEREBRAL CORTEX	(50)	(48)	(46)
OLFACTORY NEUROBLASTOMA, METASTA			1 (2%)
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)

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

TABLE A2
(CONTINUED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(49)
TRANSITIONAL-CELL CARCINOMA, INV			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	7	3	30
MORIBUND SACRIFICE	2	6	20
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	41	
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2
(CONCLUDED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	27	48	44
TOTAL PRIMARY TUMORS	42	93	79
TOTAL ANIMALS WITH BENIGN TUMORS	23	35	17
TOTAL BENIGN TUMORS	33	43	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	36	42
TOTAL MALIGNANT TUMORS	9	46	60
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	9
TOTAL SECONDARY TUMORS		2	11
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		4	2
TOTAL UNCERTAIN TUMORS		4	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH p-CRESIDINE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE
MICE TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	50	47	41
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	50	43	37
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(47)	(41)
ADENOCARCINOMA, NOS		1 (2%)	
SARCOMA, NOS			1 (2%)
FIBROSARCOMA		1 (2%)	
#LUNG	(50)	(40)	(37)
SQUAMOUS CELL CARCINOMA, METASTA		4 (10%)	2 (5%)
TRANSITIONAL-CELL CARCINOMA, MET		1 (3%)	
HEPATOCELLULAR CARCINOMA, METAST		2 (5%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	1 (3%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (3%)	1 (3%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(47)	(41)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#SPLEEN	(50)	(37)	(33)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA	2 (4%)	1 (3%)	
#MESENTERIC L. NODE	(44)	(26)	(16)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#LIVER	(50)	(41)	(37)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE B1
(CONTINUED)

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
DIGESTIVE SYSTEM			
#LIVER	(50)	(41)	(37)
HEPATOCELLULAR ADENOMA	5 (10%)		
HEPATOCELLULAR CARCINOMA	10 (20%)	11 (27%)	3 (8%)
#PANCREAS	(50)	(30)	(31)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (3%)	
#DUODENAL GLAND	(50)	(30)	(29)
ADENOMA, NOS		1 (3%)	
URINARY SYSTEM			
#URINARY BLADDER	(50)	(42)	(35)
SQUAMOUS CELL CARCINOMA		27 (64%)	28 (80%)
TRANSITIONAL-CELL CARCINOMA		13 (31%)	3 (9%)
LEIOMYOSARCOMA		2 (5%)	4 (11%)
*PROSTATIC URETHRA	(50)	(47)	(41)
SQUAMOUS CELL CARCINOMA, INVASIV		2 (4%)	
TRANSITIONAL-CELL CARCINOMA, INV		1 (2%)	
ENDOCRINE SYSTEM			
#THYROID	(39)	(31)	(29)
FOLLICULAR-CELL ADENOMA	1 (3%)		
FOLLICULAR-CELL CARCINOMA	1 (3%)		
REPRODUCTIVE SYSTEM			
#PROSTATE	(41)	(37)	(26)
SQUAMOUS CELL CARCINOMA, INVASIV		6 (16%)	2 (8%)
TRANSITIONAL-CELL CARCINOMA, INV		3 (8%)	1 (4%)
LEIOMYOSARCOMA, INVASIVE		1 (3%)	1 (4%)
*SEMINAL VESICLE	(50)	(47)	(41)
TRANSITIONAL-CELL CARCINOMA, INV		1 (2%)	
*COAGULATING GLAND	(50)	(47)	(41)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	

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

TABLE B1
(CONTINUED)

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
TRANSITIONAL-CELL CARCINOMA, INV		1 (2%)	
#TESTIS	(50)	(41)	(37)
EMBRYONAL CARCINOMA	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(36)	(32)
SARCOMA, NOS, METASTATIC			1 (3%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(47)	(41)
CYSTADENOMA, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(47)	(41)
SQUAMOUS CELL CARCINOMA, INVASIV		4 (9%)	3 (7%)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
TRANSITIONAL-CELL CARCINOMA, INV		1 (2%)	
LEIOMYOSARCOMA, INVASIVE			1 (2%)
*PERITONEAL CAVITY	(50)	(47)	(41)
SQUAMOUS CELL CARCINOMA, INVASIV			2 (5%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(47)	(41)
SQUAMOUS CELL CARCINOMA, INVASIV		4 (9%)	1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA		2 (4%)	2 (5%)
TRANSITIONAL-CELL CARCINOMA, INV			2 (5%)
ADENOCARCINOMA, NOS, INVASIVE		1 (2%)	
LEIOMYOSARCOMA, INVASIVE		1 (2%)	

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

TABLE B1
(CONCLUDED)

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	3	37	40
MORIBUND SACRIFICE		5	7
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	42	7	
ANIMAL MISSING		1	3
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	42	32
TOTAL PRIMARY TUMORS	33	60	40
TOTAL ANIMALS WITH BENIGN TUMORS	12	3	
TOTAL BENIGN TUMORS	13	3	
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	42	32
TOTAL MALIGNANT TUMORS	20	57	40
TOTAL ANIMALS WITH SECONDARY TUMORS#		27	14
TOTAL SECONDARY TUMORS		38	18
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	47	47	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	47	47	48
INTEGUMENTARY SYSTEM			
*SKIN	(47)	(47)	(48)
KERATOACANTHOMA	1 (2%)		
*SUBCUT TISSUE	(47)	(47)	(48)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(47)	(47)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)
#LUNG	(46)	(47)	(44)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	3 (7%)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (7%)	3 (6%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(47)	(47)	(48)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)		
MALIGNANT LYMPHOMA, MIXED TYPE		5 (11%)	
#SPLEEN	(45)	(44)	(38)
HEMANGIOSARCOMA		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#MANDIBULAR L. NODE	(38)	(38)	(28)
HEMANGIOMA		1 (3%)	

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

TABLE B2
(CONTINUED)

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
#ABDOMINAL LYMPH NODE	(38)	(38)	(28)
SQUAMOUS CELL CARCINOMA, METASTA		1 (3%)	
#MESENTERIC L. NODE	(38)	(38)	(28)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
#LIVER	(46)	(45)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(46)	(45)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
HEPATOCELLULAR ADENOMA		1 (2%)	
HEPATOCELLULAR CARCINOMA		13 (29%)	6 (14%)
#STOMACH	(46)	(40)	(36)
ADENOCARCINOMA, NOS		1 (3%)	
URINARY SYSTEM			
#KIDNEY/PELVIS	(46)	(45)	(45)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	1 (2%)
#URINARY BLADDER	(45)	(47)	(48)
NEOPLASM, NOS			1 (2%)
NEOPLASM, NOS, MALIGNANT		1 (2%)	
CARCINOMA,NOS			1 (2%)
SQUAMOUS CELL CARCINOMA		21 (45%)	43 (90%)
TRANSITIONAL-CELL CARCINOMA		20 (43%)	
SARCOMA, NOS			1 (2%)
LEIOMYOSARCOMA		2 (4%)	2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(33)	(32)	(26)
ADENOMA, NOS	1 (3%)		

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

TABLE B2
(CONTINUED)

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
#ADRENAL/CAPSULE	(40)	(42)	(39)
ADENOMA, NOS	1 (3%)		
#THYROID	(29)	(32)	(37)
FOLLICULAR-CELL ADENOMA	1 (3%)	2 (6%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(45)	(46)	(36)
HEMANGIOSARCOMA		1 (2%)	
#OVARY	(40)	(41)	(35)
PAPILLARY ADENOMA	1 (3%)		
HEMANGIOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(44)	(45)	(39)
SQUAMOUS CELL CARCINOMA, INVASIV			1 (3%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(47)	(47)	(48)
PAPILLARY ADENOMA		1 (2%)	
PAPILLARY ADENOCARCINOMA		1 (2%)	
PAPILLARY CYSTADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(47)	(47)	(48)
SQUAMOUS CELL CARCINOMA, INVASIV		2 (4%)	2 (4%)
*PERITONEAL CAVITY	(47)	(47)	(48)
SQUAMOUS CELL CARCINOMA, INVASIV			2 (4%)

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

TABLE B2
(CONCLUDED)

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(47)	(47)	(48)
SQUAMOUS CELL CARCINOMA, INVASIV			2 (4%)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
LEIOMYOSARCOMA, INVASIVE		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	21	41
MORIBUND SACRIFICE	3	4	8
SCHEDULED SACRIFICE	5		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	25	1
ANIMAL MISSING	2		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	45	45
TOTAL PRIMARY TUMORS	15	83	59
TOTAL ANIMALS WITH BENIGN TUMORS	5	7	2
TOTAL BENIGN TUMORS	6	7	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	45	44
TOTAL MALIGNANT TUMORS	9	76	56
TOTAL ANIMALS WITH SECONDARY TUMORS#		6	9
TOTAL SECONDARY TUMORS		7	11
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH p-CRESIDINE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MALE RATS TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	48	49	47
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(47)
EPIDERMAL INCLUSION CYST	1 (2%)		
*SUBCUT TISSUE	(48)	(50)	(47)
ABSCESS, NOS	3 (6%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(48)	(50)	(47)
HYPERPLASIA, EPITHELIAL			5 (11%)
POLYP		1 (2%)	
*NASAL TURBINATE	(48)	(50)	(47)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#LUNG/BRONCHUS	(48)	(49)	(45)
CALCIFICATION, NOS			1 (2%)
#LUNG	(48)	(49)	(45)
BRONCHOPNEUMONIA, ACUTE			1 (2%)
INFLAMMATION, ACUTE FOCAL			2 (4%)
PNEUMONIA, CHRONIC MURINE		3 (6%)	
METAPLASIA, NOS			2 (4%)
#LUNG/ALVEOLI	(48)	(49)	(45)
CALCIFICATION, FOCAL			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(48)	(49)	(45)
INFARCT, NOS	1 (2%)		

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

TABLE C1
(CONTINUED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
ATROPHY, NOS			1 (2%)
HEMATOPOIESIS		1 (2%)	
#THYMUS	(32)	(33)	(23)
HYPERPLASIA, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(45)
PERIARTERITIS		1 (2%)	
CALCIFICATION, FOCAL			1 (2%)
#MYOCARDIUM	(48)	(49)	(45)
DEGENERATION, NOS		6 (12%)	1 (2%)
CALCIFICATION, FOCAL			2 (4%)
*BLOOD VESSEL	(48)	(50)	(47)
MEDIAL CALCIFICATION			2 (4%)
*CORONARY ARTERY	(48)	(50)	(47)
CALCIFICATION, FOCAL			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(45)	(48)	(43)
HYPERPLASIA, INTRADUCTAL			1 (2%)
DYSPLASIA, NOS		1 (2%)	
#LIVER	(48)	(49)	(46)
METAMORPHOSIS FATTY	2 (4%)		1 (2%)
BASOPHILIC CYTO CHANGE		5 (10%)	1 (2%)
CLEAR-CELL CHANGE		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	1 (2%)	
#PANCREAS	(44)	(48)	(40)
INFLAMMATION, NOS	2 (5%)		
#PANCREATIC ACINUS	(44)	(48)	(40)
ATROPHY, NOS			1 (3%)
#STOMACH	(48)	(49)	(46)
ULCER, NOS		1 (2%)	1 (2%)
CALCIFICATION, FOCAL			2 (4%)

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

TABLE C1
(CONTINUED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
HYPERPLASIA, BASAL CELL		8 (16%)	
#GASTRIC MUCOSA	(48)	(49)	(46)
CALCIFICATION, NOS			1 (2%)
#GASTRIC MUSCULARIS	(48)	(49)	(46)
INFLAMMATION, NECROTIZING			1 (2%)
CALCIFICATION, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(48)	(49)	(46)
HYDRONEPHROSIS		1 (2%)	3 (7%)
HEMORRHAGE			1 (2%)
GLOMERULONEPHRITIS, NOS			3 (7%)
INFLAMMATION, INTERSTITIAL			1 (2%)
NEPHROPATHY	35 (73%)		
NEPHROSIS, NOS		26 (53%)	14 (30%)
NECROSIS, MEDULLARY			3 (7%)
CALCIFICATION, NOS			3 (7%)
CALCIFICATION, FOCAL			3 (7%)
HYPERPLASIA, TUBULAR CELL			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
#KIDNEY/MEDULLA	(48)	(49)	(46)
AMYLOIDOSIS			1 (2%)
#RENAL PAPILLA	(48)	(49)	(46)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
#KIDNEY/TUBULE	(48)	(49)	(46)
CAST, NOS			1 (2%)
FIBROSIS			1 (2%)
DEGENERATION, NOS			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
#KIDNEY/PELVIS	(48)	(49)	(46)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER	(48)	(48)	(47)
INFLAMMATION, ACUTE FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL		11 (23%)	1 (2%)
HYPERPLASIA, PAPILLARY			1 (2%)
POLYP, INFLAMMATORY			3 (6%)

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

TABLE C1
(CONTINUED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(48)	(38)
HYPERPLASIA, NODULAR		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		
HYPERPLASIA, BASOPHILIC		1 (2%)	1 (3%)
#PITUITARY/BASOPHIL	(45)	(48)	(38)
HYPERPLASIA, NODULAR		1 (2%)	
#ADRENAL CORTEX	(46)	(48)	(44)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(46)	(48)	(44)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	3 (7%)		
#PANCREATIC ISLETS	(44)	(48)	(40)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(47)
HEMORRHAGIC CYST		1 (2%)	
#PROSTATE	(45)	(48)	(46)
INFLAMMATION, ACUTE			5 (11%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
*SEMINAL VESICLE	(48)	(50)	(47)
ATROPHY, NOS			1 (2%)
#TESTIS	(48)	(47)	(46)
MINERALIZATION	1 (2%)		
ATROPHY, NOS	4 (8%)		2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)		2 (4%)
#TESTIS/TUBULE	(48)	(47)	(46)
DEGENERATION, NOS			7 (15%)
*EPIDIDYMIS	(48)	(50)	(47)
ABSCESS, NOS	1 (2%)		

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

TABLE C1
(CONCLUDED)

	CONTROL(UNTR) 01-0220	LOW DOSE 01-0260	HIGH DOSE 01-0265
NERVOUS SYSTEM			
#BRAIN	(46)	(48)	(43)
GLIOSIS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(48)	(50)	(47)
CATARACT	1 (2%)		
*EYE/RETINA	(48)	(50)	(47)
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS	2 (4%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(48)	(50)	(47)
MINERALIZATION		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF	1		
AUTO/NECROPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY	2		3

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN FEMALE RATS TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	49	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(49)
HYPERPLASIA, EPITHELIAL			8 (16%)
*NASAL TURBINATE	(50)	(50)	(49)
INFLAMMATION, NOS	1 (2%)		
#LUNG	(50)	(48)	(48)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		
ABSCESS, NOS	2 (4%)		
PNEUMONIA, CHRONIC MURINE	1 (2%)		
GRANULOMA, NOS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(46)	(43)
OSTEOSCLEROSIS			2 (5%)
#SPLEEN	(50)	(49)	(47)
HEMATOPOIESIS	7 (14%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(48)	(47)
ENDOCARDIOSIS		1 (2%)	
#MYOCARDIUM	(50)	(48)	(47)
FIBROSIS, FOCAL			1 (2%)

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

TABLE C2
(CONTINUED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(46)	(48)	(43)
DYSPLASIA, NOS		1 (2%)	
#LIVER	(50)	(48)	(48)
INFLAMMATION, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	4 (8%)		2 (4%)
BASOPHILIC CYTO CHANGE			1 (2%)
HYPERPLASIA, FOCAL	9 (18%)	1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(48)	(48)
NECROSIS, NOS		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(48)	(48)
HYPERPLASIA, FOCAL			2 (4%)
#STOMACH	(49)	(48)	(46)
ULCER, NOS			1 (2%)
HYPERPLASIA, PAPILLARY	1 (2%)		
HYPERPLASIA, BASAL CELL		2 (4%)	
#GASTRIC MUCOSA	(49)	(48)	(46)
ULCER, NOS			1 (2%)
#DUODENUM	(47)	(49)	(46)
ULCER, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(46)
HYDRONEPHROSIS			2 (4%)
GLOMERULONEPHRITIS, NOS	1 (2%)		2 (4%)
PYELONEPHRITIS, FOCAL			1 (2%)
PYELONEPHRITIS SUPPURATIVE			1 (2%)
PYELONEPHRITIS, CHRONIC		1 (2%)	
NEPHROPATHY	18 (37%)		
NEPHROSIS, NOS		2 (4%)	1 (2%)
NECROSIS, MEDULLARY			2 (4%)
HYPERPLASIA, EPITHELIAL			3 (7%)
#KIDNEY/MEDULLA	(49)	(49)	(46)
CALCIFICATION, FOCAL			1 (2%)

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

TABLE C2
(CONTINUED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
#RENAL PAPILLA	(49)	(49)	(46)
CALCIFICATION, FOCAL			1 (2%)
#KIDNEY/TUBULE	(49)	(49)	(46)
CALCIFICATION, FOCAL			1 (2%)
#KIDNEY/PELVIS	(49)	(49)	(46)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
#URINARY BLADDER	(47)	(49)	(46)
INFLAMMATION, ACUTE			2 (4%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL		10 (20%)	1 (2%)
HYPERPLASIA, PAPILLARY		1 (2%)	
POLYP, INFLAMMATORY			5 (11%)
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(45)	(40)
MINERALIZATION	1 (3%)		
HYPERPLASIA, NOS		1 (2%)	
#ZONA GLOMERULOSA	(48)	(48)	(44)
METAMORPHOSIS FATTY			1 (2%)
#THYROID	(43)	(42)	(40)
HYPERPLASIA, C-CELL	1 (2%)		
#PARATHYROID	(31)	(28)	(22)
HYPERPLASIA, NODULAR	1 (3%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
GALACTOCELE	2 (4%)		
HYPERPLASIA, NOS	1 (2%)		
#UTERUS	(48)	(47)	(45)
ABSCESS, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(47)	(45)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C2
(CONCLUDED)

	CONTROL(UNTR) 02-0220	LOW DOSE 02-0260	HIGH DOSE 02-0265
INFLAMMATION, ACUTE			1 (2%)
#OVARY	(49)	(47)	(43)
INFLAMMATION, NOS	1 (2%)		
ABSCESS, NOS		1 (2%)	
DEGENERATION, CYSTIC	2 (4%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(46)
HYDROCEPHALUS, NOS			1 (2%)
GLIOSIS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(49)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	11		
AUTO/NECROPSY/HISTO PERF	1		
AUTO/NECROPSY/NO HISTO		1	1
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH p-CRESIDINE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MALE MICE TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	50	47	41
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	43	37
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(47)	(41)
ABSCESS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(40)	(37)
INFLAMMATION, NOS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(37)	(33)
ATROPHY, NOS		17 (46%)	
#MESENTERIC L. NODE	(44)	(26)	(16)
HEMATOPOIESIS	1 (2%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(40)	(36)
MINERALIZATION		1 (3%)	
DEGENERATION, NOS		1 (3%)	
*CORONARY ARTERY	(50)	(47)	(41)
MEDIAL CALCIFICATION			1 (2%)
*PULMONARY ARTERY	(50)	(47)	(41)
MEDIAL CALCIFICATION			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(41)	(37)
NECROSIS, COAGULATIVE	1 (2%)		

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

TABLE D1
(CONTINUED)

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
#PANCREATIC ACINUS	(50)	(30)	(31)
ATROPHY, NOS	1 (2%)		
HYPERTROPHY, FOCAL	1 (2%)		
#GASTRIC MUCOSA	(50)	(32)	(33)
CALCIFICATION, NOS			1 (3%)
#GASTRIC MUSCULARIS	(50)	(32)	(33)
CALCIFICATION, NOS			1 (3%)
URINARY SYSTEM			
#KIDNEY	(50)	(43)	(36)
HYDRONEPHROSIS	1 (2%)	29 (67%)	31 (86%)
#URINARY BLADDER	(50)	(42)	(35)
HYPERPLASIA, EPITHELIAL			3 (9%)
DYSPLASIA, NOS			1 (3%)
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(50)	(30)	(31)
INFLAMMATION, NOS	3 (6%)		
HYPERPLASIA, ADENOMATOUS	1 (2%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(41)	(37)
ATROPHY, NOS	1 (2%)		
#TESTIS/TUBULE	(50)	(41)	(37)
MINERALIZATION	2 (4%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D1
(CONCLUDED)

	CONTROL(UNTR) 05-0220	LOW DOSE 05-0260	HIGH DOSE 05-0265
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(47)	(41)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(47)	(41)
ATROPHY, NOS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	22	1	1
ANIMAL MISSING/NO NECROPSY		1	3
NECROPSY PERF/NO HISTO PERFORMED			2
AUTO/NECROPSY/NO HISTO		4	2
AUTOLYSIS/NO NECROPSY		2	6

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN FEMALE MICE TREATED WITH p-CRESIDINE

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	47	47	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	47	47	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(47)	(47)	(48)
INFLAMMATION, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(46)	(47)	(44)
THROMBOSIS, NOS		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(39)	(44)	(39)
MYELOFIBROSIS		14 (32%)	
MYELOPOIESIS			3 (8%)
#SPLEEN	(45)	(44)	(38)
ATROPHY, NOS		9 (20%)	2 (5%)
HYPERPLASIA, RETICULUM CELL		2 (5%)	
HYPERPLASIA, LYMPHOID		2 (5%)	
HEMATOPOIESIS	1 (2%)		2 (5%)
#MEDIASTINAL L.NODE	(38)	(38)	(28)
HYPERPLASIA, LYMPHOID		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(45)	(47)	(42)
PERIARTERITIS			1 (2%)
#MYOCARDIUM	(45)	(47)	(42)
CALCIFICATION, NOS			1 (2%)

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

TABLE D2
(CONTINUED)

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
*ARTERY	(47)	(47)	(48)
INFLAMMATION, NOS		1 (2%)	
*CORONARY ARTERY	(47)	(47)	(48)
MEDIAL CALCIFICATION			1 (2%)
*MEDIASTINAL ARTERY	(47)	(47)	(48)
MEDIAL CALCIFICATION			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(46)	(45)	(43)
ABSCESS, CHRONIC			1 (2%)
METAMORPHOSIS FATTY	1 (2%)	2 (4%)	
ANGIECTASIS		1 (2%)	
#PANCREAS	(45)	(42)	(33)
CYSTIC DUCTS		1 (2%)	
#PANCREATIC ACINUS	(45)	(42)	(33)
ATROPHY, NOS		1 (2%)	
#STOMACH	(46)	(40)	(36)
ULCER, NOS			1 (3%)
HYPERKERATOSIS		1 (3%)	
#GASTRIC MUCOSA	(46)	(40)	(36)
INFLAMMATION, ACUTE FOCAL		1 (3%)	
CALCIFICATION, FOCAL		1 (3%)	
#GASTRIC MUSCULARIS	(46)	(40)	(36)
CALCIFICATION, FOCAL			1 (3%)
URINARY SYSTEM			
#KIDNEY	(46)	(45)	(45)
HYDRONEPHROSIS		18 (40%)	37 (82%)
GLOMERULONEPHRITIS, NOS	1 (2%)	1 (2%)	
PYELONEPHRITIS, ACUTE		1 (2%)	1 (2%)
PYELONEPHRITIS, CHRONIC			1 (2%)
NEPHROPATHY		1 (2%)	
NEPHROSIS, NOS			1 (2%)

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

TABLE D2
(CONTINUED)

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
GLOMERULOSCLEROSIS, NOS		1 (2%)	
INFARCT, NOS			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
#URINARY BLADDER	(45)	(47)	(48)
HYPERPLASIA, EPITHELIAL		2 (4%)	
DYSPLASIA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(47)	(47)	(48)
HYPERPLASIA, NOS	1 (2%)		
#UTERUS	(45)	(46)	(36)
HYDROMETRA		1 (2%)	
#UTERUS/ENDOMETRIUM	(45)	(46)	(36)
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, CYSTIC		14 (30%)	1 (3%)
#OVARY/OVIDUCT	(45)	(46)	(36)
DEGENERATION, NOS	1 (2%)		
#OVARY	(40)	(41)	(35)
THROMBOSIS, NOS		1 (2%)	
PLASMA-CELL INFILTRATE		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(44)	(45)	(39)
HYDROCEPHALUS, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D2
(CONCLUDED)

	CONTROL(UNTR) 06-0220	LOW DOSE 06-0260	HIGH DOSE 06-0265
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(47)	(47)	(48)
PERIARTERITIS			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	30		1
ANIMAL MISSING/NO NECROPSY	2		
AUTO/NECROPSY/HISTO PERF	1		1
AUTOLYSIS/NO NECROPSY	1	3	2

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

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

June 29, 1978

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

The reviewer agreed with the conclusion in the report that *p*-Cresidine was carcinogenic in both rats and mice, under the conditions of test. He said that the nature of the tumors observed clearly indicate that they were treatment-related. He noted that the *p*-Cresidine was dissolved in acetone but that there was no acetone control group. This shortcoming, however, did not interefer with the conclusion on the carcinogenicity of *p*-Cresidine. Based on the results of the study, he said that *p*-Cresidine would appear to pose a carcinogenic risk to humans. The reviewer moved that the report on the bioassay of *p*-Cresidine be accepted as written. The motion was approved without objection.

Clearinghouse Members present:
Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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