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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 3-CHLORO-p-TOLUIDINE
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 3-chloro-p-toluidine 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 3-chloro-p-toluidine was conducted by Litton Bionetics, Inc., Bethesda, Maryland, 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. N. P. Page (1,2), Dr. E. K. Weisburger (1) and Dr. J. H. Weisburger (1,3). The principal investigators for the contract were Dr. S. M. Garner (4,5) and Dr. B. M. Ulland (4,5). Mr. S. Johnson (4) was the coprincipal investigator for the contract. Animal treatment and observation were supervised by Mr. R. Cypher (4), Mr. D. S. Howard (4) and Mr. H. D. Thornett (4); Mr. H. Paulin (4) analyzed dosed feed mixtures. Ms. J. Blalock (4) was responsible for data collection and assembly.

Histopathologic examinations were performed by Dr. W. Busey (6), at Experimental Pathology Laboratories, Inc., the pathology narratives were written by Dr. W. Busey (6), and the diagnoses included in this report represent the interpretation of this pathologist. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (9,10) and Mr. R. M. Helfand (9), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (11).

This report was prepared at METREK, a Division of The MITRE Corporation (9) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (9), task leader Ms. P. Walker (9), senior biologist Mr. M. Morse (9), biochemist Mr. S. C. Drill (9), chemist Dr. N. Zimmerman (9) and technical editor Ms. P. A. Miller (9). 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 (1,12), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,13), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay for the possible carcinogenicity of 3-chloro-p-toluidine was conducted using Fischer 344 rats and B6C3F1 mice. 3-Chloro-p-toluidine was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The time-weighted average dietary concentrations of 3-chloro-p-toluidine administered to rats of both sexes were 3269 and 1635 ppm for the high and low dose groups, respectively. The high and low dietary concentrations of 3-chloro-p-toluidine administered to mice were, respectively, 1200 and 600 ppm for males and 600 and 300 ppm for females. The compound was administered in the diet for 78 weeks, followed by an observation period of 24 weeks for high dose male rats, 25 weeks for all other dosed rats, and 12 weeks for mice.

There were no significant positive associations between the concentrations of 3-chloro-p-toluidine administered and mortality in either species. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in high dose rats and mice of both sexes, indicating that the concentrations administered to these animals may have approximated the maximum tolerated dosages. The unusual incidences of nonneoplastic spleen and liver lesions in high dose rats supports this assumption.

Under the conditions of this bioassay there was no convincing evidence for the carcinogenicity of 3-chloro-p-toluidine in Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

3-Chloro-p-toluidine (Figure 1) (NCI No. C02040), a dye intermediate and avicide, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer observed among workers in the dye manufacturing industry (Anthony and Thomas, 1970; Wynder et al., 1963). Aromatic amines, of which 3-chloro-p-toluidine is one example, are among several classes of chemicals believed to contribute to this increased cancer risk (Clayson and Garner, 1976).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 3-chloro-4-methylbenzenamine.* It is also called 1-amino-3-chloro-4-methylbenzene; 4-amino-2-chlorotoluene (CH_3=1); 2-chloro-4-aminotoluene (CH_3=1); 3-chloro-4-methylaniline (NH_2=1); and CPT.

3-Chloro-p-toluidine is used as an intermediate in the production of at least one dye, Palatine Fast Yellow 6GN (Society of Dyers and Colourists, 1956).

3-Chloro-p-toluidine is strongly nephrotoxic to birds of several species, especially starlings, and is therefore used as a selective avicide for starling control (Mull and Giri, 1972; Metcalf, 1967).

Specific production data for 3-chloro-p-toluidine are not available; however, this compound is produced in commercial quantities (in

*The CAS registry number is 95-74-9.

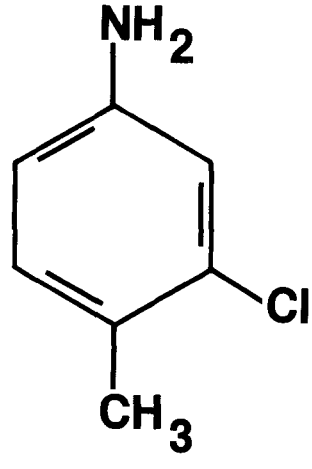


FIGURE 1
CHEMICAL STRUCTURE OF 3-CHLORO-p-TOLUIDINE

excess of 1000 pounds or $1000 in value annually) by one U.S. company (Stanford Research Institute, 1977).

The potential for exposure to 3-chloro-p-toluidine is greatest for workers in the chemical and dye manufacturing industries and pest control workers.

II. MATERIALS AND METHODS

A. Chemicals

3-Chloro-p-toluidine was purchased from E.I. duPont de Nemours & Company, Wilmington, Delaware. Chemical analysis was performed by Litton Bionetics, Inc., Bethesda, Maryland. Thin-layer chromatographic (TLC) plates, developed utilizing two solvent systems (benzene:methanol and diethyl ether:ethyl acetate:acetic acid), each revealed one spot. Visualization was by visible and ultraviolet light, I_2 vapor and ferric chloride-potassium ferricyanide spray. Gas-liquid chromatography showed one peak and infrared (IR) analysis was consistent with the structure of 3-chloro-p-toluidine.

TLC and IR analyses performed after a six-month interval showed no significant changes from the original analyses. These results suggested that this compound was of high purity with good stability.

Throughout this report, the term 3-chloro-p-toluidine is used to refer to this material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). 3-Chloro-p-toluidine was administered to the dosed animals as a component of the diet.

The chemical was removed from its container and a proper amount was blended with an aliquot of the ground feed using a mortar and

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

The stability of 3-chloro-p-toluidine in feed was determined spectrophotometrically. Ten days after preparation of diets containing 1500 and 3000 ppm concentrations of 3-chloro-p-toluidine, 61.6 $\pm$ 0.6 percent of the initial concentrations were detected in the feed, using the methods indicated. Analysis of the data generated by the analytical methods used does not permit a distinction to be made between stability and the extent of extraction.

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. Rats were obtained from Laboratory Supply Company, Inc., Indianapolis, Indiana; A.R. Schmidt, Madison, Wisconsin; and Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts; and A.R. Schmidt, Madison, Wisconsin. There was no indication that animals from a specific supplier were assigned to a specific group.

Rats and mice were approximately 4 weeks old when received. Upon receipt, animals were examined for visible signs of disease or parasites. Obviously ill or runted animals were culled. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals which did not manifest clinical signs of disease were placed on test at this time. Animals were assigned to groups and distributed among cages so that the average body weight per cage was approximately equal for a given species and sex.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 22° to 26°C and the relative humidity was maintained between 45 and 55 percent. Incoming air was filtered through HEPA filters (Flanders Filters, McLean, Virginia) at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided 8 hours per day (9:00 a.m. to 5:00 p.m.).

All rats were housed four per cage by sex and all mice five per cage by sex. Throughout the study dosed and control animals of both species were housed in polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) suspended from aluminum racks. Racks were fitted with a continuous stainless steel mesh lid over which a sheet of filter paper was firmly secured. Filter paper was changed at 2-week intervals, when the racks were sanitized. Clean cages and bedding were provided twice weekly. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used in polycarbonate cages for the entire bioassay.

Acidulated water (pH 2.5) was supplied to animals in water bottles filled by an automated metering device that was checked daily for diluting accuracy. Water bottles were changed twice weekly and sipper tubes were washed at weekly intervals. During the period of chemical administration, dosed and control animals received treated or untreated Wayne Lab-Blox® meal as appropriate. The feed was supplied in hanging stainless steel hoppers which were refilled three times per week and sanitized weekly. Food and water were available ad libitum for both species.

All dosed and control rats were housed in a room with other rats receiving diets containing* 2-nitro-p-phenylenediamine (5307-14-2); 5-chloro-o-toluidine (95-79-4); and nitrofen (1836-75-5).

All dosed and control mice were housed in a room with other mice receiving diets containing 2-nitro-p-phenylenediamine (5307-14-2); Michler's ketone (90-94-8); p-chloroaniline (106-47-8); 4,4'-methylenebis(N,N-dimethyl)-benzenamine (101-61-1); 1-phenyl-2-thiourea (103-85-5); trimethylthiourea (2489-77-2); dibutyltin diacetate (1067-33-0); 5-chloro-o-toluidine (95-79-4); and N-phenyl-p-phenylenediamine hydrochloride (2198-59-6).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of 3-chloro-p-toluidine for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with

*CAS registry numbers are given in parentheses.

both rats and mice. Rats were distributed among six groups, each consisting of five males and five females. 3-Chloro-p-toluidine was incorporated into the basal laboratory diet and supplied ad libitum to five of the six rat groups in concentrations of 315, 680, 1465, 3155, and 6800 ppm. The remaining rat group served as a control group, receiving only the basal laboratory diet.

Mice were distributed among six groups, each consisting of five males and five females. 3-Chloro-p-toluidine was incorporated into the basal laboratory diet and supplied ad libitum to five of the six mouse groups in concentrations of 810, 1180, 1740, 2550, and 3750 ppm. The sixth mouse group served as a control group, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 4 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet. Individual body weights and food consumption data were recorded twice weekly throughout the study. Upon termination of the observation period, all survivors were sacrificed and necropsied.

At the end of the subchronic test, mean body weight gain of male and female rat groups receiving 6800 ppm was 9 percent less than the mean body weight gain of their control groups. The mean body weight gain of male rats receiving 3155 ppm was 17 percent greater than that of their controls, while female rats receiving the same concentration displayed a mean body weight gain 6 percent less than that

of their controls. No deaths were reported for any rat group. The high concentration selected for administration to dosed rats in the chronic bioassay was 6000 ppm.

At the end of the subchronic test, mean body weight gain among male mice receiving 1740 ppm was the same as that of their controls, while female mice receiving the same concentration displayed a mean weight gain 5 percent less than that of their controls. The mean body weight gain among male mice receiving 1180 ppm was the same as that of their controls, while female mice receiving the same concentration displayed a mean body weight gain 3 percent less than that of their control. No deaths were reported in any mouse group. The high concentrations selected for administration to dosed mice in the chronic bioassay were 1200 and 600 ppm for males and females, respectively.

F. Experimental Design

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

All rats were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The initial dietary concentrations of 3-chloro-p-toluidine administered were 6000 and 3000 ppm. Throughout this report those rats initially receiving the former concentration are referred to as the high

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
3-CHLORO-p-TOLUIDINE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	3-CHLORO-p-TOLUIDINE CONCENTRATION[a]	OBSERVATION PERIOD		TIME-WEIGHTED AVERAGE CONCENTRATION[b]
			TREATED (WEEKS)	UNTREATED (WEEKS)	
MALE					
CONTROL	20	0	0	103	0
LOW DOSE	50	3000 1500 0	7 71	 25	1635
HIGH DOSE	50	6000 3000 0	7 71	 24	3269
FEMALE					
CONTROL	20	0	0	103	0
LOW DOSE	50	3000 1500 0	7 71	 25	1635
HIGH DOSE	50	6000 3000 0	7 71	 25	3269

[a] Concentrations given in parts per million.

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
3-CHLORO-p-TOLUIDINE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	3-CHLORO-p-TOLUIDINE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	90
LOW DOSE	50	600	78	
		0		12
HIGH DOSE	50	1200	78	
		0		12
FEMALE				
CONTROL	20	0	0	90
LOW DOSE	50	300	78	
		0		12
HIGH DOSE	50	600	78	
		0		12

[a] Concentrations given in parts per million.

dose groups and those initially receiving the latter concentration are referred to as the low dose groups. At the start of week 8 the dietary concentrations of 3-chloro-p-toluidine were adjusted to 3000 and 1500 ppm. Dosed rats were supplied with feed containing 3-chloro-p-toluidine for 78 weeks followed by a 25-week observation period; except high dose males, which were observed for 24 weeks.

All mice were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The concentrations of 3-chloro-p-toluidine utilized for male mice were 1200 and 600 ppm. Throughout this report, those male mice receiving the former concentration are referred to as the high dose group and those receiving the latter concentration are referred to as the low dose group. The dietary concentrations of 3-chloro-p-toluidine utilized for female mice were 600 and 300 ppm. Throughout this report those female mice receiving the former concentration are referred to as the high dose group and those receiving the latter concentration are referred to as the low dose group. Dosed mice were supplied with feed containing 3-chloro-p-toluidine for 78-weeks followed by a 12-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice daily for mortality. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group. Body weights

were recorded once a week for the first 6 weeks, every 2 weeks for the next 12 weeks, and at monthly intervals thereafter.

All moribund animals or animals that developed large, palpable masses that jeopardized their health were sacrificed. A necropsy was performed on each animal regardless of whether it died, was sacrificed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide asphyxiation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of all major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in a 10 percent neutral buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, tunica vaginalis, 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 recorded in each group at the time that the test was initiated.

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

Mean group body weight depression was apparent in high dose male and in female rats during the period of compound administration (Figure 2).

No abnormal clinical signs were recorded.

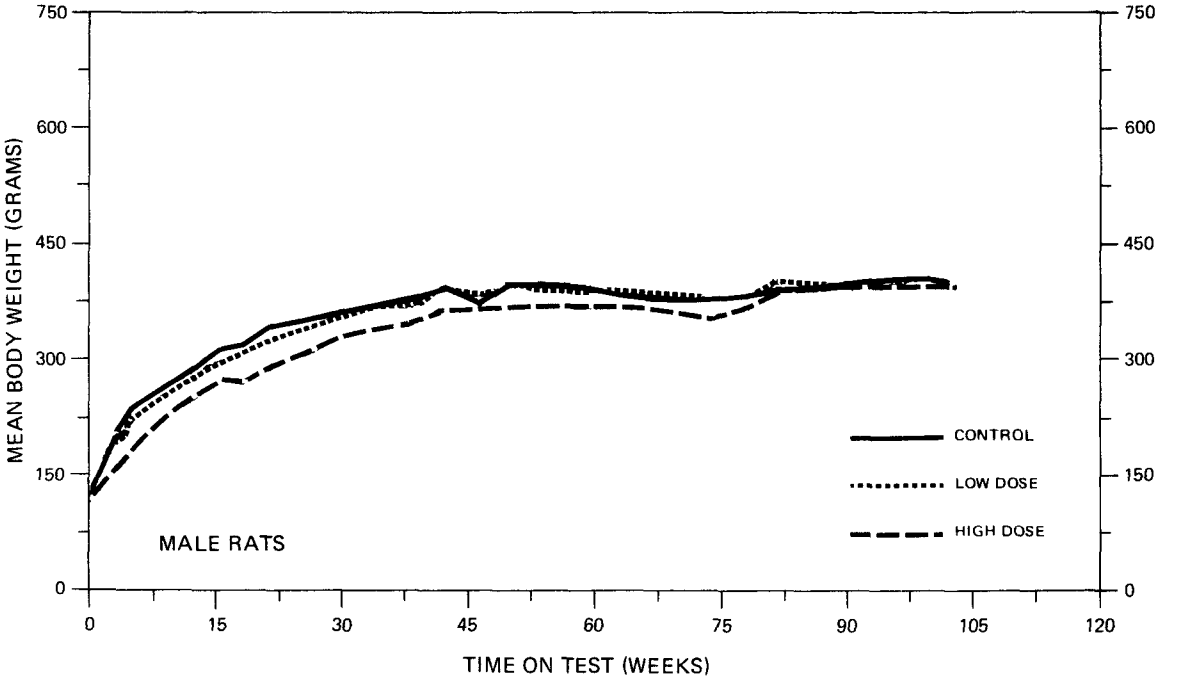
B. Survival

The estimated probabilities of survival for male and female rats in the control and 3-chloro-p-toluidine-dosed groups are shown in Figure 3. For both males and females, the Tarone test did not indicate a significant association between dosage and mortality.

For males adequate numbers of rats were at risk from late-developing tumors, as 46/50 (92 percent) of the high dose, 43/50 (86 percent) of the low dose, and 13/20 (65 percent) of the control group survived on test until the end of the experiment. For females survival was also adequate, as 48/50 (96 percent) of the high dose, 44/50 (88 percent) of the low dose, and 17/20 (85 percent) of the control group survived on test until the end of the experiment.

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).



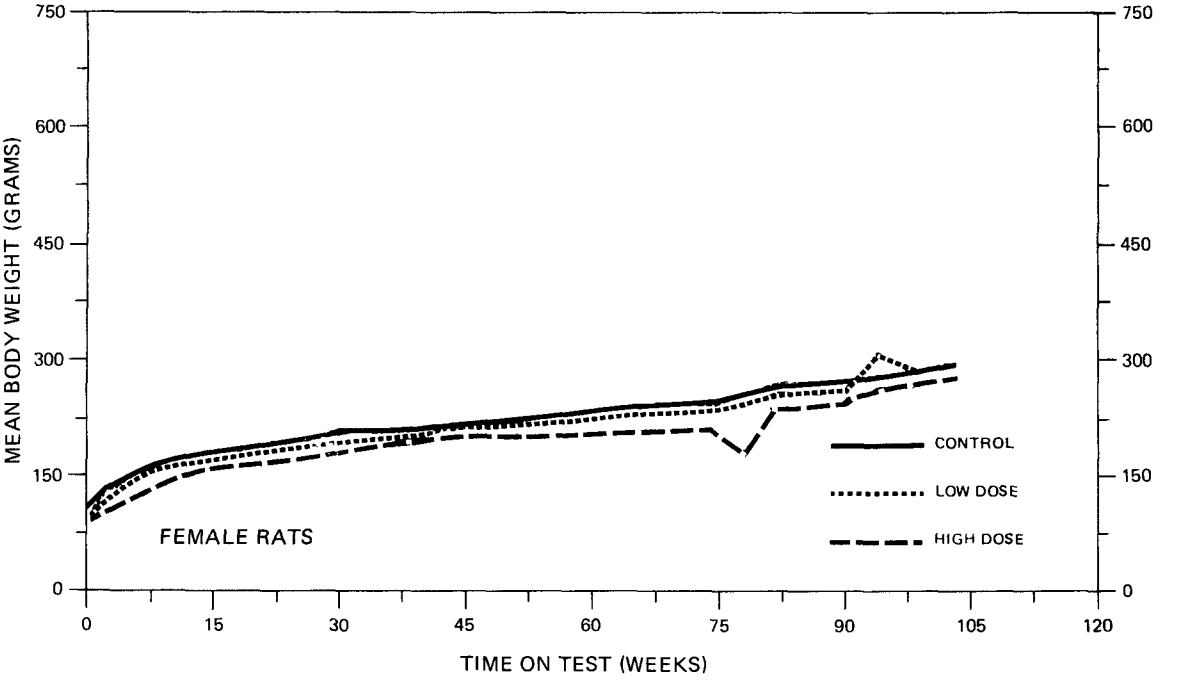
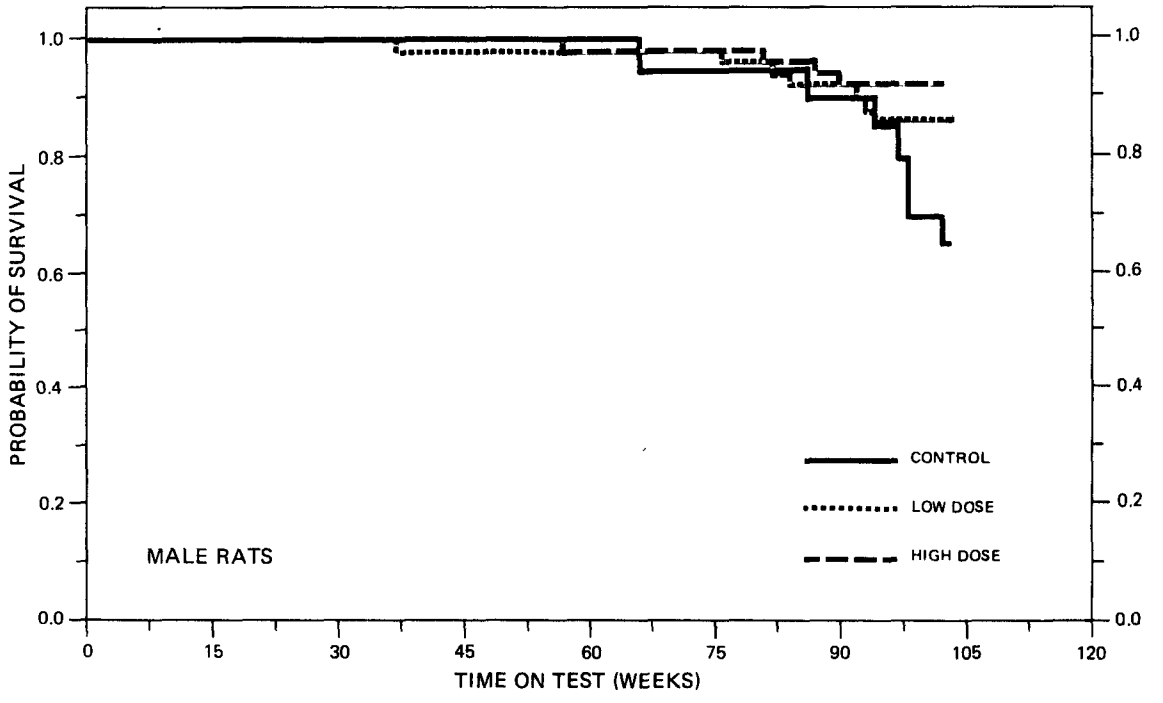


FIGURE 2
GROWTH CURVES FOR 3-CHLORO-p-TOLUIDINE CHRONIC STUDY RATS



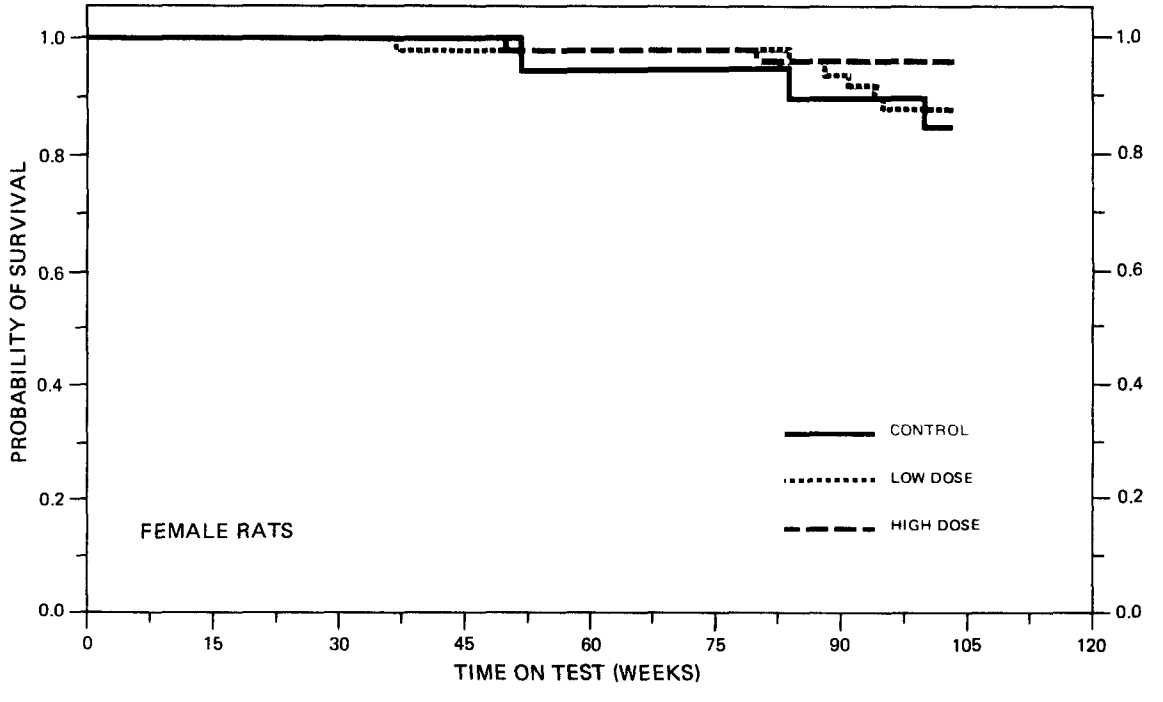


FIGURE 3
SURVIVAL COMPARISONS OF 3-CHLORO-p-TOLUIDINE CHRONIC STUDY RATS

A variety of neoplasms was seen in both the male and female rats. These neoplasms were generally equally distributed among the control and dosed groups.

Endometrial stromal polyps were seen in the female rats from both of the dosed groups. No endometrial stromal polyps were recognized in the control females; however, this lesion is common in aged female Fischer 344 rats, and the variation in its incidence among the control and dosed rats is probably due to the low number of control females. Nonneoplastic lesions were of the types commonly observed in aging Fischer 344 rats, except for those of the spleen and liver. A high incidence of fibrosis of the splenic capsule (i.e., 25/50 [50 percent] in high dose males and 37/50 [74 percent] in high dose females) and hepatic fatty metamorphosis (i.e., 35/50 [70 percent] in high dose males and 34/50 [68 percent] in high dose females) was observed, primarily in high dose rats.

Based on the results of this pathologic examination, 3-chloro-p-toluidine was not carcinogenic in male or female Fischer 344 rats under the conditions of this bioassay; however, administration of the compound was toxic to the spleen and liver.

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

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 3-CHLORO-p-TOLUIDINE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	1/20(0.05)	5/48(0.10)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.083	1.200
Lower Limit	---	0.259	0.106
Upper Limit	---	96.358	61.724
Weeks to First Observed Tumor	103	84	102
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/20(0.20)	0/50(0.00)	0/50(0.00)
P Values[c]	P = 0.001(N)	P = 0.005(N)	P = 0.005(N)
Departure from Linear Trend[e]	P = 0.004	---	---
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	0.427	0.427
Weeks to First Observed Tumor	66	---	---
Pituitary: Chromophobe Adenoma[b]	2/18(0.11)	2/42(0.05)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.429	0.191
Lower Limit	---	0.034	0.003
Upper Limit	---	5.612	3.512
Weeks to First Observed Tumor	98	103	102

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Pheochromocytoma[b]	1/18(0.06)	1/47(0.02)	5/48(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.383	1.875
Lower Limit	---	0.005	0.236
Upper Limit	---	29.452	86.718
Weeks to First Observed Tumor	103	103	57
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/16(0.06)	4/39(0.10)	0/43(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.641	0.000
Lower Limit	---	0.185	0.000
Upper Limit	---	78.628	6.936
Weeks to First Observed Tumor	98	103	---
Pancreatic Islets: Islet-Cell Adenoma[b]	1/19(0.05)	5/46(0.11)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.065	0.000
Lower Limit	---	0.259	0.000
Upper Limit	---	95.429	7.102
Weeks to First Observed Tumor	102	103	---

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	18/20(0.90)	48/49(0.98)	49/50(0.98)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.088	1.089
Lower Limit	---	0.959	0.960
Upper Limit	---	1.174	1.174
Weeks to First Observed Tumor	86	76	81

[a]Treated groups received time-weighted average doses of 1635 or 3269 ppm 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% 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 3-CHLORO-p-TOLUIDINE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/19(0.00)	2/48(0.04)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.122	0.501
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	102
Pituitary: Chromophobe Adenoma[b]	4/17(0.24)	10/42(0.24)	9/45(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.012	0.850
Lower Limit	---	0.354	0.286
Upper Limit	---	3.962	3.408
Weeks to First Observed Tumor	103	37	80
Mammary Gland: Fibroadenoma[b]	1/20(0.05)	6/50(0.12)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.400	1.200
Lower Limit	---	0.325	0.106
Upper Limit	---	108.021	61.724
Weeks to First Observed Tumor	103	103	102

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	0/19(0.00)	4/50(0.08)	9/50(0.18)
P Values[c]	P = 0.018	N.S.	P = 0.044
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.368	1.045
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	102

[a]Treated groups received time-weighted average doses of 1635 or 3269 ppm 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% confidence interval on the relative risk of the treated group to the control group.

tumors were observed in at least one of the control or 3-chloro-p-toluidine-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for male rats indicated a significant positive association between the administration of 3-chloro-p-toluidine and an increased tumor incidence.

For female rats the Cochran-Armitage test indicated a significant ($P = 0.018$) positive association between dosage and the incidence of endometrial stromal polyps of the uterus. The Fisher exact tests, however, were not significant under the Bonferroni criterion. It should also be noted that these tumors occurred in 28/284 (10 percent) of the untreated female Fischer 344 rats in the historical control observed at this laboratory for the NCI Carcinogenesis Testing Program as compared with the lower incidence of 0/19 observed in the controls of this bioassay.

Thus, based upon these statistical results there was no convincing evidence that 3-chloro-p-toluidine was a carcinogen in male or female Fischer 344 rats under the conditions of this experiment.

The possibility of a negative association between dose and the combined incidence of leukemia or malignant lymphoma was noted in male rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the

observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by 3-chloro-p-toluidine that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Distinct and consistent dose-related mean group body weight depression was apparent in male mice. Mean body weight depression, relative to the controls, was apparent throughout a major portion of the bioassay for high dose females. This was not true for low dose females (Figure 4).

No abnormal clinical signs were recorded.

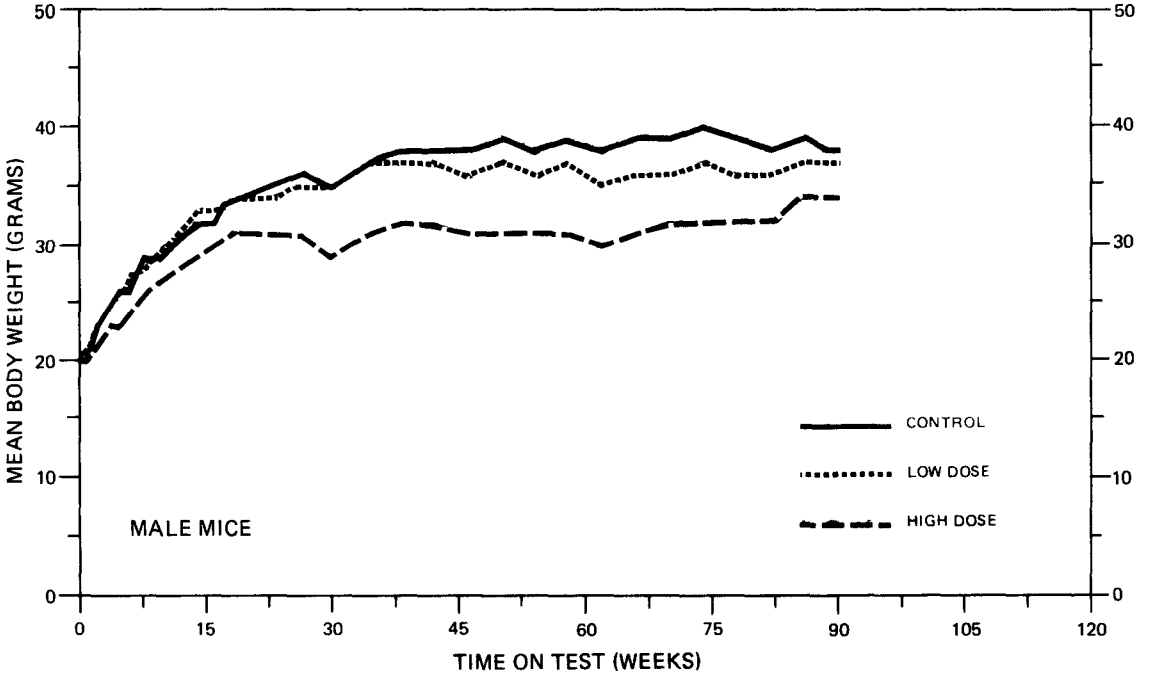
B. Survival

The estimated probabilities of survival for male and female mice in the control and 3-chloro-p-toluidine-dosed groups are shown in Figure 5. The Tarone test did not indicate a significant association between dosage and mortality for either male or female mice.

For males adequate numbers of mice were at risk from late-developing tumors, as 48/50 (96 percent) of the high dose, 44/50 (88 percent) of the low dose, and 20/20 in the control group survived on test until the end of the experiment. For females survival was also adequate, as 44/50 (88 percent) of the high dose, 44/50 (88 percent) of the low dose, and 20/20 in the control group survived on test until the end of the experiment.

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).



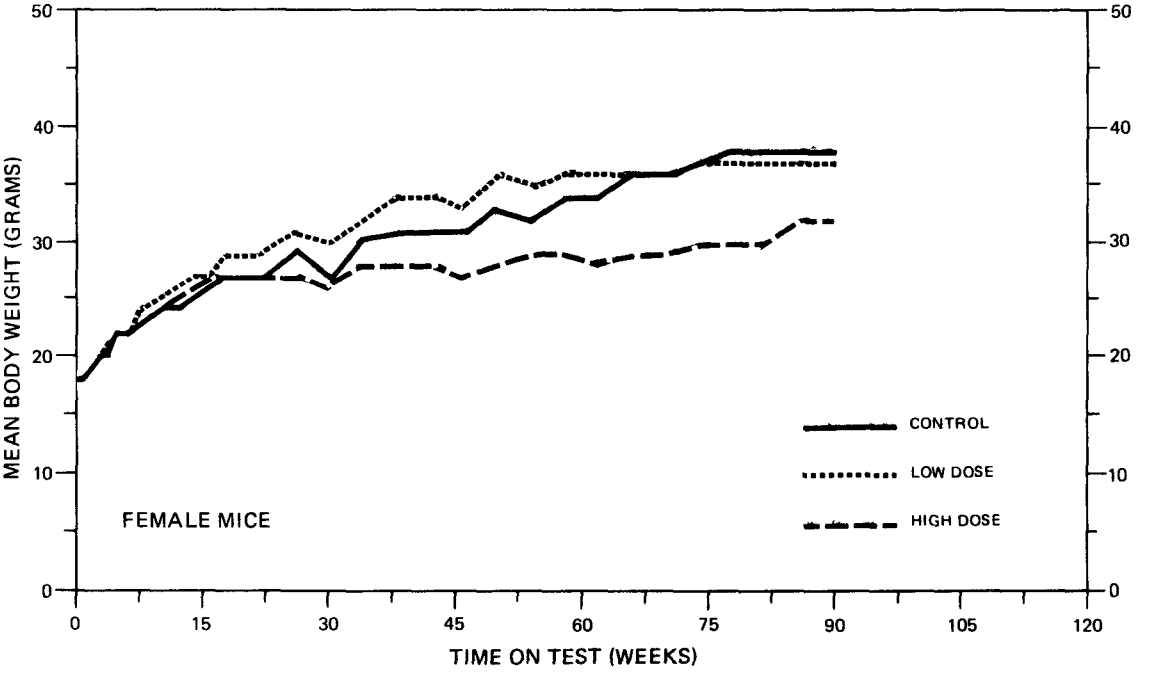
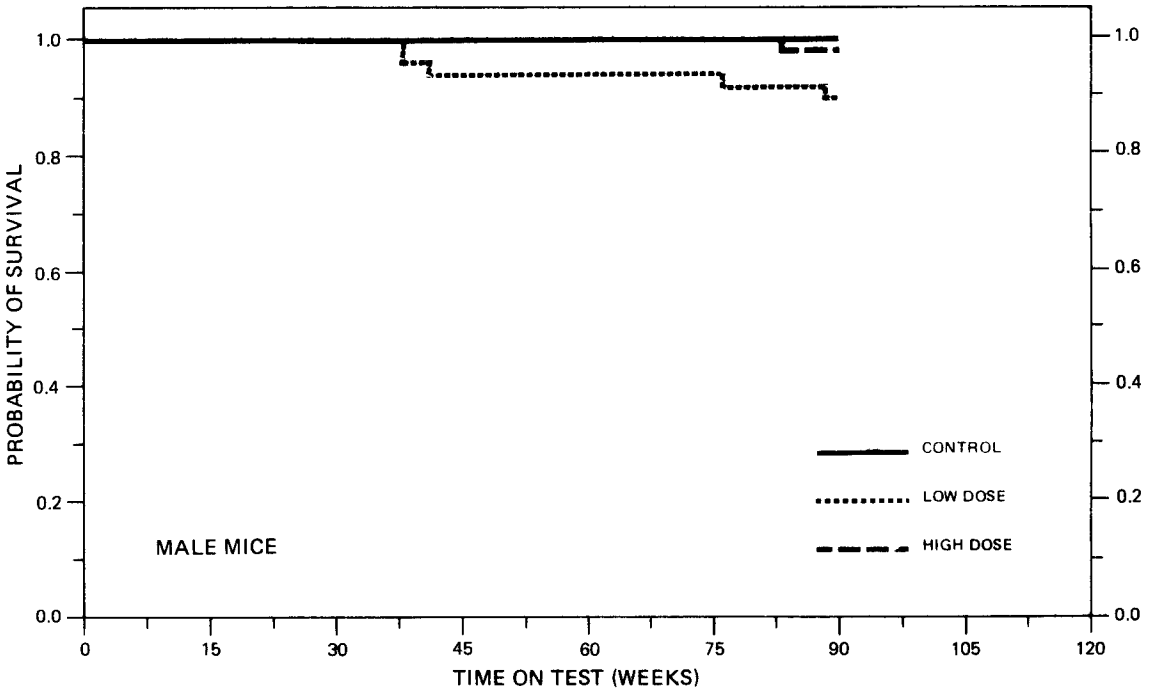


FIGURE 4
GROWTH CURVES FOR 3-CHLORO-p-TOLUIDINE CHRONIC STUDY MICE



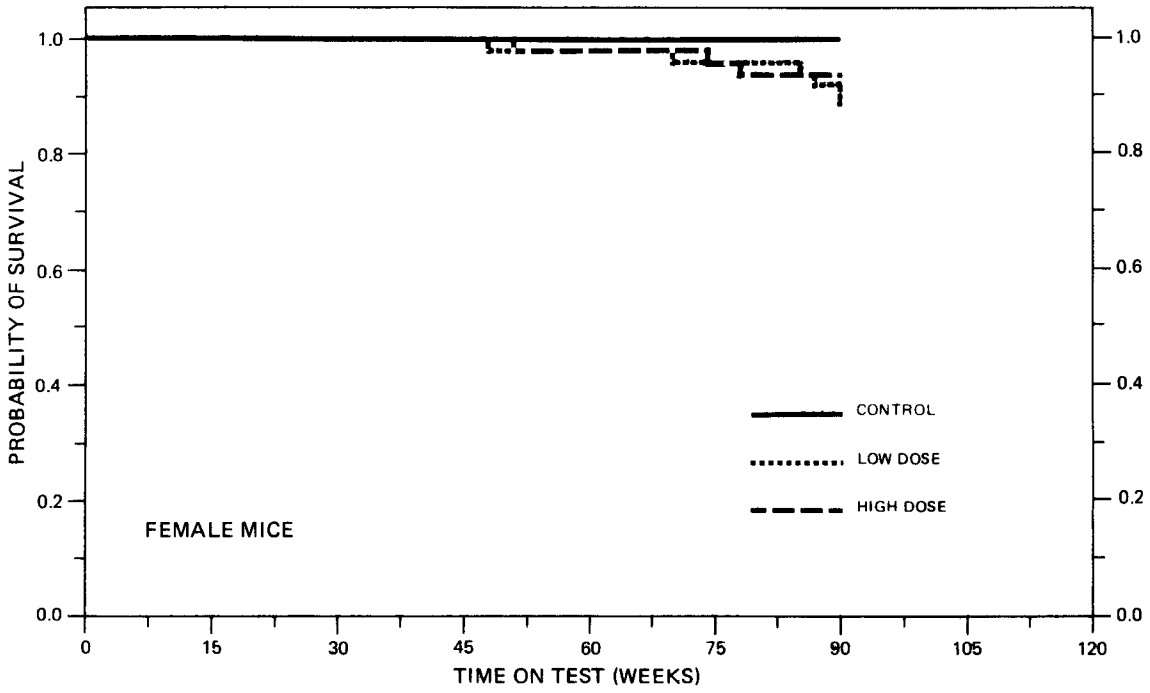


FIGURE 5
SURVIVAL COMPARISONS OF 3-CHLORO-p-TOLUIDINE CHRONIC STUDY MICE

A variety of neoplasms was present in both the dosed and control groups. No meaningful differences were noted in the incidence of neoplasms among the control and dosed mice. Nonneoplastic lesions were of the types commonly observed in aging B6C3F1 mice.

Based on the results of this pathologic examination, 3-chloro-p-toluidine was not carcinogenic in B6C3F1 mice under the conditions of this bioassay.

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 3-chloro-p-toluidine-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site in mice of either sex indicated a significant positive association between the administration of 3-chloro-p-toluidine and an increased tumor incidence. Thus, at the dose levels used in this experiment there was no evidence that 3-chloro-p-toluidine was a carcinogen in B6C3F1 mice.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 3-CHLORO-p-TOLUIDINE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	0/20(0.00)	3/49(0.06)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.255	0.255
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	90	83
Liver: Hepatocellular Carcinoma[b]	3/20(0.15)	6/47(0.13)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.851	0.408
Lower Limit	---	0.208	0.061
Upper Limit	---	4.897	2.857
Weeks to First Observed Tumor	90	90	90
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	4/20(0.20)	10/47(0.21)	7/49(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.064	0.714
Lower Limit	---	0.361	0.211
Upper Limit	---	4.230	3.052
Weeks to First Observed Tumor	90	90	90

TABLE 5 (CONCLUDED)

[a]Treated groups received doses of 600 or 1200 ppm 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% confidence interval on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 3-CHLORO-p-TOLUIDINE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	2/20(0.10)	0/50(0.00)	4/46(0.09)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.030	---	---
Relative Risk (Control)[d]	---	0.000	0.870
Lower Limit	---	0.000	0.139
Upper Limit	---	1.345	9.144
Weeks to First Observed Tumor	90	---	90
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/20(0.10)	4/50(0.08)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.800	0.638
Lower Limit	---	0.128	0.081
Upper Limit	---	8.436	7.284
Weeks to First Observed Tumor	90	90	74
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	3/49(0.06)	0/45(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.255	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	87	---

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	0/20(0.00)	4/49(0.08)	2/45(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.394	0.136
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	87	90

[a]Treated groups received doses of 300 or 600 ppm 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% 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 $P < 0.05$;

of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by 3-chloro-p-toluidine that could not be established under the conditions of this test.

V. DISCUSSION

There were no significant positive associations between the concentrations of 3-chloro-p-toluidine administered and mortality in either species. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in high dose rats and mice of both sexes, indicating that the concentrations administered to these animals may have approximated the maximum tolerated dosages. The unusual incidences of nonneoplastic spleen and liver lesions in high dose rats supports this assumption.

In female rats endometrial stromal polyps of the uterus were observed in dosed but not in control groups (i.e., 0/19, 4/50, and 9/50 in the control, low dose, and high dose groups, respectively). There was a statistically significant positive association between dosage and the incidence of these uterine tumors; however, the Fisher exact tests were not significant. In addition, it should be noted that the incidence of these tumors in the control female rats in this bioassay (i.e., 0 percent) was considerably lower than the incidence seen in historical untreated controls from this laboratory (i.e., 10 percent). There were no other statistically significant positive associations between the administration of 3-chloro-p-toluidine and tumor incidence in rats of either sex.

No biologically unusual tumors were detected in mice of either sex, and there were no statistically significant positive associations between compound administration and tumor incidence.

Under the conditions of this bioassay, there was no convincing evidence for the carcinogenicity of 3-chloro-p-toluidine in Fischer 344 rats or B6C3F1 mice.

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Review of the Bioassay of 3-Chloro-*p*-Toluidine* 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 3-Chloro-*p*-Toluidine for carcinogenicity.

The reviewer agreed with the conclusion in the report that 3-Chloro-*p*-Toluidine was not carcinogenic under the conditions of test. The compound was obtained from the commercial producer and was analyzed for purity and stability, both over time and in the dietary mixture. Although she noted the small control group sizes and dosage changes during the chronic phase, she still considered the study valid. The reviewer moved that the report on the bioassay of 3-Chloro-*p*-Toluidine 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.

✪U.S. GOVERNMENT PRINTING OFFICE: 1978-260-899/(198

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 3-CHLORO-p-TOLUIDINE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
UNDIFFERENTIATED CARCINOMA			1 (2%)
ADNEXAL ADENOMA		1 (2%)	
NEUROFIBROMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA		2 (4%)	2 (4%)
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
*LUNG	(20)	(48)	(50)
UNDIFFERENTIATED CARCINOMA METAS			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	5 (10%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (10%)		
LEUKEMIA,NOS	1 (5%)		
UNDIFFERENTIATED LEUKEMIA	1 (5%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*LIVER	(20)	(47)	(50)
HEPATOCELLULAR CARCINOMA		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
#STOMACH	(19)	(49)	(48)
SARCOMA, NOS		2 (4%)	
#SMALL INTESTINE	(20)	(47)	(49)
ADENOMA, NOS	1 (5%)		
#LARGE INTESTINE	(19)	(46)	(49)
LEIOMYOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(49)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(42)	(47)
CHROMOPHOBE ADENOMA	2 (11%)	2 (5%)	1 (2%)
#ADRENAL	(18)	(47)	(48)
PHEOCHROMOCYTOMA	1 (6%)	1 (2%)	5 (10%)
#THYROID	(16)	(39)	(43)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA		3 (8%)	
C-CELL CARCINOMA	1 (6%)	1 (3%)	
#PANCREATIC ISLETS	(19)	(46)	(50)
ISLET-CELL ADENOMA	1 (5%)	5 (11%)	
REPRODUCTIVE SYSTEM			
#PREPUTIAL GLAND	(20)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
#TESTIS	(20)	(49)	(50)
INTERSTITIAL-CELL TUMOR	18 (90%)	48 (98%)	49 (98%)
NERVOUS SYSTEM			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
MESOTHELIOMA, NOS			2 (4%)
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	4	3
MORIBUND SACRIFICE	3	3	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	43	46
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	49	50
TOTAL PRIMARY TUMORS	29	74	67
TOTAL ANIMALS WITH BENIGN TUMORS	19	49	50
TOTAL BENIGN TUMORS	24	68	62
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	5	3
TOTAL MALIGNANT TUMORS	5	5	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(48)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
C-CELL CARCINOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
**MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)		
#SPLENIC CAPSULE	(19)	(49)	(50)
MESOTHELIOMA, NOS		1 (2%)	
#UTERUS	(19)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(18)	(50)	(50)
NEOPLASTIC NODULE			1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
URINARY SYSTEM			
#URINARY BLADDER	(18)	(45)	(42)
PAPILLOMA, NOS		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(42)	(45)
CHROMOPHOBE ADENOMA	4 (24%)	10 (24%)	9 (20%)
#ADRENAL	(19)	(49)	(50)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(15)	(43)	(47)
C-CELL ADENOMA	1 (7%)		1 (2%)
C-CELL CARCINOMA			1 (2%)
#PANCREATIC ISLETS	(19)	(49)	(48)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA	1 (5%)	6 (12%)	3 (6%)
*PREPUTIAL GLAND	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#UTERUS	(19)	(50)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS		2 (4%)	
ENDOMETRIAL STROMAL POLYP		4 (8%)	9 (18%)
#CERVIX UTERI	(19)	(50)	(50)
FIBROMA			1 (2%)
#OVARY	(19)	(49)	(48)
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(18)	(49)	(49)
GLIOMA, NOS		1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
MENINGIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	3	1
MORIBUND SACRIFICE	1	3	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	44	48
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	22	28
TOTAL PRIMARY TUMORS	7	33	33
TOTAL ANIMALS WITH BENIGN TUMORS	6	19	25
TOTAL BENIGN TUMORS	6	24	29
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	7	3
TOTAL MALIGNANT TUMORS	1	8	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 3-CHLORO-p-TOLUIDINE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 22-2125	LOW DOSE 22-2123	HIGH DOSE 22-2121
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(49)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(49)
NEOPLASM, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)
LEUKEMIA,NOS		1 (2%)	
#SPLEEN	(19)	(40)	(46)
ANGIOSARCOMA		1 (3%)	
#SMALL INTESTINE	(20)	(47)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(47)	(49)
NEOPLASM, NOS, MALIGNANT			1 (2%)

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2125	LOW DOSE 22-2123	HIGH DOSE 22-2121
HEPATOCELLULAR ADENOMA	1 (5%)	4 (9%)	4 (8%)
HEPATOCELLULAR CARCINOMA	3 (15%)	6 (13%)	3 (6%)
HEPATOBLASTOMA		1 (2%)	
ANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(20)	(36)	(43)
FOLLICULAR-CELL ADENOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(20)	(45)	(48)
INTERSTITIAL-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 22-2125	LOW DOSE 22-2123	HIGH DOSE 22-2121
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@		2	1
MORIBUND SACRIFICE		3	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	20	44	48
ANIMAL MISSING		1	1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	15	14
TOTAL PRIMARY TUMORS	5	18	14
TOTAL ANIMALS WITH BENIGN TUMORS	2	7	8
TOTAL BENIGN TUMORS	2	7	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	8	6
TOTAL MALIGNANT TUMORS	3	11	6
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			3
ANIMALS NECROPSIED	20	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)		3 (7%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(47)
MALIGNANT LYMPHOMA, NOS	1 (5%)	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		2 (4%)
LEUKEMIA,NOS		1 (2%)	1 (2%)
#LUNG	(20)	(50)	(46)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(45)
HEPATOCELLULAR ADENOMA		1 (2%)	2 (4%)
HEPATOCELLULAR CARCINOMA		3 (6%)	
URINARY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(34)	(32)
CHROMOPHOBE ADENOMA	1 (11%)		
#THYROID	(17)	(42)	(43)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
#OVARY	(19)	(34)	(30)
PAPILLARY CYSTADENOMA, NOS			1 (3%)
THECOMA		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(47)
LIPOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@		6	3
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	20	44	44
ANIMAL MISSING			3
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	6	11
TOTAL PRIMARY TUMORS	5	10	11
TOTAL ANIMALS WITH BENIGN TUMORS	3	2	7
TOTAL BENIGN TUMORS	3	3	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	6	4
TOTAL MALIGNANT TUMORS	2	7	4
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 3-CHLORO-p-TOLUIDINE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(20)	(48)	(50)
BRONCHIECTASIS		1 (2%)	
#LUNG	(20)	(48)	(50)
ATELECTASIS	1 (5%)	1 (2%)	
PNEUMONIA, CHRONIC MURINE	4 (20%)	20 (42%)	11 (22%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(47)	(50)
CONGESTION, NOS		1 (2%)	
HEMATOPOIESIS		1 (2%)	1 (2%)
HYPOPLASIA, LYMPHOID			1 (2%)
#SPLENIC CAPSULE	(20)	(47)	(50)
FIBROSIS			1 (2%)
FIBROSIS, FOCAL		1 (2%)	24 (48%)
HYPERPLASIA, NOS		1 (2%)	
#CERVICAL LYMPH NODE	(16)	(38)	(39)
INFLAMMATION, NOS		1 (3%)	
#MESENTERIC L. NODE	(16)	(38)	(39)
CYST, NOS	1 (6%)		
NECROSIS, NOS		1 (3%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(47)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
FIBROSIS, DIFFUSE	1 (5%)		
DEGENERATION, NOS			1 (2%)
HYPERTROPHY, NOS		1 (2%)	
*PULMONARY ARTERY	(20)	(50)	(50)
HYPERTROPHY, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(47)	(50)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	2 (10%)	5 (11%)	35 (70%)
#LIVER/PERIPORTAL	(20)	(47)	(50)
FIBROSIS	1 (5%)		
#BILE DUCT	(20)	(47)	(50)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS	1 (5%)	2 (4%)	
#PANCREATIC ACINUS	(19)	(46)	(50)
ATROPHY, NOS	1 (5%)	5 (11%)	6 (12%)
#SMALL INTESTINE	(20)	(47)	(49)
HYPERPLASIA, LYMPHOID	1 (5%)	3 (6%)	2 (4%)
#LARGE INTESTINE	(19)	(46)	(49)
NEMATODIASIS	4 (21%)	11 (24%)	7 (14%)
URINARY SYSTEM			
*KIDNEY	(20)	(49)	(49)
INFLAMMATION, CHRONIC	13 (65%)	38 (78%)	33 (67%)
#KIDNEY/CORTEX	(20)	(49)	(49)
HEMORRHAGIC CYST			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(18)	(47)	(48)
HYPERPLASIA, FOCAL		1 (2%)	

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

TABLE C-1 (CONTINUED)

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
#ADRENAL MEDULLA	(18)	(47)	(48)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(16)	(39)	(43)
HYPERPLASIA, NOS		1 (3%)	
#PANCREATIC ISLETS	(19)	(46)	(50)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
#PROSTATE	(20)	(37)	(48)
INFLAMMATION, NOS	1 (5%)	1 (3%)	
#TESTIS	(20)	(49)	(50)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
NECROSIS, FAT	1 (5%)	2 (4%)	1 (2%)
ALL OTHER SYSTEMS			
THORAX			
CYST, NOS		1	

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 11-1125	LOW DOSE 11-1123	HIGH DOSE 11-1121
ABSCESS, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/NO HISTO		1	

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(48)	(50)
ATELECTASIS			1 (2%)
EDEMA, NOS			1 (2%)
PNEUMONIA, CHRONIC MURINE	2 (11%)	7 (15%)	8 (16%)
#LUNG/ALVEOLI	(19)	(48)	(50)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(49)	(50)
HEMOSIDEROSIS		2 (4%)	1 (2%)
HEMATOPOIESIS			5 (10%)
#SPLENIC CAPSULE	(19)	(49)	(50)
CYST, NOS		1 (2%)	2 (4%)
FIBROSIS			3 (6%)
FIBROSIS, FOCAL		3 (6%)	34 (68%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	1 (2%)
FIBROSIS	1 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(18)	(50)	(50)
HEMORRHAGIC CYST	1 (6%)		

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
INFLAMMATION, NOS		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY		4 (8%)	34 (68%)
BASOPHILIC CYTO CHANGE	1 (6%)	5 (10%)	1 (2%)
ANGIECTASIS			1 (2%)
#BILE DUCT	(18)	(50)	(50)
HYPERPLASIA, NOS	1 (6%)	1 (2%)	
#PANCREATIC ACINUS	(19)	(49)	(48)
ATROPHY, NOS	1 (5%)	4 (8%)	4 (8%)
#SMALL INTESTINE	(19)	(50)	(49)
FIBROSIS, FOCAL		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (5%)	5 (10%)	
#LARGE INTESTINE	(19)	(49)	(49)
NEMATODIASIS	2 (11%)	12 (24%)	6 (12%)
*RECTUM	(20)	(50)	(50)
NECROSIS, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(19)	(50)	(50)
INFLAMMATION, CHRONIC	2 (11%)	7 (14%)	16 (32%)
DEGENERATION PIGMENTARY		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(42)	(45)
CYST, NOS		1 (2%)	
#ADRENAL	(19)	(49)	(50)
HEMORRHAGIC CYST	1 (5%)	1 (2%)	
LIPOIDOSIS	1 (5%)	2 (4%)	
#ADRENAL CORTEX	(19)	(49)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA	(19)	(49)	(50)
CYST, NOS			1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
#THYROID	(15)	(43)	(47)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
CYST, NOS		2 (4%)	
*PREPUTIAL GLAND	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
#UTERUS	(19)	(50)	(50)
HYDROMETRA		1 (2%)	2 (4%)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS	3 (16%)		
PYOMETRA			2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
#UTERUS/ENDOMETRIUM	(19)	(50)	(50)
HYPERPLASIA, CYSTIC	1 (5%)		
#OVARY	(19)	(49)	(48)
CYST, NOS	4 (21%)	1 (2%)	2 (4%)
PAROVARIAN CYST		2 (4%)	4 (8%)
NECROSIS, FAT		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 11-1126	LOW DOSE 11-1124	HIGH DOSE 11-1122
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	4	
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO	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 3-CHLORO-p-TOLUIDINE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 22-2125	LOW DOSE 22-2123	HIGH DOSE 22-2121
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(49)
INFLAMMATION, FOCAL		1 (2%)	
ACARIASIS	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(49)
PNEUMONIA, CHRONIC MURINE	2 (10%)	5 (10%)	7 (14%)
PNEUMONIA INTERSTITIAL CHRONIC			3 (6%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (5%)	2 (4%)	1 (2%)
EPITHELIALIZATION			1 (2%)
HYPERPLASIA, LYMPHOID			2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(40)	(46)
CONGESTION, NOS		1 (3%)	1 (2%)
AMYLOID, NOS	1 (5%)		
HYPERPLASIA, RETICULUM CELL			2 (4%)
HYPERPLASIA, LYMPHOID	1 (5%)	2 (5%)	4 (9%)
#LYMPH NODE	(13)	(39)	(43)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID	1 (8%)		
#MESENTERIC L. NODE	(13)	(39)	(43)
INFLAMMATION, HEMORRHAGIC	1 (8%)	1 (3%)	
HYPERPLASIA, RETICULUM CELL			3 (7%)
HYPERPLASIA, LYMPHOID	1 (8%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2125	LOW DOSE 22-2123	HIGH DOSE 22-2121
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(48)	(48)
INFLAMMATION, FOCAL		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(47)	(49)
INFLAMMATION, ACUTE			1 (2%)
NECROSIS, DIFFUSE		1 (2%)	
HEPATOCYTOMEGALY	1 (5%)	2 (4%)	
ANGIECTASIS	1 (5%)		
#PANCREAS	(20)	(45)	(48)
INFLAMMATION, NECROTIZING		1 (2%)	
#SMALL INTESTINE	(20)	(47)	(49)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (5%)		1 (2%)
#LARGE INTESTINE	(20)	(47)	(49)
NEMATODIASIS		3 (6%)	6 (12%)
HYPERPLASIA, LYMPHOID	1 (5%)		
URINARY SYSTEM			
#KIDNEY	(20)	(48)	(49)
GLOMERULONEPHRITIS, MEMBRANOUS		1 (2%)	
#RENAL PAPILLA	(20)	(48)	(49)
INFLAMMATION, NECROTIZING		1 (2%)	
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(20)	(45)	(48)
HYPERPLASIA, NODULAR		1 (2%)	
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(20)	(49)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 22-2125	LOW DOSE 22-2123	HIGH DOSE 22-2121
#TESTIS	(20)	(45)	(48)
DEGENERATION, NOS	1 (5%)		3 (6%)
ATROPHY, NOS		1 (2%)	
#TESTIS/TUBULE	(20)	(45)	(48)
DEGENERATION, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(48)	(49)
HYDROCEPHALUS, INTERNAL	1 (5%)		
CORPORA AMYLACEA	8 (40%)	14 (29%)	14 (29%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
MINERALIZATION			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	14	10
ANIMAL MISSING/NO NECROPSY		1	1

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 3-CHLORO-p-TOLUIDINE

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			3
ANIMALS NECROPSIED	20	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(20)	(50)	(46)
BRONCHIECTASIS			1 (2%)
#LUNG	(20)	(50)	(46)
PNEUMONIA, CHRONIC MURINE	2 (10%)	10 (20%)	17 (37%)
FIBROSIS, DIFFUSE			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#LUNG/ALVEOLI	(20)	(50)	(46)
HYPERPLASIA, ADENOMATOUS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(47)	(43)
HEMOSIDEROSIS		1 (2%)	
#SPLEEN	(18)	(41)	(45)
HEMOSIDEROSIS	2 (11%)	3 (7%)	3 (7%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	2 (4%)
HYPERPLASIA, LYMPHOID	1 (6%)	6 (15%)	8 (18%)
HEMATOPOIESIS		3 (7%)	2 (4%)
#LYMPH NODE	(12)	(43)	(38)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (3%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
#SUBMANDIBULAR L.NODE	(12)	(43)	(38)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#MESENTERIC L. NODE	(12)	(43)	(38)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#CARDIAC VALVE	(18)	(47)	(45)
SCLEROSIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(19)	(46)	(41)
INFLAMMATION, NOS		1 (2%)	
#LIVER	(20)	(49)	(45)
INFLAMMATION, FOCAL		2 (4%)	1 (2%)
INFLAMMATION, MULTIFOCAL	1 (5%)	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
CYTOPLASMIC VACUOLIZATION			1 (2%)
BASOPHILIC CYTO CHANGE	1 (5%)	1 (2%)	
HEPATOCYTOMEGALY		1 (2%)	2 (4%)
ANGIECTASIS			1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
#BILE DUCT	(20)	(49)	(45)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (5%)		
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
#PANCREAS	(19)	(46)	(38)
CYSTIC DUCTS	1 (5%)		1 (3%)
INFLAMMATION, ACUTE		1 (2%)	
ATROPHY, NOS	1 (5%)		
HYPERPLASIA, LYMPHOID			1 (3%)
#SMALL INTESTINE	(20)	(48)	(45)
AMYLOIDOSIS	1 (5%)		
HYPERPLASIA, ADENOMATOUS	1 (5%)		
#ILEUM	(20)	(48)	(45)
INFLAMMATION, NOS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
HYPERPLASIA, LYMPHOID		1 (2%)	
#LARGE INTESTINE	(20)	(49)	(42)
HYPERPLASIA, RETICULUM CELL			1 (2%)
#COLON	(20)	(49)	(42)
ULCER, CHRONIC		1 (2%)	
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(45)
HYDRONEPHROSIS		1 (2%)	1 (2%)
GLOMERULONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
SCAR		1 (2%)	
AMYLOID, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#KIDNEY/GLOMERULUS	(20)	(50)	(45)
AMYLOIDOSIS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(34)	(32)
ANGIECTASIS	1 (11%)		
#ADRENAL CORTEX	(18)	(39)	(42)
METAMORPHOSIS FATTY		1 (3%)	
#THYROID	(17)	(42)	(43)
DEGENERATION, NOS	1 (6%)		
#PARATHYROID	(5)	(16)	(20)
THYROGLOSSAL DUCT CYST	1 (20%)		
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(49)	(44)
MINERALIZATION			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
CYST, NOS	1 (5%)	1 (2%)	
PYOMETRA		2 (4%)	
NECROSIS, NOS			1 (2%)
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#UTERUS/ENDOMETRIUM	(19)	(49)	(44)
CYST, NOS	10 (53%)	13 (27%)	20 (45%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, CYSTIC	1 (5%)	1 (2%)	3 (7%)
#UTERUS/MYOMETRIUM	(19)	(49)	(44)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
#OVARY	(19)	(34)	(30)
CYST, NOS	1 (5%)	3 (9%)	2 (7%)
FOLLICULAR CYST, NOS			1 (3%)
PAROVARIAN CYST	2 (11%)	1 (3%)	2 (7%)
HEMORRHAGIC CYST		1 (3%)	
INFLAMMATION, GRANULOMATOUS		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(50)	(46)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL	1 (5%)		
#BRAIN/EPENDYMA	(20)	(50)	(46)
INFLAMMATION, FOCAL		1 (2%)	
#BRAIN	(20)	(50)	(46)
CORPORA AMYLACEA	5 (25%)	10 (20%)	8 (17%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(50)	(47)
INFLAMMATION, NOS	1 (5%)		

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 22-2126	LOW DOSE 22-2124	HIGH DOSE 22-2122
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(47)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
ALL OTHER SYSTEMS			
SITE UNKNOWN			
HYPERPLASIA, LYMPHOID	1		
ADIPOSE TISSUE			
INFLAMMATION, PYOGRANULOMATOUS		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	7	1
ANIMAL MISSING/NO NECROPSY			3
AUTO/NECROPSY/HISTO PERF			1

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

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