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1979

BIOASSAY OF 4'-(CHLOROACETYL)-ACETANILIDE FOR POSSIBLE CARCINOGENICITY

CAS No. 140-49-8

NCI-CG-TR-177

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

BIOASSAY OF

4'-(CHLOROACETYL)-ACETANILIDE

FOR POSSIBLE CARCINOGENICITY

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

Carcinogenesis Technical report series

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DHEW Publication No. (NIH) 79-1733

REPORT ON THE BIOASSAY OF 4'-(CHLOROACETYL)-ACETANILIDE
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 4'-(chloroacetyl)-acetanilide 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 4'-(chloroacetyl)-acetanilide was conducted by Litton Bionetics, Inc., Kensington, 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. F. M. Garner (4) 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. Chemical analysis was performed by Midwest Research Institute (6) and the analytical results were reviewed by Dr. N. Zimmerman (7).

Histopathologic examinations were performed by Dr. B. C. Zook (4) at Litton Bionetics, Inc., the pathology narratives were written by Dr. B. C. Zook (4), and the diagnoses included in this report represent the interpretation of this pathologist. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (8).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (9); the statistical analysis was performed by Mr. R. M. Helfand (7) and Dr. J. P. Dirkse, III (10) 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 (7) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (7), task leader Ms. P. Walker (7), senior biologist Mr. M. Morse (7), biochemist Mr. S. C. Drill (7), and technical editor Ms. P. A. Miller (7). 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. R. A. Griesemer (1), Dr. T. E. Hamm (1), Dr. W. V. Hartwell (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), 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 4'-(chloroacetyl)-acetanilide was conducted using Fischer 344 rats and B6C3F1 mice. 4'-(Chloroacetyl)-acetanilide 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 high and low dietary concentrations of 4'-(chloroacetyl)-acetanilide were, respectively, 2000 and 1000 ppm for rats and 10,000 and 5,000 ppm for mice. The compound was administered for 87 weeks of a 102-week period in rats and for 90 weeks of a 105-week period in mice. Mice were killed at the end of the last week of compound administration, while rats were observed for 1 week after compound administration ceased.

There were no significant positive associations between the concentrations of 4'-(chloroacetyl)-acetanilide administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Dose-related mean body weight depression was observed for males and females of both species, indicating that the concentrations of 4'-(chloroacetyl)-acetanilide administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

None of the statistical tests for any site in rats of either sex or in male mice indicated a significant positive association between compound administration and tumor incidence. Although there was a significant positive association between the concentration of the compound administered and the incidences of hepatocellular adenomas in female mice, the Fisher exact comparisons were not significant.

Under the conditions of this bioassay, 4'-(chloroacetyl)-acetanilide was not carcinogenic when administered in the diet to Fischer 344 rats or B6C3F1 mice of either sex.

TABLE OF CONTENTS

TABLE OF CONTENTS (Concluded)

LIST OF ILLUSTRATIONS

LIST OF TABLES

LIST OF TABLES (Concluded)

I. INTRODUCTION

4'-(Chloroacetyl)-acetanilide (Figure 1) (NCI No. C03770), an intermediate in the synthesis of dyes and pharmaceutical compounds, was selected for bioassay by the National Cancer Institute because of the increased incidence of bladder cancer observed among dye manufacturing industry workers (Anthony and Thomas, 1970; Wynder et al., 1963). Aromatic amines, such as 4'-(chloroacetyl)-acetanilide, are among several classes of chemicals thought to contribute to the increased cancer risk in this industry (Clayson and Garner, 1976), and 4'-(chloroacetyl)-acetanilide is especially suspect because it is structurally similar to the possible human renal pelvic carcinogen, phenacetin (Juusela, 1973).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is N'-(chloroacetyl)-N-phenylacetamide.* It is also called 4'-(Cl-acetyl)acetanilide.

4'-(Chloroacetyl)-acetanilide is used in the synthesis of cationic azo dyes for nylon (James, 1975a,b,c), and acrylic polyester and polyamide fibers and leather (Kruckenberg, 1976; Kruckenberg, 1973; Harris, 1969). It has also been used to prepare choleretic agents (Bourdon et al., 1971; Ranisteano and Bourdon, 1969) and antimicrobial agents (Geigy, 1962).

*The CAS registry number is 140-49-8.

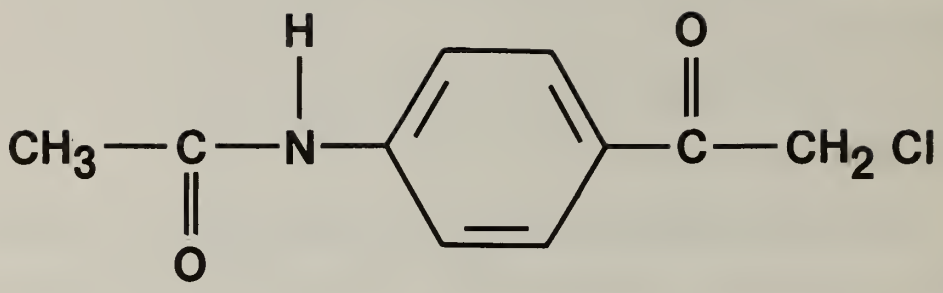


FIGURE 1
CHEMICAL STRUCTURE OF 4'-(CHLOROACETYL)-ACETANILIDE

Specific production data for 4'-(chloroacetyl)-acetanilide are not available; however, this compound is produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by one U.S. company (U.S. International Trade Commission, 1977).

The potential for exposure to 4'-(chloroacetyl)-acetanilide is greatest for workers in the chemical and dye manufacturing industries.

II. MATERIALS AND METHODS

A. Chemicals

Three batches of 4'-(chloroacetyl)-acetanilide were purchased. The first batch was obtained from Carroll Products, Wood River Junction, Rhode Island. Chemical analysis was performed by Midwest Research Institute, Kansas City, Missouri. The experimentally determined range in melting point of 211° to 213°C closely approximated the literature value of 213° to 214°C (Leiserson and Weissberger, 1948). Thin-layer chromatography (TLC) was performed utilizing two solvent systems (i.e., benzene:isopropanol and chloroform:dioxane). Each plate was visualized with ultraviolet light and iodine vapor and revealed the presence of two impurities. The results of elemental analysis deviated from the theoretical (i.e., suggested low carbon and nitrogen content and high chlorine content), based on the molecular formula of the compound, $C_{10}H_{10}NO_2Cl$. High pressure liquid chromatography (HPLC) indicated the presence of one peak with a shoulder at a shorter retention time using one solvent system [i.e., acetonitrile in 0.1 M $(NH_4)_2CO_3$] and a shoulder at a longer retention time using another (i.e., chloroform:hexane). The results of infrared (IR) and nuclear magnetic resonance (MNR) analyses were consistent with those expected based upon the structure of the compound. Ultraviolet/visible (UV/VIS) analysis revealed λ_{max} at 292.5 and 220.5 nm with respective molar extinction coefficients of approximately 2×10^4 and 9.3×10^3. No literature reference was found for comparison.

A second batch of the compound was purchased from Eastman Kodak Company, Rochester, New York. Chemical analysis was performed by Midwest Research Institute. The results of elemental analysis again deviated from those expected on a theoretical basis. TLC was performed utilizing two solvent systems (i.e., acetone:chloroform and benzene:isopropanol). Each plate was visualized with ultraviolet light and iodine and each indicated the presence of three contaminants, one of greater and two of lesser motility than the major spot. High pressure liquid chromatography indicated the presence of two impurities, accounting for approximately 1.5 percent of the total. The experimentally determined range in melting point of this batch was 214° to 217°C. UV/VIS analysis revealed λ_{max} at 292 and 220 nm with respective molar extinction coefficients of 21×10^3 and 10×10^3. The results of IR and NMR analyses were consistent with those expected based upon the structure of the compound.

Another batch of 4'-(chloroacetyl)-acetanilide was purchased from Carroll Products and analyzed by Midwest Research Institute. TLC was performed utilizing two solvent systems (i.e., benzene: isopropenol and chloroform:dioxane). Each plate was visualized with 254 and 366 nm ultraviolet light and iodine vapor. Four impurities appeared on the plate developed with the first solvent system and one impurity appeared on the other. The experimentally determined range in melting point was 214° to 215°C. The results of IR and NMR

analyses were consistent with those expected based upon the structure of the compound. UV/VIS analysis revealed λ_{max} at 221 and 292 nm with respective molar extinction coefficients of 8 x 10^3 and 19.2 x 10^3.

Throughout this report, the term 4'-(chloroacetyl)-acetanilide is used to represent this material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois). 4'-(Chloroacetyl)-acetanilide 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.

Dosed feed preparations containing 1000 and 10,000 ppm of 4'-(chloroacetyl)-acetanilide were analyzed spectrophotometrically. The mean result immediately after preparation was 101 percent of theoretical (ranging from 92 to 110 percent).

C. Animals

The two animal species, Fischer 344 rats and B6C3F1 mice, used in the carcinogenicity bioassay were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. Rats were supplied by the Frederick Cancer Research Center, Frederick, Maryland. Mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts.

Rats and mice were approximately 4 weeks old when received. Upon receipt, animals were examined and any obviously ill or runted animals were killed. 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

Animals were housed by species in rooms with a temperature range of 22° to 26°C and a range in relative humidity of 45 to 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.).

Rats were housed four per cage by sex and mice were housed 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 piece of stainless steel mesh 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. Water bottles were changed and washed 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.

Dosed and control rats were housed in a room with other rats receiving diets containing* 2,4-dimethoxyaniline hydrochloride (54150-69-5) and nithiazide (139-94-6); and with other rats intubated with trimethylphosphate (512-56-1).

Dosed and control mice were housed in a room with mice receiving diets containing nithiazide (139-94-6); 2,4-dimethoxyaniline hydrochloride (54150-69-5); 1-phenyl-3-methyl-5-pyrazolone (89-25-8);

*CAS registry numbers are given in parentheses.

p-phenylenediamine dihydrochloride (624-18-0); and 4-nitro-o-phenylenediamine (99-56-9); and other mice intubated with 2-(chloromethyl) pyridine hydrochloride (6959-47-3); trimethylphosphate (512-56-1); 3-(chloromethyl)pyridine hydrochloride (3099-31-8); and pivalolactone (1955-45-9).

E. Selection of Initial Concentrations

To establish the concentrations of 4'-(chloroacetyl)-acetanilide for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Rats were distributed among eleven groups, each consisting of five males and five females. 4'-(Chloroacetyl)-acetanilide was incorporated into the basal laboratory diet and supplied ad libitum to nine of the eleven rat groups in concentrations of 1000, 1470, 2150, 3160, 4640, 6810, 10,000, 14,700 and 21,500 ppm. The two remaining rat groups served as control groups, receiving only the basal laboratory diet.

Mice were distributed among eight groups, each consisting of five males and five females. 4'-(Chloroacetyl)-acetanilide was incorporated into the basal laboratory diet and supplied ad libitum to seven of the eight mouse groups in concentrations of 2150, 3160, 4640, 6810, 10,000, 14,700 and 21,500 ppm. The remaining mouse group served as a control group, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 7 weeks, followed by a 1-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 study all survivors were killed and necropsied.

The following table indicates the mean body weight gain, relative to controls, survival and incidence of rough coats and arched backs observed in each of the dosed rat groups at the end of the subchronic test.

RAT SUBCHRONIC STUDY RESULTS

	Mean Body Weight Gain (%)*		Survival**		Observation of Rough Coats and Arched Backs**	
ppm	Males	Females	Males	Females	Males	Females
21,500	--	-57	0/5	1/5	0/5	0/5
14,700	-150	-85	2/5	2/5	5/5	5/5
10,000	-125	-62	5/5	5/5	5/5	5/5
6,810	-27	-37	5/5	5/5	0/5	0/5
4,640	-40	-28	5/5	5/5	0/5	0/5
3,160	-59	-23	5/5	5/5	0/5	0/5
2,150	-14	-9	5/5	5/5	0/5	0/5
1,470	-9	-2	5/5	5/5	0/5	0/5
1,000	-4	-5	5/5	5/5	0/5	0/5
0	--	--	5/5	5/5	0/5	0/5

The high concentration selected for administration to dosed rats in the chronic bioassay was 2000 ppm.

The following table indicates the mean body weight gain, relative to controls, and survival observed in each of the dosed mouse groups at the end of the subchronic test.

*+ is indicative of mean body weight gain greater than that of controls.
- is indicative of mean body weight gain less than that of controls.
**Number of animals observed/number of animals originally in group.

MOUSE SUBCHRONIC STUDY RESULTS

ppm	Mean Body Weight Gain (%)* Males	Females	Survival** Males	Females
21,500	+2	-2	5/5	5/5
14,700	+6	+5	5/5	5/5
10,000	+4	+3	5/5	5/5
6,810	-2	-1	5/5	5/5
4,640	-1	+2	5/5	5/5
3,160	+1	+1	5/5	5/5
2,150	-2	+1	5/5	5/5
0	--	--	5/5	5/5

No abnormal clinical signs were recorded for any mouse group. The high concentration selected for administration to dosed mice in the chronic bioassay was 10,000 ppm.

F. Experimental Design

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

Rats were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The dietary concentrations of 4'-(chloroacetyl)-acetanilide administered to rats were 2000 and 1000 ppm. Throughout this report those rats receiving the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to

*+ is indicative of mean body weight gain greater than that of controls.
- is indicative of mean body weight gain less than that of controls.
** Number of animals observed/number of animals originally in group.

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
4'-(CHLOROACETYL)-ACETANILIDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	4'-(CHLOROACETYL)-ACETANILIDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	103
LOW DOSE	50	1000	42	
		0		15
		1000	45	
		0		1
HIGH DOSE	50	2000	42	
		0		15
		2000	45	
		0		1
FEMALE				
CONTROL	20	0	0	103
LOW DOSE	50	1000	42	
		0		15
		1000	45	
		0		1
HIGH DOSE	50	2000	42	
		0		15
		2000	45	
		0		1

[a]Concentrations given in parts per million.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
4'-(CHLOROACETYL)-ACETANILIDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	4'-(CHLOROACETYL)-ACETANILIDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	105
LOW DOSE	50	5,000	57	
		0		15
		5,000	33	
HIGH DOSE	50	10,000	57	
		0		15
		10,000	33	
FEMALE				
CONTROL	20	0	0	105
LOW DOSE	50	5,000	57	
		0		15
		5,000	33	
HIGH DOSE	50	10,000	57	
		0		15
		10,000	33	

[a]Concentrations given in parts per million.

as the low dose groups. Dosed rats were supplied with feed containing 4'-(chloroacetyl)-acetanilide for the first 42 weeks of the chronic study. Due to a shortage of 4'-(chloroacetyl)-acetanilide, dosed feed was not available for the next 15 weeks. Use of dosed feed was then resumed and continued for 45 weeks, followed by a 1-week observation period.

All mice were approximately 6 weeks old at the time the test was initiated and were placed on test simultaneously. The dietary concentrations of 4'-(chloroacetyl)-acetanilide administered were 10,000 and 5000 ppm. Throughout this report those mice receiving the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to as the low dose groups. Dosed mice were supplied with feed containing 4'-(chloroacetyl)-acetanilide for the first 57 weeks of the chronic study. Due to a shortage of 4'-(chloroacetyl)-acetanilide, dosed feed was not available for the next 15 weeks. Use of dosed feed was then resumed and continued for 33 weeks.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment and body weights were recorded at monthly intervals throughout the bioassay. All animals were inspected twice daily. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group.

All moribund animals or animals that developed large, palpable masses that jeopardized their health were killed. A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was killed at the end of the bioassay. The animals were euthanized with carbon dioxide, 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, 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

Distinct and consistent dose-related mean body weight depression was apparent in male rats throughout the bioassay. Female rats evidenced dose-related mean body weight depression from week 62 until termination of the bioassay (Figure 2).

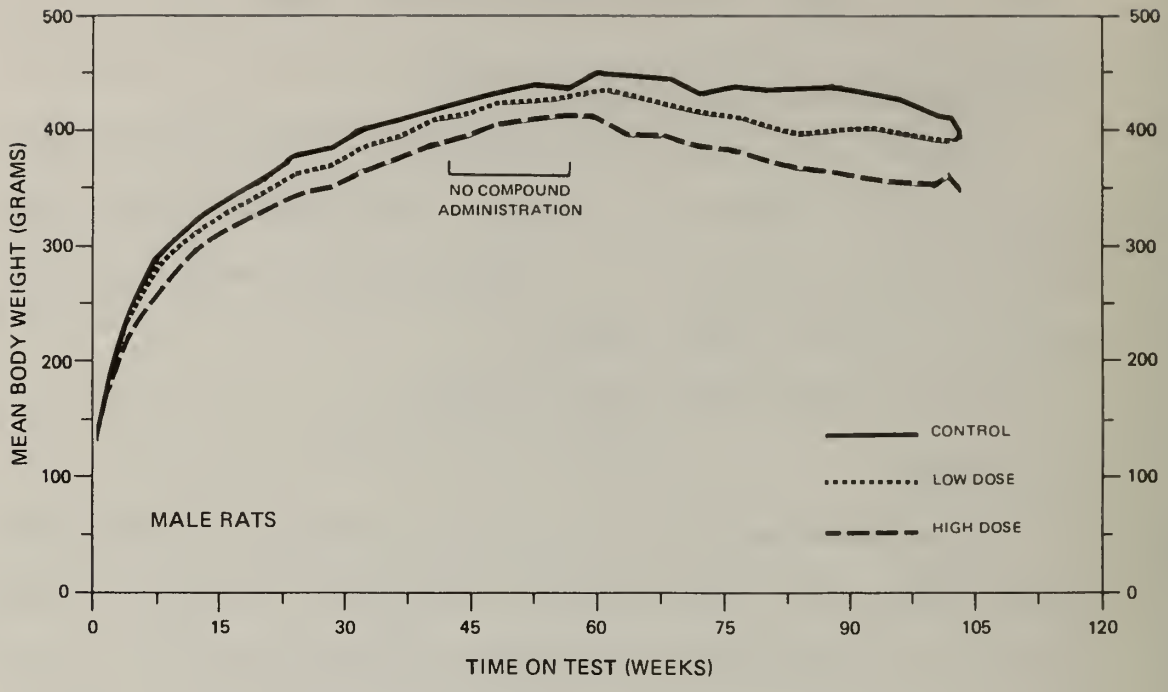
No other clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 4'-(chloroacetyl)-acetanilide-dosed groups are shown in Figure 3. For both males and females, the Tarone test did not indicate a significant positive association between dosage and mortality. For males, the test for departure from linear trend was significant ($P = 0.0128$) as the Cox test indicated a significant negative association in comparing the low dose and control groups.

There were adequate numbers of male rats at risk from late-developing tumors as 72 percent (36/50) of the high dose, 88 percent (44/50) of the low dose, and 65 percent (13/20) of the controls survived on test until the termination of the study.

For female rats, with 92 percent (46/50) of the high dose, 80 percent (40/50) of the low dose, and 80 percent (16/20) of the controls surviving on test until the termination of the study, there were adequate numbers at risk from late-developing tumors.



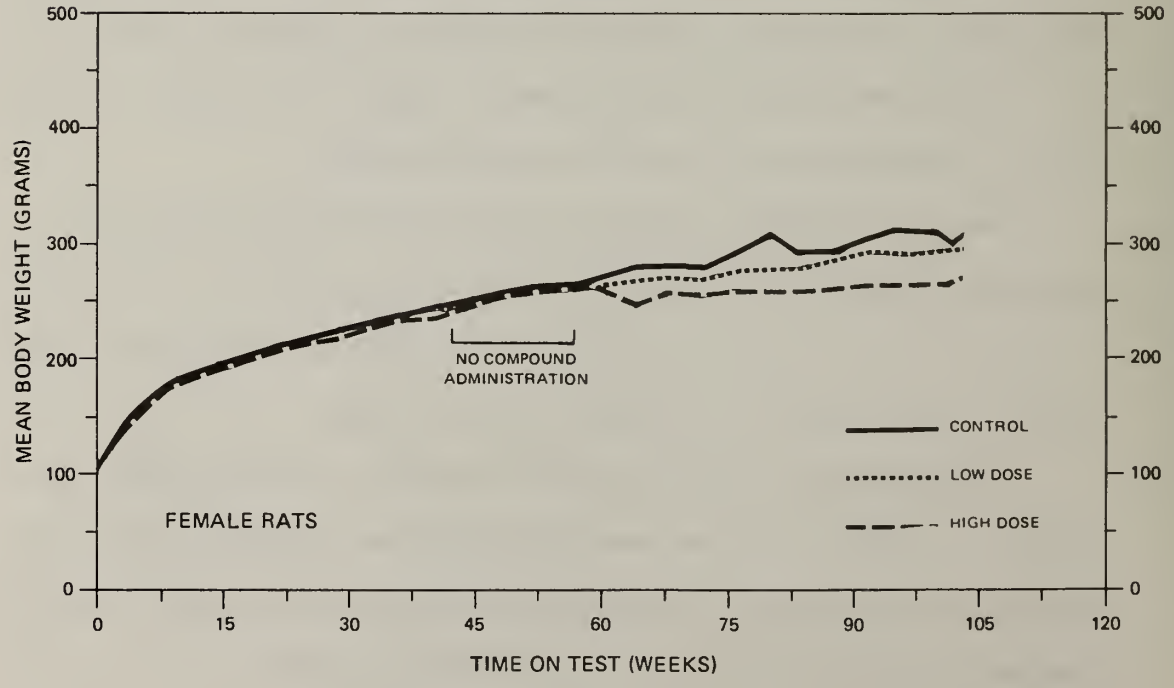
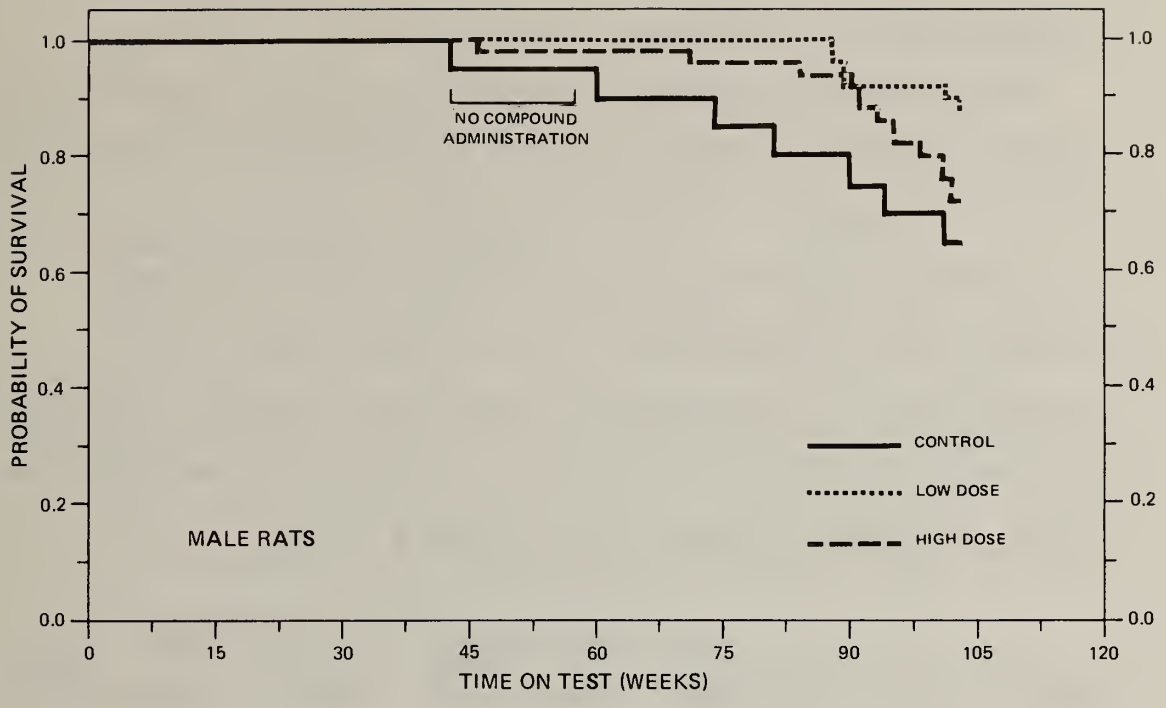


FIGURE 2
GROWTH CURVES FOR 4'-(CHLOROACETYL)-ACETANILIDE CHRONIC STUDY RATS



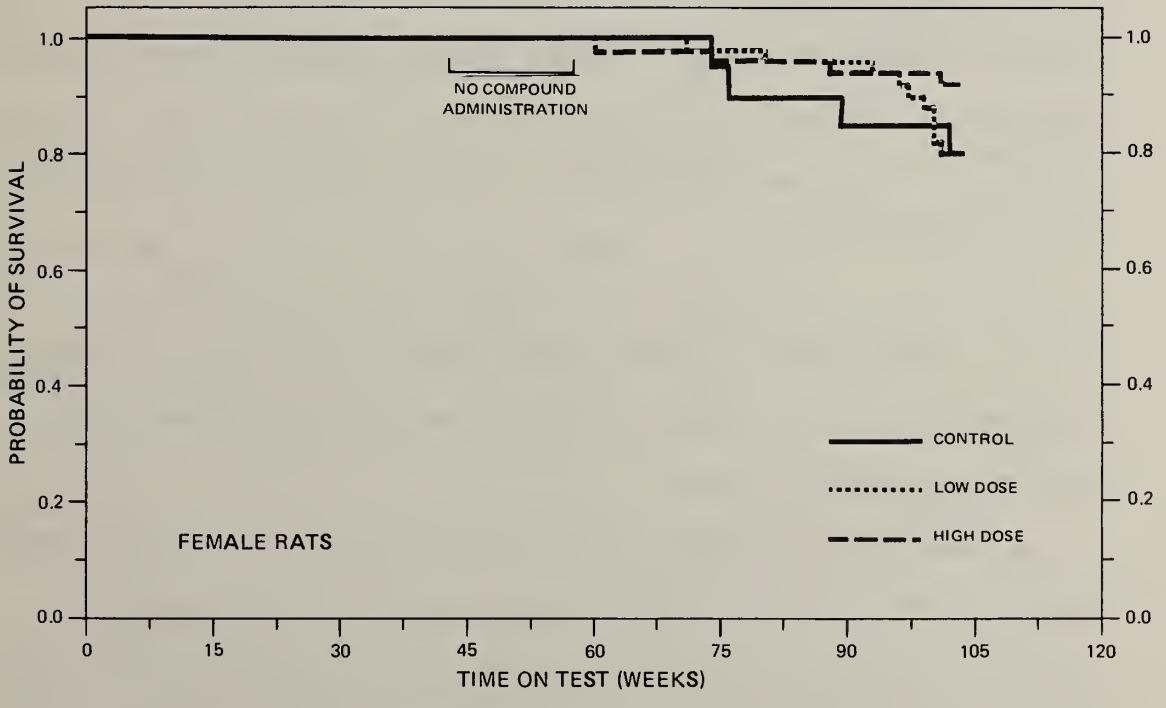


FIGURE 3
SURVIVAL COMPARISONS OF 4'-(CHLOROACETYL)-ACETANILIDE CHRONIC STUDY RATS

C. Pathology

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

A variety of tumors occurred both in the control and dosed groups. A few neoplasms occurred only in dosed groups or with a greater frequency in dosed groups compared with controls. Alveolar/bronchiolar neoplasms were observed in a slightly increased incidence in high dose males, as shown in the following table:

	Males			Females		
LUNG	Control	Low Dose	High Dose	Control	Low Dose	High Dose
No. of Animals with Tissues Examined Histopathologically	(20)	(50)	(50)	(20)	(50)	(50)
Alveolar/Bronchiolar Adenoma	1(5%)	3(6%)	7(14%)	2(10%)	4(8%)	1(2%)
Alveolar/Bronchiolar Carcinoma	0	1(2%)	1(2%)	0	0	0

All of the neoplasms which were observed have been reported to occur spontaneously in this strain of rats. None of the neoplasms were considered compound-related.

A number of inflammatory and degenerative lesions were encountered both in control and dosed rats. The lesions are all recognized as spontaneous in older rats of this strain, and no nonneoplastic lesions, including those in the kidney, were considered compound-related.

Based on the results of this pathologic examination, 4'-(chloroacetyl)-acetanilide was not carcinogenic in male or female Fischer 344 rats under the conditions of this bioassay.

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 4'-(chloroacetyl)-acetanilide-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between the administration of 4'-(chloroacetyl)-acetanilide and an increased tumor incidence. Thus, at the dose levels used in this experiment, there was no evidence that 4'-(chloroacetyl)-acetanilide was a carcinogen in Fischer 344 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,

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	1/20(0.05)	4/50(0.08)	8/50(0.16)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.600	3.200
Lower Limit	---	0.175	0.482
Upper Limit	---	77.169	138.771
Weeks to First Observed Tumor	103	103	91
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/20(0.20)	7/50(0.14)	7/50(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.700	0.700
Lower Limit	---	0.207	0.207
Upper Limit	---	2.994	2.994
Weeks to First Observed Tumor	60	88	71
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	1/20(0.05)	2/50(0.04)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.800	1.200
Lower Limit	---	0.045	0.106
Upper Limit	---	46.273	61.724
Weeks to First Observed Tumor	94	103	103

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	0/16(0.00)	6/40(0.15)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.029	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.679	0.113
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	95
Adrenal: Pheochromocytoma[b]	2/20(0.10)	5/50(0.10)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.000	0.800
Lower Limit	---	0.184	0.128
Upper Limit	---	10.007	8.436
Weeks to First Observed Tumor	103	103	98
Pancreatic Islets: Islet-Cell Adenoma[b]	0/20(0.00)	3/49(0.06)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.255	0.125
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	103

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Testis: Interstitial-Cell Tumor[b]	17/19(0.89)	46/50(0.92)	42/50(0.84)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.028	0.939
Lower Limit	---	0.898	0.817
Upper Limit	---	1.275	1.247
Weeks to First Observed Tumor	74	88	93

[a]Treated groups received doses of 1000 or 2000 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 4'-(CHLOROACETYL)-ACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	2/20(0.10)	4/50(0.08)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.800	0.200
Lower Limit	---	0.128	0.004
Upper Limit	---	8.436	3.681
Weeks to First Observed Tumor	103	96	103
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/20(0.20)	6/50(0.12)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.600	0.400
Lower Limit	---	0.164	0.085
Upper Limit	---	2.659	1.984
Weeks to First Observed Tumor	76	80	60
Pituitary: Chromophobe Adenoma[b]	5/18(0.28)	9/44(0.20)	16/48(0.33)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.736	1.200
Lower Limit	---	0.269	0.515
Upper Limit	---	2.491	3.697
Weeks to First Observed Tumor	76	101	101

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma or C-Cell Adenoma[b]	1/18(0.06)	3/48(0.06)	2/44(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.125	0.818
Lower Limit	---	0.100	0.046
Upper Limit	---	57.811	47.190
Weeks to First Observed Tumor	103	103	103
Mammary Gland: Fibroadenoma[b]	2/20(0.10)	3/50(0.06)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.600	0.600
Lower Limit	---	0.076	0.076
Upper Limit	---	6.860	6.860
Weeks to First Observed Tumor	103	97	103
Mammary Gland: Adenoma NOS or Acinar-Cell Adenoma[b]	0/20(0.00)	0/50(0.00)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.250
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	103

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	0/20(0.00)	8/50(0.16)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.009	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.952	0.123
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	99	103

[a]Treated groups received doses of 1000 or 2000 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 $P < 0.05$.

indicating the theoretical possibility of tumor induction in rats by 4'-(chloroacetyl)-acetanilide 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 body weight depression was apparent in both male and female mice throughout the bioassay (Figure 4).

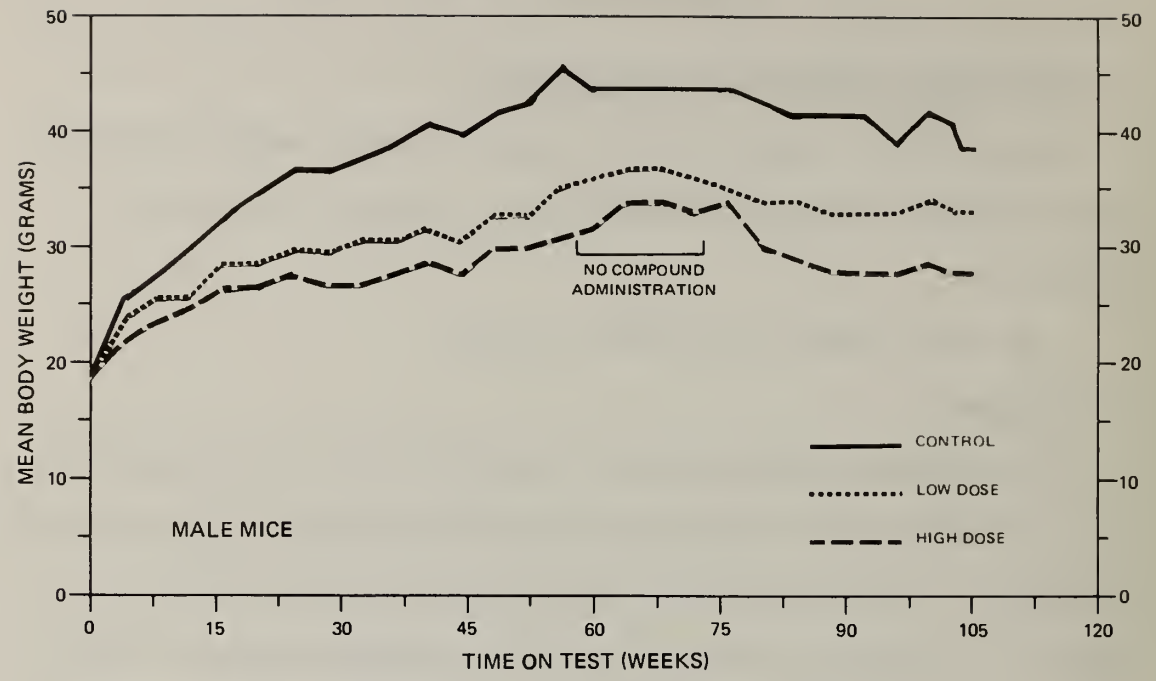
No other clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 4'-(chloroacetyl)-acetanilide-dosed groups are shown in Figure 5. For both male and female mice, the Tarone test did not indicate a significant positive association between dosage and mortality. For males the test for departure from linear trend was significant ($P = 0.0287$) as the Cox test indicated a significant negative association in comparing the low dose and control groups.

There were adequate numbers of male mice at risk from late-developing tumors, as 80 percent (40/50) of the high dose, 86 percent (43/50) of the low dose and 65 percent (13/20) of the controls survived on test until termination of the study.

For females, 86 percent (43/50) of the high dose, 78 percent (39/50) of the low dose and 70 percent (14/20) of the controls survived on test until the termination of the study. Thus, there were adequate numbers of females at risk from late-developing tumors.



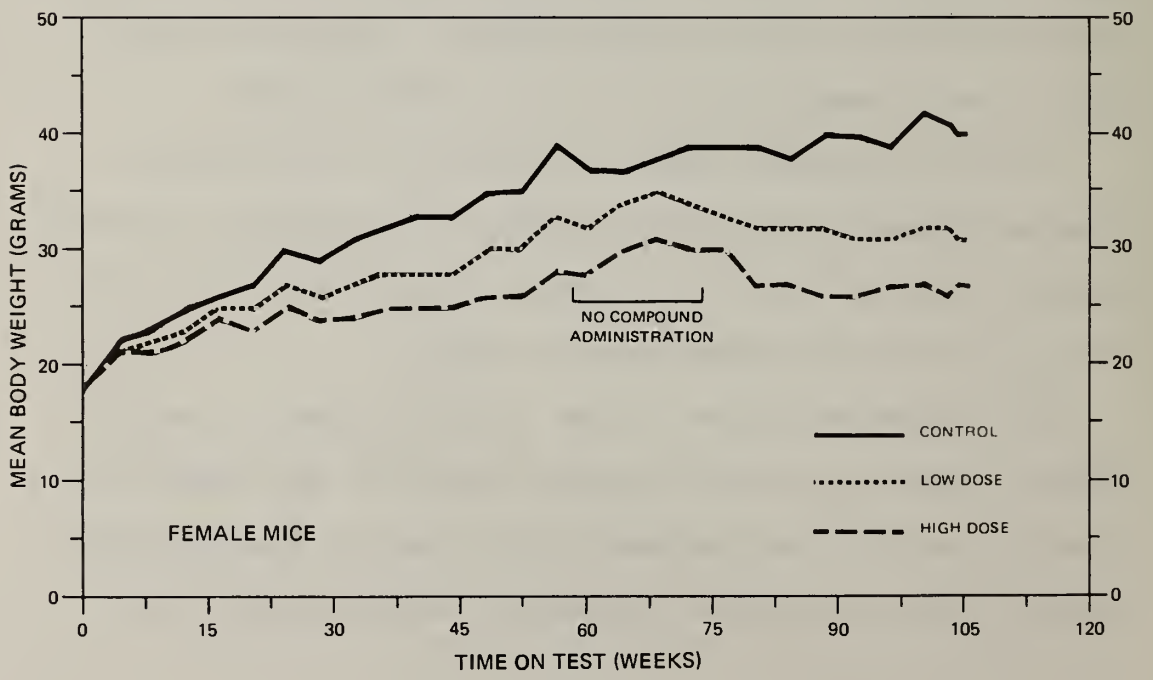
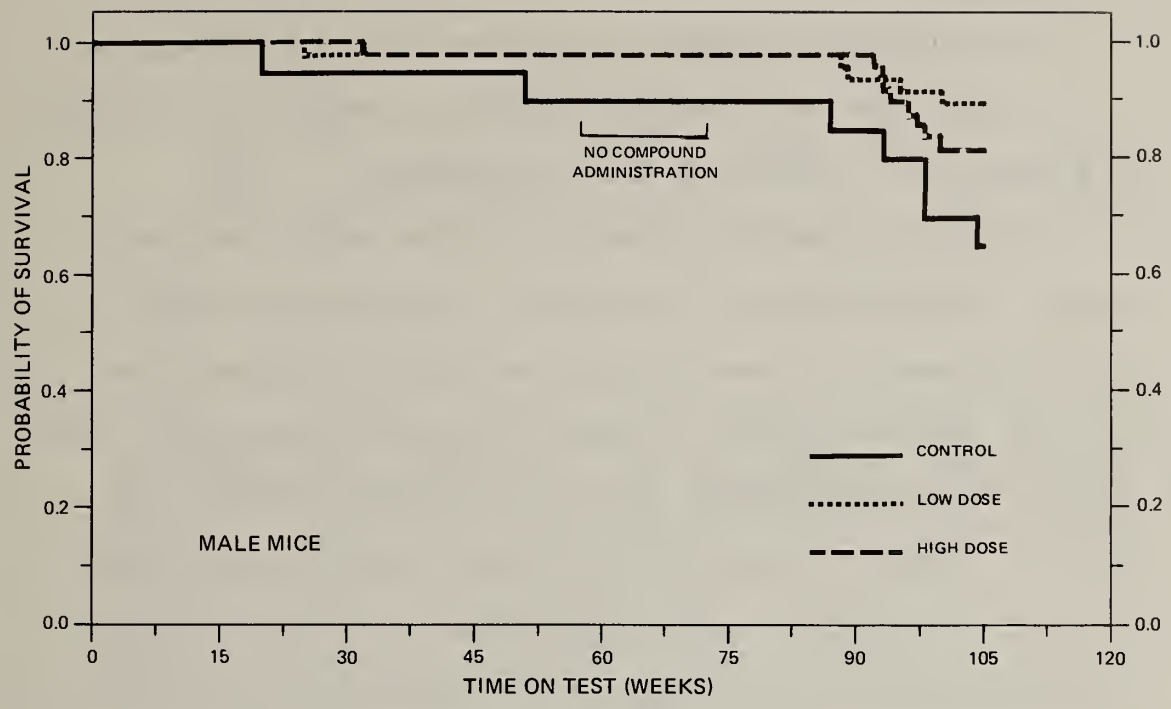


FIGURE 4
GROWTH CURVES FOR 4'-(CHLOROACETYL)-ACETANILIDE CHRONIC STUDY MICE



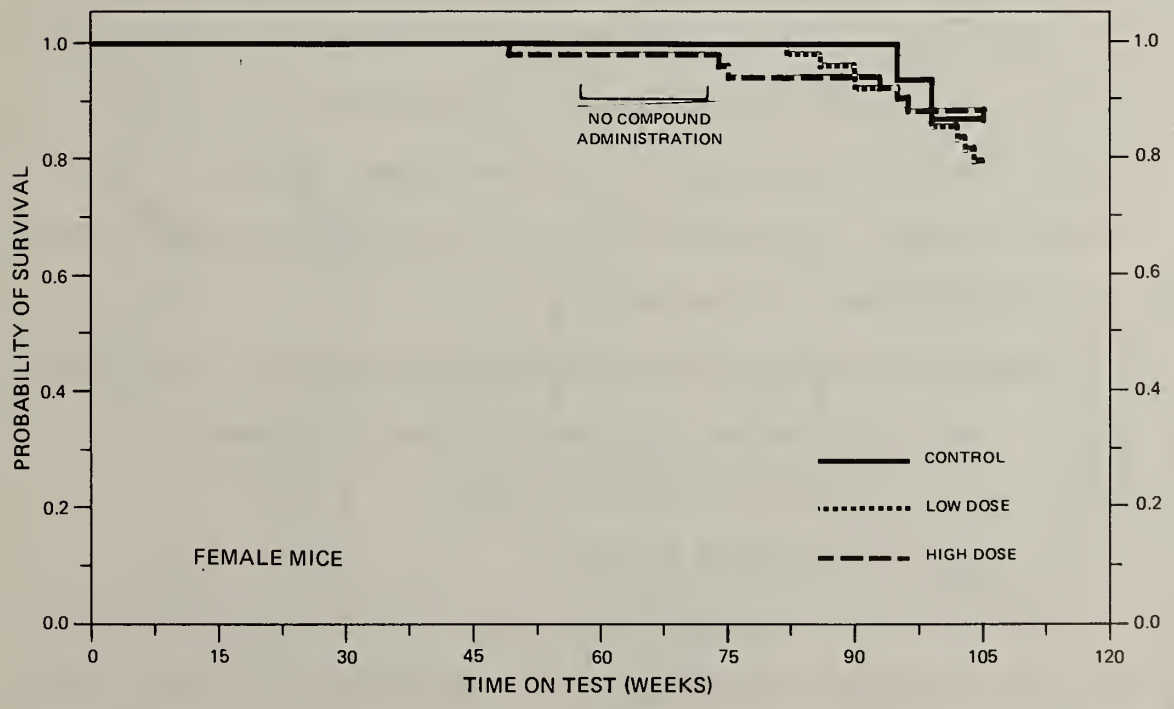


FIGURE 5
SURVIVAL COMPARISONS OF 4'-(CHLOROACETYL)-ACETANILIDE CHRONIC STUDY MICE

C. Pathology

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

A variety of tumors occurred both in the control and dosed groups. A few neoplasms occurred only in dosed groups or with greater frequency in dosed groups compared with controls. Hepatocellular adenomas occurred in slightly increased incidences in dosed females compared to controls (i.e., 0/16, 2/44 [5 percent], and 8/50 [16 percent] in the control, low dose, and high dose, respectively). The neoplasms observed have been reported to occur spontaneously in this strain of mice. No neoplasms were considered to be compound-related.

Nonneoplastic lesions were observed in all groups. They were generally common chronic inflammatory, degenerative, or fibrotic lesions, and none, including those in the kidney, appeared to be compound-related. These lesions were not considered to significantly alter the lifespan of the animals.

Based on the results of this pathologic examination, 4'-(chloroacetyl)-acetanilide was not carcinogenic in male or female 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

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	3/19(0.16)	6/44(0.14)	4/46(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.864	0.551
Lower Limit	---	0.213	0.106
Upper Limit	---	4.945	3.503
Weeks to First Observed Tumor	105	105	97
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/19(0.05)	5/45(0.11)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.111	0.000
Lower Limit	---	0.265	0.000
Upper Limit	---	97.475	7.546
Weeks to First Observed Tumor	105	25	---
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	3/19(0.16)	6/45(0.13)	0/46(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.844	0.000
Lower Limit	---	0.208	0.000
Upper Limit	---	4.841	0.679
Weeks to First Observed Tumor	105	105	---

TABLE 5 (CONCLUDED)

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[a]Treated groups received doses of 5000 or 10,000 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 4'-(CHLOROACETYL)-ACETANILIDE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	0/15(0.00)	5/41(0.12)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.026	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.492	0.018
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	86	105
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/16(0.19)	15/45(0.33)	3/50(0.06)
P Values[c]	P = 0.021(N)	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.010	---	---
Relative Risk (Control)[d]	---	1.778	0.320
Lower Limit	---	0.611	0.049
Upper Limit	---	8.695	2.224
Weeks to First Observed Tumor	95	82	74
Circulatory System: Hemangiosarcoma[b]	3/16(0.19)	0/45(0.00)	0/50(0.00)
P Values[c]	P = 0.003(N)	P = 0.016(N)	P = 0.012(N)
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	0.582	0.526
Weeks to First Observed Tumor	105	---	---

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Adenoma[b]	0/16(0.00)	2/44(0.05)	8/50(0.16)
P Values[c]	P = 0.020	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.113	0.775
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	93

[a]Treated groups received doses of 5000 or 10,000 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 $P < 0.05$.

tumors were observed in at least one of the control or 4'-(chloroacetyl)-acetanilide-dosed groups and where such tumors were observed in at least 5 percent of the group.

For females the Cochran-Armitage test indicated a significant ($P = 0.020$) positive association between dose and the incidence of hepatocellular adenomas. However, the Fisher exact tests comparing high dose to control and low dose to control were not significant.

None of the statistical tests for any site in male mice indicated a significant positive association between chemical administration and tumor incidence.

In male mice, the Cochran-Armitage test indicated a significant negative association between dose and the combined incidence of hepatocellular carcinomas or hepatocellular adenomas. The Fisher exact test comparing the high dose group to the control group also indicated a significant negative association at this site.

For female mice, the Cochran-Armitage test indicated a significant negative association between dose and the incidence of hemangiosarcomas of the circulatory system. In addition, the Fisher exact tests comparing low dose to control and high dose to control both indicated a significant negative association. The Cochran-Armitage test also showed a significant negative association between dose and the combined incidence of leukemia or malignant lymphoma. The Fisher exact tests were not significant; however, the test for departure from linear trend was significant ($P = 0.010$).

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by 4'-(chloroacetyl)-acetanilide that could not be established under the conditions of this test.

V. DISCUSSION

There were no significant positive associations between the concentrations of 4'-(chloroacetyl)-acetanilide administered and mortality in rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Dose-related mean body weight depression was observed for males and females of both species, indicating that the concentrations of 4'-(chloroacetyl)-acetanilide administered to the animals in this bioassay may have approximated the maximum tolerated concentrations.

None of the statistical tests for any site in rats of either sex or in male mice indicated a significant positive association between compound administration and tumor incidence. Although there was a significant positive association between the concentration of the compound administered and the incidences of hepatocellular adenomas in female mice, the Fisher exact comparisons were not significant.

Under the conditions of this bioassay, 4'-(chloroacetyl)-acetanilide was not carcinogenic when administered in the diet to Fischer 344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH
4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
PAPILLOMA, NOS			2 (4%)
TRICHOEPITHELIOMA		1 (2%)	
SEBACEOUS ADENOCARCINOMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
BASAL-CELL TUMOR			1 (2%)
FIBROMA			1 (2%)
FIBROSARCOMA		1 (2%)	1 (2%)
LIPOMA		1 (2%)	
FIBROADENOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	3 (6%)	7 (14%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMIA,NOS	1 (5%)	3 (6%)	3 (6%)
UNDIFFERENTIATED LEUKEMIA	2 (10%)	4 (8%)	4 (8%)
GRANULOCYTIC LEUKEMIA	1 (5%)		
#SPLEEN	(20)	(50)	(49)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
#MANDIBULAR L. NODE	(17)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
#MESENTERIC L. NODE	(17)	(50)	(49)
LEIOMYOSARCOMA, METASTATIC			1 (2%)

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
FIBROMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR ADENOMA		2 (4%)	2 (4%)
HEPATOCELLULAR CARCINOMA	1 (5%)		1 (2%)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
#PANCREAS	(20)	(49)	(49)
ACINAR-CELL CARCINOMA			1 (2%)
#STOMACH	(20)	(49)	(47)
LEIOMYOSARCOMA			1 (2%)
#SMALL INTESTINE	(20)	(49)	(48)
LEIOMYOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(40)	(44)
CHROMOPHOBE ADENOMA		6 (15%)	2 (5%)
#ADRENAL	(20)	(50)	(50)
PHEOCHROMOCYTOMA	2 (10%)	5 (10%)	4 (8%)
#THYROID	(17)	(48)	(49)
C-CELL ADENOMA		2 (4%)	1 (2%)
CYSTADENOMA, NOS			1 (2%)
#PANCREATIC ISLETS	(20)	(49)	(49)
ISLET-CELL ADENOMA		3 (6%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
#TESTIS	(19)	(50)	(50)
INTERSTITIAL-CELL TUMOR	17 (89%)	46 (92%)	42 (84%)
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
GLIOMA, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(50)
MESOTHELIOMA, NOS	1 (5%)		
*PLEURA	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
*PERICARDIUM	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
*MESENTERY	(20)	(50)	(50)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATHS	4	4	8
MORIBUND SACRIFICE	3	2	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	44	36
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	50	48
TOTAL PRIMARY TUMORS	27	83	78
TOTAL ANIMALS WITH BENIGN TUMORS	17	49	45
TOTAL BENIGN TUMORS	21	72	65
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	10	12
TOTAL MALIGNANT TUMORS	5	11	13
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	2
TOTAL SECONDARY TUMORS		1	6
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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH
4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
TRICHOEPITHELIOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	
OSTEOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	4 (8%)	1 (2%)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMIA, NOS	2 (10%)	3 (6%)	1 (2%)
UNDIFFERENTIATED LEUKEMIA	2 (10%)	2 (4%)	1 (2%)
#LIVER	(20)	(49)	(50)
UNDIFFERENTIATED LEUKEMIA		1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEPATOCELLULAR ADENOMA	1 (5%)	1 (2%)	1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
#SMALL INTESTINE	(19)	(50)	(50)
LEIOMYOMA		1 (2%)	
URINARY SYSTEM			
#URINARY BLADDER	(18)	(45)	(47)
PAPILLOMA, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(44)	(48)
CHROMOPHOBE ADENOMA	5 (28%)	9 (20%)	16 (33%)
#ADRENAL	(20)	(49)	(50)
CORTICAL ADENOMA	1 (5%)		
PHEOCHROMOCYTOMA			2 (4%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(18)	(48)	(44)
FOLLICULAR-CELL ADENOMA		1 (2%)	
C-CELL ADENOMA		1 (2%)	2 (5%)
C-CELL CARCINOMA	1 (6%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS			2 (4%)
ACINAR-CELL ADENOMA			1 (2%)
FIBROADENOMA	2 (10%)	3 (6%)	3 (6%)
#UTERUS	(20)	(50)	(50)
ENDOMETRIAL STROMAL POLYP		8 (16%)	2 (4%)
#UTERUS/ENDOMETRIUM	(20)	(50)	(50)
CYSTADENOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(50)
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	8	2
MORIBUND SACRIFICE	1	2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	40	46
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	31	29
TOTAL PRIMARY TUMORS	16	41	38
TOTAL ANIMALS WITH BENIGN TUMORS	9	23	24
TOTAL BENIGN TUMORS	11	30	32
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	11	6
TOTAL MALIGNANT TUMORS	5	11	6
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH
4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	5	3
ANIMALS NECROPSIED	19	45	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	45	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(44)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (11%)	5 (11%)	3 (7%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(45)	(47)
MALIGNANT LYMPHOMA, NOS		2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#MESENTERIC L. NODE	(16)	(44)	(43)
HEMANGIOSARCOMA	1 (6%)		
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#THYMUS	(1)	(4)	(1)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (25%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(45)	(46)
HEPATOCELLULAR ADENOMA	3 (16%)	4 (9%)	

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
HEPATOCELLULAR CARCINOMA		2 (4%)	
HEMANGIOMA	1 (5%)		
HEMANGIOSARCOMA, METASTATIC	1 (5%)		
#STOMACH	(19)	(42)	(46)
PAPILLOMA, NOS		1 (2%)	
#DUODENUM	(19)	(42)	(45)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(42)	(43)
CORTICAL ADENOMA		1 (2%)	
PHEOCHROMOCYTOMA			1 (2%)
#PANCREATIC ISLETS	(19)	(45)	(45)
ISLET-CELL ADENOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EAR	(19)	(45)	(47)
MALIGNANT MELANOMA	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	5	5	8
MORIBUND SACRIFICE	2		1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	12	40	38
ANIMAL MISSING	1	5	3
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	19	5
TOTAL PRIMARY TUMORS	11	20	5
TOTAL ANIMALS WITH BENIGN TUMORS	5	11	4
TOTAL BENIGN TUMORS	7	11	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	9	1
TOTAL MALIGNANT TUMORS	4	9	1
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
4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	4	5	
ANIMALS NECROPSIED	16	45	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	16	45	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(15)	(41)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		5 (12%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(16)	(45)	(50)
MALIGNANT LYMPHOMA, NOS		5 (11%)	2 (4%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (13%)	3 (7%)	
LEUKEMIA,NOS		1 (2%)	1 (2%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
LYMPHOCYTIC LEUKEMIA		1 (2%)	
#SPLEEN	(16)	(43)	(47)
HEMANGIOSARCOMA	2 (13%)		
MALIGNANT LYMPHOMA, MIXED TYPE	1 (6%)		
#LYMPH NODE	(16)	(44)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
DIGESTIVE SYSTEM			
#LIVER	(16)	(44)	(50)
HEPATOCELLULAR ADENOMA		2 (5%)	8 (16%)
HEMANGIOSARCOMA	1 (6%)		
#SMALL INTESTINE	(14)	(42)	(48)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(9)	(24)	(20)
CHROMOPHOBE ADENOMA		1 (4%)	
REPRODUCTIVE SYSTEM			
NONE			
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 B2 (CONCLUDED)

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	10	7
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	35	43
ANIMAL MISSING	4	5	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	21	12
TOTAL PRIMARY TUMORS	6	23	14
TOTAL ANIMALS WITH BENIGN TUMORS		8	9
TOTAL BENIGN TUMORS		8	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	15	4
TOTAL MALIGNANT TUMORS	6	15	5
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 4'-(CHLOROACETYL)-ACETANILIDE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
EDEMA, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
BRONCHOPNEUMONIA, NOS			1 (2%)
INFLAMMATION, NOS	1 (5%)		
PNEUMONIA, ASPIRATION		1 (2%)	
BRONCHOPNEUMONIA, ACUTE	1 (5%)		1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
PNEUMONIA, CHRONIC MURINE		3 (6%)	11 (22%)
HYPERPLASIA, ADENOMATOUS	1 (5%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(50)	(50)
MYELOFIBROSIS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(20)	(50)	(49)
INFARCT, NOS		1 (2%)	
HYPERPLASIA, RETICULUM CELL			1 (2%)
#MESENTERIC L. NODE	(17)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
THROMBOSIS, NOS			1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
THROMBUS, ORGANIZED			1 (2%)
#MYOCARDIUM	(20)	(50)	(50)
FIBROSIS	3 (15%)	2 (4%)	6 (12%)
FIBROSIS, FOCAL	1 (5%)	1 (2%)	
#ENDOCARDIUM	(20)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
CHOLANGIOFIBROSIS	1 (5%)		
NECROSIS, FOCAL			2 (4%)
METAMORPHOSIS FATTY	1 (5%)	4 (8%)	4 (8%)
HYPERPLASIA, FOCAL		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(50)	(50)
METAMORPHOSIS FATTY	2 (10%)		1 (2%)
#LIVER/PERIPORTAL	(20)	(50)	(50)
NECROSIS, NOS			1 (2%)
#BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)		1 (2%)
#PANCREAS	(20)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS		1 (2%)	1 (2%)
FIBROSIS, FOCAL		1 (2%)	
#PANCREATIC DUCT	(20)	(49)	(49)
FIBROSIS			1 (2%)
#PANCREATIC ACINUS	(20)	(49)	(49)
HYPERPLASIA, FOCAL		1 (2%)	
#STOMACH	(20)	(49)	(47)
ULCER, NOS			1 (2%)
#COLON	(20)	(49)	(49)
ULCER, CHRONIC			1 (2%)
NEMATODIASIS			10 (20%)
PARASITISM	4 (20%)	4 (8%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
ATROPHY, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS	1 (5%)		
INFLAMMATION, CHRONIC	9 (45%)	14 (28%)	5 (10%)
NEPHROPATHY, TOXIC	1 (5%)		
#URINARY BLADDER	(18)	(43)	(46)
POLYP, INFLAMMATORY			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(40)	(44)
CYST, NOS		1 (3%)	
HYPERPLASIA, CHROMOPHOBE-CELL	1 (6%)	2 (5%)	1 (2%)
METAPLASIA, OSSEOUS		1 (3%)	
#ADRENAL MEDULLA	(20)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(17)	(48)	(49)
FOLLICULAR CYST, NOS		1 (2%	
HYPERPLASIA, C-CELL		4 (8%	1 (2%)
#PARATHYROID	(10)	(35)	(25)
HYPERPLASIA, NOS		1 (3%)	
#PANCREATIC ISLETS	(20)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(14)	(44)	(43)
INFLAMMATION, SUPPURATIVE	1 (7%)		
*SEMINAL VESICLE	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 11-1315	LOW DOSE 11-1313	HIGH DOSE 11-1311
#TESTIS	(19)	(50)	(50)
ATROPHY, NOS	3 (16%)	4 (8%)	7 (14%)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
COMPRESSION			1 (2%)
ATROPHY, PRESSURE		1 (2%)	
#MEDULLA OBLONGATA	(20)	(50)	(49)
ABSCESS, NOS	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
NECROSIS, FAT	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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 4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
PNEUMONIA, ASPIRATION	1 (5%)	2 (4%)	2 (4%)
PNEUMONIA, CHRONIC MURINE	1 (5%)	3 (6%)	8 (16%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
#LUNG/ALVEOLI	(20)	(50)	(50)
HYPERTROPHY, NOS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(45)	(49)
RUPTURE		1 (2%)	
HYPERPLASIA, RETICULUM CELL	1 (5%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL			1 (2%)
FIBROSIS		2 (4%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(49)	(50)
FIBROSIS		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
HYPERPLASIA, EPITHELIAL		1 (2%)	
#LIVER	(20)	(49)	(50)
THROMBOSIS, NOS		1 (2%)	
FIBROSIS	1 (5%)		
DEGENERATION, NOS			1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	2 (10%)	1 (2%)	
HEMATOPOIESIS	1 (5%)		
#LIVER/CENTRILOBULAR	(20)	(49)	(50)
NECROSIS, NOS		1 (2%)	
#BILE DUCT	(20)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREAS	(19)	(46)	(49)
FIBROSIS, FOCAL		1 (2%)	1 (2%)
#COLON	(20)	(49)	(50)
PARASITISM	2 (10%)	11 (22%)	11 (22%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
CALCULUS, NOS		1 (2%)	
PYELONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)	3 (6%)
PYELONEPHRITIS, HEALED	1 (5%)		
FIBROSIS		1 (2%)	
NEPHROPATHY, TOXIC		1 (2%)	
NECROSIS, MEDULLARY	1 (5%)		
#URINARY BLADDER	(18)	(45)	(47)
CALCULUS, NOS	1 (6%)		
INFLAMMATION, CHRONIC	1 (6%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(44)	(48)
CYST, NOS		2 (5%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
HEMORRHAGIC CYST	1 (6%)		
HYPERPLASIA, CHROMOPHOBE-CELL		2 (5%)	3 (6%)
#ADRENAL	(20)	(49)	(50)
METAMORPHOSIS FATTY		1 (2%)	1 (2%)
#ADRENAL CORTEX	(20)	(49)	(50)
INFARCT, NOS	1 (5%)		
#THYROID	(18)	(48)	(44)
HYPERPLASIA, C-CELL	1 (6%)	1 (2%)	2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
NECROSIS, FAT			1 (2%)
#UTERUS	(20)	(50)	(50)
HYDROMETRA		1 (2%)	
HEMORRHAGE		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, CYSTIC	1 (5%)		
#OVARY	(20)	(48)	(50)
CYST, NOS		1 (2%)	3 (6%)
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(50)
COMPRESSION		2 (4%)	4 (8%)
HEMORRHAGE		1 (2%)	
GLIOSIS	1 (5%)		
ATROPHY, PRESSURE		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE/CONJUNCTIVA	(20)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 11-1316	LOW DOSE 11-1314	HIGH DOSE 11-1312
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	7	7

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH 4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	5	3
ANIMALS NECROPSIED	19	45	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	45	47
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(45)	(47)
INFLAMMATION, CHRONIC	1 (5%)		
*SUBCUT TISSUE	(19)	(45)	(47)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(18)	(37)	(41)
METAPLASIA, SQUAMOUS			1 (2%)
#LUNG	(19)	(44)	(46)
PNEUMONIA, ASPIRATION		1 (2%)	
BRONCHOPNEUMONIA, ACUTE			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
PNEUMONIA, CHRONIC MURINE		4 (9%)	4 (9%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
PERIVASCULITIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(18)	(40)	(35)
HYPERPLASIA, HEMATOPOIETIC	1 (6%)		
#SPLEEN	(19)	(45)	(43)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID		3 (7%)	
HEMATOPOIESIS	1 (5%)		
MYELOPOIESIS	1 (5%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
#MANDIBULAR L. NODE	(16)	(44)	(43)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
#CERVICAL LYMPH NODE	(16)	(44)	(43)
ABSCESS, NOS			1 (2%)
PLASMACYTOSIS			1 (2%)
#MEDIASTINAL L.NODE	(16)	(44)	(43)
ABSCESS, NOS			1 (2%)
#MESENTERIC L. NODE	(16)	(44)	(43)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
GRANULOMA, PYOGENIC		1 (2%)	
PLASMACYTOSIS		2 (5%)	4 (9%)
HYPERPLASIA, LYMPHOID		5 (11%)	
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(45)	(46)
INFLAMMATION, FOCAL			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (5%)		
HEPATOCYTOMEGALY		1 (2%)	
MEGALOCYTOSIS		1 (2%)	
#LIVER/CENTRILOBULAR	(19)	(45)	(46)
NECROSIS, NOS			1 (2%)
#LIVER/HEPATOCYTES	(19)	(45)	(46)
HYPERPLASIA, NODULAR		1 (2%)	
HYPERPLASIA, DIFFUSE			1 (2%)
#BILE DUCT	(19)	(45)	(46)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
#PANCREAS	(19)	(45)	(45)
DILATATION/DUCTS	1 (5%)		
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
INFLAMMATION, CHRONIC	1 (5%)		
INFLAMMATION, CHRONIC FOCAL	1 (5%)		
#PANCREATIC ACINUS	(19)	(45)	(45)
ATROPHY, NOS	2 (11%)		
#STOMACH	(19)	(42)	(46)
INFLAMMATION, CHRONIC			1 (2%)
#SMALL INTESTINE	(19)	(42)	(45)
ULCER, NOS			1 (2%)
INFLAMMATION, FOCAL			2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
#S.INTESTINE/MUCOSA	(19)	(42)	(45)
HYPERPLASIA, FOCAL		1 (2%)	
#PEYERS PATCH	(19)	(42)	(45)
HYPERPLASIA, NOS		2 (5%)	
#DUODENUM	(19)	(42)	(45)
HYPERPLASIA, NOS		1 (2%)	
#ILEUM	(19)	(42)	(45)
ULCER, NOS			1 (2%)
AMYLOIDOSIS	1 (5%)		
#COLON	(19)	(41)	(44)
ULCER, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
PARASITISM	5 (26%)	20 (49%)	4 (9%)
#CECUM	(19)	(41)	(44)
HYPERPLASIA, NOS		1 (2%)	
*RECTUM	(19)	(45)	(47)
ULCER, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(45)	(47)
PYELONEPHRITIS, ACUTE	1 (5%)		

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
INFLAMMATION, CHRONIC DIFFUSE	1 (5%)		
PERIVASCULITIS		2 (4%)	
NEPHROPATHY, TOXIC			1 (2%)
NEPHROSIS, NOS	1 (5%)		
CALCINOSIS, NOS		1 (2%)	
#KIDNEY/GLOMERULUS	(19)	(45)	(47)
AMYLOIDOSIS	1 (5%)		
ENDOCRINE SYSTEM			
#THYROID	(16)	(29)	(29)
FOLLICULAR CYST, NOS	1 (6%)	1 (3%)	
REPRODUCTIVE SYSTEM			
#TESTIS	(19)	(43)	(43)
HEMORRHAGIC CYST		1 (2%)	
CALCIFICATION, NOS	1 (5%)		
ATROPHY, NOS	1 (5%)		
NERVOUS SYSTEM			
#BRAIN	(19)	(44)	(45)
CORPORA AMYLACEA	8 (42%)	14 (32%)	14 (31%)
CALCIFICATION, FOCAL		1 (2%)	
PSAMMOMA BODIES			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(19)	(45)	(47)
NECROSIS, FAT	1 (5%)		

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 22-2315	LOW DOSE 22-2313	HIGH DOSE 22-2311
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(19)	(45)	(47)
AMYLOIDOSIS	1 (5%)		
OMENTUM			
ABSCESS, NOS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	3	13
ANIMAL MISSING/NO NECROPSY	1	5	3
AUTO/NECROPSY/HISTO PERF	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 4'-(CHLOROACETYL)-ACETANILIDE

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	4	5	
ANIMALS NECROPSIED	16	45	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	16	45	50
INTEGUMENTARY SYSTEM			
*SKIN	(16)	(45)	(50)
INFLAMMATION, NOS			1 (2%)
*SUBCUT TISSUE	(16)	(45)	(50)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(15)	(41)	(48)
FOREIGN BODY, NOS			1 (2%)
#LUNG	(15)	(41)	(48)
THROMBOSIS, NOS			1 (2%)
EDEMA, NOS	1 (7%)		
PNEUMONIA, ASPIRATION	1 (7%)		
PNEUMONIA, CHRONIC MURINE	1 (7%)	8 (20%)	16 (33%)
HEMOSIDEROSIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(12)	(40)	(35)
HYPERPLASIA, NEUTROPHILIC			2 (6%)
#SPLEEN	(16)	(43)	(47)
HYPERPLASIA, LYMPHOID	1 (6%)	2 (5%)	
HEMATOPOIESIS		1 (2%)	
#LYMPH NODE	(16)	(44)	(49)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#MANDIBULAR L. NODE	(16)	(44)	(49)
HYPERPLASIA, RETICULUM CELL		1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
#MESENTERIC L. NODE	(16)	(44)	(49)
LYMPHANGIECTASIS			1 (2%)
CONGESTION, NOS	1 (6%)		
ABSCESS, NOS	1 (6%)		
PLASMACYTOSIS			6 (12%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		2 (5%)	
CIRCULATORY SYSTEM			
#HEART	(16)	(42)	(45)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(16)	(44)	(50)
THROMBOSIS, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
AMYLOIDOSIS			1 (2%)
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(16)	(44)	(50)
NECROSIS, NOS			1 (2%)
#LIVER/HEPATOCYTES	(16)	(44)	(50)
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	2 (4%)
#S.INTESTINE/MUCOSA	(14)	(42)	(48)
HYPERPLASIA, NOS		1 (2%)	
#PEYERS PATCH	(14)	(42)	(48)
HYPERPLASIA, NOS			2 (4%)
#COLON	(13)	(44)	(48)
PARASITISM	1 (8%)	15 (34%)	14 (29%)
#CECUM	(13)	(44)	(48)
PARASITISM			2 (4%)
HYPERPLASIA, LYMPHOID			3 (6%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
URINARY SYSTEM			
#KIDNEY	(16)	(44)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
PERIARTERITIS			1 (2%)
AMYLOIDOSIS			1 (2%)
METAPLASIA, OSSEOUS	1 (6%)		
ENDOCRINE SYSTEM			
#ADRENAL	(15)	(41)	(46)
CYTOPLASMIC VACUOLIZATION	1 (7%)		
REPRODUCTIVE SYSTEM			
#UTERUS	(16)	(41)	(45)
HYDROMETRA		4 (10%)	3 (7%)
PYOMETRA			1 (2%)
#UTERUS/ENDOMETRIUM	(16)	(41)	(45)
CYST, NOS	1 (6%)	1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	8 (50%)	7 (17%)	5 (11%)
#OVARY	(12)	(37)	(38)
CYST, NOS	4 (33%)	6 (16%)	5 (13%)
HEMATOMA, NOS			1 (3%)
INFLAMMATION, HEMORRHAGIC		1 (3%)	
ABSCESS, CHRONIC		1 (3%)	
CORPORA AMYLACEA	1 (8%)		
NERVOUS SYSTEM			
#BRAIN	(16)	(44)	(48)
CORPORA AMYLACEA	3 (19%)	9 (20%)	14 (29%)
CALCIFICATION, FOCAL			2 (4%)
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 22-2316	LOW DOSE 22-2314	HIGH DOSE 22-2312
MUSCULOSKELETAL SYSTEM			
*BONE	(16)	(45)	(50)
FIBROUS OSTEODYSTROPHY			1 (2%)
BODY CAVITIES			
*PERITONEUM	(16)	(45)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	6
ANIMAL MISSING/NO NECROPSY	4	5	

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

Review of the Bioassay of 4'-(Chloroacetyl)-Acetanilide* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

August 31, 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 4'-(Chloroacetyl)-Acetanilide for carcinogenicity.

The primary reviewer indicated that 4'-(Chloroacetyl)-Acetanilide was not carcinogenic in rats or mice, under the conditions of test. After a brief description of the experimental design, he said that the study was adequate on which to base the conclusion in the report.

The secondary reviewer noted the small number of control animals used. Despite the deficiency, he considered the study to be adequate.

A motion was approved unanimously that the report on the bioassay of 4'-(Chloroacetyl)-Acetanilide be accepted as written.

Members present were:

Arnold Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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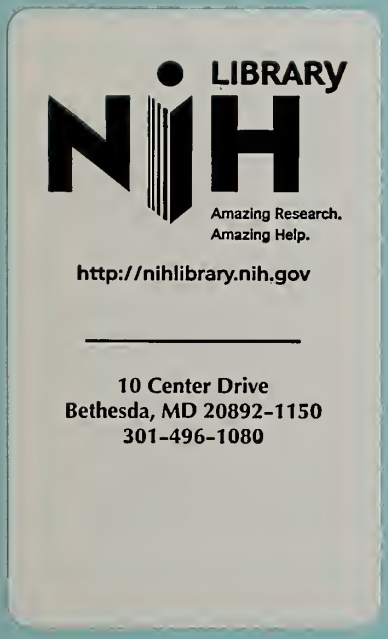
* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.



DHEW Publication No. (NIH) 79-1733