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# BIOASSAY OF IODOFORM FOR POSSIBLE CARCINOGENICITY

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

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# IODOFORM

# FOR POSSIBLE CARCINOGENICITY

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 IODOFORM 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 iodoform 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 iodoform was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

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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 (6) and Dr. J.

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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), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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## SUMMARY

A bioassay for possible carcinogenicity of technical-grade iodoform was conducted using Osborne-Mendel rats and B6C3F1 mice. Iodoform in corn oil was administered by gavage, at either of two dosages, to groups of 50 male and 50 female animals of each species. Administration of the chemical occurred 5 days a week, for a period of 78 weeks, followed by an observation period of 34 weeks for rats and 13 or 14 weeks for mice. The high and low time-weighted average dosages of iodoform were, respectively, 142 and 71 mg/kg/day for male rats, 55 and 27 mg/kg/day for female rats, and 93 and 47 mg/kg/day for male and female mice. For each species, 20 animals of each sex were placed on test as vehicle controls. These animals were gavaged with pure corn oil at the same rate as the high dose group of the same sex. Twenty animals of each sex were placed on test as untreated controls for each species. These animals were not intubated.

A significant positive association between dosage and mortality was observed in male rats but not in female rats or in mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

No statistical significance could be attributed to the incidences of any neoplasms in rats or mice of either sex when compared to their respective controls.

Under the conditions of this bioassay, no convincing evidence was provided for the carcinogenicity of iodoform in Osborne-Mendel rats or B6C3F1 mice.

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# I. INTRODUCTION

Iodoform (NCI No. C04568), a halogenated alkane with antiseptic and anti-infective properties, was selected for bioassay by the National Cancer Institute because of its use in pharmaceutical preparations and its structural similarity to methyl iodide, which has produced sarcomas in BD rats (Druckrey et al., 1970; Preussmann, 1968), and to chloroform, a compound which has been found to induce hepatomas in NLC mice (Eschenbrenner, 1945; Rudali, 1967).

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is triiodo-methane.*

In the past, iodoform was used by humans chiefly as a topical anti-infective (Windholz, 1976). The mild antibacterial action of the compound results from its gradual release of elemental iodine (Goodman and Gilman, 1970). Use of iodoform for the dressing of wounds was fairly extensive but in recent times it has been replaced almost altogether by more effective antiseptic agents (Goodman and Gilman, 1970).

Iodoform may still be used in veterinary medicine as an antiseptic and also as a disinfectant on superfical lesions and in the female reproductive tract (Windholz, 1976).

Specific production figures for iodoform are not available. Iodoform is produced in two grades: technical or nonmedicinal; and

*The CAS registry number is 75-48-8.

N.F. (National Formulary). Of these, only technical-grade iodoform is produced in commercial quantities (greater than 1000 pounds or $1000 in value annually) in the United States (Stanford Research Institute, 1976).

Since iodoform is no longer used to any great extent in the treatment of humans, the potential for exposure is greatest for workers in iodoform production facilities and for those persons using the compound for research purposes.

Iodoform is considered moderately toxic (Sax, 1975); the lowest published toxic dose in humans is 114 mg/kg (U.S. Department of Health, Education, and Welfare, 1976). Poisoning, which is often the result of absorption of iodoform through a wound, produces vomiting, rapid pulse, sometimes accompanied by a slight fever, and all degrees of cerebral depression or excitation (Gosselin et al., 1976). Absorption of large amounts of the compound may result in depression of the central nervous system, and damage to the kidneys, liver, and heart (Irish, 1967).

## II. MATERIALS AND METHODS

### A. Chemicals

One batch of technical-grade iodoform (Figure 1) (triiodomethane) was purchased from Merck and Company, Inc., Rahway, New Jersey. Chemical analysis was performed by Hazleton Laboratories America, Inc., Vienna Virginia. The experimentally determined melting point was 115°C, while the literature value is 120°C (Windholtz, 1976). The results of analysis via reaction with silver nitrate and titration with thiocyanate also suggested a compound of extremely high purity.

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

### B. Dosage Preparation

Fresh solutions of iodoform in Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) were prepared weekly, sealed, and stored in dark bottles at 1°C. These iodoform solutions were considered generally stable for ten days under the indicated storage conditions. The concentrations of iodoform in corn oil ranged from 1.8 to 9.0 percent for the rat bioassay and 0.6 to 1.0 percent for the mouse bioassay.

### C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon

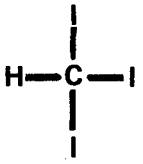



**FIGURE 1**
**CHEMICAL STRUCTURE OF IODOFORM**

tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various treated and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors, while mice were housed in groups of ten in solid-bottom, polypropylene cages equipped with non-woven filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) were provided once

each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food (Wayne Lab-Blox®, Allied Mills, Inc., Chicago, Illinois) and water were available ad libitum.

The iodoform-dosed and vehicle control rats were housed in the same room as other rats intubated with* 3-sulfolene (77-79-2) and hexachloroethane (67-72-1). The untreated control rats were housed with other rats intubated with 1,1,2-trichloroethane (79-00-5) and tetrachloroethylene (127-18-4).

All mice utilized in the iodoform bioassay, including controls, were housed with other mice intubated with allyl chloride (107-05-1); 1,1,2,2-tetrachloroethane (79-34-5); chloroform (67-66-3); chloropicrin (76-06-2); carbon disulfide (75-15-0); dibromochloropropane (96-12-8); 1,2-dibromoethane (106-93-4); 1,2-dichloroethane (107-06-2); 1,1-dichloroethane (75-34-3); trichloroethylene (79-01-6); 3-sulfolene (77-79-2); methylchloroform (71-55-6); 1,1,2-trichloroethane (79-00-5); tetrachloroethylene (127-18-4); hexachloroethane (67-72-1); trichlorofluoromethane (75-69-4) and carbon tetrachloride (56-23-5).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg body weight basis utilizing the most recently observed group

*CAS registry numbers are given in parentheses.

mean body weight as a guide for determining the dose. Mean body weights for each group were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. All animals of one sex within a treated group received the same dose. Animals were gavaged with the test solution under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

In order to estimate the maximum tolerated dosage of iodoform for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Iodoform mixed with corn oil was introduced by gavage to five of the six rat groups at dosages of 56, 100, 178, 316 and 562 mg/kg/day and five of the six mouse groups at dosages of 18, 32, 56, 100, and 178 mg/kg/day. The sixth group of each species served as a control group, receiving only the corn oil by gavage. Intubation was performed 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

A dosage inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent was selected as the initial high dose. When weight gain criteria were not applicable, mortality data alone were utilized.

Deaths occurred in all groups of treated female rats and in all male groups receiving 316 mg/kg/day or more. All the male and female

rats receiving dosages of 562 mg/kg/day died before the end of the experiment. Mean body weight was depressed in male rats receiving dosages of 316 mg/kg/day and in female rats receiving dosages of 56 mg/kg/day or higher. The initial high doses selected for the chronic bioassay were 180 and 36 mg/kg/day for males and females, respectively.

All male mice receiving 56 mg/kg/day or less survived. One of the five male mice receiving 100 mg/kg/day died and all the male mice receiving 178 mg/kg/day died. All treated female mice survived, except for four of the five female mice treated with 178 mg/kg/day. The only significant mean body weight depression observed was in female mice receiving 178 mg/kg/day. The initial high dose selected for both male and female mice in the chronic bioassay was 56 mg/kg/day.

G. Experimental Design

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

All rats were approximately 7 weeks old when they were started on test. Vehicle control and treated rats shared the same median date of birth while untreated control rats were approximately 2 weeks younger than the other groups and were started on test a corresponding 2 weeks after the other groups. Male rats initially received

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
IODOFORM GAVAGE EXPERIMENT

| | INITIAL GROUP SIZE | IODOFORM DOSAGE[a] | OBSERVATION PERIOD TREATED (WEEKS) | OBSERVATION PERIOD UNTREATED (WEEKS) | TIME-WEIGHTED AVERAGE DOSAGE[b] |
|---|---|---|---|---|---|
| MALE | | | | | |
| UNTREATED CONTROL | 20 | 0 | 0 | 112 | 0 |
| VEHICLE CONTROL | 20 | 0 | 78 | 34 | 0 |
| LOW DOSE | 50 | 90 | 28 | | 71 |
| | | 60 | 50 | | |
| | | 0 | | 34 | |
| HIGH DOSE | 50 | 180 | 28 | | 142 |
| | | 120 | 50 | | |
| | | 0 | | 34 | |
| FEMALE | | | | | |
| UNTREATED CONTROL | 20 | 0 | 0 | 112 | 0 |
| VEHICLE CONTROL | 20 | 0 | 78 | 34 | 0 |
| LOW DOSE | 50 | 18 | 18 | | 27 |
| | | 30 | 60 | | |
| | | 0 | | 34 | |
| HIGH DOSE | 50 | 36 | 18 | | 55 |
| | | 60 | 60 | | |
| | | 0 | | 34 | |

[a]Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
IODOFORM GAVAGE EXPERIMENT

| | INITIAL GROUP SIZE | IODOFORM DOSAGE[a] | OBSERVATION PERIOD TREATED (WEEKS) | OBSERVATION PERIOD UNTREATED (WEEKS) | TIME-WEIGHTED AVERAGE DOSAGE[b] |
|---|---|---|---|---|---|
| MALE | | | | | |
| UNTREATED CONTROL | 20 | 0 | 0 | 90 | 0 |
| VEHICLE CONTROL | 20 | 0 | 78 | 12 | 0 |
| LOW DOSE | 50 | 28 | 8 | | 47 |
| | | 40 | 10 | | |
| | | 50 | 60 | | |
| | | 0 | | 13 | |
| HIGH DOSE | 50 | 56 | 8 | | 93 |
| | | 80 | 10 | | |
| | | 100 | 60 | | |
| | | 0 | | 13 | |
| FEMALE | | | | | |
| UNTREATED CONTROL | 20 | 0 | 0 | 90 | 0 |
| VEHICLE CONTROL | 20 | 0 | 78 | 12 | 0 |
| LOW DOSE | 50 | 28 | 8 | | 47 |
| | | 40 | 10 | | |
| | | 50 | 60 | | |
| | | 0 | | 13 | |
| HIGH DOSE | 50 | 56 | 8 | | 93 |
| | | 80 | 10 | | |
| | | 100 | 60 | | |
| | | 0 | | 14 | |

[a]Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

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

iodoform dosages of 90 and 180 mg/kg/day. Throughout this report those male rats initially receiving the former dosage are referred to as the low dose group, while those initially receiving the latter dosage are referred to as the high dose group. In week 29 the dosages were lowered to 60 and 120 mg/kg/day for low and high dose males, respectively. The dosages were maintained at these levels for the remainder of the period of compound administration. The doses initially utilized for female rats were 18 and 36 mg/kg/day. Throughout this report those female rats initially receiving the former dosage are referred to as the low dose group while those initially receiving the latter dosage are referred to as the high dose group. In week 19 the dosages were increased to 30 and 60 mg/kg/day for low and high dose female rats, respectively. These dosages were maintained for the remainder of the period of compound administration.

Mice were all approximately 5 weeks old when they were started on test. The vehicle control and treated mice shared the same median date of birth. The untreated control mice were approximately 4 weeks younger than the other groups and were started on test a corresponding 4 weeks later. For the first 8 weeks of the experiment male and female mice received dosages of 28 and 56 mg/kg/day. Throughout this report those mice initially receiving the former dosage are referred to as the low dose groups, while those initially receiving the latter dosage are referred to as the high dose groups. In week 9 dosages were raised to 40 and 80 mg/kg/day for low and high dose mice,

respectively. In week 19 the dosages were again raised, to 50 and 100 mg/kg/day for low and high dose mice, respectively. These dosages remained unchanged for both male and female mice for the remainder of the period of compound administration.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

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

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

Slides were prepared from the following tissues: skin, lungs, 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, mammary gland, testis, prostate, and brain.

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

## I. 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.

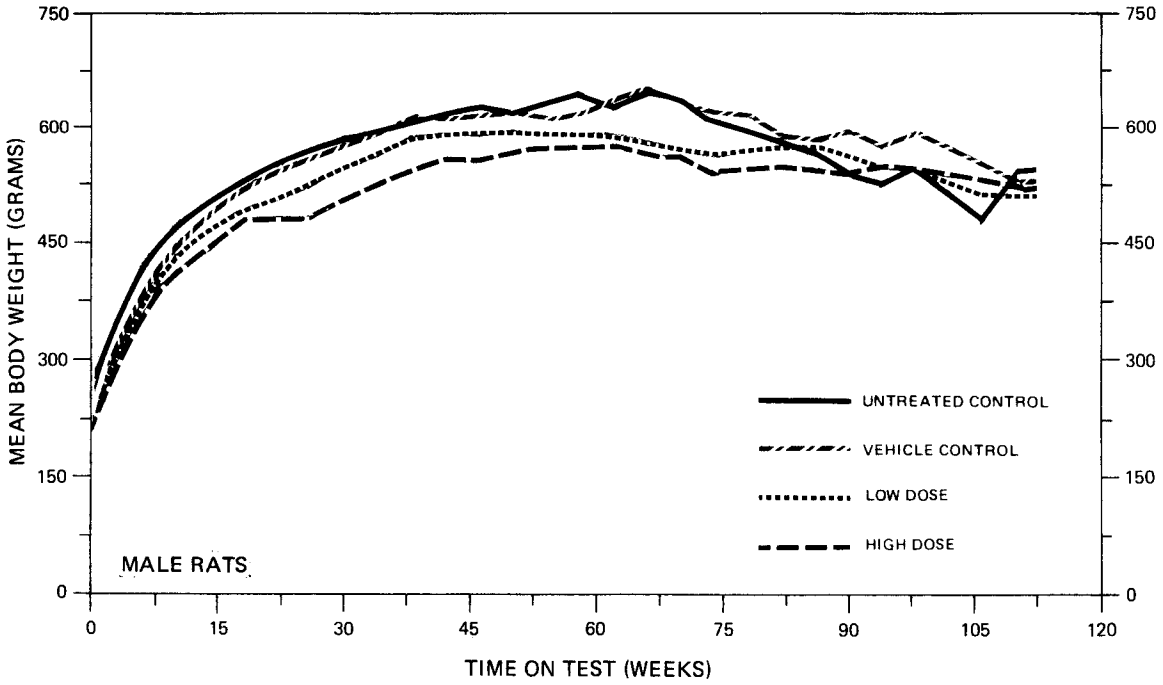
## III. CHRONIC TESTING RESULTS: RATS

### A. Body Weights and Clinical Observations

No mean body weight depression was evident during this bioassay for female rats, but a slight compound-related mean body weight depression was observed among male rats during the dosing period (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

During the first 18 weeks of the study the appearance and behavior of the treated rats were generally comparable with those of the untreated controls. From week 20 to the end of the first year, a hunched appearance was observed with greater frequency in the high dose males and females than in the low dose and control groups, but was noted at a comparable rate in all groups during the remainder of the study.

Respiratory signs, involving labored respiration, wheezing, and/or nasal discharge, were observed at a low incidence in all groups during the first year, increasing as the animals aged; by week 110 most of the surviving rats exhibited respiratory symptoms. Clinical signs associated with aging were noted at a comparable frequency in treated and control rats during the last 10 months of the study. These signs included sores on the body or extremities, alopecia, rough fur, abdominal urine stains, squinted or reddened eyes, swollen areas of the body, tissue masses, and palpable nodules. Isolated



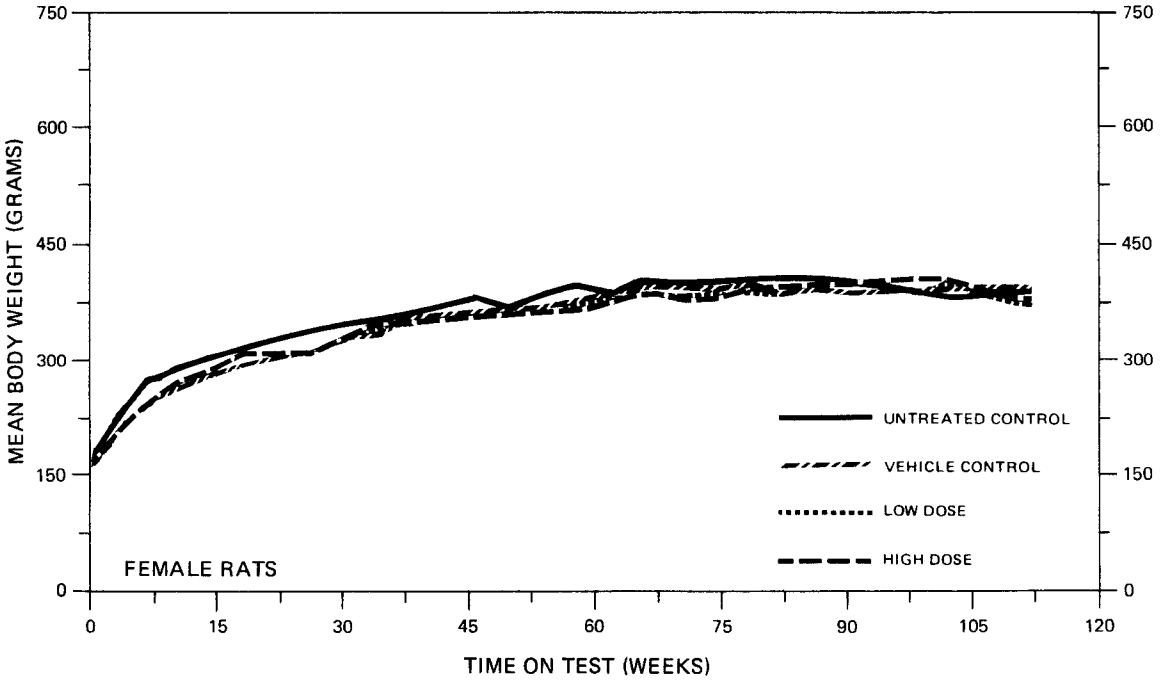




**FIGURE 2**
**GROWTH CURVES FOR IODOFORM CHRONIC STUDY RATS**

observations in one to three rats included tremors, transient salivation, incoordination, ataxia, red vaginal discharge, abnormal gait, and head tilt.

B. Survival

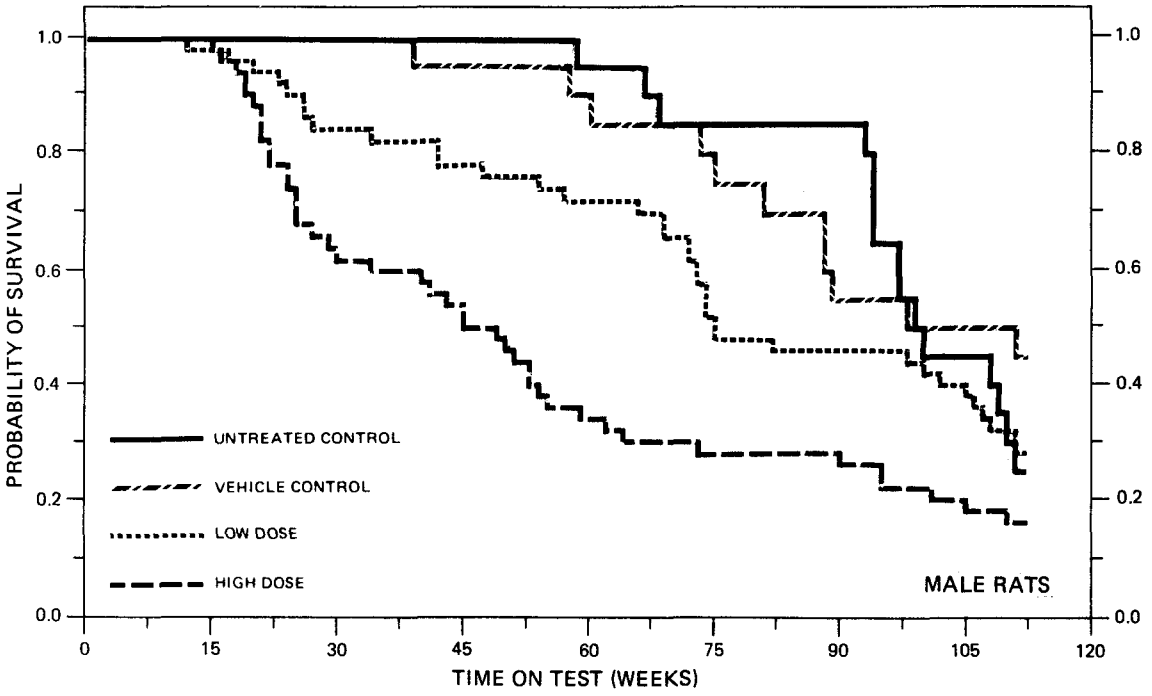
The estimated probabilities of survival for male and female rats in the control and iodoform-dosed groups are shown in Figure 3. For male rats the Tarone test indicated a significant ($P < 0.001$) positive association between increased dosage and mortality. For female rats no statistically significant association between dose and mortality was observed.

The survival of the dosed males was low, with 50 percent (25/50) of the high dose male rats dead by week 46 and 52 percent (26/50) of the low dose male rats dead by week 76. For each of the control groups, however, 50 percent (10/20) of the rats survived on test at least 100 weeks.

There were adequate numbers of females at risk from late-developing tumors as 54 percent (27/50) of the high dose, 38 percent (19/50) of the low dose, 80 percent (16/20) of the vehicle control and 60 percent (12/20) of the untreated control females survived on test until the end of the study.

C. Pathology

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



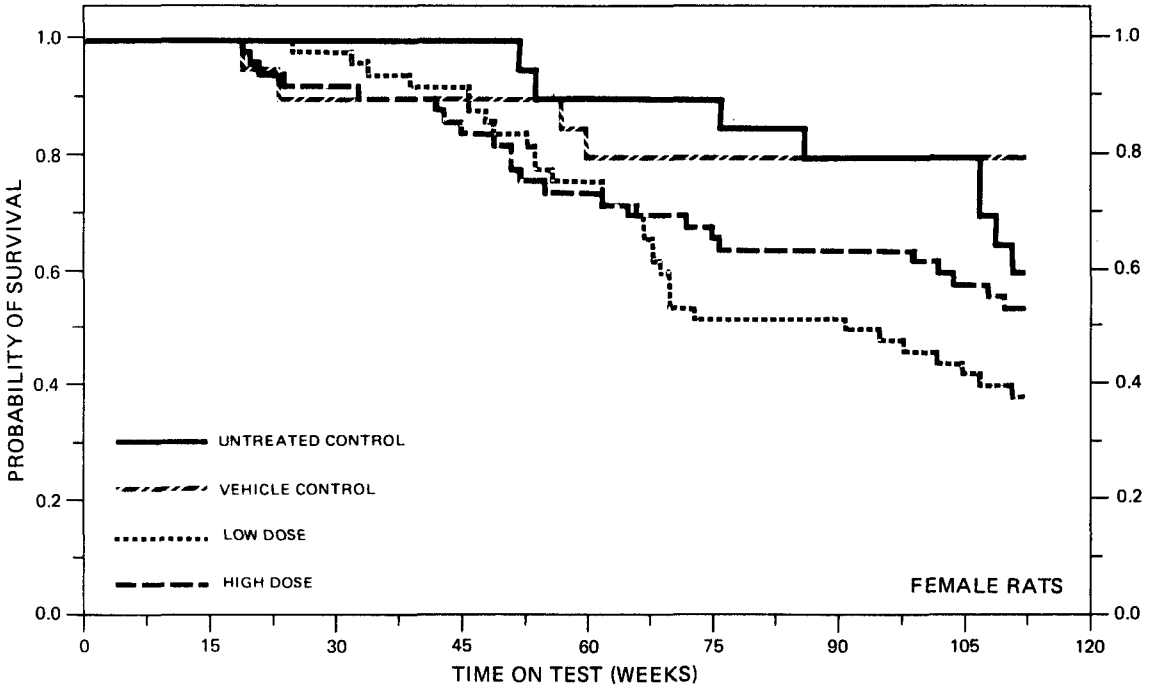




**FIGURE 3**
**SURVIVAL COMPARISONS OF IODOFORM CHRONIC STUDY RATS**

Follicular-cell tumors of the thyroid gland occurred in treated rats and pooled vehicle controls of both sexes but not in matched vehicle controls. Each of the other types of tumors observed in this bioassay has been encountered previously as a naturally occurring lesion in the aged Osborne-Mendel rat.

Inflammatory, degenerative, and proliferative lesions as seen in the control and chemically treated rats were similar in number and kind to those lesions occurring spontaneously in untreated aged rats.

This histopathologic examination did not provide evidence that iodoform was carcinogenic to Osborne-Mendel rats under the conditions of this experiment.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. For males (Table 3) because of the high early mortality in the high dose group the statistical analyses were based either on rats which survived at least 52 weeks or, in the case of the combined incidence of follicular-cell carcinomas or follicular-cell adenomas of the thyroid, on rats which survived at least 50 weeks (the time at which the first tumor of interest was detected). For females (Table 4) the standard analyses were performed. 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 iodoform-dosed groups and where such tumors were observed in at least 5 percent of the group.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH IODOFORM WHICH SURVIVED AT LEAST 52 WEEKS[a,e]

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Pituitary: Chromophobe Adenoma[b] | 6/36(0.17) | 4/18(0.22) | 7/36(0.19) | 4/20(0.20) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 1.167 | 1.200 |
| Lower Limit | --- | --- | 0.363 | 0.276 |
| Upper Limit | --- | --- | 3.697 | 4.348 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.875 | 0.900 |
| Lower Limit | --- | --- | 0.258 | 0.198 |
| Upper Limit | --- | --- | 3.560 | 4.141 |
| Weeks to First Observed Tumor | 105 | 111 | 72 | 95 |
| Thyroid: Follicular-Cell Carcinoma[b] | 1/34(0.03) | 0/16(0.00) | 6/35(0.17) | 3/17(0.18) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 5.829 | 6.000 |
| Lower Limit | --- | --- | 0.722 | 0.520 |
| Upper Limit | --- | --- | 245.698 | 293.063 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | Infinite | Infinite |
| Lower Limit | --- | --- | 0.735 | 0.604 |
| Upper Limit | --- | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | 111 | --- | 74 | 112 |

TABLE 3 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b,e] | 2/34(0.06) | 0/16(0.00) | 8/35(0.23) | 4/18(0.22) |
| P Values[c] | N.S. | N.S. | P = 0.046*<br>P = 0.037** | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 3.886 | 3.778 |
| Lower Limit | --- | --- | 0.851 | 0.595 |
| Upper Limit | --- | --- | 35.305 | 37.389 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | Infinite | Infinite |
| Lower Limit | --- | --- | 1.112 | 0.882 |
| Upper Limit | --- | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | 111 | --- | 74 | 50 |
| Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b] | 1/34(0.03) | 1/16(0.06) | 3/35(0.09) | 3/20(0.15) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 2.914 | 5.100 |
| Lower Limit | --- | --- | 0.235 | 0.520 |
| Upper Limit | --- | --- | 140.599 | 293.063 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 1.371 | 2.400 |
| Lower Limit | --- | --- | 0.117 | 0.259 |
| Upper Limit | --- | --- | 66.206 | 137.988 |
| Weeks to First Observed Tumor | 111 | 111 | 111 | 112 |

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 71 or 142 mg/kg by gavage.

[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 corresponding 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 pooled vehicle control group (*) or the matched vehicle control group (**) is given beneath the incidence of tumors in that 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]For sites where the first tumor of interest was observed earlier than 52 weeks, the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

TABLE 4

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

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Pituitary: Chromophobe Adenoma[b] | 12/40(0.30) | 5/20(0.25) | 8/45(0.18) | 9/47(0.19) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.593 | 0.638 |
| Lower Limit | --- | --- | 0.236 | 0.267 |
| Upper Limit | --- | --- | 1.411 | 1.478 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.711 | 0.766 |
| Lower Limit | --- | --- | 0.243 | 0.273 |
| Upper Limit | --- | --- | 2.485 | 2.618 |
| Weeks to First Observed Tumor | 89 | 112 | 62 | 104 |
| Thyroid: Follicular-Cell Carcinoma[b] | 1/40(0.02) | 0/20(0.00) | 4/40(0.10) | 2/42(0.05) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 4.000 | 1.905 |
| Lower Limit | --- | --- | 0.420 | 0.103 |
| Upper Limit | --- | --- | 191.652 | 109.644 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | Infinite | Infinite |
| Lower Limit | --- | --- | 0.483 | 0.146 |
| Upper Limit | --- | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | 111 | --- | 91 | 104 |

TABLE 4 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Mammary Gland: Adenocarcinoma NOS[b] | 1/40(0.02) | 1/20(0.05) | 6/50(0.12) | 4/50(0.08) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 4.800 | 3.200 |
| Lower Limit | --- | --- | 0.620 | 0.335 |
| Upper Limit | --- | --- | 215.902 | 154.289 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 2.400 | 1.600 |
| Lower Limit | --- | --- | 0.325 | 0.175 |
| Upper Limit | --- | --- | 108.021 | 77.169 |
| Weeks to First Observed Tumor | 112 | 112 | 32 | 76 |
| Mammary Gland: Fibroadenoma[b] | 10/40(0.25) | 4/20(0.20) | 10/50(0.20) | 8/50(0.16) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.800 | 0.640 |
| Lower Limit | --- | --- | 0.334 | 0.244 |
| Upper Limit | --- | --- | 1.934 | 1.634 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 1.000 | 0.800 |
| Lower Limit | --- | --- | 0.339 | 0.250 |
| Upper Limit | --- | --- | 3.991 | 3.327 |
| Weeks to First Observed Tumor | 106 | 112 | 73 | 75 |

TABLE 4 (CONCLUDED)

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Uterus: Endometrial Stromal Polyp[b] | 2/39(0.05) | 1/19(0.05) | 2/47(0.04) | 3/48(0.06) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.830 | 1.219 |
| Lower Limit | --- | --- | 0.063 | 0.147 |
| Upper Limit | --- | --- | 11.016 | 14.035 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.809 | 1.187 |
| Lower Limit | --- | --- | 0.046 | 0.105 |
| Upper Limit | --- | --- | 46.702 | 61.031 |
| Weeks to First Observed Tumor | 111 | 112 | 112 | 112 |

[a]Treated groups received time-weighted average doses of 27 or 55 mg/kg by gavage.

[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 corresponding 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 pooled vehicle control group (*) or the matched vehicle control group (**) is given beneath the incidence of tumors in that 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.

Two types of control groups were used for statistical analyses: the vehicle control group (designated in this section as the "matched" vehicle control group) and a pooled vehicle control group, combining the vehicle controls from the studies of iodoform and hexachloroethane. The pooled control rats were of the same strain, were housed in the same room, were started on test within 2 weeks of each other and tested concurrently for more than one year, received the same vehicle, and were diagnosed by the same pathologists.

Thyroid tumors were found in both male and female rats. For males for the combined incidence of follicular-cell carcinomas or follicular-cell adenomas of the thyroid, the Fisher exact test comparisons of low dose to both the pooled and the matched control had marginal test results which were not significant under the Bonferroni criterion. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, 11/200 (6 percent) of the male vehicle control Osborne-Mendel rats had one of these tumors--compared to the 8/35 (23 percent) and 4/18 (22 percent) observed in the low dose and high dose groups, respectively.

No statistical test for any site in either males or females was significant under the Bonferroni criterion. Thus, there was no convincing statistical evidence of the carcinogenicity of iodoform in rats.

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

observed tumor incidence rates. In all 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 all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by iodoform that could not be established under the conditions of this test.

## IV. CHRONIC TESTING RESULTS: MICE

### A. Body Weights and Clinical Observations

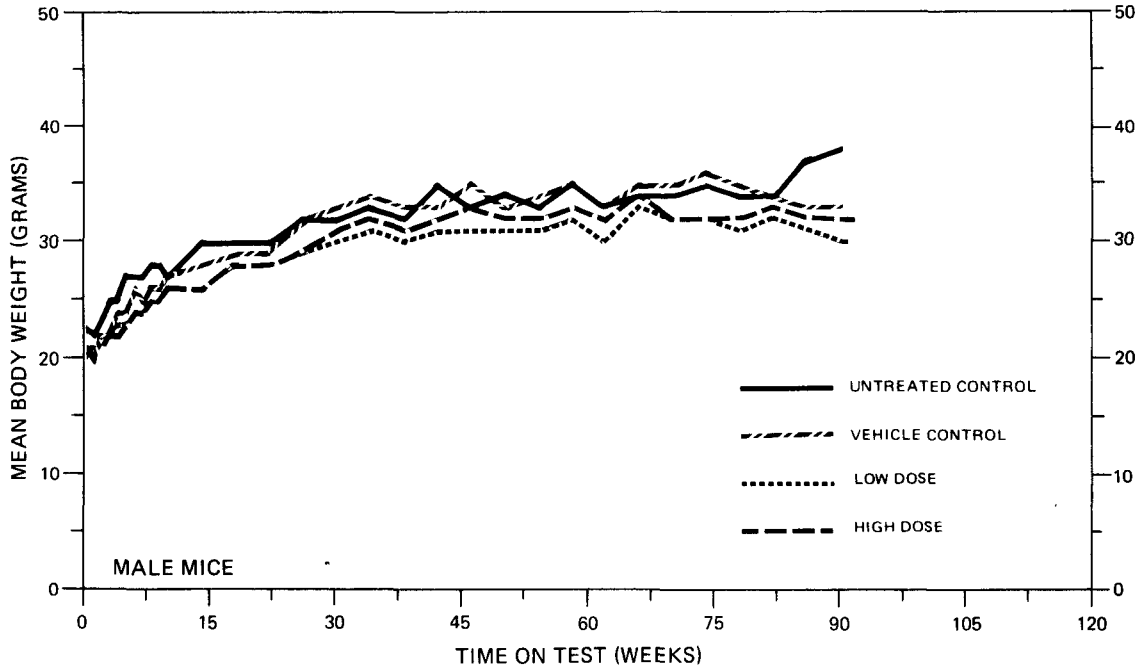
Distinct patterns of compound-related mean body weight depression were not apparent during this bioassay (Figure 4).

Throughout the study, there was no evidence of compound effect with regard to physical appearance and behavior among the iodoform-treated mice. Clinical signs often observed in group-housed laboratory mice were noted at comparable rates in control and treated mice, with the incidences increasing gradually in all groups as the study approached termination. These common signs included sores and/or desquamation on parts of the body, alopecia, stains on the fur, external genital irritation, bloating, palpable nodules, and tissue masses.

### B. Survival

The estimated probabilities of survival for male and female mice in the control and iodoform-dosed groups are shown in Figure 5. For both male and female mice no statistically significant positive association between dosage and mortality was observed.

There were adequate numbers of male mice at risk from late-developing tumors as 60 percent (30/50) of the high dose, 68 percent (34/50) of the low dose, and 60 percent (12/20) of the vehicle con-control mice lived on test until the end of the study. Survival among the untreated control mice was unexpectedly low, as only 10 percent (2/20) lived on test until the end of the study.



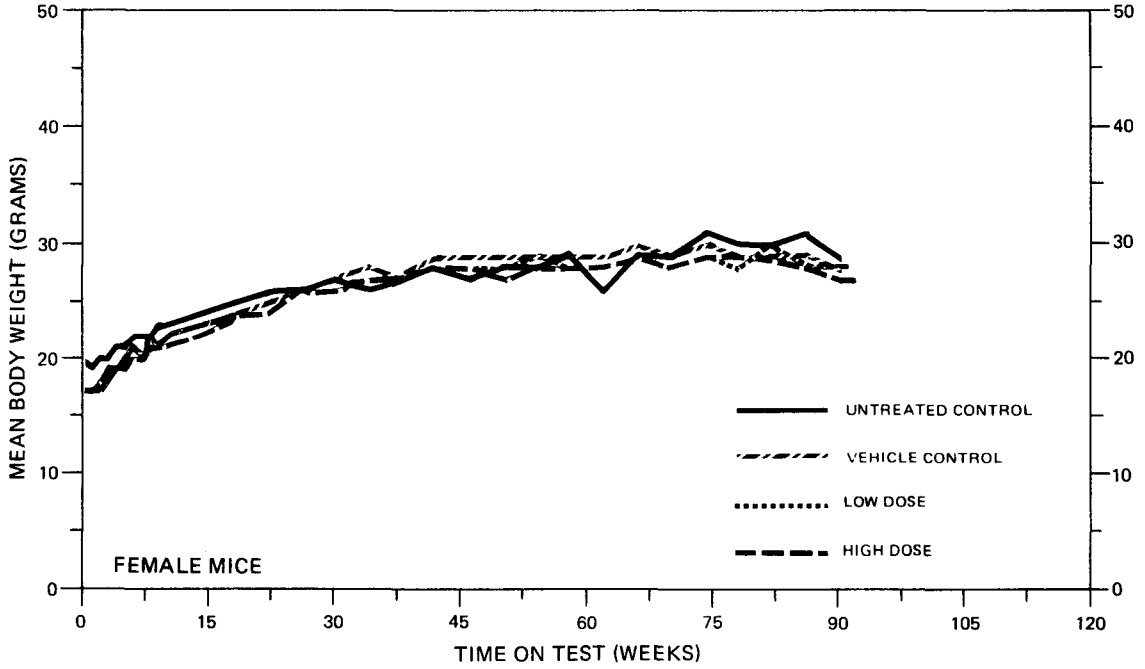
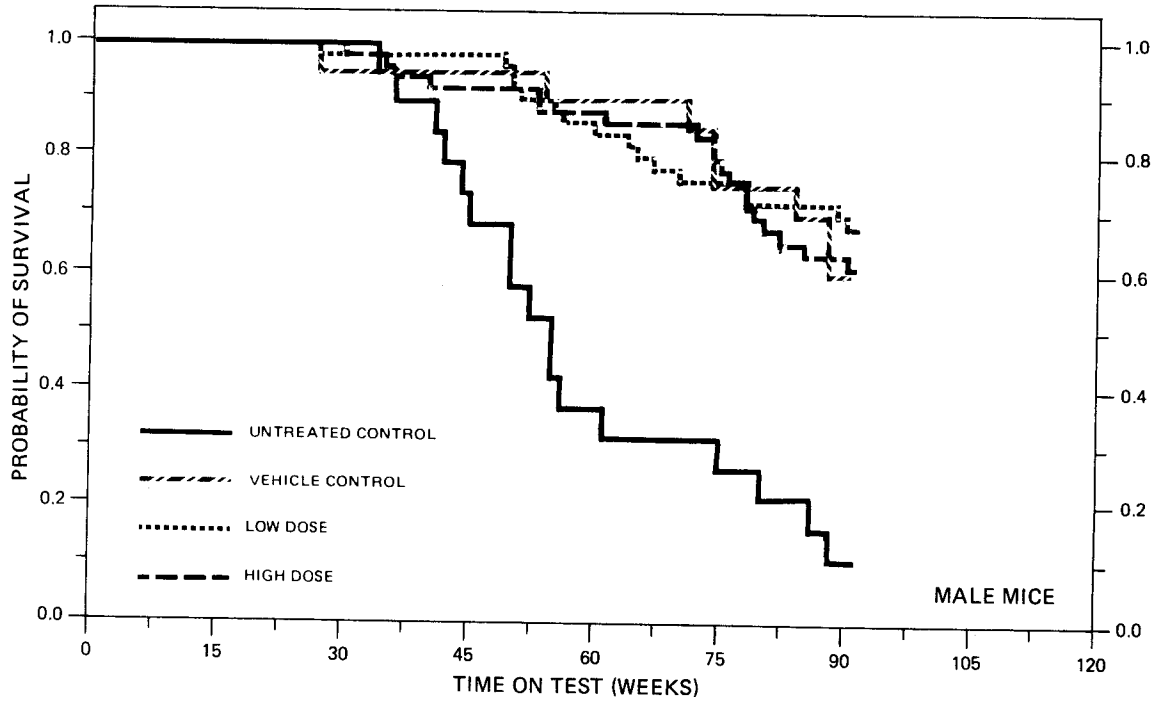




**FIGURE 4**
**GROWTH CURVES FOR IODOFORM CHRONIC STUDY MICE**



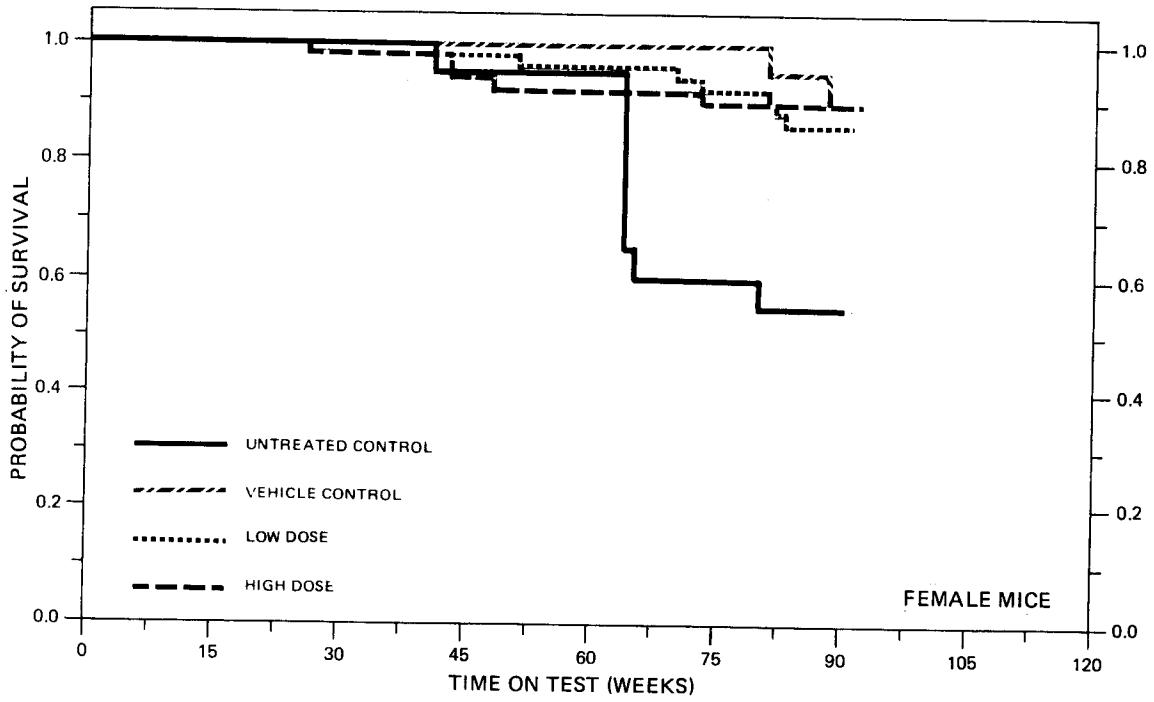




**FIGURE 5**
**SURVIVAL COMPARISONS OF IODOFORM CHRONIC STUDY MICE**

There were adequate numbers of female mice at risk from late-developing tumors as 86 percent (43/50) of the high dose, 86 percent (43/50) of the low dose, and 90 percent (18/20) of the vehicle control mice lived on test until the end of the study. Fifty-five percent (11/20) of the untreated controls survived on test until the study was terminated, despite the death of seven animals in weeks 64 and 65. Six of these mice had congestion of the lungs; the other was autolyzed.

C. Pathology

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

The incidence of malignant lymphoma, a neoplasm occurring commonly in the B6C3F1 mouse, were increased in high dose male mice (i.e, 2/19 [11 percent] controls, 3/50 [6 percent] low dose, and 10/50 [20 percent] high dose). A large variety of other neoplasms were found in various organs of mice in both the control and treated groups; however, they were of the usual number and type observed in hybrid mice of this age and strain.

The inflammatory, degenerative, and proliferative lesions were of the usual type observed in mice of this age and strain and were essentially comparable in incidence in the control and treated groups, except for an increase in amyloidosis of the liver, spleen, kidney, and adrenal gland in untreated control males.

This histopathologic examination did not provide convincing evidence for the carcinogenicity of iodoform in B6C3F1 mice, although exposure to the compound may have been associated with an increased incidence of malignant lymphoma in high dose males.

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 for every type of tumor that was observed in more than 5 percent of any of the iodoform-dosed groups of either sex is included.

Two types of control groups were used for statistical analyses: the vehicle control group (designated in this section as the "matched" vehicle control group) and a pooled vehicle control group, combining the vehicle controls from the studies of iodoform and 1,1,2-trichloroethane. The pooled control mice were of the same strain, were given the same vehicle, were housed in the same room, were started on test in the same month and tested concurrently for at least one year, and were diagnosed by the same pathologists.

No statistical tests from any site in male or female mice showed a positive association between administration and tumor incidence. Based upon these results there was no statistical evidence of the carcarcinogenicity of iodoform in 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

TABLE 5

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

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Lung: Alveolar/Bronchiolar Carcinoma[b] | 0/39(0.00) | 0/19(0.00) | 3/50(0.06) | 1/49(0.02) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | Infinite | Infinite |
| Lower Limit | --- | --- | 0.472 | 0.043 |
| Upper Limit | --- | --- | Infinite | Infinite |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | Infinite | Infinite |
| Lower Limit | --- | --- | 0.238 | 0.021 |
| Upper Limit | --- | --- | Infinite | Infinite |
| Weeks to First Observed Tumor | --- | --- | 90 | 91 |
| Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b] | 1/39(0.03) | 1/19(0.05) | 4/50(0.08) | 4/49(0.08) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 3.120 | 3.184 |
| Lower Limit | --- | --- | 0.327 | 0.333 |
| Upper Limit | --- | --- | 150.411 | 153.393 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 1.520 | 1.551 |
| Lower Limit | --- | --- | 0.167 | 0.171 |
| Upper Limit | --- | --- | 73.309 | 74.767 |
| Weeks to First Observed Tumor | 90 | 90 | 90 | 91 |

TABLE 5 (CONTINUED)

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Hematopoietic: Malignant Lymphoma[b] | 4/39(0.10) | 2/19(0.11) | 3/50(0.06) | 10/50(0.20) |
| P Values[c] | P = 0.009 | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.585 | 1.950 |
| Lower Limit | --- | --- | 0.091 | 0.616 |
| Upper Limit | --- | --- | 3.266 | 7.953 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.570 | 1.900 |
| Lower Limit | --- | --- | 0.073 | 0.468 |
| Upper Limit | --- | --- | 6.511 | 16.901 |
| Weeks to First Observed Tumor | 66 | 74 | 70 | 40 |
| Liver: Hepatocellular Carcinoma[b] | 5/39(0.13) | 3/19(0.16) | 5/49(0.10) | 7/50(0.14) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.796 | 1.092 |
| Lower Limit | --- | --- | 0.198 | 0.325 |
| Upper Limit | --- | --- | 3.228 | 4.061 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.646 | 0.887 |
| Lower Limit | --- | --- | 0.144 | 0.234 |
| Upper Limit | --- | --- | 3.881 | 4.945 |
| Weeks to First Observed Tumor | 88 | 88 | 90 | 91 |

TABLE 5 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 47 or 93 mg/kg by gavage.

[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 corresponding 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 pooled vehicle control group (*) or the matched vehicle control group (**) is given beneath the incidence of tumors in that 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 IODOFORM[a]

| TOPOGRAPHY:MORPHOLOGY | POOLED VEHICLE CONTROL | MATCHED VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| Hematopoietic: Malignant Lymphoma[b] | 9/40(0.22) | 5/20(0.25) | 5/49(0.10) | 4/45(0.09) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.454 | 0.395 |
| Lower Limit | --- | --- | 0.130 | 0.096 |
| Upper Limit | --- | --- | 1.383 | 1.298 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.408 | 0.356 |
| Lower Limit | --- | --- | 0.109 | 0.081 |
| Upper Limit | --- | --- | 1.614 | 1.502 |
| Weeks to First Observed Tumor | 69 | 81 | 70 | 91 |
| Liver: Hepatocellular Carcinoma[b] | 1/40(0.02) | 1/20(0.05) | 1/49(0.02) | 0/45(0.00) |
| P Values[c] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Vehicle Control)[d] | --- | --- | 0.816 | 0.000 |
| Lower Limit | --- | --- | 0.011 | 0.000 |
| Upper Limit | --- | --- | 62.794 | 16.555 |
| Relative Risk (Matched Vehicle Control)[d] | --- | --- | 0.408 | 0.000 |
| Lower Limit | --- | --- | 0.005 | 0.000 |
| Upper Limit | --- | --- | 31.413 | 8.288 |
| Weeks to First Observed Tumor | 90 | 90 | 91 | --- |

TABLE 6 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 47 or 93 mg/kg by gavage.

[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 corresponding 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 pooled vehicle control group (*) or the matched vehicle control group (**) is given beneath the incidence of tumors in that 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.

observed tumor incidence rates. In all 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 all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by iodoform that could not be established under the conditions of this test.

# V. DISCUSSION

There was a significant positive association between the dosage of iodoform administered and mortality in male rats; this was not the case for female rats or mice of either sex. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

The possibility that female rats and mice of both sexes did not receive dosages of iodoform approximating the maximum tolerated dosages must be considered, as intubation with the compound had no significant effect upon the mean body weights for these treated animals when compared to their respective controls.

Of the neoplasms of histopathologic interest observed in treated animals (i.e., follicular-cell thyroid tumors in rats and malignant lymphomas in high dose male mice), neither showed a significant positive association between administration of the compound and tumor incidence and neither of these neoplasms was unusual in these species. Because of poor survival in male rats, however, the possibility that compound administration resulted in thyroid tumors cannot be excluded.

No neoplasms occurred in statistically significant increased incidences when treated rats and mice were compared to their respective controls.

Under the conditions of this bioassay, no convincing evidence was provided for the carcinogenicity of iodoform in Osborne-Mendel rats or in B6C3F1 mice.

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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH IODOFORM

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH IODOFORM

| | CONTROL(UNTR) 01-141M | CONTROL(VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS NECROPSIED | 20 | 20 | 49 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 20 | 20 | 49 | 50 |
| INTEGUMENTARY SYSTEM | | | | |
| *SUBCUT TISSUE | (20) | (20) | (49) | (50) |
| FIBROMA | 1 (5%) | | 1 (2%) | |
| FIBROSARCOMA | | 1 (5%) | | |
| HEMANGIOMA | | | 1 (2%) | |
| NEUROFIBROSARCOMA | | 1 (5%) | | |
| NEUROFIBROSARCOMA, METASTATIC | | 1 (5%) | | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (20) | (19) | (49) | (50) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | 1 (2%) | |
| NEUROFIBROSARCOMA, METASTATIC | | 1 (5%) | | |
| HEMATOPOIETIC SYSTEM | | | | |
| *MULTIPLE ORGANS | (20) | (20) | (49) | (50) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (5%) | 1 (2%) | |
| #SPLEEN | (19) | (19) | (47) | (50) |
| HEMANGIOSARCOMA | 2 (11%) | | | 1 (2%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | 1 (2%) |
| #LYMPH NODE | (19) | (17) | (41) | (37) |
| NEUROFIBROSARCOMA, METASTATIC | | 1 (6%) | | |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |
| DIGESTIVE SYSTEM | | | | |
| #SALIVARY GLAND | (14) | (16) | (31) | (13) |
| NEUROFIBROSARCOMA, METASTATIC | | 1 (6%) | | |

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

TABLE A1 (CONTINUED)

| | CONTROL (UNTR) 01-141M | CONTROL (VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| URINARY SYSTEM | | | | |
| #KIDNEY | (19) | (20) | (49) | (50) |
| MIXED TUMOR, MALIGNANT | 1 (5%) | | | |
| ENDOCRINE SYSTEM | | | | |
| #PITUITARY | (19) | (19) | (43) | (33) |
| CHROMOPHOBE ADENOMA | 3 (16%) | 4 (21%) | 7 (16%) | 4 (12%) |
| CHROMOPHOBE CARCINOMA | 1 (5%) | | | |
| #ADRENAL | (19) | (19) | (48) | (49) |
| PHEOCHROMOCYTOMA | | 1 (5%) | | |
| #THYROID | (19) | (17) | (43) | (37) |
| FOLLICULAR-CELL ADENOMA | | | 2 (5%) | 1 (3%) |
| FOLLICULAR-CELL CARCINOMA | 1 (5%) | | 6 (14%) | 3 (8%) |
| C-CELL ADENOMA | | 1 (6%) | 1 (2%) | 3 (8%) |
| C-CELL CARCINOMA | | | 2 (5%) | |
| NEUROFIBROSARCOMA, METASTATIC | | 1 (6%) | | |
| #PANCREATIC ISLETS | (19) | (19) | (48) | (45) |
| ISLET-CELL ADENOMA | 2 (11%) | 1 (5%) | | |
| REPRODUCTIVE SYSTEM | | | | |
| *MAMMARY GLAND | (20) | (20) | (49) | (50) |
| ADENOCARCINOMA, NOS | | 1 (5%) | 1 (2%) | |
| FIBROADENOMA | 1 (5%) | | | |
| NERVOUS SYSTEM | | | | |
| #BRAIN | (19) | (20) | (48) | (50) |
| CHROMOPHOBE CARCINOMA, METASTATI | 1 (5%) | | | |
| SPECIAL SENSE ORGANS | | | | |
| NONE | | | | |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |

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

TABLE A1 (CONCLUDED)

| | CONTROL (UNTR) 01-141M | CONTROL (VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| BODY CAVITIES | | | | |
| NONE | | | | |
| ALL OTHER SYSTEMS | | | | |
| *MULTIPLE ORGANS | (20) | (20) | (49) | (50) |
| FIBROUS HISTIOCYTOMA, MALIGNANT | | 1 (5%) | | 1 (2%) |
| ANIMAL DISPOSITION SUMMARY | | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| NATURAL DEATH@ | 14 | 11 | 36 | 42 |
| MORIBUND SACRIFICE | 1 | | | |
| SCHEDULED SACRIFICE | | | | |
| ACCIDENTALLY KILLED | | | | |
| TERMINAL SACRIFICE | 5 | 9 | 14 | 8 |
| ANIMAL MISSING | | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | | |
| TUMOR SUMMARY | | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 9 | 7 | 17 | 10 |
| TOTAL PRIMARY TUMORS | 12 | 12 | 23 | 14 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 6 | 4 | 11 | 7 |
| TOTAL BENIGN TUMORS | 7 | 7 | 13 | 8 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 5 | 4 | 10 | 5 |
| TOTAL MALIGNANT TUMORS | 5 | 5 | 10 | 6 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | 1 | | |
| TOTAL SECONDARY TUMORS | 1 | 5 | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH IODOFORM

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS NECROPSIED | 20 | 20 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 20 | 20 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | | |
| *SUBCUT TISSUE | (20) | (20) | (50) | (50) |
| FIBROSARCOMA | 1 (5%) | | | |
| RESPIRATORY SYSTEM | | | | |
| #TRACHEA | (20) | (20) | (50) | (49) |
| FOLLICULAR-CELL CARCINOMA, METAS | | | 1 (2%) | |
| #LUNG | (20) | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS, METASTATIC | | | | 1 (2%) |
| HEMANGIOSARCOMA, METASTATIC | | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | | |
| #SPLEEN | (20) | (20) | (49) | (50) |
| HEMANGIOSARCOMA | | | 1 (2%) | 2 (4%) |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (20) | (20) | (49) | (49) |
| NEOPLASTIC NODULE | 1 (5%) | 1 (5%) | | |
| HEPATOCELLULAR CARCINOMA | | 1 (5%) | | |
| HEMANGIOSARCOMA | | | 1 (2%) | |
| URINARY SYSTEM | | | | |
| #KIDNEY | (20) | (20) | (49) | (50) |
| MIXED TUMOR, MALIGNANT | | 1 (5%) | | |

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

TABLE A2 (CONTINUED)

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| HAMARTOMA + | 1 (5%) | | | |
| ENDOCRINE SYSTEM | | | | |
| #PITUITARY | (20) | (20) | (45) | (47) |
| CHROMOPHOBE ADENOMA | 8 (40%) | 5 (25%) | 8 (18%) | 9 (19%) |
| #ADRENAL | (20) | (20) | (49) | (50) |
| PHEOCHROMOCYTOMA | | | | 1 (2%) |
| HEMANGIOSARCOMA, METASTATIC | | | | 1 (2%) |
| #THYROID | (19) | (20) | (40) | (42) |
| FOLLICULAR-CELL CARCINOMA | | | 4 (10%) | 2 (5%) |
| C-CELL ADENOMA | 2 (11%) | 1 (5%) | | |
| C-CELL CARCINOMA | | 1 (5%) | 1 (3%) | |
| #PANCREATIC ISLETS | (20) | (20) | (47) | (50) |
| ISLET-CELL ADENOMA | 1 (5%) | | 2 (4%) | |
| REPRODUCTIVE SYSTEM | | | | |
| *MAMMARY GLAND | (20) | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS | | 1 (5%) | 6 (12%) | 4 (8%) |
| FIBROADENOMA | 3 (15%) | 4 (20%) | 10 (20%) | 8 (16%) |
| *CLITORAL GLAND | (20) | (20) | (50) | (50) |
| ADENOCARCINOMA, NOS | | | | 1 (2%) |
| #UTERUS | (20) | (19) | (47) | (48) |
| ADENOCARCINOMA, NOS | | 1 (5%) | | |
| ENDOMETRIAL STROMAL POLYP | 1 (5%) | 1 (5%) | 2 (4%) | 3 (6%) |
| #CERVIX UTERI | (20) | (19) | (47) | (48) |
| SQUAMOUS CELL CARCINOMA | | | | 1 (2%) |
| #OVARY | (20) | (19) | (47) | (50) |
| GRANULOSA-CELL TUMOR | | | 1 (2%) | |
| NERVOUS SYSTEM | | | | |
| NONE | | | | |
| SPECIAL SENSE ORGANS | | | | |
| NONE | | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| NONE | | | | |
| ALL OTHER SYSTEMS | | | | |
| *MULTIPLE ORGANS | (20) | (20) | (50) | (50) |
| FIBROUS HISTIOCYTOMA, MALIGNANT | | | 1 (2%) | |
| ANIMAL DISPOSITION SUMMARY | | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| NATURAL DEATH@ | 8 | 4 | 30 | 23 |
| MORIBUND SACRIFICE | | | 1 | |
| SCHEDULED SACRIFICE | | | | |
| ACCIDENTALLY KILLED | | | | |
| TERMINAL SACRIFICE | 12 | 16 | 19 | 27 |
| ANIMAL MISSING | | | | |

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| TUMOR SUMMARY | | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 13 | 10 | 27 | 23 |
| TOTAL PRIMARY TUMORS | 18 | 17 | 37 | 31 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 13 | 9 | 20 | 18 |
| TOTAL BENIGN TUMORS | 16 | 11 | 22 | 21 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 1 | 5 | 12 | 9 |
| TOTAL MALIGNANT TUMORS | 1 | 5 | 14 | 10 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | 1 | 1 |
| TOTAL SECONDARY TUMORS | | | 1 | 3 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 1 | 1 | 1 | |
| TOTAL UNCERTAIN TUMORS | 1 | 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 IODOFORM

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH IODOFORM

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS MISSING | 1 | | | |
| ANIMALS NECROPSIED | 15 | 19 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 15 | 19 | 49 | 50 |
| INTEGUMENTARY SYSTEM | | | | |
| *SKIN | (15) | (19) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (15) | (19) | (50) | (49) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | | 1 (2%) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (7%) | 1 (5%) | 1 (2%) | 3 (6%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | 3 (6%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | | |
| *MULTIPLE ORGANS | (15) | (19) | (50) | (50) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (5%) | 1 (2%) | 6 (12%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 2 (4%) | 2 (4%) |
| #SPLEEN | (15) | (19) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 1 (7%) | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (7%) | | | |
| #LYMPH NODE | (15) | (19) | (48) | (45) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (7%) | | | |
| #CERVICAL LYMPH NODE | (15) | (19) | (48) | (45) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | | 1 (2%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | 1 (2%) |
| #MESENTERIC L. NODE | (15) | (19) | (48) | (45) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (5%) | | 1 (2%) |
| #LIVER | (15) | (19) | (49) | (50) |
| LYMPHOMA METASTATIC | 1 (7%) | | | |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |

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

TABLE B1 (CONTINUED)

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| DIGESTIVE SYSTEM | | | | |
| #SALIVARY GLAND | (15) | (18) | (48) | (40) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | | 1 (3%) |
| #LIVER | (15) | (19) | (49) | (50) |
| HEPATOCELLULAR CARCINOMA | | 3 (16%) | 5 (10%) | 7 (14%) |
| HEMANGIOMA | | | | 1 (2%) |
| HEMANGIOSARCOMA | | | | 1 (2%) |
| #STOMACH | (15) | (19) | (50) | (49) |
| CARCINOMA,NOS | | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | | 1 (2%) |
| URINARY SYSTEM | | | | |
| NONE | | | | |
| ENDOCRINE SYSTEM | | | | |
| #THYROID | (15) | (17) | (41) | (38) |
| FOLLICULAR-CELL ADENOMA | | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | | |
| NONE | | | | |
| NERVOUS SYSTEM | | | | |
| NONE | | | | |
| SPECIAL SENSE ORGANS | | | | |
| *EYE/LACRIMAL GLAND | (15) | (19) | (50) | (50) |
| ADENOMA, NOS | | | 1 (2%) | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| NONE | | | | |

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

TABLE B1 (CONCLUDED)

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| ANIMAL DISPOSITION SUMMARY | | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| NATURAL DEATH@ | 17 | 8 | 15 | 15 |
| MORIBUND SACRIFICE | | | 1 | 4 |
| SCHEDULED SACRIFICE | | | | |
| ACCIDENTALLY KILLED | | | | 1 |
| TERMINAL SACRIFICE | 2 | 12 | 34 | 30 |
| ANIMAL MISSING | 1 | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | | |
| TUMOR SUMMARY | | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 2 | 5 | 14 | 23 |
| TOTAL PRIMARY TUMORS | 4 | 6 | 14 | 27 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 1 | 1 | 3 | 5 |
| TOTAL BENIGN TUMORS | 1 | 1 | 3 | 5 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 2 | 4 | 11 | 20 |
| TOTAL MALIGNANT TUMORS | 3 | 5 | 11 | 22 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | | | 1 |
| TOTAL SECONDARY TUMORS | 1 | | | 3 |
| 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 IODOFORM

| | CONTROL (UNTR) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS MISSING | | | | 2 |
| ANIMALS NECROPSIED | 18 | 20 | 49 | 45 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 18 | 20 | 49 | 45 |
| INTEGUMENTARY SYSTEM | | | | |
| *SKIN | (18) | (20) | (49) | (45) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (18) | (20) | (49) | (45) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | 1 (5%) | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | | |
| *NERVE TRACT | (18) | (20) | (49) | (45) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (5%) | | |
| #BRAIN | (16) | (20) | (49) | (45) |
| MALIGNANT LYMPHOMA, NOS | 1 (6%) | | | |
| *MULTIPLE ORGANS | (18) | (20) | (49) | (45) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | 3 (6%) | 2 (4%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (5%) | | 2 (4%) |
| #SPLEEN | (18) | (20) | (49) | (45) |
| MALIGNANT LYMPHOMA, NOS | 1 (6%) | | | |
| LYMPHOMA METASTATIC | 1 (6%) | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 3 (15%) | | |
| #LYMPH NODE | (18) | (20) | (47) | (45) |
| FIBROUS HISTIOCYTOMA, MALIGNANT | | | 1 (2%) | |
| MALIGNANT LYMPHOMA, NOS | 2 (11%) | | | |
| #MESENTERIC L. NODE | (18) | (20) | (47) | (45) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (5%) | | |
| #LIVER | (18) | (20) | (49) | (45) |
| LYMPHOMA METASTATIC | 1 (6%) | | | |

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

TABLE B2 (CONTINUED)

| | CONTROL(UNTR) 02-F121 | CONTROL(VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (5%) | | |
| #PANCREAS | (18) | (20) | (49) | (45) |
| LYMPHOMA METASTATIC | 1 (6%) | | | |
| #SMALL INTESTINE | (18) | (20) | (49) | (45) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 1 (2%) | |
| #KIDNEY | (18) | (20) | (49) | (45) |
| LYMPHOMA METASTATIC | 2 (11%) | | | |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | 1 (2%) | |
| #OVARY | (18) | (20) | (49) | (44) |
| LYMPHOMA METASTATIC | 2 (11%) | | | |
| #ADRENAL | (18) | (20) | (49) | (45) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (5%) | | |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (18) | (20) | (49) | (45) |
| HEPATOCELLULAR CARCINOMA | | 1 (5%) | 1 (2%) | |
| ENDOMETRIAL STROMAL SARCOMA, MET | | | 1 (2%) | |
| HEMANGIOMA | | | 1 (2%) | |
| HEMANGIOSARCOMA | | | 1 (2%) | |
| URINARY SYSTEM | | | | |
| #KIDNEY | (18) | (20) | (49) | (45) |
| ENDOMETRIAL STROMAL SARCOMA, MET | | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | | |
| #PITUITARY | (16) | (19) | (39) | (43) |
| CHROMOPHOBE ADENOMA | | | 1 (3%) | |
| #ADRENAL | (18) | (20) | (49) | (45) |
| CORTICAL ADENOMA | 1 (6%) | | | |

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

TABLE B2 (CONTINUED)

| | CONTROL (UNTR) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | | |
| *MAMMARY GLAND | (18) | (20) | (49) | (45) |
| ADENOCARCINOMA, NOS | | | 1 (2%) | 1 (2%) |
| #UTERUS | (18) | (20) | (48) | (44) |
| LEIOMYOSARCOMA | | | 1 (2%) | |
| ENDOMETRIAL STROMAL POLYP | | | 1 (2%) | |
| ENDOMETRIAL STROMAL SARCOMA | | | 1 (2%) | |
| #OVARY | (18) | (20) | (49) | (44) |
| CYSTADENOMA, NOS | | | 1 (2%) | |
| NERVOUS SYSTEM | | | | |
| *CRANIAL NERVE | (18) | (20) | (49) | (45) |
| NEUROFIBROSARCOMA | | | 1 (2%) | |
| 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) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | | |
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| NATURAL DEATH@ | 9 | 2 | 7 | 5 |
| MORIBUND SACRIFICE | | | | |
| SCHEDULED SACRIFICE | | | | |
| ACCIDENTALLY KILLED | | | | |
| TERMINAL SACRIFICE | 11 | 18 | 43 | 43 |
| ANIMAL MISSING | | | | 2 |
| @ INCLUDES AUTOLYZED ANIMALS | | | | |
| TUMOR SUMMARY | | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 4 | 7 | 14 | 5 |
| TOTAL PRIMARY TUMORS | 5 | 10 | 18 | 5 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 1 | 1 | 5 | |
| TOTAL BENIGN TUMORS | 1 | 1 | 5 | |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 3 | 6 | 10 | 5 |
| TOTAL MALIGNANT TUMORS | 4 | 9 | 13 | 5 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 3 | | 1 | |
| TOTAL SECONDARY TUMORS | 7 | | 2 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |

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

# APPENDIX C

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH IODOFORM

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH IODOFORM

| | CONTROL (UNTR) 01-141M | CONTROL (VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS NECROPSIED | 20 | 20 | 49 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 20 | 20 | 49 | 50 |
| INTEGUMENTARY SYSTEM | | | | |
| *SKIN | (20) | (20) | (49) | (50) |
| EPIDERMAL INCLUSION CYST | 1 (5%) | | | |
| INFLAMMATION, NOS | 1 (5%) | | | |
| *SUBCUT TISSUE | (20) | (20) | (49) | (50) |
| EPIDERMAL INCLUSION CYST | 1 (5%) | | | |
| THROMBUS, ORGANIZED | | | 1 (2%) | |
| ABSCESS, NOS | | | 2 (4%) | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (20) | (19) | (49) | (50) |
| PNEUMONIA, CHRONIC MURINE | 16 (80%) | 11 (58%) | 30 (61%) | 32 (64%) |
| CALCIUM DEPOSIT | | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | | |
| #SPLEEN | (19) | (19) | (47) | (50) |
| HEMATOPOIESIS | 1 (5%) | 1 (5%) | | |
| CIRCULATORY SYSTEM | | | | |
| #HEART | (20) | (19) | (49) | (50) |
| CALCIUM DEPOSIT | 2 (10%) | | 4 (8%) | 1 (2%) |
| #MYOCARDIUM | (20) | (19) | (49) | (50) |
| FIBROSIS | 1 (5%) | 2 (11%) | 4 (8%) | 1 (2%) |
| DEGENERATION, NOS | | 2 (11%) | 5 (10%) | 1 (2%) |
| #ENDOCARDIUM | (20) | (19) | (49) | (50) |
| HYPEREPLASIA, NOS | 1 (5%) | | | 1 (2%) |

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

TABLE C1 (CONTINUED)

| | CONTROL (UNTR) 01-141M | CONTROL (VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| *AORTA | (20) | (20) | (49) | (50) |
| MEDIAL CALCIFICATION | 3 (15%) | 4 (20%) | 9 (18%) | 2 (4%) |
| *CORONARY ARTERY | (20) | (20) | (49) | (50) |
| MEDIAL CALCIFICATION | 2 (10%) | 2 (10%) | | |
| *MESENTERIC ARTERY | (20) | (20) | (49) | (50) |
| MEDIAL CALCIFICATION | 1 (5%) | 2 (10%) | 3 (6%) | 2 (4%) |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (20) | (20) | (49) | (50) |
| THROMBUS, ORGANIZED | | | 1 (2%) | |
| INFLAMMATION, NOS | 1 (5%) | | | |
| PELIOSIS HEPATIS | | 1 (5%) | | 1 (2%) |
| METAMORPHOSIS FATTY | 1 (5%) | 2 (10%) | 2 (4%) | 2 (4%) |
| *BILE DUCT | (20) | (20) | (49) | (50) |
| HYPERPLASIA, NOS | | 1 (5%) | 3 (6%) | |
| #PANCREAS | (19) | (19) | (48) | (45) |
| PERIARTERITIS | | | 2 (4%) | |
| #ESOPHAGUS | (19) | (20) | (49) | (50) |
| RUPTURE | | | | 2 (4%) |
| INFLAMMATION, NOS | | | | 2 (4%) |
| #STOMACH | (20) | (20) | (49) | (50) |
| INFLAMMATION, FOCAL | | 1 (5%) | | |
| CALCIUM DEPOSIT | 3 (15%) | 3 (15%) | 5 (10%) | 1 (2%) |
| URINARY SYSTEM | | | | |
| #KIDNEY | (19) | (20) | (49) | (50) |
| PYELONEPHRITIS, NOS | 2 (11%) | 1 (5%) | | |
| INFLAMMATION, CHRONIC | 13 (68%) | 11 (55%) | 23 (47%) | 8 (16%) |
| CALCIUM DEPOSIT | 1 (5%) | | 5 (10%) | 2 (4%) |
| #URINARY BLADDER | (19) | (18) | (48) | (37) |
| INFLAMMATION, NOS | 1 (5%) | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | | |
| #ADRENAL | (19) | (19) | (48) | (49) |
| CYST, NOS | | 1 (5%) | | |

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

TABLE C1 (CONTINUED)

| | CONTROL (UNTR) 01-141M | CONTROL (VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| THROMBUS, ORGANIZED | | | 1 (2%) | |
| #ADRENAL CORTEX | (19) | (19) | (48) | (49) |
| DEGENERATION, NOS | | 1 (5%) | 2 (4%) | 1 (2%) |
| #ADRENAL MEDULLA | (19) | (19) | (48) | (49) |
| CYST, NOS | | 1 (5%) | | |
| #THYROID | (19) | (17) | (43) | (37) |
| FOLLICULAR CYST, NOS | 1 (5%) | | 4 (9%) | 1 (3%) |
| HYPERPLASIA, FOLLICULAR-CELL | | | 1 (2%) | |
| #PARATHYROID | (19) | (10) | (41) | (23) |
| HYPERPLASIA, NOS | 1 (5%) | 3 (30%) | 4 (10%) | 1 (4%) |
| REPRODUCTIVE SYSTEM | | | | |
| #PROSTATE | (19) | (19) | (39) | (25) |
| INFLAMMATION, NOS | 2 (11%) | 2 (11%) | 3 (8%) | |
| #TESTIS | (19) | (19) | (48) | (50) |
| CALCIUM DEPOSIT | | | 4 (8%) | 1 (2%) |
| CALCIFICATION, NOS | | | 1 (2%) | |
| ATROPHY, NOS | 8 (42%) | 4 (21%) | 11 (23%) | 6 (12%) |
| *EPIDIDYMIS | (20) | (20) | (49) | (50) |
| EPIDERMAL INCLUSION CYST | | | 1 (2%) | |
| NECROSIS, FAT | | 2 (10%) | 4 (8%) | |
| NERVOUS SYSTEM | | | | |
| NONE | | | | |
| SPECIAL SENSE ORGANS | | | | |
| *EYE/CORNEA | (20) | (20) | (49) | (50) |
| INFLAMMATION, NOS | | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | | |
| *SKELETAL MUSCLE | (20) | (20) | (49) | (50) |
| INFLAMMATION, NOS | 1 (5%) | | | |

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

TABLE C1 (CONCLUDED)

| | CONTROL (UNTR) 01-141M | CONTROL (VEH) 01-111M | LOW DOSE 01-112M | HIGH DOSE 01-113M |
|---|---|---|---|---|
| BODY CAVITIES | | | | |
| *PERICARDIUM | (20) | (20) | (49) | (50) |
| INFLAMMATION, NOS | | 2 (10%) | 1 (2%) | |
| *MESENTERY | (20) | (20) | (49) | (50) |
| PERIARTERITIS | 2 (10%) | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | | |
| NO LESION REPORTED | | 1 | 7 | 10 |
| AUTOLYSIS/NO NECROPSY | | | 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 IODOFORM

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS NECROPSIED | 20 | 20 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 20 | 20 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | | |
| *SKIN | (20) | (20) | (50) | (50) |
| INFLAMMATION, NOS | 1 (5%) | | 1 (2%) | |
| HYPERKERATOSIS | | | 1 (2%) | |
| *SUBCUT TISSUE | (20) | (20) | (50) | (50) |
| ABSCESS, NOS | | | 2 (4%) | |
| NECROSIS, FAT | | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (20) | (20) | (50) | (50) |
| PNEUMONIA, CHRONIC MURINE | 19 (95%) | 18 (90%) | 37 (74%) | 37 (74%) |
| HEMATOPOIETIC SYSTEM | | | | |
| #SPLEEN | (20) | (20) | (49) | (50) |
| LEUKOCYTOSIS, NOS | | | | 1 (2%) |
| HEMATOPOIESIS | 3 (15%) | | | 3 (6%) |
| #CERVICAL LYMPH NODE | (20) | (18) | (44) | (44) |
| INFLAMMATION, NOS | | | 1 (2%) | 1 (2%) |
| #THYMUS | (16) | (13) | (34) | (26) |
| CYST, NOS | | | 2 (6%) | |
| INFLAMMATION, NOS | | | 1 (3%) | |
| CIRCULATORY SYSTEM | | | | |
| #MYOCARDIUM | (20) | (20) | (50) | (49) |
| INFLAMMATION, NOS | | | 3 (6%) | |
| #ENDOCARDIUM | (20) | (20) | (50) | (49) |
| HYPERPLASIA, NOS | 1 (5%) | | | |

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

TABLE C2 (CONTINUED)

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| *AORTA | (20) | (20) | (50) | (50) |
| MEDIAL CALCIFICATION | 1 (5%) | | | |
| DIGESTIVE SYSTEM | | | | |
| #SALIVARY GLAND | (16) | (17) | (27) | (34) |
| CYST, NOS | | 1 (6%) | | |
| #LIVER | (20) | (20) | (49) | (49) |
| INFLAMMATION, NOS | 1 (5%) | | 1 (2%) | |
| PELIOSIS HEPATIS | | | | 1 (2%) |
| METAMORPHOSIS FATTY | 2 (10%) | 1 (5%) | 4 (8%) | |
| #LIVER/PERIPORTAL | (20) | (20) | (49) | (49) |
| METAMORPHOSIS FATTY | | | 1 (2%) | |
| *BILE DUCT | (20) | (20) | (50) | (50) |
| HYPERPLASIA, NOS | 2 (10%) | 1 (5%) | | 1 (2%) |
| #ESOPHAGUS | (20) | (20) | (50) | (45) |
| INFLAMMATION, NOS | | | 3 (6%) | |
| #STOMACH | (20) | (20) | (48) | (50) |
| ULCER, FOCAL | 3 (15%) | | 2 (4%) | |
| #COLON | (20) | (18) | (34) | (33) |
| NEMATODIASIS | | | | 1 (3%) |
| URINARY SYSTEM | | | | |
| #KIDNEY | (20) | (20) | (49) | (50) |
| HYDRONEPHROSIS | | | | 1 (2%) |
| PYELONEPHRITIS, NOS | | 1 (5%) | | |
| INFLAMMATION, CHRONIC | 6 (30%) | 1 (5%) | 10 (20%) | 5 (10%) |
| CALCIUM DEPOSIT | 1 (5%) | 1 (5%) | 4 (8%) | |
| #URINARY BLADDER | (20) | (20) | (40) | (41) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | | |
| #ADRENAL | (20) | (20) | (49) | (50) |
| CALCIUM DEPOSIT | 1 (5%) | | | |

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

TABLE C2 (CONTINUED)

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| ANGIECTASIS | | 2 (10%) | | 1 (2%) |
| #ADRENAL CORTEX | (20) | (20) | (49) | (50) |
| DEGENERATION, NOS | | 3 (15%) | 1 (2%) | 6 (12%) |
| ANGIECTASIS | 5 (25%) | 1 (5%) | 3 (6%) | 1 (2%) |
| #THYROID | (19) | (20) | (40) | (42) |
| FOLLICULAR CYST, NOS | 2 (11%) | 2 (10%) | 2 (5%) | 2 (5%) |
| HYPERPLASIA, C-CELL | | | | 1 (2%) |
| HYPERPLASIA, FOLLICULAR-CELL | | | | 1 (2%) |
| #PARATHYROID | (20) | (13) | (50) | (33) |
| HYPERPLASIA, NOS | | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | | |
| *MAMMARY GLAND | (20) | (20) | (50) | (50) |
| NECROSIS, FAT | 1 (5%) | | | |
| *VAGINA | (20) | (20) | (50) | (50) |
| INFLAMMATION, NOS | 1 (5%) | | | |
| POLYP, INFLAMMATORY | | 1 (5%) | | |
| #UTERUS | (20) | (19) | (47) | (48) |
| HYDROMETRA | | | 2 (4%) | 1 (2%) |
| INFLAMMATION, NOS | | | 1 (2%) | 1 (2%) |
| PYOMETRA | | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (20) | (19) | (47) | (48) |
| INFLAMMATION, NOS | 2 (10%) | | | |
| HYPERPLASIA, CYSTIC | | | 1 (2%) | 1 (2%) |
| #OVARY/OVIDUCT | (20) | (19) | (47) | (48) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| #OVARY | (20) | (19) | (47) | (50) |
| CYST, NOS | 1 (5%) | 1 (5%) | 2 (4%) | 1 (2%) |
| NERVOUS SYSTEM | | | | |
| #BRAIN/MENINGES | (20) | (20) | (50) | (50) |
| INFLAMMATION, NOS | | | 1 (2%) | |
| SPECIAL SENSE ORGANS | | | | |
| *EYE | (20) | (20) | (50) | (50) |
| SYNECHIA, POSTERIOR | | | | 1 (2%) |

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

TABLE C2 (CONCLUDED)

| | CONTROL (UNTR) 01-141F | CONTROL (VEH) 01-111F | LOW DOSE 01-114F | HIGH DOSE 01-115F |
|---|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| *PERICARDIUM | (20) | (20) | (50) | (50) |
| INFLAMMATION, NOS | | 2 (10%) | 4 (8%) | 1 (2%) |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | | |
| NO LESION REPORTED | | | 3 | 5 |

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

# APPENDIX D

## SUMMARY OF THE INCIDENCE OF NQNNEOPLASTIC LESIONS IN MICE TREATED WITH IODOFORM

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH IODOFORM

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS MISSING | 1 | | | |
| ANIMALS NECROPSIED | 15 | 19 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 15 | 19 | 49 | 50 |
| INTEGUMENTARY SYSTEM | | | | |
| *SKIN | (15) | (19) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | 1 (2%) | |
| ABSCESS, CHRONIC | 1 (7%) | | | |
| *SUBCUT TISSUE | (15) | (19) | (50) | (50) |
| EDEMA, NOS | 1 (7%) | | | |
| ABSCESS, NOS | | 1 (5%) | | |
| GRANULOMA, NOS | | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | | |
| #TRACHEA | (15) | (19) | (44) | (40) |
| INFLAMMATION, NOS | | | | 1 (3%) |
| #LUNG | (15) | (19) | (50) | (49) |
| CONGESTION, NOS | 9 (60%) | | | 2 (4%) |
| INFLAMMATION, NOS | 1 (7%) | | | |
| PNEUMONIA, CHRONIC MURINE | | 2 (11%) | 13 (26%) | 12 (24%) |
| HEMATOPOIETIC SYSTEM | | | | |
| #BONE MARROW | (15) | (19) | (48) | (48) |
| NECROSIS, NOS | | | 1 (2%) | |
| HYPERPLASIA, HEMATOPOIETIC | 1 (7%) | | | |
| #SPLEEN | (15) | (19) | (50) | (50) |
| AMYLOIDOSIS | 7 (47%) | 2 (11%) | 9 (18%) | 5 (10%) |
| HYPERPLASIA, LYMPHOID | 1 (7%) | | | 1 (2%) |
| #LYMPH NODE | (15) | (19) | (48) | (45) |
| CONGESTION, NOS | 2 (13%) | | | |
| LYMPHOID DEPLETION | 1 (7%) | | | |

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

TABLE D1 (CONTINUED)

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| HYPERPLASIA, LYMPHOID | 1 (7%) | | 1 (2%) | |
| #CERVICAL LYMPH NODE | (15) | (19) | (48) | (45) |
| CYST, NOS | | | 1 (2%) | |
| ANGIECTASIS | | 1 (5%) | | |
| #SUPERIOR DEEP CERVIC | (15) | (19) | (48) | (45) |
| ANGIECTASIS | | 1 (5%) | | |
| #BRONCHIAL LYMPH NODE | (15) | (19) | (48) | (45) |
| ABSCESS, NOS | | | | 1 (2%) |
| #MESENTERIC L. NODE | (15) | (19) | (48) | (45) |
| CONGESTION, NOS | | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | | | | 2 (4%) |
| CIRCULATORY SYSTEM | | | | |
| #HEART | (15) | (19) | (50) | (50) |
| MINERALIZATION | | | 3 (6%) | |
| *AORTA | (15) | (19) | (50) | (50) |
| INFLAMMATION, ACUTE | 1 (7%) | | | |
| DIGESTIVE SYSTEM | | | | |
| #SALIVARY GLAND | (15) | (18) | (48) | (40) |
| CYST, NOS | | | | 1 (3%) |
| #LIVER | (15) | (19) | (49) | (50) |
| INFARCT, NOS | | | 1 (2%) | 1 (2%) |
| AMYLOIDOSIS | 7 (47%) | 2 (11%) | 6 (12%) | 2 (4%) |
| ANGIECTASIS | 1 (7%) | | | |
| #LIVER/CENTRILOBULAR | (15) | (19) | (49) | (50) |
| NECROSIS, NOS | | | | 1 (2%) |
| NECROSIS, FOCAL | | | 1 (2%) | |
| #PANCREAS | (15) | (19) | (50) | (49) |
| AMYLOIDOSIS | | | 6 (12%) | |
| #ESOPHAGUS | (15) | (19) | (50) | (48) |
| RUPTURE | | | | 1 (2%) |
| INFLAMMATION, SUPPURATIVE | | | | 1 (2%) |

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

TABLE D1 (CONTINUED)

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| #STOMACH | (15) | (19) | (50) | (49) |
| HYPERKERATOSIS | | | | 1 (2%) |
| #LARGE INTESTINE | (15) | (19) | (48) | (47) |
| NEMATODIASIS | | | 2 (4%) | |
| #COLON | (15) | (19) | (48) | (47) |
| NEMATODIASIS | | 3 (16%) | | |
| URINARY SYSTEM | | | | |
| #KIDNEY | (15) | (19) | (50) | (50) |
| MINERALIZATION | | | 1 (2%) | |
| HYDRONEPHROSIS | | 1 (5%) | | |
| LYMPHOCYTIC INFILTRATE | 2 (13%) | | | |
| PYELONEPHRITIS SUPPURATIVE | | | 2 (4%) | |
| INFLAMMATION, ACUTE SUPPURATIVE | 2 (13%) | | | |
| INFLAMMATION, CHRONIC | 4 (27%) | 1 (5%) | 9 (18%) | 6 (12%) |
| FIBROSIS, DIFFUSE | 2 (13%) | | | |
| AMYLOIDOSIS | 3 (20%) | | | |
| CALCIFICATION, FOCAL | | | | 1 (2%) |
| #KIDNEY/TUBULE | (15) | (19) | (50) | (50) |
| CYTOPLASMIC VACUOLIZATION | 2 (13%) | | | |
| #URINARY BLADDER | (15) | (19) | (50) | (49) |
| INFLAMMATION, NOS | | 1 (5%) | | |
| HYPERPLASIA, EPITHELIAL | | | | 3 (6%) |
| ENDOCRINE SYSTEM | | | | |
| #ADRENAL | (15) | (19) | (50) | (50) |
| AMYLOIDOSIS | 3 (20%) | | | 2 (4%) |
| #THYROID | (15) | (17) | (41) | (38) |
| HYPERPLASIA, FOLLICULAR-CELL | | | 2 (5%) | |
| REPRODUCTIVE SYSTEM | | | | |
| #PROSTATE | (15) | (18) | (50) | (50) |
| INFLAMMATION, ACUTE | 1 (7%) | | | |
| GRANULOMA, SPERMATIC | | | | 1 (2%) |

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

TABLE DI (CONTINUED)

| | CONTROL (UNTR) 02-M121 | CONTROL (VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| #TESTIS | (15) | (18) | (49) | (50) |
| ATROPHY, NOS | | | 1 (2%) | |
| *EPIDIDYMIS | (15) | (19) | (50) | (50) |
| GRANULOMA, SPERMATIC | | 1 (5%) | | |
| NECROSIS, FAT | | | 2 (4%) | |
| NERVOUS SYSTEM | | | | |
| #BRAIN/MENINGES | (15) | (19) | (50) | (48) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| INFLAMMATION, ACUTE | 1 (7%) | | | |
| #BRAIN/EPENDYMA | (15) | (19) | (50) | (48) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| #BRAIN | (15) | (19) | (50) | (48) |
| COMPRESSION | | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | | |
| *EYE | (15) | (19) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | | 1 (2%) |
| *EYE/CORNEA | (15) | (19) | (50) | (50) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| *PLEURA | (15) | (19) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | | 1 (2%) |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |

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

TABLE DI (CONCLUDED)

| | CONTROL(UNTR) 02-M121 | CONTROL(VEH) 02-M111 | LOW DOSE 02-M112 | HIGH DOSE 02-M113 |
|---|---|---|---|---|
| SPECIAL MORPHOLOGY SUMMARY | | | | |
| NO LESION REPORTED | 1 | 8 | 12 | 13 |
| ANIMAL MISSING/NO NECROPSY | 1 | | | |
| AUTO/NECROPSY/NO HISTO | | | 1 | |
| AUTOLYSIS/NO NECROPSY | 4 | 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 IODOFORM

| | CONTROL (UNTR) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 20 | 20 | 50 | 50 |
| ANIMALS MISSING | | | | 2 |
| ANIMALS NECROPSIED | 18 | 20 | 49 | 45 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY** | 18 | 20 | 49 | 45 |
| INTEGUMENTARY SYSTEM | | | | |
| *SKIN | (18) | (20) | (49) | (45) |
| ACANTHOSIS | 8 (44%) | | | |
| RESPIRATORY SYSTEM | | | | |
| #TRACHEA | (18) | (20) | (47) | (44) |
| INFLAMMATION, NOS | | | 1 (2%) | 1 (2%) |
| *LUNG | (18) | (20) | (49) | (45) |
| CONGESTION, NOS | 9 (50%) | | | |
| EDEMA, NOS | 1 (6%) | | | |
| HEMORRHAGE | | | 1 (2%) | 3 (7%) |
| INFLAMMATION, NOS | 4 (22%) | | | |
| PNEUMONIA, CHRONIC MURINE | 1 (6%) | 2 (10%) | 5 (10%) | 4 (9%) |
| HEMATOPOIETIC SYSTEM | | | | |
| #BONE MARROW | (18) | (20) | (49) | (45) |
| HEMORRHAGE | 1 (6%) | | | |
| HYPERPLASIA, HEMATOPOIETIC | 2 (11%) | | | |
| #SPLEEN | (18) | (20) | (49) | (45) |
| INFLAMMATION, ACUTE | 1 (6%) | | | |
| AMYLOIDOSIS | | | 1 (2%) | |
| HYPERPLASIA, RETICULUM CELL | | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | 5 (28%) | | 1 (2%) | 2 (4%) |
| #LYMPH NODE | (18) | (20) | (47) | (45) |
| INFLAMMATION, CHRONIC | 1 (6%) | | | |
| HYPERPLASIA, LYMPHOID | 2 (11%) | | | |
| #CERVICAL LYMPH NODE | (18) | (20) | (47) | (45) |
| INFLAMMATION, NOS | | | 1 (2%) | |

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

TABLE D2 (CONTINUED)

| | CONTROL (UNTR) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| HYPERPLASIA, LYMPHOID | | | 2 (4%) | |
| #MESENTERIC L. NODE | (18) | (20) | (47) | (45) |
| INFLAMMATION, NOS | | | 2 (4%) | |
| ANGIECTASIS | | | | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | | 2 (4%) | 2 (4%) |
| CIRCULATORY SYSTEM | | | | |
| #HEART | (18) | (20) | (49) | (45) |
| PERIARTERITIS | | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (18) | (20) | (49) | (45) |
| THROMBUS, ORGANIZED | | | | 1 (2%) |
| LYMPHOCYTIC INFILTRATE | 2 (11%) | | | |
| INFLAMMATION, ACUTE/CHRONIC | 1 (6%) | | | |
| NECROSIS, NOS | | | 1 (2%) | |
| INFARCT, NOS | | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | | | 2 (4%) |
| #LIVER/CENTRILOBULAR | (18) | (20) | (49) | (45) |
| NECROSIS, NOS | | | 1 (2%) | |
| #PANCREAS | (18) | (20) | (49) | (45) |
| CYSTIC DUCTS | | | 6 (12%) | 2 (4%) |
| ATROPHY, NOS | | | 1 (2%) | |
| #PANCREATIC DUCT | (18) | (20) | (49) | (45) |
| DILATATION, NOS | | 1 (5%) | | |
| #PANCREATIC ACINUS | (18) | (20) | (49) | (45) |
| ATROPHY, NOS | | | 1 (2%) | |
| #STOMACH | (18) | (20) | (49) | (45) |
| INFLAMMATION, FOCAL | | | | 1 (2%) |
| ULCER, ACUTE | 1 (6%) | | | |
| #SMALL INTESTINE | (18) | (20) | (49) | (45) |
| HYPERPLASIA, LYMPHOID | 1 (6%) | | | |
| #COLON | (18) | (20) | (48) | (43) |
| NEMATODIASIS | | 3 (15%) | | |

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

TABLE D2 (CONTINUED)

| | CONTROL (UNTR) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| URINARY SYSTEM | | | | |
| #KIDNEY | (18) | (20) | (49) | (45) |
| HYDRONEPHROSIS | 1 (6%) | | | |
| CYST, NOS | | | | 1 (2%) |
| PYELONEPHRITIS, NOS | | 1 (5%) | | |
| LYMPHOCYTIC INFILTRATE | 4 (22%) | | | |
| INFLAMMATION, CHRONIC | 1 (6%) | | 1 (2%) | |
| ATROPHY, NOS | | 1 (5%) | | |
| #URINARY BLADDER | (18) | (19) | (48) | (44) |
| LYMPHOCYTIC INFILTRATE | 1 (6%) | | | |
| ENDOCRINE SYSTEM | | | | |
| #ADRENAL CORTEX | (18) | (20) | (49) | (45) |
| DEGENERATION, NOS | | | | 1 (2%) |
| HYPERPLASIA, NOS | 1 (6%) | | | |
| REPRODUCTIVE SYSTEM | | | | |
| *MAMMARY GLAND | (18) | (20) | (49) | (45) |
| GALACTOCELE | | | 1 (2%) | |
| #UTERUS | (18) | (20) | (48) | (44) |
| HYDROMETRA | | 2 (10%) | 2 (4%) | 1 (2%) |
| INFLAMMATION, NOS | | 2 (10%) | | |
| PYOMETRA | | | 1 (2%) | |
| INFLAMMATION, ACUTE SUPPURATIVE | 1 (6%) | | | |
| ANGIECTASIS | | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (18) | (20) | (48) | (44) |
| HYPERPLASIA, CYSTIC | 15 (83%) | 9 (45%) | 39 (81%) | 41 (93%) |
| #OVARY | (18) | (20) | (49) | (44) |
| CYST, NOS | 2 (11%) | 2 (10%) | 4 (8%) | 7 (16%) |
| FOLLICULAR CYST, NOS | 1 (6%) | | 1 (2%) | 6 (14%) |
| ABSCESS, NOS | | | | 1 (2%) |
| ATROPHY, NOS | 2 (11%) | | | |
| NERVOUS SYSTEM | | | | |
| #BRAIN | (16) | (20) | (49) | (45) |
| MALACIA | | | | 1 (2%) |

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

TABLE D2 (CONCLUDED)

| | CONTROL (UNTR) 02-F121 | CONTROL (VEH) 02-F111 | LOW DOSE 02-F114 | HIGH DOSE 02-F115 |
|---|---|---|---|---|
| SPECIAL SENSE ORGANS | | | | |
| *EYE | (18) | (20) | (49) | (45) |
| PHTHISIS BULBI | | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| *PERITONEUM | (18) | (20) | (49) | (45) |
| INFLAMMATION, NOS | | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | | |
| *MULTIPLE ORGANS | (18) | (20) | (49) | (45) |
| AMYLOIDOSIS | | | 1 (2%) | |
| SPECIAL MORPHOLOGY SUMMARY | | | | |
| NO LESION REPORTED | | 2 | 1 | 2 |
| ANIMAL MISSING/NO NECROPSY | | | | 2 |
| AUTOLYSIS/NO NECROPSY | 2 | | 1 | 3 |

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

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

April 26, 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 Iodoform for carcinogenicity.

The primary reviewer said that the study did not provide evidence that Iodoform was carcinogenic in rats or mice, under the conditions of test. After a brief description of the experimental design, he commented that the subchronic study was deficient in that it provided little help in establishing chronic dose levels. He noted the numerous dose changes which occurred during the chronic phase and the fact that a maximum tolerated dose may not have been achieved. The only statistically significant neoplasm observed was a follicular-cell tumor of the thyroid in low dose male rats.

The secondary reviewer opined that the dose levels administered were sufficiently high, based on an inspection of survival curves. He concurred with the conclusion in the report that Iodoform was not carcinogenic under the conditions of test.

It was moved that the report on the bioassay of Iodoform be accepted as written. The motion was seconded and approved unanimously.

Members present were:

Michael Shimkin (Acting Chairman), University of California at San Diego
Joseph Highland, Environmental Defense Fund
George Roush, Jr., Monsanto Company
Louise Strong, University of Texas Health Sciences Center
John Weisburger, American Health Foundation

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

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