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BIOASSAY OF DIBENZO-p-DIOXIN FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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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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FOREWORD: This report presents the results of the bioassay of dibenzo-p-dioxin conducted for the Carcinogenesis Testing Program, Divison of Cancer Cause and Prevention, National Cancer Institute (NCI), 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 greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as 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 that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic for animals requires a wider analysis.

CONTRIBUTORS: The bioassay of dibenzo-p-dioxin was conducted at the Illinois Institute of Technology Research Institute (IITRI), Chicago, Illinois, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program.

The project director was Mr. A. Shefner (1), Dr. M. E. King (1) was the principal investigator for this study, and Dr. P. Holmes (1) assembled the data. Doses of the test chemical were selected by Dr. King, Mr. Shefner, and Dr. R. R. Bates (2,3). Mr. T. Kruckeberg (1) and Mr. K. Kaltenborn (1) were in charge of animal care.

Histopathologic examinations were performed by Dr. A. R. Roesler (1). Tumor diagnoses were reviewed by Dr. R. L. Schueler (4), who also prepared the interpretive pathology summary included in this report. Pathologists at NCI and at Tracor Jitco have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (5). The statistical analyses were performed by Dr. J. R. Joiner (4), and Ms. P. L. Yong (4) using methods selected for the bioassay program by Dr. J. J. Gart (6). Chemicals used in this bioassay were synthesized and analyzed under the direction of Dr. A. Gray (1), with the assistance of Mr. S. Cepa (1) and Mr. V. DaPinto (1). Further analyses were conducted under the direction of Dr. E. Murrill (7). The results of the analytical work were reviewed by Dr. S. S. Olin (4).

This report was prepared at Tracor Jitco (4) under the direction of Dr. L. A. Campbell , Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Waitz, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

The following scientists at NCI (2) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of dibenzo-p-dioxin (UDD) for possible carcinogenicity was conducted by administering the test chemical in feed to Osborne-Mendel rats and B6C3F1 mice.

Groups of 35 rats of each sex were administered UDD at one of two doses, either 5,000 or 10,000 ppm, for 110 weeks. Groups of 50 mice of each sex were administered the same doses for 87 or 90 weeks. Controls consisted of groups of 35 untreated rats of each sex and 50 untreated mice of each sex. All surviving male rats were killed at 110 weeks, all surviving female rats at 111 to 117 weeks, all surviving male mice at 92 to 97 weeks, and all surviving female mice at 91 to 93 weeks.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls; the depression in the amount of weight gained in the dosed male mice was, however, relatively slight. Except for the male rats, survival at the end of the bioassay was lower in the dosed groups of both rats or mice than in the corresponding control groups. At week 90, at least 57% of the rats and 54% of the mice were still alive. Because the mean body weights and survival rats of the dosed animals were lower than those of corresponding controls and because there was an increase in the incidence of hepatotoxic lesions, the 10,000-ppm concentration administered to the rats and mice is considered to be maximum tolerated dose.

No tumors were induced in rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

It is concluded that under the conditions of this bioassay, UDD was not carcinogenic for Osborne-Mendel rats or B6C3F1 mice.

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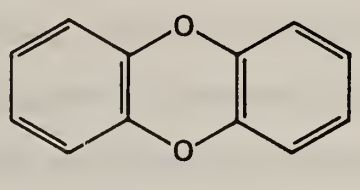
I. INTRODUCTION

Unsubstituted dibenzo-p-dioxin, (CAS 262-12-4; NCI C03656) is an analog of a series of chlorinated dibenzo-p-dioxins that were selected for carcinogenesis testing. The synonym for unsubstituted dibenzo-p-dioxin -- UDD -- is used throughout this report. The chlorinated compounds are formed as unwanted by-products during the synthesis of chlorophenols, and were discovered in the late 1960's as contaminants in the industrial microbicide pentachlorophenol, and in a widely used agricultural herbicide, 2,4,5-trichloro- phenoxyacetic acid (2,4,5-T) (Crossland and Shea, 1973). Certain members of the chlorinated series were shown to be highly toxic and teratogenic (Sparschu et al., 1971; Schwetz et al., 1973). Chronic carcinogenicity studies were begun with these compounds because of evidence that they were both widely distributed and persistent in the environment (Kearney et al., 1972). The unsubstituted dibenzo-p-dioxin has been reported to be a photodecomposition product of chlorinated dibenzo-p-dioxins (Crosby et al., 1971; Kearney et al., 1972).



Dibenzo-p-dioxin

Except for a preliminary report of the present bioassay (King et al., 1973), no previous information is available on the toxicity of UDD. Studies for the acute and subacute toxicities of the 2,7-dichloro-, 2,3,7,8-tetrachloro-, hexachloro-, and octachlorodibenzo-p-dioxin analogs of UDD have shown that the 2,3,7,8-tetrachloro analog (TCDD) is the most toxic, having an LD_{50} of 0.022 mg/kg in Sherman rats (Schwetz et al., 1973). The principal target organs of TCDD in rats, guinea pigs, and mice are the liver and thymus (International Agency for Research on Cancer, 1977), and evidence has been presented for the induction of carcinomas of the ear duct, kidney, and liver by TCDD administered in the diet to Sprague-Dawley rats (Van Miller et al., 1977).

The series of chlorinated dibenzodioxins was selected for carcinogenesis testing because of the wide distribution of some of them in the environment and the possibility of their entrance into the food chain, causing long-term human exposure. UDD was included in the series because of interest in it as the unsubstituted analog.

II. MATERIALS AND METHODS

A. Chemical

The batch of UDD used for this bioassay was synthesized by the IITRI Chemistry Division. Analysis by Midwest Research Institute, Kansas City, Missouri, confirmed the identity of the chemical and indicated a purity of approximately 99.5% by vapor-phase chromatography (vpc). Results of mass spectrometry suggested a phenoxydibenzo-p-dioxin structure for an impurity accounting for 0.5% of the total vpc peak area. One other trace impurity (less than 0.02%) was detected by vpc, but no chlorinated compounds were detected. Elemental analyses were correct for $C_{12}H_8O_2$, the molecular formula of UDD. The melting point of this white crystalline material was 124.5 to 126.0°C (120 to 122°C given in the literature [Gilman and Dietrich, 1957]). Infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with the spectra given in Sadtler Standard Spectra (Sadtler Research Laboratories, Philadelphia, Pa.). Hereinafter this materials is referred to as "UDD".

B. Dietary Preparation

Test diets were prepared by incorporating a known quantity of UDD into a 2-week supply of ground Wayne® Lab Blox animal feed (Allied Mills, Inc., Chicago, Ill.). Diets were mixed in a Patterson-Kelly twin-shell blender for approximately 1 hour, and were stored in sealed plastic containers at room temperature for no more than 2 weeks.

Analyses were performed to assess the accuracy of concentrations in two individual batches of test diet. These batches had been stored at room temperature and were analyzed several months after preparation. Ninety-eight percent of the expected concentration was found at the 10,000 ppm level and 80% of the expected concentration at 5,000 ppm.

C. Animals

Osborne-Mendel rats and B6C3F1 mice of each sex, obtained through a contract with the Division of Cancer Treatment, NCI, were used in the chronic study. Animals were obtained at various times from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. The rats and mice were received at the laboratory

at approximately 4 weeks of age and were placed in quarantine for 1 week. Those animals with no visible signs of disease were assigned to dosed or control groups according to a series of random numbers and were earmarked for individual identification. Due to a loss of male rats occasioned by an air-conditioning failure, all groups of male rats were restarted 1 year after the beginning of the first tests, using new groups of 4-week-old animals obtained from Charles River Breeding Laboratories and quarantined for 1 week.

D. Animal Maintenance

The rats and mice were housed in temperature- and humidity-controlled rooms. The temperature was maintained at 22 to 23°C and the relative humidity at 40 to 50%. Fluorescent lighting was provided for 12 hours each day. Air in the animal rooms was changed 15 to 20 times per hour and exchanged through fiberglass filters (Air Filter Equipment Corp., Chicago, Ill.).

The rats were housed 4 per cage and the mice 10 per cage in suspended polypropylene cages (Maryland Plastics, Federalsburg, Maryland), covered with a wire mesh screen and a polyester filter (Research Equipment Co., Inc., Bryan, Tex.). Bedding used in the

cages was Absorb-dri® hardwood chips (Lab Products, Inc., Garfield, N. J.). Tap water was available ad libitum in glass water bottles with sipper tubes and was replenished twice per week. The control animals were fed Wayne® Lab Blox animal meal (Allied Mills, Inc.), and the test animals received the same diets, to which was added the test chemical. The diets were available ad libitum and were replenished as necessary, but at least once per week.

The cages, cage lids, and water bottles were sanitized weekly at 82°C; the feed hoppers, every 2 weeks at the same temperature. The detergent used was liquid Spearhead® (Economics Laboratory, Inc., St. Paul, Minn.). The dishwasher used was a flight-type conveyor belt washer (G. S. Blakeslee & Co., Chicago, Ill). The bedding was replaced each week. The racks were washed once per month in a Metalwash Rack Washer (Metalwash Machinery Corp., Elizabeth, N. J.) and were also rotated once per month. The rats and the mice were housed in separate rooms. The untreated controls and the UDD-dosed animals were housed in the same room as animals administered the following test compounds:

Drinking Water Studies

(CAS 123-91-1) 1,4-dioxane

Feed Studies

(CAS 3268-87-9) 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin
(CAS 33857-26-0) 2,7-dichlorodibenzo-p-dioxin (DCDD)

E. Chronic Studies

The test groups, doses administered, and durations of the chronic studies are shown in tables 1 and 2. No subchronic studies were conducted. The concentrations of 5,000 and 10,000 ppm were chosen for use in the chronic studies because they were the highest amounts used in the Carcinogenesis Testing Program at the time these studies were initiated.

F. Clinical and Pathologic Examinations

All animals were observed twice daily. Body weights were measured monthly. Moribund animals and animals that survived to the end of the bioassay were killed using sodium pentobarbitol and necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization.

Table 1. UDD Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	UDD in Diet (ppm)	Time on Study Dosed (weeks)	Time on Study Observed (weeks)
Male (b)				
Control	35	0	110	0
Low-Dose	35	5,000	110	0
High-Dose	35	10,000	110	0
Female (c)				
Control	35	0	110	6-7
Low-Dose	35	5,000	110	6-7
High-Dose	35	10,000	110	1-2

(a) Rats were 5 weeks of age when placed on study.

(b) These groups were put on study 1 year after the study began, to replace the original groups of male rats that died during an air conditioning failure. The low-dose group was placed on study 8 weeks after the control group, and the high-dose group was placed on study 6 weeks after the control group.

(c) Female controls were started 4 weeks after the female dosed groups.

Table 2. UDD Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	UDD in Diet (ppm)	Time on Study Dosed (weeks)	Time on Study Observed (weeks)
Male				
Control (b)	50	0	90	2-3
Low-Dose	50	5,000	90	7
High-Dose	50	10,000	87	6-7
Female				
Control (b)	50	0	90	1-2
Low-Dose	50	5,000	90	2-3
High-Dose	50	10,000	90	1-2

(a) Mice were 5 weeks of age when placed on study.

(b) Controls were placed on study 2-1/2 weeks after the dosed groups.

The following tissues were taken at necropsy: lung, heart, liver, spleen, kidney, adrenal, gonads, brain, stomach, nasal septum, skin, and tissue masses. Two years after the start of the bioassay, a new necropsy protocol was instituted, and the tissues that were taken therefore included: skin, lymph node (mandibular and mesenteric), salivary gland, mammary gland, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroids, esophagus, stomach, duodenum, colon, liver, gall bladder (mice), pancreas, spleen, kidney, adrenal, gonads, nasal cavity, brain, pituitary, spinal cord, skeletal muscle, sciatic nerve, and tissue masses. The tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. All tissues were examined microscopically by the pathologist, except for some tissues that were lost during necropsy or histologic processing.

A few tissues from some animals were not examined, particularly from those animals that may have died early, been missing, or been in advanced states of cannibalization or autolysis. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

G. Data Recording and Statistical Analyses

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

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for

a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each

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

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

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When

such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

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

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true

binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the dosed group than in the control.

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

the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of dosed groups of male and female rats were lower than those of the corresponding control groups (figure 1). Depressions in weight gains were similar in the low- and high-dose groups of both sexes, particularly toward the end of the bioassay. Some fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation. No clinical signs other than those of lowered body weights were reported.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered UDD in the diet at the doses of this bioassay, together with those of the controls, are shown in figure 2.

In male rats, the low-dose group was started on study 8 weeks after the control group, and the high-dose group was started 6

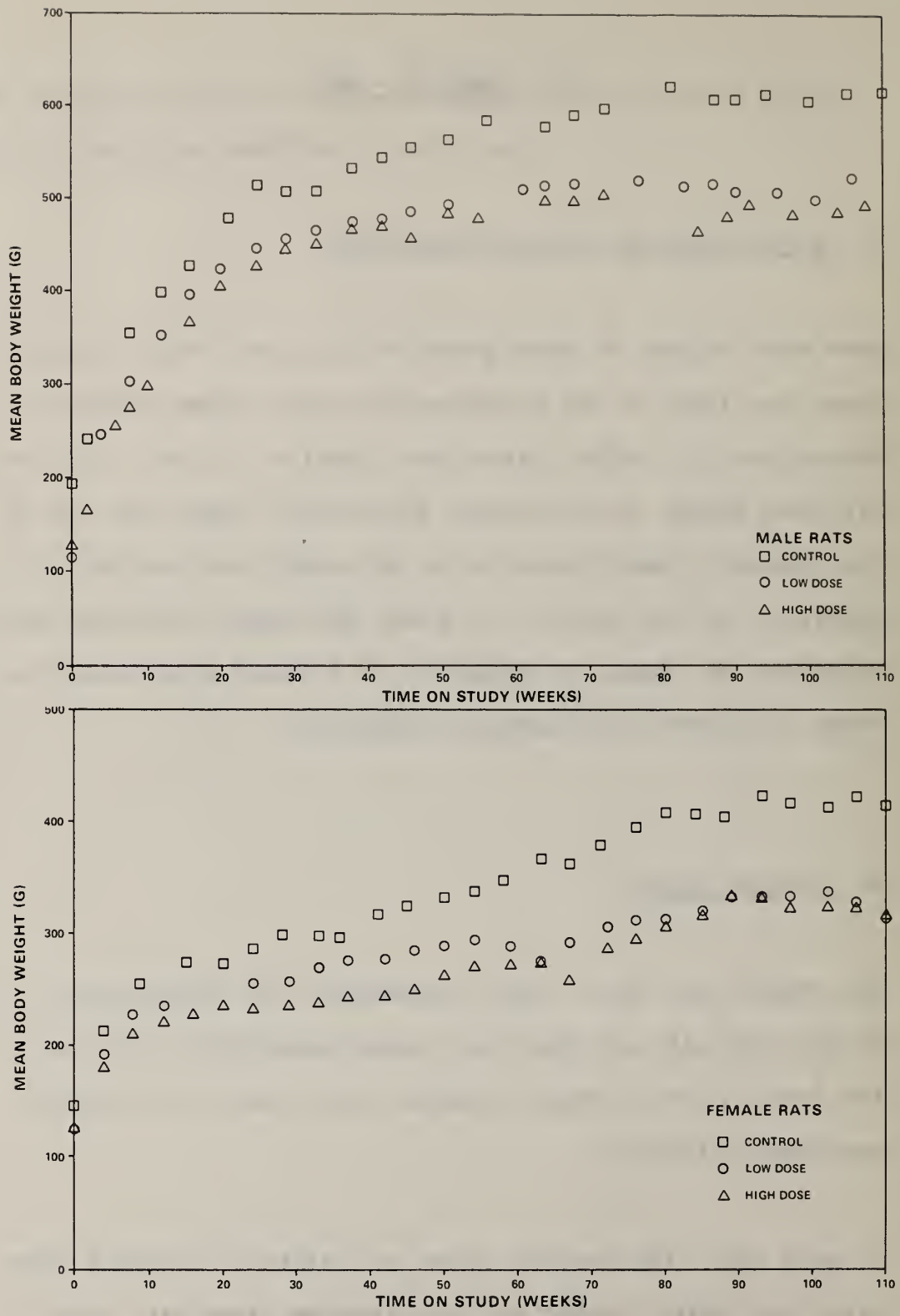


Figure 1. Growth Curves for Rats Administered UDD in the Diet

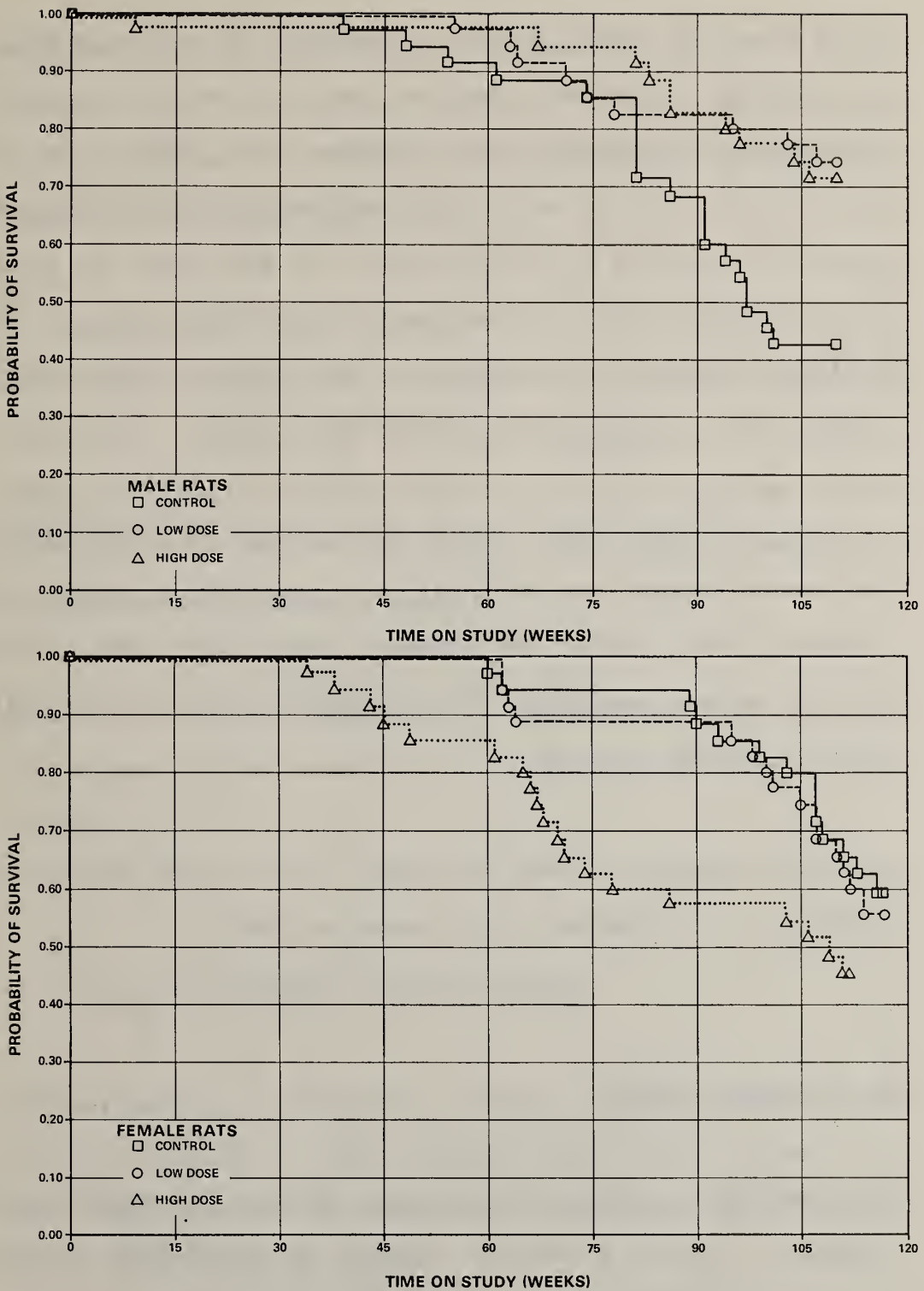


Figure 2. Survival Curves for Rats Administered UDD in the Diet

weeks after the control group. In females, the two dosed groups were started at the same time, but the controls were started 4 weeks after the dosed groups. However, the Tarone test for dose-related trend in mortality is applied as if the different groups were started at the same time. In male rats, the result of the Tarone test is significant (P = 0.011), but in the negative direction. In females, the result of the Tarone test is significant in the positive direction (P = 0.007).

In male rats, 29/35 (83%) of each dosed group, and 24/35 (69%) of the control group were still alive at week 90 on study. In females, 20/35 (57%) of the high-dose group, 31/35 (89%) of the low-dose group, and 32/35 (92%) of the control group were still alive at week 90 on study.

Sufficient numbers of dosed and control rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

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

Neoplasms occurred in a variety of tissues in dosed and control rats and were of the usual types seen in aged Osborne-Mendel rats. There was no evidence that any neoplasms were induced by administration of UDD in the diet.

In some male and more frequently in female rats there was a dose-related increase in incidence of hepatotoxic pathologic alterations characterized by fatty metamorphosis or necrosis. Other nonneoplastic lesions were of the usual types seen in aged Osborne-Mendel rats and were seen in comparable numbers in control and dosed groups of animals.

Based on the histopathologic examination, UDD was not carcinogenic in Osborne-Mendel rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In male rats, the low-dose group was started on study 8 weeks after the control group, and the high-dose group was started 6 weeks after the control group. In females, the two dosed groups were started at the same time, but the controls were started 4 weeks after the dosed groups. However, the Cochran-Armitage test for dose-related trend in the incidence of tumors is applied as if the different groups were started at the same time.

In each sex, the results of the Cochran-Armitage test and the Fisher exact test are not significant in the positive direction. In male rats, significant results in the negative direction are observed in the incidences of fibroma of the subcutaneous tissue, cortical adenoma and pheochromocytoma of the adrenal, and C-cell adenoma of the thyroid. In female rats, significant results in the negative direction are observed in the incidences of chromophobe adenoma of the pituitary, cortical adenoma or carcinoma of the adrenal, and fibroadenoma of the mammary gland. Significant results in the negative direction in the incidence of tumors in the female rats may have been occasioned by the shortened survival in the high-dose groups compared with that in the controls, but in male rats survival was lowest in the control groups.

In each of the 95% confidence intervals of relative risk, shown

in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that most of the intervals have upper limits greater than one, indicating the theoretical possibility of the induction of tumors by UDD, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male and female mice were generally lower than those of corresponding controls throughout the bioassay, although the effect of the UDD was slight in the males (figure 3). Some fluctuation in the growth curve may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation. No clinical signs other than those of lowered body weight were reported.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered UDD in the diet at the doses of this bioassay, together with those of the controls, are shown in figure 4.

In each sex, the control group was started on study 2-1/2 weeks after the dosed groups; however, the Tarone test for dose-related trend in mortality is applied as if the dosed and control groups

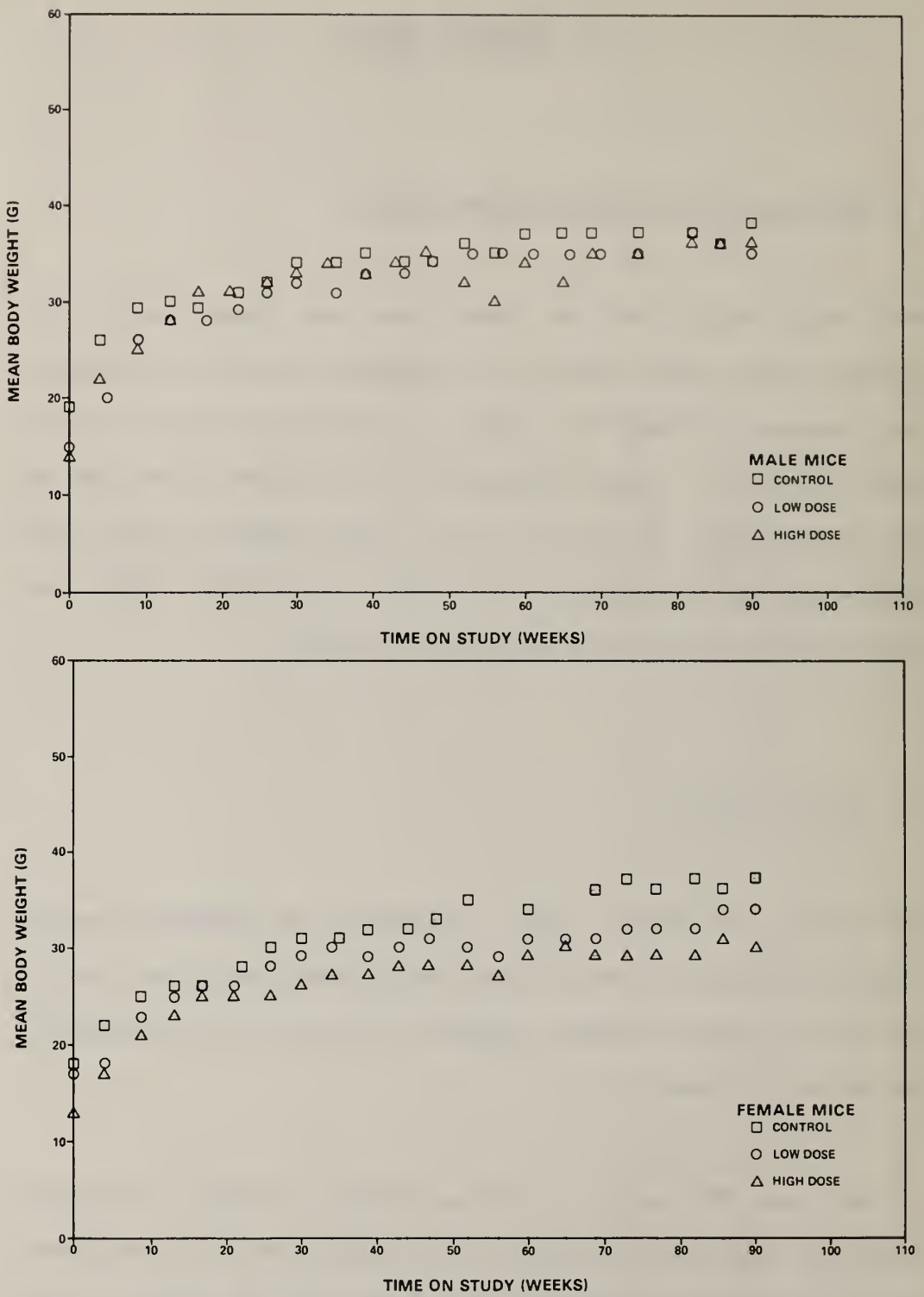


Figure 3. Growth Curves for Mice Administered UDD in the Diet

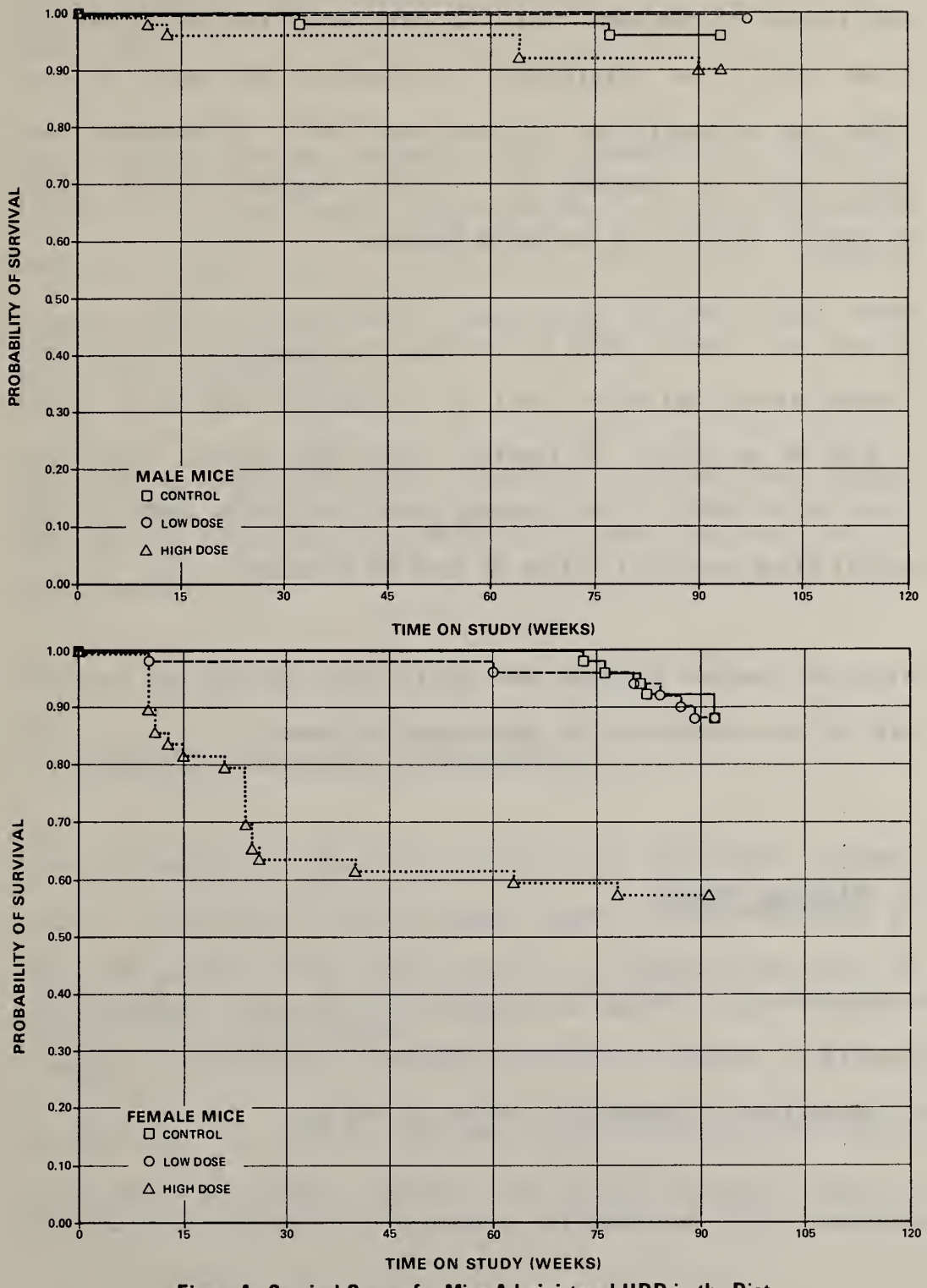


Figure 4. Survival Curves for Mice Administered UDD in the Diet

were started at the same time. In male mice, the result of the Tarone test is not significant. In females, the result of the Tarone test is significant (P less than 0.001). A departure from linear trend is observed (P = 0.006), because of the steep decrease in survival of the dosed animals.

In male mice, 46/50 (92%) of the high-dose group, all 50 of the low-dose group, and 48/50 (96%) of the controls were still alive at week 90 on study. In females, 27/50 (54%) of the high-dose group, 44/50 (88%) of the low-dose group, and 44/50 (88%) of the control group were still alive at week 90 on study.

Sufficient numbers of dosed and control mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

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

Neoplasms which occurred in a variety of tissues of dosed and

control mice were of the usual types and incidences seen in aged B6C3F1 mice.

Toxic hepatic lesions including liver degeneration, necrosis, fibrosis, and/or cirrhosis were observed in slightly increased numbers in several of the dosed mice, mainly in the high-dose females. Other nonneoplastic lesions were of the usual types seen in aged B6C3F1 mice.

Based on the histopathologic evaluation, there was no evidence that UDD was carcinogenic in B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In each sex, the control group was started on study 2-1/2 weeks after the dosed groups; however, the Cochran-Armitage test for

dose-related trend in the incidence of tumors is applied as if the dosed and control groups were started at the same time.

In male mice, the Fisher exact comparison of the incidence of alveolar/bronchiolar carcinomas between the low-dose and control groups indicates a P value of 0.027, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The result of the Cochran-Armitage test for dose-related trend in this incidence of tumors and that of the Fisher exact test comparing the incidence in the high-dose group with that in the control group are not significant.

In females, the results of the statistical tests on the incidences of tumors are not significant.

A significant dose-related trend in the negative direction is observed in the incidence of squamous-cell papillomas of the stomach in male mice, in which the incidence in the control group is 5/49 (10%), but no such tumor is observed in either of the dosed groups.

In each of the 95% confidence intervals of relative risk, shown in the tables (except for the incidence of alveolar/bronchiolar

carcinomas in the low-dose male mice), the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals (except that for the incidence of squamous-cell papilloma of the stomach in male mice) has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by UDD, which could not be detected under the conditions of this bioassay.

V. DISCUSSION

Toxicity of UDD for rats and mice at the doses of 5,000 and 10,000 ppm administered in the diet in this bioassay was indicated by lowered mean body weights and survivals of most of the dosed groups when compared with control groups. The mean body weights of the dosed male and female rats and the dosed female mice were lower than those of the corresponding controls; the depression in the amount of weight gained in the dosed male mice was, however, relatively slight. Survivals of the high-dose groups of female rats and male and female mice at the end of the bioassay were lower than those of the corresponding control groups; the survivals of the dosed groups of male rats were higher than that of the corresponding control group, but the survival of the control male rats may have been abnormally low. At week 90, at least 57% of the rats and 54% of the mice were still alive. In some male and, more frequently, female rats there was a dose-related increase in the incidence of hepatotoxic alterations characterized by fatty metamorphosis or necrosis. Also, in mice, toxic hepatic lesions including liver degeneration, necrosis, fibrosis and/or cirrhosis were observed in slightly increased numbers in the dosed mice -- particularly in the high-dose females. Thus the 10,000-ppm concentration

administered to the rats and mice is considered to be the maximum tolerated dose.

No tumors were induced in rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups.

Unlike 2,3,7,8-tetrachlorodibenzo-p-dioxin, which has been reported to be highly toxic in Sherman rats (Schwetz et al., 1973) and to be carcinogenic in Sprague-Dawley rats (Van Miller et al., 1977), UDD, the unsubstituted analog, was observed in the present bioassay to have a very low toxicity for Osborne-Mendel rats and B6C3F1 mice, and to be noncarcinogenic for both species. However, the degeneration and necrosis of the liver observed in the rats and mice administered UDD is similar to the liver damage observed in rats and mice administered TCDD (International Agency for Research on Cancer, 1977).

It is concluded that under the conditions of this bioassay, UDD was not carcinogenic for Osborne-Mendel rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED UDD IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	34	33	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	33	33	35
INTEGUMENTARY SYSTEM			
*SKIN	(34)	(33)	(35)
TRICHOEPITHELIOMA			1 (3%)
*SUBCUT TISSUE	(34)	(33)	(35)
FIBROMA	3 (9%)		
FIBROSARCOMA		1 (3%)	1 (3%)
LIPOMA	1 (3%)		
RESPIRATORY SYSTEM			
#LUNG	(30)	(33)	(35)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (3%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (3%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(34)	(33)	(35)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)	
#SPLEEN	(31)	(33)	(35)
SARCOMA, NOS	1 (3%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(31)	(32)	(35)
HEPATOCELLULAR ADENOMA	1 (3%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(31)	(33)	(33)
PAPILLOMA, NOS			2 (6%)
URINARY SYSTEM			
#KIDNEY	(31)	(33)	(35)
LIPOSARCOMA	1 (3%)		
MIXED TUMOR, MALIGNANT	1 (3%)		
#URINARY BLADDER	(28)	(31)	(30)
TRANSITIONAL-CELL CARCINOMA			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(21)	(16)
ADENOMA, NOS	2 (13%)		
CHROMOPHOBE ADENOMA	1 (6%)		1 (6%)
#ADRENAL	(31)	(30)	(34)
CORTICAL ADENOMA	7 (23%)	4 (13%)	2 (6%)
PHEOCHROMOCYTOMA	6 (19%)		2 (6%)
#THYROID	(29)	(33)	(33)
FOLLICULAR-CELL ADENOMA	2 (7%)		
FOLLICULAR-CELL CARCINOMA	1 (3%)		1 (3%)
C-CELL ADENOMA	3 (10%)		
CYSTADENOMA, NOS		2 (6%)	
#PARATHYROID	(25)	(27)	(27)
ADENOMA, NOS	2 (8%)		
#PANCREATIC ISLETS	(24)	(33)	(31)
ISLET-CELL ADENOMA	1 (4%)	2 (6%)	1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(34)	(33)	(35)
ADENOMA, NOS			1 (3%)
NERVOUS SYSTEM			
#BRAIN	(31)	(30)	(35)
ASTROCYTOMA		1 (3%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH OOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*TUNICA VAGINALIS	(34)	(33)	(35)
MESOTHELIOMA, NOS	2 (6%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LIPOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	35	35	35
NATURAL DEATH@	20	9	9
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE	1	1	
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	25	25
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	11	11
TOTAL PRIMARY TUMORS	37	11	14
TOTAL ANIMALS WITH BENIGN TUMORS	17	8	8
TOTAL BENIGN TUMORS	30	8	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	3	3
TOTAL MALIGNANT TUMORS	5	3	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	35	33	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	31	33	33
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(35)	(33)	(33)
FIBROMA	1 (3%)		
FIBROSARCOMA	1 (3%)		
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#RENAL LYMPH NODE	(25)	(23)	(14)
ADENOCARCINOMA, NOS, METASTATIC		1 (4%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(31)	(32)	(32)
NEOPLASTIC NODULE			1 (3%)
HEPATOCELLULAR CARCINOMA			1 (3%)
URINARY SYSTEM			
#KIDNEY	(31)	(32)	(32)
FIBROSARCOMA, METASTATIC	1 (3%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(19)	(11)
ADENOMA, NOS		1 (5%)	
CHROMOPHOBE ADENOMA	4 (22%)	1 (5%)	
#ADRENAL	(30)	(31)	(30)
CORTICAL ADENOMA	11 (37%)	8 (26%)	3 (10%)
CORTICAL CARCINOMA			1 (3%)
#ADRENAL CORTEX	(30)	(31)	(30)
CYSTADENOMA, NOS			2 (7%)
#THYROID	(28)	(28)	(24)
FOLLICULAR-CELL CARCINOMA		1 (4%)	
C-CELL ADENOMA	4 (14%)		1 (4%)
C-CELL CARCINOMA		1 (4%)	
#THYROID FOLLICLE	(28)	(28)	(24)
CYSTADENOMA, NOS	2 (7%)		
#PANCREATIC ISLETS	(29)	(28)	(21)
ISLET-CELL ADENOMA	1 (3%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(35)	(33)	(33)
ADENOMA, NOS	3 (9%)		1 (3%)
ADENOCARCINOMA, NOS	1 (3%)		
FIBROMA	1 (3%)	1 (3%)	
FIBROADENOMA	13 (37%)	8 (24%)	5 (15%)
#UTERUS	(30)	(30)	(27)
ADENOCARCINOMA, NOS	1 (3%)	1 (3%)	1 (4%)
PAPILLARY CYSTADENOMA, NOS	1 (3%)		
LEIOMYOMA			1 (4%)
ENDOMETRIAL STROMAL POLYP		1 (3%)	1 (4%)
#UTERUS/ENDOMETRIUM	(30)	(30)	(27)
ADENOCARCINOMA, NOS		1 (3%)	
#OVARY	(26)	(29)	(21)
GRANULOSA-CELL TUMOR			1 (5%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUBULAR ADENOMA	1 (4%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(35)	(33)	(33)
ADENOCARCINOMA, NOS	1 (3%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(35)	(33)	(33)
FIBROSARCOMA	1 (3%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	35	35	35
NATURAL DEATH@	14	15	19
MORIBUND SACRIFICE		5	
SCHEDULED SACRIFICE	4	13	
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	2	16
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	19	13
TOTAL PRIMARY TUMORS	47	24	19
TOTAL ANIMALS WITH BENIGN TUMORS	24	17	12
TOTAL BENIGN TUMORS	42	20	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	4	2
TOTAL MALIGNANT TUMORS	5	4	3
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	
TOTAL SECONDARY TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2
TOTAL UNCERTAIN TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
MICE ADMINISTERED UDD IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(48)
PAPILLOMA, NOS	1 (2%)		
FIBROSARCOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(48)
SEBACEOUS ADENOMA	1 (2%)		
LEIOMYOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL SEPTUM	(50)	(50)	(48)
MENINGIOMA, METASTATIC			1 (2%)
#LUNG	(49)	(48)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	8 (16%)	6 (13%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		5 (10%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
#SPLEEN	(48)	(48)	(44)
HEMANGIOMA		3 (6%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(48)
HEPATOCELLULAR ADENOMA	4 (8%)	1 (2%)	2 (4%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	4 (8%)	7 (14%)	3 (6%)
*BILE DUCT	(50)	(50)	(48)
BILE DUCT CARCINOMA	1 (2%)		
#STOMACH	(49)	(49)	(45)
SQUAMOUS CELL PAPILLOMA	5 (10%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(39)	(37)	(31)
PAPILLARY CYSTADENOMA, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
#BRAIN	(48)	(49)	(42)
MENINGIOMA			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 B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2		5
MORIBUND SACRIFICE		50	45
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	48		
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	19	16
TOTAL PRIMARY TUMORS	26	22	16
TOTAL ANIMALS WITH BENIGN TUMORS	17	10	8
TOTAL BENIGN TUMORS	20	10	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	11	8
TOTAL MALIGNANT TUMORS	6	12	8
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	49	40
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	39
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(40)
FIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(49)	(40)
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(47)	(37)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	2 (4%)	5 (14%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(40)
MALIGNANT LYMPHOMA, NOS	4 (8%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	3 (6%)	1 (3%)
GRANULOCYTIC LEUKEMIA			1 (3%)
#SPLEEN	(50)	(46)	(39)
HEMANGIOMA			1 (3%)
#LYMPH NODE	(5)	(11)	(6)
HEMANGIOSARCOMA, METASTATIC	1 (20%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(47)	(38)
HEPATOCELLULAR CARCINOMA		1 (2%)	
ANGIOSARCOMA		1 (2%)	
#STOMACH	(48)	(47)	(33)
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)	
URINARY SYSTEM			
#URINARY BLADDER	(2)	(2)	
PAPILLOMATOSIS	2 (100%)		
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*VAGINA	(50)	(49)	(40)
HEMANGIOSARCOMA	1 (2%)		
#OVARY	(20)	(33)	(21)
GRANULOSA-CELL TUMOR		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(50)	(49)	(40)
LYMPHANGIOMA	1 (2%)		
*MESENTERY	(50)	(49)	(40)
HEMANGIOSARCOMA			1 (3%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	5	6	22
MORIBUND SACRIFICE		44	27
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	45		
ANIMAL MISSING			1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	12	9
TOTAL PRIMARY TUMORS	15	13	9
TOTAL ANIMALS WITH BENIGN TUMORS	7	3	6
TOTAL BENIGN TUMORS	7	3	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	9	3
TOTAL MALIGNANT TUMORS	8	9	3
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	
TOTAL SECONDARY TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN RATS ADMINISTERED UDD IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	34	33	35
ANIMALS EXAMINED HISTOPATHOLOGICALLY	33	33	35
INTEGUMENTARY SYSTEM			
*SKIN	(34)	(33)	(35)
EPIDERMAL INCLUSION CYST		2 (6%)	
*SUBCUT TISSUE	(34)	(33)	(35)
GRANULOMA, NOS	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(34)	(33)	(35)
INFLAMMATION, CHRONIC		1 (3%)	3 (9%)
*NASAL TURBINATE	(34)	(33)	(35)
INFLAMMATION, ACUTE	5 (15%)		
INFLAMMATION, ACUTE SUPPURATIVE	6 (18%)		
INFLAMMATION, CHRONIC	2 (6%)		
#TRACHEA	(30)	(33)	(35)
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC	7 (23%)	2 (6%)	3 (9%)
INFLAMMATION, CHRONIC SUPPURATIV	2 (7%)		
#LUNG	(30)	(33)	(35)
CONGESTION, NOS	1 (3%)	3 (9%)	
EDEMA, NOS	1 (3%)		
PNEUMONIA, ASPIRATION			1 (3%)
BRONCHOPNEUMONIA, ACUTE			1 (3%)
PNEUMONIA, CHRONIC MURINE	8 (27%)	7 (21%)	21 (60%)
#LUNG/ALVEOLI	(30)	(33)	(35)
HEMORRHAGE			1 (3%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(31)	(33)	(35)
HYPERPLASIA, HEMATOPOIETIC	4 (13%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(31)	(33)	(35)
HEMOSIDEROSIS	3 (10%)	1 (3%)	
ATROPHY, NOS		1 (3%)	
LYMPHOID DEPLETION			1 (3%)
HYPERPLASIA, HEMATOPOIETIC		2 (6%)	
HEMATOPOIESIS	3 (10%)		1 (3%)
#SPLENIC FOLLICLES	(31)	(33)	(35)
ATROPHY, NOS	1 (3%)		
#SPLENIC RED PULP	(31)	(33)	(35)
HEMOSIDEROSIS		1 (3%)	4 (11%)
HYPERPLASIA, NOS			1 (3%)
#MANDIBULAR L. NODE	(22)	(29)	(30)
HYPERPLASIA, LYMPHOID	5 (23%)		
#CERVICAL LYMPH NODE	(22)	(29)	(30)
HEMORRHAGE		1 (3%)	
INFLAMMATION, CHRONIC			1 (3%)
#BRONCHIAL LYMPH NODE	(22)	(29)	(30)
HEMORRHAGE	1 (5%)		
INFLAMMATION, CHRONIC			1 (3%)
#LUMBAR LYMPH NODE	(22)	(29)	(30)
INFLAMMATION, CHRONIC		1 (3%)	
#MESENTERIC L. NODE	(22)	(29)	(30)
HYPERPLASIA, LYMPHOID		1 (3%)	
#RENAL LYMPH NODE	(22)	(29)	(30)
INFLAMMATION, CHRONIC		1 (3%)	
#THYMUS	(3)	(25)	(20)
ATROPHY, NOS	3 (100%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(30)	(33)	(35)
INFLAMMATION, CHRONIC	4 (13%)		1 (3%)
INFLAMMATION, CHRONIC FOCAL			1 (3%)
INFLAMMATION, CHRONIC DIFFUSE		1 (3%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DEGENERATION, NOS		1 (3%)	
#ENDOCARDIUM	(30)	(33)	(35)
DEGENERATION, MUCOID		1 (3%)	1 (3%)
METAPLASIA, OSSEOUS		1 (3%)	
*AORTA	(34)	(33)	(35)
MINERALIZATION		1 (3%)	
*ABDOMINAL AORTA	(34)	(33)	(35)
PERIARTERITIS			1 (3%)
*PULMONARY ARTERY	(34)	(33)	(35)
CALCIFICATION, DYSTROPHIC	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(31)	(32)	(35)
CYST, NOS	1 (3%)		
CONGESTION, CHRONIC PASSIVE	1 (3%)		
ABSCESS, NOS		1 (3%)	
CIRRHOSIS, CARDIAC	1 (3%)		
METAMORPHOSIS FATTY	2 (6%)	1 (3%)	
FOCAL CELLULAR CHANGE		1 (3%)	2 (6%)
CLEAR-CELL CHANGE			6 (17%)
HYPERPLASIA, NOS	5 (16%)		
ANGIECTASIS	1 (3%)		
HEMATOPOIESIS		1 (3%)	1 (3%)
#LIVER/CENTRILOBULAR	(31)	(32)	(35)
NECROSIS, NOS		1 (3%)	1 (3%)
METAMORPHOSIS FATTY		2 (6%)	11 (31%)
*BILE DUCT	(34)	(33)	(35)
HYPERPLASIA, NOS	8 (24%)		
#PANCREAS	(24)	(33)	(31)
PERIARTERITIS	1 (4%)	1 (3%)	
#PANCREATIC ACINUS	(24)	(33)	(31)
ATROPHY, FOCAL			1 (3%)
#GASTRIC MUSCULARIS	(31)	(33)	(33)
MINERALIZATION		1 (3%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(31)	(33)	(35)
HYDRONEPHROSIS		2 (6%)	2 (6%)
CYST, NOS			1 (3%)
MULTIPLE CYSTS			1 (3%)
PYELONEPHRITIS, NOS		2 (6%)	
INFLAMMATION, INTERSTITIAL		2 (6%)	
INFLAMMATION, CHRONIC	23 (74%)		
PYELONEPHPITIS, CHRONIC	1 (3%)		
NEPHROPATHY		17 (52%)	21 (60%)
NECROSIS, MEDULLARY		1 (3%)	
#URINARY BLADDER	(28)	(31)	(30)
INFLAMMATION, CHRONIC	2 (7%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	
HYPERPLASIA, EPITHELIAL		1 (3%)	
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(21)	(16)
CYST, NOS	2 (13%)		
#ADRENAL	(31)	(30)	(34)
ECTOPIA		1 (3%)	
HYPERPLASIA, FOCAL	1 (3%)		
ANGIECTASIS	1 (3%)		
#ADRENAL CORTEX	(31)	(30)	(34)
LIPOIDOSIS	11 (35%)	2 (7%)	
#THYROID	(29)	(33)	(33)
HYPERPLASIA, C-CELL		1 (3%)	2 (6%)
#PARATHYROID	(25)	(27)	(27)
HYPERPLASIA, NOS	4 (16%)	1 (4%)	2 (7%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(34)	(33)	(35)
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, CYSTIC		1 (3%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PROSTATE	(29)	(31)	(30)
INFLAMMATION, ACUTE	2 (7%)		
INFLAMMATION, CHRONIC	4 (14%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	3 (10%)
*SEMINAL VESICLE	(34)	(33)	(35)
DILATATION, NOS	1 (3%)		
INFLAMMATION, CHRONIC	1 (3%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	
#TESTIS	(32)	(33)	(34)
ABSCESS, NOS	1 (3%)		
PERIARTERITIS	2 (6%)		
ATROPHY, NOS	9 (28%)	8 (24%)	13 (38%)
ATROPHY, FOCAL		1 (3%)	
ASPERMATOGENESIS	1 (3%)		
HYPERPLASIA, INTERSTITIAL CELL			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(34)	(33)	(35)
INFARCT, NOS		1 (3%)	
*MESENTERY	(34)	(33)	(35)
PERIARTERITIS	1 (3%)	1 (3%)	
ALL OTHER SYSTEMS			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
AUTO/NECROPSY/HISTO PERF	1	1	
AUTO/NECROPSY/NO HISTO	1		
AUTOLYSIS/NO NECROPSY	1	2	

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	35	33	33
ANIMALS EXAMINED HISTOPATHOLOGICALLY	31	33	33
INTEGUMENTARY SYSTEM			
*SKIN	(35)	(33)	(33)
ULCER, NOS			1 (3%)
*SUBCUT TISSUE	(35)	(33)	(33)
INFLAMMATION, CHRONIC		1 (3%)	
GRANULOMA, FOREIGN BODY	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(35)	(33)	(33)
INFLAMMATION, NOS			1 (3%)
INFLAMMATION, ACUTE			1 (3%)
INFLAMMATION, CHRONIC		3 (9%)	
INFLAMMATION, CHRONIC DIFFUSE			1 (3%)
INFLAMMATION, CHRONIC NECROTIZIN			1 (3%)
HYPERPLASIA, NOS			1 (3%)
*NASAL SEPTUM	(35)	(33)	(33)
INFLAMMATION, CHRONIC			3 (9%)
INFLAMMATION, CHRONIC DIFFUSE			1 (3%)
*NASAL TURBINATE	(35)	(33)	(33)
INFLAMMATION, ACUTE	1 (3%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
#TRACHEA	(29)	(31)	(28)
INFLAMMATION, NOS	5 (17%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC		3 (10%)	1 (4%)
INFLAMMATION, CHRONIC DIFFUSE		1 (3%)	
HYPERPLASIA, EPITHELIAL		1 (3%)	
METAPLASIA, SQUAMOUS		1 (3%)	1 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LUNG	(30)	(33)	(33)
EMPHYSEMA, NOS		1 (3%)	
ATELECTASIS		7 (21%)	1 (3%)
CONGESTION, NOS	2 (7%)		1 (3%)
BRONCHOPNEUMONIA, NOS		1 (3%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
PNEUMONIA, CHRONIC MURINE	6 (20%)	25 (76%)	19 (58%)
BRONCHOPNEUMONIA CHRONIC SUPPURA		1 (3%)	
GRANULOMA, NOS	1 (3%)		
FIBROSIS		1 (3%)	
HYPERPLASIA, ADENOMATOUS		3 (9%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(31)	(27)	(27)
HYPERPLASIA, HEMATOPOIETIC	4 (13%)		
#SPLEEN	(30)	(30)	(29)
INFLAMMATION, ACUTE	4 (13%)		
INFLAMMATION, CHRONIC	1 (3%)		
HEMOSIDEROSIS	2 (7%)		1 (3%)
ATROPHY, NOS	1 (3%)		
LYMPHOID DEPLETION		2 (7%)	5 (17%)
HYPERPLASIA, HEMATOPOIETIC		1 (3%)	
HEMATOPOIESIS	6 (20%)	5 (17%)	2 (7%)
GRANULOPOIESIS		1 (3%)	
#MANDIBULAR L. NODE	(25)	(23)	(14)
HEMORRHAGIC CYST	1 (4%)		
INFLAMMATION, ACUTE	1 (4%)		
PLASMA-CELL INFILTRATE	3 (12%)		
HYPERPLASIA, LYMPHOID	5 (20%)		
#CERVICAL LYMPH NODE	(25)	(23)	(14)
INFLAMMATION, NOS		1 (4%)	
#BRONCHIAL LYMPH NODE	(25)	(23)	(14)
INFLAMMATION, CHRONIC		1 (4%)	
#MESENTERIC L. NODE	(25)	(23)	(14)
HYPERPLASIA, LYMPHOID	1 (4%)		
#THYMUS	(9)		
CYST, NOS	2 (22%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	9 (100%)		
CIRCULATORY SYSTEM			
#HEART	(31)	(30)	(32)
CALCIFICATION, DYSTROPHIC	1 (3%)		
#ENDOCARDIUM	(31)	(30)	(32)
INFLAMMATION, CHRONIC			1 (3%)
FIBROSIS, FOCAL			1 (3%)
*MESENTERIC ARTERY	(35)	(33)	(33)
THROMBOSIS, NOS	1 (3%)		
INFLAMMATION, CHRONIC	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(31)	(32)	(32)
CYST, NOS			2 (6%)
CONGESTION, NOS	1 (3%)		
ABSCESS, NOS		1 (3%)	
HEPATITIS, TOXIC			1 (3%)
NECROSIS, NOS	1 (3%)		1 (3%)
NECROSIS, FOCAL	1 (3%)	4 (13%)	1 (3%)
NECROSIS, DIFFUSE		1 (3%)	1 (3%)
METAMORPHOSIS FATTY		16 (50%)	18 (56%)
LIPOIDOSIS	2 (6%)		
MEGALOCYTOSIS			1 (3%)
HYPERPLASIA, NOS	7 (23%)		
ANISOCYTOSIS		1 (3%)	
HEMATOPOIESIS	1 (3%)	3 (9%)	1 (3%)
#LIVER/CENTRILOBULAR	(31)	(32)	(32)
NECROSIS, NOS		2 (6%)	3 (9%)
METAMORPHOSIS FATTY	1 (3%)	3 (9%)	7 (22%)
ANGIECTASIS		1 (3%)	
#LIVER/PERIPORTAL	(31)	(32)	(32)
FIBROSIS			3 (9%)
METAMORPHOSIS FATTY			1 (3%)
*BILE DUCT	(35)	(33)	(33)
DILATATION, NOS	1 (3%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MULTIPLE CYSTS			1 (3%)
INFLAMMATION, CHRONIC	1 (3%)		
HYPERPLASIA, NOS	13 (37%)		1 (3%)
HYPERPLASIA, FOCAL		1 (3%)	4 (12%)
#PANCREAS	(29)	(28)	(21)
INFLAMMATION WITH FIBROSIS	1 (3%)		
#PANCREATIC DUCT	(29)	(28)	(21)
HYPERPLASIA, NOS	3 (10%)		
#PANCREATIC ACINUS	(29)	(28)	(21)
ATROPHY, NOS		2 (7%)	1 (5%)
ATROPHY, FOCAL		2 (7%)	1 (5%)
#STOMACH	(31)	(31)	(28)
CALCIFICATION, DYSTROPHIC	1 (3%)		
HYPERKERATOSIS			1 (4%)
URINARY SYSTEM			
#KIDNEY	(31)	(32)	(32)
MINERALIZATION	17 (55%)		
CAST, NOS			3 (9%)
PYELONEPHRITIS, NOS	1 (3%)		
INFLAMMATION, INTERSTITIAL		1 (3%)	3 (9%)
PYELONEPHRITIS, ACUTE	1 (3%)		
INFLAMMATION, ACUTE			1 (3%)
INFLAMMATION, CHRONIC	5 (16%)		
INFLAMMATION, CHRONIC FOCAL		1 (3%)	
GLOMERULOSCLEROSIS, NOS		2 (6%)	1 (3%)
NECROSIS, MEDULLARY		2 (6%)	5 (16%)
HYPERPLASIA, EPITHELIAL		1 (3%)	
#KIDNEY/MEDULLA	(31)	(32)	(32)
MINERALIZATION	1 (3%)		
#KIDNEY/TUBULE	(31)	(32)	(32)
DILATATION, NOS		3 (9%)	4 (13%)
CAST, NOS		10 (31%)	4 (13%)
CYST, NOS	4 (13%)		
#URINARY BLADDER	(25)	(15)	(8)
INFLAMMATION, NOS	1 (4%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE	1 (4%)		
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(19)	(11)
CYST, NOS	3 (17%)		
#ADRENAL	(30)	(31)	(30)
ANGIECTASIS	8 (27%)		
#ADRENAL CORTEX	(30)	(31)	(30)
HEMORRHAGIC CYST			1 (3%)
LIPOIDOSIS	9 (30%)		
HYPERPLASIA, NOS	1 (3%)		
#THYROID	(28)	(28)	(24)
CYSTIC FOLLICLES	1 (4%)		
FOLLICULAR CYST, NOS	1 (4%)	1 (4%)	
HYPERPLASIA, C-CELL	3 (11%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(35)	(33)	(33)
CYST, NOS		1 (3%)	
#UTERUS	(30)	(30)	(27)
PYOMETRA			1 (4%)
INFLAMMATION, ACUTE	2 (7%)		
ABSCESS, NOS			1 (4%)
ATROPHY, NOS			2 (7%)
#UTERUS/ENDOMETRIUM	(30)	(30)	(27)
CYST, NOS	2 (7%)		
INFLAMMATION, ACUTE	2 (7%)		
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, CYSTIC			2 (7%)
#OVARY	(26)	(29)	(21)
CYSTIC FOLLICLES	1 (4%)		
FOLLICULAR CYST, NOS	1 (4%)	1 (3%)	1 (5%)
NERVOUS SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE	(35)	(33)	(33)
INFLAMMATION, ACUTE	2 (6%)		
CATARACT	1 (3%)		
*EYE/CORNEA	(35)	(33)	(33)
INFLAMMATION, ACUTE	1 (3%)		
*EYE/RETINA	(35)	(33)	(33)
INFLAMMATION, NOS	21 (60%)		
*EYE/LACRIMAL GLAND	(35)	(33)	(33)
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
*HARDERIAN GLAND	(35)	(33)	(33)
ABSCESS, NOS	1 (3%)		
INFLAMMATION, CHRONIC		1 (3%)	1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (3%)	
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(35)	(33)	(33)
GRANULOMA, FOREIGN BODY	1 (3%)		
BODY CAVITIES			
*ABDOMINAL WALL	(35)	(33)	(33)
INFLAMMATION, CHRONIC	1 (3%)		
*PERITONEAL CAVITY	(35)	(33)	(33)
INFLAMMATION, CHRONIC DIFFUSE		1 (3%)	
*PLEURA	(35)	(33)	(33)
INFLAMMATION, CHRONIC		1 (3%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/NO HISTO	4		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AUTOLYSIS/NO NECROPSY		2	2

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MICE ADMINISTERED UDD IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(48)
ULCER, FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
ACANTHOSIS			6 (13%)
RESPIRATORY SYSTEM			
#TRACHEA	(45)	(46)	(41)
HYPERPLASIA, EPITHELIAL			2 (5%)
#LUNG	(49)	(48)	(48)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL			1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC		6 (13%)	2 (4%)
HYPERPLASIA, ADENOMATOUS		2 (4%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(48)	(48)	(44)
ATROPHY, FOCAL			1 (2%)
LYMPHOID DEPLETION		1 (2%)	2 (5%)
HYPERPLASIA, LYMPHOID		2 (4%)	3 (7%)
#LUMBAR LYMPH NODE	(1)	(31)	(25)
INFLAMMATION, CHRONIC			1 (4%)
#MESENTERIC L. NODE	(1)	(31)	(25)
INFLAMMATION, CHRONIC			1 (4%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#AXILLARY LYMPH NODE	(1)	(31)	(25)
INFLAMMATION, CHRONIC			1 (4%)
#INGUINAL LYMPH NODE	(1)	(31)	(25)
INFLAMMATION, CHRONIC			2 (8%)
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(46)
PERIARTERITIS			1 (2%)
#MYOCARDIUM	(49)	(50)	(46)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(48)
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		5 (10%)	
HEPATITIS, TOXIC		1 (2%)	1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY		2 (4%)	1 (2%)
BASOPHILIC CYTO CHANGE		1 (2%)	
#STOMACH	(49)	(49)	(45)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS		1 (2%)	
#GASTRIC MUSCULARIS	(49)	(49)	(45)
NECROSIS, DIFFUSE			1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(48)
INFLAMMATION, INTERSTITIAL			2 (4%)
GLOMERULOSCLEROSIS, NOS			1 (2%)
#URINARY BLADDER		(9)	
CALCULUS, NOS		1 (11%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC DIFFUSE		1 (11%)	
ENDOCRINE SYSTEM			
#THYROID	(39)	(37)	(31)
ATROPHY, FOCAL			1 (3%)
#PARATHYROID	(15)	(10)	(17)
CYST, NOS			1 (6%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(48)
DILATATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		1 (2%)
*TESTIS	(49)	(49)	(45)
GRANULOMA, SPERMATIC	1 (2%)		
ATROPHY, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(48)
INFLAMMATION, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	26	18	16
AUTO/NECROPSY/NO HISTO	1		
AUTOLYSIS/NO NECROPSY			2

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED UDD IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	49	40
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	39
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(40)
ACARIASIS			2 (5%)
RESPIRATORY SYSTEM			
#TRACHEA	(45)	(44)	(24)
HYPERPLASIA, EPITHELIAL			1 (4%)
#LUNG/BRONCHIOLE	(50)	(47)	(37)
HYPERPLASIA, EPITHELIAL			1 (3%)
#LUNG	(50)	(47)	(37)
CONGESTION, NOS		1 (2%)	1 (3%)
INFLAMMATION, NOS	2 (4%)		
INFLAMMATION, INTERSTITIAL		1 (2%)	2 (5%)
BRONCHOPNEUMONIA, ACUTE			2 (5%)
LOBAR PNEUMONIA, ACUTE			1 (3%)
PNEUMONIA, CHRONIC MURINE		2 (4%)	3 (8%)
PNEUMONIA INTERSTITIAL CHRONIC			6 (16%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(43)	(24)
HYPERPLASIA, HEMATOPOIETIC		3 (7%)	
#SPLEEN	(50)	(46)	(39)
LYMPHOID DEPLETION			2 (5%)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	2 (5%)
HYPERPLASIA, LYMPHOID	6 (12%)	7 (15%)	5 (13%)
HEMATOPOIESIS		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(5)	(11)	(6)
HYPERPLASIA, LYMPHOID	1 (20%)		
#BRONCHIAL LYMPH NODE	(5)	(11)	(6)
INFLAMMATION, NOS		1 (9%)	
#LUMBAR LYMPH NODE	(5)	(11)	(6)
INFLAMMATION, CHRONIC		1 (9%)	1 (17%)
#RENAL LYMPH NODE	(5)	(11)	(6)
INFLAMMATION, CHRONIC		1 (9%)	1 (17%)
HYPERPLASIA, LYMPHOID		1 (9%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(47)	(38)
ABSCESS, NOS		2 (4%)	
INFLAMMATION, ACUTE/CHRONIC			1 (3%)
INFLAMMATION, CHRONIC			1 (3%)
FIBROSIS			3 (8%)
CIRRHOSIS, NOS			2 (5%)
HEPATITIS, TOXIC			5 (13%)
NECROSIS, NOS			3 (8%)
MEGALOCYTOSIS			1 (3%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC			1 (3%)
HEMATOPOIESIS		3 (6%)	
GRANULOPOIESIS		2 (4%)	
#LIVER/HEPATOCYTES	(50)	(47)	(38)
NECROSIS, NOS	1 (2%)		
*BILE DUCT	(50)	(49)	(40)
HYPERPLASIA, NOS			1 (3%)
#PANCREAS	(26)	(45)	(25)
DILATATION/DUCTS	1 (4%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV			1 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ACINUS	(26)	(45)	(25)
ATROPHY, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(47)	(39)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		
INFLAMMATION, INTERSTITIAL		7 (15%)	5 (13%)
GLOMERULOSCLEROSIS, NOS		2 (4%)	
#KIDNEY/GLOMERULUS	(50)	(47)	(39)
AMYLOIDOSIS	1 (2%)		
#KIDNEY/TUBULE	(50)	(47)	(39)
NECROSIS, NOS			1 (3%)
HYPOPLASIA, NOS			1 (3%)
ENDOCRINE SYSTEM			
#ADRENAL MEDULLA	(43)	(29)	(35)
CYST, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(49)	(48)	(26)
HYDROMETRA	4 (8%)		
PYOMETRA		1 (2%)	
ATROPHY, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(49)	(48)	(26)
INFLAMMATION, SUPPURATIVE		6 (13%)	3 (12%)
HYPERPLASIA, DIFFUSE	1 (2%)		
HYPERPLASIA, CYSTIC	48 (98%)	37 (77%)	18 (69%)
#UTERUS/MYOMETRIUM	(49)	(48)	(26)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#OVARY/OVIDUCT	(49)	(48)	(26)
PUS		1 (2%)	1 (4%)
PUS			1 (4%)
#OVARY	(20)	(33)	(21)
CYST, NOS	5 (25%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
FOLLICULAR CYST, NOS	5 (25%)	2 (6%)	2 (10%)
HEMORRHAGIC CYST			2 (10%)
ABSCESS, NOS		1 (3%)	
ABSCESS, CHRONIC			1 (5%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(47)	(44)	(27)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(49)	(40)
INFLAMMATION, CHRONIC		4 (8%)	
INFLAMMATION, CHRONIC FOCAL			1 (3%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
LIPOGRANULOMA	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	3	2
ANIMAL MISSING/NO NECROPSY			1
AUTO/NECROPSY/HISTO PERF			2
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY		1	9

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED UDD IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered UDD in the Diet (a)

Topography: Morphology	Control	Low Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	3/34 (9)	0/33 (0)	0/35 (0)
P Values (c,d)	P = 0.036 (N)	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.687	1.594
Weeks to First Observed Tumor	96	--	--
Stomach: Papilloma, NOS (b)	0/31 (0)	0/33 (0)	2/33 (6)
P Values (c,d)	N.S.	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.282
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	110

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	2/16 (13)	0/21 (0)	0/16 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		2.475	3.190
Weeks to First Observed Tumor	110	--	--
Adrenal: Cortical Adenoma (b)	7/31 (23)	4/30 (13)	2/34 (6)
P Values (c,d)	P = 0.039 (N)	N.S.	N.S.
Relative Risk (f)		0.590	0.261
Lower Limit		0.141	0.028
Upper Limit		2.068	1.245
Weeks to First Observed Tumor	91	110	110

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma (b)	6/31 (19)	0/30 (0)	2/34 (6)
P Values (c,d)	P = 0.047 (N)	P = 0.013 (N)	N.S.
Departure from Linear Trend (e)	P = 0.038		
Relative Risk (f)		0.000	0.304
Lower Limit		0.000	0.032
Upper Limit		0.631	1.554
Weeks to First Observed Tumor	86	--	110
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	3/29 (10)	0/33 (0)	1/33 (3)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.293
Lower Limit		0.000	0.006
Upper Limit		1.437	3.417
Weeks to First Observed Tumor	97	--	110

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: Cystadenoma, NOS (b)	0/29 (0)	2/33 (6)	0/33 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.265	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	110	--
Thyroid: C-cell Adenoma (b)	3/29 (10)	0/33 (0)	0/33 (0)
P Values (c,d)	P = 0.029 (N)	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.437	1.437
Weeks to First Observed Tumor	110	--	--

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Parathyroid: Adenoma, NOS (b)	2/25 (8)	0/27 (0)	0/27 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		3.057	3.057
Weeks to First Observed Tumor	110	--	--
Pancreatic Islets: Islet-cell Adenoma (b)	1/24 (4)	2/33 (6)	1/31 (3)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.455	0.774
Lower Limit		0.081	0.010
Upper Limit		83.169	58.826
Weeks to First Observed Tumor	97	110	110

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Tunica Vaginalis: Mesothelioma, NOS (b)	2/34 (6)	0/33 (0)	0/35 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		3.435	3.246
Weeks to First Observed Tumor	81	--	--

(a) Dosed groups received 5,000 or 10,000 ppm.

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

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

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered UDD in the Diet (a)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	4/18 (22)	1/19 (5)	0/11 (0)
P Values (c,d)	P = 0.045 (N)	N.S.	N.S.
Relative Risk (f)		0.237	0.000
Lower Limit		0.005	0.000
Upper Limit		2.106	1.589
Weeks to First Observed Tumor	116	116	--
Adrenal: Cortical Adenoma (b)	11/30 (37)	8/31 (26)	3/30 (10)
P Values (c,d)	P = 0.012 (N)	N.S.	P = 0.015 (N)
Relative Risk (f)		0.704	0.273
Lower Limit		0.289	0.055
Upper Limit		1.643	0.909
Weeks to First Observed Tumor	115	95	67

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Adrenal: Cortical Adenoma or Carcinoma (b)	11/30 (37)	8/31 (26)	4/30 (13)
P Values (c,d)	P = 0.027 (N)	N.S.	P = 0.036 (N)
Relative Risk (f)		0.704	0.364
Lower Limit		0.289	0.096
Upper Limit		1.643	1.072
Weeks to First Observed Tumor	115	95	67
Adrenal Cortex: Cystadenoma, NOS (b)	0/30 (0)	0/31 (0)	2/30 (7)
P Values (c,d)	N.S.	--	N.S.
Relative Risk (f)		--	Infinite
Lower Limit		--	0.301
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	111

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-cell Adenoma or Carcinoma (b)	4/28 (14)	1/28 (4)	1/24 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.250	0.292
Lower Limit		0.005	0.006
Upper Limit		2.322	2.680
Weeks to First Observed Tumor	115	114	111
Thyroid Follicle: Cystadenoma, NOS (b)	2/28 (7)	0/28 (0)	0/24 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		3.310	3.834
Weeks to First Observed Tumor	116	--	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Mammary Gland: Adenoma, NOS (b)	3/35 (9)	0/33 (0)	1/33 (3)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.354
Lower Limit		0.000	0.007
Upper Limit		1.737	4.136
Weeks to First Observed Tumor	113	--	111
Mammary Gland: Fibroadenoma (b)	13/35 (37)	8/33 (24)	5/33 (15)
P Values (c,d)	P = 0.027 (N)	N.S.	P = 0.037 (N)
Relative Risk (f)		0.653	0.408
Lower Limit		0.272	0.129
Upper Limit		1.466	1.069
Weeks to First Observed Tumor	107	95	111

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered UDD in the Diet (a)

(continued)

(a) Dosed groups received 5,000 or 10,000 ppm.

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

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

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED UDD IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered UDD in the Diet (a)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/49 (0)	5/48 (10)	1/48 (2)
P Values (c,d)	N.S.	P = 0.027	N.S.
Departure from Linear Trend (e)	P = 0.008		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.289	0.055
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	97	93
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	8/49 (16)	11/48 (23)	6/48 (13)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.404	0.766
Lower Limit		0.565	0.236
Upper Limit		3.665	2.322
Weeks to First Observed Tumor	92	97	93

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Spleen: Hemangioma (b)	0/48 (0)	3/48 (6)	1/44 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.601	0.059
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	97	93
Liver: Hepatocellular Carcinoma (b)	4/49 (8)	7/50 (14)	3/48 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.715	0.766
Lower Limit		0.467	0.118
Upper Limit		7.525	4.285
Weeks to First Observed Tumor	93	97	94

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered UDD in the Diet (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	8/49 (16)	8/50 (16)	5/48 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.980	0.638
Lower Limit		0.349	0.176
Upper Limit		2.757	2.047
Weeks to First Observed Tumor	92	97	93
Stomach: Squamous-cell Papilloma (b)	5/49 (10)	0/49 (0)	0/45 (0)
P Values (c,d)	P = 0.007 (N)	P = 0.028 (N)	P = 0.035 (N)
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		0.792	0.861
Weeks to First Observed Tumor	92	--	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered UDD in the Diet (a)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/50 (6)	2/47 (4)	5/37 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.709	2.252
Lower Limit		0.061	0.467
Upper Limit		5.913	13.614
Weeks to First Observed Tumor	91	92	91
Hematopoietic System: Lymphoma or Leukemia (b)	6/50 (12)	6/49 (12)	2/40 (5)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.020	0.417
Lower Limit		0.293	0.043
Upper Limit		3.556	2.176
Weeks to First Observed Tumor	76	87	91

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered UDD in the Diet (a)

(continued)

(a) Dosed groups received 5,000 or 10,000 ppm.

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

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

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

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

August 31, 1978

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

The primary reviewer agreed with the conclusion in the report that Dibenzo-p-Dioxin was not carcinogenic in rats or mice, under the conditions of test. After a brief description of the experimental design, he noted the inadequate procedure by which the chronic dose levels were selected and the poor survival among high dose treated female mice. Despite the shortcomings, the primary reviewer said that the study still appeared to be valid. Based on the results of the bioassay, he said that Dibenzo-p-Dioxin would not appear to pose a carcinogenic risk to man.

The secondary reviewer agreed with the primary reviewer's critique.

A motion was approved unanimously that the report on the bioassay of Dibenzo-p-Dioxin be accepted as written.

Members present were:

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

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

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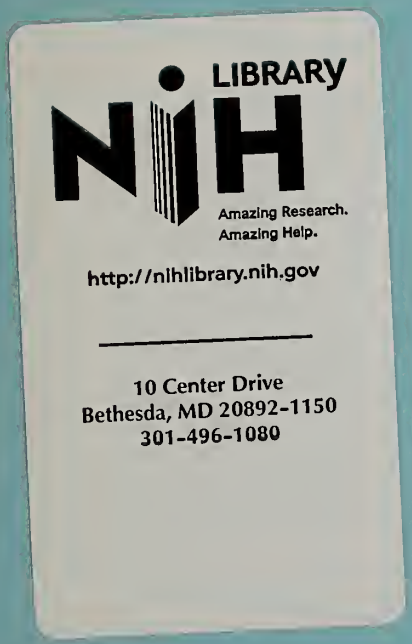

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