

National Cancer Institute
CARCINOGENESIS
Technical Report Series
NO. 123
1979

**BIOASSAY OF
2,7-DICHLORODIBENZO-p-DIOXIN (DCDD)
FOR POSSIBLE CARCINOGENICITY**

CAS No. 33857-26-0

NCI-CG-TR-123

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



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

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DHEW Publication No. (NIH) 79-1378

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FOREWORD: This report presents the results of the bioassay of 2,7-dichlorodibenzo-p-dioxin (DCDD) 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. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicates 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 in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of 2,7-dichlorodibenzo-p-dioxin (DCDD) was conducted by the Illinois Institute of Technology Research Institute (IITRI) (1), Chicago, Illinois, initially under direct contract to NCI (2) and currently under a subcontract to Tracor Jitco., Inc. (3), Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program.

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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. DePinto (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 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.

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SUMMARY

A bioassay of 2,7-dichlorodibenzo-p-dioxin (DCDD) 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 DCDD at one of two doses, either 5,000 or 10,000 ppm, for 110 weeks. Groups of 50 mice of each sex were administered these same doses for 90 weeks. Controls consisted of 35 untreated rats of each sex and 50 untreated mice of each sex. All surviving male rats were killed at 110 to 112 weeks, all surviving female rats at 110 to 117 weeks, all surviving male mice at 92 to 101 weeks, and all surviving female mice at 91 to 98 weeks.

Mean body weights of most of the dosed groups of rats and mice were lower than those of corresponding controls both when placed on study and for much of the study period; however, survival of any group was not significantly affected by administration of the test chemical. Sufficient numbers of dosed and control rats and mice of each sex were at risk for the development of late-appearing tumors.

No tumors were induced in male or female rats or female mice at incidences that were significantly higher in the dosed groups than in the corresponding control groups. Both low- and high-dose rats had toxic hepatic lesions characterized by centrilobular fatty metamorphosis and/or necrosis.

In the male mice, hepatocellular adenomas or carcinomas occurred at incidences that were dose related ($P = 0.008$), and, in direct comparisons, were higher in the low-dose group ($P = 0.008$) and the high-dose group ($P = 0.010$) than in the control group (controls 8/49, low-dose 20/50, high-dose 17/42). However, the historical incidence of this lesion in control male B6C3F1 mice at this laboratory does not permit a clear association of the lesion with the administration of the test compound. There were also significant increases in the incidence of combinations of leukemias and lymphomas and of hemangiosarcomas and hemangiomas in the low-dose male mice, but these findings were not supported by the high-dose animals.

It is concluded that under the conditions of this bioassay, DCDD was not carcinogenic for Osborne-Mendel rats of either sex or for female B6C3F1 mice. The marginal increased incidences of combinations of leukemias and lymphomas, of hemangiosarcomas and hemangiomas, and of hepatocellular carcinomas and adenomas in male B3C3F1 mice are, however, considered as suggestive of a carcinogenic effect of 2,7-dichlorodibenzo-p-dioxin in these animals.

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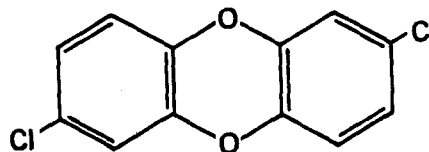
I. INTRODUCTION

2,7-Dichlorodibenzo-p-dioxin (CAS 33857-26-0; NCI C03667), referred to in this report as DCDD, is a chlorinated dibenzodioxin.

Chlorinated dibenzodioxins have been found as by-products in the manufacture of pentachlorophenol and in the herbicide 2,4,5-tri-

chlorophenoxyacetic acid (2,4,5-T) and its esters. Pentachlorophenol is a microbicidal agent that is used as a wood preservative, for slime control in herbicide formulations, and in the manufacture of paper pulp; 2,4,5-T has been used as a herbicide on national forests, rangelands, pastures, in the agricultural industry, and as a component of Agent Orange, a wartime defoliant (Stecher, 1968; EPA, 1971; Crossland and Shea, 1973).

As a result of these applications, certain dibenzodioxins have been dispersed in the environment where they are slowly degraded. Laboratory experiments to test photodegradation indicate that 2,3,7,8-tetrachlorodibenzodioxin is degraded to 2,3,7-trichlorodibenzodioxin and DCDD; photodegradation occurs in organic



2, 7 – Dichlorodibenzo-p-dioxin

solvents, but not in aqueous suspensions or on wet or dry soil (Crosby et al., 1971; Kearney et al., 1972).

In acute oral toxicity studies, doses of 1 to 2 g DCDD/kg did not kill female rats (International Agency for Research on Cancer, 1977). Except for this information and that in a preliminary report of the present bioassay (King et al., 1973), no other data are available on the toxicity of DCDD. Studies on the acute and subacute toxicities of the 2,3,7,8-tetrachloro-, hexachloro-, and octachlorodibenzo-p-dioxin analogs of DCDD have shown that the 2,3,7,8-tetrachloro analog (TCDD) is the most toxic, having an acute LD₅₀ 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 and Allen, 1977).

DCDD was selected for the Carcinogenesis Testing Program as one of a series of chlorinated dibenzo-p-dioxins because some of these compounds, due to their dispersion and persistence in the environment, may have entered the food chain, causing long-term human exposure.

II. MATERIALS AND METHODS

A. Chemical

The batch of DCDD used for this bioassay was synthesized by the Chemistry Division of IITRI. It was prepared by heating sodium 2,4-dichlorophenoxide with copper catalyst in bis(2-ethoxyethyl)ether at 180°C (Aniline, 1973).

The identity of the chemical was confirmed by mass spectrometry and by comparison of gas chromatographic retention time with that of an authentic sample obtained from Dr. David Firestone of the Food and Drug Administration. Three impurities with peak areas 3 to 6% of the major peak were detected, all with longer retention times. One of the impurities was identified by mass spectrometry as a trichlorodibenzodioxin. No tetrachlorodibenzodioxin was detected by mass spectrometry.

B. Dietary Preparation

Test diets were prepared by incorporating a known quantity of DCDD into a 2-week supply of powdered Wayne® Sterilizable 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 in two individual batches of test diet several months after preparation. Ninety percent of the expected concentration was found at the 10,000 ppm level and 110% 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. All animals were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Rats and mice were received at the laboratory at approximately 4 weeks of age. They were placed in quarantine for 1 week. Those animals with no visible signs of disease were earmarked and assigned to dosed or control groups.

D. Animal Maintenance

The rats and mice were housed in rooms maintained at 22 to 23°C; the relative humidity ranged from 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.).

Control and dosed rats and mice were housed in groups of 4 and 10, respectively, in suspended polypropylene cages (Maryland Plastics, Federalsburg, Maryland), which were covered with a wire mesh screen and a polyester filter (Research Equipment Co., Inc., Bryan, Tex.). The bedding used in the cages was Absorb-dri[®] hardwood chips (Lab Products, Inc., Garfield, N. J.). Tap water was made 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 dosed animals received the same diets, to which was added the test chemical. The diets were made 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.)

The racks were rotated in the test rooms once per month. The rats and the mice were housed in separate rooms. The untreated controls were housed in the same room with the dosed animals. The animals fed DCDD were in the same room with the 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-octachlorodibenzodioxin
(CAS 262-12-4) dibenzo-p-dioxin (UDD)

E. Chronic Studies

The test groups, doses administered, and durations of the chronic studies are shown in tables 1 and 2. Dosed and control male rats originally placed on study died, due to a failure of the air-conditioning system. The male groups in this report were placed on study 1 year later than the female rats and male and

Table 1. DCDD Chronic Feeding Studies in Rats

<u>Sex and Test Group</u>	<u>Initial No. of Animals (a)</u>	<u>DCDD in Diet (ppm)</u>	<u>Time on Study</u>	
			<u>Dosed (weeks)</u>	<u>Observed (weeks)</u>
<u>Male</u>				
Control (b)	35	0		110
Low-Dose	35	5,000	110	1-2
High-Dose	35	10,000	110	1
<u>Female</u>				
Control (b)	35	0		116-117
Low-Dose	35	5,000	110	
High-Dose	35	10,000	110	

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

(b) Male controls were started 4 weeks earlier than the dosed male groups; female controls were started 17 weeks earlier than the dosed female groups.

Table 2. DCDD Chronic Feeding Studies in Mice

<u>Sex and Test Group</u>	<u>Initial No. of Animals (a)</u>	<u>DCDD in Diet (ppm)</u>	<u>Time on Study</u>	
			<u>Dosed (weeks)</u>	<u>Observed (weeks)</u>
<u>Male</u>				
Control (b)	50	0	90	2-3
Low-Dose	50	5,000	90	10-11
High-Dose	50	10,000	90	9
<u>Female</u>				
Control (b)	50	0	90	1-2
Low-Dose	50	5,000	90	2-3
High-Dose	50	10,000	90	8

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

(b) Controls were placed on study 16 weeks before the dosed groups.

female mice. The doses were set at 5,000 and 10,000 ppm for both species, based on the maximum dose levels permitted by NCI protocols for administration of materials presumed to be nontoxic. A subchronic study was not conducted. In an acute oral LD₅₀ study, DCDD in doses of 1 to 2 g/kg did not kill female rats (IARC, 1977).

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 pentobarbital and necropsied.

The tissues taken at necropsy 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.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. 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)

Among male rats the mean body weights of both dosed groups were lower than those of the corresponding controls at the time the animals were placed on study and throughout the test period. After week 50, mean body weights of dosed groups of female rats were also lower than those of controls and were dose related (figure 1). Fluctuation in the growth curves 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 DCDD in the diet at the doses of this bioassay, together with those of the controls, are shown in figure 2. In male rats, the dosed groups were started on study 4 weeks after the control group, and in females, the dosed groups were started 17 weeks after the

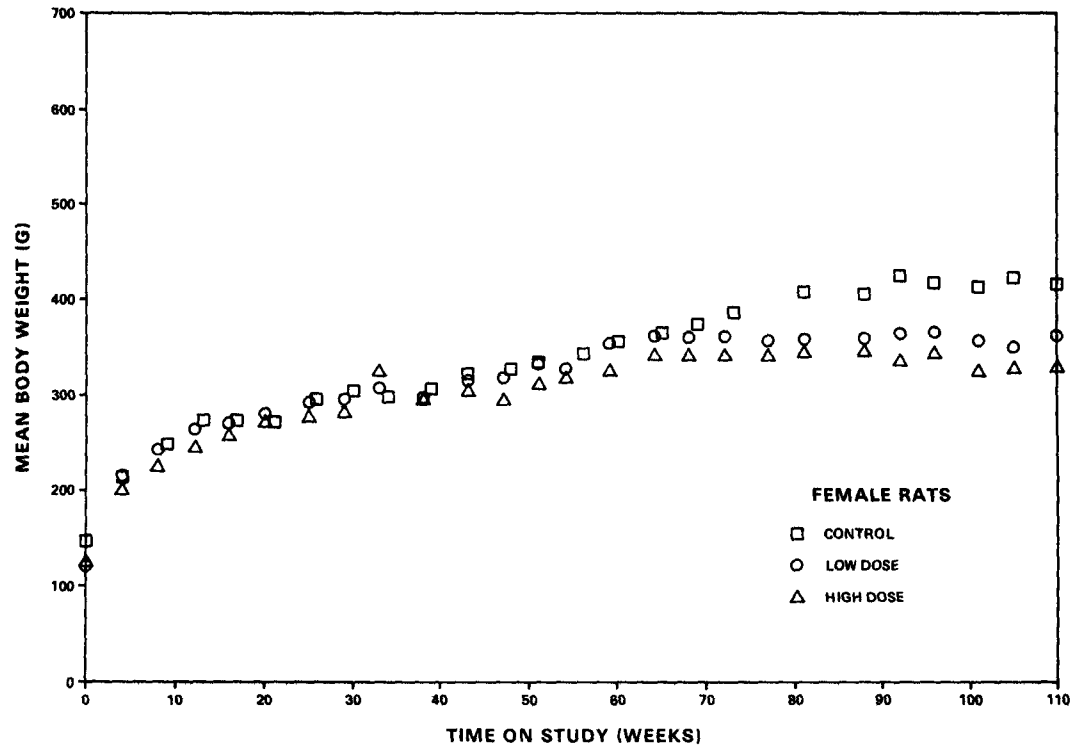
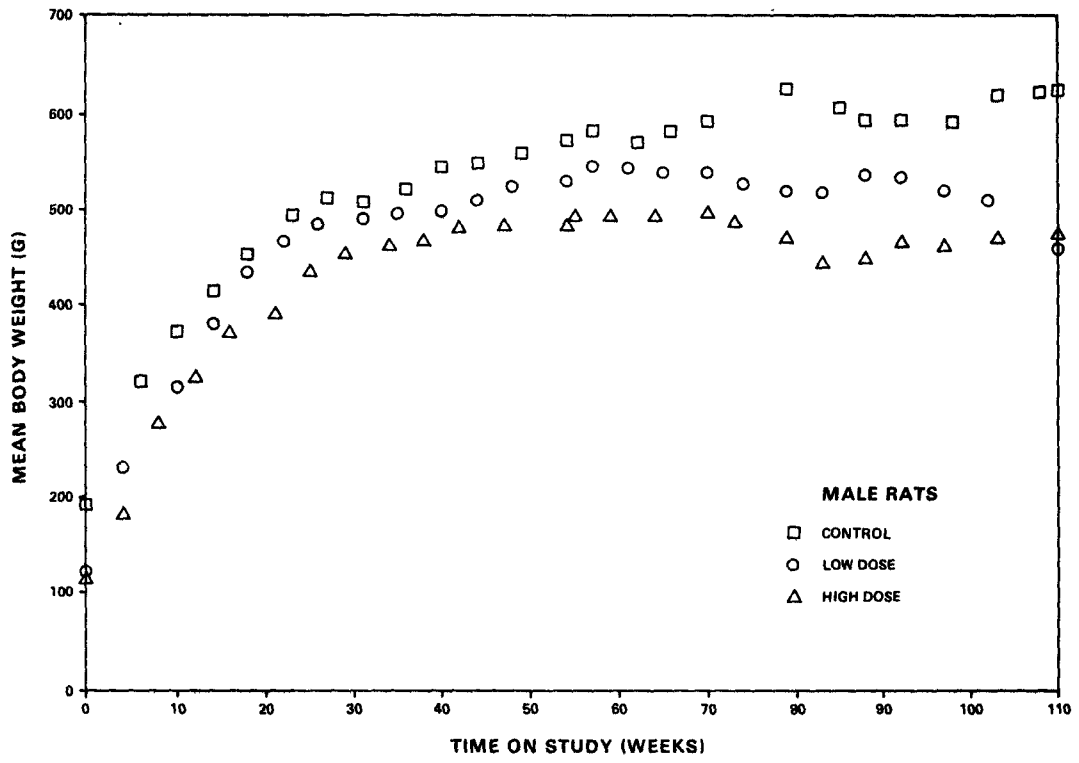


Figure 1. Growth Curves for Rats Administered DCDD in the Diet

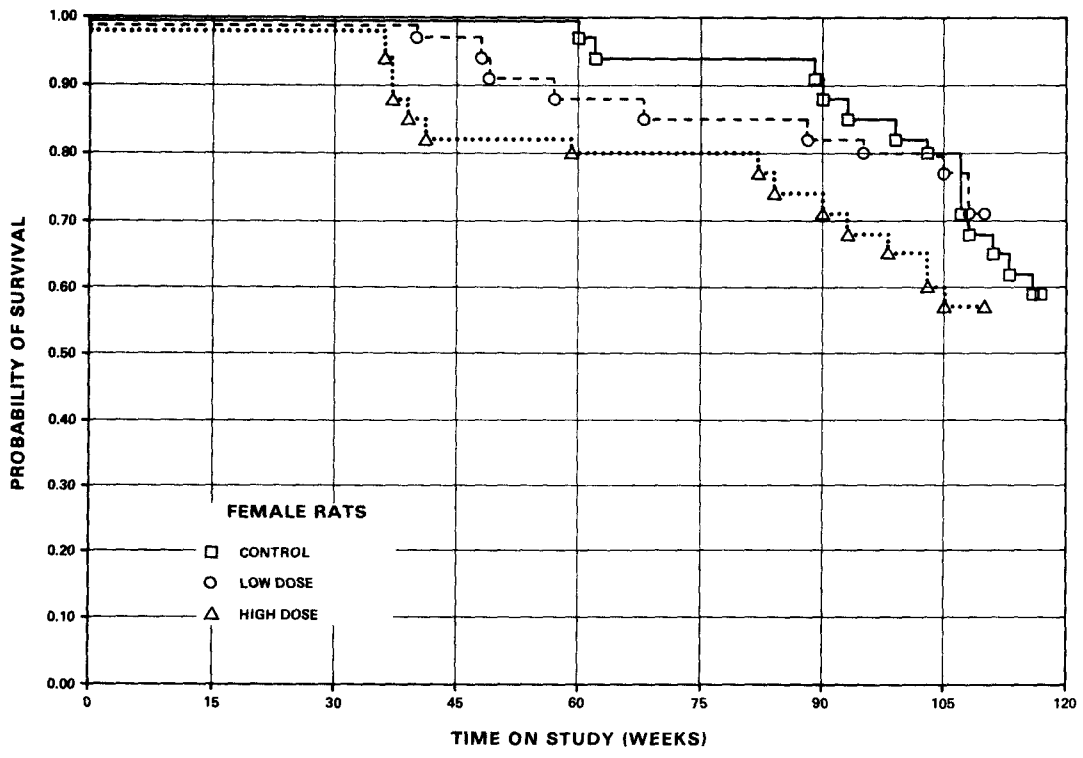
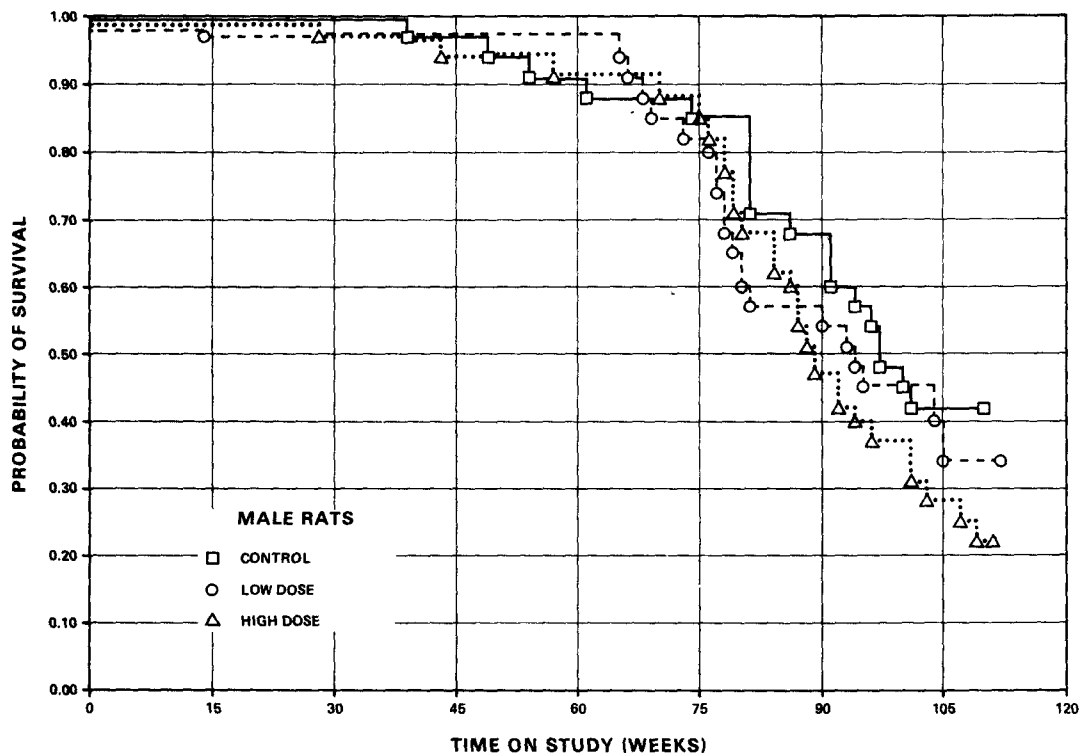


Figure 2. Survival Curves for Rats Administered DCDD in the Diet

controls; however, the Tarone test for dose-related trend in mortality is applied as if the three groups of each sex were started at the same time. The control and high-dose male rats were terminated at 110 weeks while the low-dose males were terminated at 112 weeks. In female rats, the differences in time on study were more pronounced; the controls were terminated at 116 to 117 weeks, whereas the dosed groups were terminated at 110 weeks. All animals were censored at 110 weeks in the application of the Cox and Tarone tests. The results of the Tarone tests are not significant in either sex, although substantial mortality occurred in the high-dose group from weeks 36 to 40 compared with the other groups. The results of the Cox test comparing the mortality of the control group with that of each dosed group also are not significant in either sex.

In male rats, 29/35 (83%) of the high-dose animals, 26/35 (74%) of the low-dose animals, and 30/35 (86%) of the controls were still alive at week 78 on study. In females, 28/35 (80%) of the high-dose animals, 30/35 (86%) of the low-dose animals, and 33/35 (94%) of the controls were still alive at week 78 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.

A variety of tumors were observed in both the control and dosed rats, each of which has been previously seen in untreated aging Osborne-Mendel rats.

Both low- and high-dose rats had toxic hepatic lesions characterized by centrilobular fatty metamorphosis (33-48%) and/or necrosis (6-20%). Other nonneoplastic lesions were of the types usually seen in aged Osborne-Mendel rats.

Based on the histopathologic examination, DCDD was not carcinogenic in Osborne-Mendel rats of each sex 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 control group was started on study 4 weeks before the dosed groups, and in females, the control group was started 17 weeks before the dosed groups; however, the Cochran-Armitage test for dose-related trend in the incidence of tumors is applied as if the three groups of each sex were started at the same time.

The results of the Cochran-Armitage test and those of the Fisher exact test are not significant in the positive direction in either sex. Several significant results in the negative direction are observed in each sex; in females, this may be due to the earlier termination of the dosed groups compared with the control group.

In all of the intervals 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 DCDD, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Among both male and female mice the mean body weights of both dosed groups were lower than those of the corresponding controls at the time the animals were placed on study. During the study, mean body weights of dosed female mice were lower than those of corresponding controls and were essentially the same in the low- and high-dose groups (figure 3). Mean body weights of the male mice were unaffected by administration of the test chemical. Some fluctuation in the growth curves 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 in the dosed females were reported.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered DCDD in the diet at the doses of this bioassay, together with those of the

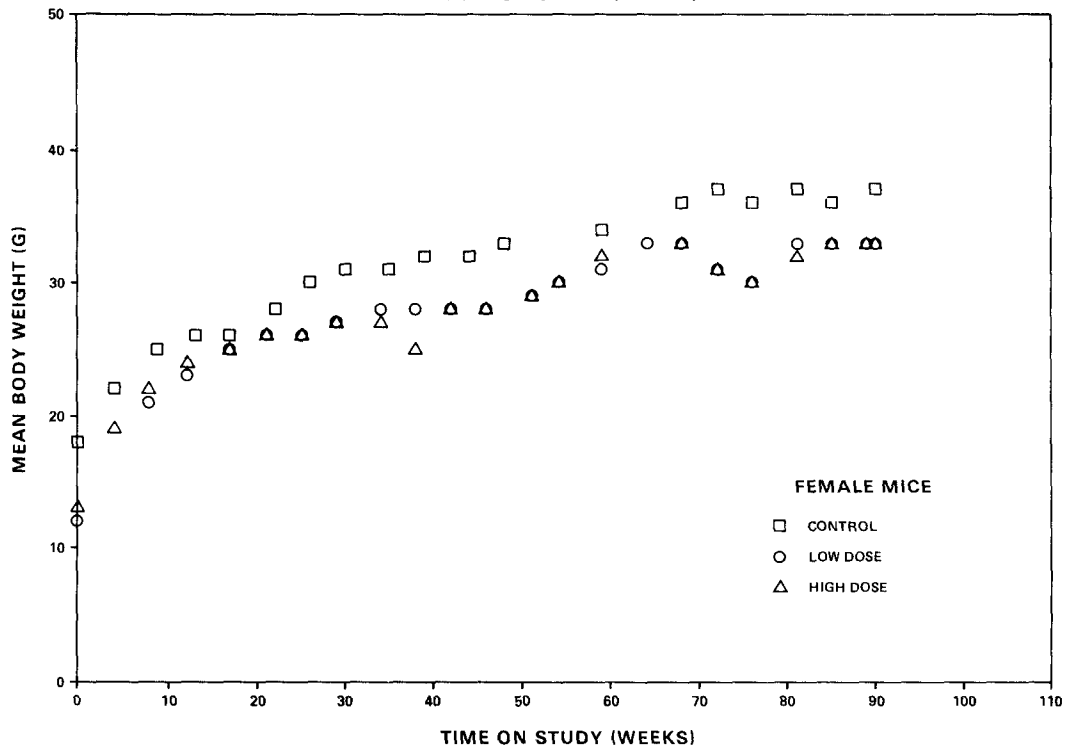
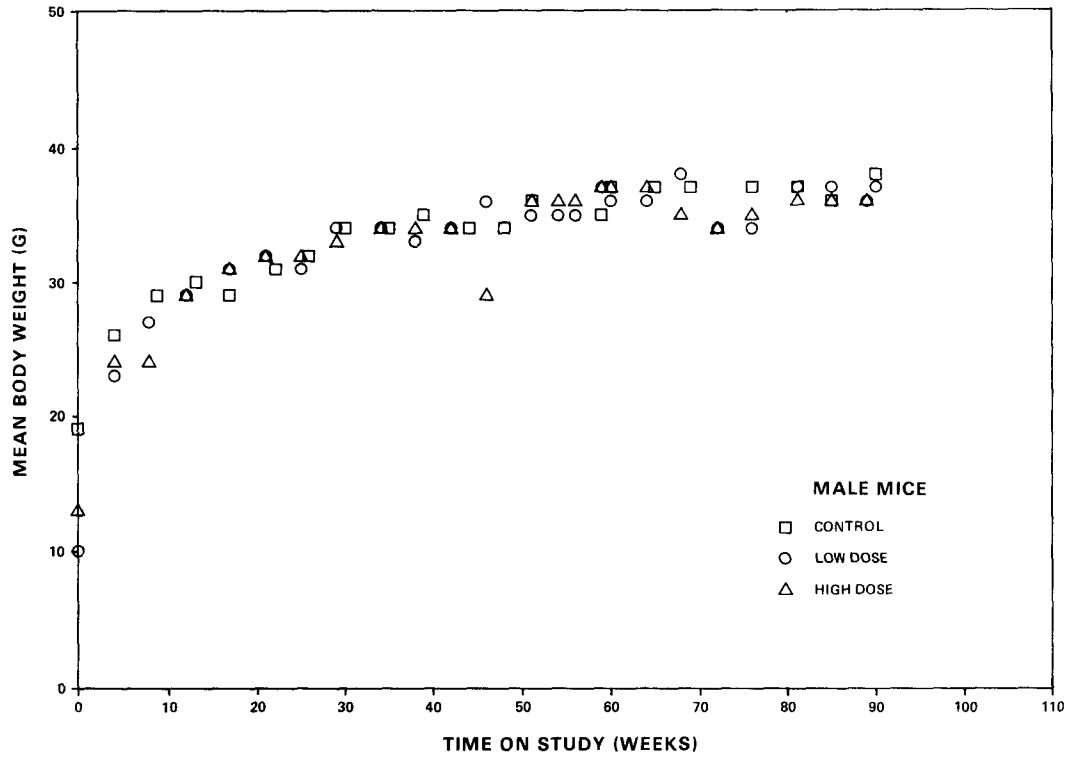


Figure 3. Growth Curves for Mice Administered DCDD in the Diet

controls, are shown in figure 4. In each sex, the control group was started on study 16 weeks before the dosed groups; however, the Tarone test for dose-related trend in mortality is applied as if the three groups of each sex were started at the same time. There are substantial differences in the time on study for both male and female groups. Control males were terminated at 92 to 93 weeks, while dosed males were terminated at 99 to 101 weeks. Control and low-dose females were terminated at 91 to 93 weeks, whereas the high-dose females were terminated at week 98. The Cox and Tarone tests are applied only to the first 91 weeks on study. The results of the Tarone test are not significant in male mice but indicate a probability trend of P less than 0.001 in female mice.

In male mice, 38/50 (76%) of the high-dose animals, 36/50 (72%) of the low-dose animals, and 48/50 (96%) of the controls lived to the end of the study. In females, 28/50 (56%) of the high-dose animals, 46/50 (92%) of the low-dose animals, and 45/50 (90%) of the controls lived to the end of the study. Sufficient numbers of dosed and control mice of each sex were at risk for the development of late-appearing tumors.

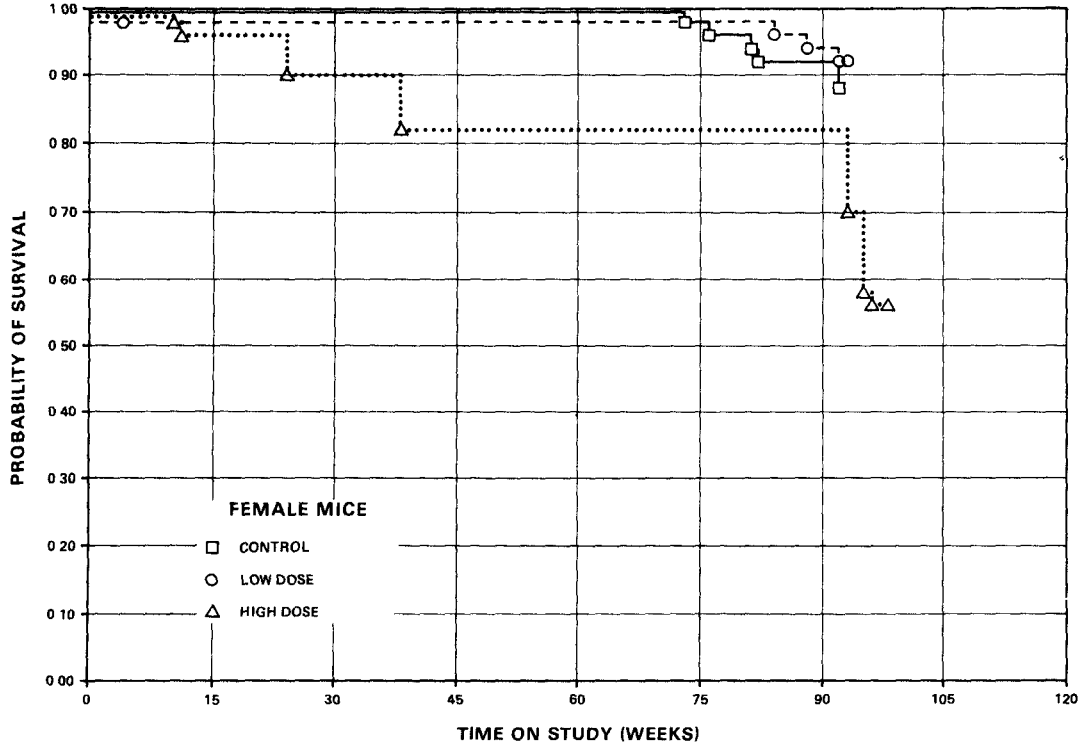
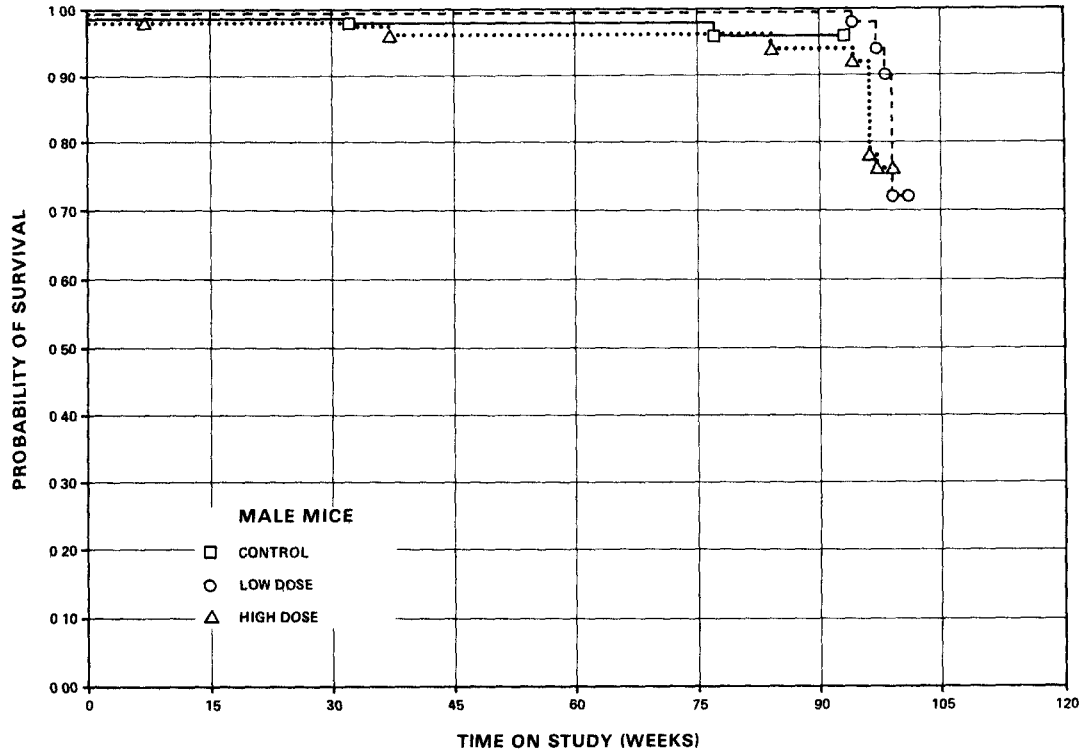


Figure 4. Survival Curves for Mice Administered DCDD in the Diet

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.

A variety of tumors were observed in both the control and dosed mice, each of which has been previously seen in untreated aging B6C3F1 mice.

The incidence of hepatocellular carcinomas in male mice was 4/49 (8%) in the controls, 5/50 (10%) in the low-dose group, and 5/42 (12%) in the high-dose group; the incidence of hepatocellular adenomas was 4/49 (8%) in the controls, 15/50 (30%) in the low-dose group, and 12/42 (29%) in the high-dose group. In contrast, the female mice administered DCDD in the diet did not respond with an increased incidence of either hepatocellular neoplasm. Both male and female mice, however, showed increased incidences of focal necrosis of the liver in the dosed groups.

Based on the pathology examination, exposure to DCDD may have been associated with an increased incidence of liver tumors in male 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 16 weeks after the dosed groups; however, the Cochran-Armitage test for dose-related trend in the incidence of tumors is applied as if the three groups of each sex were started at the same time.

In male mice, the result of the Cochran-Armitage test for the incidence of animals with either hepatocellular adenomas or carcinomas is significant ($P = 0.008$). The Fisher exact comparisons of the incidence in the control group with those in the low- and high-dose groups show P values of 0.008 and 0.010, respectively. In the current historical records at this laboratory the incidence of such liver tumors in control groups is 32/125 (26%), with individual group incidences of 8/49 (16%), 9/25(36%), and two groups with 7/25 (28%), compared with 17/42 (40%) in the high-dose group and 20/50 (40%) in the low-dose group of this study.

The result of the Fisher exact test comparing the incidence of animals with either lymphoma or leukemia of the hematopoietic system in the low-dose male mice with that of the control group is significant ($P = 0.006$), but a significant incidence is not indicated in the high-dose group. The result of the Cochran-Armitage test for this incidence of tumors is not significant.

In the incidence of male mice with either hemangiosarcomas or hemangiomas of all sites, the Fisher exact comparison of the incidences in the low-dose and control groups shows a P value of 0.028, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The high-dose group does not have a significant incidence. The result of the Cochran-Armitage test for this incidence of tumors is not significant.

In female mice, the results of the Cochran-Armitage test and those of the Fisher exact test for tumor incidence at any site are not significant. A significant trend in the negative direction is observed in the incidence of squamous-cell papillomas of the stomach in male mice.

In some of the intervals 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 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 DCDD, which could not be detected under the conditions of this test.

V. DISCUSSION

The mean body weights of the dosed male rats and male and female mice were lower than those of the corresponding controls at the time the animals were placed on study. While the mean body weights of the dosed male rats remained lower than those of their corresponding controls throughout the study, the mean body weights of the dosed female rats were lower than their corresponding controls only after week 50. Mean body weights of the dosed female, but not the male, mice were lowered throughout the study. The survival in any of the dosed groups, however, was not significantly affected by administration of the test chemical. In the mice the tests for difference in survival were applied only to the first 91 weeks on study since control males were terminated at 92 to 93 weeks, while dosed males were terminated at 99 to 101 weeks. Control and low-dose females were terminated at 91 to 93 weeks, whereas the high-dose females were terminated at week 98.

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

In the male mice, hepatocellular adenomas or carcinomas occurred at incidences that in direct comparisons were higher in the low-dose group ($P = 0.008$) and the high-dose group ($P = 0.010$) than in the control group (controls 8/49, low-dose 20/50, high-dose 17/42). In recent findings at this laboratory the incidence of such liver tumors in control groups is 32/125 (26%), with individual group incidences of 8/49 (16%), 9/25 (36%), and two groups with 7/25 (28%), compared with 17/42 (40%) in the high-dose group and 20/50 (40%) in the low-dose group in this study. The occurrence of increased incidences of hepatocellular adenomas or carcinomas in the dosed groups of male mice cannot, therefore, be clearly related to the administration of the test chemical.

Leukemias or lymphomas occurred in the male mice at incidences that were significant ($P = 0.006$) in a direct comparison of the low-dose and control groups. Similarly, hemangiosarcomas or hemangiomas at all sites occurred in male mice at incidences that were significant ($P = 0.028$) in a direct comparison of the low-dose and control groups. However, the incidences of these hematopoietic tumors or vascular tumors did not show dose-related trends and were not higher in high-dose groups than in corresponding control groups. Thus, the occurrence of these

tumors in the dosed groups of male mice cannot be clearly related to administration of the test chemical.

Unlike 2,3,7,8-tetrachlorodibenzo-p-dioxin, which has been reported to be highly toxic when tested in Sherman rats (Schwetz et al., 1973) and to be carcinogenic in Sprague-Dawley rats (Van Miller et al., 1977), DCDD was observed in the present bioassay to have a relatively low toxicity for Osborne-Mendel rats and B6C3F1 mice. The necrosis observed in both rats and mice and the fatty metamorphosis observed in the rats administered DCDD is similar, however, 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 DCDD was not carcinogenic for Osborne-Mendel rats of either sex or for female B6C3F1 mice. The marginal increased incidences of combinations of leukemias and lymphomas, of hemangiosarcomas and hemangiomas, and of hepatocellular carcinomas and adenomas in male B6C3F1 mice is considered as suggestive of a carcinogenic effect of 2,7-dichlorodibenzo-p-dioxin in these animals.

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APPENDIX A

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

TABLE A1.

**SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS
ADMINISTERED DCDD IN THE DIET**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	34	35	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	33	34	33
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(34)	(35)	(34)
FIBROMA	3 (9%)		
FIBROSARCOMA		1 (3%)	
LIPOMA	1 (3%)		
RESPIRATORY SYSTEM			
*LUNG	(30)	(34)	(33)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (3%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (3%)		
CORTICAL CARCINOMA, METASTATIC			1 (3%)
HEMATOPOIETIC SYSTEM			
*BRAIN	(31)	(34)	(31)
MALIGNANT RETICULOSIS		1 (3%)	
*MULTIPLE ORGANS	(34)	(35)	(34)
MALIGNANT LYMPHOMA, UNDIFFER-TYPE		1 (3%)	
*SPLEEN	(31)	(34)	(32)
SARCOMA, NOS	1 (3%)		
HEMANGIOSARCOMA		2 (6%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*LIVER	(31)	(34)	(33)
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
HEPATOCELLULAR CARCINOMA			1 (3%)
*STOMACH	(31)	(34)	(33)
LEIOMYOSARCOMA			1 (3%)
URINARY SYSTEM			
*KIDNEY	(31)	(34)	(33)
LIPCSARCOMA	1 (3%)		
MIXED TUMOR, MALIGNANT	1 (3%)		
ENDOCRINE SYSTEM			
*PITUITARY	(16)	(22)	(17)
ADENOMA, NOS	2 (13%)		
CHROMOPHOBE ADENOMA	1 (6%)		1 (6%)
*ADRENAL	(31)	(34)	(32)
CORTICAL ADENOMA	7 (23%)	4 (12%)	2 (6%)
CORTICAL CARCINOMA		1 (3%)	1 (3%)
PHEOCHROMOCYTOMA	6 (19%)	2 (6%)	
*THYROID	(29)	(34)	(32)
FOLLICULAR ADENOCARCINOMA			1 (3%)
FOLLICULAR-CELL ADENOMA	2 (7%)		
FOLLICULAR-CELL CARCINOMA	1 (3%)	1 (3%)	
C-CELL ADENOMA	3 (10%)	3 (9%)	
*PARATHYROID	(25)	(24)	(26)
ADENOMA, NOS	2 (8%)		
*PANCREATIC ISLETS	(24)	(33)	(29)
ISLET-CELL ADENOMA	1 (4%)	1 (3%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY FIBROSCARCOMA, METASTATIC	(34)	(35) 1 (3%)	(34)
*TUNICA VAGINALIS MESOTHELIOMA, NOS	(34) 2 (6%)	(35)	(34)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE LIPOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	35	35	35
NATURAL DEATH	20	20	26
MOBUND SACRIFICE		3	1
**SCHEDULED SACRIFICE	1	1	
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	11	8
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

** Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	14	6
TOTAL PRIMARY TUMORS	37	18	7
TOTAL ANIMALS WITH BENIGN TUMORS	17	10	3
TOTAL BENIGN TUMORS	30	11	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	7	4
TOTAL MALIGNANT TUMORS	5	7	4
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			

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS
ADMINISTERED DCDD 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	30
INTEGUMENTARY SYSTEM			
*SKIN	(35)	(33)	(33)
FIBROMA		1 (3%)	
LEIOMYOSARCOMA, METASTATIC			1 (3%)
*SUBCUT TISSUE	(35)	(33)	(33)
FIBROMA	1 (3%)		
FIBROSARCOMA	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(35)	(33)	(33)
SQUAMOUS CELL CARCINOMA			1 (3%)
HEMATOPOIETIC SYSTEM			
*SPLEEN	(30)	(33)	(29)
HEMANGIOMA			1 (3%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*PANCREAS	(29)	(32)	(26)
LEIOMYOSARCOMA, INVASIVE			1 (4%)
*STOMACH	(31)	(33)	(27)
PAPILLOMA, NOS			1 (4%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
LEICMYCSARCOMA			1 (4%)
URINARY SYSTEM			
*KIDNEY	(31)	(33)	(30)
FIBROSARCOMA, METASTATIC	1 (3%)		
ENDOCRINE SYSTEM			
*PITUITARY	(18)	(25)	(20)
CHROMOPHOBE ADENOMA	4 (22%)	3 (12%)	7 (35%)
*ADRENAL	(30)	(33)	(29)
CORTICAL ADENOMA	11 (37%)	7 (21%)	9 (31%)
*THYROID	(28)	(32)	(25)
FOLLICULAR-CELL CARCINOMA		2 (6%)	2 (8%)
C-CELL ADENOMA	4 (14%)		
CYSTADENOMA, NOS		1 (3%)	
*THYROID FOLLICLE	(28)	(32)	(25)
CYSTADENOMA, NOS	2 (7%)		
*PANCREATIC ISLETS	(29)	(32)	(26)
ISLET-CELL ADENOMA	1 (3%)		
ISLET-CELL CARCINOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(35)	(33)	(33)
ADENOMA, NOS	3 (9%)	5 (15%)	
ADENOCARCINOMA, NOS	1 (3%)	1 (3%)	
FIBROSARCOMA	1 (3%)	1 (3%)	
FIBROADENOMA	13 (37%)	7 (21%)	4 (12%)
*UTERUS	(30)	(32)	(30)
ADENOCARCINOMA, NOS	1 (3%)		
PAPILLARY CYSTADENOMA, NOS	1 (3%)		
LEIOMYOSARCOMA			1 (3%)
*OVARY	(26)	(31)	(26)
GRANULOSA-CELL TUMOR		2 (6%)	

* 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%)	1 (3%)	
NERVOUS SYSTEM			
NCNE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND ADENOCARCINOMA, NOS	(35) 1 (3%)	(33)	(33)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL FIBROSARCOMA	(35) 1 (3%)	(33)	(33)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	35	35	35
NATURAL DEATH@	14	10	14
MORIEUND SACRIFICE			1
**SCHEDULED SACRIFICE	4		1
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	25	19
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

** Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	22	16
TOTAL PRIMARY TUMORS	47	32	27
TOTAL ANIMALS WITH BENIGN TUMORS	24	19	15
TOTAL BENIGN TUMORS	42	26	22
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	4	5
TOTAL MALIGNANT TUMORS	5	4	5
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		2
TOTAL SECONDARY TUMORS	1		2
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 DCDD IN THE DIET

TABLE B1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	45
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(45)
PAPILLOMA, NOS	1 (2%)		
HEMANGIOSARCOMA, METASTATIC			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(45)
SERFACEOUS ADENOMA	1 (2%)		
LEIOMYOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
*LUNG	(49)	(49)	(44)
ALVEOLAR/BRONCHIOLAR ADENOMA	8 (16%)	2 (4%)	5 (11%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		3 (6%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(45)
MALIG. LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	2 (4%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)	1 (2%)
MONOCYTIC LEUKEMIA		1 (2%)	
MAST-CELL LEUKEMIA		1 (2%)	
*SPLEEN	(48)	(48)	(43)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA		4 (8%)	1 (2%)
*MESENTERIC L. NODE	(1)	(42)	(36)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*LIVER	(49)	(50)	(42)
HEPATOCELLULAR ADENOMA	4 (8%)	15 (30%)	12 (29%)
HEPATOCELLULAR CARCINOMA	4 (8%)	5 (10%)	5 (12%)
HEMANGIOSARCOMA		1 (2%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)
*BILE DUCT	(49)	(50)	(42)
BILE DUCT CARCINOMA	1 (2%)		
*STOMACH	(49)	(47)	(43)
SQUAMOUS CELL PAPILLOMA	5 (10%)		
*COLON		(37)	(36)
ADENOCARCINOMA, NOS		1 (3%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
*THYROID	(39)	(43)	(43)
PAPILLARY ADENOMA			1 (2%)
PAPILLARY CYSTADENOMA, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(45)
PAPILLARY ADENOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	2	5	11
MORIBUND SACRIFICE		9	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	48	36	38
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	30	25
TOTAL PRIMARY TUMORS	26	40	27
TOTAL ANIMALS WITH BENIGN TUMORS	17	19	17
TOTAL BENIGN TUMORS	20	19	18
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	17	9
TOTAL MALIGNANT TUMORS	6	21	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			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			

TABLE B2.

**SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE
ADMINISTERED DCDD IN THE DIET**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROSARCOMA			1 (2%)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
HEMANGIOMA			1 (2%)
*SUBCUT TISSUE	(50)	(49)	(48)
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(47)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	2 (4%)	
HEMATOPCIE TIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(48)
MALIGNANT LYMPHOMA, NOS	4 (8%)	1 (2%)	
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)	7 (14%)	3 (6%)
LYMPHOCYTIC LEUKEMIA		2 (4%)	
GRANULOCYTIC LEUKEMIA		1 (2%)	
*SPLEEN	(50)	(48)	(46)
HEMANGIOSARCOMA			1 (2%)
*LYMPH NODE	(5)	(37)	(37)
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)	(48)	(47)
HEPATOCYLLULAR CARCINOMA		1 (2%)	
# STOMACH	(48)	(48)	(39)
PAPILLOMA, NOS		2 (4%)	1 (3%)
PAPILLOMATOSIS		1 (2%)	
SQUAMOUS CELL PAPILLOMA	1 (2%)		
URINARY SYSTEM			
# URINARY BLADDER	(2)	(36)	(34)
PAPILLOMATOSIS	2 (100%)		
ENDOCRINE SYSTEM			
# PARATHYROID	(20)	(25)	(29)
ADENOCARCINOMA, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
* VAGINA	(50)	(49)	(48)
HEMANGIOSARCOMA	1 (2%)		
# UTERUS	(49)	(46)	(45)
LEIOMYOMA			1 (2%)
# OVARY	(20)	(43)	(41)
LUTEOMA		1 (2%)	
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 LYMPHANGIOMA	(50) 1 (2%)	(49)	(48)
*ABDOMINAL VISCERA NEOPLASM, NOS	(50)	(49) 1 (2%)	(48)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	5	4	10
MORIBUND SACRIFICE			12
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	45	46	28
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	18	9
TOTAL PRIMARY TUMORS	15	19	12
TOTAL ANIMALS WITH BENIGN TUMORS	7	6	3
TOTAL BENIGN TUMORS	7	6	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	12	8
TOTAL MALIGNANT TUMORS	8	12	9
TOTAL ANIMALS WITH SECONDARY TUMORS [#]	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- EFFICACY 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 DCDD IN THE DIET

TABLE C1.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
ADMINISTERED DCDD IN THE DIET**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	35	35	35
ANIMALS NECROPSIED	34	35	34
ANIMALS EXAMINED HISTOPATHOLOGICALLY	33	34	33
INTEGUMENTARY SYSTEM			
*SKIN	(34)	(35)	(34)
SEBACEOUS CYST		1 (3%)	
*SUBCUT TISSUE	(34)	(35)	(34)
GRANULOMA, NOS	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(34)	(35)	(34)
INFLAMMATION, CHRONIC		7 (20%)	10 (29%)
INFLAMMATION, CHRONIC SUPPURATIV		3 (9%)	
*NASAL TURBINATE	(34)	(35)	(34)
INFLAMMATION, ACUTE	5 (15%)		
INFLAMMATION, ACUTE SUPPURATIVE	6 (18%)		
INFLAMMATION, CHRONIC	2 (6%)		
*TRACHEA	(30)	(34)	(33)
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC	7 (23%)	10 (29%)	9 (27%)
INFLAMMATION, CHRONIC SUPPURATIV	2 (7%)	1 (3%)	1 (3%)
#LUNG/BRONCHIOLE	(30)	(34)	(33)
HYPERPLASIA, FOCAL			1 (3%)
*LUNG	(30)	(34)	(33)
CONGESTION, NOS	1 (3%)		1 (3%)
EDEMA, NOS	1 (3%)		
BRONCHOPNEUMONIA, NOS		1 (3%)	1 (3%)
PNEUMONIA, CHRONIC MURINE	8 (27%)	22 (65%)	21 (64%)
INFLAMMATION, CHRONIC			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
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(31)	(34)	(31)
ATROPHY, NOS		1 (3%)	
HYPERPLASIA, HEMATOPOIETIC	4 (13%)		
#SPLEEN	(31)	(34)	(32)
INFARCT HEMORRHAGIC			1 (3%)
HEMOSIDROSIS	3 (10%)		3 (9%)
ATROPHY, NOS			2 (6%)
DEPLETION		2 (6%)	3 (9%)
LYMPHOID DEPLETION			2 (6%)
HYPERPLASIA, HEMATOPOIETIC		4 (12%)	3 (9%)
HYPERPLASIA, ERYTHROID		1 (3%)	
HEMATOPOIESIS	3 (10%)	1 (3%)	
#SPLENIC FOLLICLES	(31)	(34)	(32)
ATROPHY, NOS	1 (3%)		
#LYMPH NODE	(22)	(22)	(28)
INFLAMMATION, CHRONIC		1 (5%)	
#MANDIBULAR L. NODE	(22)	(22)	(28)
HYPERPLASIA, LYMPHOID	5 (23%)		
#CERVICAL LYMPH NODE	(22)	(22)	(28)
INFLAMMATION, CHRONIC			2 (7%)
HYPERPLASIA, NOS		1 (5%)	
#BRONCHIAL LYMPH NODE	(22)	(22)	(28)
HEMORRHAGE	1 (5%)		
#THYMUS	(3)	(17)	(25)
ATROPHY, NOS	3 (100%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(30)	(34)	(33)
INFLAMMATION, CHRONIC	4 (13%)		1 (3%)
INFLAMMATION, CHRONIC FOCAL		4 (12%)	1 (3%)
INFLAMMATION, CHRONIC DIFFUSE		1 (3%)	
#ENDOCARDIUM	(30)	(34)	(33)
DEGENERATION, MUCOID		1 (3%)	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
*AORTA	(34)	(35)	(34)
MINERALIZATION		1 (3%)	2 (6%)
*PULMONARY ARTERY	(34)	(35)	(34)
CALCIFICATION, DYSTROPHIC	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(31)	(34)	(33)
CYST, NOS	1 (3%)		
CONGESTION, CHRONIC PASSIVE	1 (3%)		
ABSCCESS, NOS		1 (3%)	
CIRRHOISIS, CARDIAC	1 (3%)		
METAMORPHOSIS FATTY	2 (6%)		
FOCAL CELLULAR CHANGE		1 (3%)	1 (3%)
HYPERPLASIA, NOS	5 (16%)		
ANGIECTASIS	1 (3%)		
*LIVER/CENTRILOBULAR	(31)	(34)	(33)
CONGESTION, NOS		1 (3%)	1 (3%)
NECROSIS, NOS		2 (6%)	2 (6%)
METAMORPHOSIS FATTY		13 (38%)	16 (48%)
#BILE DUCT	(31)	(34)	(33)
CYST, NOS			2 (6%)
HYPERPLASIA, NOS	8 (26%)		
#PANCREAS	(24)	(35)	(29)
PERIPANCREATITIS	1 (4%)	4 (12%)	1 (3%)
#PANCREATIC ACINUS	(24)	(33)	(29)
ATROPHY, NOS		1 (3%)	
ATROPHY, FOCAL			2 (7%)
#STOMACH	(31)	(34)	(33)
DIVERTICULUM			1 (3%)
INFLAMMATION, CHRONIC		1 (3%)	
ACANTHOSIS		1 (3%)	
#GASTRIC SUBMUCOSA	(31)	(34)	(33)
MINERALIZATION		1 (3%)	
*ANUS	(34)	(35)	(34)
INFLAMMATION, NECROTIZING		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)	(34)	(33)
CAST, NOS			1 (3%)
HYDRONEPHROSIS		1 (3%)	
PYELONEPHRITIS, NOS			1 (3%)
INFLAMMATION, INTERSTITIAL		2 (6%)	5 (15%)
INFLAMMATION, CHRONIC	23 (74%)		1 (3%)
PYELONEPHRITIS, CHRONIC	1 (3%)		
NEPHROPATHY		21 (62%)	2 (6%)
*KIDNEY/TUBULE	(31)	(34)	(33)
DILATATION, NOS		1 (3%)	2 (6%)
CAST, NOS		1 (3%)	2 (6%)
HEMORRHAGE			1 (3%)
*KIDNEY/PELVIS	(31)	(34)	(33)
HEMORRHAGE			1 (3%)
HYPERPLASIA, EPITHELIAL			3 (9%)
*URINARY BLADDER	(28)	(32)	(27)
INFLAMMATION, SUPPURATIVE			1 (4%)
INFLAMMATION, CHRONIC	2 (7%)		
INFLAMMATION, CHRONIC SUPPURATIVE		1 (3%)	1 (4%)
HYPERPLASIA, EPITHELIAL			1 (4%)
ENDOCRINE SYSTEM			
*PITUITARY	(16)	(22)	(17)
CYST, NOS	2 (13%)		
*ADRENAL	(31)	(34)	(32)
CONGESTION, NOS		1 (3%)	
LIPOIDOSIS		2 (6%)	3 (9%)
HYPERPLASIA, FOCAL	1 (3%)		1 (3%)
ANGIECTASIS	1 (3%)		
*ADRENAL CORTEX	(31)	(34)	(32)
LIPOIDOSIS	11 (35%)		
*THYROID	(29)	(34)	(32)
CYST, NOS			1 (3%)
GOITER COLLOID			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
HYPERPLASIA, FOCAL			1 (3%)
*PARATHYROID HYPERPLASIA, NOS	(25) 4 (16%)	(24) 1 (4%)	(26)
REPRODUCTIVE SYSTEM			
*PENIS INFLAMMATION, CHRONIC SUPPURATIVE	(34)	(35) 1 (3%)	(34)
*PROSTATE INFLAMMATION, SUPPURATIVE	(29)	(31) 1 (3%)	(27) 1 (4%)
INFLAMMATION, ACUTE	2 (7%)		
INFLAMMATION, CHRONIC	4 (14%)		
INFLAMMATION, CHRONIC SUPPURATIVE		1 (3%)	
*SEMINAL VESICLE DILATATION, NOS	(34) 1 (3%)	(35)	(34)
INFLAMMATION, SUPPURATIVE		1 (3%)	
ABSCCESS, NOS		1 (3%)	
INFLAMMATION, CHRONIC	1 (3%)		
INFLAMMATION, CHRONIC SUPPURATIVE			1 (3%)
ATROPHY, NOS		1 (3%)	
HYPERPLASIA, EPITHELIAL			1 (3%)
*TESTIS ABSCCESS, NOS	(32) 1 (3%)	(33)	(33)
PERIARTERITIS	2 (6%)		
ATROPHY, NOS	9 (28%)	9 (27%)	10 (30%)
ATROPHY, FOCAL			1 (3%)
ASPERMATOGENESIS	1 (3%)		
*TESTIS/TUBULE MINERALIZATION	(32)	(33) 1 (3%)	(33) 1 (3%)
*SPERMATOGENIC EPITHE LIAL ATROPHY, NOS	(32)	(33)	(33) 1 (3%)
*EPIDIDYMISS GRANULOMA, SPERMATIC	(34)	(35) 1 (3%)	(34)
*MUSCULARIS OF VAS DE DEFERENTIS MINERALIZATION	(34)	(35) 1 (3%)	(34)
NERVOUS SYSTEM			
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 SENSE ORGANS			
*ZYMBAL'S GLAND HYPERPLASIA, CYSTIC	(34)	(35) 1 (3%)	(34)
MUSCULOSKELETAL SYSTEM			
*JOINT OF WRIST INFLAMMATION, CHRONIC	(34)	(35)	(34) 1 (3%)
BODY CAVITIES			
*ABDOMINAL CAVITY PERITONITIS	(34)	(35)	(34) 1 (3%)
*MESENTERY PERIARTERITIS	(34) 1 (3%)	(35)	(34)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF	1		
AUTO/NECROPSY/NO HISTO	1	1	1
AUTOLYSIS/NO NECROPSY	1		1

TABLE C2.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
ADMINISTERED DCDD 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	30
INTEGUMENTARY SYSTEM			
*SKIN	(35)	(33)	(33)
ULCER, NOS		1 (3%)	
HYPERKERATOSIS			3 (9%)
ACANTHOSIS			3 (9%)
*SUBCUT TISSUE	(35)	(33)	(33)
GRANULOMA, FOREIGN BODY	1 (3%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(35)	(33)	(33)
INFLAMMATION, SUPPURATIVE		1 (3%)	
INFLAMMATION, HEMORRHAGIC		1 (3%)	
INFLAMMATION, CHRONIC		1 (3%)	
INFLAMMATION, CHRONIC DIFFUSE		2 (6%)	
INFLAMMATION, CHRONIC SUPPURATIVE		1 (3%)	1 (3%)
INFLAMMATION PROLIFERATIVE		3 (9%)	1 (3%)
*NASAL TURBINATE	(35)	(33)	(33)
INFLAMMATION, ACUTE	1 (3%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
*TRACHEA	(29)	(33)	(29)
INFLAMMATION, NOS	5 (17%)		
INFLAMMATION, SUPPURATIVE		1 (3%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
INFLAMMATION, CHRONIC		9 (27%)	1 (3%)
INFLAMMATION PROLIFERATIVE		3 (9%)	6 (21%)
*LUNG	(30)	(33)	(28)
CONGESTION, NOS	2 (7%)		
BRONCHOPNEUMONIA, NOS		3 (9%)	3 (11%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, INTERSTITIAL		1 (3%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (3%)		
ABSCESS, NOS		1 (3%)	2 (7%)
PNEUMONIA, CHRONIC MURINE	6 (20%)	14 (42%)	10 (36%)
PNEUMONIA INTERSTITIAL CHRONIC			1 (4%)
GRANULOMA, NOS	1 (3%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(31)	(32)	(26)
HYPERPLASIA, HEMATOPOIETIC	4 (13%)		
#SPLEEN	(30)	(33)	(29)
INFLAMMATION, ACUTE	4 (13%)		
INFLAMMATION, CHRONIC	1 (3%)		
HEMOSIDEROSIS	2 (7%)	5 (15%)	2 (7%)
ATROPHY, NOS	1 (3%)		
DEPLETION			2 (7%)
LYMPHOID DEPLETION		3 (9%)	
HEMATOPOIESIS	6 (20%)	3 (9%)	3 (10%)
#MANDIBULAR L. NODE	(25)	(25)	(25)
HEMORRHAGIC CYST	1 (4%)		
INFLAMMATION, ACUTE	1 (4%)		
PLASMA-CELL INFILTRATE	3 (12%)		
HYPERPLASIA, LYMPHOID	5 (20%)		
#CERVICAL LYMPH NODE	(25)	(25)	(25)
INFLAMMATION, CHRONIC		3 (12%)	
HYPERPLASIA, LYMPHOID		1 (4%)	
#MESENTERIC L. NODE	(25)	(25)	(25)
HYPERPLASIA, LYMPHOID	1 (4%)		
#THYMUS	(9)	(1)	
CYST, NOS	2 (22%)		
ATROPHY, NOS	9 (100%)		
CIRCULATORY SYSTEM			
#HEART	(31)	(29)	(30)
CALCIFICATION, DYSTROPHIC	1 (3%)		
#MYOCARDIUM	(31)	(29)	(30)
FIBROSIS, FOCAL		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
#ENDOCARDIUM	(31)	(29)	(30)
INFLAMMATION WITH FIBROSIS		1 (3%)	
DEGENERATION, MUCOID			1 (3%)
*AORTA	(35)	(33)	(33)
MEDIAL CALCIFICATION		1 (3%)	
*MESENTERIC ARTERY	(35)	(33)	(33)
THROMBOSIS, NOS	1 (3%)		
INFLAMMATION, CHRONIC	1 (3%)		
DIGESTIVE SYSTEM			
#LIVER	(31)	(33)	(30)
CONGESTION, NOS	1 (3%)		
CIRRHOSIS, NOS			1 (3%)
NECROSIS, NOS	1 (3%)	1 (3%)	
NECROSIS, FOCAL	1 (3%)	1 (3%)	
METAMORPHOSIS FATTY		6 (18%)	10 (33%)
LIPCIDOSIS	2 (6%)		
HYPERPLASIA, NODULAR			1 (3%)
HYPERPLASIA, NOS	7 (23%)		
HEMATOPOIESIS	1 (3%)	2 (6%)	1 (3%)
#LIVER/CENTRILOBULAR	(31)	(33)	(30)
NECROSIS, NOS		2 (6%)	6 (20%)
METAMORPHOSIS FATTY	1 (3%)	13 (39%)	10 (33%)
#BILE DUCT	(31)	(33)	(30)
DILATATION, NOS	1 (3%)		
CYST, NOS		2 (6%)	1 (3%)
INFLAMMATION, CHRONIC	1 (3%)		
HYPERPLASIA, NOS	13 (42%)		
#PANCREAS	(29)	(32)	(26)
INFLAMMATION WITH FIBROSIS	1 (3%)		
PERIARTERITIS			2 (8%)
#PANCREATIC DUCT	(29)	(32)	(26)
HYPERPLASIA, NOS	3 (10%)		
#PANCREATIC ACINUS	(29)	(32)	(26)
ATROPHY, NOS		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
*STOMACH	(31)	(33)	(27)
CALCIFICATION, DYSTROPHIC	1 (3%)		
*GASTRIC MUCOSA	(31)	(33)	(27)
CALCIFICATION, NOS		1 (3%)	
*CECUM	(19)	(27)	(25)
ULCER, NOS			1 (4%)
URINARY SYSTEM			
*KIDNEY	(31)	(33)	(30)
MINERALIZATION	17 (55%)		
CAST, NOS		9 (27%)	7 (23%)
CYST, NOS			1 (3%)
HEMORRHAGE			1 (3%)
PYELONEPHRITIS, NOS	1 (3%)		
INFLAMMATION, INTERSTITIAL		5 (15%)	9 (30%)
PYELONEPHRITIS, ACUTE	1 (3%)		
INFLAMMATION, CHRONIC	5 (16%)		
NEPHROPATHY			1 (3%)
*KIDNEY/MEDULLA	(31)	(33)	(30)
MINERALIZATION	1 (3%)		
*KIDNEY/TUBULE	(31)	(33)	(30)
DILATATION, NOS		12 (36%)	7 (23%)
CAST, NOS		3 (9%)	
CYST, NOS	4 (13%)		
*URINARY BLADDER	(25)	(29)	(23)
INFLAMMATION, NOS	1 (4%)		
INFLAMMATION, HEMORRHAGIC		1 (3%)	
INFLAMMATION, ACUTE	1 (4%)		
ENDOCRINE SYSTEM			
*PITUITARY	(18)	(25)	(20)
CYST, NOS	3 (17%)		
COLLOID CYST		1 (4%)	
HEMORRHAGIC CYST		1 (4%)	
*ADRENAL	(30)	(33)	(29)
HEMORRHAGIC CYST		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
LIFOIDOSIS		2 (6%)	
ANGIECTASIS	8 (27%)		
#ADRENAL CORTEX	(30)	(33)	(29)
LIPCIDOSIS	9 (30%)		
HYPERPLASIA, NOS	1 (3%)		
#THYPCID	(28)	(32)	(25)
CYSTIC FOLLICLES	1 (4%)		
FOLLICULAR CYST, NOS	1 (4%)		
HYPERPLASIA, C-CELL	3 (11%)		1 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(35)	(33)	(33)
ABSCISS, NOS			1 (3%)
#UTERUS	(30)	(32)	(30)
EYOMETRA		1 (3%)	1 (3%)
INFLAMMATION, ACUTE	2 (7%)		
#UTERUS/ENDOMETRIUM	(30)	(32)	(30)
CYST, NOS	2 (7%)		
INFLAMMATION, ACUTE	2 (7%)		
HYPERPLASIA, NOS			1 (3%)
#OVARY	(26)	(31)	(26)
CYSTIC FOLLICLES	1 (4%)		
FOLLICULAR CYST, NOS	1 (4%)	1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(35)	(33)	(33)
INFLAMMATION, ACUTE	2 (6%)		
CATARACT	1 (3%)		
*EYE/CCRNEA	(35)	(33)	(33)
INFLAMMATION, ACUTE	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
*EYE/RETINA INFLAMMATION, NOS	(35) 21 (60%)	(33)	(33)
*EYE/LACRIMAL GLAND INFLAMMATION, ACUTE SUPPURATIVE	(35) 1 (3%)	(33)	(33)
*HARDERIAN GLAND ABSCESS, NOS	(35) 1 (3%)	(33)	(33)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE GRANULOMA, FOREIGN BODY	(35) 1 (3%)	(33)	(33)
BODY CAVITIES			
*ABDOMINAL WALL INFLAMMATION, CHRONIC	(35) 1 (3%)	(33)	(33)
*PERITONEUM INFLAMMATION, CHRONIC	(35)	(33)	(33) 1 (3%)
*MESENTERY PERIARTERITIS	(35)	(33)	(33) 1 (3%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			

APPENDIX D

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

TABLE D1.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
ADMINISTERED DCDD IN THE DIET**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	45
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	45
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(44)
CONGESTION, NOS		1 (2%)	1 (2%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, INTERSTITIAL			2 (5%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*BLOOD CFLLS	(50)	(50)	(45)
LEUKOCYTOsis, NOS			1 (2%)
#BONE MARROW	(48)	(43)	(39)
HYPERPLASIA, GRANULOCYTTIC			1 (3%)
*SPLEEN	(48)	(48)	(43)
DEFLECTION			2 (5%)
HYPERPLASIA, LYMPHOID			2 (5%)
HEMATOPOIESIS			1 (2%)
#MESENTERIC L. NODE	(1)	(42)	(36)
HYPERPLASIA, NOS		2 (5%)	
HYPERPLASIA, LYMPHOID		2 (5%)	5 (14%)
CIRCULATORY SYSTEM			
*AORTA	(50)	(50)	(45)
INFLAMMATION, CHRONIC			1 (2%)
* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*CORONARY ARTERY INFLAMMATION, CHRONIC	(50)	(50)	(45) 1 (2%)
DIGESTIVE SYSTEM			
#LIVER NECROSIS, FOCAL HYPERPLASIA, NODULAR HEMATOPOIESIS	(49)	(50) 1 (2%)	(42) 2 (5%) 2 (5%) 1 (2%)
#PANCREAS ABSCESS, NOS	(42)	(48)	(40) 1 (3%)
#PEYERS PATCH HYPERPLASIA, LYMPHOID	(5)	(45) 1 (2%)	(39) 2 (5%)
URINARY SYSTEM			
*KIDNEY INFLAMMATION, INTERSTITIAL PYELONEPHRITIS SUPPURATIVE	(49)	(48) 1 (2%)	(42) 1 (2%)
*URINARY BLADDER INFLAMMATION, CHRONIC		(47) 1 (2%)	(37) 1 (3%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND DILATATION, NOS CYST, NOS INFLAMMATION, CHRONIC SUPPURATIVE	(50) 1 (2%)	(50) 1 (2%)	(45) 1 (2%) 1 (2%)
#TESTIS GRANULOMA, SPERMATIC ATROPHY, FOCAL	(49) 1 (2%)	(49) 1 (2%)	(44)
NERVOUS SYSTEM			
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 SENSE ORGANS			
*HARDERIAN GLAND HYPERPLASIA, PAPILLARY	(50)	(50) 1 (2%)	(45)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM INFLAMMATION, CHRONIC FOCAL INFLAMMATION, CHRONIC DIFFUSE	(50)	(50) 1 (2%)	(45) 1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	26	15	8
AUT/NECROPSY/HISTO PERF			1

TABLE D2.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
ADMINISTERED DCDD IN THE DIET**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
# LUNG	(50)	(47)	(47)
INFLAMMATION, NOS	2 (4%)		
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
# BONE MARROW	(48)	(47)	(38)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
# SPLEEN	(50)	(48)	(46)
HEMOSIDEROSIS			3 (7%)
LYMPHOID DEPLETION			3 (7%)
HYPERPLASIA, LYMPHOID	6 (12%)		5 (11%)
MASTOCYTOSIS			1 (2%)
HEMATOPOIESIS		1 (2%)	1 (2%)
# LYMPH NODE	(5)	(37)	(37)
HYPERPLASIA, LYMPHOID	1 (20%)		
# MESENTERIC L. NODE	(5)	(37)	(37)
EDEMA, NOS		1 (3%)	1 (3%)
INFLAMMATION, ACUTE/CHRONIC			1 (3%)
HYPERPLASIA, LYMPHOID		2 (5%)	3 (8%)
# THYMUS		(5)	(1)
HYPERPLASIA, LYMPHOID		3 (60%)	1 (100%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND INFLAMMATION, CHRONIC FOCAL		(43) 1 (2%)	(38)
#LIVER	(50)	(48)	(47)
HEMATOMA, NOS			1 (2%)
INFLAMMATION, DIFFUSE			1 (2%)
HEPATITIS, TOXIC			1 (2%)
PELIOSIS HEPATIS			1 (2%)
NECROSIS, FOCAL			10 (21%)
METAMORPHOSIS FATTY			1 (2%)
CALCIFICATION, FOCAL		1 (2%)	
MEGALOCYTOSIS			1 (2%)
HYPERPLASIA, NOS	1 (2%)		
HEMATOPOIESIS		5 (10%)	5 (11%)
#LIVER/HEPATOCYTES NECROSIS, NOS	(50) 1 (2%)	(48)	(47)
#PANCREAS DILATATION/DUCTS	(26) 1 (4%)	(45) 1 (2%)	(44) 1 (2%)
#STOMACH	(48)	(48)	(39)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
HYPERPLASIA, FOCAL		2 (4%)	
#PFYERS PATCH HYPERPLASIA, LYMPHOID	(1)	(44) 2 (5%)	(36) 2 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(47)	(47)
LYMPHOCYtic INFLAMMATORY INFILTR INFLAMMATION, INTERSTITIAL	2 (4%)		6 (13%)
#KIDNEY/GLOMERULUS AMYLOIDOSIS	(50) 1 (2%)	(47)	(47)
ENDOCRINE SYSTEM			
NONE			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*CLITELFIS INFLAMMATION, CHRONIC SUPPURATIV	(50)	(49)	(48) 1 (2%)
#UTERUS HYPERMETRA ATROPHY, NOS	(49) 4 (8%)	(46)	(45) 1 (2%)
#UTERUS/ENDOMETRIUM HYPERPLASIA, DIFFUSE HYPERPLASIA, CYSTIC	(49) 1 (2%) 48 (98%)	(46) 20 (43%)	(45) 10 (22%)
#OVARY CYST, NOS FOLLICULAR CYST, NOS ABSCFSS, NOS	(20) 5 (25%) 5 (25%)	(43) 1 (2%) 2 (5%)	(41) 6 (15%) 3 (7%)
NERVOUS SYSTEM			
NCNE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM INFLAMMATION, CHRONIC INFLAMMATION, CHRONIC FOCAL	(50)	(49)	(48) 1 (2%) 1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE LIPCGRANULOMA	1		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	10	10
AUT/NECROPSY/HISTO PERF			1
AUTCLYSIS/NO NECROPSY		1	2
* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

APPENDIX E

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

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

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	3/34 (9)	0/35 (0)	0/34 (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		1.594	1.639
Weeks to First Observed Tumor	96	--	--
Spleen: Hemangiosarcoma (b)	0/31 (0)	2/34 (6)	0/32 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.274	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	112	--

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Adrenal: Cortical Adenoma or Carcinoma (b)	7/31 (23)	5/34 (15)	3/32 (9)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.651	0.415
Lower Limit		0.182	0.076
Upper Limit		2.133	1.638
Weeks to First Observed Tumor	91	104	109
Adrenal: Pheochromocytoma (b)	6/31 (19)	2/34 (6)	0/32 (0)
P Values (c,d)	P = 0.006 (N)	N.S.	P = 0.011 (N)
Relative Risk (f)		0.304	0.000
Lower Limit		0.032	0.000
Upper Limit		1.554	0.593
Weeks to First Observed Tumor	86	104	--

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	3/29 (10)	1/34 (3)	0/32 (0)
P Values (c,d)	P = 0.048 (N)	N.S.	N.S.
Relative Risk (f)		0.284	0.000
Lower Limit		0.006	0.000
Upper Limit		3.321	1.480
Weeks to First Observed Tumor	97	77	--
Thyroid: Papillary Adenocarcinoma, Follicular-cell Adenoma, or Follicular-cell Carcinoma (b)	3/29 (10)	1/34 (3)	1/32 (3)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.284	0.302
Lower Limit		0.006	0.006
Upper Limit		3.321	3.518
Weeks to First Observed Tumor	97	77	101

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Thyroid: C-cell Adenoma (b)	3/29 (10)	3/34 (9)	0/32 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.853	0.000
Lower Limit		0.124	0.000
Upper Limit		5.927	1.480
Weeks to First Observed Tumor	110	95	--
<hr/>			
Parathyroid: Adenoma, NOS (b)	2/25 (8)	0/24 (0)	0/26 (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		3.421	3.170
Weeks to First Observed Tumor	110	--	--

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Pituitary: Adenoma, NOS, or Chromophobe Adenoma (b)	3/16 (19)	0/22 (0)	1/17 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.314
Lower Limit		0.000	0.006
Upper Limit		1.157	3.436
Weeks to First Observed Tumor	110	--	111
<hr/>			
Tunica Vaginalis: Mesothelioma, NOS (b)	2/34 (6)	0/35 (0)	0/34 (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		3.246	3.338
Weeks to First Observed Tumor	81	--	--

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

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Pituitary: Chromophobe Adenoma (b)	4/18 (22)	3/25 (12)	7/20 (35)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.540	1.575
Lower Limit		0.091	0.488
Upper Limit		2.825	6.098
Weeks to First Observed Tumor	116	110	103
Adrenal: Cortical Adenoma (b)	11/30 (37)	7/33 (21)	9/29 (31)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.579	0.846
Lower Limit		0.222	0.368
Upper Limit		1.415	1.894
Weeks to First Observed Tumor	115	110	90

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Thyroid: Follicular-cell Carcinoma (b)	0/28 (0)	2/32 (6)	2/25 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.264	0.339
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	110	108
Thyroid: C-cell Adenoma (b)	4/28 (14)	0/32 (0)	0/25 (0)
P Values (c,d)	P = 0.015 (N)	P = 0.042 (N)	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		0.925	1.171
Weeks to First Observed Tumor	115	--	--

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Thyroid or Thyroid Follicle: Cystadenoma, NOS (b)	2/28 (7)	1/32 (3)	0/25 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.437	0.000
Lower Limit		0.008	0.000
Upper Limit		7.961	3.688
69 Weeks to First Observed Tumor	116	110	--
Thyroid or Thyroid Follicle: Follicular-cell Carcinoma or Cystadenoma, NOS (b)	2/28 (7)	3/32 (9)	2/25 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.312	1.120
Lower Limit		0.163	0.087
Upper Limit		14.810	14.392
Weeks to First Observed Tumor	116	110	106

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Adenoma, NOS (b)	3/35 (9)	5/33 (15)	0/33 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.768	0.000
Lower Limit		0.375	0.000
Upper Limit		10.552	1.737
Weeks to First Observed Tumor	113	110	--
Mammary Gland: Fibroadenoma (b)	13/35 (37)	7/33 (21)	4/33 (12)
P Values (c,d)	P = 0.011 (N)	N.S.	P = 0.017 (N)
Relative Risk (f)		0.571	0.326
Lower Limit		0.222	0.087
Upper Limit		1.336	0.932
Weeks to First Observed Tumor	107	110	103

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Mammary Gland: Adenoma, NOS, or Fibroadenoma (b)	14/35 (40)	12/33 (36)	4/33 (12)
P Values (c,d)	P = 0.009 (N)	N.S.	P = 0.009 (N)
Relative Risk (f)		0.909	0.303
Lower Limit		0.455	0.082
Upper Limit		1.783	0.849
16 Weeks to First Observed Tumor	107	110	103
Mammary Gland: Adenoma, NOS, Fibroadenoma, or Adenocarcinoma, NOS (b)	15/35 (43)	12/33 (36)	4/33 (12)
P Values (c,d)	P = 0.005 (N)	N.S.	P = 0.005 (N)
Relative Risk (f)		0.848	0.283
Lower Limit		0.432	0.077
Upper Limit		1.630	0.779
Weeks to First Observed Tumor	93	110	103

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Ovary: Granulosa-cell Tumor (b)	0/26 (0)	2/31 (6)	0/26 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.254	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	110	--

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(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 the 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 DCDD IN THE DIET

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

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/49 (0)	3/49 (6)	0/44 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.016		
Relative Risk (f)		Infinite	--
Lower Limit		0.602	--
Upper Limit		Infinite	--
95 Weeks to First Observed Tumor	--	97	--
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	8/49 (16)	5/49 (10)	5/44 (11)
P Values(c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.625	0.696
Lower Limit		0.172	0.192
Upper Limit		2.007	2.222
Weeks to First Observed Tumor	92	97	97

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Leukemia (b)	0/50 (0)	3/50 (6)	1/45 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.601	0.060
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	98	94
Hematopoietic System: Lymphoma (b)	0/50 (0)	4/50 (8)	2/45 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.927	0.329
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	99	99

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Leukemia or Lymphoma (b)	0/50 (0)	7/50 (14)	3/45 (7)
P Values(c,d)	N.S.	P = 0.006	N.S.
Departure from Linear Trend (e)	P = 0.016		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.941	0.669
Upper Limit		Infinite	Infinite
97 Weeks to First Observed Tumor	--	98	94
All Sites: Hemangiosarcoma (b)	0/50 (0)	4/50 (8)	1/45 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.031		
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.927	0.060
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	97	99

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
All Sites: Hemangiosarcoma or Hemangioma (b)	0/50 (0)	5/50 (10)	1/45 (2)
P Values(c,d)	N.S.	P = 0.028	N.S.
Departure from Linear Trend (e)	P = 0.011		
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.261	0.060
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	97	99
Liver: Hepatocellular Carcinoma (b)	4/49 (8)	5/50 (10)	5/42 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.225	1.458
Lower Limit		0.280	0.335
Upper Limit		5.833	6.884
Weeks to First Observed Tumor	93	99	99

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Liver: Hepatocellular Carcinoma or Adenoma (b)	8/49 (16)	20/50 (40)	17/42 (40)
P Values (c,d)	P = 0.008	P = 0.008	P = 0.010
Relative Risk (f)		2.450	2.479
Lower Limit		1.156	1.138
Upper Limit		5.757	5.862
Weeks to First Observed Tumor	92	97	99
Stomach: Squamous-cell Papilloma (b)	5/49 (10)	0/47 (0)	0/43 (0)
P Values(c,d)	P = 0.008 (N)	P = 0.031 (N)	P = 0.039 (N)
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		0.825	0.900
Weeks to First Observed Tumor	92	--	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice
Administered DCDD 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 the 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 F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered DCDD in the Diet (a)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Lung: Alveolar/Bronchiolar Adenoma (b)	3/50 (6)	2/47 (4)	0/47 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.709	0.000
Lower Limit		0.061	0.000
Upper Limit		5.913	1.766
Weeks to First Observed Tumor	91	92	--
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101 Stomach: Papilloma, NOS, Papillomatosis, or Squamous-cell Papilloma (b)	1/48 (2)	3/48 (6)	1/39 (3)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.000	1.231
Lower Limit		0.252	0.016
Upper Limit		154.112	94.143
Weeks to First Observed Tumor	91	92	93

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

(continued)

<u>Topography: Morphology</u>	<u>Control</u>	<u>Low Dose</u>	<u>High Dose</u>
Hematopoietic System: Leukemia or Lymphoma (b)	6/50 (12)	11/49 (22)	4/48 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.044		
Relative Risk (f)		1.871	0.694
Lower Limit		0.692	0.153
Upper Limit		5.683	2.739
Weeks to First Observed Tumor	76	88	93

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(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 the 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 2,7-Dichlorodibenzo-*p*-Dioxin (DCDD)*
for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

October 25, 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, and State health officials. 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 2,7-Dichlorodibenzo-*p*-Dioxin (DCDD) for carcinogenicity.

The reviewer for the report on the bioassay of DCDD said that, under the conditions of test, the compound was not carcinogenic in either sex of treated rats or female mice. An increased incidence of a variety of tumors, including hepatocellular neoplasms and leukemias, were observed among treated male mice. These findings led the Program staff to conclude that the evidence was suggestive of a carcinogenic effect in male mice. There was no objection to a recommendation that the report on the bioassay of DCDD be accepted as written.

Clearinghouse Members present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Kenneth Wilcox, Michigan State Health Department

* 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.

