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BIOASSAY OF A MIXTURE OF 1, 2, 3, 6, 7, 8-HEXACHLORODIBENZO-p-DIOXIN AND 1, 2, 3, 7, 8, 9-HEXACHLORODIBENZO-p-DIOXIN (Gavage) FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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BIOASSAY OF

A MIXTURE OF

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HEXACHLORODIBENZO-p-DIOXINS

FOR POSSIBLE CARCINOGENICITY

(Gavage Study)

Carcinogenesis Testing Program
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FOREWORD

This report presents the results of the bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins conducted for the Carcinogenesis Testing Program, National Cancer Institute (NCI), National Toxicology Program (NTP). 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 a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that a 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 in animals requires a wider analysis.

CONTRIBUTORS

This bioassay was conducted at the Illinois Institute of Technology Research Institute (IITRI), Chicago, Illinois, initially under direct contract to NCI and later 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. O. G. Fitzhugh (2,3). Mr. T. Kruckeberg (1) and Mr. K. Kaltenborn (1) were in charge of animal care.

Necropsies were performed by Dr. A. R. Roesler (1). Histopathologic evaluations were performed by Dr. W. R. Richter (1). The pathology report

and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). Statistical analyses were performed by Dr. J. R. Joiner (3) and Ms. S. Vatsan (3) using methods selected for the bioassay program by Dr. J. J. Gart (5). 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 chemical analyses were conducted at Midwest Research Institute (6). The results of the chemical analytical work were reviewed by Dr. S. S. Olin (3).

This report was prepared at Tracor Jitco (3) under the direction of Dr. C. R. Angel, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. R. L. Schueler, pathologist; Dr. D. J. Beach, reports manager; Dr. A. C. Jacobs, bioscience writer; and Dr. W. D. Theriault and Ms. M. Glasser, technical editors.

The following scientists at NCI (7) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Jr., Dr. Michael P. Dieter, Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Y. Jack Lee, Dr. Harry Mahar, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Marcelina B. Powers, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins (HCDD) for possible carcinogenicity was conducted by administering the test material by gavage to Osborne-Mendel rats and B6C3F1 mice for 104 weeks.

Fifty rats and 50 mice of each sex were administered HCDD suspended in a vehicle of 9:1 corn oil-acetone 2 days per week for 104 weeks at doses of 1.25, 2.5, or 5 μg/kg/wk for rats and male mice and 2.5, 5, or 10 μg/kg/wk for female mice. Seventy-five rats and 75 mice of each sex served as vehicle controls. In addition, one untreated control group containing 25 rats and 25 mice of each sex was present in the HCDD treatment room, and one untreated control group containing 25 rats and 25 mice of each sex was present in the vehicle-control room. All surviving animals were killed at 105 to 108 weeks.

In rats, a dose-related depression in mean body weight gain became evident in the males after week 68 of the bioassay and in the females after week 33. In mice, the mean body weight gain in the dosed groups was comparable with that of the vehicle-control groups. No other toxic clinical signs were reported in either the rats or the mice. Administration of HCDD had no adverse effect on the survival of either species.

In male rats, hepatocellular carcinomas or neoplastic nodules occurred at low incidences that were dose related (P=0.003). In a direct comparison, the incidence of these tumors in the high-dose group was higher (P=0.022) than that in the corresponding vehicle-control group, but the Bonferroni requirement of P=0.017 for the multiple comparison of three dosed groups with a control group was not met.

In female rats, hepatocellular carcinomas, adenomas, or neoplastic nodules occurred at incidences that were dose related (P less than 0.001), and in direct comparisons the incidences of these tumors in the mid- and high-dosed groups were significantly higher (P=0.006 and P less than 0.001, respectively) than those in the corresponding vehicle-control group.

In male mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P=0.001), and in a direct comparison the incidence of these tumors in the high-dose group was significantly higher (P=0.001) than that in the corresponding vehicle-control group.

In female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P=0.002), and the incidence of these tumors in the high-dose group was significantly higher (P=0.004) than that in the corresponding vehicle-control group.

Complex nonneoplastic toxic liver lesions were seen in all dosed groups of rats and mice. Compound-associated hyperplastic lesions of the lung were also found in both male and female rats.

Under the conditions of this bioassay, HCDD administered by gavage was carcinogenic, causing increased the incidences of hepatocellular carcinomas or neoplastic nodules in female Osborne-Mendel rats and inducing hepatocellular carcinomas and adenomas in male and female B6C3F1 mice. HCDD was not demonstrated to be carcinogenic for male rats.

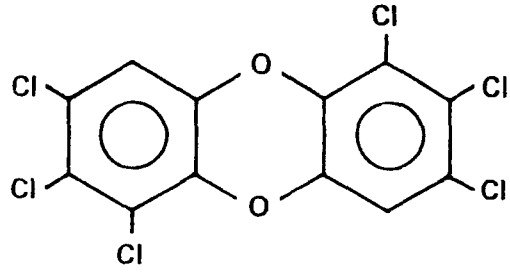
TABLE OF CONTENTS

APPENDIXES

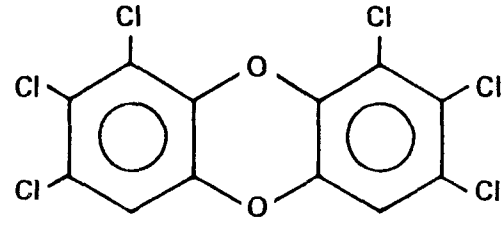
TABLES

FIGURES

I. INTRODUCTION



1, 2, 3, 6, 7, 8-HCDD
CAS 57653-85-7



1, 2, 3, 7, 8, 9-HCDD
CAS 19408-74-3

Hexachlorodibenzo-p-dioxins (HCDD) (NCI C03703) are formed during the manufacture of certain chlorophenols. They have been found in trichlorophenol (Woolson et al., 1972), tetrachlorophenol (Woolson et al., 1972; Firestone et al., 1972), and pentachlorophenol (Woolson et al., 1972; Firestone et al., 1972) and in the chlorophenol-derived herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (Woolson et al., 1972). From 1967 to 1970, the concentration of HCDD in commercial pentachlorophenol ranged from 0.03 to 38 ppm (Firestone et al., 1972). Since then, HCDD levels in pentachlorophenol have been less than 1 ppm (Blaser et al., 1976).

HCDD was first identified in 1967. It was called the "chick edema factor" following research into the cause of a disease that killed millions of chickens in the eastern and midwestern United States (Firestone, 1973). The disease was characterized by a buildup of fluid in the pericardial sac and abdominal cavity or at subcutaneous sites. Liver damage was also seen in these animals. The chick embryo later became the animal test system used to detect HCDD or other dioxins in commercial fatty acids (Firestone, 1978).

Using x-ray crystallography, Cantrell et al. (1969) identified 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (one of the isomers used in the

present study) as one of the toxic components in fats that had been used in animal feeds. The presence of HCDD in animal feeds was traced to impurities in the pentachlorophenol that had been used in the preservation of animal hides. The fats from these hides, which contained HCDD residues, had subsequently been processed and used in animal feeds (Firestone, 1973).

Schwetz et al. (1973) found that a single oral dose of 100 μg/kg HCDD was lethal to male Sprague-Dawley rats. Pregnant Sprague-Dawley rats treated with oral doses of 100 μg/kg/day for 10 consecutive days had severe weight losses and gross evidence of liver changes. Doses of 10 or 100 μg/ kg/day of HCDD were fetotoxic, and a dose of 100μg/kg was teratogenic.

HCDD was assigned for testing with a series of the chlorodibenzo-p-dioxins in the early 1970's after TCDD, a contaminant in 2,4,5-T, was found to be a potent teratogen (Courtney et al., 1970; Sparschu et al., 1971). Preliminary toxicological analyses showed the dioxins to be among the most toxic substances known. Long-term animal bioassays were initiated for all of the dioxins identified at that time because these compounds had been released into the environment along with the herbicides and microbicides they contaminated. A mixture of two HCDD isomers was used in the present study (1,2,3,6,7,8-HCDD and 1,2,3,7,8,9-HCDD). A chronic dermal bioassay of the same batch of HCDD isomers used in the present study was conducted concurrently (NCI, 1980).

II. MATERIALS AND METHODS

A. Chemical

HCDD (Lot No. IIT 102) was synthesized at the Chemistry Division of IIT Research Institute (IITRI), Chicago, Illinois (Appendix E). The white crystalline solid used for the subchronic and chronic gavage studies was approximately 98.6% hexachlorodibenzo-p-dioxin and consisted of a 1:2 mixture of the 1, 2, 3, 6, 7, 8 - (CAS 57653-85-7) and the 1, 2, 3, 7, 8, 9- (CAS 19408-74-3) isomers -- 31% and 67% of total HCDD, respectively.

After separation and purification, the isomers were identified by comparing x-ray powder patterns with theoretical calculations and with the reported x-ray data for the 1,2,3,7,8,9 - isomer (Cantrell et al., 1969). The melting point, gas-liquid chromatography, proton magnetic resonance, and mass spectrometry were also used to characterize the two isomers (Gray et al., 1975). The mixture of the two HCDD isomers used in the present study was similar to the HCDD synthesized by an alternate route (Kende and DeCamp, 1975).

The following impurities were identified by vapor-phase chromatography and mass spectrometry: bromopentachlorodibenzo-p-dioxin, less than 0.004%; dichlorodibenzo-p-dioxin, 0.004%; trichlorodibenzo-p-dioxin, 0.004%; tetrachlorodibenzo-p-dioxin, 0.07%-0.09%; and pentachlorodibenzo-p-dioxin (at least two isomers), 0.04%. No octachlorodibenzo-p-dioxin was found in HCDD by either vapor-phase chromatography or mass spectrometry (Appendix F). Results from subsequent mass spectrometry measurements of fractions separated by vapor-phase chromatography indicated that HCDD used in these tests contained 0.09% ($\pm$0.03%) tetrachlorodibenzo-p-dioxin.

HCDD was stored in brown glass vials at room temperature in an unlighted glove-box hood and was exposed to light only when samples were removed at 3-month intervals for preparation of stock suspensions in acetone.

B. Dosage Preparation

HCDD is insoluble in corn oil and in most other solvents but is partially soluble in acetone. Therefore, HCDD was administered as a suspension in a 9:1 corn oil-acetone solution. Fresh stock suspensions in acetone (Mallinkrodt, Inc., St. Louis, Mo.) containing 100 μg/ml were prepared every 3 months, and working suspensions were prepared every 2 weeks from the stock suspensions. The stock suspensions in acetone were shaken well, suitable aliquots were added to corn oil (Tek-Lad Laboratories, Madison, Wis.), and additional acetone was added to give concentrations of the test chemical of 0.125 to 5.0 μg/ml in 9:1 corn oil-acetone. The working suspensions of HCDD were administered at volumes of 0.05 ml/100 g body weight to rats and 0.05 ml/10 g to mice.

The suspensions of HCDD in either acetone alone or in the corn oil-acetone vehicle were kept in brown glass bottles with Teflon-lined caps. The bottles were sealed with tape, triple-bagged in plastic, and stored at 4°C at all times, except when samples were removed for administration to the rats and mice.

Concentrations of HCDD in the stock suspensions in acetone were determined by analyzing samples when the stock suspensions were freshly prepared and at the end of the 3-month periods of use. The mean concentration of 16 samples containing a theoretical level of 100 μg/ml was 109.3±19.2 μg/ml.

Concentrations of HCDD in suspensions prepared in the corn oil-acetone vehicle could not be determined by the methods used due to difficulty in quantitative chromatographic separation of the chemical from components in the corn oil.

C. Animals

Osborne-Mendel rats and B6C3F1 mice, obtained from the Charles River Breeding Laboratory, Inc., Wilmington, Massachusetts, were used in acute, subchronic, and chronic studies. The animals used in the chronic studies were approximately 4 weeks old when received and were acclimated in the laboratory for 2 weeks before the start of the bioassay. Animals with no

visible signs of disease were earmarked for individual identification and assigned to dosed or control groups according to a table of random numbers.

Because of animal supply limitations, five shipments of rats and three shipments of mice were used over a 7-week period. The animals from each shipment were evenly distributed among all test and control groups. All animals were the same age when placed on test and were dosed or observed for the same period of time, regardless of shipment date.

D. Animal Maintenance

Rats and mice were housed in rooms with the temperature maintained at 20° to 22°C, and the relative humidity was 45% to 55%. Negative air pressure in the animal rooms relative to the hallways was maintained with 15 changes of room air per hour. The exhaust system included a series of HEPA filters through which all air from the animal rooms and hoods was passed before being released from the facility. Fluorescent lighting was provided 12 hours each day.

Rats were housed 3 per cage and mice 10 per cage in polystyrene cages (Maryland Plastics, Federalsburg, Md.) covered with a special tight-fitting polystyrene lid adapted to hold two metal filter housings and a water bottle. The filter housings contained FG 50 filters, one of which was left open to the room atmosphere while the other was attached to a hose that led to a pipe running the length of the shelf on the rack. Pipes on each of four shelves of the rack led to a large vertical pipe at the end of the rack. The large pipe was connected by flexible hose to the HEPA-filtered exhaust system. This arrangement provided a constant flow of air that was filtered both as it entered and as it left the cages.

Because of the possible toxicity of the test chemical for laboratory personnel, the cages (including lids) housing the groups of animals dosed with HCDD were used only once and were discarded every week. The used cages and lids were triple-sealed in plastic bags and incinerated, as was all waste material from the animal rooms and the hoods. The glass water bottles and stainless steel sipper tubes from the used cages were rinsed in the same rooms, using the organic solvent chlorothene, N.U. (Central Solvents,

Chicago, Ill.) to dilute out any dioxin present, and were then sanitized at 82°C in an automatic washer. (Clorothene N.U. is the trademark for a formulation of 1,1,1-trichloroethane with an inhibitor.) The polycarbonate cages in the room housing the vehicle-control groups of animals were recycled three times, and the water bottles and sipper tubes used in these rooms were not rinsed in chlorothene before washing. After 4 weeks of use, the cages housing the control animals were also incinerated. Disposable clothing was worn by all personnel and, after use, it was incinerated by the procedure used for cages and other waste material.

Animals were provided with fresh Absorb-Dri® hardwood chip bedding (Lab Products, Inc., Garfield, N.J.) once a week. They were fed Wayne® Lab Blox (Allied Mills, Inc., Chicago, Ill.) in pellet form and were provided with fresh food when their cages were changed. Tap water was provided ad libitum. Clean water bottles were provided once a week, and the bottles were refilled once a week.

For the chronic study, dosed groups of rats and mice were housed in one room, and vehicle-control groups were housed in a separate room. An untreated-control group, serving as the room environmental-control group, was housed in each room.

E. Acute Studies

Groups of four male and four female 9-week-old Osborne-Mendel rats and 10-week-old B6C3F1 mice were administered single doses of 0.5 to 10 mg/kg body weight of test chemical by gavage and were observed for 9 weeks. The test chemical was composed of 96.8% HCDD isomers, 2.0% pentachloro isomers, and 1.2% heptachloro isomers. The rates of mortality, given in Table 1, indicate an approximate oral LD_{50} of 1.8 mg/kg for male rats, 0.8 mg/kg for female rats, 0.75 mg/kg for male mice, and 0.5 mg/kg for female mice.

F. Subchronic Studies

The amounts of test chemical to be used in the chronic studies were determined by administering HCDD in corn oil-acetone by gavage to groups of 10 male and 10 female 6-week-old rats mice once per week for 13 weeks.

Table 1. Doses and Mortality in Rats and Mice Administered a Single Dose of HCDD by Gavage Followed By 9 Weeks Observation

Dose (mg/kg)	Mortality (a)			
	Osborne-Mendel Rats		B6C3F1 Mice	
	Males	Females	Males	Females
10	4/4	4/4	4/4	4/4
5	3/4	4/4	4/4	4/4
2.5	3/4	4/4	4/4	3/4
1	1/4	4/4	4/4	3/4
0.5	2/4	0/4	0/4	3/4

(a) Number of animals dying/Number of animals in group.

The animals were weighed every week for the first 7 or 8 weeks and every 2 weeks thereafter and were observed daily for deaths. The doses administered and the mean body weights of the dosed groups relative to the control groups at week 10 are given in Table 2. Dose-related decrements in weight gain among rats were more marked in the males than in the females. All dosed groups of mice had lower weight gains than did their controls, but the effects were not clearly dose related.

At the end of the study, necropsies and histologic examinations of tissues were performed on 9 male rats administered 5 μg/kg, 10 female rats administered 10 μg/kg, and 10 male and 9 female mice administered 10μ g/kg. Fewer rats and mice in other dosed groups underwent these procedures.

In the rats, 4/9 males administered 5 μg/kg and 5/10 females administered 10 μ g/kg exhibited threshold to moderate hepatotoxicity. Splenic hyperplasia occurred in about half of the male rats given 50 or 100 μg/kg and in about half of the females that were examined at each dose. Cortical atrophy of the thymus was observed in 1 of 2 male rats and 1 of 2 female rats administered 50 μg/kg and in 1 of 10 females administered 10 μg/kg.

In mice, significant histopathologic changes of the liver were observed in 2/2 males and 2/2 females administered 50 μ g/kg; among animals administered 10 μ g/kg, threshold to moderate changes were observed in 5/10 males and threshold changes alone in 2/2 females. No changes were observed in males administered 1.25μ g/kg or in females administered either 1.25 or 2.5 μg/kg.

Low, mid, and high doses selected for male and female rats and male mice in the chronic study were 1.25, 2.5, and 5 μ g/kg/wk, respectively; doses of HCDD selected for female mice were 2.5, 5, and 10 μ g/kg/wk.

G. Chronic Studies

The test groups, doses administered, and durations of the chronic gavage studies in rats and mice are shown in Tables 3 and 4. Animals dosed with HCDD were housed in one room with untreated control group No. 2. Three vehicle control groups were housed in a second room with untreated control group No. 1. The vehicle control groups of each sex and species were shared

Table 2. Doses and Mean Body Weights of Rats and Mice Administered HCDD by Gavage Once per Week for 13 weeks for the Subchronic Study (a)

Doses (μg/kg/wk)	Mean Weight at Week 10 as Percent of Control(b)	
	Male	Female
RATS		
0(c)	100	100
2.5	93	94
5	82	87
10	80	92
50	75	90
100	79	83
MICE		
0(c)	100	100
1.25	83	87
2.5	84	84
5	89	88
10	85	82
50	81	81

(a) All survived except one male that received 2.5 μg/kg.
(b) Data obtained at week 10 were used because data at week 14 were incomplete.
(c) Vehicle controls received volumes of corn oil-acetone equal to the volumes of the test suspension administered.

Table 3. Design for Chronic HCDD Gavage Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Room	HCDD Dose(b) (μg/kg/wk)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Males					
Untreated-Control No. 1	25	1C9	0		106
Untreated-Control No. 2	25	1B3	0		106
Untreated-Control No. 3(c)	25	1A6	0		106
Vehicle-Controls(d,e,f)	75	1C9	0		105
Low-Dose	50	1B3	1.25	104	2
Mid-Dose	50	1B3	2.5	104	3
High-Dose	50	1B3	5	104	3
Females					
Untreated-Control No. 1	25	1C9	0		106
Untreated-Control No. 2	25	1B3	0		106
Untreated-Control No. 3(c)	25	1A6	0		106
Vehicle-Control(d,e,f)	75	1C9	0		105
Low-Dose	50	1B3	1.25	104	3
Mid-Dose	50	1B3	2.5	104	3
High-Dose	50	1B3	5	104	3

(a) Rats from five shipments covering a 7-week period were evenly distributed among untreated controls, vehicle controls, and dosed groups. All animals were dosed or observed for the same period of time, regardless of the starting date.
(b) HCDD was administered 2 days per week as a suspension in 9:1 corn oil-acetone at a volume of 0.05 ml/10 g body weight.
(c) Untreated-control No. 3 was an environmental control for the room in which studies on TCDD were being carried out.
(d) Vehicle controls received volumes of corn oil-acetone equal to the volumes of test suspension administered.
(e) Three groups of 25 vehicle controls were all in the same room and all started at the same age. These are identified in Appendixes A, B, C, and D.
(f) Vehicle-controls were shared with a gavage study on TCDD carried out in a different room.

Table 4. Design for Chronic HCDD Gavage Studies in Mice

Sex and Test Group	Initial No. of Animals(a)	Room	HCDD Dose(b) (μg/kg/wk)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Males					
Untreated-Control No. 1	25	1C9	0	0	107
Untreated-Control No. 2	25	1B3	0	0	107
Untreated-Control No. 3(c)	25	1A6	0	0	107
Vehicle-Controls(d,e,f)	75	1C9	0	0	105
Low-Dose	50	1B3	1.25	104	4
Mid-Dose	50	1B3	2.5	104	3
High-Dose	50	1B3	5	104	4
Females					
Untreated-Control No. 1	25	1C9	0		108
Untreated-Control No. 2	25	1B3	0		108
Untreated-Control No. 3(c)	25	1A6	0		108
Vehicle-Control(d,e,f)	75	1C9	0		106
Low-Dose	50	1B3	2.5	104	4
Mid-Dose	50	1B3	5.0	104	4
High-Dose	50	1B3	10	104	3

(a) Mice from three shipments covering a 7-week period were evenly distributed among the untreated controls, vehicle controls, and dosed groups. All groups were dosed or observed for the same period of time, regardless of starting date.

(b) HCDD was administered 2 days per week as a suspension in 9:1 corn oil-acetone at a volume of 0.05 ml/10 g body weight.

(c) Untreated-control No. 3 was an environmental control for the room in which studies on TCDD were being carried out.

(d) Vehicle controls received volumes of corn oil-acetone equal to the volumes of test suspension administered.

(e) Three groups of 25 vehicle controls were all in the same room and all started at the same age. They are identified in Appendixes A, B, C, and D.

(f) Vehicle-controls were shared with a gavage study on TCDD carried out in a different room.

with a study of TCDD which was housed in a third room with untreated control group No. 3. For statistical analysis, the three vehicle control groups of each sex and species are treated as single groups of 75 animals.

H. Clinical Examinations and Pathology

Animals were observed twice daily for clinical signs and mortality. Body weights were recorded every 2 weeks for the first 12 weeks and every month thereafter. Moribund animals and those that survived to the end of the study were killed using sodium pentobarbital and necropsied.

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from killed animals and from animals found dead. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were taken at necropsy: skin, mandibular lymph node, salivary gland, mammary gland, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, colon, liver, gall bladder (mice), pancreas, spleen, kidney, adrenal, urinary bladder, ovary, testis, uterus, prostate, gonads, nasal cavity, brain, pituitary, spinal cord, skeletal muscle, sciatic nerve, and all tissue masses.

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.

I. Data Recording and Statistical Analyses

Data on this experiment have been recorded in 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).

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 were performed using the method of Cox (1972) to compare each dosed group with the control group for equality and Tarone's (1975) extensions of Cox's methods to test for an overall dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is reported only 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 (e.g., skin or mammary tumors) before histologic sampling 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 are compared simultaneously with those for a control group, a correction may be made to ensure an overall significance level of 0.05. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.017 (0.05/3). When this correction was used, it is discussed in the narrative section. It is not 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. When the trend is assumed to be linear, 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 relationship. This method also provides a two-tailed test of departure from linear trend.

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 killed 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 were one-tailed when life-table methods were used and, unless otherwise noted, were in the direction of a positive dose relationship. Significant departures from linearity were also noted (P less than 0.05, two-tailed test).

The approximate 95% 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 lower and upper limits of this confidence interval 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 has occurred (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). 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 the dosed groups of male rats during the first 68 weeks of the bioassay and of the dosed groups of females during the first 33 weeks were essentially the same as those of corresponding vehicle-control groups; thereafter, weight gains of mid- and high-dosed groups were depressed, and the depressions in weight were dose related (Figure 1). No other significant clinical signs were reported.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered HCDD by gavage at the doses of this bioassay, together with those of the pooled vehicle controls and of the pooled untreated controls, are shown by the Kaplan and Meier curves in Figure 2. The pooled vehicle-control group was formed by combining all three vehicle-control groups. The two untreated groups that were either in the vehicle-control room or in the HCDD-dosed group room were pooled into one group. The untreated control groups served as environmental controls, and survival in these groups was not significantly different from that in the other groups. The result of the Tarone test does not show a decrease in survival in male rats.

In male rats, 19/50 (38%) of the high-dose group, 19/50 (38%) of the mid-dose group, 18/50 (36%) of the low-dose animals, 29/75 (39%) of the pooled vehicle-control group, and 24/50 (48%) of the pooled untreated control group lived to the end of the study. In female rats, 37/50 (74%) of the high-dose group, 36/50 (72%) of the mid-dose group, 36/50 (72%) of the low-dose group, 39/75 (52%) of the combined vehicle-control group, and 33/50 (66%) of the pooled untreated control group lived to the end of the study. Sufficient numbers of rats in control and dosed groups of each sex were at risk for the development of late-appearing tumors.

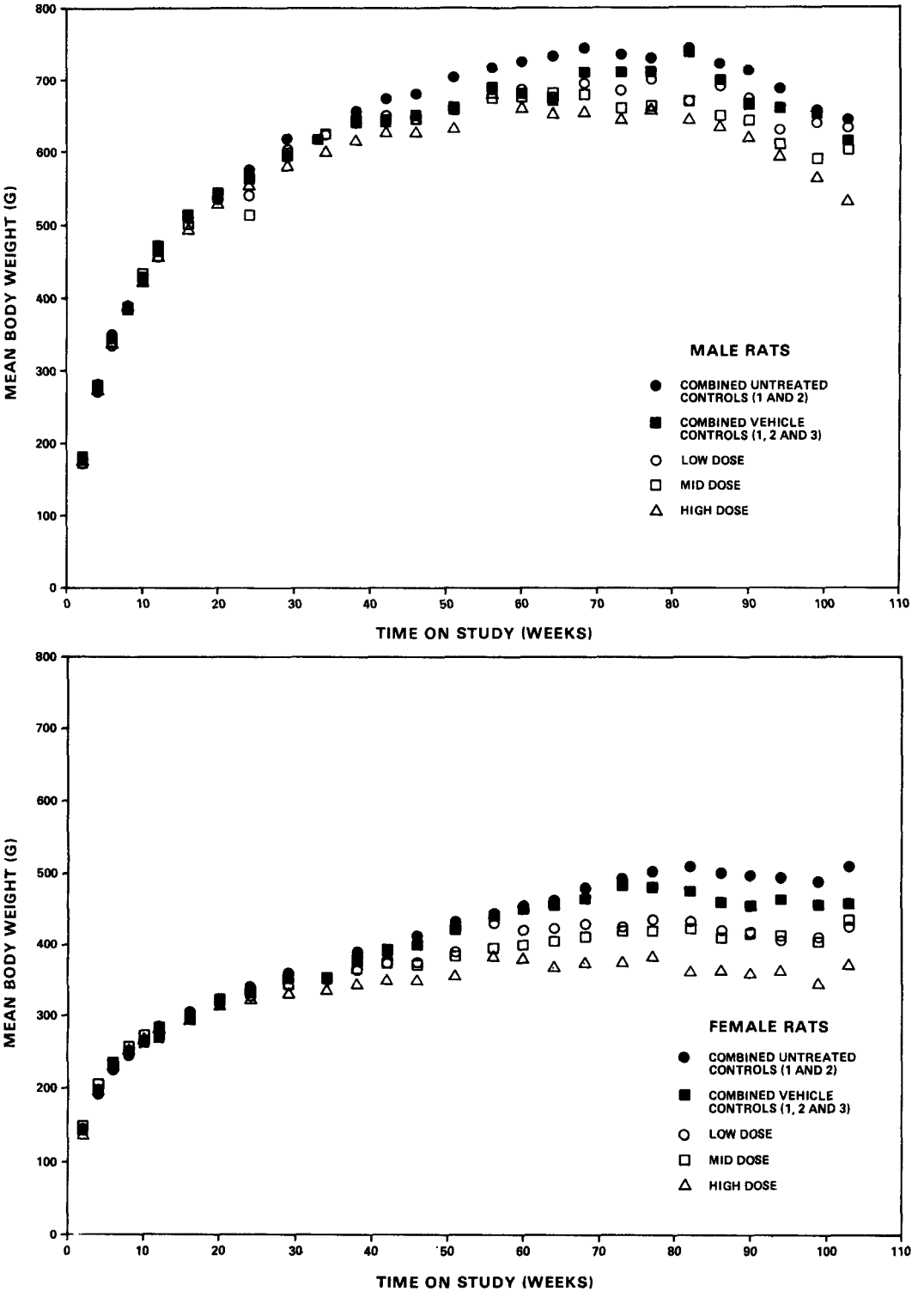


Figure 1. Growth Curves for Rats Administered HCDD by Gavage

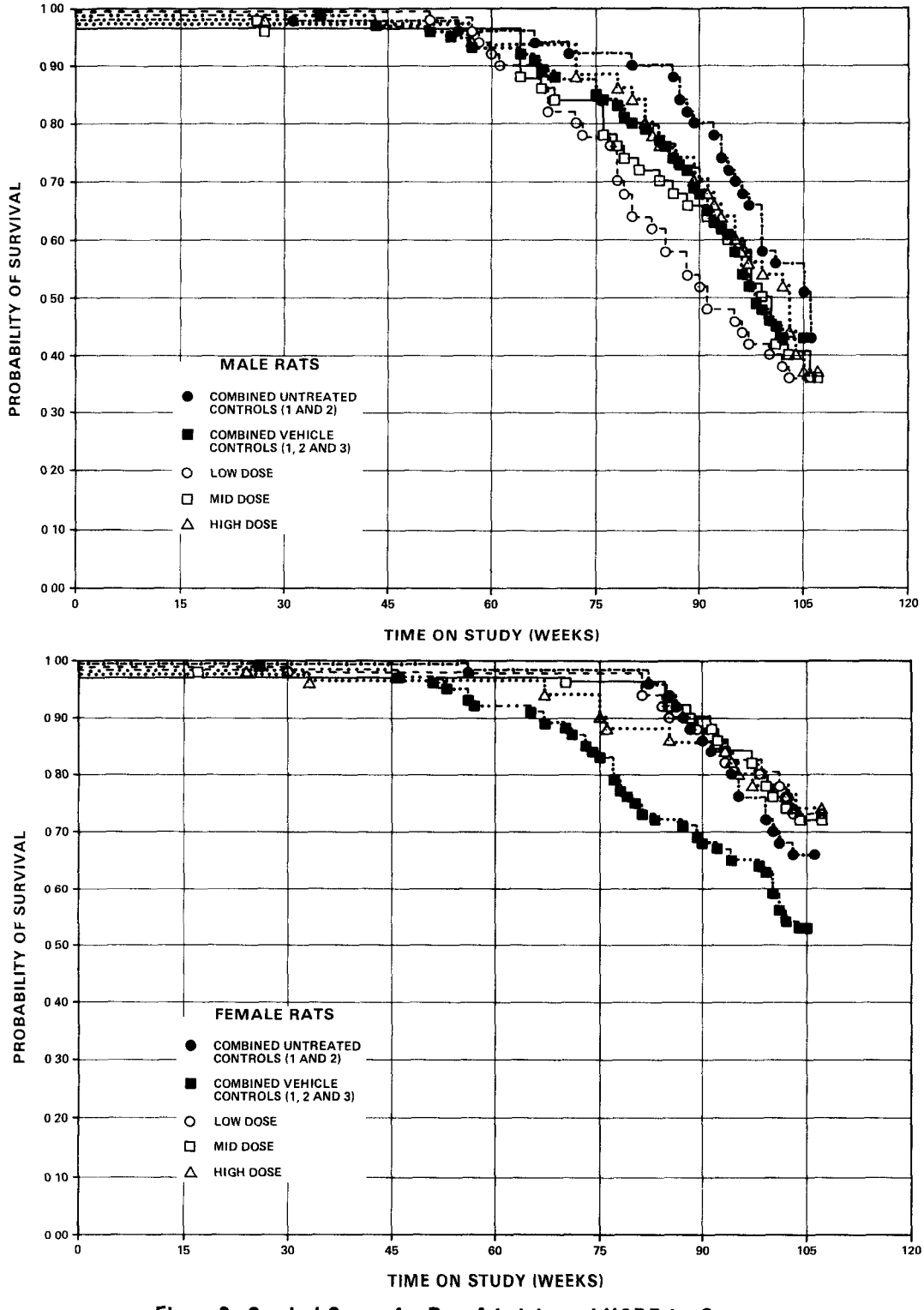


Figure 2. Survival Curves for Rats Administered HCDD by Gavage

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 to A4; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 to C4.

A variety of neoplasms were seen in dosed and control rats and, except for those of the liver, the tumors were not related to chemical administration.

Hepatic neoplasms were found in both dosed and control animals. As shown in Table 5, increased incidences of neoplastic nodules and hepatocellular carcinomas were dose related in female rats and toxic hepatic lesions were dose related in both sexes.

The neoplastic nodules were composed of hypertrophic hepatocytes with eosinophilic cytoplasm forming a solid pattern. These nodules compressed adjacent liver tissue and distorted or interrupted the normal lobular pattern of the liver. They were usually multiple in the liver. The carcinomas were composed of hepatocytes forming trabecular patterns. All four female rats with hepatocellular carcinomas also had neoplastic nodules. Metastases were not found. All liver tumors occurred in livers with toxic lesions.

The complex nonneoplastic liver lesions seen in dosed rats were recorded as "toxic hepatitis." The severity of these lesions was dose related. The lesions were not inflammatory and included degenerative hepatocyte changes (lipidosis, cytomegaly, etc.), eosinophilic foci of cellular alteration, mild fibrosis, and bile duct hyperplasia.

In addition to the hepatic lesions, a large number of degenerative, proliferative, and inflammatory changes were present in animals of the dosed and control groups. For the most part, these nonneoplastic lesions are commonly seen in aged rats and, except for those of the liver and lung, could not be related to chemical administration. Hyperplastic lung lesions, recorded as adenomatous hyperplasia, were seen in 1/147 untreated and vehicle-control males, 9/49 low-dose males, 13/49 mid-dose males, 23/47 high-dose males, 0/150 untreated and vehicle-control females, 24/50 low-dose females, 21/49 mid-dose females, and 21/49 high-dose females. The hyperplastic lesions were characterized by hypertrophy and hyperplasia of

Table 5. Incidences of Neoplastic Nodules, Hepatocellular Carcinomas, and Toxic Hepatic Lesions In Rats Administered HHCD by Gavage

Tumor	Vehicle Control	Untreated Control	Low Dose	Mid Dose	High Dose
MALE					
Number of Tissues Examined	(74)	(75)	(48)	(50)	(48)
Hepatocellular Carcinoma	0	0	0	0	1
Neoplastic Nodule	0	2	0	1	3
Toxic Hepatitis	0	0	28	35	34
FEMALE					
Number of Tissues Examined	(75)	(73)	(50)	(50)	(50)
Hepatocellular Carcinoma	0	0	0	0	4
Neoplastic Nodule	5	1	10	12	30
Toxic Hepatitis	0	0	33	37	44

epithelial cells in terminal bronchioles and adjacent alveoli. Pigment-filled macrophages were frequently present in affected alveoli. Most of the lesions were focal, present in small numbers, and classified as trace to mild in severity.

The histopathologic examination provided evidence that HCDD was carcinogenic in female Osborne-Mendel rats, inducing neoplastic nodules and hepatocellular carcinomas under conditions of this bioassay. HCDD also induced toxic nonneoplastic liver and lung lesions in male and female rats.

D. Statistical Analyses of Results (Rats)

Tables 6 and 7 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 groups. The untreated-control groups are not included in the statistical analyses tables; however, data on the untreated-control groups are presented in the appendixes.

The result of the Cochran-Armitage test for dose-related trend in the incidence of male rats with either neoplastic nodules or hepatocellular carcinomas of the liver is significant (P=0.003). The Fisher exact comparison of the incidences of these tumors in the high-dose and vehicle-control groups indicates a P value of 0.022, which is above the 0.017 level required for significance when an overall significance level of P=0.05 is required. Evidence associating administration of HCDD with liver tumors is not conclusive in male rats. Untreated-control group Number 2 of male rats had an incidence of 2/25 (8%) neoplastic nodules, which is the same proportion observed in the high-dose group when the incidence of neoplastic nodules and hepatocellular carcinomas are combined.

A significantly larger number of liver tumors was observed in female mid- and high-dose rats (P=0.006 and P less than 0.001, respectively) than in the vehicle controls. An increased incidence in the low-dose group compared with the vehicle-control group was observed, but the significance level of P=0.026 is above the P=0.017 required by the Bonferroni inequality when three dosed groups are compared with a single control group and an overall significance level of P=0.05 was chosen. The Cochran-Armitage test

indicates a significant positive linear trend (P less than 0.001) in the development of these tumors in relation to the administration of the chemical.

Life table analysis, based upon the time when liver tumors were observed in female rats, indicates a significantly shortened time to observation in the high-dose group (P less than 0.001) compared with the vehicle control. The historical incidence of untreated female Osborne-Mendel rats with these liver tumors is 8/470 (1.7%) compared with 5/25 (7%) in the vehicle controls on this study.

In male rats, the Fisher exact comparison of the incidences of follicular-cell adenomas of the thyroid in low-dose and vehicle-control groups shows a P value of 0.044. This value is above the 0.017 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The incidences in the mid- and high-dose groups are not significant when compared with that of the vehicle-control group, and the result of the Cochran-Armitage test for dose-related trend in incidence is not significant. The incidence of this tumor in the untreated-control groups was 6/74 (8%), a rate that is larger than the 3/49 (6%) seen in the high-dose group.

Significant trends in the negative direction are observed in the incidences of pheochromocytomas of the adrenal (P=0.022) and fibroadenomas of the mammary gland in the male rats (P=0.036).

In summary of the statistical analysis, the incidence of liver tumors in female rats is related to the administration of HCDD.

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered HCDD by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	3/75 (4)	3/50 (6)	3/50 (6)	4/49 (8)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.500	1.500	2.041
Lower Limit		0.208	0.208	0.359
Upper Limit		10.741	10.741	13.333
Weeks to First Observed Tumor	76	83	104	90
Integumentary System: Fibrosarcoma of the Subcutaneous Tissue (b)	9/75 (12)	3/50 (6)	1/50 (2)	4/49 (8)
P Value (c,d)	N.S.	N.S.	P=0.040(N)	N.S.
Relative Risk (e)		0.500	0.167	0.680
Lower Limit		0.090	0.004	0.160
Upper Limit		1.883	1.142	2.280
Weeks to First Observed Tumor	65	83	87	77
Circulatory System: Hemangioma/ Hemangiosarcoma (b)	7/75 (9)	2/50 (4)	0/50 (0)	3/49 (6)
P Value (c,d)	N.S.	N.S.	P=0.025(N)	N.S.
Relative Risk (e)		0.429	0.000	0.656
Lower Limit		0.045	0.000	0.114
Upper Limit		2.132	0.775	2.709
Weeks to First Observed Tumor	75	87	—	83
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	0/74 (0)	0/49 (0)	1/50 (2)	4/48 (8)
P Value (c,d)	P=0.003	--	N.S.	P=0.022
Relative Risk (e)		--	Infinite	Infinite
Lower Limit		--	0.079	1.417
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	104	106

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered HCDD by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Pituitary: Chromophobe Adenoma or Adenoma, NOS(b)	2/61 (3)	1/42 (2)	1/43 (2)	4/41 (10)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.726	0.709	2.976
Lower Limit		0.013	0.012	0.447
Upper Limit		13.436	13.134	31.517
Weeks to First Observed Tumor	81	108	100	91
Adrenal: Cortical Adenoma (b)	6/72 (8)	2/47 (4)	4/47 (9)	4/47 (9)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.511	1.021	1.021
Lower Limit		0.052	0.222	0.222
Upper Limit		2.702	4.049	4.049
Weeks to First Observed Tumor	92	83	81	57
Adrenal: Pheochromocytoma (b)	5/72 (7)	1/47 (2)	0/47 (0)	0/47 (0)
P Value (c,d)	P=0.022(N)	N.S.	N.S.	N.S.
Relative Risk (e)		0.306	0.000	0.000
Lower Limit		0.077	0.000	0.000
Upper Limit		2.609	1.215	1.215
Weeks to First Observed Tumor	104	108	--	--
Thyroid: Follicular-cell Adenoma (b)	1/69 (1)	5/49 (10)	4/47 (9)	3/49 (6)
P Value (c,d)	N.S.	P=0.044	N.S.	N.S.
Relative Risk (e)		7.041	5.872	4.224
Lower Limit		0.821	0.604	0.350
Upper Limit		325.699	282.686	217.085
Weeks to First Observed Tumor	104	105	81	105

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered HCDD by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Thyroid: C-cell Adenoma (b)	2/69 (3)	2/49 (4)	3/47 (6)	3/49 (6)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.408	2.202	2.112
Lower Limit		0.105	0.261	0.251
Upper Limit		18.787	25.436	24.431
Weeks to First Observed Tumor	81	108	104	107
Mammary Gland: Fibroadenoma (b)	5/75 (7)	3/50 (6)	1/50 (2)	0/49 (0)
P Value (c,d)	P=0.036(N)	N.S.	N.S.	N.S.
Relative Risk (e)		0.900	0.300	0.000
Lower Limit		0.145	0.006	0.000
Upper Limit		4.391	2.562	1.216
Weeks to First Observed Tumor	93	88	111	--

(a) Dosed groups received 1.25, 2.5, or 5 μg/kg/wk.
(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 vehicle-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 the control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the vehicle-control group.

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered HCDD by Gavage(a)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	4/75 (5)	2/50 (4)	3/50 (6)	0/50 (0)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.750	1.125	0.000
Lower Limit		0.070	0.171	0.000
Upper Limit		5.001	6.340	1.622
Weeks to First Observed Tumor	80	94	94	--
Liver: Neoplastic Nodule, Hepatocellular Carcinoma(b)	5/75 (7)	10/50 (20)	12/50 (24)	30/50 (60)
P Value (c,d)	P is less than 0.001	P=0.026	P=0.006	P is less than 0.001
Relative Risk (e)		3.000	3.600	9.000
Lower Limit		0.995	1.263	3.830
Upper Limit		10.486	12.188	26.359
Weeks to First Observed Tumor	92	91	95	72
Pituitary: Chromophobe Adenoma (b)	5/66 (8)	2/45 (4)	3/47 (6)	5/45 (11)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.587	0.843	1.467
Lower Limit		0.058	0.136	0.356
Upper Limit		3.391	4.093	5.982
Weeks to First Observed Tumor	92	105	95	72
Adrenal: Cortical Adenoma (b)	11/73 (15)	3/48 (6)	9/50 (18)	8/50 (16)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.415	1.194	1.062
Lower Limit		0.077	0.470	0.397
Upper Limit		1.468	2.916	2.672
Weeks to First Observed Tumor	77	101	94	104

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered HCDD by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Thyroid: C-cell Adenoma (b)	7/73 (10)	4/48 (8)	4/48 (8)	3/49 (6)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.869	0.869	0.638
Lower Limit		0.195	0.195	0.111
Upper Limit		3.208	3.208	2.636
Weeks to First Observed Tumor	105	104	102	104
Thyroid: Follicular-cell Carcinoma or Adenoma (b)	5/73 (7)	3/48 (6)	0/48 (0)	1/49 (2)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.912	0.000	0.298
Lower Limit		0.147	0.000	0.006
Upper Limit		4.443	1.207	2.542
Weeks to First Observed Tumor	92	105	—	—
Mammary Gland: Fibroadenoma (b)	27/75 (36)	13/50 (26)	16/50 (32)	12/50 (24)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.722	0.889	0.667
Lower Limit		0.379	0.499	0.340
Upper Limit		1.291	1.512	1.217
Weeks to First Observed Tumor	53	81	85	76

(a) Dosed groups received 1.25, 2.5, or 5 μg/kg/wk.
(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 vehicle-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 the control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the vehicle-control group.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed groups of male mice were similar to those of the corresponding vehicle-control group throughout the bioassay (Figure 3). Mean body weights of the dosed females were similar to those of corresponding vehicle-controls. No other clinical signs were reported.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered HCDD by gavage at the doses of this bioassay, together with those estimates of the pooled vehicle controls and of the combined untreated controls, are shown by the Kaplan and Meier curves in Figure 4. The two untreated control groups that were in either the vehicle-control room or the room housing the HCDD-dosed group were pooled into one group. The three vehicle-control groups were pooled into one vehicle-control group. Although included in the graphs, survivals of the untreated-control groups are not included in the statistical analysis of survival. The result of the Tarone test for dose-related trend in mortality is not significant in either sex. The results of the Cox test comparing the survival between each of the dosed groups with their respective pooled vehicle-control group are also not significant, thus indicating comparable survival among all groups in either sex.

In male mice, 23/50 (46%) of the high-dose group, 26/50 (52%) of the mid-dose group, 29/50 (58%) of the low-dose animals, 38/75 (51%) of the pooled vehicle-control group, and 32/50 (64%) of the pooled untreated control group lived to the end of the study. In females, 36/50 (72%) of the high-dose animals, 33/50 (66%) of the mid-dose animals, 31/50 (62%) of the low-dose group, 58/75 (77%) of the pooled vehicle-control group, and 36/50 (72%) of the pooled untreated control

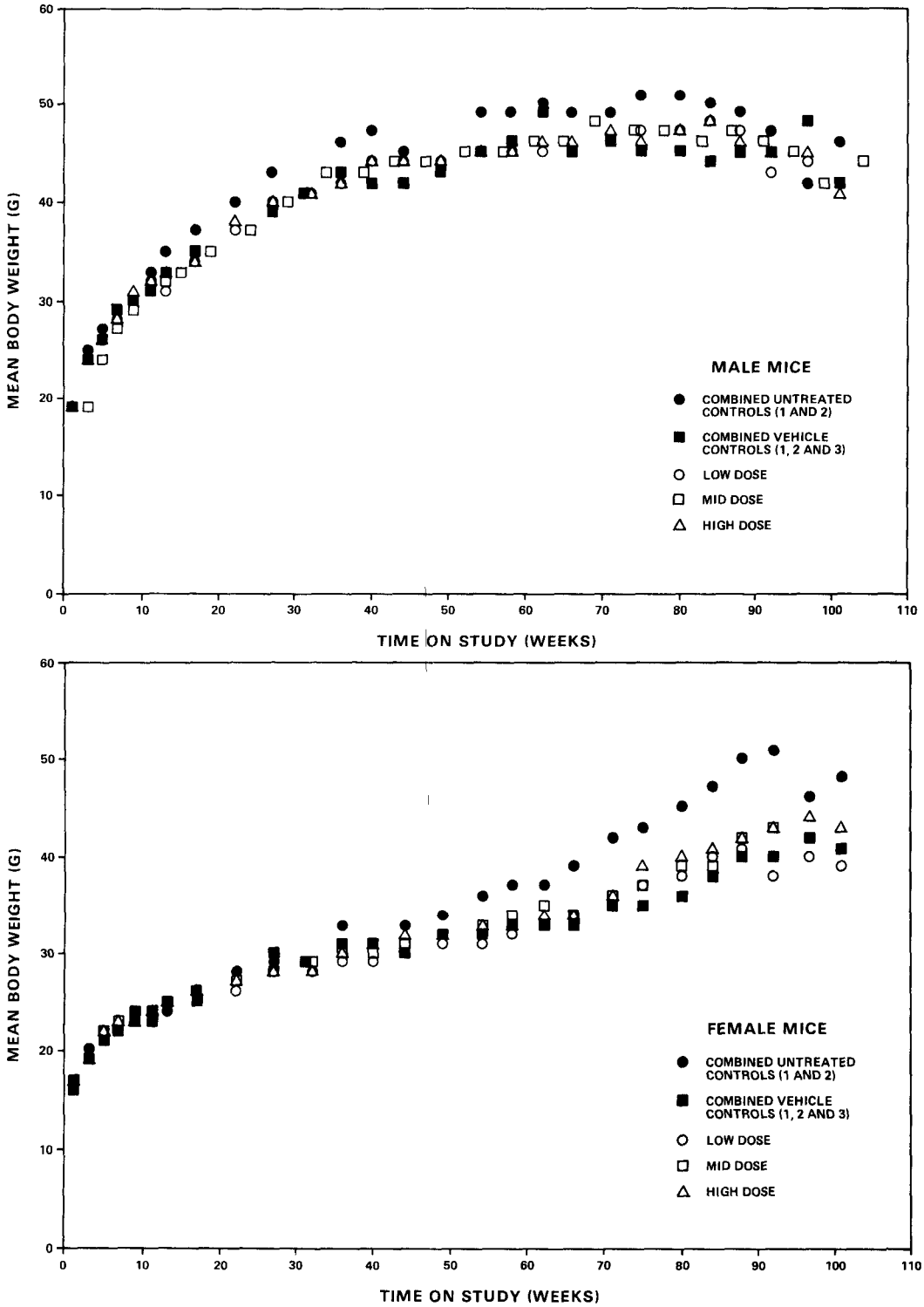


Figure 3. Growth Curves for Mice Administered HCDD by Gavage

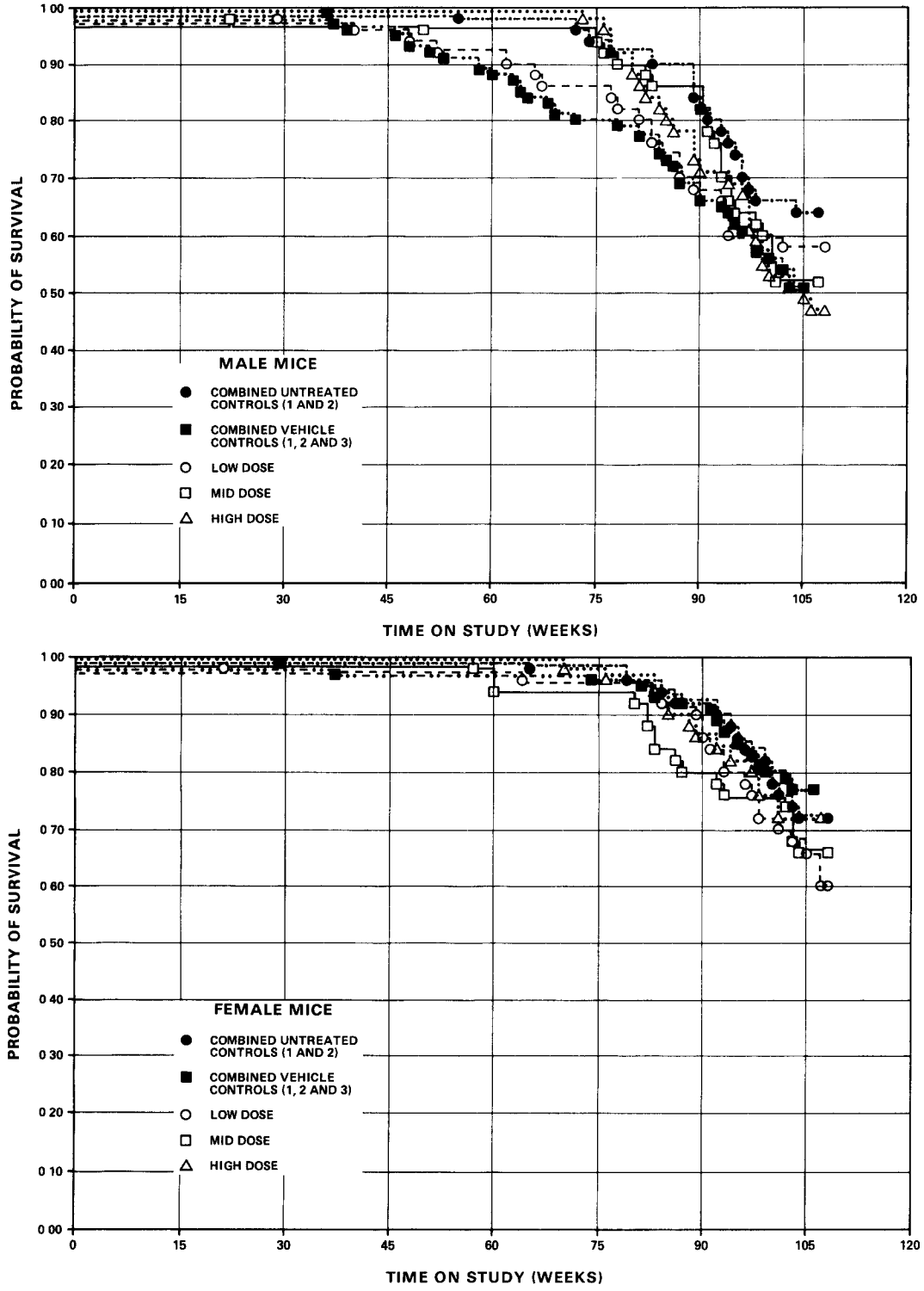


Figure 4. Survival Curves for Mice Administered HCDD by Gavage

group animals lived to the end of the study. Sufficient numbers of mice in control and dosed groups 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 to B4; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 to D4.

A variety of tumors occurred in both the control and dosed groups. Except for tumors of the liver, the incidences of the individual tumor types are not unusual.

An increased incidence of hepatocellular tumors occurred in dosed male and female mice. The number of hepatocellular carcinomas and adenomas found in the dosed and control groups are presented in Table 8. The hepatocellular adenomas, consisting of cells with uniform cell type and devoid of lobular architecture, compressed the surrounding normal liver. The individual tumor cells were similar in appearance to normal liver cells, although there was some variation in cytoplasmic staining and in cell size from surrounding cells. The hepatocellular carcinomas displayed greater deviation from normal in cellular characteristics and growth patterns and, because of their histologic appearance, they were judged to have the capacity for progressive growth, invasion, and metastasis. The cells in these tumors were pleomorphic, varied in staining characteristics, displayed increased mitosis, and were disorganized in their growth, appearing in sheets or cords of multiple cell layers and occasionally separated into cords by wide vascular channels (trabecular). A few tumors in control and dosed mice metastasized to the lungs.

In addition to neoplastic lesions, a large number of degenerative, proliferative, and inflammatory changes were present in animals of the dosed and control groups. For the most part, these nonneoplastic lesions are commonly seen in aged mice. However, degenerative, inflammatory, and hypertrophic changes were induced by the compound in the livers of male and female mice. These lesions were more severe in the male mice.

Table 8. Incidences of Hepatocellular Carcinomas and Adenomas in Mice Administered HCCD by Gavage

Tumor	Vehicle Control	Untreated Control	Low Dose	Mid Dose	High Dose
MALE					
Number of Tissues Examined	(73)	(75)	(50)	(48)	(48)
Hepatocellular Carcinoma	8	12	9	5	9
Hepatocellular Adenoma	7	15	5	9	15
FEMALE					
Number of Tissues Examined	(73)	(74)	(48)	(47)	(47)
Hepatocellular Carcinoma	1	0	0	2	2
Hepatocellular Adenoma	2	2	4	4	9

Toxic hepatitis, the severity of which was dose-related, consisted of degenerative hepatocytic changes and/or necrosis associated with mild fibrosis and infiltration. Cellular hypertrophy (cytomegaly) involved focal increase in cell size of groups of hepatocytes usually in the centrilobular area. Intranuclear inclusions were seen in some cells, and oval cell (bile ductular or biliary) hyperplasia, not recorded in the tables, was seen in high-dose mice. Macrophages containing pigment were noted in dosed male mice. The degenerative changes included cloudy swelling and lipidosis.

The histopathologic examination indicates that under conditions of this bioassay HCDD was carcinogenic in male and female B6C3F1 mice, inducing hepatocellular neoplasms. Toxic nonneoplastic lesions were seen in the livers of dosed male and female mice.

D. Statistical Analyses of Results (Mice)

Tables 9 and 10 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. The untreated-control groups are not included in the statistical analyses tables because the test conditions of the vehicle-control groups resemble more closely those of the dosed groups. The untreated controls were intended only as environmental controls and indicated no differences in survival from the other groups. The three vehicle control groups that were combined were comparable in tumor incidence.

In male mice, the result of the Cochran-Armitage test for dose-related trend in incidence of hepatocellular carcinomas or adenomas is significant (P=0.001). The Fisher exact test shows that the incidence of these tumors in the high-dose group is significantly higher (P=0.001) than that in the vehicle-control group.

In female mice, the result of the Cochran-Armitage test for dose-related trend of hepatocellular carcinomas or adenomas is significant (P=0.002), and the direct comparison of the high-dose with the vehicle-control group indicates a significant increase (P=0.004) in the incidence of this tumor.

These statistical results indicate that the incidences of liver tumors in male mice and female mice are associated with the administration of HCDD.

Table 9. Analyses of the Incidence of Primary Tumors in Male Mice Administered HCDD by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Integumentary System: Fibroma of the Subcutaneous Tissue (b)	1/73 (1)	4/50 (8)	1/50 (2)	2/48 (4)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		5.840	1.460	3.042
Lower Limit		0.599	0.019	0.162
Upper Limit		281.464	112.322	175.643
Weeks to First Observed Tumor	90	108	75	97
Integumentary System: Fibrosarcoma (b)	8/73 (11)	1/50 (2)	6/50 (12)	6/48 (13)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.183	1.095	1.141
Lower Limit		0.004	0.331	0.345
Upper Limit		1.293	3.358	3.490
Weeks to First Observed Tumor	87	91	78	81
Circulatory System: Hemangioma/Hemangiosarcoma (b)	1/73 (1)	1/50 (2)	2/50 (4)	4/48 (8)
P Value (c,d)	P=0.033	N.S.	N.S.	N.S.
Relative Risk (e)		1.460	2.920	6.083
Lower Limit		0.019	0.156	0.624
Upper Limit		112.341	168.786	292.954
Weeks to First Observed Tumor	96	67	100	85
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	10/71 (14)	11/50 (22)	10/50 (20)	7/48 (15)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.562	1.420	1.035
Lower Limit		0.650	0.571	0.357
Upper Limit		3.762	3.494	2.782
Weeks to First Observed Tumor	88	94	75	77

Table 9. Analyses of the Incidence of Primary Tumors in Male Mice Administered HCDD by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Hematopoietic System:				
All Lymphomas (b)	8/73 (11)	7/50 (14)	4/50 (8)	8/48 (17)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.278	0.730	1.521
Lower Limit		0.419	0.168	0.531
Upper Limit		3.753	2.556	4.307
Weeks to First Observed Tumor	71	83	94	86
Liver: Hepatocelluar Adenoma (b)	7/73(10)	5/50(10)	9/49(18)	15/48(31)
P Value (c), (d)	P=0.001	N.S.	N.S.	P=0.003
Relative Risk (Matched Control) (e)		1.043	1.915	3.259
Lower Limit		0.274	0.678	1.357
Upper Limit		3.581	5.622	8.648
Weeks to First Observed Tumor	88	94	75	80
Liver: Hepatocellular Carcinoma (b)	8/73 (11)	9/50 (18)	5/49 (10)	9/48 (19)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.642	0.931	1.711
Lower Limit		0.602	0.252	0.627
Upper Limit		4.535	3.016	4.710
Weeks to First Observed Tumor	86	67	91	94
Liver: Hepatocellular Carcinoma (b)	8/73 (11)	9/50 (18)	5/49 (10)	9/48 (19)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.642	0.931	1.711
Lower Limit		0.602	0.252	0.627
Upper Limit		4.535	3.016	4.710
Weeks to First Observed Tumor	86	67	91	94

Table 9. Analyses of the Incidence of Primary Tumors in Male Mice Administered HCDD by Gavage (a)

(continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	15/73 (21)	14/50 (28)	14/49 (29)	24/48 (50)
P Value (c,d)	P=0.001	N.S.	N.S.	P=0.001
Relative Risk (e)		1.363	1.390	2.433
Lower Limit		0.667	0.682	1.376
Upper Limit		2.728	2.779	4.327
Weeks to First Observed Tumor	86	67	91	80

(a) Dosed groups received 1.25, 2.5, or 5 μg/kg/wk.
(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 vehicle-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 the control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the vehicle-control group.

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Administered HCDD by Gavage (a)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	2/74 (3)	2/49 (4)	5/48 (10)	1/48 (2)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.510	3.854	0.771
Lower Limit		0.112	0.659	0.013
Upper Limit		20.157	39.017	14.334
Weeks to First Observed Tumor	99	105	105	99
Hematopoietic System: All Lymphomas (b)	18/74 (24)	10/49 (20)	5/49 (10)	15/49 (31)
P Value (c,d)	N.S.	N.S.	P=0.039(N)	N.S.
Departure from Linear Trend (f)	P=0.048			
Relative Risk (e)		0.839	0.420	1.259
Lower Limit		0.376	0.129	1.259
Upper Limit		1.737	1.080	2.362
Weeks to First Observed Tumor	76	85	61	77
All Sites: Hemangioma or Hemangiosarcoma (b)	2/74 (3)	4/49 (8)	3/49 (6)	0/49 (0)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		3.020	2.265	0.000
Lower Limit		0.450	0.268	0.000
Upper Limit		32.239	26.213	5.108
Weeks to First Observed Tumor	104	101	109	--
Liver: Hepatocellular Adenoma (b)	2/73 (3)	4/48 (8)	4/47 (9)	9/47 (19)
P Value (c), (d)	P=0.002	N.S.	N.S.	P=0.003
Relative Risk (e)		3.042	3.106	6.989
Lower Limit		0.453	0.463	1.527
Upper Limit		32.446	33.108	63.779
Weeks to First Observed Tumor	104	93	106	104

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Administered HCDD by Gavage (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	1/73 (1)	0/48 (0)	2/47 (4)	2/47 (4)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	3.106	3.106
Lower Limit		0.000	0.166	0.166
Upper Limit		28.344	179.333	179.333
Weeks to First Observed Tumor	91	—	104	104
Liver: Hepatocellular Adenoma Carcinoma or (b)	3/73 (4)	4/48 (8)	6/47 (13)	10/47 (21)
P Value (c,d)	P=0.002	N.S.	N.S.	P=0.004
Relative Risk (e)		2.028	3.106	5.177
Lower Limit		0.357	0.697	1.416
Upper Limit		13.234	18.287	27.743
Weeks to First Observed Tumor	91	108	104	104
Pituitary: Chromophobe Adenoma (b)	1/62 (2)	2/41 (5)	0/40 (0)	0/41 (0)
P Value (c,d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		3.024	0.000	0.000
Lower Limit		0.162	0.000	0.000
Upper Limit		173.984	28.776	28.089
Weeks to First Observed Tumor	108	107	--	--

(a) Dosed groups received 2.5, 5, or 10 μg/kg/wk.
(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 vehicle-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 the control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the vehicle-control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

V. DISCUSSION

In rats, a dose-related decrement in mean body weight gain became evident in mid- and high-dose males after week 68 of the bioassay and in females after week 33. In mice, weight gain in the dosed groups was comparable with that of the vehicle-control groups throughout the bioassay. No other clinical signs were reported for either rats or mice. Administration of HCDD had no adverse effect on the survival of rats or mice of either sex.

In male rats, hepatocellular carcinomas or neoplastic nodules occurred at incidences that were dose related (P=0.003), and in a direct comparison the incidence in the high-dose group was higher (P=0.022) than that in the corresponding vehicle-control group. The level of significance of P=0.022 for the direct comparison did not meet the Bonferroni requirement of P=0.017 for the multiple comparison of three dosed groups with a control group.

In female rats, hepatocellular carcinomas, adenomas, or neoplastic nodules occurred at incidences that were dose related (P less than 0.001), and in direct comparisons the incidences in the mid- and high-dose groups were significantly higher (P=0.006 and P less than 0.001, respectively) than the incidence in the corresponding vehicle-control group.

In male mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P=0.001), and in a direct comparison the incidence of these tumors in the high-dose group was significantly higher (P=0.001) than that in the corresponding vehicle-control group.

In the female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P=0.002). The Fisher exact test shows that the incidence of these tumors in the high-dose group is significantly higher (P=0.004) than that in the vehicle-control group.

Hepatotoxic effects in the subchronic study were the determining factors in the selection of dose levels for the chronic study. Although some liver damage was expected at the highest dose in the chronic study, complex nonneoplastic liver lesions were seen in 60% to 80% of all dosed groups of rats. These hepatotoxic lesions are similar to those reported by McConnell

et al. (1978) in subchronic studies in mice and guinea pigs. Compound-associated hyperplastic lesions of the lungs were also found in both male and female rats, and HCDD was also hepatotoxic for B6C3F1 mice.

Although much has been published about the structurally related 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the literature on HCDD is limited and not all of the references specify which isomer was used. Biological effects of HCDD appear to parallel, qualitatively, the biological effects of TCDD. Toxicity appears to be partly correlated with the degree of chlorination at the 2,3,7, or 8 positions (McConnell and Moore, 1976). The isomers of HCDD used in the present study (1,2,3,6,7,8 and 1,2,3,7,8,9) are both chlorinated at those four lateral ring positions. Crystalline 1,2,3,7,8,9-HCDD has specifically been shown to cause chick edema (Cantrell et al., 1969).

Studies of aryl hydrocarbon hydroxylase enzyme induction indicate that TCDD is the most potent inducer; 1,2,3,4,7,8-HCDD was more effective than 1,2,3,7,8,9-HCDD, which in turn was more effective than 1,2,3,6,7,8-HCDD; but 1,2,4,5,7,9-HCDD had no effect (Bradlaw et al., 1975). 1,2,3,7,8,9-HCDD was 20% as effective as TCDD in inducing aryl hydrocarbon hydroxylase (Poland et al., 1976).

The relative individual contributions of the two HCDD isomers to the carcinogenic effects observed in the present study are not known. The possible contribution of the 1.38% pentachlorodibenzo-p-dioxin impurities is also unknown.

VI. CONCLUSIONS

Under the conditions of this bioassay, HCDD administered by gavage was carcinogenic, increasing the incidences of hepatocellular carcinomas or neoplastic nodules in female Osborne-Mendel rats and inducing hepatocellular carcinomas or adenomas in male and female B6C3F1 mice. HCDD was not demonstrated to be carcinogenic for male rats.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED HCDD BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	25	25	25	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	25	25	25	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(25)	(25)	(25)	(25)
KERATOACANTHOMA		2 (8%)			
FIBROMA	1 (4%)				
*SUBCUT TISSUE	(25)	(25)	(25)	(25)	(25)
SARCOMA, NOS				1 (4%)	
FIBROMA		2 (8%)	2 (8%)	1 (4%)	2 (8%)
FIBROSARCOMA	1 (4%)	4 (16%)		5 (20%)	1 (4%)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (4%)				1 (4%)
LIPOMA	2 (8%)	1 (4%)	1 (4%)	1 (4%)	1 (4%)
NEUROBLASTOMA					1 (4%)
RESPIRATORY SYSTEM					
#LUNG	(25)	(25)	(25)	(25)	(25)
SQUAMOUS CELL CARCINOMA				1 (4%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (8%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (4%)		
MIXED TUMOR, METASTATIC	1 (4%)				
NEUROBLASTOMA, METASTATIC					1 (4%)
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
MALIGNANT LYMPHOMA, NOS		1 (4%)			
MALIG LYMPHOMA, HISTIOCYTIC TYPE			1 (4%)		
#SPLEEN	(25)	(23)	(25)	(23)	(24)
FIBROMA					1 (4%)
FIBROSARCOMA					1 (4%)
FIBROSARCOMA, INVASIVE			1 (4%)		

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

A1. MALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE					1 (4%)
#LYMPH NODE	(20)	(17)	(18)	(19)	(22)
MALIGNANT LYMPHOMA, NOS		1 (6%)			
CIRCULATORY SYSTEM					
*SUBCUT TISSUE	(25)	(25)	(25)	(25)	(25)
HEMANGIOMA					1 (4%)
#SPLEEN	(25)	(23)	(25)	(23)	(24)
HEMANGIOMA		2 (9%)	1 (4%)		2 (8%)
HEMANGIOSARCOMA			1 (4%)	2 (9%)	
#LYMPH NODE	(20)	(17)	(18)	(19)	(22)
HEMANGIOSARCOMA				1 (5%)	
DIGESTIVE SYSTEM					
#LIVER	(25)	(25)	(25)	(25)	(25)
NEOPLASTIC NODULE		2 (8%)			
#SMALL INTESTINE	(23)	(24)	(23)	(25)	(24)
FIBROSARCOMA, INVASIVE			1 (4%)		
URINARY SYSTEM					
#KIDNEY	(25)	(25)	(25)	(24)	(25)
MIXED TUMOR, BENIGN	1 (4%)				
MIXED TUMOR, MALIGNANT	3 (12%)				
ENDOCRINE SYSTEM					
#PITUITARY	(24)	(21)	(21)	(20)	(22)
CHROMOPHOBE ADENOMA		2 (10%)		1 (5%)	1 (5%)
NEUROFIBROSARCOMA	1 (4%)				
#ADRENAL	(25)	(25)	(24)	(24)	(24)
CORTICAL ADENOMA	2 (8%)	3 (12%)	3 (13%)	1 (4%)	1 (4%)
PHEOCHROMOCYTOMA		1 (4%)		1 (4%)	3 (13%)
#THYROID	(25)	(25)	(24)	(23)	(24)
FOLLICULAR-CELL ADENOMA	4 (16%)	2 (8%)			1 (4%)

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

A1. MALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
FOLLICULAR-CELL CARCINOMA		1 (4%)	1 (4%)		
C-CELL ADENOMA		3 (12%)		2 (9%)	
C-CELL CARCINOMA			1 (4%)		
#PANCREATIC ISLETS	(23)	(24)	(23)	(24)	(23)
ISLET-CELL ADENOMA	2 (9%)	2 (8%)		1 (4%)	1 (4%)
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(25)	(25)	(25)	(25)	(25)
ADENOCARCINOMA, NOS		1 (4%)			
FIBROADENOMA	2 (8%)	3 (12%)		1 (4%)	4 (16%)
*PREPUTIAL GLAND	(25)	(25)	(25)	(25)	(25)
ADENOCA/SQUAMOUS METAPLASIA				1 (4%)	
#PROSTATE	(25)	(24)	(22)	(24)	(25)
HIBERNOMA		1 (4%)			
#TESTIS	(25)	(25)	(24)	(24)	(25)
INTERSTITIAL-CELL TUMOR	1 (4%)				
NERVOUS SYSTEM					
#BRAIN	(25)	(25)	(23)	(25)	(25)
NEOPLASM, NOS, MALIGNANT					1 (4%)
MENINGIOMA					1 (4%)
SPECIAL SENSE ORGANS					
NONE					
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
*ABDOMINAL CAVITY	(25)	(25)	(25)	(25)	(25)
MIXED TUMOR, MALIGNANT	1 (4%)				

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

A1. MALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
*MESENTERY	(25)	(25)	(25)	(25)	(25)
FIBROSARCOMA			1 (4%)		
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
FIBROSARCOMA			1 (4%)		
OSTEOSARCOMA		1 (4%)			
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
NATURAL DEATH@	7	9	6	6	4
MORIBUND SACRIFICE	5	3	8	9	9
SCHEDULED SACRIFICE	6	12	9	4	9
ACCIDENTALLY KILLED	1			3	1
TERMINAL SACRIFICE	6	1	2	3	2
ANIMAL MISSING					
@ INCLUDES AUTOLYZED ANIMALS					
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	16	20	12	14	16
TOTAL PRIMARY TUMORS	22	35	16	20	25
TOTAL ANIMALS WITH BENIGN TUMORS	10	16	8	7	12
TOTAL BENIGN TUMORS	15	24	9	9	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	9	6	9	6
TOTAL MALIGNANT TUMORS	7	9	7	11	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1		1
TOTAL SECONDARY TUMORS	1		2		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 MALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS NECROPSIED	25	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(25)	(50)	(50)	(49)
PAPILLOMA, NOS		1 (2%)		
*SUBCUT TISSUE	(25)	(50)	(50)	(49)
CARCINOMA,NOS		1 (2%)		
BASAL-CELL TUMOR	1 (4%)			
KERATOACANTHOMA	1 (4%)			
FIBROMA		3 (6%)	3 (6%)	4 (8%)
FIBROSARCOMA	3 (12%)	3 (6%)	1 (2%)	4 (8%)
LIPOMA		2 (4%)	2 (4%)	1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(25)	(49)	(50)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	
FIBROSARCOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(25)	(50)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
ERYTHROCYTIC LEUKEMIA		1 (2%)		
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(25)	(50)	(50)	(49)
HEMANGIOSARCOMA	1 (4%)			1 (2%)
#SPLEEN	(25)	(50)	(49)	(47)
HEMANGIOMA				1 (2%)

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

A2. MALE RATS (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HEMANGIOSARCOMA		2 (4%)		1 (2%)
#ENDOCARDIUM	(25)	(50)	(50)	(49)
FIBROSARCOMA, METASTATIC				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(25)	(47)	(47)	(47)
FIBROADENOMA				1 (2%)
#LIVER	(24)	(49)	(50)	(48)
NEOPLASTIC NODULE			1 (2%)	3 (6%)
HEPATOCELLULAR CARCINOMA				1 (2%)
LIPOMA		1 (2%)		
#PANCREAS	(23)	(48)	(47)	(48)
ADENOMA, NOS			1 (2%)	
#GASTRIC SEROSA	(25)	(50)	(49)	(49)
FIBROSARCOMA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(25)	(49)	(47)	(49)
MIXED TUMOR, BENIGN				1 (2%)
MIXED TUMOR, MALIGNANT			1 (2%)	1 (2%)
#KIDNEY/PELVIS	(25)	(49)	(47)	(49)
TRANSITIONAL-CELL CARCINOMA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(42)	(43)	(41)
ADENOMA, NOS				1 (2%)
CHROMOPHOBE ADENOMA		1 (2%)	1 (2%)	3 (7%)
#ADRENAL	(24)	(47)	(47)	(47)
CORTICAL ADENOMA	4 (17%)	2 (4%)	4 (9%)	4 (9%)
PHEOCHROMOCYTOMA	1 (4%)	1 (2%)		
#ADRENAL/CAPSULE	(24)	(47)	(47)	(47)
TRANSITIONAL-CELL CARCINOMA, INV				1 (2%)

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

A2. MALE RATS (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
LIPOMA				1 (2%)
#THYROID	(22)	(49)	(47)	(49)
ADENOMA, NOS			1 (2%)	
FOLLICULAR-CELL ADENOMA		5 (10%)	4 (9%)	3 (6%)
C-CELL ADENOMA		2 (4%)	3 (6%)	3 (6%)
#PANCREATIC ISLETS	(23)	(48)	(47)	(48)
ISLET-CELL ADENOMA		2 (4%)	2 (4%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(49)
ADENOMA, NOS	1 (4%)		1 (2%)	1 (2%)
FIBROADENOMA		3 (6%)	1 (2%)	
FIBROADENOCARCINOMA				1 (2%)
#TESTIS	(25)	(49)	(50)	(48)
INTERSTITIAL-CELL TUMOR		1 (2%)		
INTERSTITIAL-CELL TUMOR, MALIGNA				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(25)	(49)	(47)	(48)
EPENDYMOMA			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*TUNICA VAGINALIS	(25)	(50)	(50)	(49)
MESOTHELIOMA, NOS		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR, METASTA				1 (2%)

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

A2. MALE RATS (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
FIBROMA				1 (2%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATHə	8	18	23	20
MORIBUND SACRIFICE	5	14	8	11
SCHEDULED SACRIFICE	7	17	15	17
ACCIDENTALLY KILLED	1			
TERMINAL SACRIFICE	4	1	4	2
ANIMAL MISSING				
ə INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	22	22	25
TOTAL PRIMARY TUMORS	12	34	31	40
TOTAL ANIMALS WITH BENIGN TUMORS	8	20	16	18
TOTAL BENIGN TUMORS	8	26	24	25
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	7	6	9
TOTAL MALIGNANT TUMORS	4	7	6	12
TOTAL ANIMALS WITH SECONDARY TUMORS#				3
TOTAL SECONDARY TUMORS				4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1	3
TOTAL UNCERTAIN TUMORS		1	1	3
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 A3.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	25	25	25	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	25	25	25	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(25)	(25)	(25)	(25)
LIPOMA					1 (4%)
*SUBCUT TISSUE	(25)	(25)	(25)	(25)	(25)
FIBROMA			2 (8%)	3 (12%)	1 (4%)
LIPOMA	1 (4%)	1 (4%)	1 (4%)		
HIBERNOMA	1 (4%)				
FIBROADENOMA					1 (4%)
RESPIRATORY SYSTEM					
#LUNG	(25)	(25)	(25)	(25)	(24)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (4%)				
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (4%)				
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (4%)				
#SPLEEN	(24)	(24)	(25)	(25)	(25)
FIBROMA					1 (4%)
#MANDIBULAR L. NODE	(23)	(21)	(21)	(19)	(21)
SQUAMOUS CELL CARCINOMA, METASTA		1 (5%)			
#RENAL LYMPH NODE	(23)	(21)	(21)	(19)	(21)
SARCOMA, NOS		1 (5%)			
CIRCULATORY SYSTEM					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
HEMANGIOSARCOMA			1 (4%)	1 (4%)	

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

TABLE A3. FEMALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#SPLEEN	(24)	(24)	(25)	(25)	(25)
HEMANGIOMA			1 (4%)	1 (4%)	
DIGESTIVE SYSTEM					
#LIVER	(24)	(24)	(25)	(25)	(25)
ISLET-CELL CARCINOMA, METASTATIC		1 (4%)			
NEOPLASTIC NODULE		1 (4%)		2 (8%)	1 (4%)
#COLON	(25)	(23)	(24)	(25)	(24)
ADENOMA, NOS	1 (4%)				
URINARY SYSTEM					
#KIDNEY	(25)	(25)	(24)	(25)	(25)
MIXED TUMOR, BENIGN	1 (4%)				
MIXED TUMOR, MALIGNANT					1 (4%)
ENDOCRINE SYSTEM					
#PITUITARY	(24)	(23)	(23)	(22)	(22)
ADENOMA, NOS					1 (5%)
CHROMOPHOBE ADENOMA	5 (21%)	2 (9%)	3 (13%)	1 (5%)	1 (5%)
#ADRENAL	(25)	(24)	(25)	(24)	(25)
CORTICAL ADENOMA	4 (16%)		6 (24%)	5 (21%)	3 (12%)
PHEOCHROMOCYTOMA			1 (4%)		
GANGLIONEUROMA	1 (4%)				
#THYROID	(25)	(24)	(24)	(25)	(24)
ADENOMA, NOS		1 (4%)			
FOLLICULAR-CELL ADENOMA					2 (8%)
FOLLICULAR-CELL CARCINOMA				1 (4%)	1 (4%)
C-CELL ADENOMA	3 (12%)	3 (13%)		4 (16%)	
#PANCREATIC ISLETS	(24)	(24)	(25)	(24)	(23)
ISLET-CELL ADENOMA			1 (4%)		
ISLET-CELL CARCINOMA		1 (4%)			
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(25)	(25)	(25)	(25)	(25)
ADENOCARCINOMA, NOS			2 (8%)	2 (8%)	1 (4%)

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

TABLE A3. FEMALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
HIBERNOMA	1 (4%)				
FIBROADENOMA	8 (32%)	9 (36%)	5 (20%)	12 (48%)	9 (36%)
#UTERUS	(25)	(25)	(23)	(24)	(21)
LEIOMYOMA		1 (4%)	2 (9%)		
LEIOMYOSARCOMA				1 (4%)	
#UTERUS/ENDOMETRIUM	(25)	(25)	(23)	(24)	(21)
ADENOCA/SQUAMOUS METAPLASIA			1 (4%)		
NERVOUS SYSTEM					
NONE					
SPECIAL SENSE ORGANS					
*EYE/LACRIMAL GLAND	(25)	(25)	(25)	(25)	(25)
SQUAMOUS CELL CARCINOMA		1 (4%)			
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
NONE					
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
ADENOCA/SQUAMOUS METAPLASIA, MET			1 (4%)		
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
NATURAL DEATH@	3	4	3	4	4
MORIBUND SACRIFICE	7	3	8	8	7
SCHEDULED SACRIFICE	11	16	12	8	12
ACCIDENTALLY KILLED					
TERMINAL SACRIFICE	4	2	2	5	2
ANIMAL MISSING					

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A3. FEMALE RATS (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	19	14	17	21	16
TOTAL PRIMARY TUMORS	29	21	26	33	24
TOTAL ANIMALS WITH BENIGN TUMORS	18	11	15	19	15
TOTAL BENIGN TUMORS	27	17	22	26	20
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	3	4	5	3
TOTAL MALIGNANT TUMORS	2	3	4	5	3
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1		
TOTAL SECONDARY TUMORS		2	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1		2	1
TOTAL UNCERTAIN TUMORS		1		2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC					
TOTAL UNCERTAIN TUMORS					

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

TABLE A4.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS NECROPSIED	25	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(25)	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)	
FIBROMA		2 (4%)	3 (6%)	
FIBROSARCOMA		2 (4%)	1 (2%)	1 (2%)
LIPOSARCOMA	1 (4%)			
LEIOMYOMA			1 (2%)	
RHABDOMYOSARCOMA				1 (2%)
FIBROADENOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(25)	(50)	(49)	(50)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA				1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (4%)			
SARCOMA, NOS, METASTATIC	1 (4%)			1 (2%)
HEMATOPOIETIC SYSTEM				
#LIVER	(25)	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
*MESENTERY	(25)	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(25)	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)		
#SPLEEN	(25)	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	2 (4%)	1 (2%)

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

TABLE A4. FEMALE RATS (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#HEART	(25)	(49)	(49)	(50)
FIBROSARCOMA		1 (2%)		
RHABDOMYOSARCOMA	1 (4%)			
DIGESTIVE SYSTEM				
#LIVER	(25)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (4%)			
BILE DUCT ADENOMA			1 (2%)	1 (2%)
NEOPLASTIC NODULE	2 (8%)	10 (20%)	12 (24%)	30 (60%)
HEPATOCELLULAR CARCINOMA				4 (8%)
SARCOMA, NOS, METASTATIC			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(25)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, INVASIVE				1 (2%)
MIXED TUMOR, BENIGN		1 (2%)		
#KIDNEY/PELVIS	(25)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA				1 (2%)
#URINARY BLADDER	(22)	(47)	(49)	(45)
TRANSITIONAL-CELL CARCINOMA		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(45)	(47)	(45)
ADENOMA, NOS				1 (2%)
CHROMOPHOBE ADENOMA	3 (14%)	2 (4%)	3 (6%)	5 (11%)
#ADRENAL	(24)	(48)	(50)	(50)
CORTICAL ADENOMA	3 (13%)	3 (6%)	9 (18%)	8 (16%)
PHEOCHROMOCYTOMA	2 (8%)			
#THYROID	(24)	(48)	(48)	(49)
FOLLICULAR-CELL ADENOMA	1 (4%)	3 (6%)		1 (2%)
C-CELL ADENOMA	3 (13%)	4 (8%)	4 (8%)	3 (6%)
#PANCREATIC ISLETS	(24)	(49)	(50)	(50)
ISLET-CELL ADENOMA		2 (4%)	2 (4%)	1 (2%)

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

TABLE A4. FEMALE RATS (CONTROL AND DOSED GROUPS) NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)		1 (2%)
ADENOCARCINOMA, NOS			1 (2%)	1 (2%)
FIBROADENOMA	6 (24%)	13 (26%)	16 (32%)	12 (24%
#UTERUS	(24)	(47)	(49)	(47)
ADENOCARCINOMA, NOS	1 (4%)			
LEIOMYOMA	1 (4%)		2 (4%)	1 (2%)
#OVARY	(23)	(47)	(49)	(47)
THECOMA				1 (2%)
GRANULOSA-CELL TUMOR		1 (2%)		
SERTOLI-CELL TUMOR		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(50)
ADENOCARCINOMA, NOS				1 (2%)
SARCOMA, NOS				1 (2%)

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

TABLE A4. FEMALE RATS (CONTROL AND DOSED GROUPS) NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATH@	4	8	8	9
MORIBUND SACRIFICE	8	5	6	4
SCHEDULED SACRIFICE	11	30	26	30
ACCIDENTALLY KILLED	1	1		
TERMINAL SACRIFICE	1	6	10	7
ANIMAL MISSING				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	36	33	41
TOTAL PRIMARY TUMORS	25	50	59	78
TOTAL ANIMALS WITH BENIGN TUMORS	13	29	29	27
TOTAL BENIGN TUMORS	1^	34	43	37
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	5	4	10
TOTAL MALIGNANT TUMORS	4	5	4	11
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1	3
TOTAL SECONDARY TUMORS	2		1	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	10	12	30
TOTAL UNCERTAIN TUMORS	2	11	12	30
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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED HCDD BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	25	25	25	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	25	25	25	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(25)	(25)	(25)	(25)
FIBROMA	2 (8%)				
*SUBCUT TISSUE	(25)	(25)	(25)	(25)	(25)
SARCOMA, NOS			1 (4%)	1 (4%)	
FIBROMA	1 (4%)		2 (8%)	1 (4%)	
FIBROSARCOMA	4 (16%)			3 (12%)	1 (4%)
RESPIRATORY SYSTEM					
#LUNG	(25)	(25)	(25)	(25)	(23)
HEPATOCELLULAR CARCINOMA, METAST		2 (8%)	1 (4%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (16%)	1 (4%)	1 (4%)	2 (8%)	1 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (4%)	1 (4%)	2 (8%)	
NEPHROBLASTOMA, METASTATIC		1 (4%)			
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
MALIG LYMPHOMA, UNDIFFER-TYPE		1 (4%)	1 (4%)		
MALIG LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)				3 (12%)
MALIG LYMPHOMA, HISTIOCYTIC TYPE	2 (8%)	1 (4%)	3 (12%)	1 (4%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (4%)	2 (8%)		
#SPLEEN	(25)	(23)	(25)	(24)	(21)
MALIG LYMPHOMA, HISTIOCYTIC TYPE			2 (8%)	1 (4%)	
#LYMPH NODE	(19)	(15)	(21)	(16)	(16)
FIBROSARCOMA	1 (5%)				
#BRACHIAL LYMPH NODE	(19)	(15)	(21)	(16)	(16)
FIBROSARCOMA, METASTATIC	1 (5%)				

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

TABLE B1. MALE MICE (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
*MESENTERY	(25)	(25)	(25)	(25)	(25)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (4%)			
CIRCULATORY SYSTEM					
*SPINAL CORD	(25)	(25)	(25)	(25)	(25)
HEMANGIOMA	1 (4%)				
#SPLEEN	(25)	(23)	(25)	(24)	(21)
HEMANGIOMA	2 (8%)	2 (9%)			
HEMANGIOSARCOMA		1 (4%)			
#LIVER	(25)	(25)	(25)	(25)	(25)
HEMANGIOSARCOMA		1 (4%)			
#TESTIS	(25)	(25)	(25)	(24)	(24)
HEMANGIOMA	1 (4%)				
DIGESTIVE SYSTEM					
#SALIVARY GLAND	(25)	(23)	(25)	(25)	(25)
FIBROSARCOMA					1 (4%)
#LIVER	(25)	(25)	(25)	(25)	(25)
HEPATOCELLULAR ADENOMA	5 (20%)	4 (16%)	6 (24%)	3 (12%)	2 (8%)
HEPATOCELLULAR CARCINOMA	3 (12%)	4 (16%)	5 (20%)	3 (12%)	1 (4%)
URINARY SYSTEM					
#KIDNEY	(25)	(25)	(25)	(25)	(25)
ADENOMA, NOS	1 (4%)		1 (4%)		
NEPHROBLASTOMA		1 (4%)			
ENDOCRINE SYSTEM					
#ADRENAL	(24)	(22)	(25)	(24)	(21)
PHEOCHROMOCYTOMA				1 (4%)	
#THYROID	(25)	(24)	(20)	(24)	(23)
ADENOMA, NOS			1 (5%)		

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

TABLE B1. MALE MICE (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#PANCREATIC ISLETS	(24)	(22)	(23)	(25)	(21)
ISLET-CELL ADENOMA					1 (5%)
REPRODUCTIVE SYSTEM					
*PREPUTIAL GLAND	(25)	(25)	(25)	(25)	(25)
ADENOMA, NOS					2 (8%)
#TESTIS	(25)	(25)	(25)	(24)	(24)
INTERSTITIAL-CELL TUMOR					1 (4%)
NERVOUS SYSTEM					
NONE					
SPECIAL SENSE ORGANS					
*HARDERIAN GLAND	(25)	(25)	(25)	(25)	(25)
ADENOMA, NOS				1 (4%)	
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
NONE					
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
SARCOMA, NOS, METASTATIC			1 (4%)		
OSTEOSARCOMA		1 (4%)			

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

TABLE B1. MALE MICE (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
NATURAL DEATH@	6	8	8	11	10
MORIBUND SACRIFICE	4		2	1	5
SCHEDULED SACRIFICE	8	10	10	5	8
ACCIDENTALLY KILLED					
TERMINAL SACRIFICE	7	7	5	8	2
ANIMAL MISSING					
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	17	21	16	11
TOTAL PRIMARY TUMORS	28	20	26	19	13
TOTAL ANIMALS WITH BENIGN TUMORS	14	7	11	6	6
TOTAL BENIGN TUMORS	17	7	11	8	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	10	14	11	6
TOTAL MALIGNANT TUMORS	11	13	15	11	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3	2		
TOTAL SECONDARY TUMORS	1	3	2		
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 MALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	23	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	23	50	50	48
INTEGUMENTARY SYSTEM				
*SKIN	(23)	(50)	(50)	(48)
FIBROSARCOMA			1 (2%)	
*SUBCUT TISSUE	(23)	(50)	(50)	(48)
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (2%)
SARCOMA, NOS		2 (4%)	2 (4%)	
FIBROMA		4 (8%)	1 (2%)	2 (4%)
FIBROSARCOMA	4 (17%)	1 (2%)	5 (10%)	6 (13%)
RESPIRATORY SYSTEM				
#LUNG	(23)	(50)	(50)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	3 (6%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (17%)	9 (18%)	9 (18%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (4%)	2 (4%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(23)	(50)	(50)	(48)
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (9%)	2 (4%)	2 (4%)	5 (10%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		1 (2%)
#SPLEEN	(21)	(48)	(49)	(47)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		
#MESENTERIC L. NODE	(16)	(34)	(28)	(30)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)		

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

TABLE B2. MALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#SMALL INTESTINE	(21)	(44)	(46)	(39)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)			
*MESENTERY	(23)	(50)	(50)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
#THYMUS	(11)	(35)	(28)	(31)
HEPATOCELLULAR CARCINOMA, METAST			1 (4%)	
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (3%)
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(23)	(50)	(50)	(48)
HEMANGIOMA				1 (2%)
HEMANGIOSARCOMA			1 (2%)	
#SPLEEN	(21)	(48)	(49)	(47)
HEMANGIOMA	1 (5%)		1 (2%)	2 (4%)
#HEART/VENTRICLE	(23)	(49)	(49)	(48)
HEMANGIOMA				1 (2%)
#LIVER	(23)	(50)	(49)	(48)
HEMANGIOMA				1 (2%)
HEMANGIOSARCOMA	1 (4%)	1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(23)	(50)	(49)	(48)
HEPATOCELLULAR ADENOMA	2 (9%)	5 (10%)	9 (18%)	15 (31%)
HEPATOCELLULAR CARCINOMA	4 (17%)	9 (18%)	5 (10%)	9 (19%)
INFILTRATING DUCT CARCINOMA			1 (2%)	
#PANCREAS	(23)	(48)	(46)	(40)
INFILTRATING DUCT CARCINOMA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(23)	(50)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	

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

TABLE B2. MALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)	
#URINARY BLADDER	(22)	(47)	(43)	(46)
PAPILLOMA, NOS		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(17)	(38)	(28)	(30)
CHROMOPHOBE ADENOMA				1 (3%)
#ADRENAL	(23)	(48)	(47)	(43)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)	
PHEOCHROMOCYTOMA	1 (4%)			
FIBROSARCOMA			1 (2%)	
#THYROID	(22)	(46)	(47)	(42)
ADENOMA, NOS	1 (5%)	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM				
#PROSTATE	(21)	(44)	(46)	(46)
ADENOCARCINOMA, NOS			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*STERNUM	(23)	(50)	(50)	(48)
OSTEOSARCOMA				1 (2%)
BODY CAVITIES				
NONE				

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

TABLE B2. MALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(23)	(50)	(50)	(48)
SARCOMA, NOS	1 (4%)			
FIBROSARCOMA				1 (2%)
THORACIC CAVITY				
MESOTHELIOMA, MALIGNANT			1	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATH@	7	14	18	19
MORIBUND SACRIFICE	2	7	6	7
SCHEDULED SACRIFICE	5	25	17	16
ACCIDENTALLY KILLED				1
TERMINAL SACRIFICE	10	4	9	7
ANIMAL MISSING	1			
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	13	33	29	38
TOTAL PRIMARY TUMORS	23	44	45	55
TOTAL ANIMALS WITH BENIGN TUMORS	6	19	16	22
TOTAL BENIGN TUMORS	9	21	21	28
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	18	20	21
TOTAL MALIGNANT TUMORS	14	23	24	27
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	4	4
TOTAL SECONDARY TUMORS		1	8	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE B3.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	24	25	24	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	24	25	24	25
INTEGUMENTARY SYSTEM					
*SUBCUT TISSUE	(25)	(24)	(25)	(24)	(25)
BASAL-CELL CARCINOMA	1 (4%)				
FIBROMA		1 (4%)			
FIBROSARCOMA	2 (8%)			1 (4%)	
RESPIRATORY SYSTEM					
#LUNG	(25)	(23)	(24)	(24)	(25)
ADENOCARCINOMA, NOS, METASTATIC			2 (8%)		
HEPATOCELLULAR CARCINOMA, METAST					1 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (8%)	2 (9%)	2 (8%)		2 (8%)
THYMOMA, METASTATIC					1 (4%)
FIBROSARCOMA, METASTATIC				1 (4%)	
OSTEOSARCOMA, METASTATIC	1 (4%)				
HEMATOPOIETIC SYSTEM					
*MULTIPLE ORGANS	(25)	(24)	(25)	(24)	(25)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (4%)		1 (4%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)	2 (8%)	1 (4%)	1 (4%)	1 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	7 (28%)	2 (8%)	2 (8%)		6 (24%)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (4%)	1 (4%)	
#LYMPH NODE	(21)	(17)	(21)	(17)	(21)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (6%)	
#CERVICAL LYMPH NODE	(21)	(17)	(21)	(17)	(21)
ADENOCARCINOMA, NOS			1 (5%)		
#RETROPHARYNGEAL LYMP	(21)	(17)	(21)	(17)	(21)
FIBROSARCOMA, METASTATIC				1 (6%)	

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

TABLE B3. FEMALE MICE (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#MESENTERIC L. NODE	(21)	(17)	(21)	(17)	(21)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)				
#JEJUNUM	(22)	(19)	(23)	(24)	(23)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (4%)	
#THYMUS	(19)	(18)	(13)	(20)	(20)
THYMOMA, MALIGNANT					1 (5%)
CIRCULATORY SYSTEM					
*SUBCUT TISSUE	(25)	(24)	(25)	(24)	(25)
HEMANGIOMA		1 (4%)		1 (4%)	
#SPLEEN	(24)	(24)	(24)	(24)	(25)
HEMANGIOMA	1 (4%)				
#UTERUS	(23)	(23)	(24)	(24)	(23)
HEMANGIOMA				1 (4%)	
HEMANGIOSARCOMA		1 (4%)			
DIGESTIVE SYSTEM					
#LIVER	(25)	(24)	(25)	(24)	(25)
HEPATOCELLULAR ADENOMA		2 (8%)		1 (4%)	1 (4%)
HEPATOCELLULAR CARCINOMA			1 (4%)		1 (4%)
THYMOMA, METASTATIC					1 (4%)
URINARY SYSTEM					
#KIDNEY	(25)	(24)	(25)	(24)	(25)
THYMOMA, METASTATIC					1 (4%)
ENDOCRINE SYSTEM					
#PITUITARY	(21)	(22)	(16)	(18)	(22)
CHROMOPHOBE ADENOMA		1 (5%)	1 (6%)		
#ADRENAL	(24)	(23)	(24)	(24)	(25)
CORTICAL ADENOMA			1 (4%)		

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

TABLE B3. FEMALE MICE (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#THYROID	(22)	(21)	(24)	(23)	(21)
ADENOMA, NOS			1 (4%)		
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(25)	(24)	(25)	(24)	(25)
ADENOMA, NOS					1 (4%)
FIBROADENOMA			1 (4%)		
#UTERUS	(23)	(23)	(24)	(24)	(23)
LIPOMA	1 (4%)				1 (4%)
LEIOMYOMA				1 (4%)	
#CERVIX UTERI	(23)	(23)	(24)	(24)	(23)
LEIOMYOMA			1 (4%)		
#OVARY	(23)	(19)	(22)	(22)	(19)
CYSTADENOMA, NOS				1 (5%)	1 (5%)
LIPOMA			1 (5%)		
NERVOUS SYSTEM					
NONE					
SPECIAL SENSE ORGANS					
NONE					
MUSCULOSKELETAL SYSTEM					
*VERTEBRA	(25)	(24)	(25)	(24)	(25)
OSTEOSARCOMA	1 (4%)				
BODY CAVITIES					
NONE					
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(24)	(25)	(24)	(25)
ADENOCARCINOMA, NOS			1 (4%)		

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

TABLE B3. FEMALE MICE (CONTROL GROUPS): NEOPLASMS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
FIBROSARCOMA				1 (4%)	
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
NATURAL DEATH@	6	5	6	4	4
MORIBUND SACRIFICE	1	2	3	3	2
SCHEDULED SACRIFICE	6	13	13	4	14
ACCIDENTALLY KILLED					
TERMINAL SACRIFICE	12	5	3	14	5
ANIMAL MISSING					
@ INCLUDES AUTOLYZED ANIMALS					
TUMOR SUMMARY					
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	10	11	9	13
TOTAL PRIMARY TUMORS	17	12	16	11	16
TOTAL ANIMALS WITH BENIGN TUMORS	4	6	6	5	4
TOTAL BENIGN TUMORS	4	7	8	5	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	5	6	6	10
TOTAL MALIGNANT TUMORS	13	5	8	6	10
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		2	1	2
TOTAL SECONDARY TUMORS	1		2	2	4
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 B4.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED HCDO BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS NECROPSIED	25	49	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	49	48	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(25)	(49)	(49)	(49)
ADENOMA, NOS		1 (2%)		
SARCOMA, NOS				1 (2%)
FIBROMA		1 (2%)	1 (2%)	
FIBROSARCOMA			1 (2%)	2 (4%)
FIBROUS HISTIOCYTOMA				1 (2%)
OSTEOSARCOMA				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(25)	(49)	(48)	(48)
NEOPLASM, NOS		1 (2%)		
ADENOCARCINOMA, NOS, METASTATIC	1 (4%)	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	5 (10%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(25)	(49)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	1 (4%)			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3 (12%)	4 (8%)	3 (6%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (8%)	2 (4%)	2 (4%)	7 (14%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		
GRANULOCYTIC SARCOMA				1 (2%)
#SPLEEN	(23)	(48)	(47)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#LYMPH NODE	(22)	(42)	(36)	(30)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)		1 (3%)
#PYLORIC LYMPH NODE	(22)	(42)	(36)	(30)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		

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

TABLE B4. FEMALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY/CAPSULE	(24)	(49)	(48)	(46)
SARCOMA, NOS, INVASIVE				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(41)	(40)	(41)
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS			1 (3%)	
CHROMOPHOBE ADENOMA	1 (5%)	2 (5%)		
#ADRENAL	(24)	(46)	(46)	(47)
CORTICAL ADENOMA	1 (4%)			
PHEOCHROMOCYTOMA	1 (4%)			
#ADRENAL/CAPSULE	(24)	(46)	(46)	(47)
SARCOMA, NOS, INVASIVE				1 (2%)
#THYROID	(25)	(44)	(40)	(42)
ADENOMA, NOS	1 (4%)		1 (3%)	
PAPILLARY ADENOMA		1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(49)	(49)	(49)
ADENOMA, NOS				1 (2%)
#UTERUS	(25)	(45)	(45)	(45)
FIBROMA	1 (4%)			
LEIOMYOMA	2 (8%)	1 (2%)		
LEIOMYOSARCOMA			1 (2%)	
#OVARY	(23)	(46)	(40)	(36)
MUCINOUS CYSTADENOMA			1 (3%)	
LUTEOMA			1 (3%)	
GRANULOSA-CELL TUMOR			1 (3%)	1 (3%)
NERVOUS SYSTEM				
NONE				

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

TABLE B4. FEMALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(25)	(49)	(49)	(49)
ADENOCARCINOMA, NOS	1 (4%)	1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(49)	(49)	(49)
SARCOMA, NOS				1 (2%)
THORAX				
SARCOMA, NOS			1	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATH@	4	13	16	11
MORIBUND SACRIFICE		6	1	3
SCHEDULED SACRIFICE	16	16	22	27
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	5	15	11	9
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B4. FEMALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#MESENTERIC L. NODE	(22)	(42)	(36)	(30)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (3%)
#LIVER	(24)	(48)	(47)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
*MESENTERY	(25)	(49)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#THYMUS	(21)	(32)	(32)	(30)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (3%)		
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(25)	(49)	(49)	(49)
HEMANGIOSARCOMA		1 (2%)		
*SUBCUT TISSUE	(25)	(49)	(49)	(49)
HEMANGIOMA		2 (4%)		
#SPLEEN	(23)	(48)	(47)	(46)
HEMANGIOMA			3 (6%)	
#OVARY	(23)	(46)	(40)	(36)
HEMANGIOMA		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(25)	(47)	(47)	(44)
FIBROSARCOMA		1 (2%)		
#LIVER	(24)	(48)	(47)	(47)
HEPATOCELLULAR ADENOMA		4 (8%)	4 (9%)	9 (19%)
HEPATOCELLULAR CARCINOMA			2 (4%)	2 (4%)
#HEPATIC CAPSULE	(24)	(48)	(47)	(47)
SARCOMA, NOS, INVASIVE				1 (2%)
#PANCREAS	(23)	(47)	(46)	(44)
ADENOMA, NOS	1 (4%)			
#COLON	(25)	(47)	(44)	(43)
LEIOMYOMA				1 (2%)

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

TABLE B4. FEMALE MICE (CONTROL AND DOSED GROUPS): NEOPLASMS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	24	22	28
TOTAL PRIMARY TUMORS	15	30	29	38
TOTAL ANIMALS WITH BENIGN TUMORS	8	14	12	13
TOTAL BENIGN TUMORS	8	16	16	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	13	12	21
TOTAL MALIGNANT TUMORS	7	13	12	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		1
TOTAL SECONDARY TUMORS	1	1		3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1	1
TOTAL UNCERTAIN TUMORS		1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED HCDD BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	25	25	25	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	25	25	25	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(25)	(25)	(25)	(25)
ABSCESS, NOS				1 (4%)	
GRANULOMA, NOS			1 (4%)		
HYPERKERATOSIS			1 (4%)		
*SUBCUT TISSUE	(25)	(25)	(25)	(25)	(25)
HEMORRHAGIC CYST				1 (4%)	1 (4%)
NECROSIS, NOS				1 (4%)	
RESPIRATORY SYSTEM					
*NASAL CAVITY	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, SUPPURATIVE			1 (4%)		
INFLAMMATION, ACUTE SUPPURATIVE			1 (4%)		
INFLAMMATION, CHRONIC FOCAL				3 (12%)	
*LARYNX	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC		1 (4%)			
INFLAMMATION, CHRONIC FOCAL					1 (4%)
#TRACHEA	(25)	(25)	(25)	(25)	(23)
INFLAMMATION, CHRONIC FOCAL	2 (8%)				1 (4%)
#LUNG/BRONCHIOLE	(25)	(25)	(25)	(25)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR			7 (28%)		
ABSCESS, NOS			1 (4%)		
GRANULOMA, FOREIGN BODY			1 (4%)		
#LUNG	(25)	(25)	(25)	(25)	(25)
ATELECTASIS		1 (4%)			
CONGESTION, NOS	4 (16%)	8 (32%)	1 (4%)	7 (28%)	5 (20%)
EDEMA, NOS	1 (4%)	2 (8%)			

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
INFLAMMATION, INTERSTITIAL			2 (8%)		
PNEUMONIA, ASPIRATION			1 (4%)		
BRONCHOPNEUMONIA SUPPURATIVE	1 (4%)				
INFLAMMATION, ACUTE FOCAL			2 (8%)		
INFLAMMATION, ACUTE DIFFUSE			1 (4%)		
PNEUMONIA, CHRONIC MURINE	16 (64%)	22 (88%)	6 (24%)	20 (80%)	15 (60%)
PNEUMONIA INTERSTITIAL CHRONIC				1 (4%)	
GRANULOMA, NOS				1 (4%)	
INFLAMMATION, FOCAL GRANULOMATOU					1 (4%)
ALVEOLAR MACROPHAGES	1 (4%)	2 (8%)		1 (4%)	1 (4%)
HYPERPLASIA, ADENOMATOUS		1 (4%)			
#LUNG/ALVEOLI	(25)	(25)	(25)	(25)	(25)
COLLAPSE	1 (4%)				
CALCIFICATION, NOS					1 (4%)
CALCIFICATION, FOCAL	2 (8%)				
HEMATOPOIETIC SYSTEM					
*MAMMARY GLAND	(25)	(25)	(25)	(25)	(25)
ADENOSIS				1 (4%)	
#BONE MARROW	(24)	(24)	(23)	(24)	(23)
METAMORPHOSIS FATTY		1 (4%)	3 (13%)		
FIBROUS OSTEODYSTROPHY			1 (4%)		
HYPOPLASIA, NOS			1 (4%)		
ATROPHY, NOS		1 (4%)	1 (4%)		1 (4%)
MYELOFIBROSIS	4 (17%)	1 (4%)	1 (4%)		2 (9%)
#SPLEEN	(25)	(23)	(25)	(23)	(24)
CONGESTION, NOS	2 (8%)	5 (22%)		4 (17%)	3 (13%)
HEMORRHAGE					1 (4%)
INFLAMMATION, CHRONIC		1 (4%)			
HEMOSIDEROSIS	4 (16%)	3 (13%)	1 (4%)	3 (13%)	
ATROPHY, NOS			3 (12%)		
HYPERPLASIA, LYMPHOID			1 (4%)		
HEMATOPOIESIS	5 (20%)	5 (22%)	6 (24%)	10 (43%)	8 (33%)
ERYTHROPOIESIS			5 (20%)		
#SPLENIC RED PULP	(25)	(23)	(25)	(23)	(24)
ATROPHY, NOS			1 (4%)		
#LYMPH NODE	(20)	(17)	(18)	(19)	(22)
CONGESTION, NOS		1 (6%)		1 (5%)	1 (5%)

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
EDEMA, NOS		1 (6%)		1 (5%)	1 (5%)
INFLAMMATION, CHRONIC				1 (5%)	
HYPERPLASIA, LYMPHOID				2 (11%)	
#SUBMANDIBULAR L.NODE	(20)	(17)	(18)	(19)	(22)
HYPERPLASIA, LYMPHOID					1 (5%)
#MANDIBULAR L. NODE	(20)	(17)	(18)	(19)	(22)
CONGESTION, NOS		1 (6%)			
#CERVICAL LYMPH NODE	(20)	(17)	(18)	(19)	(22)
HYPERPLASIA, NOS			8 (44%)		
#MESENTERIC L. NODE	(20)	(17)	(18)	(19)	(22)
HEMORRHAGE			1 (6%)		
INFLAMMATION, CHRONIC			1 (6%)		
#RENAL LYMPH NODE	(20)	(17)	(18)	(19)	(22)
HEMORRHAGE	1 (5%)				
PIGMENTATION, NOS	1 (5%)				
LYMPHOID DEPLETION	1 (5%)				
HYPERPLASIA, NOS				1 (5%)	
HYPERPLASIA, HEMATOPOIETIC	1 (5%)				
#PANCREAS	(23)	(24)	(23)	(24)	(23)
HEMATOPOIESIS					1 (4%)
#COLON	(24)	(24)	(23)	(25)	(24)
HYPERPLASIA, LYMPHOID			1 (4%)		
#ADRENAL CORTEX	(25)	(25)	(24)	(24)	(24)
HEMATOPOIESIS	1 (4%)				
#THYMUS	(9)	(8)	(15)	(17)	(15)
BRANCHIAL CYST					1 (7%)
INFLAMMATION, CHRONIC					1 (7%)
CIRCULATORY SYSTEM					
#HEART	(25)	(25)	(24)	(24)	(25)
CALCIFICATION, NOS	1 (4%)	1 (4%)			
#HEART/ATRIUM	(25)	(25)	(24)	(24)	(25)
THROMBUS, ORGANIZED	1 (4%)	1 (4%)			

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
THROMBUS, MURAL	1 (4%)				
#MYOCARDIUM	(25)	(25)	(24)	(24)	(25)
INFLAMMATION, FOCAL			1 (4%)		
INFLAMMATION, CHRONIC	2 (8%)	6 (24%)		1 (4%)	3 (12%)
INFLAMMATION, CHRONIC FOCAL	13 (52%)	8 (32%)	3 (13%)	9 (38%)	10 (40%)
CALCIFICATION, NOS	1 (4%)				
CALCIFICATION, FOCAL				1 (4%)	
*BLOOD VESSEL	(25)	(25)	(25)	(25)	(25)
MEDIAL CALCIFICATION					2 (8%)
*ARTERY	(25)	(25)	(25)	(25)	(25)
MEDIAL CALCIFICATION	4 (16%)	2 (8%)		1 (4%)	
*AORTA	(25)	(25)	(25)	(25)	(25)
MEDIAL CALCIFICATION			1 (4%)		
*PULMONARY ARTERY	(25)	(25)	(25)	(25)	(25)
MEDIAL CALCIFICATION			1 (4%)		
#PANCREAS	(23)	(24)	(23)	(24)	(23)
PERIARTERITIS	1 (4%)		1 (4%)		
#TESTIS	(25)	(25)	(24)	(24)	(25)
PERIARTERITIS	7 (28%)	1 (4%)	1 (4%)	2 (8%)	2 (8%)
DIGESTIVE SYSTEM					
#SALIVARY GLAND	(22)	(24)	(22)	(24)	(24)
INFLAMMATION, CHRONIC FOCAL					1 (4%)
ATROPHY, FOCAL			1 (5%)		1 (4%)
#LIVER	(25)	(25)	(25)	(25)	(25)
TRAUMATIC ABNORMALITY					1 (4%)
CONGESTION, NOS		2 (8%)	1 (4%)	2 (8%)	2 (8%)
HEMORRHAGE					1 (4%)
INFLAMMATION, NOS					1 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)		1 (4%)
CIRRHOSIS, BILIARY					1 (4%)
DEGENERATION, NOS		3 (12%)	1 (4%)		
CLOUDY SWELLING	1 (4%)	1 (4%)			1 (4%)
DEGENERATION, HYDROPIC			1 (4%)	1 (4%)	
NECROSIS, NOS		2 (8%)			2 (8%)

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
NECROSIS, FOCAL	1 (4%)	1 (4%)	1 (4%)		1 (4%)
NECROSIS, COAGULATIVE			1 (4%)		
METAMORPHOSIS FATTY	2 (8%)	2 (8%)	2 (8%)	4 (16%)	5 (20%)
LIPOIDOSIS			2 (8%)		
CYTOPLASMIC VACUOLIZATION	2 (8%)	4 (16%)	1 (4%)	1 (4%)	1 (4%)
HEPATOCYTOMEGALY			1 (4%)		
CYTOLOGIC DEGENERATION	1 (4%)	2 (8%)		2 (8%)	
HYPERTROPHY, FOCAL				1 (4%)	1 (4%)
ANGIECTASIS				1 (4%)	1 (4%)
#LIVER/CENTRILOBULAR	(25)	(25)	(25)	(25)	(25)
CONGESTION, NOS	1 (4%)				
DEGENERATION, HYDROPIC			2 (8%)		
NECROSIS, NOS	1 (4%)	2 (8%)	1 (4%)		
NECROSIS, COAGULATIVE			1 (4%)		
METAMORPHOSIS FATTY	6 (24%)	3 (12%)	1 (4%)	5 (20%)	3 (12%)
LIPOIDOSIS			3 (12%)		
#LIVER/PERIPORTAL	(25)	(25)	(25)	(25)	(25)
FIBROSIS				1 (4%)	
#LIVER/HEPATOCYTES	(25)	(25)	(25)	(25)	(25)
CLOUDY SWELLING					1 (4%)
METAMORPHOSIS FATTY	3 (12%)				
HYPERTROPHY, FOCAL	1 (4%)				
#BILE DUCT	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC			1 (4%)		
HYPERPLASIA, NOS	13 (52%)	7 (28%)	8 (32%)	11 (44%)	9 (36%)
#PANCREAS	(23)	(24)	(23)	(24)	(23)
CONGESTION, NOS				1 (4%)	
INFLAMMATION, CHRONIC FOCAL	2 (9%)				
ATROPHY, NOS	1 (4%)				
ATROPHY, FOCAL	1 (4%)	3 (13%)	1 (4%)	1 (4%)	
#PANCREATIC ACINUS	(23)	(24)	(23)	(24)	(23)
HYPERPLASIA, FOCAL		1 (4%)			
#STOMACH	(24)	(24)	(25)	(23)	(24)
MINERALIZATION			2 (8%)		
ULCER, FOCAL	1 (4%)				
INFLAMMATION, NECROTIZING			1 (4%)		
INFLAMMATION, CHRONIC	1 (4%)		1 (4%)		1 (4%)
INFLAMMATION, CHRONIC FOCAL			1 (4%)		

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
GRANULATION, TISSUE	1 (4%)				
NECROSIS, FOCAL			1 (4%)		
HYPERPLASIA, EPITHELIAL					1 (4%)
#GASTRIC MUCOSA	(24)	(24)	(25)	(23)	(24)
DILATATION, NOS			4 (16%)		
CALCIFICATION, NOS	4 (17%)	4 (17%)	2 (8%)	1 (4%)	3 (13%)
CALCIFICATION, FOCAL			1 (4%)	1 (4%)	
HYPERPLASIA, EPITHELIAL			1 (4%)		
HYPERPLASIA, FOCAL					1 (4%)
#GASTRIC SUBMUCOSA	(24)	(24)	(25)	(23)	(24)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)		
#STOMACH WALL	(24)	(24)	(25)	(23)	(24)
CALCIFICATION, NOS	1 (4%)				
#SMALL INTESTINE	(23)	(24)	(23)	(25)	(24)
CONGESTION, NOS	1 (4%)				
INFLAMMATION, ACUTE			1 (4%)		
INFLAMMATION, CHRONIC			1 (4%)		
POSTMORTEM CHANGE	1 (4%)				
#INTESTINAL VILLUS	(23)	(24)	(23)	(25)	(24)
CONGENITAL ABNORMAL FUSION		1 (4%)			
#DUODENUM	(23)	(24)	(23)	(25)	(24)
INFLAMMATION, ACUTE			1 (4%)		
#COLON	(24)	(24)	(23)	(25)	(24)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (8%)			1 (4%)	1 (4%)
INFLAMMATION, CHRONIC	2 (8%)				
INFLAMMATION, CHRONIC FOCAL		1 (4%)		2 (8%)	2 (8%)
NEMATODIASIS				1 (4%)	
#COLONIC MUSCULARIS P	(24)	(24)	(23)	(25)	(24)
CALCIFICATION, FOCAL				1 (4%)	
URINARY SYSTEM					
#KIDNEY	(25)	(25)	(25)	(24)	(25)
PYELONEPHRITIS, NOS		1 (4%)			
PYELONEPHRITIS, ACUTE			1 (4%)		
INFLAMMATION, CHRONIC	24 (96%)	25 (100%)	23 (92%)	21 (88%)	23 (92%)

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
GLOMERULONEPHRITIS, CHRONIC			1 (4%)		
#KIDNEY/PELVIS	(25)	(25)	(25)	(24)	(25)
MINERALIZATION	2 (8%)	2 (8%)	3 (12%)	2 (8%)	4 (16%)
INFLAMMATION, NOS	1 (4%)	2 (8%)	1 (4%)		
INFLAMMATION, CHRONIC	1 (4%)				
HYPERPLASIA, EPITHELIAL	5 (20%)	10 (40%)	10 (40%)	8 (33%)	7 (28%)
METAPLASIA, SQUAMOUS			1 (4%)		
#URINARY BLADDER	(24)	(24)	(24)	(24)	(24)
EDEMA, NOS	1 (4%)				
INFLAMMATION, CHRONIC	1 (4%)	2 (8%)			2 (8%)
INFLAMMATION, CHRONIC FOCAL					1 (4%)
HYPERPLASIA, EPITHELIAL	2 (8%)	4 (17%)	1 (4%)	2 (8%)	3 (13%)
ENDOCRINE SYSTEM					
#PITUITARY	(24)	(21)	(21)	(20)	(22)
MULTIPLE CYSTS					1 (5%)
HYPERPLASIA, NOS	1 (4%)			1 (5%)	
HYPERPLASIA, CHROMOPHOBE-CELL		1 (5%)	2 (10%)		
ANGIECTASIS			1 (5%)		
#ADRENAL	(25)	(25)	(24)	(24)	(24)
CONGESTION, NOS		1 (4%)			
METAMORPHOSIS FATTY			1 (4%)		
LIPOIDOSIS			1 (4%)		
ANGIECTASIS			1 (4%)	1 (4%)	
#ADRENAL CORTEX	(25)	(25)	(24)	(24)	(24)
ECTOPIA			1 (4%)		
FIBROSIS, FOCAL					1 (4%)
METAMORPHOSIS FATTY	5 (20%)	7 (28%)	3 (13%)	4 (17%)	7 (29%)
LIPOIDOSIS			6 (25%)		
HEMOSIDEROSIS					1 (4%)
HYPERPLASIA, NODULAR		1 (4%)		2 (8%)	1 (4%)
HYPERPLASIA, NOS		1 (4%)		1 (4%)	
ANGIECTASIS			2 (8%)	1 (4%)	
#THYROID	(25)	(25)	(24)	(23)	(24)
ATROPHY, PRESSURE			1 (4%)		
HYPERPLASIA, C-CELL	2 (8%)		1 (4%)	1 (4%)	1 (4%)
HYPERPLASIA, FOLLICULAR-CELL			2 (8%)		
#PARATHYROID	(21)	(22)	(22)	(13)	(15)
HYPERPLASIA, NOS	7 (33%)	4 (18%)	7 (32%)	2 (15%)	5 (33%)

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(25)	(25)	(25)	(25)	(25)
GALACTOCELE		2 (8%)			1 (4%)
CYST, NOS		1 (4%)			
HYPERPLASIA, NOS		1 (4%)	1 (4%)		1 (4%)
*BULBOURETHRAL GLAND	(25)	(25)	(25)	(25)	(25)
RETENTION OF CONTENT			2 (8%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (4%)				
HYPERPLASIA, EPITHELIAL			1 (4%)		
#PROSTATE	(25)	(24)	(22)	(24)	(25)
RETENTION OF CONTENT			6 (27%)		
INFLAMMATION, FOCAL	1 (4%)				
INFLAMMATION, SUPPURATIVE	2 (8%)	1 (4%)		1 (4%)	1 (4%)
INFLAMMATION, ACUTE		1 (4%)			
INFLAMMATION, ACUTE SUPPURATIVE	1 (4%)		1 (5%)	1 (4%)	1 (4%)
INFLAMMATION, CHRONIC	1 (4%)	1 (4%)	1 (5%)		3 (12%)
INFLAMMATION, CHRONIC FOCAL		1 (4%)		3 (13%)	
INFLAMMATION, CHRONIC SUPPURATIV		4 (17%)	1 (5%)	1 (4%)	1 (4%)
ABSCESS, CHRONIC					1 (4%)
HYPERPLASIA, NOS			2 (9%)		
HYPERPLASIA, FOCAL				1 (4%)	
#PROSTATIC GLAND	(25)	(24)	(22)	(24)	(25)
INFLAMMATION, CHRONIC FOCAL				1 (4%)	
*SEMINAL VESICLE	(25)	(25)	(25)	(25)	(25)
RETENTION OF CONTENT			8 (32%)		
INFLAMMATION, NECROTIZING	1 (4%)				
HYPERPLASIA, NOS			1 (4%)		
HYPERPLASIA, EPITHELIAL		1 (4%)			1 (4%)
#PERIPROSTATIC TISSUE	(25)	(24)	(22)	(24)	(25)
INFLAMMATION, NOS					1 (4%)
#TESTIS	(25)	(25)	(24)	(24)	(25)
DEGENERATION, NOS	11 (44%)	12 (48%)	4 (17%)	10 (42%)	9 (36%)
ATROPHY, NOS			1 (4%)		
ATROPHY, FOCAL			1 (4%)		
#TESTIS/TUBULE	(25)	(25)	(24)	(24)	(25)
DEGENERATION, NOS		1 (4%)			

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

TABLE C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
*EPIDIDYMIS	(25)	(25)	(25)	(25)	(25)
SPERMATOCELE	1 (4%)				1 (4%)
ABSCESS, NOS					1 (4%)
INFLAMMATION, GRANULOMATOUS					1 (4%)
FIBROSIS	1 (4%)				
NECROSIS, FOCAL				1 (4%)	
ASPERMATOGENESIS			1 (4%)		
NERVOUS SYSTEM					
#BRAIN	(25)	(25)	(23)	(25)	(25)
GLIOSIS				1 (4%)	
#BRAIN STEM	(25)	(25)	(23)	(25)	(25)
GLIOSIS					1 (4%)
SPECIAL SENSE ORGANS					
*EYE	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC	1 (4%)			1 (4%)	
*EYE/CORNEA	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, NOS				1 (4%)	
INFLAMMATION, ACUTE	2 (8%)				
INFLAMMATION, CHRONIC	1 (4%)				
*EYE/LACRIMAL GLAND	(25)	(25)	(25)	(25)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			2 (8%)	
MUSCULOSKELETAL SYSTEM					
*COSTOCHONDRAL SYNCHO	(25)	(25)	(25)	(25)	(25)
HYPEROSTOSIS		1 (4%)			
BODY CAVITIES					
*EPICARDIUM	(25)	(25)	(25)	(25)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)		
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
NECROSIS, NOS			1 (4%)		

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

C1. MALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
SPECIAL MORPHOLOGY SUMMARY					
NONE					

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS NECROPSIED	25	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(25)	(50)	(50)	(49)
EDEMA, NOS			1 (2%)	
ULCER, CHRONIC			1 (2%)	
GRANULATION, TISSUE			1 (2%)	
FIBROSIS			1 (2%)	
HYPERKERATOSIS		1 (2%)	1 (2%)	1 (2%)
ACANTHOSIS	1 (4%)			1 (2%)
*SUBCUT TISSUE	(25)	(50)	(50)	(49)
ULCER, NOS				1 (2%)
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
GRANULATION, TISSUE			1 (2%)	
FIBROSIS			1 (2%)	
NECROSIS, NOS				2 (4%)
RESPIRATORY SYSTEM				
*NASAL CAVITY	(25)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			2 (4%)	
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (4%)	3 (6%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
*LARYNX	(25)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
#TRACHEA	(25)	(49)	(49)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	1 (2%)	
INFLAMMATION, ACUTE				1 (2%)

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)	3 (6%)
#LUNG/BRONCHUS	(25)	(49)	(50)	(49)
INFLAMMATION, NOS	1 (4%)			
HYPERPLASIA, EPITHELIAL				1 (2%)
HYPERPLASIA, ADENOMATOUS		6 (12%)	7 (14%)	14 (29%)
#LUNG/BRONCHIOLE	(25)	(49)	(50)	(49)
INFLAMMATION, MULTIFOCAL	1 (4%)			
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, ADENOMATOUS		3 (6%)	6 (12%)	9 (18%)
#LUNG	(25)	(49)	(50)	(49)
ATELECTASIS			1 (2%)	
CONGESTION, NOS	5 (20%)	7 (14%)	6 (12%)	8 (16%)
EDEMA, NOS	1 (4%)	3 (6%)	2 (4%)	2 (4%)
HEMORRHAGE		1 (2%)		
BRONCHOPNEUMONIA, FOCAL		1 (2%)	1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE	1 (4%)		2 (4%)	1 (2%)
BRONCHOPNEUMONIA, ACUTE				1 (2%)
ABSCESS, NOS	1 (4%)			
PNEUMONIA, CHRONIC MURINE	14 (56%)	33 (67%)	30 (60%)	37 (76%)
PNEUMONIA INTERSTITIAL CHRONIC	1 (4%)	1 (2%)		
GRANULOMA, NOS		1 (2%)		
NECROSIS, FOCAL			2 (4%)	
CALCIFICATION, FOCAL	1 (4%)	1 (2%)	1 (2%)	
ALVEOLAR MACROPHAGES	2 (8%)	3 (6%)	3 (6%)	2 (4%)
HYPERPLASIA, ADENOMATOUS			1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)	3 (6%)
#LUNG/ALVEOLI	(25)	(49)	(50)	(49)
CALCIFICATION, FOCAL	1 (4%)	3 (6%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(25)	(48)	(47)	(48)
METAMORPHOSIS FATTY			1 (2%)	
ATROPHY, NOS	1 (4%)	1 (2%)	1 (2%)	1 (2%)
MYELOFIBROSIS	1 (4%)	4 (8%)	5 (11%)	
APLASIA, HEMATOPOIETIC		1 (2%)		
#SPLEEN	(25)	(50)	(49)	(47)
CONGESTION, NOS	2 (8%)	6 (12%)	7 (14%)	1 (2%)

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	1 (4%)	1 (2%)	1 (2%)	
NECROSIS, FOCAL	1 (4%)		1 (2%)	
INFARCT, NOS				1 (2%)
HEMOSIDEROSIS	3 (12%)	1 (2%)	3 (6%)	2 (4%)
HEMATOPOIESIS	6 (24%)	9 (18%)	11 (22%)	8 (17%)
#LYMPH NODE	(22)	(37)	(41)	(38)
CONGESTION, NOS	1 (5%)			
EDEMA, NOS	1 (5%)	1 (3%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
DEGENERATION, LIPOID				1 (3%)
CHOLESTEROL DEPOSIT				1 (3%)
HYPERPLASIA, LYMPHOID			1 (2%)	
#MANDIBULAR L. NODE	(22)	(37)	(41)	(38)
CONGESTION, NOS	1 (5%)			
INFLAMMATION, NOS	1 (5%)			
ABSCESS, NOS		1 (3%)		
HYPERPLASIA, LYMPHOID	1 (5%)	1 (3%)	2 (5%)	1 (3%)
#RENAL LYMPH NODE	(22)	(37)	(41)	(38)
HYPERPLASIA, LYMPHOID	1 (5%)			
#LIVER	(24)	(49)	(50)	(48)
HEMATOPOIESIS			1 (2%)	2 (4%)
#COLONIC SUBMUCOSA	(25)	(48)	(48)	(47)
HYPERPLASIA, LYMPHOID	1 (4%)			
#ADRENAL	(24)	(47)	(47)	(47)
HEMATOPOIESIS			1 (2%)	
#THYMUS	(15)	(19)	(15)	(31)
BRANCHIAL CYST	1 (7%)			
CONGESTION, NOS				2 (6%)
INFLAMMATION, CHRONIC	1 (7%)			
CIRCULATORY SYSTEM				
#LYMPH NODE	(22)	(37)	(41)	(38)
LYMPHANGIECTASIS		1 (3%)	1 (2%)	
#HEART	(25)	(50)	(50)	(49)
CALCIFICATION, NOS		4 (8%)	3 (6%)	

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
CALCIFICATION, FOCAL		2 (4%)	1 (2%)	
#HEART/ATRIUM	(25)	(50)	(50)	(49)
THROMBUS, MURAL			1 (2%)	
#MYOCARDIUM	(25)	(50)	(50)	(49)
INFLAMMATION, MULTIFOCAL				1 (2%)
INFLAMMATION, CHRONIC	4 (16%)	7 (14%)	4 (8%)	6 (12%)
INFLAMMATION, CHRONIC FOCAL	10 (40%)	20 (40%)	21 (42%)	21 (43%)
DEGENERATION, NOS			1 (2%)	
CALCIFICATION, NOS	2 (8%)			1 (2%)
CALCIFICATION, FOCAL				1 (2%)
*BLOOD VESSEL	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION	2 (8%)	1 (2%)	2 (4%)	
*ARTERY	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION	3 (12%)	8 (16%)	7 (14%)	5 (10%)
*AORTA	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION		1 (2%)		
#PANCREAS	(23)	(48)	(47)	(48)
PERIARTERITIS			1 (2%)	1 (2%)
#TESTIS	(25)	(49)	(50)	(48)
PERIARTERITIS	8 (32%)	9 (18%)	10 (20%)	8 (17%)
#THYMUS	(15)	(19)	(15)	(31)
PERIARTERITIS			1 (7%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(25)	(47)	(47)	(47)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
ATROPHY, NOS	1 (4%)	1 (2%)		
#LIVER	(24)	(49)	(50)	(48)
CONGESTION, NOS	1 (4%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (8%)		1 (2%)	
FIBROSIS			1 (2%)	
CIRRHOSIS, BILIARY				1 (2%)
HEPATITIS, TOXIC		28 (57%)	35 (70%)	34 (71%)
CLOUDY SWELLING	3 (13%)	1 (2%)		

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
NECROSIS, NOS		1 (2%)		1 (2%)
NECROSIS, FOCAL	1 (4%)			
METAMORPHOSIS FATTY	4 (17%)	9 (18%)	2 (4%)	4 (8%)
CYTOPLASMIC VACUOLIZATION	1 (4%)			1 (2%)
CYTOLOGIC DEGENERATION	1 (4%)			
HYPERTROPHY, FOCAL			2 (4%)	1 (2%)
ANGIECTASIS		1 (2%)		
#HEPATIC LOBULE	(24)	(49)	(50)	(48)
METAMORPHOSIS FATTY			1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(24)	(49)	(50)	(48)
NECROSIS, NOS	1 (4%)			
METAMORPHOSIS FATTY	7 (29%)	10 (20%)	9 (18%)	7 (15%)
#LIVER/HEPATOCYTES	(24)	(49)	(50)	(48)
CLOUDY SWELLING	1 (4%)			
METAMORPHOSIS FATTY		1 (2%)		
HYPERTROPHY, FOCAL			1 (2%)	3 (6%)
#BILE DUCT	(24)	(49)	(50)	(48)
INFLAMMATION, FOCAL		1 (2%)		
HYPERPLASIA, NOS	8 (33%)	3 (6%)	2 (4%)	1 (2%)
HYPERPLASIA, FOCAL				1 (2%)
#PANCREAS	(23)	(48)	(47)	(48)
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)	3 (6%)	4 (8%)
GRANULATION, TISSUE		1 (2%)		
ATROPHY, NOS	1 (4%)	1 (2%)	1 (2%)	4 (8%)
ATROPHY, FOCAL	2 (9%)	1 (2%)		2 (4%)
#STOMACH	(25)	(50)	(49)	(49)
ULCER, NOS		1 (2%)		
CALCIFICATION, NOS		5 (10%)	1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERKERATOSIS				1 (2%)
#GASTRIC MUCOSA	(25)	(50)	(49)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
INFLAMMATION, CHRONIC FOCAL				1 (2%)
EROSION	1 (4%)			
FIBROSIS, FOCAL	1 (4%)			
DEGENERATION, NOS			1 (2%)	
CALCIFICATION, NOS	7 (28%)	6 (12%)	9 (18%)	5 (10%)

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HYPERPLASIA, FOCAL		1 (2%)		1 (2%)
HYPERKERATOSIS	1 (4%)			
ACANTHOSIS	1 (4%)		1 (2%)	
METAPLASIA, SQUAMOUS			1 (2%)	
#GASTRIC SUBMUCOSA	(25)	(50)	(49)	(49)
INFLAMMATION, CHRONIC	1 (4%)			
#GASTRIC SEROSA	(25)	(50)	(49)	(49)
CALCIFICATION, NOS	1 (4%)			
#LARGE INTESTINE	(25)	(48)	(48)	(47)
NEMATODIASIS				1 (2%)
#COLON	(25)	(48)	(48)	(47)
INFLAMMATION, FOCAL			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		3 (6%)	1 (2%)	4 (9%)
INFLAMMATION, CHRONIC		2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	3 (12%)	2 (4%)		4 (9%)
NEMATODIASIS	1 (4%)			
*ANUS	(25)	(50)	(50)	(49)
STEATITIS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(25)	(49)	(47)	(49)
PYELONEPHRITIS, NOS		1 (2%)		
INFLAMMATION, CHRONIC	22 (88%)	42 (86%)	41 (87%)	44 (90%)
NEPHROPATHY		2 (4%)		1 (2%)
CYTOLOGIC DEGENERATION	1 (4%)			
#KIDNEY/MEDULLA	(25)	(49)	(47)	(49)
CALCULUS, NOS		1 (2%)		
#KIDNEY/PELVIS	(25)	(49)	(47)	(49)
MINERALIZATION	1 (4%)			
INFLAMMATION, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL	6 (24%)		2 (4%)	1 (2%)
#URINARY BLADDER	(24)	(47)	(46)	(47)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		
INFLAMMATION, CHRONIC		2 (4%)		
HYPERPLASIA, EPITHELIAL		3 (6%)	1 (2%)	1 (2%)

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(42)	(43)	(41)
MULTIPLE CYSTS			1 (2%)	
CONGESTION, NOS	1 (5%)			1 (2%)
HYPERPLASIA, CHROMOPHOBE-CELL	1 (5%)			1 (2%)
#ADRENAL	(24)	(47)	(47)	(47)
HEMORRHAGIC CYST			1 (2%)	1 (2%)
DEGENERATION, LIPOID			1 (2%)	
NECROSIS, NOS		1 (2%)		
METAMORPHOSIS FATTY				1 (2%)
ANGIECTASIS		3 (6%)	1 (2%)	1 (2%)
#ADRENAL CORTEX	(24)	(47)	(47)	(47)
CONGESTION, NOS				1 (2%)
HEMORRHAGIC CYST			1 (2%)	
DEGENERATION, LIPOID		1 (2%)		
METAMORPHOSIS FATTY	7 (29%)	8 (17%)	12 (26%)	12 (26%)
LIPOIDOSIS	1 (4%)			
HYPERPLASIA, NODULAR	2 (8%)	2 (4%)		5 (11%)
HYPERPLASIA, NOS				2 (4%)
#THYROID	(22)	(49)	(47)	(49)
CYSTIC FOLLICLES			1 (2%)	2 (4%)
FOLLICULAR CYST, NOS			1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)		1 (2%)
HYPERPLASIA, C-CELL	1 (5%)		2 (4%)	
#PARATHYROID	(20)	(39)	(38)	(37)
HYPERPLASIA, NOS	9 (45%)	18 (46%)	11 (29%)	12 (32%)
#PANCREATIC ISLETS	(23)	(48)	(47)	(48)
HYPERPLASIA, FOCAL				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(49)
HYPERPLASIA, NOS	1 (4%)	1 (2%)		
#PROSTATE	(25)	(47)	(48)	(47)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, SUPPURATIVE	1 (4%)	2 (4%)		3 (6%)

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		3 (6%)		
ABSCESS, NOS				1 (2%)
INFLAMMATION, CHRONIC	1 (4%)	5 (11%)	3 (6%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL	4 (16%)	2 (4%)	2 (4%)	4 (9%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		2 (4%)
*SEMINAL VESICLE	(25)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			2 (4%)	
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)		
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
HYPERPLASIA, NOS				1 (2%)
#TESTIS	(25)	(49)	(50)	(48)
DEGENERATION, NOS	14 (56%)	22 (45%)	22 (44%)	17 (35%)
ATROPHY, NOS			3 (6%)	
ASPERMATOGENESIS			2 (4%)	
#TESTIS/TUBULE	(25)	(49)	(50)	(48)
DEGENERATION, NOS			1 (2%)	1 (2%)
*EPIDIDYMIS	(25)	(50)	(50)	(49)
DEGENERATION, NOS				1 (2%)
*VAS DEFERENS	(25)	(50)	(50)	(49)
CYST, NOS	1 (4%)			
HYPERPLASIA, NOS				1 (2%)
*MUSCULARIS OF VAS DE	(25)	(50)	(50)	(49)
CALCIFICATION, NOS		1 (2%)	1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(25)	(49)	(47)	(48)
HYDROCEPHALUS, NOS		1 (2%)		
GLIOSIS			1 (2%)	
#BASAL GANGLIA	(25)	(49)	(47)	(48)
CALCIFICATION, FOCAL	1 (4%)			
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(25)	(50)	(50)	(49)
INFLAMMATION, NOS			2 (4%)	

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

C2. MALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, FOCAL	1 (4%)			
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)	
*EYE/RETINA	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC				1 (2%)
*EYE/LACRIMAL GLAND	(25)	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC	1 (4%)			
*PLEURA	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC	1 (4%)			
*MESENTERY	(25)	(50)	(50)	(49)
INFLAMMATION, ACUTE		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(49)
CONGESTION, NOS	1 (4%)	1 (2%)		
HEMORRHAGE			2 (4%)	
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY				1

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

TABLE C3.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	25	25	25	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	25	25	25	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(25)	(25)	(25)	(25)
ULCER, NOS					1 (4%)
INFLAMMATION, ACUTE NECROTIZING				1 (4%)	1 (4%)
INFLAMMATION, CHRONIC					1 (4%)
ACANTHOSIS					1 (4%)
RESPIRATORY SYSTEM					
*NASAL CAVITY	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, SUPPURATIVE					1 (4%)
INFLAMMATION, ACUTE SUPPURATIVE					1 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (4%)		1 (4%)	2 (8%)	1 (4%)
*LARYNX	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC FOCAL		1 (4%)		2 (8%)	
REACTION, FOREIGN BODY					1 (4%)
#TRACHEA	(25)	(25)	(22)	(24)	(25)
INFLAMMATION, CHRONIC FOCAL		1 (4%)	2 (9%)		1 (4%)
#LUNG	(25)	(25)	(25)	(25)	(24)
CONGESTION, NOS		2 (8%)	2 (8%)		1 (4%)
CONGESTION, ACUTE			1 (4%)		
EDEMA, NOS	1 (4%)	1 (4%)			
HEMORRHAGE			1 (4%)		
INFLAMMATION, INTERSTITIAL			1 (4%)		
BRONCHOPNEUMONIA SUPPURATIVE					1 (4%)
ABSCESS, NOS				1 (4%)	
PNEUMONIA, CHRONIC MURINE	15 (60%)	17 (68%)	15 (60%)	23 (92%)	19 (79%)
INFLAMMATION, GRANULOMATOUS				1 (4%)	
INFLAMMATION, FOCAL GRANULOMATOU					1 (4%)
GRANULOMA, FOREIGN BODY		1 (4%)			

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
CRYSTALS, NOS					1 (4%)
ALVEOLAR MACROPHAGES				3 (12%)	
#ALVEOLAR WALL	(25)	(25)	(25)	(25)	(24)
CALCIFICATION, FOCAL				1 (4%)	
HEMATOPOIETIC SYSTEM					
*MAMMARY GLAND	(25)	(25)	(25)	(25)	(25)
ADENOSIS			1 (4%)		
#BONE MARROW	(24)	(24)	(21)	(25)	(23)
METAMORPHOSIS FATTY	2 (8%)				
FIBROUS OSTEODYSTROPHY	5 (21%)		1 (5%)		
MYELOFIBROSIS		1 (4%)			
#SPLEEN	(24)	(24)	(25)	(25)	(25)
CONGESTION, NOS	1 (4%)	9 (38%)		1 (4%)	1 (4%)
EDEMA, NOS					1 (4%)
HEMORRHAGE					1 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (4%)			
INFARCT, NOS					1 (4%)
HEMOSIDEROSIS		3 (13%)		6 (24%)	4 (16%)
HYPOPLASIA, NOS			1 (4%)		
ATROPHY, NOS	1 (4%)				
HEMATOPOIESIS	4 (17%)	8 (33%)	9 (36%)	11 (44%)	6 (24%)
ERYTHROPOIESIS	1 (4%)		1 (4%)		
#SPLENIC RED PULP	(24)	(24)	(25)	(25)	(25)
ATROPHY, NOS	1 (4%)				
#LYMPH NODE	(23)	(21)	(21)	(19)	(21)
HYPERPLASIA, LYMPHOID				1 (5%)	
#SUBMANDIBULAR L.NODE	(23)	(21)	(21)	(19)	(21)
CONGESTION, NOS	1 (4%)				
#CERVICAL LYMPH NODE	(23)	(21)	(21)	(19)	(21)
HYPERPLASIA, NOS			1 (5%)		
#MESENTERIC L. NODE	(23)	(21)	(21)	(19)	(21)
HYPERPLASIA, NOS					1 (5%)
#LIVER	(24)	(24)	(25)	(25)	(25)
HEMATOPOIESIS	2 (8%)			5 (20%)	1 (4%)

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#THYMUS	(6)	(14)	(19)	(19)	(18)
ECTOPIA					2 (11%)
BRANCHIAL CYST			1 (5%)		
CIRCULATORY SYSTEM					
#HEART	(24)	(25)	(24)	(25)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (4%)	
ENDOCARDITIS, VERRUCOUS			1 (4%)		
ENDOCARDIOSIS	1 (4%)				1 (4%)
#MYOCARDIUM	(24)	(25)	(24)	(25)	(25)
INFLAMMATION, ACUTE/CHRONIC	1 (4%)				
INFLAMMATION, CHRONIC					1 (4%)
INFLAMMATION, CHRONIC FOCAL	3 (13%)	7 (28%)	3 (13%)	5 (20%)	4 (16%)
INFLAMMATION PROLIFERATIVE			1 (4%)		
#ENDOCARDIUM	(24)	(25)	(24)	(25)	(25)
FIBROSIS					1 (4%)
*ARTERY	(25)	(25)	(25)	(25)	(25)
MEDIAL CALCIFICATION	1 (4%)	1 (4%)			
*CORONARY ARTERY	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, ACUTE NECROTIZING			1 (4%)		
#PANCREAS	(24)	(24)	(25)	(24)	(23)
PERIARTERITIS			1 (4%)		
#UTERUS	(25)	(25)	(23)	(24)	(21)
THROMBOSIS, NOS				1 (4%)	
#ADRENAL	(25)	(24)	(25)	(24)	(25)
HEMANGIOMATOSIS	1 (4%)				
DIGESTIVE SYSTEM					
#SALIVARY GLAND	(24)	(24)	(25)	(23)	(22)
INFLAMMATION, CHRONIC FOCAL	1 (4%)			2 (9%)	
ATROPHY, FOCAL			1 (4%)		
#LIVER	(24)	(24)	(25)	(25)	(25)
TRAUMATIC ABNORMALITY					1 (4%)

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
CONGESTION, NOS					2 (8%)
HEMORRHAGE					1 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)		
INFLAMMATION, MULTIFOCAL		1 (4%)			
INFLAMMATION, CHRONIC FOCAL		1 (4%)		1 (4%)	
FIBROSIS				1 (4%)	
CLOUDY SWELLING		1 (4%)		1 (4%)	2 (8%)
DEGENERATION, HYDROPIC			1 (4%)	1 (4%)	
NECROSIS, NOS					1 (4%)
NECROSIS, FOCAL				1 (4%)	
NECROSIS, CENTRAL			1 (4%)		
METAMORPHOSIS FATTY	1 (4%)	4 (17%)	5 (20%)	5 (20%)	4 (16%)
LIPOIDOSIS	2 (8%)				
CYTOPLASMIC VACUOLIZATION	2 (8%)	5 (21%)		1 (4%)	
CYTOLOGIC DEGENERATION	3 (13%)				
HYPERTROPHY, NOS	1 (4%)				
HYPERTROPHY, FOCAL		2 (8%)		2 (8%)	1 (4%)
ANGIECTASIS	3 (13%)	1 (4%)		1 (4%)	
#LIVER/CENTRILOBULAR	(24)	(24)	(25)	(25)	(25)
CONGESTION, NOS			1 (4%)		
INFLAMMATION, ACUTE/CHRONIC	1 (4%)				
DEGENERATION, NOS				1 (4%)	
NECROSIS, NOS				1 (4%)	
METAMORPHOSIS FATTY	2 (8%)	1 (4%)		2 (8%)	1 (4%)
LIPOIDOSIS			1 (4%)		
#LIVER/HEPATOCYTES	(24)	(24)	(25)	(25)	(25)
CLOUDY SWELLING			2 (8%)		
DEGENERATION, HYDROPIC				1 (4%)	
METAMORPHOSIS FATTY		1 (4%)		1 (4%)	2 (8%)
#BILE DUCT	(24)	(24)	(25)	(25)	(25)
DILATATION, NOS		1 (4%)			
INFLAMMATION, NOS	1 (4%)	1 (4%)			
HYPERPLASIA, NOS	9 (38%)	12 (50%)	8 (32%)	7 (28%)	14 (56%)
HYPERPLASIA, FOCAL	1 (4%)		2 (8%)		
#PANCREAS	(24)	(24)	(25)	(24)	(23)
FIBROSIS, DIFFUSE			1 (4%)		
ATROPHY, FOCAL				1 (4%)	
#STOMACH	(25)	(24)	(25)	(24)	(24)
INFLAMMATION, ACUTE					1 (4%)
HYPERKERATOSIS				1 (4%)	

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ACANTHOSIS				1 (4%)	
#GASTRIC MUCOSA	(25)	(24)	(25)	(24)	(24)
CALCIFICATION, NOS	1 (4%)	1 (4%)		1 (4%)	
METAPLASIA, SQUAMOUS		1 (4%)			
#GASTRIC SUBMUCOSA	(25)	(24)	(25)	(24)	(24)
FIBROSIS				1 (4%)	
#SMALL INTESTINE	(25)	(23)	(23)	(23)	(24)
CONGESTION, NOS					1 (4%)
EDEMA, NOS					1 (4%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (4%)				
INFLAMMATION, ACUTE NECROTIZING			1 (4%)		
#INTESTINAL VILLUS	(25)	(23)	(23)	(23)	(24)
CONGENITAL ABNORMAL FUSION	1 (4%)				
#COLON	(25)	(23)	(24)	(25)	(24)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)				3 (13%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (4%)				
INFLAMMATION, CHRONIC					2 (8%)
INFLAMMATION, CHRONIC FOCAL	1 (4%)				1 (4%)
NEMATODIASIS				1 (4%)	1 (4%)
URINARY SYSTEM					
#KIDNEY	(25)	(25)	(24)	(25)	(25)
CAST, NOS					1 (4%)
HYDRONEPHROSIS	1 (4%)				
PYELONEPHRITIS, NOS					1 (4%)
PYELONEPHRITIS SUPPURATIVE					1 (4%)
INFLAMMATION, CHRONIC	16 (64%)	11 (44%)	16 (67%)	7 (28%)	8 (32%)
NECROSIS, FOCAL	1 (4%)				
CALCIFICATION, NOS	1 (4%)				
HYPERPLASIA, FOCAL		1 (4%)			
#KIDNEY/TUBULE	(25)	(25)	(24)	(25)	(25)
MINERALIZATION	2 (8%)			1 (4%)	2 (8%)
#KIDNEY/PELVIS	(25)	(25)	(24)	(25)	(25)
MINERALIZATION	14 (56%)	15 (60%)	13 (54%)	20 (80%)	18 (72%)
INFLAMMATION, CHRONIC		1 (4%)		1 (4%)	
HYPERPLASIA, EPITHELIAL	12 (48%)	10 (40%)	11 (46%)	15 (60%)	14 (56%)

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#URINARY BLADDER	(25)	(25)	(21)	(23)	(22)
CALCULUS, NOS	1 (4%)				
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (5%)		
INFLAMMATION, ACUTE					1 (5%)
INFLAMMATION, CHRONIC			1 (5%)	1 (4%)	
INFLAMMATION, CHRONIC FOCAL		1 (4%)		1 (4%)	
HYPERPLASIA, EPITHELIAL				1 (4%)	
ENDOCRINE SYSTEM					
#PITUITARY	(24)	(23)	(23)	(22)	(22)
CONGESTION, NOS			2 (9%)	1 (5%)	
HYPERPLASIA, NOS			1 (4%)	1 (5%)	
HYPERPLASIA, CHROMOPHOBE-CELL	4 (17%)	4 (17%)	1 (4%)	2 (9%)	2 (9%)
ANGIECTASIS			1 (4%)		
#ADRENAL	(25)	(24)	(25)	(24)	(25)
CONGESTION, NOS	1 (4%)	2 (8%)	1 (4%)	2 (8%)	3 (12%)
HEMORRHAGIC CYST	3 (12%)	1 (4%)	3 (12%)	2 (8%)	1 (4%)
METAMORPHOSIS FATTY		1 (4%)			1 (4%)
LIPOIDOSIS					1 (4%)
ANGIECTASIS	4 (16%)	2 (8%)	1 (4%)	2 (8%)	
#ADRENAL CORTEX	(25)	(24)	(25)	(24)	(25)
CONGESTION, NOS	1 (4%)				
HEMORRHAGIC CYST				1 (4%)	
METAMORPHOSIS FATTY	2 (8%)	3 (13%)	1 (4%)	2 (8%)	3 (12%)
LIPOIDOSIS	1 (4%)	1 (4%)		1 (4%)	
PIGMENTATION, NOS	1 (4%)				
HYPERPLASIA, NODULAR	1 (4%)	3 (13%)	4 (16%)	1 (4%)	3 (12%)
HYPERPLASIA, FOCAL				1 (4%)	
ANGIECTASIS	1 (4%)		1 (4%)		
#ZONA RETICULARIS	(25)	(24)	(25)	(24)	(25)
FIBROSIS	2 (8%)				
DEGENERATION, NOS	1 (4%)				
PIGMENTATION, NOS	1 (4%)				
ATROPHY, NOS	1 (4%)				
#THYROID	(25)	(24)	(24)	(25)	(24)
INFLAMMATION, NOS				1 (4%)	
NECROSIS, FOCAL		1 (4%)			
CALCIFICATION, NOS		1 (4%)			

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
HYPERPLASIA, C-CELL	1 (4%)	1 (4%)		3 (12%)	1 (4%)
#PARATHYROID	(20)	(16)	(18)	(16)	(17)
ECTOPIA			1 (6%)		
HYPERPLASIA, NOS	1 (5%)	1 (6%)		1 (6%)	
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(25)	(25)	(25)	(25)	(25)
DILATATION/DUCTS			1 (4%)		
GALACTOCELE				2 (8%)	1 (4%)
HEMORRHAGE					1 (4%)
INFLAMMATION, ACUTE NECROTIZING	1 (4%)				
NECROSIS, NOS				1 (4%)	1 (4%)
NECROSIS, FOCAL				1 (4%)	
HYPERPLASIA, NOS					2 (8%)
#UTERUS	(25)	(25)	(23)	(24)	(21)
DILATATION, NOS			1 (4%)		
HEMORRHAGE			1 (4%)		
HEMORRHAGIC CYST				1 (4%)	
INFLAMMATION, NOS	2 (8%)				
INFLAMMATION, SUPPURATIVE					1 (5%)
INFLAMMATION, CHRONIC	1 (4%)				1 (5%)
POLYP, INFLAMMATORY		2 (8%)			
METAPLASIA, SQUAMOUS					3 (14%)
#UTERUS/ENDOMETRIUM	(25)	(25)	(23)	(24)	(21)
INFLAMMATION, SUPPURATIVE		3 (12%)			
INFLAMMATION, VESICULAR ABSCESS, NOS			1 (4%)	2 (8%)	1 (5%)
INFLAMMATION, CHRONIC	3 (12%)	2 (8%)	2 (9%)	2 (8%)	1 (5%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (4%)				
INFLAMMATION CHRONIC CYSTIC	1 (4%)	3 (12%)	1 (4%)	4 (17%)	2 (10%)
FIBROSIS				1 (4%)	
HYPERPLASIA, NOS	4 (16%)			1 (4%)	
HYPERPLASIA, FOCAL		1 (4%)			
HYPERPLASIA, CYSTIC	1 (4%)		1 (4%)		
METAPLASIA, SQUAMOUS				1 (4%)	
#UTERUS/MYOMETRIUM	(25)	(25)	(23)	(24)	(21)
HYPERPLASIA, NOS					1 (5%)
#OVARY	(25)	(25)	(21)	(25)	(23)
CYST, NOS	1 (4%)	1 (4%)	1 (5%)		

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

TABLE C3. FEMALE RATS (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ATRESIA	6 (24%)				
ATROPHY, NOS	15 (60%)	7 (28%)		9 (36%)	2 (9%)
HYPERPLASIA, NOS	6 (24%)		2 (10%)		
CORPUS LUTEUM	1 (4%)	2 (8%)		1 (4%)	
#OVARY/FOLLICLE	(25)	(25)	(21)	(25)	(23)
ATRESIA		1 (4%)			
NERVOUS SYSTEM					
#MIDBRAIN	(24)	(23)	(25)	(25)	(24)
CALCIFICATION, NOS			1 (4%)		
SPECIAL SENSE ORGANS					
*EYE/CORNEA	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC FOCAL	1 (4%)				
*EYE/CRYSTALLINE LENS	(25)	(25)	(25)	(25)	(25)
FIBROSIS	1 (4%)				
*EYE/LACRIMAL GLAND	(25)	(25)	(25)	(25)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (16%)	7 (28%)	4 (16%)	5 (20%)	3 (12%)
INFLAMMATION, CHRONIC		3 (12%)			
*HARDERIAN GLAND	(25)	(25)	(25)	(25)	(25)
SCLEROSIS	1 (4%)				
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
NONE					
ALL OTHER SYSTEMS					
NONE					
SPECIAL MORPHOLOGY SUMMARY					
NONE					

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

TABLE C4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS NECROPSIED	25	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(25)	(50)	(50)	(50)
EDEMA, NOS				1 (2%)
ULCER, CHRONIC	1 (4%)			
*SUBCUT TISSUE	(25)	(50)	(50)	(50)
NECROSIS, NOS			1 (2%)	
RESPIRATORY SYSTEM				
*NASAL CAVITY	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC SUPPURATIV	2 (8%)			
*LARYNX	(25)	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		2 (4%)		
HYPERPLASIA, EPITHELIAL				1 (2%)
#TRACHEA	(24)	(49)	(47)	(49)
INFLAMMATION, FOCAL			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL		2 (4%)		
HYPERPLASIA, EPITHELIAL				1 (2%)
#LUNG/BRONCHUS	(25)	(50)	(49)	(50)
BRONCHIECTASIS		1 (2%)		
HYPERPLASIA, ADENOMATOUS		1 (2%)	9 (18%)	
#LUNG/BRONCHIOLE	(25)	(50)	(49)	(50)
HYPERPLASIA, ADENOMATOUS		23 (46%)	13 (27%)	21 (42%)
#LUNG	(25)	(50)	(49)	(50)
CONGESTION, NOS	3 (12%)	4 (8%)	5 (10%)	6 (12%)

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
EDEMA, NOS		1 (2%)		1 (2%)
HEMORRHAGE		1 (2%)		1 (2%)
PNEUMONIA, ASPIRATION		1 (2%)	1 (2%)	
ABSCESS, NOS	1 (4%)	2 (4%)		
PNEUMONIA, CHRONIC MURINE	19 (76%)	41 (82%)	46 (94%)	40 (80%)
PNEUMONIA INTERSTITIAL CHRONIC				1 (2%)
GRANULOMA, NOS	1 (4%)	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)		
NECROSIS, NOS	1 (4%)			
NECROSIS, FOCAL		1 (2%)		
CRYSTALS, NOS	1 (4%)			
PIGMENTATION, NOS	1 (4%)			
HEMOSIDEROSIS				1 (2%)
FOAM-CELL				1 (2%)
ALVEOLAR MACROPHAGES		3 (6%)	1 (2%)	2 (4%)
HYPERPLASIA, ADENOMATOUS			1 (2%)	3 (6%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (4%)		1 (2%)	
METAPLASIA, SQUAMOUS	1 (4%)		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(25)	(50)	(50)	(50)
CONGESTION, NOS	3 (12%)	9 (18%)	17 (34%)	7 (14%)
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
HEMOSIDEROSIS	5 (20%)	2 (4%)	8 (16%)	5 (10%)
HEMATOPOIESIS	7 (28%)	10 (20%)	8 (16%)	6 (12%)
#SPLENIC CAPSULE	(25)	(50)	(50)	(50)
HEMORRHAGIC CYST				1 (2%)
#LYMPH NODE	(19)	(44)	(39)	(39)
INFLAMMATION, CHRONIC		1 (2%)		
FIBROSIS		1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)	1 (3%)	
#SUBMANDIBULAR L.NODE	(19)	(44)	(39)	(39)
CONGESTION, NOS	1 (5%)			
#MANDIBULAR L. NODE	(19)	(44)	(39)	(39)
CONGESTION, NOS	1 (5%)			
NECROSIS, NOS		1 (2%)		
PIGMENTATION, NOS				1 (3%)
HYPERPLASIA, NOS		1 (2%)		

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#PANCREATIC L.NODE	(19)	(44)	(39)	(39)
INFLAMMATION, CHRONIC		1 (2%)		
HEMOSIDEROSIS		1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)		
#LIVER	(25)	(50)	(50)	(50)
HEMATOPOIESIS	3 (12%)	9 (18%)	3 (6%)	2 (4%)
#COLON	(24)	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
#ADRENAL	(24)	(48)	(50)	(50)
HEMATOPOIESIS	1 (4%)	1 (2%)		1 (2%)
#THYMUS	(16)	(33)	(29)	(21)
ECTOPIA	1 (6%)		1 (3%)	
COLLOID CYST	1 (6%)			
CONGESTION, NOS			1 (3%)	
HYPERPLASIA, NOS			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(25)	(49)	(49)	(50)
NECROSIS, FOCAL				1 (2%)
CALCIFICATION, FOCAL				1 (2%)
#MYOCARDIUM	(25)	(49)	(49)	(50)
INFLAMMATION, MULTIFOCAL				1 (2%)
INFLAMMATION, CHRONIC	1 (4%)	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL	3 (12%)	5 (10%)	10 (20%)	11 (22%)
#ENDOCARDIUM	(25)	(49)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)	
*ARTERY	(25)	(50)	(50)	(50)
MEDIAL CALCIFICATION		1 (2%)	1 (2%)	
*PULMONARY ARTERY	(25)	(50)	(50)	(50)
MEDIAL CALCIFICATION				1 (2%)
#PANCREAS	(24)	(49)	(50)	(50)
PERIARTERITIS			1 (2%)	

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(24)	(48)	(47)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
INFLAMMATION, CHRONIC	1 (4%)			
INFLAMMATION, CHRONIC FOCAL	1 (4%)			
FIBROSIS				1 (2%)
ATROPHY, NOS		1 (2%)		1 (2%)
ATROPHY, FOCAL	1 (4%)		1 (2%)	1 (2%)
#LIVER	(25)	(50)	(50)	(50)
HEMORRHAGE	1 (4%)			
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)	
CIRRHOSIS, BILIARY	1 (4%)			1 (2%)
HEPATITIS, TOXIC		33 (66%)	37 (74%)	44 (88%)
CLOUDY SWELLING	6 (24%)	3 (6%)		
NECROSIS, NOS	2 (8%)			
NECROSIS, FOCAL	1 (4%)			
METAMORPHOSIS FATTY	5 (20%)	3 (6%)	7 (14%)	
HEMOSIDEROSIS		2 (4%)	1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (4%)		1 (2%)	1 (2%)
BASOPHILIC CYTO CHANGE	1 (4%)			
HYPERTROPHY, FOCAL		1 (2%)	3 (6%)	2 (4%)
ANGIECTASIS	3 (12%)		1 (2%)	
#LIVER/CENTRILOBULAR	(25)	(50)	(50)	(50)
DEGENERATION, NOS	1 (4%)			
NECROSIS, NOS		1 (2%)	1 (2%)	
METAMORPHOSIS FATTY	1 (4%)	6 (12%)	1 (2%)	1 (2%)
CYTOLOGIC DEGENERATION			1 (2%)	
#LIVER/HEPATOCYTES	(25)	(50)	(50)	(50)
METAMORPHOSIS FATTY		2 (4%)	1 (2%)	
HYPERTROPHY, NOS		1 (2%)		
HYPERTROPHY, FOCAL		2 (4%)	2 (4%)	3 (6%)
#BILE DUCT	(25)	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, CHRONIC				1 (2%)
HYPERPLASIA, NOS	8 (32%)	2 (4%)	1 (2%)	2 (4%)
#PANCREAS	(24)	(49)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)	

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ATROPHY, NOS		2 (4%)	3 (6%)	
ATROPHY, FOCAL		3 (6%)	3 (6%)	2 (4%)
#ESOPHAGUS	(24)	(49)	(48)	(49)
HYPERKERATOSIS				1 (2%)
#STOMACH	(25)	(49)	(49)	(49)
INFLAMMATION, FOCAL	1 (4%)			
ULCER, FOCAL				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
#GASTRIC MUCOSA	(25)	(49)	(49)	(49)
CALCIFICATION, NOS		1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	
HYPERKERATOSIS			1 (2%)	
ACANTHOSIS			1 (2%)	
#GASTRIC SEROSA	(25)	(49)	(49)	(49)
HEMORRHAGE			1 (2%)	
#DUODENUM	(24)	(48)	(48)	(50)
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
#COLON	(24)	(49)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (17%)	1 (2%)		
INFLAMMATION, CHRONIC	4 (17%)	2 (4%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (4%)	2 (4%)	4 (8%)	
NEMATODIASIS		2 (4%)	3 (6%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(25)	(50)	(50)	(50)
CALCULUS, NOS			2 (4%)	
CONGESTION, NOS				1 (2%)
HEMORRHAGE		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
INFLAMMATION, CHRONIC	15 (60%)	34 (68%)	40 (80%)	41 (82%)
PYELONEPHRITIS, CHRONIC			1 (2%)	
FIBROSIS			1 (2%)	
GLOMERULOSCLEROSIS, NOS				1 (2%)
CALCIFICATION, NOS		4 (8%)	2 (4%)	1 (2%)
#KIDNEY/CORTEX	(25)	(50)	(50)	(50)
POLYCYSTIC KIDNEY	1 (4%)			

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#KIDNEY/MEDULLA	(25)	(50)	(50)	(50)
CALCULUS, NOS		1 (2%)		
CALCIFICATION, FOCAL				1 (2%)
#KIDNEY/TUBULE	(25)	(50)	(50)	(50)
MINERALIZATION	2 (8%)			
HEMOSIDEROSIS				2 (4%)
#KIDNEY/PELVIS	(25)	(50)	(50)	(50)
MINERALIZATION	18 (72%)			
INFLAMMATION, CHRONIC	1 (4%)			
CALCIFICATION, NOS		2 (4%)	1 (2%)	2 (4%)
HYPERPLASIA, EPITHELIAL	16 (64%)	4 (8%)	2 (4%)	3 (6%)
#URINARY BLADDER	(22)	(47)	(49)	(45)
EDEMA, NOS		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	1 (5%)			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (5%)	1 (2%)	1 (2%)	
#U. BLADDER/MUCOSA	(22)	(47)	(49)	(45)
METAPLASIA, SQUAMOUS		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(45)	(47)	(45)
CYST, NOS	1 (5%)			
CONGESTION, NOS		2 (4%)		
HEMORRHAGIC CYST		1 (2%)		
CHOLESTEROL DEPOSIT	1 (5%)			
HYPERPLASIA, CHROMOPHOBE-CELL	1 (5%)	7 (16%)	2 (4%)	3 (7%)
#ADRENAL	(24)	(48)	(50)	(50)
CONGESTION, NOS	6 (25%)	2 (4%)	2 (4%)	
HEMORRHAGIC CYST	2 (8%)	6 (13%)	4 (8%)	1 (2%)
METAMORPHOSIS FATTY	1 (4%)	2 (4%)	2 (4%)	2 (4%)
LIPOIDOSIS		1 (2%)		
HEMOSIDEROSIS		1 (2%)		
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, NODULAR	1 (4%)	1 (2%)	1 (2%)	
ANGIECTASIS	3 (13%)	2 (4%)	1 (2%)	5 (10%)
#ADRENAL CORTEX	(24)	(48)	(50)	(50)
HEMORRHAGIC CYST		1 (2%)		1 (2%)

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
METAMORPHOSIS FATTY		9 (19%)	5 (10%)	11 (22%)
ATROPHY, NOS	1 (4%)		1 (2%)	4 (8%)
HYPERPLASIA, NODULAR	1 (4%)	4 (8%)	7 (14%)	4 (8%)
HYPERPLASTIC NODULE				1 (2%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)	
#THYROID	(24)	(48)	(48)	(49)
COLLOID CYST			1 (2%)	
ABSCESS, NOS			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)	
HYPERPLASIA, C-CELL		3 (6%)	2 (4%)	1 (2%)
#THYROID FOLLICLE	(24)	(48)	(48)	(49)
HYPERPLASIA, EPITHELIAL		1 (2%)		
#PANCREATIC ISLETS	(24)	(49)	(50)	(50)
CLOUDY SWELLING				2 (4%)
DEGENERATION, HYDROPIC				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(50)
GALACTOCELE	1 (4%)			
NECROSIS, NOS				1 (2%)
HYPERPLASIA, NOS	1 (4%)			
*VAGINA	(25)	(50)	(50)	(50)
CYTOLOGIC DEGENERATION				1 (2%)
HYPERTROPHY, NOS				1 (2%)
#UTERUS	(24)	(47)	(49)	(47)
HEMORRHAGE	1 (4%)			
INFLAMMATION, SUPPURATIVE	1 (4%)			
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, CHRONIC	3 (13%)			
INFLAMMATION, CHRONIC SUPPURATIV	1 (4%)	1 (2%)	1 (2%)	
FIBROSIS, FOCAL			2 (4%)	1 (2%)
NECROSIS, FOCAL	1 (4%)			
HEMOSIDEROSIS	1 (4%)		1 (2%)	
HYPERPLASIA, EPITHELIAL	2 (8%)			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	
POLYP		4 (9%)	1 (2%)	
METAPLASIA, SQUAMOUS		2 (4%)		
#CERVIX UTERI	(24)	(47)	(49)	(47)
ACANTHOSIS				2 (4%)

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#UTERUS/ENDOMETRIUM	(24)	(47)	(49)	(47)
INFLAMMATION, SUPPURATIVE		1 (2%)		1 (2%)
INFLAMMATION, VESICULAR	1 (4%)		1 (2%)	
INFLAMMATION, CHRONIC	1 (4%)	11 (23%)	7 (14%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		2 (4%)		3 (6%)
INFLAMMATION CHRONIC CYSTIC		2 (4%)	2 (4%)	3 (6%)
FIBROSIS	1 (4%)			
SCAR		1 (2%)		
HYPERPLASIA, NOS	1 (4%)		3 (6%)	1 (2%)
HYPERPLASIA, CYSTIC				2 (4%)
METAPLASIA, SQUAMOUS		1 (2%)	1 (2%)	1 (2%)
#OVARY/OVIDUCT	(24)	(47)	(49)	(47)
INFLAMMATION, SUPPURATIVE		1 (2%)		
#OVARY/PAROVARIAN	(24)	(47)	(49)	(47)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
#OVARY	(23)	(47)	(49)	(47)
CYST, NOS			1 (2%)	1 (2%)
CORPUS LUTEUM CYST			1 (2%)	
HEMORRHAGIC CYST		1 (2%)		
ABSCESS, NOS			1 (2%)	
ATROPHY, NOS	5 (22%)	8 (17%)	19 (39%)	18 (38%)
CORPUS LUTEUM		4 (9%)	1 (2%)	1 (2%)
NERVOUS SYSTEM				
#BASAL GANGLIA	(25)	(50)	(50)	(50)
GLIOSIS				1 (2%)
NECROSIS, FOCAL				1 (2%)
CALCIFICATION, NOS				1 (2%)
#PONS	(25)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
SPECIAL SENSE ORGANS				
*EYE	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		
*EYE/CORNEA	(25)	(50)	(50)	(50)
FIBROSIS	1 (4%)			

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

TABLE C4. FEMALE RATS (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
SCAR	1 (4%)			
*EYE/CRYSTALLINE LENS	(25)	(50)	(50)	(50)
DEGENERATION, NOS	1 (4%)			
*EYE/LACRIMAL GLAND	(25)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (8%)	8 (16%)	4 (8%)	3 (6%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(50)
CONGESTION, NOS	1 (4%)			
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF				

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED HCDD BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	25	25	25	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	25	25	25	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(25)	(25)	(25)	(25)
HYPERPLASIA, CYSTIC			1 (4%)		
*SUBCUT TISSUE	(25)	(25)	(25)	(25)	(25)
DILATATION, NOS			1 (4%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)				
ABSCESS, NOS	1 (4%)				
INFLAMMATION, FOCAL GRANULOMATOU			1 (4%)		
NECROSIS, NOS				1 (4%)	
CALCIFICATION, FOCAL	1 (4%)				
RESPIRATORY SYSTEM					
*NASAL CAVITY	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC		1 (4%)			
#TRACHEA	(24)	(23)	(22)	(25)	(24)
INFLAMMATION, NOS					1 (4%)
#LUNG/BRONCHUS	(25)	(25)	(25)	(25)	(23)
INFLAMMATION, CHRONIC					1 (4%)
#LUNG/BRONCHIOLE	(25)	(25)	(25)	(25)	(23)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (16%)	2 (8%)	2 (8%)	5 (20%)	4 (17%)
#LUNG	(25)	(25)	(25)	(25)	(23)
CONGESTION, NOS	3 (12%)	4 (16%)	5 (20%)	5 (20%)	4 (17%)
EDEMA, NOS		2 (8%)	1 (4%)		
HEMORRHAGE	1 (4%)				
BRONCHOPNEUMONIA, NOS				1 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)		
PNEUMONIA, ASPIRATION			1 (4%)		

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

TABLE D1. MALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
PNEUMONIA, CHRONIC MURINE	2 (8%)				
HYPERPLASIA, ADENOMATOUS	2 (8%)		1 (4%)	2 (8%)	
HEMATOPOIETIC SYSTEM					
#BONE MARROW	(25)	(25)	(24)	(25)	(22)
MYELOFIBROSIS	1 (4%)				
#SPLEEN	(25)	(23)	(25)	(24)	(21)
CONGESTION, NOS				1 (4%)	1 (5%)
AMYLOIDOSIS			1 (4%)	1 (4%)	
HYPERPLASIA, LYMPHOID			1 (4%)		
HEMATOPOIESIS	4 (16%)		2 (8%)	3 (13%)	2 (10%)
#LYMPH NODE	(19)	(15)	(21)	(16)	(16)
CONGESTION, NOS		1 (7%)	1 (5%)		
EDEMA, NOS		1 (7%)	1 (5%)		
HYPERPLASIA, NOS	1 (5%)			3 (19%)	
MEGAKARYOCYTOSIS				1 (6%)	
HYPERPLASIA, LYMPHOID	2 (11%)	1 (7%)		2 (13%)	1 (6%)
HEMATOPOIESIS			1 (5%)	1 (6%)	
#SUBMANDIBULAR L.NODE	(19)	(15)	(21)	(16)	(16)
CONGESTION, NOS	1 (5%)				
HYPERPLASIA, LYMPHOID	1 (5%)				
#PANCREATIC L.NODE	(19)	(15)	(21)	(16)	(16)
CONGESTION, NOS				1 (6%)	
HYPERPLASIA, LYMPHOID	1 (5%)				
HEMATOPOIESIS				1 (6%)	2 (13%)
#MESENTERIC L. NODE	(19)	(15)	(21)	(16)	(16)
CYST, NOS				1 (6%)	
FIBROSIS				1 (6%)	
HYPERPLASIA, LYMPHOID	2 (11%)				
#RENAL LYMPH NODE	(19)	(15)	(21)	(16)	(16)
FIBROSIS	1 (5%)				
HYPERPLASIA, LYMPHOID	1 (5%)			1 (6%)	
#INGUINAL LYMPH NODE	(19)	(15)	(21)	(16)	(16)
HYPERPLASIA, LYMPHOID	1 (5%)				
#LIVER	(25)	(25)	(25)	(25)	(25)
HEMATOPOIESIS		1 (4%)	3 (12%)		

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

TABLE D1. MALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
CIRCULATORY SYSTEM					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
EMBOLUS, SEPTIC					1 (4%)
#MYOCARDIUM	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC FOCAL	2 (8%)		1 (4%)	4 (16%)	1 (4%)
INFLAMMATION, CHRONIC DIFFUSE		1 (4%)		1 (4%)	1 (4%)
*BLOOD VESSEL	(25)	(25)	(25)	(25)	(25)
PERIVASCULITIS				1 (4%)	
*MESENTERY	(25)	(25)	(25)	(25)	(25)
PERIARTERITIS					1 (4%)
DIGESTIVE SYSTEM					
#SALIVARY GLAND	(25)	(23)	(25)	(25)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (20%)	7 (30%)	5 (20%)	2 (8%)	3 (12%)
INFLAMMATION, CHRONIC FOCAL	1 (4%)				
#LIVER	(25)	(25)	(25)	(25)	(25)
CONGESTION, NOS	1 (4%)	1 (4%)	1 (4%)		1 (4%)
HEMORRHAGE	1 (4%)				
HEMORRHAGIC CYST	1 (4%)				
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (4%)	1 (4%)		1 (4%)
INFLAMMATION, DIFFUSE					1 (4%)
FIBROSIS			1 (4%)		
FIBROSIS, FOCAL	1 (4%)			1 (4%)	
CLOUDY SWELLING		1 (4%)			
NECROSIS, NOS	1 (4%)	1 (4%)	3 (12%)		
NECROSIS, FOCAL	1 (4%)		1 (4%)	1 (4%)	1 (4%)
AMYLOIDOSIS				1 (4%)	
METAMORPHOSIS FATTY	1 (4%)	2 (8%)			1 (4%)
CYTOLOGIC DEGENERATION	1 (4%)				
HYPERTROPHY, FOCAL		1 (4%)			
ANGIECTASIS				1 (4%)	1 (4%)
#LIVER/CENTRILOBULAR	(25)	(25)	(25)	(25)	(25)
DEGENERATION, NOS			1 (4%)	1 (4%)	
NECROSIS, NOS		1 (4%)		1 (4%)	
METAMORPHOSIS FATTY	1 (4%)	2 (8%)	1 (4%)		
HYPERTROPHY, NOS		1 (4%)			

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

TABLE D1. MALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#PANCREAS	(24)	(22)	(23)	(25)	(21)
DILATATION/DUCTS		1 (5%)			
INFLAMMATION, CHRONIC FOCAL		1 (5%)	1 (4%)		
ATROPHY, NOS		1 (5%)			
#ESOPHAGUS	(21)	(24)	(22)	(25)	(19)
INFLAMMATION, CHRONIC				1 (4%)	
#STOMACH	(25)	(22)	(25)	(24)	(22)
INFLAMMATION, CHRONIC					1 (5%)
#GASTRIC MUCOSA	(25)	(22)	(25)	(24)	(22)
HYPERPLASIA, NOS	1 (4%)				1 (5%)
#COLON	(25)	(22)	(24)	(24)	(20)
INFLAMMATION, CHRONIC				1 (4%)	
INFLAMMATION, CHRONIC FOCAL	4 (16%)	4 (18%)	4 (17%)	2 (8%)	1 (5%)
URINARY SYSTEM					
#KIDNEY	(25)	(25)	(25)	(25)	(25)
CALCULUS, NOS			1 (4%)		
CONGESTION, NOS		1 (4%)	3 (12%)		
PYELONEPHRITIS, NOS	1 (4%)				1 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	17 (68%)	13 (52%)	8 (32%)	15 (60%)	7 (28%)
INFLAMMATION, SUPPURATIVE				1 (4%)	
PYELONEPHRITIS SUPPURATIVE					1 (4%)
INFLAMMATION, CHRONIC FOCAL	2 (8%)	1 (4%)		1 (4%)	
GLOMERULOSCLEROSIS, NOS			1 (4%)		
#KIDNEY/TUBULE	(25)	(25)	(25)	(25)	(25)
CALCULUS, NOS		1 (4%)			
CALCIFICATION, NOS					1 (4%)
#URINARY BLADDER	(24)	(23)	(23)	(24)	(23)
CALCULUS, NOS			1 (4%)	1 (4%)	2 (9%)
CONGESTION, NOS					1 (4%)
INFLAMMATION, NOS			1 (4%)		
INFLAMMATION, FOCAL	1 (4%)				
INFLAMMATION, SUPPURATIVE				1 (4%)	
INFLAMMATION, ACUTE SUPPURATIVE		1 (4%)			1 (4%)
INFLAMMATION, CHRONIC					1 (4%)
INFLAMMATION, CHRONIC FOCAL	3 (13%)	1 (4%)	1 (4%)	2 (8%)	

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

TABLE D1. MALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
HYPERPLASIA, EPITHELIAL		1 (4%)	1 (4%)	1 (4%)	1 (4%)
ENDOCRINE SYSTEM					
#ADRENAL	(24)	(22)	(25)	(24)	(21)
ATROPHY, NOS			1 (4%)		
#ADRENAL CORTEX	(24)	(22)	(25)	(24)	(21)
HYPERPLASIA, NODULAR				1 (4%)	
#THYROID	(25)	(24)	(20)	(24)	(23)
CYSTIC FOLLICLES			1 (5%)	1 (4%)	
#PANCREATIC ISLETS	(24)	(22)	(23)	(25)	(21)
HYPERPLASIA, NOS	3 (13%)	1 (5%)			
HYPERPLASIA, FOCAL		1 (5%)			
REPRODUCTIVE SYSTEM					
*PREPUTIAL GLAND	(25)	(25)	(25)	(25)	(25)
DILATATION, NOS				1 (4%)	
CYST, NOS					1 (4%)
ABSCESS, NOS				1 (4%)	
HYPERPLASIA, NOS					1 (4%)
HYPERPLASIA, CYSTIC				1 (4%)	
METAPLASIA, SQUAMOUS					1 (4%)
#PROSTATE	(22)	(23)	(24)	(22)	(22)
INFLAMMATION, ACUTE SUPPURATIVE				1 (5%)	2 (9%)
INFLAMMATION, CHRONIC					1 (5%)
INFLAMMATION, CHRONIC FOCAL	1 (5%)	2 (9%)	1 (4%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (5%)				
*SEMINAL VESICLE	(25)	(25)	(25)	(25)	(25)
DILATATION, NOS				1 (4%)	
FIBROSIS		1 (4%)			
NECROSIS, NOS		1 (4%)			
#TESTIS	(25)	(25)	(25)	(24)	(24)
INFLAMMATION, CHRONIC	1 (4%)				
FIBROSIS, FOCAL	1 (4%)				
DEGENERATION, NOS	1 (4%)	1 (4%)	1 (4%)	1 (4%)	
CALCIFICATION, FOCAL				1 (4%)	

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

TABLE D1. MALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ATROPHY, NOS			1 (4%)		
*VAS DEFERENS	(25)	(25)	(25)	(25)	(25)
RETENTION OF CONTENT				1 (4%)	
INFLAMMATION, CHRONIC				1 (4%)	
NERVOUS SYSTEM					
#BRAIN	(25)	(25)	(25)	(25)	(25)
CALCIFICATION, FOCAL			2 (8%)		
#CEREBRAL CORTEX	(25)	(25)	(25)	(25)	(25)
CALCIFICATION, FOCAL				1 (4%)	
METAPLASIA, OSSEOUS				1 (4%)	
#BASAL GANGLIA	(25)	(25)	(25)	(25)	(25)
CALCIFICATION, NOS		1 (4%)			
CALCIFICATION, FOCAL	11 (44%)	9 (36%)	6 (24%)	9 (36%)	4 (16%)
SPECIAL SENSE ORGANS					
*EYE/LACRIMAL GLAND	(25)	(25)	(25)	(25)	(25)
HYPERPLASIA, CYSTIC	1 (4%)				
MUSCULOSKELETAL SYSTEM					
NONE					
BODY CAVITIES					
*EPICARDIUM	(25)	(25)	(25)	(25)	(25)
INFLAMMATION, CHRONIC FOCAL		1 (4%)			
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(25)	(25)	(25)	(25)
CONGESTION, NOS			1 (4%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (12%)	4 (16%)	3 (12%)	3 (12%)	4 (16%)
SITE UNKNOWN					
HEMORRHAGIC CYST			1		

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

TABLE D1. MALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ADIPOSE TISSUE					
INFLAMMATION, CHRONIC	1				
FIBROSIS	1				
SPECIAL MORPHOLOGY SUMMARY					
AUTO/NECROPSY/HISTO PERF				1	2

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	23	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	23	50	50	48
INTEGUMENTARY SYSTEM				
*SKIN	(23)	(50)	(50)	(48)
ULCER, FOCAL			1 (2%)	
ACANTHOSIS				1 (2%)
*SUBCUT TISSUE	(23)	(50)	(50)	(48)
DERMAL INCLUSION CYST			1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
GRANULATION, TISSUE				1 (2%)
FIBROSIS		1 (2%)		1 (2%)
NECROSIS, NOS				1 (2%)
METAPLASIA, OSSEOUS		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(23)	(48)	(48)	(39)
INFLAMMATION, CHRONIC		1 (2%)		
#LUNG/BRONCHUS	(23)	(50)	(50)	(48)
INFLAMMATION, CHRONIC	1 (4%)			
#LUNG/BRONCHIOLE	(23)	(50)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (17%)	8 (16%)	6 (12%)	4 (8%)
#LUNG	(23)	(50)	(50)	(48)
ATELECTASIS		1 (2%)	1 (2%)	
CONGESTION, NOS	7 (30%)	6 (12%)	10 (20%)	12 (25%)
EDEMA, NOS	1 (4%)	1 (2%)	1 (2%)	2 (4%)
HEMORRHAGE				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
PNEUMONIA, ASPIRATION			1 (2%)	
ABSCESS, NOS		1 (2%)		
PNEUMONIA INTERSTITIAL CHRONIC			1 (2%)	

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
FIBROSIS		1 (2%)		
ALVEOLAR MACROPHAGES	1 (4%)	1 (2%)	1 (2%)	2 (4%)
HYPERPLASIA, ADENOMATOUS	2 (9%)		2 (4%)	2 (4%)
#LUNG/ALVEOLI	(23)	(50)	(50)	(48)
HEMORRHAGE		1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(23)	(50)	(50)	(48)
MYELOPROLIFERATIVE DISORDER			1 (2%)	
#SPLEEN	(21)	(48)	(49)	(47)
CONGESTION, NOS		1 (2%)		
FIBROSIS, FOCAL				1 (2%)
AMYLOIDOSIS	1 (5%)			
HEMATOPOIESIS	1 (5%)	3 (6%)	3 (6%)	5 (11%)
#LYMPH NODE	(16)	(34)	(28)	(30)
CONGESTION, NOS	2 (13%)	1 (3%)		2 (7%)
EDEMA, NOS				2 (7%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (6%)			
INFLAMMATION, CHRONIC	3 (19%)			
HYPERPLASIA, NOS	2 (13%)			
HYPERPLASIA, LYMPHOID	2 (13%)	2 (6%)		
#TRACHEAL LYMPH NODE	(16)	(34)	(28)	(30)
HEMATOPOIESIS		1 (3%)		
#PANCREATIC L.NODE	(16)	(34)	(28)	(30)
CONGESTION, NOS	1 (6%)			
HEMATOPOIESIS	1 (6%)			
#MESENTERIC L. NODE	(16)	(34)	(28)	(30)
CONGESTION, NOS	1 (6%)	2 (6%)	2 (7%)	
EDEMA, NOS		2 (6%)	1 (4%)	
NECROSIS, NOS		1 (3%)		
HYPERPLASIA, LYMPHOID	1 (6%)	1 (3%)		
#LIVER	(23)	(50)	(49)	(48)
HEMATOPOIESIS		1 (2%)		3 (6%)
*MESENTERY	(23)	(50)	(50)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)	

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#DUODENUM	(21)	(44)	(46)	(39)
HYPERPLASIA, LYMPHOID		1 (2%)		
#ADRENAL	(23)	(48)	(47)	(43)
HEMATOPOIESIS		1 (2%)		
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(23)	(50)	(50)	(48)
EMBOLUS, SEPTIC			1 (2%)	
#HEART	(23)	(49)	(49)	(48)
ABSCESS, NOS				1 (2%)
#HEART/VENTRICLE	(23)	(49)	(49)	(48)
THROMBUS, MURAL				1 (2%)
#MYOCARDIUM	(23)	(49)	(49)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (4%)	3 (6%)	5 (10%)	3 (6%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)		
#AORTIC VALVE	(23)	(49)	(49)	(48)
THROMBOSIS, NOS		1 (2%)		
#PANCREAS	(23)	(48)	(46)	(40)
PERIARTERITIS			1 (2%)	1 (3%)
#PROSTATE	(21)	(44)	(46)	(46)
PERIARTERITIS			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(22)	(46)	(48)	(44)
EDEMA, NOS				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		7 (15%)	5 (10%)	6 (14%)
FIBROSIS				1 (2%)
NECROSIS, FOCAL				1 (2%)
#LIVER	(23)	(50)	(49)	(48)
CYST, NOS		1 (2%)		
CONGESTION, NOS		1 (2%)	1 (2%)	1 (2%)

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HEMORRHAGIC CYST				1 (2%)
INFLAMMATION, NOS		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (13%)	4 (8%)	1 (2%)	3 (6%)
INFLAMMATION, MULTIFOCAL		1 (2%)		
ABSCESS, NOS				1 (2%)
INFLAMMATION, CHRONIC	1 (4%)			
INFLAMMATION, CHRONIC FOCAL				2 (4%)
FIBROSIS	1 (4%)		1 (2%)	7 (15%)
FIBROSIS, FOCAL		1 (2%)		
FIBROSIS, MULTIFOCAL				1 (2%)
CIRRHOSIS, NOS				1 (2%)
HEPATITIS, TOXIC	1 (4%)		7 (14%)	14 (29%)
DEGENERATION, NOS				1 (2%)
CLOUDY SWELLING		1 (2%)		1 (2%)
NECROSIS, NOS	1 (4%)	1 (2%)		1 (2%)
NECROSIS, FOCAL	1 (4%)	1 (2%)	1 (2%)	4 (8%)
AMYLOIDOSIS		1 (2%)		
METAMORPHOSIS FATTY	1 (4%)	5 (10%)	3 (6%)	9 (19%)
CALCIFICATION, NOS	1 (4%)			
PIGMENTATION, NOS			1 (2%)	11 (23%)
HEMOSIDEROSIS			1 (2%)	
FOCAL CELLULAR CHANGE	1 (4%)	1 (2%)		
HYPERTROPHY, NOS	1 (4%)			
HYPERTROPHY, FOCAL		1 (2%)	4 (8%)	4 (8%)
ANGIECTASIS				1 (2%)
#LIVER/CENTRILOBULAR	(23)	(50)	(49)	(48)
INFLAMMATION, NOS			1 (2%)	
CLOUDY SWELLING			1 (2%)	
NECROSIS, NOS		2 (4%)	2 (4%)	7 (15%)
METAMORPHOSIS FATTY		7 (14%)	2 (4%)	
HYPERTROPHY, NOS		2 (4%)	2 (4%)	3 (6%)
#LIVER/PERIPORTAL	(23)	(50)	(49)	(48)
FIBROSIS		2 (4%)		
#LIVER/KUPFFER CELL	(23)	(50)	(49)	(48)
HYPERPLASIA, NOS			1 (2%)	
#BILE DUCT	(23)	(50)	(49)	(48)
HYPERPLASIA, NOS			1 (2%)	
#PANCREAS	(23)	(48)	(46)	(40)
HEMORRHAGIC CYST		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (3%)

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, CHRONIC FOCAL	1 (4%)	1 (2%)		
FIBROSIS	1 (4%)	1 (2%)		
NECROSIS, FAT	1 (4%)			1 (3%)
ATROPHY, FOCAL	1 (4%)			
#ESOPHAGUS	(23)	(45)	(45)	(41)
INFLAMMATION, NOS				1 (2%)
#SMALL INTESTINE	(21)	(44)	(46)	(39)
INFLAMMATION, CHRONIC	1 (5%)			
#DUODENUM	(21)	(44)	(46)	(39)
INFLAMMATION, CHRONIC		1 (2%)		
#COLON	(22)	(49)	(45)	(43)
INFLAMMATION, CHRONIC FOCAL	5 (23%)	10 (20%)	4 (9%)	7 (16%)
NEMATODIASIS		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(23)	(50)	(49)	(48)
CAST, NOS				1 (2%)
CONGESTION, NOS		1 (2%)	1 (2%)	3 (6%)
PYELONEPHRITIS, NOS		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	12 (52%)	23 (46%)	24 (49%)	24 (50%)
PYELONEPHRITIS SUPPURATIVE		4 (8%)		
INFLAMMATION, CHRONIC FOCAL	2 (9%)	5 (10%)	1 (2%)	7 (15%)
FIBROSIS, FOCAL		1 (2%)		
INFARCT, NOS		1 (2%)		
METAPLASIA, OSSEOUS		1 (2%)		
#KIDNEY/PELVIS	(23)	(50)	(49)	(48)
DILATATION, NOS		1 (2%)		
#URINARY BLADDER	(22)	(47)	(43)	(46)
CALCULUS, NOS		1 (2%)		
EDEMA, NOS			1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (5%)			
INFLAMMATION, CHRONIC	2 (9%)	4 (9%)		
INFLAMMATION, CHRONIC FOCAL	3 (14%)	1 (2%)		2 (4%)
HYPERPLASIA, EPITHELIAL	2 (9%)	3 (6%)	3 (7%)	2 (4%)

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(23)	(48)	(47)	(43)
HYPERPLASIA, NODULAR	2 (9%)			
#ZONA RETICULARIS	(23)	(48)	(47)	(43)
FIBROSIS		1 (2%)		
PIGMENTATION, NOS		1 (2%)		
#PANCREATIC ISLETS	(23)	(48)	(46)	(40)
HYPERPLASIA, FOCAL		1 (2%)		
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(23)	(50)	(50)	(48)
INFLAMMATION, CHRONIC	2 (9%)			
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
ACANTHOSIS		1 (2%)		
#PROSTATE	(21)	(44)	(46)	(46)
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, CHRONIC	2 (10%)	4 (9%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (5%)	2 (5%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
*SEMINAL VESICLE	(23)	(50)	(50)	(48)
DILATATION, NOS				1 (2%)
#TESTIS	(22)	(50)	(49)	(48)
SPERMATOCELE				1 (2%)
HEMORRHAGE				1 (2%)
FIBROSIS				1 (2%)
DEGENERATION, NOS	2 (9%)	3 (6%)		7 (15%)
NECROSIS, CASEOUS				1 (2%)
CALCIFICATION, NOS		1 (2%)		1 (2%)
CALCIFICATION, FOCAL		1 (2%)	1 (2%)	1 (2%)
*VAS DEFERENS	(23)	(50)	(50)	(48)
SPERMATOCELE		1 (2%)		
NERVOUS SYSTEM				
#BRAIN	(23)	(50)	(50)	(48)
CALCIFICATION, FOCAL			1 (2%)	

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#BASAL GANGLIA	(23)	(50)	(50)	(48)
CALCIFICATION, FOCAL	8 (35%)	14 (28%)	10 (20%)	12 (25%)
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(23)	(50)	(50)	(48)
INFLAMMATION, SUPPURATIVE	1 (4%)			
MUSCULOSKELETAL SYSTEM				
*SKULL	(23)	(50)	(50)	(48)
HEALED FRACTURE		1 (2%)		
*RIB	(23)	(50)	(50)	(48)
ABSCESS, NOS		1 (2%)		
*SKELETAL MUSCLE	(23)	(50)	(50)	(48)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
BODY CAVITIES				
*MEDIASTINUM	(23)	(50)	(50)	(48)
ABSCESS, NOS		1 (2%)		
FIBROSIS		1 (2%)		
NECROSIS, NOS		1 (2%)		
*PLEURA	(23)	(50)	(50)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)		
ABSCESS, NOS				1 (2%)
FIBROSIS				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(23)	(50)	(50)	(48)
CONGESTION, NOS			1 (2%)	2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (13%)	7 (14%)	6 (12%)	4 (8%)
SITE UNKNOWN				
ABSCESS, NOS	1			
GRANULATION, TISSUE			1	

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

TABLE D2. MALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
FIBROSIS			1	
CONNECTIVE TISSUE				
STEATITIS	1			
SPECIAL MORPHOLOGY SUMMARY				
ANIMAL MISSING/NO NECROPSY	1			
AUTO/NECROPSY/HISTO PERF			1	1
AUTOLYSIS/NO NECROPSY	1			2

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

TABLE D3.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
ANIMALS NECROPSIED	25	24	25	24	25
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	24	25	24	25
INTEGUMENTARY SYSTEM					
*SKIN	(25)	(24)	(25)	(24)	(25)
INFLAMMATION, CHRONIC			1 (4%)		
*SUBCUT TISSUE	(25)	(24)	(25)	(24)	(25)
STEATITIS				1 (4%)	
NECROSIS, FAT				1 (4%)	
RESPIRATORY SYSTEM					
*NASAL CAVITY	(25)	(24)	(25)	(24)	(25)
INFLAMMATION, CHRONIC		1 (4%)			
INFLAMMATION, CHRONIC FOCAL			1 (4%)		
#LUNG/BRONCHIOLE	(25)	(23)	(24)	(24)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (16%)	4 (17%)	4 (17%)	4 (17%)	4 (16%)
#LUNG	(25)	(23)	(24)	(24)	(25)
ATELECTASIS				1 (4%)	
CONGESTION, NOS	2 (8%)	4 (17%)	2 (8%)	1 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (4%)	1 (4%)	
INFLAMMATION, INTERSTITIAL			2 (8%)		
PNEUMONIA INTERSTITIAL CHRONIC					1 (4%)
NECROSIS, NOS				1 (4%)	
HYPERPLASIA, ADENOMATOUS		1 (4%)			
HEMATOPOIETIC SYSTEM					
#BONE MARROW	(25)	(24)	(23)	(24)	(24)
INFLAMMATION WITH FIBROSIS					1 (4%)
FIBROUS OSTEODYSTROPHY					1 (4%)
MYELOFIBROSIS	14 (56%)	19 (79%)	14 (61%)	20 (83%)	16 (67%

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

TABLE D3. FEMALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#SPLEEN	(24)	(24)	(24)	(24)	(25)
HEMORRHAGIC CYST		1 (4%)			
AMYLOIDOSIS	1 (4%)				
HEMOSIDEROSIS		2 (8%)		1 (4%)	1 (4%)
HYPERPLASIA, LYMPHOID		1 (4%)		1 (4%)	1 (4%)
HEMATOPOIESIS	2 (8%)	6 (25%)	1 (4%)	1 (4%)	2 (8%)
#SPLENIC CAPSULE	(24)	(24)	(24)	(24)	(25)
FIBROSIS		1 (4%)			
#LYMPH NODE	(21)	(17)	(21)	(17)	(21)
EDEMA, NOS			1 (5%)		
HYPERPLASIA, NOS			2 (10%)		1 (5%)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (6%)	1 (5%)	1 (6%)	
#SUBMANDIBULAR L.NODE	(21)	(17)	(21)	(17)	(21)
HYPERPLASIA, LYMPHOID		1 (6%)			
#MANDIBULAR L. NODE	(21)	(17)	(21)	(17)	(21)
HYPERPLASIA, LYMPHOID					1 (5%)
#LUMBAR LYMPH NODE	(21)	(17)	(21)	(17)	(21)
INFLAMMATION, CHRONIC		1 (6%)			
#MESENTERIC L. NODE	(21)	(17)	(21)	(17)	(21)
CONGESTION, NOS	1 (5%)				
EDEMA, NOS	1 (5%)				
#RENAL LYMPH NODE	(21)	(17)	(21)	(17)	(21)
HYPERPLASIA, LYMPHOID	1 (5%)				
#LIVER	(25)	(24)	(25)	(24)	(25)
HEMATOPOIESIS	1 (4%)	2 (8%)		1 (4%)	4 (16%)
#THYMUS	(19)	(18)	(13)	(20)	(20)
HYPERPLASIA, NOS				1 (5%)	
HYPERPLASIA, LYMPHOID		1 (6%)			
CIRCULATORY SYSTEM					
#MYOCARDIUM	(25)	(24)	(25)	(24)	(25)
INFLAMMATION, CHRONIC FOCAL	1 (4%)				
#KIDNEY	(25)	(24)	(25)	(24)	(25)
PERIARTERITIS		1 (4%)			

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

TABLE D3. FEMALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
DIGESTIVE SYSTEM					
#SALIVARY GLAND	(25)	(20)	(22)	(22)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (5%)	3 (14%)		1 (4%)
#LIVER	(25)	(24)	(25)	(24)	(25)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	3 (13%)	2 (8%)	3 (13%)	
INFLAMMATION, MULTIFOCAL	1 (4%)				
INFLAMMATION, CHRONIC	1 (4%)				
INFLAMMATION, CHRONIC FOCAL					1 (4%)
NECROSIS, FOCAL	1 (4%)		1 (4%)		
METAMORPHOSIS FATTY			1 (4%)		
CYTOLOGIC DEGENERATION				1 (4%)	
ANGIECTASIS		1 (4%)		1 (4%)	
#LIVER/CENTRILOBULAR	(25)	(24)	(25)	(24)	(25)
DEGENERATION, NOS				1 (4%)	
NECROSIS, NOS				1 (4%)	
#PANCREAS	(22)	(21)	(23)	(24)	(24)
CYST, NOS			1 (4%)		
CYSTIC DUCTS	1 (5%)				1 (4%)
INFLAMMATION, FOCAL	1 (5%)				
INFLAMMATION, CHRONIC	1 (5%)			1 (4%)	
FIBROSIS			1 (4%)		
NECROSIS, FAT			1 (4%)		
ATROPHY, NOS	2 (9%)		2 (9%)	1 (4%)	
ATROPHY, FOCAL	1 (5%)				1 (4%)
#COLON	(21)	(21)	(23)	(23)	(25)
HEMORRHAGIC CYST		1 (5%)			
INFLAMMATION, CHRONIC FOCAL	3 (14%)	3 (14%)	1 (4%)	3 (13%)	2 (8%)
URINARY SYSTEM					
#KIDNEY	(25)	(24)	(25)	(24)	(25)
HYDRONEPHROSIS					1 (4%)
CONGESTION, NOS	1 (4%)				1 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	8 (32%)	11 (46%)	10 (40%)	13 (54%)	8 (32%)
INFLAMMATION, CHRONIC	1 (4%)			1 (4%)	1 (4%)
GLOMERULONEPHRITIS, CHRONIC					1 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (4%)	2 (8%)			
CALCIFICATION, FOCAL			1 (4%)	1 (4%)	

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

TABLE D3. FEMALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ATROPHY, NOS	1 (4%)				
#KIDNEY/PELVIS	(25)	(24)	(25)	(24)	(25)
DILATATION, NOS					1 (4%)
#URINARY BLADDER	(23)	(21)	(22)	(22)	(23)
LYMPHOCYTIC INFLAMMATORY INFILTR					1 (4%)
INFLAMMATION, ACUTE				1 (5%)	
INFLAMMATION, CHRONIC		1 (5%)			3 (13%)
INFLAMMATION, CHRONIC FOCAL	7 (30%)	6 (29%)	2 (9%)	10 (45%)	6 (26%)
NECROSIS, FAT				1 (5%)	
HYPERPLASIA, EPITHELIAL		2 (10%)	2 (9%)		3 (13%)
METAPLASIA, SQUAMOUS					2 (9%)
ENDOCRINE SYSTEM					
#PITUITARY	(21)	(22)	(16)	(18)	(22)
CONGESTION, NOS			2 (13%)		
HYPERPLASIA, NOS			1 (6%)		
HYPERPLASIA, CHROMOPHOBE-CELL			1 (6%)		
#ADRENAL	(24)	(23)	(24)	(24)	(25)
CONGESTION, NOS				1 (4%)	2 (8%)
#ADRENAL CORTEX	(24)	(23)	(24)	(24)	(25)
HYPERPLASIA, NODULAR				1 (4%)	1 (4%)
#ZONA GLOMERULOSA	(24)	(23)	(24)	(24)	(25)
METAPLASIA, NOS					2 (8%)
#THYROID	(22)	(21)	(24)	(23)	(21)
CYST, NOS			2 (8%)		
CYSTIC FOLLICLES			1 (4%)		1 (5%)
INFLAMMATION, ACUTE/CHRONIC					1 (5%)
HYPERPLASIA, CYSTIC				1 (4%)	
HYPERPLASIA, C-CELL					1 (5%)
HYPERPLASIA, FOLLICULAR-CELL		1 (5%)			
REPRODUCTIVE SYSTEM					
*MAMMARY GLAND	(25)	(24)	(25)	(24)	(25)
GALACTOCELE	1 (4%)	1 (4%)		2 (8%)	
HYPERPLASIA, NOS	1 (4%)				

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

TABLE D3. FEMALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
#UTERUS	(23)	(23)	(24)	(24)	(23)
DILATATION, NOS			1 (4%)		
HEMORRHAGIC CYST				1 (4%)	
SCAR					1 (4%)
POLYP, INFLAMMATORY					1 (4%)
#UTERUS/ENDOMETRIUM	(23)	(23)	(24)	(24)	(23)
INFLAMMATION, VESICULAR	2 (9%)		1 (4%)	1 (4%)	2 (9%)
INFLAMMATION, CHRONIC					1 (4%)
INFLAMMATION CHRONIC CYSTIC	1 (4%)	2 (9%)		3 (13%)	2 (9%)
HYPERPLASIA, NOS		1 (4%)	1 (4%)		2 (9%)
HYPERPLASIA, CYSTIC	13 (57%)	15 (65%)	9 (38%)	18 (75%)	14 (61%)
#OVARY	(23)	(19)	(22)	(22)	(19)
ATRESIA					1 (5%)
HEMORRHAGE				1 (5%)	
HEMORRHAGIC CYST	2 (9%)		1 (5%)		
ATROPHY, NOS	19 (83%)	18 (95%)	15 (68%)	18 (82%)	17 (89%)
ATROPHY, CYSTIC	1 (4%)			1 (5%)	
NERVOUS SYSTEM					
#BRAIN	(25)	(24)	(25)	(24)	(24)
GLIOSIS					1 (4%)
CALCIFICATION, FOCAL				2 (8%)	
#BASAL GANGLIA	(25)	(24)	(25)	(24)	(24)
CALCIFICATION, FOCAL	11 (44%)	8 (33%)	7 (28%)	9 (38%)	10 (42%)
SPECIAL SENSE ORGANS					
*EYE/LACRIMAL GLAND	(25)	(24)	(25)	(24)	(25)
HYPERPLASIA, NOS			1 (4%)		
*HARDERIAN GLAND	(25)	(24)	(25)	(24)	(25)
INFLAMMATION, VESICULAR	1 (4%)				
MUSCULOSKELETAL SYSTEM					
NONE					

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

TABLE D3. FEMALE MICE (CONTROL GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL NO. 1	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
BODY CAVITIES					
*PLEURA	(25)	(24)	(25)	(24)	(25)
INFLAMMATION, CHRONIC FOCAL	1 (4%)				
*PERICARDIUM	(25)	(24)	(25)	(24)	(25)
INFLAMMATION, CHRONIC	1 (4%)				
ALL OTHER SYSTEMS					
*MULTIPLE ORGANS	(25)	(24)	(25)	(24)	(25)
CONGESTION, NOS	1 (4%)				1 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	11 (44%)	9 (38%)	5 (20%)	8 (33%)	8 (32%)
ADHESION, FIBROUS		1 (4%)			
SPECIAL MORPHOLOGY SUMMARY					
AUTOLYSIS/NO NECROPSY		1		1	

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

TABLE D4.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED HCDD BY GAVAGE (CONTROL AND DOSED GROUPS)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50	50
ANIMALS NECROPSIED	25	49	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	49	48	49
INTEGUMENTARY SYSTEM				
*SKIN	(25)	(49)	(49)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)		
HYPERPLASIA, NOS		1 (2%)		
*SUBCUT TISSUE	(25)	(49)	(49)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
GRANULATION, TISSUE			1 (2%)	
NECROSIS, NOS		1 (2%)		1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(25)	(48)	(42)	(44)
HYPERPLASIA, EPITHELIAL				1 (2%)
#LUNG/BRONCHIOLE	(25)	(49)	(48)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	10 (20%)	4 (8%)	6 (13%)
#LUNG	(25)	(49)	(48)	(48)
ATELECTASIS	1 (4%)			
CONGESTION, NOS		4 (8%)	7 (15%)	5 (10%)
EDEMA, NOS		1 (2%)		
HEMORRHAGE	1 (4%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	1 (2%)	1 (2%)	1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC				1 (2%)
FIBROSIS, MULTIFOCAL				1 (2%)
HEMOSIDEROSIS		1 (2%)		
ALVEOLAR MACROPHAGES			2 (4%)	1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (4%)	1 (2%)		
#LUNG/ALVEOLI	(25)	(49)	(48)	(48)
HEMORRHAGE			1 (2%)	

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

TABLE D4. FEMALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(25)	(49)	(49)	(49)
HEMATOPOIESIS			1 (2%)	
*MEDIASTINUM	(25)	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID				1 (2%)
*MAMMARY GLAND	(25)	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)		
#BONE MARROW	(23)	(48)	(46)	(48)
ATROPHY, NOS		1 (2%)	1 (2%)	1 (2%)
MYELOFIBROSIS	19 (83%)	37 (77%)	34 (74%)	26 (54%)
#SPLEEN	(23)	(48)	(47)	(46)
CONGESTION, NOS	1 (4%)		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)		
NECROSIS, FOCAL		2 (4%)		
HEMOSIDEROSIS		2 (4%)		
HYPERPLASIA, LYMPHOID	1 (4%)			
HEMATOPOIESIS	1 (4%)	4 (8%)	2 (4%)	5 (11%)
#LYMPH NODE	(22)	(42)	(36)	(30)
HYPERPLASIA, LYMPHOID	3 (14%)			
#MANDIBULAR L. NODE	(22)	(42)	(36)	(30)
PIGMENTATION, NOS				1 (3%)
HYPERPLASIA, LYMPHOID	1 (5%)		1 (3%)	
#BRONCHIAL LYMPH NODE	(22)	(42)	(36)	(30)
HYPERPLASIA, LYMPHOID			1 (3%)	
#PYLORIC LYMPH NODE	(22)	(42)	(36)	(30)
STEATITIS		1 (2%)		
NECROSIS, FAT		1 (2%)		
HISTIOCYTOSIS		1 (2%)		
#LUNG	(25)	(49)	(48)	(48)
HEMATOPOIESIS		1 (2%)		
#LIVER	(24)	(48)	(47)	(47)
HEMATOPOIESIS	2 (8%)	4 (8%)	24 (51%)	20 (43%)
#SMALL INTESTINE	(23)	(45)	(43)	(41)
HYPERPLASIA, LYMPHOID	1 (4%)			

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

TABLE D4. FEMALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#PEYER'S PATCH	(23)	(45)	(43)	(41)
HYPERPLASIA, LYMPHOID	3 (13%)			
#DUODENUM	(23)	(45)	(43)	(41)
HYPERPLASIA, LYMPHOID			2 (5%)	2 (5%)
CIRCULATORY SYSTEM				
#LUNG	(25)	(49)	(48)	(48)
PERIARTERITIS			2 (4%)	
#HEART/VENTRICLE	(25)	(49)	(47)	(47)
THROMBUS, MURAL			1 (2%)	
INFECTION, BACTERIAL			1 (2%)	
#MYOCARDIUM	(25)	(49)	(47)	(47)
INFLAMMATION, CHRONIC FOCAL			3 (6%)	1 (2%)
#OVARY	(23)	(46)	(40)	(36)
HEMANGIOMATOSIS				1 (3%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(25)	(47)	(47)	(44)
CYST, NOS		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	3 (6%)	4 (9%)	2 (5%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
ATROPHY, FOCAL				1 (2%)
#LIVER	(24)	(48)	(47)	(47)
CYST, NOS			1 (2%)	
CONGESTION, NOS			1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (13%)	7 (15%)	2 (4%)	
INFLAMMATION, MULTIFOCAL				5 (11%)
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (4%)		1 (2%)	1 (2%)
DEGENERATION, NOS		1 (2%)	1 (2%)	1 (2%)
CLOUDY SWELLING		1 (2%)		1 (2%)
DEGENERATION, HYDROPIC				1 (2%)
NECROSIS, NOS		1 (2%)		
NECROSIS, FOCAL		1 (2%)		1 (2%)
METAMORPHOSIS FATTY	2 (8%)		2 (4%)	1 (2%)

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

TABLE D4. FEMALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
CYTOLOGIC DEGENERATION			1 (2%)	1 (2%)
HYPERTROPHY, NOS				1 (2%)
HYPERTROPHY, FOCAL			1 (2%)	2 (4%)
HYPERPLASIA, NOS				1 (2%)
#LIVER/CENTRILOBULAR	(24)	(48)	(47)	(47)
NECROSIS, NOS			1 (2%)	2 (4%)
METAMORPHOSIS FATTY			1 (2%)	1 (2%)
#LIVER/KUPFFER CELL	(24)	(48)	(47)	(47)
HYPERPLASIA, NOS			1 (2%)	
#LIVER/HEPATOCYTES	(24)	(48)	(47)	(47)
HYPERTROPHY, FOCAL			1 (2%)	
#PANCREAS	(23)	(47)	(46)	(44)
DILATATION/DUCTS				1 (2%)
CYSTIC DUCTS				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	1 (2%)
FIBROSIS			1 (2%)	
METAMORPHOSIS FATTY			1 (2%)	
ATROPHY, NOS		2 (4%)	3 (7%)	
ATROPHY, FOCAL	1 (4%)	1 (2%)		
#COLON	(25)	(47)	(44)	(43)
INFLAMMATION, CHRONIC	1 (4%)			1 (2%)
INFLAMMATION, CHRONIC FOCAL	7 (28%)	6 (13%)	12 (27%)	3 (7%)
URINARY SYSTEM				
#KIDNEY	(24)	(49)	(48)	(46)
HYDRONEPHROSIS				1 (2%)
CONGESTION, NOS	1 (4%)			
PYELONEPHRITIS, NOS			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	7 (29%)	24 (49%)	24 (50%)	27 (59%)
INFLAMMATION, INTERSTITIAL		1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	1 (4%)			
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)	
INFARCT, NOS		1 (2%)		
#URINARY BLADDER	(24)	(43)	(40)	(42)
EDEMA, NOS				1 (2%)

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

TABLE D4. FEMALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	1 (4%)	1 (2%)	2 (5%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	9 (38%)	2 (5%)	8 (20%)	3 (7%)
GRANULATION, TISSUE				1 (2%)
FIBROSIS				1 (2%)
HEMOSIDEROSIS				1 (2%)
HYPERPLASIA, EPITHELIAL		2 (5%)	1 (3%)	2 (5%)
HYPERPLASIA, CYSTIC	1 (4%)			
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(41)	(40)	(41)
CONGESTION, NOS		2 (5%)	1 (3%)	
HEMORRHAGIC CYST				1 (2%)
HEMOSIDEROSIS		1 (2%)		
HYPERPLASIA, NOS		2 (5%)		2 (5%)
HYPERPLASIA, CHROMOPHOBE-CELL		2 (5%)		
#ADRENAL	(24)	(46)	(46)	(47)
HEMORRHAGE			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (2%)
ATROPHY, NOS				1 (2%)
#ADRENAL/CAPSULE	(24)	(46)	(46)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	1 (2%)
#ADRENAL CORTEX	(24)	(46)	(46)	(47)
METAMORPHOSIS FATTY	1 (4%)	1 (2%)		
#THYROID	(25)	(44)	(40)	(42)
FOLLICULAR CYST, NOS	1 (4%)			
FIBROSIS		1 (2%)		
HYPERPLASIA, FOCAL				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(49)	(49)	(49)
GALACTOCELE		4 (8%)	3 (6%)	1 (2%)
#UTERUS	(25)	(45)	(45)	(45)
DILATATION, NOS			1 (2%)	1 (2%)
CYST, NOS				1 (2%)
HEMORRHAGE		1 (2%)		
HEMORRHAGIC CYST	1 (4%)			

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

TABLE D4. FEMALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC				2 (4%)
ABSCESS, CHRONIC				1 (2%)
GRANULATION, TISSUE				1 (2%)
FIBROSIS		1 (2%)		
NECROSIS, NOS		1 (2%)		
METAPLASIA, SQUAMOUS			1 (2%)	
#UTERUS/ENDOMETRIUM	(25)	(45)	(45)	(45)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, VESICULAR	1 (4%)	2 (4%)	1 (2%)	9 (20%)
ABSCESS, NOS				1 (2%)
INFLAMMATION, CHRONIC	1 (4%)	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (4%)	1 (2%)		2 (4%)
INFLAMMATION CHRONIC CYSTIC		2 (4%)	6 (13%)	
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, CYSTIC	20 (80%)	36 (80%)	24 (53%)	17 (38%)
#OVARY/PAROVARIAN	(25)	(45)	(45)	(45)
INFLAMMATION, CHRONIC				1 (2%)
#OVARY	(23)	(46)	(40)	(36)
CYST, NOS		1 (2%)	1 (3%)	2 (6%)
MULTIPLE CYSTS	2 (9%)	2 (4%)		
HEMORRHAGIC CYST		3 (7%)	6 (15%)	4 (11%)
ATROPHY, NOS	22 (96%)	41 (89%)	34 (85%)	33 (92%)
NERVOUS SYSTEM				
#BRAIN	(25)	(49)	(47)	(48)
CALCIFICATION, FOCAL		2 (4%)		
#BASAL GANGLIA	(25)	(49)	(47)	(48)
CALCIFICATION, FOCAL	6 (24%)	6 (12%)	12 (26%)	18 (38%)
#MIDBRAIN	(25)	(49)	(47)	(48)
CALCIFICATION, FOCAL		4 (8%)		
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(25)	(49)	(49)	(49)
INFLAMMATION, CHRONIC				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE D4. FEMALE MICE (CONTROL AND DOSED GROUPS): NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*PLEURA	(25)	(49)	(49)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
NECROSIS, NOS			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(49)	(49)	(49)
CONGESTION, NOS		2 (4%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	12 (48%)	8 (16%)	8 (16%)	
SITE UNKNOWN				
INFLAMMATION, CHRONIC			1	
FIBROSIS			1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		1		
AUTO/NECROPSY/HISTO PERF			2	1
TRAUMATIC ABNORMALITY		1		
AUTO/NECROPSY/NO HISTO			1	
AUTOLYSIS/NO NECROPSY		1	1	1

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

APPENDIX E

PREPARATION OF HCDD

APPENDIX E

Preparation of HCDD

3,4,5-Trichlorophenol (Aldrich Chemical Co., Milwaukee, Wis.) was brominated at 80°-90°C in glacial acetic acid and the product, 2-bromo-3,4,5-trichlorophenol, was recrystallized from methanol-water or benzene-hexane. The potassium salt of 2-bromo-3,4,5-trichlorophenol was prepared by treating the phenol with potassium hydride in benzene. The dry potassium salt of 2-bromo-3,4,5-trichlorophenol was covered with a layer of dry potassium carbonate and heated under sublimation conditions at 240°-270°C at < 1 mm pressure for 20 hours. The crude product contained hexachlorodibenzo-p-dioxins and bromohexachlorodibenzo-p-dioxins (from the condensation of the 2,6-dibromo-3,4,5-trichlorophenol impurity in 2-bromo-3,4,5-trichlorophenol) and other minor impurities. The crude product was debrominated by hydrogenolysis with lithium aluminum hydride at 0°C to yield HCDD (Gray et al., 1975).

APPENDIX F

ANALYSIS OF HCDD

APPENDIX F

Analysis of HCDD

IIT Research Institute

A. Vapor-Phase Chromatography

Column:	OV-1, 6 ft x 1/8 in
Detector:	Flame Ionization
Oven Temperature I:	150°-250°C at 12°/minute
Results:	Two peaks occurred between 8 and 9 minutes retention time, representing 1.38% of the total peak area. Major peaks were at 9.5 minutes, comprising the remainder of the total peak area (98.62%).
Conclusion:	The peaks comprising 1.38% were identified as pentachlorodibenzo-p-dioxins on the basis of relative retention times. The major peak was identified as hexachlorodibenzo-p-dioxin, as described in the chemical section of this report and in the literature (Gray et al., 1975).

B. Vapor-Phase Chromatography/Mass Spectrometry

After completion of the bioassay, IITRI reanalyzed the HCDD. In these analyses, HCDD was found to contain approximately 0.4% pentachlorodibenzo-p-dioxin and 0.07% tetrachlorodibenzo-p-dioxin, based on vapor-phase chromatographic areas (conditions unspecified). The identities of the impurities reportedly were confirmed by mass spectrometry. Detection limits were estimated at 0.01%.

Analysis of HCDD

Midwest Research Institute

A. Vapor-Phase Chromatography

1. Electron Capture Detection

a. System 1:

Instrument: Bendix 2500
Column: 3% OV-1, 1.8m x 4 mm I.D.
Detector: Electron capture, ^{63}Ni
Oven Temperature: 160°C, isothermal
Compound Concentration: 0.032 mg/ml in benzene
Results: One peak with a retention time identical to that of an authentic sample of tetrachlorodibenzo-p-dioxin. By comparison of the area of this peak with that of a weighed solution of tetrachlorodibenzo-p-dioxin, it was calculated that the tetrachloro compound was present at a concentration of 0.07%.

b. System 2

Instrument: Varian 1400
Column: 3% OV-1, 1.8 m x 4 mm I.D.
Detector: Electron capture, $Sc^{3}H_3$
Oven Temperature I: 160°C, isothermal
Compound Concentration: Saturated (2 mg/ml in benzene)
Results: Major peak not eluted in 45 minutes. Eight minor impurities detected.

Peak	Retention Time (min)	Retention Time (Relative to Tetrachloro-dibenzo-p-dioxin	Possible Identity	Percent by Weight
1	4.2	0.11	Unknown	-
2	7.9	0.20	Dichlorodibenzo-p-dioxin	~ 0.004
3	9.5	0.24	Unknown	-
4	11.7	0.29	Unknown	-
5	17.3	0.43	Trichlorodibenzo-p-dioxin	~ 0.004
6	25.6	0.64	Unknown	-
7	34.5	0.87	Unknown	-
8	39.8	1.00	Tetrachlorodibenzo-p-dioxin	~ 0.01

Possible identities were assigned to peaks which had retention times identical to those for authentic samples of other chlorinated dibenzo-p-dioxins. Percentage compositions by

weight were calculated by comparison of the areas of the impurity peaks in the weighed sample to the area of the tentatively identified chlorinated dibenzo-p-dioxin in a weighed solution of similar concentration. No authentic sample of monochlorodibenzo-p-dioxin was available. It is possible that the first peak is the monochloro compound.No percentage compositions were calculated for the unknown peaks because of the great variation in response of electron capture detectors to different compounds.

c. System 3:

Instrument:	Varian 1400
Column:	3% OV-1, 1.8 m x 4 mm I.D.
Detector:	Electron capture, Sc^3H_3
Oven Temperature II:	225°C, isothermal
Compound Concentration:	0.032 mg/ml in benzene
Results:	Major peak and three impurities.

Peak	Retention Time (min)	Retention Time (Relative to Hexachloro-dibenzo-p-dioxin)	Identity	Area (Relative to Hexachloro-dibenzo-p-dioxin)
1	4.0	0.25	Tetrachlorodibenzo-p-dioxin	0.08
2	7.8	0.50	Unknown	-
3	8.6	0.54	Unknown	-
4	15.7	1.00	Hexachlorodibenzo-p-dioxin	1.00

Nothing else eluted in 50 minutes.

The first peak was again quantitated against an authentic sample of tetrachlorodibenzo-p-dioxin. No authentic sample of pentachlorodibenzo-p-dioxin was available. The two peaks with retention times intermediate between tetra- and hexachlorodibenzo-p-dioxin

could be pentachloro compounds, but there was no way to verify this. Octachlorodibenzo-p-dioxin was not detected; the detection limit in this sample is less than 0.004%.

d. System 4:

Instrument:	Bendix 2500
Column:	3% Dexsil 400, 1.8 m x 2 mm I.D.
Detector:	Electron capture, ^{63}Ni
Oven Temperature III:	275°C, isothermal
Compound Concentration:	0.032 mg/ml in benzene
Results:	Major peak and two impurities with longer retention times.

Peak	Retention Time (min)	Retention Time (Relative to Hexachloro-dibenzo-p-dioxin)	Identity
1	2.1	1.0	Hexachlorodibenzo-p-dioxin
2	3.5	1.7	Unknown
3	4.8	2.3	Unknown

Nothing else eluted in 20 minutes.

Under these same conditions octachlorodibenzo-p-dioxin had a retention time of 5.5 minutes and thus was not detected in the sample. This column separated two impurities with retention times intermediate between those of hexa - and octachlorodibenzo-p-dioxin. Either of these impurities could have been heptachlorodibenzo-p-dioxin, but no authentic sample was available.

2. Flame Ionization Detection

a. System 1:

Instrument:	Tracor MT 220
Column:	Stainless steel capillary coated with OV-101, 50 ft. x 0.02 in. I.D.
Oven Temperature:	190°C, isothermal
Results:	Major peak and three impurities.

Peak	Retention Time (min)	Retention Time (Relative to that of Hexachloro-dibenzo-p-dioxin)	Area (Relative to that of Hexachloro-dibenzo-p-dioxin)
1	6.0	0.50	0.2
2	6.8	0.57	0.6
3	11.3	0.94	1.40
4	12.0	1.00	100

Peak No. 3 was a shoulder on the major peak and probably did not separate from the major peak on the packed columns used with the electron capture detectors. Peaks Nos. 1 and 2 were too large to be due to the chlorinated dibenzo-p-dioxins (di-, tri-, and tetra-) observed and quantitated by electron capture, but it is possible that these are the unknown peaks detected by electron capture.

b. System 2:

Instrument:	Tracor MT 220
Column:	3% Dexsil 400, 1.8 m x 2 mm I.D.
Oven Temperature:	150° to 285°C at 10°C/min
Results:	Major peak and one impurity.

Peak	Retention Time (min)	Retention Time (Relative to that of Hexachloro-dibenzo-p-dioxin)	Area (Relative to that of Hexachloro-dibenzo-p-dioxin)
1	9.6	0.85	0.2
2	11.3	1.00	100

c. System 3:

Instrument:	Tracor MT 220
Column:	5% N,N'-bis(p-methoxybenzylidine)- α,α bi-p-toluidine (liquid crystal), 1.2 m x 2 mm I.D.
Oven Temperature:	235°C, isothermal
Results:	Two peaks (indicating the presence of two isomers).

Peak	Retention Time (min)	Retention Time (Relative to that of Larger Peak)	Area (Relative to that of Larger Peak)
1	10.9	0.81	46
2	13.4	1.00	100

B. Mass Spectrometry

1. Vapor-Phase Chromatography/Mass Spectrometry

Instrument:	Varian MAT CH4B mass spectrometer interfaced via a Watson-Biemann helium separator to a Tracor MT 2000 MF gas chromatograph. Data processed by a Varian 620/i computer.
Column:	3% OV-1, 1.8 m x 2 mm I.D.
Oven Temperature:	210°C, isothermal
Results:	Only one peak, that for the major component, was detected on the ion current monitor. Specific ion searches for other possible impurities indicated the presence of pentachlorodibenzo-p-dioxin and bromo-pentachlorodibenzo-p-dioxin; the searches gave no evidence for the presence of other chlorinated dibenzo-p-dioxins or tetrabromomonochloro- or bromohexachlorodibenzo-p-dioxin.

Peak	Mass	Relative Intensities	Calculated Relative Intensities
Pentachlorodibenzo-p-dioxin	354	74	61
	356	100	100
	358	85	66
Bromopentachloro-dibenzo-p-dioxin	434	138	98
	436	100	100
	438	51	53

Peak	Mass	Intensity Relative to Base Peak	Relative Intensities of Parent Ion Cluster	Calculated Relative Intensities
Hexachlorodi-benzo-p-dioxin	28(N_2)	100		
	262	5		
	264	9		
	325	12		
	327	20		
	329	12		
	356	7		
	388	47	57	51
	390	82	100	100
	391	10	12	13
	392	72	88	82
	394	30	37	36
	396	11	13	9

2. Direct Inlet Mass Spectrometry

Instrument:	Varian MAT CH4B mass spectrometer. Data were processed by a Varian 620/i computer.
Results:	Mass spectrum consistent with the structure of the major component. Specific ion searches for the two most intense masses in the parent ion cluster of pentachlorodibenzo-p-dioxin were positive, but these masses also occur in the fragmentation of hexachlorodibenzo-p-dioxin, so the presence of pentachlorodibenzo-p-dioxin could be neither confirmed nor denied. Specific ion searches did not detect any of the other chlorinated dibenzo-p-dioxins or bromopentachloro-, tetrabromomonochloro-, or bromohexachlorodibenzo--p-dioxins or 2-bromo-3,4,5-trichlorophenol, the starting material in the synthesis of hexachlorodibenzo-p-dioxin. Peaks were detected with masses at 436, 485, 487, 492, 513, 515, 545, and 547-554, which could not be due to the major component. The origin of these peaks was not determined.

C. Special Analyses

Subsequent to the analyses described in A and B above, the following special analyses were performed.

1. Vapor-Phase Chromatography/Mass Spectrometry with Solid Injection

Instrument:	Varian MAT CH4B mass spectrometer interfaced via a Watson-Biemann helium separator to a Tracor MT 2000 MF gas chromatograph. Data processed by a Varian 620/i computer.
Column:	3% Dexsil 400, 1.8 m x 4 mm I.D. on Chromosorb W (AW)
Oven Temperature:	300°C, isothermal
Inlet Temperature:	320°C
Helium Separator Temperature:	340°C

Sample Injection:	0.5 mg hexachlorodibenzo-p-dioxin was loaded into a solid sampler (Analabs) and injected directly onto the column.
Results:	Two minor peaks were detected on the ion current monitor before the major peak was eluted. Specific ion searches for the masses in the parent ion cluster indicated that the first minor peak was tetrachlorodibenzo-p-dioxin.

TETRACHLORODIBENZO-p-DIOXIN

Mass	Relative Intensities	Calculated Relative Intensities
320	74	76
322	100	100
324	55	50

2. Vapor-Phase Chromatography with Electron Capture Detection: Quantitation of Tetrachlorodibenzo-p-dioxin

Instrument:	Varian Aerograph 1400
Detector:	Electron capture, Sc^3H_3
Column:	3% Dexsil 400 on Chromosorb W (AW) 1.8 m x 2 mm I.D., glass
Inlet Temperature:	230°C
Detector Temperature:	270°C
Oven Temperature:	220°C
Concentration of Hexachlorodibenzo-p-dioxin:	1.1 mg/ml in benzene
Percent Tetrachlorodibenzo-p-dioxin:	$0.09 \pm 0.03(\delta)\%$

APPENDIX G

QUARTERLY ANALYSES OF STOCK SOLUTIONS

APPENDIX G

Quarterly Analyses of HCDD Stock Solutions

Stock solutions of HCDD in acetone were analyzed at the beginning and at the end of each quarter by the IITRI Chemistry Division. The method of analysis consisted of adding an internal standard (pentachlorodibenzo-p-dioxin, PCDD) to samples so that the internal standard concentration was approximately the same as that of the sample being analyzed. The solution containing sample and standard was then injected onto a Dexsil 300 column (2m x 1/8 in.) at 275°C with a carrier/gas (N_2/CH_4) flow rate of 50 ml/minute in a gas chromatograph equipped with an electron capture detector. Quantitation was achieved by manually measuring the area under the resultant peaks with a planimeter and comparing with standard curves for the internal standard and test compound. The standard curve was represented by a third order polynomial equation fitting response to amounts.

The theoretical concentration for the stock solution was 100 µg/ml. The actual concentration as measured by the above method varied from 78 to 108 µg/ml. The mean was 109.3 µg/ml and the coefficient of variation was 17.6% The corn oil:acetone working solutions of HCDD were not analyzed because efforts to develop a method that would quantitatively separate the dioxins from the corn oil were not successful.

Review of the Bioassay of 1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin (HCDD)* (gavage) for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

February 15, 1980

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 1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin (HCDD) for carcinogenicity.

The primary reviewer for the report on the bioassay of HCDD by gavage said that the compound was a mixture of two isomers and belonged to the family of dioxins. After a brief description of the experimental conditions of test, the reviewer commented on the high incidence of toxic hepatitis exhibited by treated animals. Liver tumors were induced by HCDD in female rats and both sexes of mice. The reviewer said a shortcoming of the study was the contamination of HCDD with about 0.1 percent of TCDD, a known carcinogen. However, the contamination probably made little difference since it was the commercial material that was tested. He added that HCDD is probably carcinogenic by itself. The reviewer concluded that a substantial exposure to HCDD is likely to pose a risk to human beings.

The secondary reviewer questioned the statement in the report regarding the toxicity of HCDD. He said it is necessary to state more explicitly the parameters for toxicity. The primary reviewer moved that the report on the bioassay of HCDD by gavage be accepted as written. The motion was seconded and approved unanimously.

Members present were:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
David B. Clayson, Eppley Institute for Research in Cancer
Joseph Highland, Environmental Defense Fund
William Lijinsky, Federick Cancer Research Center
Henry C. Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Louise Strong, University of Texas Health Sciences Center

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

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