NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 209

CARCINOGENESIS BIOASSAY OF 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN

(CAS NO. 1746-01-6)

IN OSBORNE-MENDEL RATS AND B6C3F$_1$ MICE (GAVAGE STUDY)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

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NTP Technical Report

on the

CARCINOGENESIS BIOASSAY

OF

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(GAVAGE STUDY)

NATIONAL TOXICOLOGY PROGRAM
Research Triangle Park
Box 12233
North Carolina 27709
and
Bethesda, Maryland 20205

February 1982

NTP-80-31
NIH Publication No. 82-1765

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

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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 chronic study began in February 1975 and ended in March 1977.

The project director was Mr. A. Shefner (1); Dr. M. E. King (1) was the principal investigator for this study; and Dr. P. Holmes (1,2) assembled the data. Doses of the test chemical were selected by Dr. O. G. Fitzhugh (3,5). Mr. T. Kruckeberg (1) and Mr. K. Kaltenborn (1) were in charge of animal care.

Necropsies were performed under the direction of Dr. A. R. Roesler (1). Histopathologic evaluations were performed by Dr. W. Richter (1). The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978). The diagnoses represent a consensus of contracting pathologists and the NCI Pathology Working Group with final approval by the NCI Pathology Working Group.

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

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The following scientists at NCI/NTP (8) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Michael P. Dieter, Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Larry Hart, Dr. William V. Hartwell (Chemical Manager), Dr. Joseph Haseman, Dr. James E. Huff, Dr. C. W. Jameson, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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SUMMARY

A carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a contaminant in several phenoxy herbicides, was conducted by administering TCDD by gavage to Osborne-Mendel rats and B6C3F1 mice for 104 weeks.

Fifty rats and mice of each sex were given TCDD suspended in a vehicle of 9:1 corn oil-acetone 2 days per week for 104 weeks at doses of 0.01, 0.05, or 0.5 μg/kg/wk for rats and male mice and 0.04, 0.2, or 2.0 μg/kg/wk for female mice. Seventy-five rats and 75 mice of each sex served as vehicle controls. One untreated control group containing 25 rats and 25 mice of each sex was present in the TCDD 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 was observed in the males after week 55 of the bioassay and in the females after week 45. In mice, the mean body weight gain in the dosed groups was comparable to that of the vehicle-control groups.

In male rats, increased incidences of follicular-cell adenomas in the thyroid were dose related and were significantly (P=0.001) higher in the high-dose group than in the vehicle controls (1/69, 1%; 5/48, 10%; 6/50, 12%; 10/50, 20%). Similarly in the female rats, an increase (though not statistically significant) was seen in the high-dose group (3/73, 4%; 2/45, 4%; 1/49, 2%; 6/47, 13%).

In female rats, the incidence of neoplastic nodules of the liver in the high-dose group was significantly (P=0.006) higher than that in the vehicle control group (5/75, 7%; 1/49, 2%; 3/50, 6%; 12/49, 24%).

In male and female mice, incidences of hepatocellular carcinomas were dose related and the incidences in the high-dose groups were significantly (P=0.002 and 0.014, respectively) higher than those in the corresponding vehicle control groups (males: 8/73, 11%; 9/49, 18%; 8/49, 16%; 17/50, 34%; females: 1/73, 1%; 2/50, 4%; 2/48, 4%; 6/47, 13%).

In female mice, follicular-cell adenomas in the thyroid occurred at dose-related incidences, and were significantly (P=0.009) higher in the high-dose groups than those in the vehicle controls (0/69, 0%; 3/50, 6%; 1/47, 2%; 5/46, 11%).

Increased incidences of toxic hepatitis related to the administration of the test chemical were detected among high-dose rats and high-dose mice of each sex.

Under the conditions of this bioassay, 2,3,7,8-tetrachlorodibenzo-p-dioxin was carcinogenic for Osborne-Mendel rats, inducing follicular-cell thyroid adenomas in males and neoplastic nodules of the liver in females. TCDD was also carcinogenic for B6C3F1 mice, inducing hepatocellular carcinomas in males and females and follicular-cell thyroid adenomas in females.

PEER-REVIEW PANEL AND COMMENTS

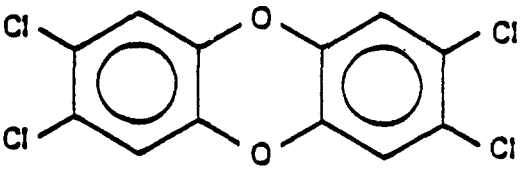
On June 27, 1980, this report underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9 a.m. in Room 1331, Switzer Building, 330 C Street, S.W., Washington, D.C. Members of the Subcommittee are: Drs. Margaret Hitchcock (Chairperson), Curtis Harper, Thomas Shepard, and Alice Whittemore. Members of the Panel are: Drs. Norman Breslow, Joseph Highland, Charles Irving, Frank Mirer, Sheldon Murphy, Svend Nielsen, Bernard Schwetz, Roy Shore, James Swenberg, and Gary Williams. Drs. Highland, Schwetz, and Swenberg were unable to attend the review.

Dr. Williams, the primary reviewer for the report on the bioassay by the gavage route of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), agreed with the conclusions that, under the conditions of this bioassay, TCDD was carcinogenic for Osborne-Mendel rats, inducing increased incidences of follicular-cell thyroid tumors in males and liver tumors in females. TCDD was also carcinogenic for B6C3F1 mice, inducing increased incidences of liver tumors in males and females and thyroid tumors in females. He opined that the high incidence of toxic hepatitis was associated with administration of TCDD in the high dose groups (the only groups displaying significant increases in liver tumor development). Dr. Williams expressed concern that in male mice the high-dose group had an incidence of hepatocellular carcinoma of only 34 percent, which is comparable to a spontaneous incidence of 28 percent in other studies with the strain. The incidence in controls in this study was 11 percent.

As the secondary reviewer, Dr. Irving agreed with the conclusions and also emphasized the incidence of toxic hepatitis in high-dose animals. Dr. Williams discussed the need to better elucidate the probable mechanism(s) by which TCDD induces thyroid and liver tumors. He stated that virtually all halogenated cyclic hydrocarbons are tumorigenic to only these sites; these tumors may arise via indirect mechanisms (endocrine disturbances).

Dr. Williams moved that the report on the bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin by the gavage route be accepted and that statements on the hepatotoxic effects of TCDD should be included in the summary and conclusions. Dr. Shepard seconded the motion and it was approved unanimously.

I. INTRODUCTION



2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Empirical Formula: $C_{12}H_4Cl_4O_2$
Percent by Weight: C 44.7, O 9.95, H 1.25, Cl 44.1
Molecular Weight: 322
Melting Point: 305°C
Decomposition Temperature: >700°C

2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD; TCDD; CAS 1746-01-6) occurs as a highly toxic impurity found in herbicides containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5,-T derivatives, as well as in other chemicals synthesized using 2,4,5-trichlorophenol (EHP, 1973; Crossland and Shea, 1973; Rappe, 1978).

The herbicide 2,4,5-T has been marketed in the United States since 1948 (Federal Register, 1978). Production increased sharply between 1960 and 1970, when a 1:1 mixture of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) was used as a defoliant in Vietnam under the names of "herbicide agent orange, herbicide orange, agent orange, and orange" (Federal Register, 1979). During this 10-year period, about 106 million pounds of 2,4,5-T were sprayed (Federal Register, 1978).

An average of 1.86 ppm TCDD (and as much as 47 ppm in a single sample) was found in surplus herbicide orange preparations stockpiled after the Vietnam war (Firestone, 1978). Commercial trichlorophenols manufactured from 1969 to 1970 contained 0.07 ppm to 6.2 ppm TCDD (Firestone et al., 1972). Woolson et al. (1972) analyzed 42 samples of 2,4,5-T manufactured from 1966 to 1970 and found that 7 contained less than 10 ppm TCDD, 13 of 42 samples contained from 10 ppm to 100 ppm TCDD, and the remaining 22 samples contained less than 0.5 ppm. After the hazardous effects of TCDD had been

publicized, manufacturers reduced the TCDD content in products to 0.5 ppm in 1971 (Kearney et al., 1973) and to 0.1 ppm in 1972 (Federal Register, 1978). The 2,4,5-trichlorophenol produced currently in the U.S. reportedly contains on the average 0.026 ppm TCDD (Ramstad et al., 1977).

Since 1974, over 95% of all 2,4,5-T produced in the U.S. has been used on rangelands and pastures for the control of woody plants (Farm Chemicals Handbook, 1977). Limited use on food crops such as rice and blueberries has been permitted (Federal Register, 1978). On February 28, 1979, the Environmental Protection Agency issued a suspension notice regarding the uses of 2,4,5-T on pastures, forests, and rights of way (Federal Register, 1979).

Local populations have been exposed to TCDD as a result of industrial accidents in Germany, The Netherlands, Czechoslovakia, Italy, Great Britain, and the United States, and through the intensive spraying campaigns with Agent Orange in Vietnam (IARC, 1977 and 1978; Crow, 1977; Hay, 1978; Firestone, 1978; Huff et al., 1980).

TCDD undergoes photodecomposition in nonpolar solvents, but not in aqueous solutions or on wet or dry soils (Crosby et al., 1971). Under laboratory conditions, TCDD in thin films of herbicide formulations applied to glass plates, leaves, and soil photodecomposes rapidly; one half of the compound is lost in approximately 6 hours (Crosby and Wong, 1977).

TCDD is apparently not taken up by plant roots or leached into groundwater nor is it found in plants after foliar applications (Kearney et al., 1973). Soil samples treated with 1, 10, or 100 ppm of TCDD and maintained in the laboratory contained as much as 71% of the original material after 1 year (Kearney et al., 1972). Between 1962 and 1970, nearly 350,000 pounds of herbicides were applied by the U.S. military to approximately one square mile at Eglin Air Force Base, Florida. During 1962-1964, a single 92-acre grid had been treated with 87,186 pounds of 2,4,5-T. After 10 years, TCDD could still be recovered from the top 6"-layer of soil (10-710 ppt) and from aquatic silt at the point where eroded soil entered water (10-35 ppt). Livers from captured field mice contained 540-1300 ppt TCDD (Young et al., 1975).

Of the chlorinated dibenzo-p-dioxin isomers tested, TCDD is the most toxic (McConnell and Moore, 1978). Schwetz et al. (1973) found that

the acute oral LD_{50} of TCDD for Sherman rats was 22 μg/kg for males and 45 μg/kg for females. The oral LD_{50} is approximately 100 μg/kg for male and female albino Charles River CD rats (Harris et al., 1973), 114 μg/kg for male C57BL/6 mice (Vos et al., 1974), and 190 μg/kg for female Porton rats (Greig et al., 1973). Deaths of the rats and mice in the acute toxicity studies usually occurred several weeks after dosing (Moore, 1978). The mean time until death was 40.4 days in female Porton rats given a single dose of 200 μg/kg TCDD (Greig et al., 1973).

Histopathologic liver changes have been observed 5 weeks after single oral doses as low as 50 μg/kg were administered to male and female CD rats and 1 week after a single dose of 50 μg/kg was administered to female CD-1 mice (Harris et al., 1973). Increased liver weights were found in male Wistar rats 7 days after single intraperitoneal doses of 0.1 μg/kg (Cunningham and Williams, 1972).

Six weekly doses of 0.2 μg/kg administered by gavage produced an increase in lipid accumulation in the liver, while doses of 1, 5, or 25 μg/kg/week for 6 weeks resulted in increased liver weights and decreased thymic weights in male C57BL/6 mice (Vos et al., 1974). The minimal toxic dose in male and female Sprague-Dawley rats was 0.1 μg/kg when administered by gavage five times per week for 13 weeks (Kociba et al., 1976). Liver degeneration and lymphoid depletion of the thymus were detected in animals given 0.1 μg/kg but not in those administered lower doses. Severe liver damage and high mortality occurred among female albino CD rats given daily oral doses of 10 μg/kg for 31 days (Harris et al., 1973). Fewer deaths and slight liver lesions occurred in another group in the same study given 1 μg/kg for 31 days, and no effects on the liver were reported in a group given 0.1 μg/kg for 31 days. In subacute feeding studies, increased liver weights were observed in male and female Sprague-Dawley rats fed 7 or 20 ppb for 42 days (Fries and Marrow, 1975).

Hematologic effects, including an increase in the packed cell volume and erythrocyte count, platelet depression, and leucocytosis, occurred in female CD rats given 10 μg/kg orally for 10 or 14 days (Weissberg and Zinkl, 1973); leucopenia was found in female CD-1 mice given TCDD at 1, 10, or 50 μg/kg; and thrombocytopenia in female CD rats given 0.1, 1, or 10 μg/kg daily for 30 days (Zinkl et al., 1973).

TCDD is eliminated slowly from rats. Twenty-two days after male and female Sprague-Dawley rats were given a single oral dose of 1.0 μg of [^{14}C]-TCDD, [^{14}C] activity was detected in the liver and fat (Rose et al., 1976). Piper et al. (1973) reported the half-life of TCDD in male Sprague-Dawley rats to be 17 days.

Van Miller et al. (1976) studied the tissue distribution and excretion of tritiated TCDD in five male Sprague-Dawley rats, three adult female rhesus monkeys, and four male infant rhesus monkeys. All of the animals in each of the three groups received the same intraperitoneal dose (400 μg TCDD/kg in corn oil) and were killed 7 days later. In the rat, 40% of the dose was retained in the liver, whereas less than 10% was retained in the livers of the monkeys. In contrast, a large percentage of the dose in monkeys was located in the skin, muscle, and fat, while similar tissues in the rat contained much lower levels of TCDD.

Results from bacterial mutagenicity tests with TCDD are conflicting (Wassom et al., 1977/1978). However, mutagenicity has been reported among plants and animals administered this chemical. Hussain et al. (1972) and Seiler (1973) reported that TCDD was mutagenic without activation in Salmonella typhimurium TA 1532 but not in Salmonella typhimurium TA 1530. Mercier et al. (1978), however, reported that TCDD was not mutagenic in Salmonella typhimurium TA 1532. These differences may be attributed to solubility problems and treatment protocols. Green (1977) gave 0.25, 0.5, 1.0, 2.0, or 4.0 μg/kg TCDD (dissolved in 1 part acetone: 9 parts corn oil) by gavage to male and female Osborne-Mendel rats twice weekly for 13 weeks and observed an increased incidence of chromosomal breaks in female rats dosed with 4 μg/kg and in males dosed with 2 μg/kg or 4 μg/kg. Jackson (1972) found that TCDD caused chromosomal aberrations in the plant Haemanthus (African blood lily).

Recently, Geiger and Neal (1981) examined the mutagenicity of TCDD (up to 20 μg/plate) using the Salmonella typhimurium histidine auxotrophs TA1535, TA100, TA1538, TA98, and TA1537. TCDD did not show mutagenicity in any of these auxotrophs in the presence of mammalian metabolic activating systems isolated from the livers of Arochlor 1254-treated rats, Arochlor 1254-treated hamsters, or TCDD-treated hamsters. Tests run in the absence

of $NADP^+$-dependence metabolic activation failed to reveal any mutagenic activity of TCDD.

Using the sex-linked recessive lethal assay in Drosophila melanogaster, negative results were obtained following intrathoracic injection studies with TCDD (NTP preliminary results).

Treatment with repeated or single doses of as little as 1-10 μg/kg of TCDD increased the frequencies of cleft palate and kidney abnormalities in mice (Courtney and Moore, 1971; Neubert and Dillmann, 1972; Neubert et al., 1973; Smith et al., 1976). In rats, embryo-lethal effects occurred under experimental conditions (Sparschu et. al., 1970; Sparschu et al., 1971), and kidney anomalies (Courtney and Moore, 1971), intestinal hemorrhages, and general edema were produced in the fetuses (Khera and Ruddick, 1973). Few follow-up studies of the effects of prenatal exposure on postnatal functions have been published. In mice, fetal kidney abnormalities caused by TCDD progressed to a hydronephrosis during the postnatal period (Moore, et al., 1973). Murray et al. (1979) completed a three generation reproduction study using Sprague-Dawley rats fed TCDD continuously in the diet (at levels of 0, 0.001, 0.01, and 0.1 μg/kg/day); significant decreases for the 0.01 and 0.1 μg/kg groups were observed in fertility, litter size, gestation survival, postnatal survival, and postnatal body weight. No apparent adverse effect on reproduction was seen at the 0.001 μg/kg dose level.

Lamb et al. (1980, 1981, 1981a, 1981b) studied the effects of simulated agent orange (2,4-D; 2,4,5-T; and TCDD) on fertility and reproduction in C57Bl/6 male mice. Mating frequency, average fertility, and percent implantation, resorption sites, and fetal malformations were not influenced by the treatment. No significant decrement in fertility or reproduction was observed, nor was any evidence of germ cell toxicity observed. Survival of offspring and neonatal development were apparently unaffected by paternal exposure.

Luster et al. (1980) examined bone marrow, immunologic parameters, and host susceptibility in B6C3F1 mice following pre- and post-natal exposure to TCDD. Mothers were given 0, 1.0, 5.0, and 15.0 μg/kg TCDD/body weight on day 14 of gestation and on days 1, 7, and 14 following birth. Neonatal body, liver, spleen, and thymus weights were decreased in the 5.0 and 15.0 μg/kg groups. RBC counts, hematocrits, and hemoglobin were decreased

at the highest TCDD level. Bone marrow toxicity occurred in the 5.0 and 15.0 μg/kg groups, as evidenced by bone-marrow hypocellularity and depressed-colony formation of macrophage-granulocyte progenitor cells and pleuripotent stem cells. Evidence was also presented of a functional depression of the thymus-dependent lymphocyte compartment. Increased susceptibility to either bacterial or syngeneic tumor cell challenge was noted in mice exposed to low levels of TCDD during pre- and postnatal development.

Two reports indicate that chronic administration of low levels of TCDD to rats is associated with an increased incidence of neoplasia (IARC Monographs, 1977; Van Miller et al. 1977; Kociba et al., 1978).

Groups of 10 male Sprague-Dawley rats were fed a diet containing TCDD for 78 weeks in the following amounts (figures in parentheses are approximately weekly doses): 0, 1 ppt (0.0003 μg/kg body weight), 5 ppt (0.001 μg/kg), 50 ppt (0.01 μg/kg), 500 ppt (0.1 μg/kg), 1 ppb (0.4 μg/kg), 5 ppb (2.0 μg/kg), 50 ppb (24 μg/kg), 500 ppb (240 μg/kg), or 1000 ppb (500 μg/kg). The three highest dose levels (50, 500, and 1000 ppb) were toxic and killed all animals by the fourth week. In the six remaining test groups, the overall incidence of neoplasms was 23/60 (38%); none occurred in the 1 ppt group. In the 5 ppt group, 5/10 animals had 6 neoplasms (ear-duct carcinoma, lymphocytic leukemia, adenocarcinoma, malignant histocytoma (with metastases), angiosarcoma, Leydig-cell adenoma); the following groups also showed neoplasms: 50 ppt, 3 observed in 3/10; 500 ppt, 4 in 4/10; 1 ppb, 5 in 4/10; 5 ppb, 10 in 7/10. Neoplasms were not observed in the controls (Van Miller et al., 1977).

Groups of 100 Sprague-Dawley rats (50 males and 50 females) for two years received diets containing 0, 22, 210, or 2,200 ppt, equivalent to 0.0, 0.001, 0.01, and 0.1 μg TCDD/kg/day. Continuous ingestion of 0.001 μg/kg/day did not cause any chemically related changes in tumor incidence or toxicity; feeding with 0.01 μg/kg/day increased the incidence ($P < 0.05$) of hepatocellular hyperplastic nodules (female: 18/50 versus 8/86 controls), focal alveolar hyperplasia in the lungs, and urinary-excretion of porphyrins (female). Dietary intake of 0.1 μg/kg/day increased the incidence ($P < 0.05$) of hepatocellular carcinomas (female: 11/49 versus 1/86) and squamous-cell carcinomas of the lung (female: 7/49 versus 0/86), hard palate/nasal

turbinates (male: 4/50 versus 0/85; female: 4/49 versus 0/86), and tongue (male: 3/50 versus 0/85). Also increased in frequency by the 0.1 μg TCDD/kg/day were adenoma of the adrenal cortex (male) and hepatocellular hyperplastic nodules (female). At this dose, the incidence of certain age-related lesions was reduced (males: acinar adenoma of the pancreas; females: granulosal cell neoplasm of the ovary, benign and malignant tumors of the mammary gland, pituitary adenoma, and benign tumors of the uterus). Also, chronic administration of TCDD caused multiple toxicologic effects including increased mortality, decreased body weight gain, slight depression of certain hematologic parameters, increased urinary excretion of porphyrins and δ-aminolevulinic acid, increased serum levels of alkaline phosphatase, glutamyl transferase and serum glutamic pyruvic transaminase, and morphologic changes of the hepatic, lymphoid, respiratory, and vascular tissues of the body (Kociba et al., 1978).

These two reports show that chronic administration of TCDD causes an increased incidence of neoplasms, but not whether this substance acts as an initiator or a promoter. This consideration is particularly important because unequivocal evidence is lacking on whether TCDD is a mutagen or is metabolized to a mutagen.

Toth et al. (1978; 1979) reported on the effects of TCDD (0, 0.007, 0.7, 7.0 μg/kg) administered by gavage to male Swiss/H/Riop mice once per week for one year. Treatment was stopped and the mice were necropsied at natural death (588, 649, 633, 424 days). Total liver tumors (benign and malignant were not reported separately) increased significantly when compared to controls at the 0.7 μg/kg dose level (0, 7/38; 0.007, 13/44; 0.7, 21/44: $P < 0.01$; 7.0, 13/43). In addition, TCDD caused chronic ulcerous skin lesions (0/38, 5/44, 13/44, 25/43) followed by "generalized lethal amyloidosis" (0/38, 5/44, 10/44, 17/43).

Kouri et al. (1978) investigated the co-carcinogenic capacity of TCDD and 3-methylcholanthrene (MCA) in C57BL/6 and DBA/2 mice. TCDD (1 or 100 μg/kg) was administered by either ip or sc injection 48 hours before or at the same time as 150 μg MCA was given sc. Mice were examined weekly for injection-site tumors (fibrosarcomas) and the experiment was terminated after 36 weeks. Because MCA alone induced a high tumor incidence (29/36, 81%) in C57BL/6 mice compared to none with ip TCDD (1 or 100 μg/kg) alone,

to that with TCDD given 48 hours previously followed by MCA (16/23, 70% for the 1 μg/kg; 21/25, 84% for the 100 μg/kg), or to the combination (27/27, 100% for the 1 μg/kg; 33/43, 71% for 100 μg/kg), these results must be considered inconclusive. In the genetically "less responsive" DBA/2 mice, sc MCA produced tumors in 1/34, 3%, and 3/30, 10%; ip or sc TCDD alone or given prior to MCA caused no apparent increase in tumor incidence. However, TCDD given simultaneously with sc MCA induced significant increases in fibrosarcomas -- 1 μg/kg sc: 21/98, 21%; 100 μg/kg sc: 46/82, 56%; and 100 μg/kg ip: 17/62, 27%. These data suggest a co-carcinogenic effect of TCDD when given with MCA; but this study may have been comprised because dioxane, a known carcinogen, was used as a solvent for TCDD.

The promoter activity of TCDD for hepatocarcinogenesis was determined in female Charles-River rats partially hepatectomized and exposed to a single dose (10 mg/kg) of N-nitrosodiethylamine (diethylnitrosamine, DEN) (Pitot et al., 1980). Rats receiving only DEN and partial hepatectomy or only TCDD exhibited few enzyme-altered foci and no hepatocellular carcinomas. Partially hepatectomized groups given DEN followed by 0.14 or 1.4 μg/kg TCDD sc once every 2 weeks for seven months developed increased numbers of foci, neoplastic nodules (3/5 low dose and 1/7 high dose), and carcinomas (5/7 high dose). In comparison, phenobarbital was less effective in causing foci, but equal in producing carcinomas (8/10). These studies by Pitot et al. (1980) demonstrate that TCDD is a promoting agent for DEN-initiated hepatocarcinogenesis.

DiGiovanni et al. (1977), using the two-stage mouse skin carcinogenesis model, applied TCDD (2 μg/mouse in 0.2 ml acetone to CD-1 mice alone or 5 minutes before DMBA (2.56 μg/mouse); starting one week later, 12-O-tetradecanoylphorbol-13-acetate (TPA, 5 μg in 0.2 ml acetone) was applied twice weekly for 32 weeks. Results are given as mice with papillomas and papillomas/mouse: TCDD/TPA, 3/21 (14%), 0.1; DMBA/TPA, 12/29 (41%), 1.8; and DMBA/TCDD/TPA, 14/22 (63%), 2.2. These data suggest that TCDD alone may be a weak tumor initiator and that TCDD plus DMBA increases the tumor rate over that of DMBA alone, resembling a co-carcinogenic effect.

Berry and co-workers (1978) obtained negative skin promotion results on female CD-1 mice following an initiation dose of DMBA (200 nmol in 0.2 ml acetone) and subsequent twice weekly applications of TCDD (0.1 μg in acetone) for 30 weeks. Further, TCDD alone did not produce papillomas;

skin rashes were noted. In dose-finding experiments, TCDD increased slightly the incidence of intrafollicular epidermis (at 1 μg/mouse) and caused gastrointestinal damage (a single 2 μg application) resulting in the death of 30 percent of treated animals (numbers of animals not given).

Cohen et al. (1979) reported on an anticarcinogenic effect of TCDD (1 μg in 0.2 ml acetone) when applied to female Sencar mice 72 hours prior to skin painting with benzo(a)pyrene (B(a)P, 100 nmol) or with 7,12-dimethylbenz(a)anthracene (DMBA, 10 nmol) followed 1 week later by twice-weekly (for 15 weeks) 2 μg applications of TPA. TCDD reduced the number of DMBA-induced papillomas (and papillomas per mouse) from 28/28 (9.1) to 3/28 (0.1), and for B(a)P from 24/28 (3.8) to 7/29 (0.3).

DiGiovanni et al. (1979, 1980) investigated the inhibitory ("anti-carcinogenic") activity of TCDD on polycyclic hydrocarbon-induced skin tumorigenesis. In a preliminary report, these authors (1979) reported that TCDD inhibited the initiation of skin papillomas by DMBA and B(a)P. The more recent study (1980) analyzed the effect of treating female CD-1 or Sencar mice with single doses of TCDD (1 μg/mouse) 3 days before, 5 minutes prior to, and 1 day after application of four tumor initiators -- DMBA (10 nmol), B(a)P (100 nmol), MCA (100 nmol) (each requiring metabolic activation), and B(a)P-diol-epoxide (200 nmol) (the apparent ultimate carcinogenic form of B(a)P). One week later, TPA (3.4 nmol) was applied twice weekly for 20 weeks. TCDD applied to Sencar mice 3 days prior to DMBA, B(a)P, or MCA markedly inhibited skin papilloma induction (% of control: 2.3, 14, and 43); when given one day after the initiator, TCDD increased the incidence when compared to controls (113%, 125%, 107%). Similar inhibitory effects occurred with B(a)P-diol-epoxide: TCDD 3 days prior, 19% of control; 5 minutes before, 50%; 1 day after, 61%.

These data allow the inference that TCDD possesses a modicum capability to initiate dermal tumors, a marked inhibitory action when applied prior to initiation/promotion, and a moderate tumor promoting index when given after initiation.

Other articles summarizing the carcinogenic activity of TCDD (and dioxins) are available (Berry et al., 1979; EHP, 1973; Huff, et al., 1980; IARC, 1977; Kimbrough, 1979; Kociba et al., 1979; McConnell, 1980).

Other long-term carcinogenesis studies on the "dioxins" that have been completed or are ongoing within the National Toxicology Program are summarized in the following paragraphs.

Dibenzo-p-dioxin, in diets containing 5,000 or 10,000 ppm, was fed to groups of 35 male and female Osborne-Mendel rats for 100-117 weeks and to groups of 50 male and female B6C3F1 mice for 91-97 weeks (NCI/NTP, 1979). No compound-related carcinogenic effects were observed. The 10,000 ppm male rats and the 5,000 and 10,000 ppm female rats had an increased incidence of fatty metamorphosis in the liver.

2,7-Dichlorodibenzo-p-dioxin was added to diets of Osborne-Mendel rats (110-117 weeks) and B6C3F1 mice (91-101 weeks) at levels of 5,000 or 10,000 ppm (NCI/NTP, 1979a). Under these conditions, 2,7-dichlorodibenzo-p-dioxin was considered to be not carcinogenic for male and female Osborne-Mendel rats or female B6C3F1 mice. For male B6C3F1 mice the combined incidences of leukemia (0/50, 3/50, 1/45) and lymphoma (0/50, 4/50, 2/45) show a significantly increased rate for the low-dose groups (0/50 versus 7/50, P=0.006); hepatocellular adenomas were significantly increased in the low- and high-dose groups when compared with the controls (4/49, 15/50: P=0.005, 12/42: P=0.011); and when the hepatocellular carcinomas (4/49, 5/50, 5/42) are added the combined tumor incidences when compared to controls were also significantly increased (8/49, 20/50: P=0.008, 17/40: P=0.010). These data support the conclusion that 2,7-dichlorodibenzo-p-dioxin was carcinogenic for male B6C3F1 mice.

A mixture of hexachlorodibenzo-p-dioxins (31% 1,2,3,6,7,8- and 67% 1,2,3,7,8,9-) was given by gavage twice per week for 104 weeks to Osborne-Mendel rats and B6C3F1 mice (NCI/NTP, 1980a). HCDD doses were 0, 1.25, 2.5, or 5 μg/kg/wk for rats and male mice and 0, 2.5, 5, or 10 μg/kg/wk for female mice. No compound-related tumors were observed in male rats; however, toxic hepatitis was observed in these animals: 0/24, 28/49, 35/50, and 34/48. HCDD induced a significantly increased incidence of neoplastic nodules in female rats when compared to vehicle controls (5/75, 10/50: P=0.026, 12/50: P=0.006, 30/50: $P < 0.001$); hepatocellular carcinoma occurred only in the high dose group (4/50). Toxic hepatitis was increased significantly in the female rats as well: 0/25, 33/50, 37/50, 44/50. In mice, the

incidence of hepatocellular adenomas increased in the high dose groups (male--7/73, 5/50, 9/49, 15/48: P=0.003; female--2/73, 4/48, 4/47, 9/47: P=0.003). The observed incidences of hepatocellular carcinomas were not significantly different from vehicle controls (male: 8/73, 9/50, 5/49, 9/48; female: 1/73, 0/48, 2/47, 2/47). When these liver tumors are combined, dose-related trends remain and significant increases are recorded for the high-dose groups (male: 15/73, 14/50, 14/49, 24/48: P=0.001; female: 3/73, 4/48, 6/47, 10/47: P=0.004).

A separate skin-painting (dermal application) study using the same hexachlorodibenzo-p-dioxin mixture was conducted with Swiss-Webster mice (NCI/NTP, 1980b). No compound-induced carcinogenic effect was observed following 104 weeks exposure to 0.01 μg HCDD (suspended in 0.1 ml acetone) thrice weekly.

A companion skin-painting investigation (NTP, 1981) was conducted with the gavage study (the subject of this report). TCDD (in 0.1 ml acetone) was applied to female Swiss-Webster mice (0.005 μg) and to male mice (0.001 μg) three times per week for 99-104 weeks. A significantly increased incidence of fibrosarcomas of the integumentary system was observed for females (2/41, 5%; 8/27, 30%: P=0.01); an increase was recorded for male mice as well, although it was not statistically significant (3/42, 7%; 6/28, 21%: P=0.084). Nonetheless, the increased rate in males may have been associated with the skin application of TCDD.

TCDD and other dioxins were selected as a class for testing in the early 1970's following reports that TCDD was a contaminant in 2,4,5-T, which was shown to be teratogenic in rats, and because human exposure to 2,4,5-T (containing dioxin) was widespread.

II. MATERIALS AND METHODS

A. Chemical

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) -- CAS No. 1746-01-6--was synthesized in the Chemistry Division of IITRI, Chicago, Illinois, by the condensation of potassium 2,4,5-trichlorophenate in the presence of the Ullman copper catalyst as described in Appendix E. IITRI reported the purity to be 99.4%, based on results of gas chromatographic analysis of the chemical. Samples analyzed at Dow Chemical Company, Midland, Michigan, were found to contain less than 1% of two impurities, tentatively identified as a trichlorodibenzo-p-dioxin and a pentachlorodibenzo-p-dioxin. The presence of 0.1% to 0.2% hexachlorodibenzo-p-dioxin was detected by gas chromatography and mass spectrometry (Stehl, 1974).

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

B. Dosage Preparation

TCDD is insoluble in corn oil and in most other solvents but is partially soluble in acetone. Therefore, TCDD was administered as a suspension in a 9:1 corn oil-acetone solution. Fresh stock suspensions in acetone (Mallinkrodt, Inc., St. Louis, MO) containing 10.0 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, and suitable aliquots were added to corn oil (Tek-Lad Laboratories, Madison, WI) and to additional acetone to give the desired concentrations of the test chemical in 9:1 corn oil-acetone. The working suspensions were administered to rats at a volume of 0.05 ml/100 g body weight and 0.05 ml/10 g body weight to mice.

The suspensions of TCDD 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.

The concentration of the TCDD in the stock suspensions in acetone was determined by analyzing samples when the stock suspensions were freshly prepared and at the end of the 3-month periods of use (Appendix F). The mean concentration of 20 determinations containing a theoretical level of 10.0 μg/ml was 12.1 (±3.6) μg/ml. The range was 6.9 to 15.7 μg/ml. Concentrations of TCDD in suspensions prepared in the corn oil-acetone vehicle could not be determined 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 of age 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. The ages of all animals at the time that they were put on test were the same. All animals were dosed or observed for the same number of weeks regardless of shipment or start date.

D. Animal Maintenance

Rats and mice were housed in rooms maintained at 20° to 22°C and 45% to 55% relative humidity with 15 changes of room air per hour. Negative air pressure in the animal rooms relative to the hallway was maintained. 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.

Animals were maintained in sealed, individually ventilated cages to ensure containment of the test chemical. Rats were housed 3 per cage and mice 10 per cage in polystyrene cages (Table 1) 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 of individually vented cages provided a constant flow of air that was filtered as it entered and as it left the cages to prevent the release of the test chemical from the cages into the room.

The cages (including lids) housing the groups of animals dosed with TCDD were discarded after 1 week of use. The polystyrene lids were changed once a month. 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.® (Table 1) to dilute out any dioxin present, and were then sanitized at 82°C in an automatic washer. The polycarbonate cages in the room housing the vehicle-control groups of animals were recycled 3 times and incinerated. The corresponding water bottles and sipper tubes used in these rooms were not rinsed in chlorothene before washing.

Disposable clothing was worn by all personnel and, after use, was incinerated by the procedure used for cages and other waste material. Respirators were worn in the animal rooms. All dosing of animals was carried out in hoods.

Animals were provided with fresh hardwood chip bedding once a week (Table 1). They were fed Wayne® Lab Blox (Table 1) 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.

Table 1. Specifications and Sources of Materials Used for Animal Maintenance

Item	Specifications	Manufacturer or Supplier
Cages	19"x10.5"x8"	Maryland Plastics Federalsburg, MD
Chlorothene N. U.®	A formulation of 1,1,1-trichloroethane	Central Solvents Chicago, IL
Feed	Wayne® Lab Blox, Pellets	Allied Mills Inc. Chicago, IL
Bedding	Absorb-Dri® hardwood chips	Lab Products, Inc. Garfield, NJ

E. Acute Studies

In acute toxicity studies, groups of four rats of either sex and groups of five mice of either sex were administered a single dose of TCDD by gavage. The rats were observed for 11 weeks and the mice for 16 weeks to determine possible delayed toxicity. Doses administered and survival of rats and mice are presented in Table 2; no deaths occurred among the mice.

The oral LD_{50} was estimated to be 165 μg/kg for male rats, 125 μg/kg for female rats, and greater than 200 μg/kg for the mice of either sex.

F. Subchronic Studies

Thirteen-week subchronic gavage studies were conducted to determine the doses of test chemical to be used in the chronic studies. Groups of 10 male and 10 female 6-week-old rats and mice were administered TCDD in corn oil-acetone by gavage twice per week for 13 weeks at one of several doses and were killed at week 15; control groups were administered the corn oil-acetone vehicle alone. The animals were weighed every week for the first 7 or 8 weeks and every 2 weeks thereafter; also, they were observed daily for deaths. The doses administered, the survival of animals in the control and dosed groups, and the mean body weights of the dosed groups relative to the control groups are given in Tables 3 and 4.

Necropsies and histologic examinations of tissues were performed at week 15 on all male rats administered 1 μg/kg/wk, all male mice administered 20 μg/kg/wk, nine female mice administered 20 μg/kg/wk, and one to five rats or mice in other dosed groups. Necropsies and tissue examinations were also performed on animals that died during the test.

A dose-related decrease in weight gain was observed in the rats. Deaths occurred in rats administered 4 or 8 μg/kg/wk. The two male rats administered 4 μg/kg/wk that died and the five females administered 4 or 8 μg/kg/wk that died all had severe toxic hepatitis. Among the survivors, almost all of the male and female rats administered 1 to 8 μg/kg/wk that were examined had hepatic lesions; 2/2 males administered 0.5 μg/kg/wk had normal livers; and 1/1 female administered 0.5 μg/kg/wk had threshold hepatotoxic effects. In the mice, weight gain was not affected adversely at

Table 2. Doses and Survival in Rats and Mice Administered a Single Dose of TCDD by Gavage Followed by 11 or 16 Weeks Observation

Dose (μg/kg)	Survival(a)			
	Osborne-Mendel Rats		B6C3F1 Mice	
	Male	Female	Male	Female
50	4/4	4/4	5/5	5/5
75	4/4	3/4	5/5	5/5
100	4/4	3/4	5/5	5/5
150	0/4	0/4	5/5	5/5
200	2/4	0/4	5/5	5/5

(a) Number of animals surviving/number of animals in group.

Table 3. Doses, Survival, and Mean Body Weights of Rats Administered TCDD by Gavage for 13 Weeks

Dose (μg/kg/wk)	Male		Female	
	Survival (a)	Mean Weight at Week 6 as % of Control (b)	Survival (a)	Mean Weight at Week 6 as % of Control (b)
0	10/10	100	10/10	100
0.5	10/10	103	10/10	94
1	10/10	94	10/10	91
2	10/10	95	10/10	95
4	8/10	80	9/10	95
8	10/10	79	6/10	84

(a) Number surviving at week 15/number in group.
(b) Data at week 6 were used because data obtained at later dates were incomplete. Weight change relative to controls was not calculated because data for initial body weights were incomplete.

Table 4. Doses, Survival, and Mean Body Weights of Mice Administered TCDD by Gavage for 13 Weeks

Dose (μg/kg/wk)	Male		Female	
	Survival (a)	Mean Weight at Week 12 as % of Control (b)	Survival (a)	Mean Weight at Week 12 as % of Control (b)
0	10/10	100	10/10	100
1	10/10	93	10/10	119
2	10/10	102	10/10	123
5	10/10	102	10/10	126
10	9/10(c)	101	10/10	124
20	9/10	101	9/10	118

(a) Number surviving at week 15/number in group.
(b) Data at week 12 were analyzed because data at week 15 were incomplete. Weight change relative to controls was not calculated because data for initial body weights were incomplete.
(c) Death of the male at 10 μg/kg/wk was attributed to bronchopneumonia.

any dose of TCDD, and deaths attributable to TCDD occurred only in animals administered 20 μg/kg/wk. Hepatic lesions were found in all of the surviving dosed male mice that were examined. Hepatic lesions were found in all surviving female mice administered 20 μg/kg/wk, in 1/2 female mice administered 10 μg/kg/wk, and in 2/2 female mice administered 5 μg/kg/wk. No hepatic lesions were observed in the female mice administered 1 or 2 μg/kg/wk.

Because of the hepatotoxic effects observed in the subchronic studies, the doses selected for rats for the chronic study were 0.01, 0.05, and 0.5 μg/kg/wk (designated in this report as "low," "mid," and "high" doses). Doses selected for mice were 0.01, 0.05, and 0.5 μg/kg/week for males and 0.04, 0.2, and 2.0 μg/kg/week for females.

G. Chronic Studies

The test groups, doses administered, and durations of the chronic gavage studies in rats and mice are shown in Tables 5 and 6. Animals dosed with TCDD were housed in one room with untreated control group No. 1. Three vehicle control groups were housed in a second room with untreated control group No. 2. The vehicle control groups of each sex and species were shared with a gavage study of HCDD (a mixture of 1,2,3,6,7,8,- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxins) 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.

Table 5. Design for Chronic TCDD Gavage Studies in Rats

Sex and Test Group	Initial(a) No. of Animals	Room	TCDD(b) Dose (μg/kg/wk)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Males					
Untreated-Control No. 1	25	1A6	0		106
Untreated-Control No. 2	25	1C9	0		106
Untreated-Control No. 3(c)	25	1B3	0		106
Vehicle-Controls(d),(e),(f)	75	1C9	0		105
Low-Dose	50	1A6	0.01	104	3
Mid-Dose	50	1A6	0.05	104	3
High-Dose	50	1A6	0.5	104	3
Females					
Untreated-Control No. 1	25	1A6	0		106
Untreated-Control No. 2	25	1C9	0		106
Untreated-Control No. 3(c)	25	1B3	0		106
Vehicle-Controls(d,e,f)	75	1C9	0		105
Low-Dose	50	1A6	0.01	104	3
Mid-Dose	50	1A6	0.05	104	3
High-Dose	50	1A6	0.5	104	3

(a) Rats from five different shipments were evenly distributed among all test and control groups. Regardless of the start date, all rats were dosed or observed for the same length of time.
(b) TCDD was administered 2 days per week (Tuesday and Friday) as a suspension in 9:1 corn oil-acetone at a volume of 0.05 ml/100 g body weight.
(c) Untreated-control No. 3 was an environmental control for the room in which studies on HCDD 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.
(f) Vehicle-controls were shared with a gavage study on HCDD carried out in a different room.

Table 6. Design for Chronic TCDD Gavage Studies in Mice

Sex and Test Group	Initial(a) No. of Animals	Room	TCDD(b) Dose (μg/kg/wk)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Males					
Untreated-Control No. 1	25	1A6	0	0	107
Untreated-Control No. 2	25	1C9	0	0	107
Untreated-Control No. 3(c)	25	1B3	0	0	107
Vehicle-Controls(d),(e),(f)	75	1C9	0	0	105
Low-Dose	50	1A6	0.01	104	3
Mid-Dose	50	1A6	0.05	104	3
High-Dose	50	1A6	0.5	104	3
Females					
Untreated-Control No. 1	25	1A6	0		108
Untreated-Control No. 2	25	1C9	0		108
Untreated-Control No. 3(c)	25	1B3	0		108
Vehicle-Controls (d,e,f)	75	1C9	0		106
Low-Dose	50	1A6	0.04	104	3
Mid-Dose	50	1A6	0.2	104	3
High-Dose	50	1A6	2.0	104	3

(a) Mice from three different shipments were evenly distributed among all test and control groups. Regardless of the start date, all mice were dosed or observed for the same length of time.
(b) TCDD was administered 2 days per week (Monday and Thursday) 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 HCDD 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.
(f) Vehicle-controls were shared with a gavage study on HCDD carried out in a different room.

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, urinary bladder, ovary or testis, prostate (male), adrenal, 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 according to the method of Cox (1972) for testing each dosed group with the control group for equality and Tarone's (1975) extentions of Cox's methods for testing 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 statistical analyses of tumor incidence 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 to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.017 (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.

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. The methods of Cox and of Tarone were used for the statistical tests of the groups. The statistical tests were one-tailed.

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

relationship. This method also provides a two-tailed test of departure from linear trend.

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 the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that, in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result 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 the test chemical might induce tumors that 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 high-dose groups of rats were lower than those of the corresponding controls after week 55 in males and after week 45 in females (Figure 1). No other clinical signs were observed.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered TCDD 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 TCDD 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 all the other groups. The result of the Tarone test for positive dose-related trend in the survival of rats over the period of the bioassay is not significant in either sex.

In male rats, 23/50 (46%) of the pooled untreated control group, 29/75 (39%) of the pooled vehicle-control group, 17/50 (34%) of the low-dose group, 20/50 (40%) of the mid-dose group, and 19/50 (38%) of the high-dose group lived to the end of the experiment at 105-108 weeks.

In female rats, 29/50 (58%) of the pooled untreated control group, 39/75 (52%) of the pooled vehicle-control group, 29/50 (58%) of the low-dose, 34/50 (68%) of the mid-dose, and 32/50 (64%) of the high-dose group lived to the end of the experiment at 105-107 weeks.

A sufficient number of rats of each sex was at risk for the development of late-appearing tumors.

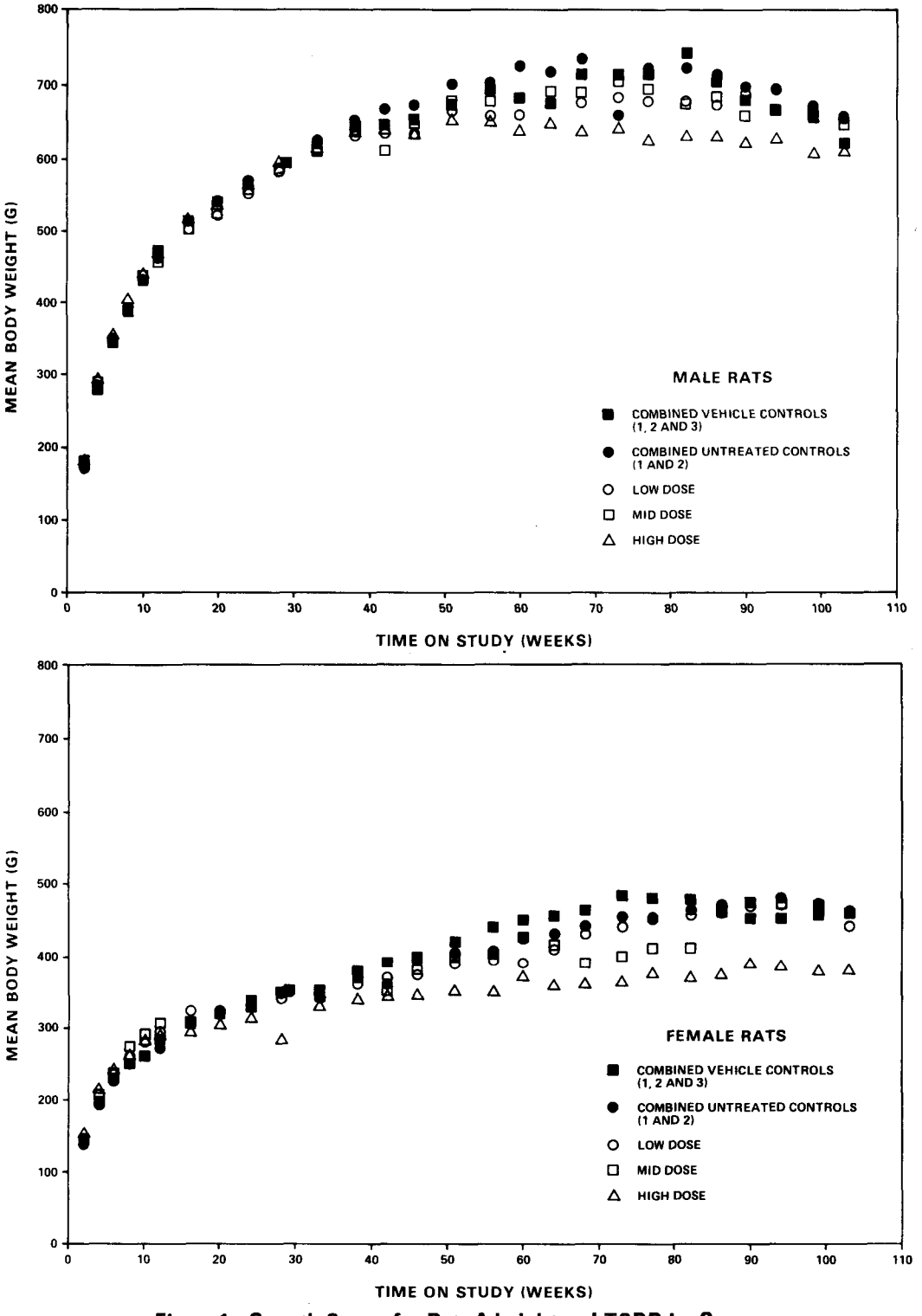


Figure 1. Growth Curves for Rats Administered TCDD by Gavage

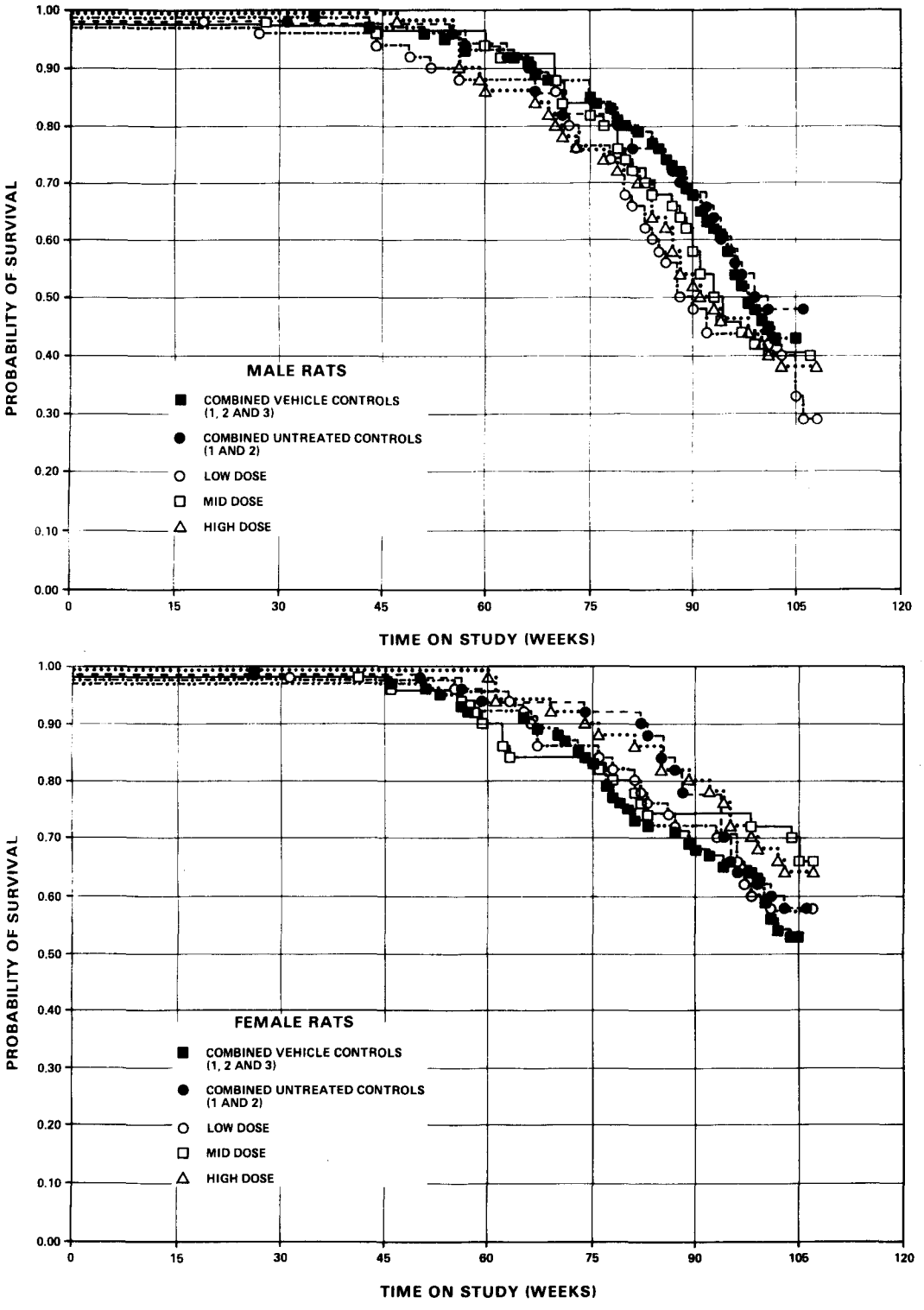


Figure 2. Survival Curves for Rats Administered TCDD by Gavage

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are tabulated in Appendix A, Tables A1 and A2; and nonneoplastic lesions are tabulated in Appendix C, Tables C1 and C2. Treated groups, vehicle controls, and untreated controls are separately tabulated and summarized.

A variety of neoplasms were seen in dosed and control Osborne-Mendel rats and, except for those of the liver and thyroid, the tumors did not appear to be related to chemical administration. The incidences of liver and thyroid neoplasms are shown in Table 7 and Table 8, respectively. The neoplastic nodules of the liver in dosed rats were usually composed of large eosinophilic cells. The carcinomas were trabecular and no metastases were found.

Toxic hepatitis was frequently found in the high-dose rats of either sex. It was characterized by central, midzonal, and often peripheral lipidosis (lipoidosis) and hydropic degeneration of the cytoplasm of the hepatocytes. In addition, proliferation of periportal bile ductules and mild fibrosis were a common finding. Foci of cellular alteration of the eosinophilic and clear cell type were seen in many high-dose rats.

The thyroid adenomas were well circumscribed follicular lesions. Carcinomas invaded the capsule or adjacent tissues.

A variety of nonneoplastic lesions were seen in tissues other than the liver or thyroid. None appeared to be related to TCDD administration.

The results of histopathologic examination indicated that, under the conditions of this bioassay, TCDD was carcinogenic in Osborne-Mendel rats, inducing hepatocellular tumors in females and thyroid tumors in males.

D. Statistical Analyses of Results (Rats)

Tables 9 and 10 contain the statistical analyses 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; however, data on the untreated-control groups are presented in the appendixes.

Table 7. Numbers of Rats with Lesions of the Liver

	Males					Females				
	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose
Number of Livers Examined	50	74	50	50	50	49	75	49	50	49
Neoplastic Nodule	0	0	0	0	3	0	5	1	3	12
Hepatocellular carcinoma	0	0	0	0	1	0	0	0	0	3
Toxic Hepatitis	0	0	1	0	14	0	0	0	1	32

Table 8. Numbers of Rats with Follicular-Cell Neoplasms of the Thyroid

	Males					Females				
	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose
Number of Thyroids Examined	49	69	48	50	50	49	73	45	49	47
Follicular:										
Adenoma	4	1	5	6	10	0	3	2	1	6
Carcinoma	1	0	0	2	1	0	2	0	0	0

The Cochran-Armitage test indicates dose-related trends in the incidence of animals with follicular-cell adenomas or carcinomas in the thyroid of male rats (P=0.005). The incidences in the mid-dose group and the high-dose group were significantly higher (P=0.004 and P<0.001, respectively) than those in the control group. The historical incidence in male Osborne-Mendel untreated control rats from all laboratories is 22/470 (5%)--lower than the incidences observed in each of the dosed groups (5/48, 10%; 8/50, 16%; and 11/50, 22%, respectively). The incidence in the untreated control group (5/49, 10%) is lower than the mid- and high-dose incidences. No historical data were available on vehicle-control groups administered corn oil plus acetone.

In female rats, a dose-related trend was observed in the incidence of animals with follicular-cell adenomas of the thyroid (P=0.022), but the Fisher exact tests are not significant. The incidences of females with either follicular cell adenomas or carcinomas are not significant for any of the tests.

The incidence of female rats with neoplastic nodules or hepatocellular carcinomas in the liver occured in a dose-related trend (P<0.001) and with a significantly higher incidence (P=0.001) among high-dose animals. The results of the test for the time to observation of tumors indicate no significant difference between the time of observation of these tumors in the vehicle-control group and in each of the dosed groups. The incidence of neoplastic nodules in untreated control groups 1 and 2 (Appendix A, Table A4) is lower than that of the vehicle control groups in this study (5/75, 7%). The historical incidence in the bioassay program of neoplastic nodules or hepatocellular carcinomas is 5/270(2%) in untreated Osborne-Mendel female rats and 18/470(2%) in corn oil vehicle controls. A similar positive dose-related trend was observed in males (P=0.005), but the results of the Fisher exact test are not significant.

The Cochran-Armitage test indicates a significant (P=0.010) dose-related trend in the incidence of male rats with fibromas in the subcutaneous tissue. The incidence in the high-dose group is also higher (P=0.048) than in the controls, but the P=0.048 is above the significance level of 0.017 required overall for a significance of 0.05 when the

Bonferroni inequality criterion is applied to compare three dosed groups with a single control group.

In female rats, the incidences of fibrosarcomas in the subcutaneous tissue of the high-dose group and adenomas in the pituitary of the low-dose group were higher (P=0.023 and P=0.044, respectively) than those in the controls. The significance observed in each of the two instances is above the level of 0.017 required by the Bonferroni multiple comparison criterion for overall significance of 0.05 when three dosed groups are compared with a single control group.

In males, the incidence of cortical adenomas in the adrenal was significantly higher (P=0.015) in the mid-dose group than in the control group, but a dose-related trend was not observed and the high-dose group incidence was not significantly higher than that of the controls. A dose-related trend (P=0.014) was observed in the incidence of females with adenomas, or with carcinomas or adenomas in the adrenal. The high-dose group incidence is higher (P=0.039) than that in the controls, but it is above the level of significance for the Bonferroni criterion.

The Cochran-Armitage test indicates departures from linear trend in the incidences of adenocarcinomas in the mammary gland of males and of chromophobe adenomas of the pituitary and astrocytomas in the brain of females that are not supported by Fisher exact tests.

The results of statistical analyses indicate that the incidences of thyroid tumors in male rats and of liver tumors in females are related to the administration of TCDD.

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

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Subcutaneous Tissue:				
Fibroma (b)	3/75(4)	1/50(2)	3/50(6)	7/50(14)
P Value (c), (d)	P=0.010	N.S.	N.S.	P=0.048
Relative Risk (e)		0.500	1.500	3.500
Lower Limit		0.010	0.208	0.841
Upper Limit		5.995	10.741	20.018
Weeks to First Observed Tumor	75	107	93	70
Subcutaneous Tissue:				
Fibrosarcoma (b)	9/75(12)	3/50(6)	3/50(6)	3/50(6)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.500	0.500	0.500
Lower Limit		0.090	0.090	0.090
Upper Limit		1.883	1.883	1.883
Weeks to First Observed Tumor	64	104	84	71
Subcutaneous Tissue:				
Fibroma or Fibrosarcoma (b)	12/75(16)	4/50(8)	5/50(10)	10/50(20)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.500	0.625	1.250
Lower Limit		0.123	0.182	0.521
Upper Limit		1.538	1.770	2.892
Weeks to First Observed Tumor	64	104	84	70

Table 9. Analyses of the Incidence of Primary Tumors in Male Rats Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Circulatory System:				
Hemangiosarcoma (b)	4/75(5)	3/50(6)	0/50(0)	4/50(8)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.125	0.000	1.500
Lower Limit		0.171	0.000	0.291
Upper Limit		6.340	1.622	7.665
Weeks to First Observed Tumor	75	78	--	56
Circulatory System:				
Hemangioma or Hemangiosarcoma (b)	7/75(9)	3/50(6)	1/50(2)	4/50(8)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.643	0.214	0.857
Lower Limit		0.111	0.005	0.192
Upper Limit		2.657	1.588	3.172
Weeks to First Observed Tumor	75	78	90	56
Liver:				
Neoplastic Nodule (b)	0/74(0)	0/50(0)	0/50(0)	3/50(6)
P Value (c), (d)	P=0.005	N.S.	N.S.	N.S.
Relative Risk (e)		--	--	Infinite
Lower Limit		--	--	0.883
Upper Limit		--	--	Infinite
Weeks to First Observed Tumor	--	--	--	79

Table 9. Analyses of the Incidence of Primary Tumors in Male Rats Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Liver:				
Neoplastic Nodule or Hepatocellular Carcinoma (b)	0/74(0)	0/50(0)	0/50(0)	3/50(6)(f)
P Value (c), (d)	P=0.005	N.S.	N.S.	N.S.
Relative Risk (e)		--	--	Infinite
Lower Limit		--	--	0.883
Upper Limit		--	--	Infinite
Weeks to First Observed Tumor	--	--	--	79
Pituitary:				
Adenoma,NOS(b)	0/61(0)	1/43(2)	2/43(5)	3/40(8)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite	Infinite
Lower Limit		0.076	0.418	0.914
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	104	89	84
Pituitary:				
Adenoma,NOS or Chromophobe Adenoma (b)	2/61(3)	1/43(2)	3/43(7)	3/40(8)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.709	2.128	2.288
Lower Limit		0.012	0.254	0.273
Upper Limit		13.134	24.489	26.248
Weeks to First Observed Tumor	79	104	70	84

Table 9. Analyses of the Incidence of Primary Tumors in Male Rats Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Adrenal:				
Cortical Adenoma (b)	6/72(8)	9/50(18)	12/49(24)	9/49(18)
P Value (c), (d)	N.S.	N.S.	P=0.015	N.S.
Relative Risk (e)		2.160	2.939	2.204
Lower Limit		0.732	1.097	0.748
Upper Limit		6.886	8.849	7.018
Weeks to First Observed Tumor	87	72	70	84
Adrenal:				
Pheochromocytoma (b)	5/72(7)	0/50(0)	1/49(2)	1/49(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	0.294	0.294
Lower Limit		0.000	0.006	0.006
Upper Limit		1.144	2.507	2.507
Weeks to First Observed Tumor	104	--	93	84
Thyroid:				
Follicular Cell Adenoma (b)	1/69(1)	5/48(10)	6/50(12)	10/50(20)
P Value (c), (d)	P=0.006	P=0.042	P=0.021	P=0.001
Relative Risk (e)		7.188	8.280	13.800
Lower Limit		0.838	1.049	2.064
Upper Limit		332.277	372.459	584.189
Weeks to First Observed Tumor	104	56	90	77

Table 9. Analyses of the Incidence of Primary Tumors in Male Rats Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Thyroid:				
Follicular-Cell Adenoma or Carcinoma (b)	1/69(1)	5/48(10)	8/50(16)	11/50(22)
P Value (c), (d)	P=0.005	P=0.042	P=0.004	P<0.001
Relative Risk (e)		7.188	11.040	15.180
Lower Limit		0.838	1.551	2.322
Upper Limit		332.277	478.431	636.936
Weeks to First Observed Tumor	104	56	89	77
Thyroid:				
C-Cell Adenoma (b)	2/69(3)	2/48(4)	4/50(8)	4/50(8)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.438	2.760	2.760
Lower Limit		0.107	0.412	0.412
Upper Limit		19.168	29.468	29.468
Weeks to First Observed Tumor	79	105	84	67
Thyroid:				
C-Cell Adenoma or Carcinoma (b)	2/69(3)	2/48(4)	5/50(10)	4/50(8)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.438	3.450	2.760
Lower Limit		0.107	0.590	0.412
Upper Limit		19.168	34.963	29.468
Weeks to First Observed Tumor	79	105	84	67

Table 9. Analyses of the Incidence of Primary Tumors in Male Rats Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Parathyroid:				
Adenoma, NOS (b)	0/20(0)	2/41(5)	1/40(3)	1/36(3)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite	Infinite
Lower Limit		0.150	0.028	0.031
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	80	88	103
Pancreatic Islets:				
Islet Cell Adenoma (b)	2/70(3)	2/49(4)	3/48(6)	1/50(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.429	2.188	0.700
Lower Limit		0.106	0.259	0.012
Upper Limit		19.061	25.288	13.029
Weeks to First Observed Tumor	96	80	81	70
Mammary Gland:				
Adenocarcinoma, NOS(b)	0/75(0)	0/50(0)	3/50(6)	1/50(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend (g)	P=0.027			
Relative Risk (e)		--	Infinite	Infinite
Lower Limit		--	0.895	0.080
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	101	70

Table 9. Analyses of the Incidence of Primary Tumors in Male Rats Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Mammary Gland:				
Fibroadenoma (b)	5/75(7)	0/50(0)	1/50(2)	0/50(0)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	0.300	0.000
Lower Limit		0.000	0.006	0.000
Upper Limit		1.192	2.562	1.192
Weeks to First Observed Tumor	91	--	104	--

(a) Dosed groups received doses of 0.01, 0.05, or 0.5 μg/kg by gavage.
(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) One high-dose animal was reported to have both a neoplastic nodule and a hepatocellular carcinoma.
(g) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

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

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Subcutaneous Tissue:				
Fibroma (b)	4/75(5)	0/50(0)	0/50(0)	1/49(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	0.000	0.383
Lower Limit		0.000	0.000	0.008
Upper Limit		1.622	1.622	3.704
Weeks to First Observed Tumor	77	--	--	85
Subcutaneous Tissue:				
Fibrosarcoma (b)	0/75(0)	2/50(4)	3/50(6)	4/49(8)
P Value (c), (d)	N.S.	N.S.	N.S.	P=0.023
Relative Risk (e)		Infinite	Infinite	Infinite
Lower Limit		0.440	0.895	1.407
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	55	58	95
Subcutaneous Tissue:				
Fibroma or Fibrosarcoma (b)	4/75(5)	2/50(4)	3/50(6)	5/49(10)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.750	1.125	1.193
Lower Limit		0.070	0.172	0.431
Upper Limit		5.001	6.340	9.153
Weeks to First Observed Tumor	77	55	58	85

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

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Liver:				
Neoplastic Nodule(b)	5/75(7)	1/49(2)	3/50(6)	12/49(24)
P Value (c), (d)	P<0.001	N.S.	N.S.	P=0.006
Relative Risk (e)		0.306	0.900	3.673
Lower Limit		0.007	0.145	1.290
Upper Limit		2.612	4.391	12.419
Weeks to First Observed Tumor	90	104	106	85
Liver:				
Neoplastic Nodule or Hepatocellular Carcinoma (b)	5/75(7)	1/49(2)	3/50(6)	14/49(29)(f)
P Value (c), (d)	P<0.001	N.S.	N.S.	P=0.001
Relative Risk (e)		0.306	0.900	4.286
Lower Limit		0.007	0.145	1.568
Upper Limit		2.612	4.391	14.133
Weeks to First Observed Tumor	90	104	106	61
Pituitary:				
Adenoma,NOS(b)	1/66(2)	5/47(11)	2/44(5)	3/43(7)
P Value (c), (d)	N.S.	P=0.044	N.S.	N.S.
Relative Risk (e)		7.021	3.000	4.605
Lower Limit		0.820	0.161	0.383
Upper Limit		324.354	172.867	235.886
Weeks to First Observed Tumor	104	76	104	99

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

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Pituitary:				
Chromophobe Adenoma (b)	5/66(8)	0/47(0)	0/44(0)	1/43(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend (g)	P=0.025			
Relative Risk (e)		0.000	0.000	0.307
Lower Limit		0.000	0.000	0.007
Upper Limit		1.114	1.187	2.603
Weeks to First Observed Tumor	92	--	--	105
Pituitary:				
Adenoma, NOS, or				
Chromophobe Adenoma (b)	6/66(9)	5/47(11)	2/44(5)	4/43(9)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.170	0.500	1.023
Lower Limit		0.298	0.051	0.223
Upper Limit		4.311	2.635	4.033
Weeks to First Observed Tumor	92	76	104	99
Adrenal:				
Cortical Adenoma (b)	11/73(15)	8/49(16)	4/49(8)	13/46(28)
P Value (c), (d)	P=0.019	N.S.	N.S.	N.S.
Relative Risk (e)		1.083	0.542	1.875
Lower Limit		0.405	0.132	0.845
Upper Limit		2.723	1.704	4.178
Weeks to First Observed Tumor	77	65	83	85

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

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Adrenal:				
Cortical Adenoma or Adenoma NOS (b)	11/73(15)	8/49(16)	4/49(8)	14/46(30)
P Value (c), (d)	P=0.008	N.S.	N.S.	P=0.039
Relative Risk (e)		1.083	0.542	2.020
Lower Limit		0.405	0.132	0.931
Upper Limit		2.723	1.704	4.430
Weeks to First Observed Tumor	77	65	83	85
Adrenal:				
Cortical Adenoma, or Carcinoma or Adenoma, NOS (b)	11/73(15)	9/49(18)	5/49(10)	14/46(30)
P Value (c), (d)	P=0.014	N.S.	N.S.	P=0.039
Relative Risk (e)		1.219	0.677	2.020
Lower Limit		0.480	0.195	0.931
Upper Limit		2.971	1.963	4.430
Weeks to First Observed Tumor	77	65	83	85
Thyroid:				
Follicular-Cell Adenoma (b)	3/73(4)	2/45(4)	1/49(2)	6/47(13)
P Value (c), (d)	P=0.022	N.S.	N.S.	N.S.
Relative Risk (e)		1.081	0.497	3.106
Lower Limit		0.093	0.010	0.697
Upper Limit		9.032	5.949	18.288
Weeks to First Observed Tumor	90	105	104	95

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

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Thyroid:				
Follicular Cell Adenoma or Carcinoma (b)	5/73(7)	2/45(4)	1/49(2)	6/47(13)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control) (e)		0.649	0.298	1.864
Lower Limit		0.064	0.006	0.500
Upper Limit		3.755	2.542	7.259
Weeks to First Observed Tumor	90	105	104	95
Thyroid:				
C-Cell Adenoma (b)	7/73(10)	1/45(2)	8/49(16)	6/47(13)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.232	1.703	1.331
Lower Limit		0.005	0.575	0.391
Upper Limit		1.709	5.134	4.314
Weeks to First Observed Tumor	77	106	81	95
Thyroid:				
C-Cell Adenoma or Carcinoma (b)	7/73(10)	3/45(7)	8/49(16)	6/47(13)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.695	1.703	1.331
Lower Limit		0.121	0.575	0.391
Upper Limit		2.858	5.134	4.314
Weeks to First Observed Tumor	77	97	81	95

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

	Vehicle Control	Low Dose	Medium Dose	High Dose
Mammary Gland:				
Adenocarcinoma, NOS (b)	3/75(4)	3/50(6)	2/50(4)	1/49(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.500	1.000	0.510
Lower Limit		0.208	0.086	0.010
Upper Limit		10.741	8.386	6.113
Weeks to First Observed Tumor	74	31	41	76
Mammary Gland:				
Fibroadenoma (b)	27/75(36)	20/50(40)	21/50(42)	17/49(35)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.111	1.167	0.964
Lower Limit		0.665	0.708	0.552
Upper Limit		1.797	1.866	1.613
Weeks to First Observed Tumor	51	76	56	60
Brain:				
Astrocytoma(b)	0/75(0)	3/47(6)	0/49(0)	0/48(0)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Departure From Linear Trend (g)	P=0.006			
Relative Risk (e)		Infinite	--	--
Lower Limit		0.952	--	--
Upper Limit		Infinite	--	--
Weeks to First Observed Tumor	--	104	--	--

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

(continued)

(a) Dosed groups received doses of 0.01, 0.05, or 0.5 μg/kg by gavage.
(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) One high-dose animal was reported to have both a neoplastic nodule and a hepatocellular carcinoma.
(g) The probability level for departure from linear trend is given when P is less 0.05 than for any comparison.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of dosed mice of either sex were comparable with the corresponding vehicle controls throughout the bioassay. After week 25, mean body weights of dosed and vehicle control mice of either sex were lower than the corresponding untreated controls (Figure 3). No other clinical signs were reported.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered TCDD 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 TCDD-dosed group were pooled into one group. The three vehicle-control groups were pooled into one vehicle-control group.

The result of the Tarone test for positive dose-related trend in mortality is not significant in either sex.

In male mice, 30/50 (60%) of the pooled untreated-control group, 38/74 (51%) of the pooled vehicle-control group, 30/50 (60%) of the low-dose group, 31/50 (62%) of the mid-dose group, and 31/50 (62%) of the high-dose group were alive at the end of the experiment at 105-107 weeks. In female mice, 34/50 (68%) of the pooled untreated-control group, 58/75 (77%) of the pooled vehicle group, 37/50 (74%) of the low-dose group, 36/50 (72%) of the mid-dose group, and 32/50 (64%) of the high-dose group lived to the end of the experiment at 106-107 weeks.

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

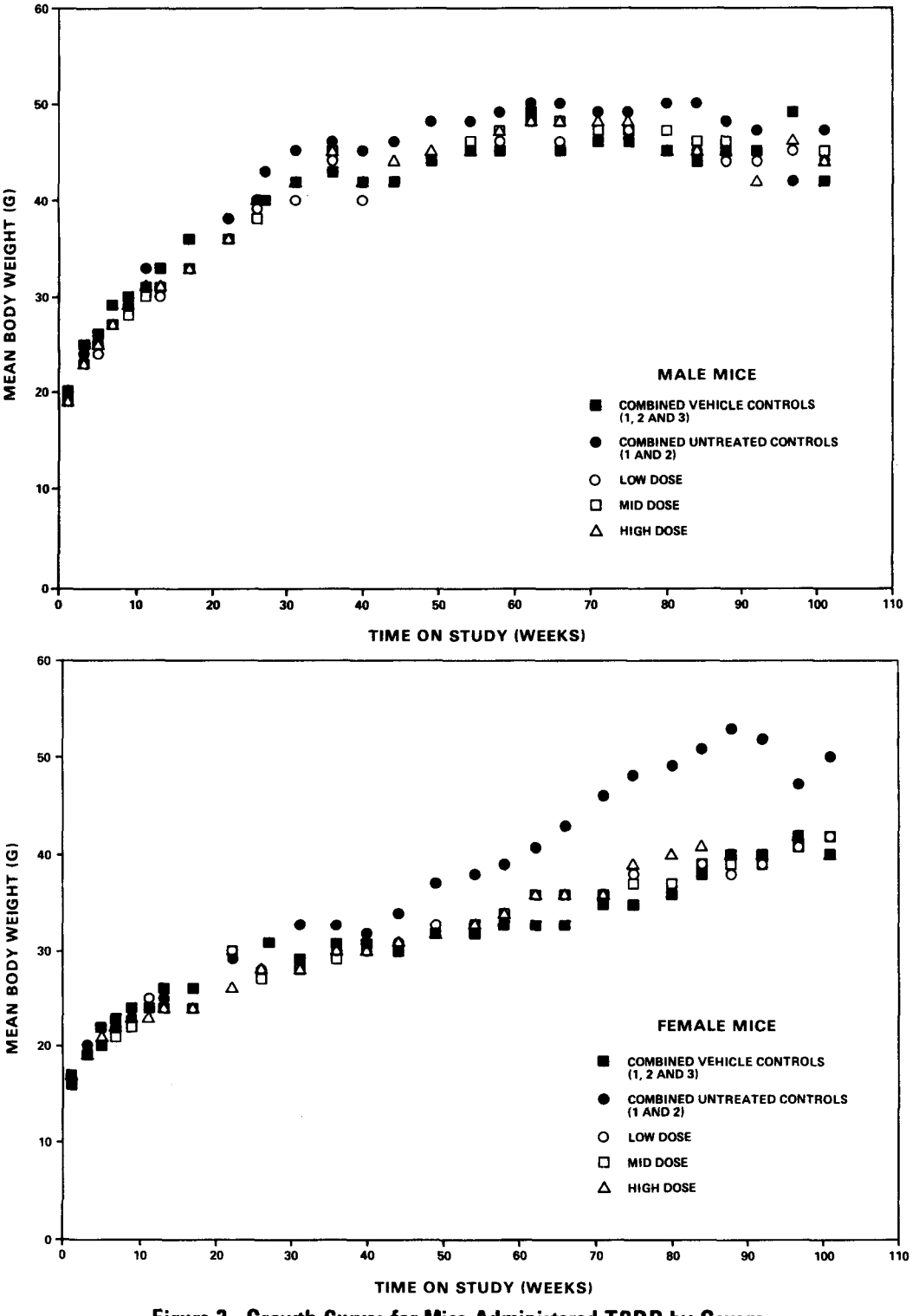


Figure 3. Growth Curves for Mice Administered TCDD by Gavage

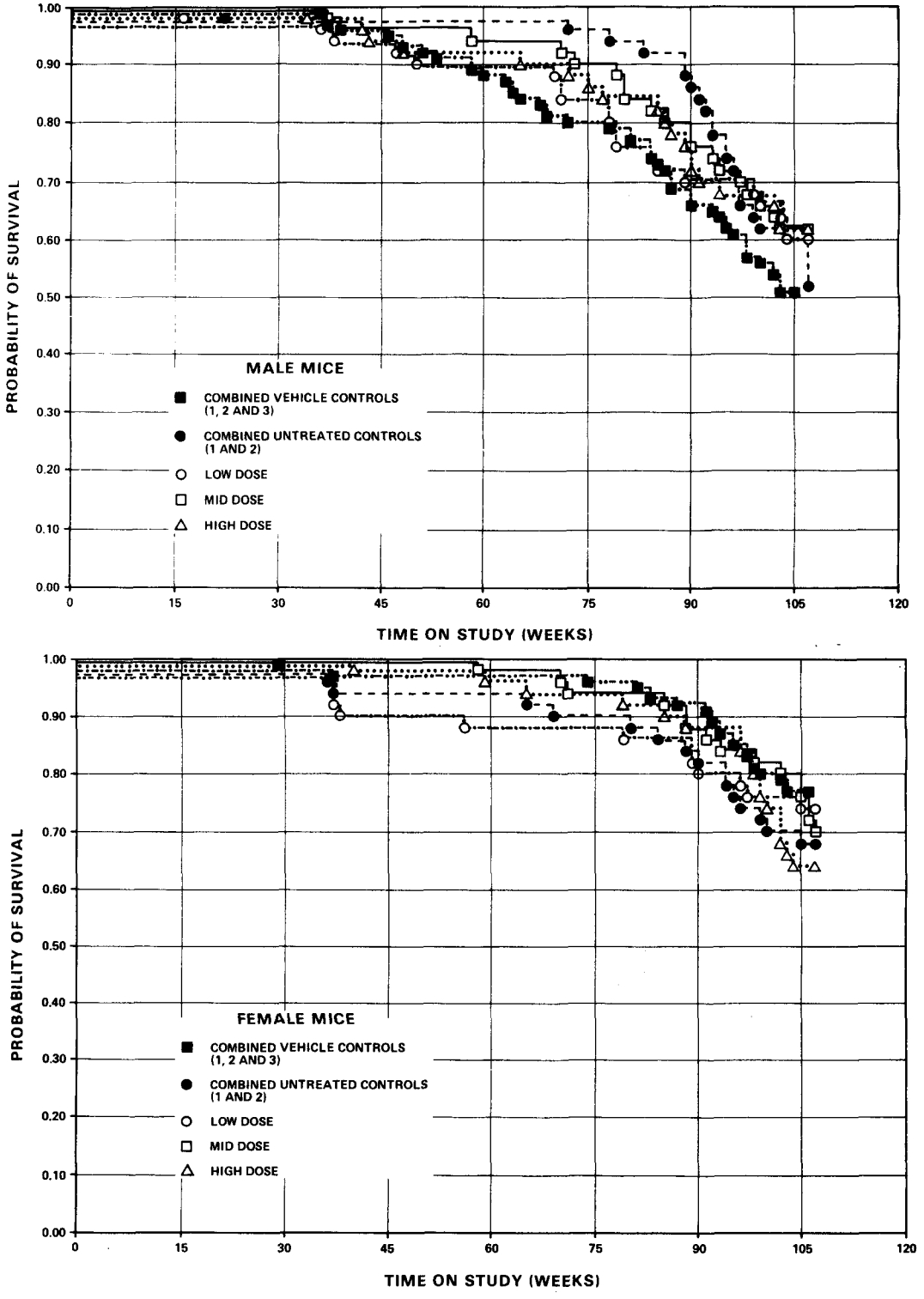


Figure 4. Survival Curves for Mice Administered TCDD by Gavage

C. Pathology (Mice)

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

A variety of tumors was seen in dosed mice. Tumors of the liver, thyroid, and hematopoietic system occurred in increased incidences in dosed mice (Tables 11, 12, and 13).

Hepatocellular adenomas were well circumscribed nodules composed of a uniform population of benign-appearing hepatocytes. Carcinomas were trabecular.

Toxic hepatic lesions, the severity of which was dose-related, were seen in dosed mice. They were recorded as "toxic hepatitis." Morphologically the lesions were characterized by cytomegaly, intranuclear inclusions, lipidosis, bile ductular hyperplasia, and pericellular fibrosis. Pigment was frequently seen in sinusoidal macrophages.

A variety of other nonneoplastic lesions was seen, none appeared to be dose related.

The results of the histopathologic examination indicated that TCDD was carcinogenic to B6C3F1 mice, inducing hepatocellular tumors and possibly tumors of the hematopoietic system and thyroid.

D. Statistical Analyses of Results (Mice)

Tables 14 and 15 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. Since the test conditions of the dosed groups are more comparable with those of the vehicle-control group than with the untreated control groups, only vehicle-control groups are shown in the statistical analyses tables; however, the data on untreated control groups are given in the appendixes.

Table 11. Numbers of Mice with Lesions of the Liver

	Males					Females				
	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose
Numbers of Livers Examined	50	73	49	49	50	50	73	50	48	47
Hepatocellular carcinoma	7	8	9	8	17	1	1	2	2	6
Hepatocellular adenoma	9	7	3	5	10	0	2	4	4	5
Toxic hepatitis	0	1	5	3	44	0	0	1	2	34

Table 12. Numbers of Mice with Follicular Lesions of the Thyroid

	Males					Females				
	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose
Number of Thyroids Examined	45	69	48	48	49	67	69	50	47	46
Follicular:										
Hyperplasia	0	0	0	0	0	0	0	1	2	0
Adenoma	0	0	3	0	0	0	0	3	1	5

Table 13. Numbers of Mice with Lymphoma

	Males					Females				
	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose	Untreated Control	Vehicle Control	Low Dose	Mid Dose	High Dose
Number of mice examined	50	73	49	49	50	50	74	50	48	47
Histiocytic lymphoma	7	5	0	3	0	9	9	4	8	14(a)
Malignant lymphoma, NOS	1	0	0	0	0	1	2	0	0	0
Malignant lymphoma, lymphocytic type	3	3	2	0	2	3	5	6	4	6(a)
Malignant lymphoma,mixed type	0	0	1	1	3	1	2	1	1	1
Total number of mice with lymphomas	11	8	3	4	5	14	18	11	13	20(a)

(a) One mouse had both lymphocytic and histiocytic lymphomas

The results of the Cochran-Armitage test indicate significant dose-related trends ($P<0.001$ for males and $P=0.005$ for females) and significantly higher ($P<0.001$ for males and $P=0.002$ for females) incidences of animals with hepatocellular adenomas or carcinomas in the high-dose groups than in the respective controls. The incidences in untreated historical control B6C3F1 mice from all laboratories were 868/3,543 (24%) in males and 171/3,617 (5%) in females as compared with 15/73 (21%) in the vehicle control group of males and 3/73 (4%) in females.

In females, follicular adenomas of the thyroid occurred with a significant ($P=0.016$) dose-related trend and with a significantly higher ($P=0.009$) incidence among the high-dose group animals. The untreated historical controls' incidence of 32/2,917 (1%) is comparable with the 0/69 (0%) observed in the vehicle-control group. In males, the results of the Fisher exact test are not significant, but there is a departure from linear trend ($P=0.008$) due to higher incidence in the low-dose group than in any other group.

In female mice, the incidence of histiocytic lymphomas in the hematopoietic system is significantly higher ($P=0.016$) in the high-dose group than in the vehicle controls. A significant ($P=0.003$) dose-related trend was also observed. The incidence in the untreated historical controls for this tumor type is 137/2,917 (5%), which is lower than the incidences observed in any of the dosed groups (4/50, 8%, 8/48, 17%; and 14/47, 30%, respectively); however, when the incidences of female mice with any type of lymphomas are analyzed, the Fisher exact test between the high-dose and the vehicle-control groups had a probability level of $P=0.029$, which is above the 0.017 level required by the Bonferroni inequality criterion when an overall significance level of 0.050 is to be maintained. When the time to tumor test was applied in females, no significant difference was observed in the time of observation of lymphomas between the vehicle-control groups and any of the dosed groups.

Positive dose-related trends were observed in the incidences of female mice with either lymphomas or leukemias ($P=0.014$) and fibrosarcomas in the subcutaneous tissue ($P=0.007$). The high-dose group incidences were also higher than those in the controls but the significance observed in either instance ($P=0.029$ and $P=0.032$, respectively) is above the level required by

the Bonferroni criterion when three dosed groups are compared with a control group.

The Cochran-Armitage test indicates a positive dose-related trend (P=0.004) in the incidence of male mice with either alveolar/bronchiolar adenomas or carcinomas in lung, but the results of the Fisher exact test are not significant.

The statistician concluded that the occurrence of liver tumors in both sexes and of thyroid tumors and possibly histiocytic lymphomas in female mice is related to the administration of TCDD.

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Administered TCDD by Gavage (a).

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Subcutaneous Tissue:				
Fibrosarcoma (b)	8/73(11)	5/49(10)	4/49(8)	3/50(6)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.931	0.745	0.548
Lower Limit		0.252	0.172	0.097
Upper Limit		3.016	2.606	2.147
Weeks to First Observed Tumor	84	79	79	87
Subcutaneous Tissue:				
Fibrosarcoma or				
Fibroma (b)	9/73(12)	6/49(12)	5/49(10)	3/50(6)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.993	0.828	0.487
Lower Limit		0.308	0.230	0.088
Upper Limit		2.905	2.564	1.832
Weeks to First Observed Tumor	84	79	79	87
Lung:				
Alveolar/Bronchiolar				
Adenoma (b)	7/71(10)	2/48(4)	4/48(8)	11/50(22)
P Value (c), (d)	P=0.006	N.S.	N.S.	N.S.
Relative Risk (e)		0.423	0.845	2.231
Lower Limit		0.044	0.190	0.849
Upper Limit		2.097	3.119	6.286
Weeks to First Observed Tumor	86	84	58	91

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Lung:				
Alveolar/Bronchiolar Adenoma or Carcinoma (b)	10/71(14)	2/48(4)	4/48(8)	13/50(26)
P Value (c), (d)	P=0.004	N.S.	N.S.	N.S.
Relative Risk (e)		0.296	0.592	1.846
Lower Limit		0.032	0.142	0.812
Upper Limit		1.305	1.912	4.292
Weeks to First Observed Tumor	86	84	58	86
Hematopoietic System:				
Histiocytic Lymphoma (b)	5/73(7)	0/49(0)	3/49(6)	0/50(0)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.000	0.894	0.000
Lower Limit		0.000	0.144	0.000
Upper Limit		1.183	4.356	1.160
Weeks to First Observed Tumor	86	--	91	--
Hematopoietic System:				
Lymphoma or Leukemia (b)	8/73(11)	3/49(6)	4/49(8)	6/50(12)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		0.559	0.745	1.095
Lower Limit		0.099	0.172	0.331
Upper Limit		2.189	2.606	3.358
Weeks to First Observed Tumor	69	78	71	85

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Circulatory System:				
Hemangiosarcoma (b)	1/73(1)	2/49(4)	1/49(2)	3/50(6)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		2.980	1.490	4.380
Lower Limit		0.159	0.019	0.363
Upper Limit		172.131	114.578	225.180
Weeks to First Observed Tumor	94	50	106	104
Liver:				
Hepatocellular Adenoma (b)	7/73(10)	3/49(6)	5/49(10)	10/50(20)
P Value (c), (d)	P=0.024	N.S.	N.S.	N.S.
Relative Risk (e)		0.638	1.064	2.086
Lower Limit		0.111	0.280	0.767
Upper Limit		2.636	3.650	5.993
Weeks to First Observed Tumor	86	104	79	34
Liver:				
Hepatocellular Carcinoma (b)	8/73(11)	9/49(18)	8/49(16)	17/50(34)
P Value (c), (d)	P=0.002	N.S.	N.S.	P=0.002
Relative Risk (e)		1.676	1.490	3.103
Lower Limit		0.614	0.520	1.382
Upper Limit		4.621	4.224	7.564
Weeks to First Observed Tumor	85	71	80	72

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Liver:				
Hepatocellular Adenoma or Carcinoma (b)	15/73(21)	12/49(24)	13/49(27)	27/50(54)
P Value (c), (d)	P<0.001	N.S.	N.S.	P<0.001
Relative Risk (e)		1.192	1.291	2.628
Lower Limit		0.555	0.618	1.521
Upper Limit		2.466	2.623	4.587
Weeks to First Observed Tumor	85	71	79	34
Thyroid:				
Follicular-Cell Adenoma (b)	0/69(0)	3/48(6)	0/48(0)	0/49(0)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Departure From Linear Trend (f)	P=0.008			
Relative Risk (e)		Infinite	--	--
Lower Limit		0.859	--	--
Upper Limit		Infinite	--	--
Weeks to First Observed Tumor	--	107	--	--
Eye/Lacrimal Gland:				
Adenoma, NOS (b)	0/73(0)	1/49(2)	1/49(2)	3/50(6)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	Infinite	Infinite
Lower Limit		0.079	0.079	0.871
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	106	98	94

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Administered TCDD by Gavage (a).
(continued)

(a) Dosed groups received doses of 0.01, 0.05, or 0.5 μg/kg by gavage.
(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 matched control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Administered TCDD by Gavage (a).

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Subcutaneous Tissue:				
Fibrosarcoma (b)	1/74(1)	1/50(2)	1/48(2)	5/47(11)
P Value (c), (d)	P=0.007	N.S.	N.S.	P=0.032
Relative Risk (e)		1.480	1.542	7.872
Lower Limit		0.019	0.020	0.917
Upper Limit		113.896	118.524	363.627
Weeks to First Observed Tumor	95	105	98	88
Lung:				
Alveolar/Bronchiolar Adenoma (b)	2/74(3)	3/49(6)	4/48(8)	1/46(2)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		2.265	3.083	0.804
Lower Limit		0.268	0.459	0.014
Upper Limit		26.213	32.886	14.938
Weeks to First Observed Tumor	99	105	105	105
Lung:				
Alveolar/Bronchiolar Adenoma or Carcinoma (b)	2/74(3)	3/49(6)	4/48(8)	2/46(4)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		2.265	3.083	1.609
Lower Limit		0.268	0.459	0.120
Upper Limit		26.213	32.886	21.428
Weeks to First Observed Tumor	99	105	105	102

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Administered TCDD by Gavage (a).
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Hematopoietic System:				
Lymphocytic Lymphoma (b)	5/74(7)	6/50(12)	4/48(8)	6/47(13)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		1.776	1.233	1.889
Lower Limit		0.476	0.256	0.507
Upper Limit		6.941	5.416	7.360
Weeks to First Observed Tumor	76	97	85	103
Hematopoietic System:				
Histiocytic Lymphoma (b)	9/74(12)	4/50(8)	8/48(17)	14/47(30)
P Value (c), (d)	P=0.003	N.S.	N.S.	P=0.016
Relative Risk (e)		0.658	1.370	2.449
Lower Limit		0.155	0.491	1.074
Upper Limit		2.207	3.697	5.829
Weeks to First Observed Tumor	87	89	102	40
Hematopoietic System:				
All Lymphoma (b)	18/74(24)	11/50(22)	13/48(27)	20/47(43)
P Value (c), (d)	P=0.011	N.S.	N.S.	P=0.029
Relative Risk (e)		0.904	1.113	1.749
Lower Limit		0.420	0.551	0.983
Upper Limit		1.830	2.155	3.067
Weeks to First Observed Tumor	76	89	85	40

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Administered TCDD by Gavage (a)
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Hematopoietic System:				
Lymphoma or Leukemia (b)	18/74(24)	12/50(24)	13/48(27)	20/47(43)
P Value (c), (d)	P=0.014	N.S.	N.S.	P=0.029
Relative Risk (e)		0.987	1.113	1.749
Lower Limit		0.474	0.551	0.983
Upper Limit		1.953	2.155	3.067
Weeks to First Observed Tumor	76	89	85	40
Liver: Hepatocellular Adenoma (b)	2/73(3)	4/50(8)	4/48(8)	5/47(11)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		2.920	3.042	3.883
Lower Limit		0.435	0.453	0.664
Upper Level		31.189	32.446	39.277
Weeks To First Observed Tumor	104	105	105	105
Liver:				
Hepatocellular Carcinoma (b)	1/73(1)	2/50(4)	2/48(4)	6/47(13)
P Value (c), (d)	P=0.008	N.S.	N.S.	P=0.014
Relative Risk (e)		2.920	3.042	9.319
Lower Limit		0.156	0.162	1.180
Upper Limit		168.814	175.643	418.407
Weeks to First Observed Tumor	91	105	105	99

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Administered TCDD by Gavage (a)
(continued)

Morphology: Topography	Vehicle Control	Low Dose	Medium Dose	High Dose
Liver:				
Hepatocellular Adenoma or Carcinoma (b)	3/73(4)	6/50(12)	6/48(13)	11/47(23)
P Value (c), (d)	P=0.005	N.S.	N.S.	P=0.002
Relative Risk (e)		2.920	3.042	5.695
Lower Limit		0.655	0.683	1.601
Upper Limit		17.238	17.924	30.086
Weeks to First Observed Tumor	91	105	105	99
Pituitary:				
Adenoma, NOS (b)	0/62(0)	2/39(5)	0/38(0)	2/33(6)
P Value (c), (d)	N.S.	N.S.	N.S.	N.S.
Relative Risk (e)		Infinite	--	Infinite
Lower Limit		0.469	--	0.554
Upper Limit		Infinite	--	Infinite
Weeks to First Observed Tumor	--	56	--	99
Thyroid:				
Follicular-Cell Adenoma (b)	0/69(0)	3/50(6)	1/47(2)	5/46(11)
P Value (c), (d)	P=0.016	N.S.	N.S.	P=0.009
Relative Risk (e)		Infinite	Infinite	Infinite
Lower Limit		0.824	0.078	1.879
Upper Limit		Infinite	Infinite	Infinite
Weeks to First Observed Tumor	--	90	107	99

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Administered TCDD by Gavage (a)
(continued)

(a) Dosed groups received doses of 0.04, 0.2, or 2.0 μg/kg by gavage.
(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.

V. DISCUSSION

In high-dose rats, a decrease in mean body weight gain became evident after week 55 in males and after week 45 in females. In mice, weight gain in the dosed groups was comparable to that of the corresponding vehicle-control group, but it was lower than that of the untreated controls. Administration of TCDD by gavage at the doses used in this study had no adverse effect on the survival of rats or mice of either sex.

Hepatotoxic effects observed in the subchronic study were the determining factor in selecting doses for the chronic study. Hepatic effects in rats and mice and goitrogenic effects in rats have been previously reported after administration of single doses of TCDD by gavage (Harris et al., 1973; and Bastomsky, 1977). The liver and thyroid were also target organs in the present chronic study; an increased incidence of liver tumors occured in female rats and in mice of either sex, and an increased incidence of follicular-cell thyroid tumors occurred in male rats and in female mice.

Follicular-cell adenomas or carcinomas in the thyroid occurred in male rats at incidences that were dose-related ($P=0.005$) and the incidences in the mid- and high-dose group were significantly higher ($P=0.004$ and $P<0.001$) than those in the vehicle controls.

Hepatocellular carcinomas or neoplastic nodules occurred in female rats at incidences that were dose related ($P<0.001$), and the incidence in the high-dose group was significantly higher ($P=0.001$) than in the vehicle controls.

An increased incidence of liver tumors in rats fed TCDD in the diet was reported by Kociba et al. (1978) while the report of the present study was in preparation. In this study, male and female Sprague-Dawley rats were fed diets containing TCDD (approximately 0.022, 0.210, or 2.2 ppb) for 2 years. The dosed groups consisted of 49 or 50 animals; the control groups consisted of 85 or 86 animals. Hepatocellular carcinomas occurred at a significantly increased incidence in the females administered 2.2 ppb (control 1/86, low-dose 0/50, mid-dose 2/50, high-dose 11/49). Hepatocellular hyperplastic nodules occurred at increased incidences in the females administered either

the mid or high dose (control: 8/86, low-dose 3/50, mid-dose 18/50, high-dose 23/50). The incidences of liver tumors in the dosed groups of male rats were not significant, but substantially increased incidences of toxic hepatitis were observed among both high-dose males and females. Squamous-cell carcinomas of the lung, hard palate/nasal turbinates, or tongue occurred at increased incidences in both the male and female rats administered the TCDD.

Hepatocellular adenomas or carcinomas occurred in male or female mice at incidences that were dose-related ($P<0.001$ and $P=0.005$, respectively), and the incidences in the high-dose groups were significantly higher ($P<0.001$ and $P=0.002$, respectively) than those in the corresponding vehicle controls. Toxic hepatitis occurred in 88% of the high-dose males and 72% of the high-dose females.

Follicular-cell adenomas in the thyroid occurred at incidences that were dose-related in female mice ($P=0.016$), and the incidence in the high-dose group was significantly higher ($P=0.009$) than that in the controls.

Histiocytic lymphomas in the hematopoietic system occurred at incidences that were dose related ($P=0.003$) in female mice, and the incidence in the high-dose group was significantly higher ($P=0.016$) than that in the vehicle controls. Lymphomas (all types) or leukemias also occurred with a dose-related trend. Although the incidence in the high-dose group was higher than that in the controls, the level of significance was above that required by the Bonferroni inequality criterion for multiple comparisons. Since it is sometimes difficult to differentiate between various types of lymphomas by histologic examination, comparison of the number of animals with total lymphomas is more appropriate than comparison of animals with histiocytic lymphomas. Thus the statistical results suggest that TCDD may have induced lymphomas or leukemia.

In a concurrent study conducted in the same laboratory as the present study, 0.005 μg TCDD in 0.1 ml acetone applied three times per week for 104 weeks to the skin of female Swiss-Webster mice was carcinogenic, causing increased incidences of fibrosarcomas in the integumentary system (NTP, 1981).

When male or female DBA/2 mice were simultaneously administered TCDD by subcutaneous injection in a single dose of 100 μg/kg body weight and an

unstated dose of methylcholanthrene (MCA) and then observed for 36 weeks, the incidence of skin tumors was greater than that induced by the administration of MCA alone (Kouri et al., 1978). The results were interpreted as evidence that MCA, and TCDD are co-carcinogens. However, the results of this study were compromised by the use of p-dioxane as a solvent for TCDD. Dioxane in drinking water has previously been found to be carcinogenic for both Sprague-Dawley rats (Argus et al., 1973), Sherman rats (Kociba et al., 1974), and in Osborne-Mendel rats and B6C3F1 mice (NCI, 1978).

VI. CONCLUSION

Under the conditions of this bioassay, 2,3,7,8-tetrachlorodibenzo-p-dioxin was carcinogenic for Osborne-Mendel rats, inducing follicular-cell thyroid adenomas in males and neoplastic nodules of the liver in females. TCDD was also carcinogenic for B6C3F1 mice, inducing hepatocellular carcinomas in males and females and follicular-cell thyroid adenomas in females.

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APPENDIX A

Summary of the Incidence of Neoplasms in Rats Administered TCDD By Gavage

TABLE A1.

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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)
KERATOACANTHOMA			1 (2%)	
*SUBCUT TISSUE	(25)	(50)	(50)	(50)
BASAL-CELL TUMOR	1 (4%)			
SEBACEOUS ADENOMA		1 (2%)		
KERATOACANTHOMA	1 (4%)			
FIBROMA		1 (2%)	3 (6%)	7 (14%)
FIBROSARCOMA	3 (12%)	3 (6%)	3 (6%)	3 (6%)
LIPOMA		2 (4%)		
FIBROADENOMA		1 (2%)	1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(25)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)		
FIBROSARCOMA, METASTATIC			1 (2%)	
MIXED TUMOR, METASTATIC			1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(25)	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#SPLEEN	(25)	(50)	(50)	(48)
FIBROSARCOMA				1 (2%)
#SMALL INTESTINE	(24)	(49)	(48)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)		

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(25)	(50)	(50)	(50)
HEMANGIOSARCOMA				1 (2%)
*SUBCUT TISSUE	(25)	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (4%)			
#SPLEEN	(25)	(50)	(50)	(48)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA		2 (4%)		
#LUNG	(25)	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#HEART	(25)	(50)	(49)	(50)
HEMANGIOSARCOMA				1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
#BASE OF HEART	(25)	(50)	(49)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#HEART/VENTRICLE	(25)	(50)	(49)	(50)
FIBROSARCOMA		1 (2%)		
HEMANGIOSARCOMA		1 (2%)		
#JEJUNUM	(24)	(49)	(48)	(49)
HEMANGIOSARCOMA				1 (2%)
#KIDNEY	(25)	(50)	(50)	(50)
HEMANGIOSARCOMA				1 (2%)
#THYMUS	(15)	(37)	(34)	(33)
HEMANGIOSARCOMA, METASTATIC		1 (3%)		
DIGESTIVE SYSTEM				
#LIVER	(24)	(50)	(50)	(50)
NEOPLASTIC NODULE				3 (6%)
HEPATOCELLULAR CARCINOMA				1 (2%)
#GASTRIC MUCOSA	(25)	(50)	(49)	(50)
ADENOMA, NOS				1 (2%)

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(25)	(50)	(50)	(50)
MIXED TUMOR, BENIGN		2 (4%)		
MIXED TUMOR, MALIGNANT				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(43)	(43)	(40)
ADENOMA, NOS		1 (2%)	2 (5%)	3 (8%)
CHROMOPHOBE ADENOMA			1 (2%)	
#ADRENAL	(24)	(50)	(49)	(49)
CORTICAL ADENOMA	4 (17%)	9 (18%)	12 (24%)	9 (18%)
PHEOCHROMOCYTOMA	1 (4%)		1 (2%)	1 (2%)
#THYROID	(22)	(48)	(50)	(50)
FOLLICULAR-CELL ADENOMA		5 (10%)	6 (12%)	10 (20%)
FOLLICULAR-CELL CARCINOMA			2 (4%)	1 (2%)
C-CELL ADENOMA		2 (4%)	4 (8%)	4 (8%)
C-CELL CARCINOMA			1 (2%)	
#PARATHYROID	(20)	(41)	(40)	(36)
ADENOMA, NOS		2 (5%)	1 (3%)	1 (3%)
#PANCREATIC ISLETS	(23)	(49)	(48)	(50)
ISLET-CELL ADENOMA		2 (4%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(50)
ADENOMA, NOS	1 (4%)			
ADENOCARCINOMA, NOS			3 (6%)	1 (2%)
PAPILLARY ADENOMA			1 (2%)	
FIBROADENOMA			1 (2%)	
*SEMINAL VESICLE	(25)	(50)	(50)	(50)
LIPOMA				1 (2%)
#TESTIS	(25)	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR			1 (2%)	
LIPOMA			1 (2%)	
NERVOUS SYSTEM				
NONE				

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(25)	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)	
BODY CAVITIES				
*MEDIASTINUM	(25)	(50)	(50)	(50)
CARCINOMA,NOS				1 (2%)
*TUNICA VAGINALIS	(25)	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(50)
MIXED TUMOR, MALIGNANT			1 (2%)	
NEURILEMOMA, MALIGNANT				1 (2%)
SITE UNKNOWN				
ADENOMA, NOS		1		
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATHS	8	15	11	12
MORIBUND SACRIFICE	5	13	19	19
SCHEDULED SACRIFICE	7	11	12	16
ACCIDENTALLY KILLED	1			
TERMINAL SACRIFICE	4	6	8	3
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	29	33	32
TOTAL PRIMARY TUMORS	12	38	53	55
TOTAL ANIMALS WITH BENIGN TUMORS	8	26	29	24
TOTAL BENIGN TUMORS	8	30	40	38
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	7	11	13
TOTAL MALIGNANT TUMORS	4	8	13	14
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	3	
TOTAL SECONDARY TUMORS		3	4	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				3
TOTAL UNCERTAIN TUMORS				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 TCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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)
SQUAMOUS CELL CARCINOMA		1 (2%)		
*SUBCUT TISSUE	(25)	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
SARCOMA, NOS		1 (2%)		1 (2%)
FIBROMA				1 (2%)
FIBROSARCOMA		2 (4%)	3 (6%)	4 (8%)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
LIPOMA			1 (2%)	
LIPOSARCOMA	1 (4%)			
#ENDOCARDIUM	(25)	(48)	(48)	(47)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(25)	(49)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA, METAST				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (4%)			
CORTICAL CARCINOMA, METASTATIC		1 (2%)	1 (2%)	
SARCOMA, NOS, METASTATIC	1 (4%)			
FIBROSARCOMA, METASTATIC		1 (2%)		
FIBROUS HISTIOCYTOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*SUBCUT TISSUE	(25)	(50)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE			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
#SPLEEN	(25)	(50)	(49)	(46)
FIBROMA				1 (2%)
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(25)	(50)	(50)	(49)
HEMANGIOSARCOMA		1 (2%)		
#SPLEEN	(25)	(50)	(49)	(46)
HEMANGIOMA		1 (2%)		
HEMANGIOSARCOMA				1 (2%)
#HEART	(25)	(48)	(48)	(47)
RHABDOMYOSARCOMA	1 (4%)			
#HEART/VENTRICLE	(25)	(48)	(48)	(47)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
#ENDOCARDIUM	(25)	(48)	(48)	(47)
FIBROMA		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(24)	(48)	(49)	(45)
FIBROSARCOMA				2 (4%)
#LIVER	(25)	(49)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (4%)			
NEOPLASTIC NODULE	2 (8%)	1 (2%)	3 (6%)	12 (24%)
HEPATOCELLULAR CARCINOMA				3 (6%)
#ESOPHAGUS	(24)	(44)	(49)	(45)
FIBROMA				1 (2%)
#STOMACH	(25)	(50)	(50)	(48)
ADENOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS				1 (2%)
#COLON	(24)	(48)	(49)	(47)
LEIOMYOSARCOMA				1 (2%)
URINARY SYSTEM				
#KIDNEY/CORTEX	(25)	(49)	(50)	(49)
ADENOMA, 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
#KIDNEY/PELVIS	(25)	(49)	(50)	(49)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(47)	(44)	(43)
ADENOMA, NOS		5 (11%)	2 (5%)	3 (7%)
CHROMOPHOBE ADENOMA	3 (14%)			1 (2%)
#ADRENAL	(24)	(49)	(49)	(46)
ADENOMA, NOS				1 (2%)
CORTICAL ADENOMA	3 (13%)	8 (16%)	4 (8%)	13 (28%)
CORTICAL CARCINOMA		1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA	2 (8%)			
#THYROID	(24)	(45)	(49)	(47)
FOLLICULAR-CELL ADENOMA	1 (4%)	2 (4%)	1 (2%)	6 (13%)
C-CELL ADENOMA	3 (13%)	1 (2%)	8 (16%)	6 (13%)
C-CELL CARCINOMA		2 (4%)		
#PANCREATIC ISLETS	(24)	(48)	(50)	(48)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(49)
ADENOCARCINOMA, NOS		3 (6%)	2 (4%)	1 (2%)
FIBROSARCOMA		1 (2%)		2 (4%)
LIPOMA		1 (2%)		
FIBROADENOMA	6 (24%)	20 (40%)	21 (42%)	17 (35%)
#UTERUS	(24)	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
ADENOCARCINOMA, NOS	1 (4%)			
LEIOMYOMA	1 (4%)			
LEIOMYOSARCOMA		2 (4%)		
#OVARY	(23)	(47)	(50)	(48)
THECOMA				1 (2%)
LUTEOMA				1 (2%)
GRANULOSA-CELL TUMOR		1 (2%)		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
NERVOUS SYSTEM				
#BRAIN	(25)	(47)	(49)	(48)
ASTROCYTOMA		3 (6%)		
*OPHTHALMIC NERVE	(25)	(50)	(50)	(49)
NEUROFIBROSARCOMA			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL WALL	(25)	(50)	(50)	(49)
FIBROMA				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)		
SARCOMA, NOS, METASTATIC				1 (2%)
FIBROSARCOMA		1 (2%)		
FIBROSARCOMA, METASTATIC				2 (4%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATHS	4	5	3	6
MORIBUND SACRIFICE	8	16	13	12
SCHEDULED SACRIFICE	11	19	21	24
ACCIDENTALLY KILLED	1			
TERMINAL SACRIFICE	1	10	13	8
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	40	36	43
TOTAL PRIMARY TUMORS	25	62	51	90
TOTAL ANIMALS WITH BENIGN TUMORS	13	29	30	37
TOTAL BENIGN TUMORS	19	41	40	57
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	19	8	15
TOTAL MALIGNANT TUMORS	4	19	8	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	2	6
TOTAL SECONDARY TUMORS	2	2	2	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	2	3	13
TOTAL UNCERTAIN TUMORS	2	2	3	13
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

APPENDIX B

Summary of the Incidence of Neoplasms in Mice Administered TCDD By Gavage

TABLE B1.

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	VEHICLE CONTROL NO. 1	VEHICLE CONTROL NO. 2
ANIMAL DISPOSITION SUMMARY					
ANIMALS INITIALLY IN STUDY	25	25	25	25	25
NATURAL DEATHa	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					

a 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 TCDD 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	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	23	49	49	50
INTEGUMENTARY SYSTEM				
*SKIN	(23)	(49)	(49)	(50)
FIBROSARCOMA			1 (2%)	
*SUBCUT TISSUE	(23)	(49)	(49)	(50)
FIBROMA		1 (2%)	1 (2%)	
FIBROSARCOMA	4 (17%)	5 (10%)	4 (8%)	3 (6%)
LIPOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(23)	(48)	(48)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (17%)	2 (4%)	4 (8%)	11 (22%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (4%)			2 (4%)
FIBROSARCOMA, METASTATIC			1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(23)	(49)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)		2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (9%)		3 (6%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	1 (2%)	1 (2%)
GRANULOCYTIC LEUKEMIA				1 (2%)
#LYMPH NODE	(16)	(25)	(32)	(36)
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (3%)
#BRONCHIAL LYMPH NODE	(16)	(25)	(32)	(36)
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (3%)
#SMALL INTESTINE	(21)	(44)	(44)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)			

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
#KIDNEY	(23)	(49)	(49)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (2%)
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(23)	(49)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)		
*SUBCUT TISSUE	(23)	(49)	(49)	(50)
HEMANGIOSARCOMA			1 (2%)	
#SPLEEN	(21)	(47)	(47)	(50)
HEMANGIOMA	1 (5%)			
HEMANGIOSARCOMA		1 (2%)		3 (6%)
#MESENTERIC L. NODE	(16)	(25)	(32)	(36)
HEMANGIOMA			1 (3%)	
*STERNUM	(23)	(49)	(49)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#LUNG	(23)	(48)	(48)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)		
#MYOCARDIUM	(23)	(44)	(48)	(50)
FIBROSARCOMA, METASTATIC			1 (2%)	
#SALIVARY GLAND	(22)	(47)	(46)	(48)
HEMANGIOMA			1 (2%)	
#LIVER	(23)	(49)	(49)	(50)
HEMANGIOSARCOMA	1 (4%)			1 (2%)
#TESTIS	(22)	(48)	(47)	(48)
HEMANGIOMA		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(23)	(49)	(49)	(50)
HEPATOCELLULAR ADENOMA	2 (9%)	3 (6%)	5 (10%)	10 (20%)
HEPATOCELLULAR CARCINOMA	4 (17%)	9 (18%)	8 (16%)	17 (34%)
FIBROSARCOMA, METASTATIC		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
#STOMACH	(22)	(47)	(46)	(50)
PAPILLOMA, NOS		1 (2%)		
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(17)	(34)	(33)	(34)
MENINGIOMA, INVASIVE				1 (3%)
#ADRENAL	(23)	(43)	(46)	(46)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)		
PHEOCHROMOCYTOMA	1 (4%)			
#THYROID	(22)	(48)	(48)	(49)
ADENOMA, NOS	1 (5%)			
FOLLICULAR-CELL ADENOMA		3 (6%)		
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
#BRAIN/MENINGES	(23)	(47)	(48)	(47)
MENINGIOMA				1 (2%)
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(23)	(49)	(49)	(50)
ADENOMA, NOS		1 (2%)	1 (2%)	3 (6%)
MUSCULOSKELETAL SYSTEM				
NONE				
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)	(49)	(49)	(50)
SARCOMA, NOS	1 (4%)			
FIBROSARCOMA			1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATHa	7	16	14	14
MORIBUND SACRIFICE	2	4	5	5
SCHEDULED SACRIFICE	5	16	17	18
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	10	14	14	13
ANIMAL MISSING	1			
a INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	13	25	27	37
TOTAL PRIMARY TUMORS	23	32	32	58
TOTAL ANIMALS WITH BENIGN TUMORS	6	12	12	17
TOTAL BENIGN TUMORS	9	13	13	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	17	17	28
TOTAL MALIGNANT TUMORS	14	19	19	34
TOTAL ANIMALS WITH SECONDARY TUMORS#		4	3	5
TOTAL SECONDARY TUMORS		5	4	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 TCDD BY GAVAGE (CONTROL GROUPS)

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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	48	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	48	47
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(25)	(50)	(48)	(47)
FIBROSARCOMA		1 (2%)	1 (2%)	5 (11%)
RESPIRATORY SYSTEM				
#LUNG	(25)	(49)	(48)	(46)
ADENOCARCINOMA, NOS, METASTATIC	1 (4%)			
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (6%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
FIBROSARCOMA, METASTATIC				2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(25)	(50)	(48)	(47)
MALIGNANT LYMPHOMA, NOS	1 (4%)			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3 (12%)	5 (10%)	4 (8%)	6 (13%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (8%)	3 (6%)	6 (13%)	10 (21%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	1 (2%)	1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)		
#LYMPH NODE	(22)	(41)	(39)	(35)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (3%)
#MANDIBULAR L. NODE	(22)	(41)	(39)	(35)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (3%)
#GASTRIC LYMPH NODE	(22)	(41)	(39)	(35)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (3%)
#LUMBAR LYMPH NODE	(22)	(41)	(39)	(35)
FIBROSARCOMA			1 (3%)	

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
#PANCREAS	(23)	(49)	(44)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#PEYER'S PATCH	(23)	(49)	(46)	(46)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)	
#KIDNEY	(24)	(50)	(47)	(45)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
#SPLEEN	(23)	(49)	(45)	(43)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA				2 (5%)
#LIVER	(24)	(50)	(48)	(47)
HEMANGIOSARCOMA			1 (2%)	
#URINARY BLADDER	(24)	(46)	(46)	(44)
HEMANGIOMA		1 (2%)		
#UTERUS	(25)	(50)	(48)	(46)
HEMANGIOMA			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(24)	(50)	(48)	(47)
HEPATOCELLULAR ADENOMA		4 (8%)	4 (8%)	5 (11%)
HEPATOCELLULAR CARCINOMA		2 (4%)	2 (4%)	6 (13%)
#PANCREAS	(23)	(49)	(44)	(43)
ADENOMA, NOS	1 (4%)			
#STOMACH	(25)	(49)	(47)	(46)
ADENOMA, NOS			1 (2%)	
URINARY 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
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(39)	(38)	(33)
ADENOMA, NOS		2 (5%)		2 (6%)
CHROMOPHOBE ADENOMA	1 (5%)			
#ADRENAL	(24)	(50)	(44)	(43)
CORTICAL ADENOMA	1 (4%)			
PHEOCHROMOCYTOMA	1 (4%)			1 (2%)
#THYROID	(25)	(50)	(47)	(46)
ADENOMA, NOS	1 (4%)			
FOLLICULAR-CELL ADENOMA		3 (6%)	1 (2%)	5 (11%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(48)	(47)
FIBROSARCOMA			1 (2%)	
FIBROADENOMA		1 (2%)		
*VAGINA	(25)	(50)	(48)	(47)
FIBROSARCOMA			1 (2%)	
#UTERUS	(25)	(50)	(48)	(46)
FIBROMA	1 (4%)			
LEIOMYOMA	2 (8%)			
#UTERUS/ENDOMETRIUM	(25)	(50)	(43)	(46)
CARCINOMA,NOS		1 (2%)		
#OVARY	(23)	(46)	(48)	(45)
PAPILLARY ADENOMA				1 (2%)
GRANULOSA-CELL TUMOR		1 (2%)	1 (2%)	
TERATOMA, BENIGN		1 (2%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(25)	(50)	(48)	(44)
MENINGIOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(25)	(50)	(48)	(47)
ADENOMA, NOS				2 (4%)

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
*HARDERIAN GLAND	(25)	(50)	(48)	(47)
ADENOCARCINOMA, NOS	1 (4%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	25	50	50	50
NATURAL DEATHS	4	9	9	17
MORIBUND SACRIFICE		4	5	1
SCHEDULED SACRIFICE	16	28	31	28
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	5	9	5	4
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
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	25	28	34
TOTAL PRIMARY TUMORS	15	32	34	52
TOTAL ANIMALS WITH BENIGN TUMORS	8	13	11	15
TOTAL BENIGN TUMORS	8	15	12	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	16	18	27
TOTAL MALIGNANT TUMORS	7	16	21	35
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			2
TOTAL SECONDARY TUMORS	1			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1	
TOTAL UNCERTAIN TUMORS		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 TCDD By Gavage

TABLE C1.

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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)
CYST, NOS				1 (2%)
EPIDERMAL INCLUSION CYST			1 (2%)	
HYPERKERATOSIS		1 (2%)		
ACANTHOSIS	1 (4%)	1 (2%)	1 (2%)	
*SUBCUT TISSUE	(25)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)	1 (2%)
ABSCESS, NOS		1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	
GRANULOMA, NOS			1 (2%)	
FIBROSIS		1 (2%)		
RESPIRATORY SYSTEM				
*NASAL CAVITY	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (4%)	1 (2%)	2 (4%)	6 (12%)
*LARYNX	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)	
#TRACHEA	(25)	(49)	(46)	(49)
INFLAMMATION, CHRONIC			2 (4%)	
INFLAMMATION, CHRONIC FOCAL			3 (7%)	
GRANULOMA, FOREIGN BODY			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)	
#LUNG/BRONCHUS	(25)	(50)	(50)	(50)
INFLAMMATION, NOS	1 (4%)			
#LUNG/BRONCHIOLE	(25)	(50)	(50)	(50)
INFLAMMATION, MULTIFOCAL	1 (4%)			

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#LUNG	(25)	(50)	(50)	(50)
CONGESTION, NOS	5 (20%)	11 (22%)	6 (12%)	8 (16%)
EDEMA, NOS	1 (4%)	1 (2%)		
HEMORRHAGE		2 (4%)	2 (4%)	
BRONCHOPNEUMONIA SUPPURATIVE	1 (4%)	1 (2%)		
BRONCHOPNEUMONIA NECROTIZING		1 (2%)		
INFLAMMATION, NECROTIZING			1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)		
ABSCESS, NOS	1 (4%)			
PNEUMONIA, CHRONIC MURINE	14 (56%)	43 (86%)	41 (82%)	39 (78%)
PNEUMONIA INTERSTITIAL CHRONIC	1 (4%)			
BRONCHOPNEUMONIA, CHRONIC				2 (4%)
GRANULOMA, NOS		1 (2%)	1 (2%)	1 (2%)
GRANULOMA, FOREIGN BODY		1 (2%)		
FIBROSIS, DIFFUSE		1 (2%)		
CHOLESTEROL DEPOSIT		1 (2%)		
CALCIFICATION, FOCAL	1 (4%)		2 (4%)	
ALVEOLAR MACROPHAGES	2 (8%)	3 (6%)		1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	7 (14%)	35 (70%)
METAPLASIA, OSSEOUS				1 (2%)
#LUNG/ALVEOLI	(25)	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (4%)			1 (2%)
#ALVEOLAR WALL	(25)	(50)	(50)	(50)
CALCIFICATION, NOS		1 (2%)		
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(25)	(49)	(47)	(45)
NECROSIS, NOS			1 (2%)	
NECROSIS, FOCAL				1 (2%)
HYPOPLASIA, NOS		1 (2%)		
ATROPHY, NOS	1 (4%)			1 (2%)
MYELOFIBROSIS	1 (4%)	1 (2%)	2 (4%)	2 (4%)
#SPLEEN	(25)	(50)	(50)	(48)
CONGESTION, NOS	2 (8%)	6 (12%)	2 (4%)	2 (4%)
INFLAMMATION, CHRONIC	1 (4%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
NECROSIS, FOCAL	1 (4%)			
INFARCT, NOS		1 (2%)		
HEMOSIDEROSIS	3 (12%)	2 (4%)	3 (6%)	5 (10%)

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIESIS	6 (24%)	15 (30%)	21 (42%)	10 (21%)
#LYMPH NODE	(22)	(39)	(39)	(43)
CONGESTION, NOS	1 (5%)			
EDEMA, NOS	1 (5%)		2 (5%)	2 (5%)
HEMORRHAGIC CYST		1 (3%)		
INFLAMMATION, CHRONIC		1 (3%)		3 (7%)
HEMOSIDEROSIS			1 (3%)	
HYPERPLASIA, LYMPHOID				1 (2%)
#SUBMANDIBULAR L.NODE	(22)	(39)	(39)	(43)
HYPERPLASIA, LYMPHOID			1 (3%)	
#MANDIBULAR L. NODE	(22)	(39)	(39)	(43)
CONGESTION, NOS	1 (5%)			
INFLAMMATION, NOS	1 (5%)			1 (2%)
HYPERPLASIA, NOS		2 (5%)	1 (3%)	
HYPERPLASIA, LYMPHOID	1 (5%)	3 (8%)		
#LYMPH NODE OF THORAX	(22)	(39)	(39)	(43)
EDEMA, NOS		1 (3%)		
HYPERPLASIA, LYMPHOID		1 (3%)		
#LUMBAR LYMPH NODE	(22)	(39)	(39)	(43)
HYPERPLASIA, LYMPHOID			1 (3%)	
#MESENTERIC L. NODE	(22)	(39)	(39)	(43)
INFLAMMATION, CHRONIC			1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)		
#RENAL LYMPH NODE	(22)	(39)	(39)	(43)
EDEMA, NOS		2 (5%)		
INFLAMMATION, CHRONIC			1 (3%)	
HYPERPLASIA, LYMPHOID	1 (5%)			
#LIVER	(24)	(50)	(50)	(50)
HEMATOPOIESIS		1 (2%)		1 (2%)
#STOMACH	(25)	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
#COLON	(25)	(48)	(46)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)		
#COLONIC SUBMUCOSA	(25)	(48)	(46)	(47)
HYPERPLASIA, LYMPHOID	1 (4%)			

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
#THYMUS	(15)	(37)	(34)	(33)
BRANCHIAL CYST	1 (7%)			
CONGESTION, NOS		4 (11%)	2 (6%)	
INFLAMMATION, CHRONIC	1 (7%)			
HYPERPLASIA, LYMPHOID			1 (3%)	
CIRCULATORY SYSTEM				
#LYMPH NODE	(22)	(39)	(39)	(43)
LYMPHANGIECTASIS			3 (8%)	1 (2%)
#RENAL LYMPH NODE	(22)	(39)	(39)	(43)
LYMPHANGIECTASIS		2 (5%)		
#HEART	(25)	(50)	(49)	(50)
CALCIFICATION, FOCAL		1 (2%)	1 (2%)	
#HEART/ATRIUM	(25)	(50)	(49)	(50)
THROMBUS, MURAL			2 (4%)	1 (2%)
#MYOCARDIUM	(25)	(50)	(49)	(50)
INFLAMMATION, FOCAL		2 (4%)		
INFLAMMATION, MULTIFOCAL			4 (8%)	4 (8%)
INFLAMMATION, CHRONIC	4 (16%)	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL	10 (40%)	12 (24%)	10 (20%)	12 (24%)
CALCIFICATION, NOS	2 (8%)	1 (2%)		
#ENDOCARDIUM	(25)	(50)	(49)	(50)
INFLAMMATION, NOS				1 (2%)
#CARDIAC VALVE	(25)	(50)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)	1 (2%)
*BLOOD VESSEL	(25)	(50)	(50)	(50)
MEDIAL CALCIFICATION	2 (8%)			
*ARTERY	(25)	(50)	(50)	(50)
MEDIAL CALCIFICATION	3 (12%)	5 (10%)	4 (8%)	1 (2%)
*AORTA	(25)	(50)	(50)	(50)
ARTERIOSCLEROSIS, NOS			1 (2%)	
MEDIAL CALCIFICATION		2 (4%)	5 (10%)	4 (8%)
*PULMONARY ARTERY	(25)	(50)	(50)	(50)
MEDIAL CALCIFICATION			2 (4%)	

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
*PANCREATIC ARTERY,	(25)	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	
MEDIAL CALCIFICATION			1 (2%)	
#PANCREAS	(23)	(49)	(48)	(50)
PERIARTERITIS		1 (2%)		4 (8%)
#SMALL INTESTINE	(24)	(49)	(48)	(49)
PERIARTERITIS			1 (2%)	
*MESENTERY	(25)	(50)	(50)	(50)
PERIARTERITIS		1 (2%)		
#TESTIS	(25)	(50)	(50)	(50)
PERIARTERITIS	8 (32%)	10 (20%)	9 (18%)	14 (28%)
#THYMUS	(15)	(37)	(34)	(33)
PERIARTERITIS			1 (3%)	1 (3%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(25)	(49)	(45)	(50)
DILATATION, NOS		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
ATROPHY, NOS	1 (4%)	1 (2%)		
ATROPHY, FOCAL		1 (2%)		
#LIVER	(24)	(50)	(50)	(50)
CALCULUS, NOS		1 (2%)		
CONGESTION, NOS	1 (4%)	5 (10%)	3 (6%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (8%)	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
FIBROSIS			1 (2%)	
HEPATITIS, TOXIC		1 (2%)		14 (28%)
CLOUDY SWELLING	3 (13%)	3 (6%)	1 (2%)	1 (2%)
NECROSIS, NOS		1 (2%)		
NECROSIS, FOCAL	1 (4%)			2 (4%)
METAMORPHOSIS FATTY	4 (17%)	5 (10%)	5 (10%)	3 (6%)
HEMOSIDEROSIS				1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (4%)			
FOCAL CELLULAR CHANGE		3 (6%)	3 (6%)	6 (12%)
CYTOLOGIC DEGENERATION	1 (4%)	1 (2%)		

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HYPERTROPHY, FOCAL			1 (2%)	
ANGIECTASIS				1 (2%)
#LIVER/CENTRILOBULAR	(24)	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)		1 (2%)
HEMORRHAGE		1 (2%)		
CLOUDY SWELLING		1 (2%)	4 (8%)	8 (16%)
NECROSIS, NOS	1 (4%)	2 (4%)	2 (4%)	
METAMORPHOSIS FATTY	7 (29%)	22 (44%)	38 (76%)	43 (86%)
ANGIECTASIS		1 (2%)		
#LIVER/HEPATOCYTES	(24)	(50)	(50)	(50)
CLOUDY SWELLING	1 (4%)			
#BILE DUCT	(24)	(50)	(50)	(50)
HYPERPLASIA, NOS	8 (33%)	20 (40%)	22 (44%)	24 (48%)
#PANCREAS	(23)	(49)	(48)	(50)
CONGESTION, NOS				1 (2%)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
FIBROSIS		1 (2%)		
ATROPHY, NOS	1 (4%)		1 (2%)	1 (2%)
ATROPHY, FOCAL	2 (9%)	5 (10%)	8 (17%)	7 (14%)
#STOMACH	(25)	(50)	(49)	(50)
DILATATION, NOS		1 (2%)		
INFLAMMATION, FOCAL			1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)
CALCIFICATION, FOCAL			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERKERATOSIS			3 (6%)	10 (20%)
ACANTHOSIS			3 (6%)	10 (20%)
#GASTRIC MUCOSA	(25)	(50)	(49)	(50)
DILATATION, NOS		3 (6%)		
CYST, NOS		5 (10%)	2 (4%)	2 (4%)
HEMORRHAGE				1 (2%)
INFLAMMATION, FOCAL				1 (2%)
ULCER, FOCAL				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
INFLAMMATION, CHRONIC		2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
EROSION	1 (4%)			

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
FIBROSIS, FOCAL	1 (4%)			
NECROSIS, FOCAL		1 (2%)		
CALCIFICATION, NOS	7 (28%)	2 (4%)	7 (14%)	4 (8%)
HYPERKERATOSIS	1 (4%)	1 (2%)	2 (4%)	
ACANTHOSIS	1 (4%)	1 (2%)	2 (4%)	
#GASTRIC SUBMUCOSA	(25)	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (4%)			
#GASTRIC SEROSA	(25)	(50)	(49)	(50)
CALCIFICATION, NOS	1 (4%)			
#COLON	(25)	(48)	(46)	(47)
INFLAMMATION, CHRONIC FOCAL	3 (12%)			
NEMATODIASIS	1 (4%)		1 (2%)	1 (2%)
URINARY SYSTEM				
#KIDNEY	(25)	(50)	(50)	(50)
CALCULUS, NOS			1 (2%)	
MINERALIZATION			1 (2%)	
HYDRONEPHROSIS		2 (4%)		
CYST, NOS		1 (2%)		
CONGESTION, NOS			1 (2%)	
PYELONEPHRITIS SUPPURATIVE			1 (2%)	
INFLAMMATION, CHRONIC	22 (88%)	47 (94%)	47 (94%)	50 (100%)
CYTOLOGIC DEGENERATION	1 (4%)			
#KIDNEY/PELVIS	(25)	(50)	(50)	(50)
MINERALIZATION	1 (4%)	2 (4%)	1 (2%)	
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
CALCIFICATION, NOS			2 (4%)	2 (4%)
CALCIFICATION, FOCAL		1 (2%)	2 (4%)	2 (4%)
HYPERPLASIA, EPITHELIAL	6 (24%)	9 (18%)	6 (12%)	4 (8%)
HYPERPLASIA, FOCAL			1 (2%)	
#URINARY BLADDER	(24)	(48)	(49)	(47)
CALCULUS, NOS			1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	3 (6%)	1 (2%)
HYPERPLASIA, EPITHELIAL		2 (4%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(43)	(43)	(40)
CONGESTION, NOS	1 (5%)	1 (2%)		

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
HYPERPLASIA, NOS		2 (5%)		
HYPERPLASIA, CHROMOPHOBE-CELL	1 (5%)	1 (2%)		
#ADRENAL	(24)	(50)	(49)	(49)
CONGESTION, NOS		1 (2%)	1 (2%)	
METAMORPHOSIS FATTY		2 (4%)	1 (2%)	1 (2%)
#ADRENAL CORTEX	(24)	(50)	(49)	(49)
METAMORPHOSIS FATTY	7 (29%)	8 (16%)	10 (20%)	8 (16%)
LIPOIDOSIS	1 (4%)	1 (2%)		
CALCIFICATION, FOCAL				1 (2%)
HYPERPLASIA, NODULAR	2 (8%)			
#THYROID	(22)	(48)	(50)	(50)
CYSTIC FOLLICLES		1 (2%)	2 (4%)	1 (2%)
FOLLICULAR CYST, NOS			1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)	2 (4%)
DEPLETION		1 (2%)		
HYPERPLASIA, NOS		2 (4%)		
HYPERPLASIA, C-CELL	1 (5%)	5 (10%)	4 (8%)	2 (4%)
#PARATHYROID	(20)	(41)	(40)	(36)
HYPERPLASIA, NOS	9 (45%)	12 (29%)	11 (28%)	5 (14%)
#PANCREATIC ISLETS	(23)	(49)	(48)	(50)
HYPERPLASIA, NOS			1 (2%)	1 (2%)
HYPERPLASIA, FOCAL				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(50)
GALACTOCELE		1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
HYPERPLASIA, NOS	1 (4%)	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)		
*BULBOURETHRAL GLAND	(25)	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		
#PROSTATE	(25)	(50)	(49)	(47)
INFLAMMATION, FOCAL		1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (4%)			
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		

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

TABLE 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%)	2 (4%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL	4 (16%)	1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	3 (6%)	1 (2%)
INFLAMMATION, CHRONIC NECROTIZIN		1 (2%)		
NECROSIS, NOS		1 (2%)		
*SEMINAL VESICLE	(25)	(50)	(50)	(50)
RETENTION OF CONTENT		2 (4%)		
INFLAMMATION, CHRONIC				2 (4%)
FIBROSIS				1 (2%)
HYPERPLASIA, NOS		1 (2%)		
#TESTIS	(25)	(50)	(50)	(50)
EDEMA, INTERSTITIAL		1 (2%)		
STEATITIS		1 (2%)		
DEGENERATION, NOS	14 (56%)	21 (42%)	20 (40%)	17 (34%)
NECROSIS, FOCAL			2 (4%)	
CALCIFICATION, NOS		1 (2%)		
CALCIFICATION, FOCAL			2 (4%)	1 (2%)
*EPIDIDYMIS	(25)	(50)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)		
*VAS DEFERENS	(25)	(50)	(50)	(50)
CYST, NOS	1 (4%)			
*SPERMATIC CORD	(25)	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(25)	(49)	(48)	(47)
CONGESTION, NOS		2 (4%)		
#BASAL GANGLIA	(25)	(49)	(48)	(47)
CALCIFICATION, FOCAL	1 (4%)			
SPECIAL SENSE ORGANS				
*EYE	(25)	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)		
*EYE/CORNEA	(25)	(50)	(50)	(50)
INFLAMMATION, FOCAL	1 (4%)			

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

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

	VEHICLE CONTROL NO. 3	LOW DOSE	MID DOSE	HIGH DOSE
INFLAMMATION, CHRONIC			1 (2%)	
*EYE/LACRIMAL GLAND	(25)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	1 (2%)	3 (6%)	3 (6%)
INFLAMMATION, MULTIFOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
MUSCULOSKELETAL SYSTEM				
*STERNUM	(25)	(50)	(50)	(50)
FIBROSIS		1 (2%)		
*SKELETAL MUSCLE	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)	
BODY CAVITIES				
*MEDIASTINUM	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (4%)			
*PLEURA	(25)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (4%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(50)
CONGESTION, NOS	1 (4%)			
ADIPOSE TISSUE				
HEMORRHAGE				1
INFLAMMATION, CHRONIC				1
FIBROSIS, FOCAL				1
PIGMENTATION, NOS				1
SPECIAL MORPHOLOGY SUMMARY				
NONE				

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

TABLE C3.

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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				2 (8%)	1 (5%)
ABSCESS, NOS			1 (4%)		
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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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)
EPIDERMAL INCLUSION CYST				1 (2%)
ULCER, CHRONIC	1 (4%)			1 (2%)
*SUBCUT TISSUE	(25)	(50)	(50)	(49)
CYST, NOS			1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
*NASAL CAVITY	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		3 (6%)	3 (6%)	
INFLAMMATION, CHRONIC SUPPURATIV	2 (8%)			
*LARYNX	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
#TRACHEA	(24)	(48)	(49)	(45)
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	2 (4%)	
#LUNG	(25)	(49)	(50)	(49)
CONGESTION, NOS	3 (12%)	4 (8%)	2 (4%)	3 (6%)
EDEMA, NOS				1 (2%)
HEMORRHAGE			1 (2%)	2 (4%)
BRONCHOPNEUMONIA SUPPURATIVE		1 (2%)		
BRONCHOPNEUMONIA NECROTIZING			1 (2%)	
ABSCESS, NOS	1 (4%)			
PNEUMONIA, CHRONIC MURINE	19 (76%)	31 (63%)	44 (88%)	43 (88%)
PNEUMONIA INTERSTITIAL CHRONIC				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
BRONCHOPNEUMONIA CHRONIC SUPPURA		1 (2%)		
GRANULOMA, NOS	1 (4%)	1 (2%)		1 (2%)
FIBROSIS			1 (2%)	
NECROSIS, NOS	1 (4%)			
CRYSTALS, NOS	1 (4%)			
PIGMENTATION, NOS	1 (4%)			
HYPERPLASIA, ADENOMATOUS		11 (22%)	15 (30%)	34 (69%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (4%)			
METAPLASIA, SQUAMOUS	1 (4%)			1 (2%)
#LUNG/ALVEOLI	(25)	(49)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
SCAR			1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(23)	(44)	(48)	(42)
ATROPHY, NOS				1 (2%)
MYELOFIBROSIS				1 (2%)
#SPLEEN	(25)	(50)	(49)	(46)
CONGESTION, NOS	3 (12%)	2 (4%)	1 (2%)	
INFARCT, NOS				1 (2%)
HEMOSIDEROSIS	5 (20%)	2 (4%)	2 (4%)	1 (2%)
ATROPHY, FOCAL				1 (2%)
HEMATOPOIESIS	7 (28%)	17 (34%)	10 (20%)	10 (22%)
#LYMPH NODE	(19)	(32)	(36)	(35)
INFLAMMATION, ACUTE				1 (3%)
INFLAMMATION, CHRONIC		2 (6%)	1 (3%)	
HEMOSIDEROSIS		1 (3%)		
HISTIOCYTOSIS				1 (3%)
HYPERPLASIA, LYMPHOID			1 (3%)	
#SUBMANDIBULAR L.NODE	(19)	(32)	(36)	(35)
CONGESTION, NOS	1 (5%)			
#MANDIBULAR L. NODE	(19)	(32)	(36)	(35)
CONGESTION, NOS	1 (5%)	1 (3%)		1 (3%)
HYPERPLASIA, LYMPHOID				2 (6%)
#LUMBAR LYMPH NODE	(19)	(32)	(36)	(35)
HYPERPLASIA, NOS		1 (3%)		
#MESENTERIC L. NODE	(19)	(32)	(36)	(35)
INFLAMMATION, NOS				1 (3%)

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
#INGUINAL LYMPH NODE	(19)	(32)	(36)	(35)
HYPERPLASIA, NOS			1 (3%)	
#LIVER	(25)	(49)	(50)	(49)
HEMATOPOIESIS	3 (12%)	3 (6%)		2 (4%)
#ADRENAL	(24)	(49)	(49)	(46)
HEMATOPOIESIS	1 (4%)	1 (2%)		
#THYMUS	(16)	(38)	(39)	(34)
ECTOPIA	1 (6%)			
ULTIMOBRANCHIAL CYST				1 (3%)
CYST, NOS		1 (3%)		
COLLOID CYST	1 (6%)			
CONGESTION, NOS		1 (3%)		
HEMORRHAGE			1 (3%)	
INFLAMMATION, CHRONIC				1 (3%)
HEMOSIDEROSIS		1 (3%)		
CIRCULATORY SYSTEM				
#HEART	(25)	(48)	(48)	(47)
THROMBOSIS, NOS		1 (2%)		
INFLAMMATION, CHRONIC FOCAL				1 (2%)
CALCIFICATION, FOCAL				1 (2%)
#BASE OF HEART	(25)	(48)	(48)	(47)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
#HEART/ATRIUM	(25)	(48)	(48)	(47)
THROMBUS, MURAL				1 (2%)
#HEART/VENTRICLE	(25)	(48)	(48)	(47)
THROMBOSIS, NOS				1 (2%)
#MYOCARDIUM	(25)	(48)	(48)	(47)
INFLAMMATION, FOCAL		1 (2%)		
INFLAMMATION, MULTIFOCAL				3 (6%)
INFLAMMATION, CHRONIC	1 (4%)			1 (2%)
INFLAMMATION, CHRONIC FOCAL	3 (12%)	3 (6%)	5 (10%)	6 (13%)
#ENDOCARDIUM	(25)	(48)	(48)	(47)
INFLAMMATION, 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
FIBROSIS, FOCAL		1 (2%)		
*ARTERY	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION				1 (2%)
*AORTA	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION			1 (2%)	
*PULMONARY ARTERY	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION			1 (2%)	
*PANCREATIC ARTERY,	(25)	(50)	(50)	(49)
MEDIAL CALCIFICATION			1 (2%)	
#KIDNEY/PELVIS	(25)	(49)	(50)	(49)
THROMBOSIS, NOS				1 (2%)
#THYMUS	(16)	(38)	(39)	(34)
PERIARTERITIS				1 (3%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(24)	(48)	(49)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
INFLAMMATION, CHRONIC	1 (4%)			
INFLAMMATION, CHRONIC FOCAL	1 (4%)			
ATROPHY, FOCAL	1 (4%)	1 (2%)		
#LIVER	(25)	(49)	(50)	(49)
CYST, NOS			2 (4%)	
CONGESTION, NOS		1 (2%)	2 (4%)	
HEMORRHAGE	1 (4%)			
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	3 (6%)	2 (4%)
INFLAMMATION, CHRONIC		1 (2%)	2 (4%)	
FIBROSIS				1 (2%)
CIRRHOSIS, BILIARY	1 (4%)			
HEPATITIS, TOXIC			1 (2%)	32 (65%)
CLOUDY SWELLING	6 (24%)	2 (4%)	1 (2%)	1 (2%)
DEGENERATION, HYDROPIC		1 (2%)		
NECROSIS, NOS	2 (8%)			
NECROSIS, FOCAL	1 (4%)	1 (2%)		
METAMORPHOSIS FATTY	5 (20%)	19 (39%)	23 (46%)	12 (24%)
CALCIFICATION, FOCAL			1 (2%)	
CYTOPLASMIC VACUOLIZATION	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
BASOPHILIC CYTO CHANGE	1 (4%)			
FOCAL CELLULAR CHANGE			8 (16%)	16 (33%)
ANGIECTASIS	3 (12%)	2 (4%)		
#LIVER/CENTRILOBULAR	(25)	(49)	(50)	(49)
DEGENERATION, NOS	1 (4%)			
CLOUDY SWELLING		1 (2%)		
NECROSIS, NOS		1 (2%)		
METAMORPHOSIS FATTY	1 (4%)		1 (2%)	1 (2%)
#BILE DUCT	(25)	(49)	(50)	(49)
HYPERPLASIA, NOS	8 (32%)	10 (20%)	10 (20%)	2 (4%)
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)	
#PANCREAS	(24)	(48)	(50)	(48)
CONGESTION, NOS		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
ADHESION, NOS				1 (2%)
ATROPHY, FOCAL		3 (6%)	3 (6%)	4 (8%)
#STOMACH	(25)	(50)	(50)	(48)
INFLAMMATION, FOCAL	1 (4%)			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)		
HYPERKERATOSIS		2 (4%)		2 (4%)
ACANTHOSIS		2 (4%)		2 (4%)
#GASTRIC MUCOSA	(25)	(50)	(50)	(48)
CALCIFICATION, NOS			1 (2%)	
#SMALL INTESTINE	(24)	(49)	(49)	(47)
INFLAMMATION, CHRONIC			1 (2%)	
#DUODENUM	(24)	(49)	(49)	(47)
INFLAMMATION, CHRONIC			1 (2%)	
#COLON	(24)	(48)	(49)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (17%)			
INFLAMMATION, CHRONIC	4 (17%)			
INFLAMMATION, CHRONIC FOCAL	1 (4%)		1 (2%)	
NEMATODIASIS		3 (6%)		
URINARY SYSTEM				
#KIDNEY	(25)	(49)	(50)	(49)
CALCULUS, NOS		2 (4%)	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
HYDRONEPHROSIS				1 (2%)
CONGESTION, NOS		1 (2%)		
PYELONEPHRITIS, NOS			1 (2%)	
INFLAMMATION, CHRONIC	15 (60%)	30 (61%)	23 (46%)	30 (61%)
CALCIFICATION, NOS			1 (2%)	
CALCIFICATION, FOCAL		1 (2%)	1 (2%)	1 (2%)
#KIDNEY/CORTEX	(25)	(49)	(50)	(49)
POLYCYSTIC KIDNEY	1 (4%)			
#KIDNEY/TUBULE	(25)	(49)	(50)	(49)
MINERALIZATION	2 (8%)			
#KIDNEY/PELVIS	(25)	(49)	(50)	(49)
MINERALIZATION	18 (72%)			
INFLAMMATION, NOS		2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (4%)			
CALCIFICATION, NOS		17 (35%)	23 (46%)	25 (51%)
CALCIFICATION, FOCAL		8 (16%)	1 (2%)	2 (4%)
HYPERPLASIA, EPITHELIAL	16 (64%)	23 (47%)	22 (44%)	30 (61%)
*URETER	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC				1 (2%)
#URINARY BLADDER	(22)	(43)	(47)	(43)
INFLAMMATION, HEMORRHAGIC			1 (2%)	
INFLAMMATION, CHRONIC	1 (5%)	2 (5%)	1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (5%)	3 (7%)	1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(22)	(47)	(44)	(43)
CYST, NOS	1 (5%)	1 (2%)		
CONGESTION, NOS		1 (2%)		1 (2%)
CHOLESTEROL DEPOSIT	1 (5%)			
HYPERPLASIA, NOS		1 (2%)	1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	1 (5%)			
#ADRENAL	(24)	(49)	(49)	(46)
CONGESTION, NOS	6 (25%)	10 (20%)	3 (6%)	2 (4%)
HEMORRHAGIC CYST	2 (8%)	3 (6%)	5 (10%)	3 (7%)
METAMORPHOSIS FATTY	1 (4%)			
HYPERPLASIA, NODULAR	1 (4%)			
ANGIECTASIS	3 (13%)			

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
#ADRENAL CORTEX	(24)	(49)	(49)	(46)
CONGESTION, NOS		4 (8%)		
METAMORPHOSIS FATTY		4 (8%)	7 (14%)	3 (7%)
ATROPHY, NOS	1 (4%)			
HYPERPLASIA, NODULAR	1 (4%)			
#THYROID	(24)	(45)	(49)	(47)
INFLAMMATION, CHRONIC				2 (4%)
HYPERPLASIA, C-CELL		8 (18%)	6 (12%)	3 (6%)
#PARATHYROID	(19)	(33)	(35)	(37)
HYPERPLASIA, NOS		1 (3%)		
#PANCREATIC ISLETS	(24)	(48)	(50)	(48)
DEGENERATION, HYDROPIC		1 (2%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(50)	(49)
GALACTOCELE	1 (4%)	1 (2%)		
HYPERPLASIA, NOS	1 (4%)		1 (2%)	
*VAGINA	(25)	(50)	(50)	(49)
INFLAMMATION, CHRONIC				1 (2%)
ACANTHOSIS				1 (2%)
#UTERUS	(24)	(50)	(50)	(49)
HEMORRHAGE	1 (4%)			
INFLAMMATION, SUPPURATIVE	1 (4%)			
INFLAMMATION, NECROTIZING		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	3 (13%)	5 (10%)	1 (2%)	10 (20%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (4%)			
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)		
FIBROSIS, FOCAL		1 (2%)	1 (2%)	
NECROSIS, FOCAL	1 (4%)			
HEMOSIDEROSIS	1 (4%)			
ATROPHY, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL	2 (8%)			
#UTERUS/ENDOMETRIUM	(24)	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, NECROTIZING				1 (2%)
INFLAMMATION, VESICULAR	1 (4%)	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
INFLAMMATION, CHRONIC	1 (4%)			1 (2%)
INFLAMMATION CHRONIC CYSTIC		1 (2%)	2 (4%)	3 (6%)
FIBROSIS	1 (4%)			
HYPERPLASIA, NOS	1 (4%)		2 (4%)	
METAPLASIA, SQUAMOUS			1 (2%)	
#OVARY	(23)	(47)	(50)	(48)
ATROPHY, NOS	5 (22%)	5 (11%)	2 (4%)	6 (13%)
LUTEINIZATION		1 (2%)	1 (2%)	1 (2%)
NERVOUS SYSTEM				
#BRAIN	(25)	(47)	(49)	(48)
HEMORRHAGE		1 (2%)		
NECROSIS, FOCAL			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(25)	(50)	(50)	(49)
FIBROSIS	1 (4%)			
SCAR	1 (4%)			
*EYE/CRYSTALLINE LENS	(25)	(50)	(50)	(49)
DEGENERATION, NOS	1 (4%)			
*EYE/LACRIMAL GLAND	(25)	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (8%)	5 (10%)	8 (16%)	14 (29%)
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(25)	(50)	(50)	(49)
INFLAMMATION, FOCAL			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(50)	(49)
CONGESTION, NOS	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
INFLAMMATION, CHRONIC				1 (2%)
TOE				
HYPERPLASIA, EPITHELIAL			1	
ADIPOSE TISSUE				
INFLAMMATION, CHRONIC		1		
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY				1

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

APPENDIX D

Summary of the Incidence of Nonneoplastic Lesions in Mice Administered TCDD By Gavage

TABLE D1.

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	23	49	49	50
INTEGUMENTARY SYSTEM				
*SKIN	(23)	(49)	(49)	(50)
SEBACEOUS CYST				1 (2%)
ULCER, NOS				1 (2%)
ULCER, FOCAL			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
*SUBCUT TISSUE	(23)	(49)	(49)	(50)
SEBACEOUS CYST			1 (2%)	1 (2%)
ABSCESS, NOS			1 (2%)	2 (4%)
FIBROSIS			1 (2%)	
NECROSIS, NOS			1 (2%)	
RESPIRATORY SYSTEM				
#TRACHEA	(23)	(49)	(47)	(43)
INFLAMMATION, CHRONIC		1 (2%)		
#LUNG/BRONCHUS	(23)	(48)	(48)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		6 (13%)	3 (6%)	7 (14%)
INFLAMMATION, CHRONIC	1 (4%)			
#LUNG/BRONCHIOLE	(23)	(48)	(48)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (17%)			
#LUNG	(23)	(48)	(48)	(50)
CONGESTION, NOS	7 (30%)	4 (8%)	8 (17%)	11 (22%)
EDEMA, NOS	1 (4%)	1 (2%)	1 (2%)	
BRONCHOPNEUMONIA, FOCAL		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		13 (27%)	11 (23%)	15 (30%)
PNEUMONIA INTERSTITIAL CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				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
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
ALVEOLAR MACROPHAGES	1 (4%)			5 (10%)
HYPERPLASIA, ADENOMATOUS	2 (9%)			1 (2%)
#LUNG/ALVEOLI	(23)	(48)	(48)	(50)
HEMORRHAGE				1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(21)	(47)	(47)	(50)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
AMYLOIDOSIS	1 (5%)			
HYPERPLASIA, LYMPHOID			1 (2%)	
HEMATOPOIESIS	1 (5%)	1 (2%)	3 (6%)	4 (8%)
#LYMPH NODE	(16)	(25)	(32)	(36)
CONGESTION, NOS	2 (13%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (6%)			
INFLAMMATION, CHRONIC	3 (19%)			1 (3%)
HYPERPLASIA, NOS	2 (13%)			
HYPERPLASIA, LYMPHOID	2 (13%)	1 (4%)		
#PANCREATIC L.NODE	(16)	(25)	(32)	(36)
CONGESTION, NOS	1 (6%)			
INFLAMMATION, CHRONIC				1 (3%)
HEMATOPOIESIS	1 (6%)			
#MESENTERIC L. NODE	(16)	(25)	(32)	(36)
CONGESTION, NOS	1 (6%)			
HEMORRHAGE			1 (3%)	
HYPERPLASIA, LYMPHOID	1 (6%)			
#SMALL INTESTINE	(21)	(44)	(44)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)	
#PEYER'S PATCH	(21)	(44)	(44)	(48)
HYPERPLASIA, LYMPHOID				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(23)	(44)	(48)	(50)
PERIARTERITIS				1 (2%)
#MYOCARDIUM	(23)	(44)	(48)	(50)
INFLAMMATION, MULTIFOCAL			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
INFLAMMATION, CHRONIC FOCAL	1 (4%)	1 (2%)		3 (6%)
#PANCREAS	(23)	(48)	(45)	(48)
PERIARTERITIS		1 (2%)		1 (2%)
#KIDNEY	(23)	(49)	(49)	(50)
PERIARTERITIS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(22)	(47)	(46)	(48)
INFLAMMATION, FOCAL				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		12 (26%)	8 (17%)	11 (23%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)	
#LIVER	(23)	(49)	(49)	(50)
CONGESTION, NOS			1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (13%)		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC	1 (4%)			
FIBROSIS	1 (4%)			
HEPATITIS, TOXIC	1 (4%)	5 (10%)	3 (6%)	44 (88%)
NECROSIS, NOS	1 (4%)			2 (4%)
NECROSIS, FOCAL	1 (4%)	1 (2%)		1 (2%)
METAMORPHOSIS FATTY	1 (4%)		5 (10%)	
CALCIFICATION, NOS	1 (4%)			
FOCAL CELLULAR CHANGE	1 (4%)			
HYPERTROPHY, NOS	1 (4%)			
HYPERTROPHY, FOCAL				1 (2%)
#LIVER/CENTRILOBULAR	(23)	(49)	(49)	(50)
NECROSIS, NOS		1 (2%)		
METAMORPHOSIS FATTY		2 (4%)	2 (4%)	
#PANCREAS	(23)	(48)	(45)	(48)
CYSTIC DUCTS		1 (2%)		
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (4%)			1 (2%)
FIBROSIS	1 (4%)			
NECROSIS, FAT	1 (4%)			
ATROPHY, FOCAL	1 (4%)	1 (2%)		
#STOMACH	(22)	(47)	(46)	(50)
INFLAMMATION, CHRONIC FOCAL		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
#SMALL INTESTINE	(21)	(44)	(44)	(48)
INFLAMMATION, CHRONIC	1 (5%)			
#COLON	(22)	(46)	(43)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	5 (23%)			
URINARY SYSTEM				
#KIDNEY	(23)	(49)	(49)	(50)
HYDRONEPHROSIS			1 (2%)	4 (8%)
CONGESTION, NOS				1 (2%)
PYELONEPHRITIS, NOS			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	12 (52%)	31 (63%)	30 (61%)	43 (86%)
INFLAMMATION, CHRONIC		2 (4%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL	2 (9%)			
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
#KIDNEY/CORTEX	(23)	(49)	(49)	(50)
CYST, NOS				1 (2%)
#KIDNEY/TUBULE	(23)	(49)	(49)	(50)
CALCIFICATION, NOS				1 (2%)
#URINARY BLADDER	(22)	(48)	(48)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (5%)			
INFLAMMATION, CHRONIC	2 (9%)	2 (4%)	3 (6%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL	3 (14%)	1 (2%)		1 (2%)
HYPERPLASIA, EPITHELIAL	2 (9%)		1 (2%)	
*URETHRA	(23)	(49)	(49)	(50)
FIBROSIS			1 (2%)	
HYPERPLASIA, NOS			1 (2%)	
ENDOCRINE SYSTEM				
#ADRENAL CORTEX	(23)	(43)	(46)	(46)
HYPERPLASIA, NODULAR	2 (9%)			
#THYROID	(22)	(48)	(48)	(49)
CYSTIC FOLLICLES			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		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
#PANCREATIC ISLETS	(23)	(48)	(45)	(48)
HYPERPLASIA, NOS				2 (4%)
HYPERPLASIA, FOCAL				1 (2%)
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(23)	(49)	(49)	(50)
INFLAMMATION, CHRONIC	2 (9%)			
#PROSTATE	(21)	(49)	(47)	(48)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC	2 (10%)	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (5%)			
INFLAMMATION, CHRONIC SUPPURATIV			2 (4%)	1 (2%)
*SEMINAL VESICLE	(23)	(49)	(49)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)	1 (2%)
#TESTIS	(22)	(48)	(47)	(48)
DEGENERATION, NOS	2 (9%)	3 (6%)	5 (11%)	5 (10%)
*EPIDIDYMIS	(23)	(49)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)		1 (2%)
*SPERMATIC CORD	(23)	(49)	(49)	(50)
INFLAMMATION, CHRONIC				1 (2%)
NERVOUS SYSTEM				
*PERIPHERAL NERVE	(23)	(49)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)		
#BRAIN	(23)	(47)	(48)	(47)
INFLAMMATION, FOCAL		1 (2%)		
CALCIFICATION, FOCAL		19 (40%)	17 (35%)	11 (23%)
#BASAL GANGLIA	(23)	(47)	(48)	(47)
CALCIFICATION, FOCAL	8 (35%)			
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(23)	(49)	(49)	(50)
INFLAMMATION, CHRONIC 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
*HARDERIAN GLAND	(23)	(49)	(49)	(50)
INFLAMMATION, SUPPURATIVE	1 (4%)			
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(23)	(49)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (13%)	2 (4%)	2 (4%)	1 (2%)
SITE UNKNOWN				
ABSCESS, NOS	1			
ADIPOSE TISSUE				
HEMORRHAGE				1
INFLAMMATION, CHRONIC		2		
INFLAMMATION, CHRONIC NECROTIZIN		1		
FIBROSIS		1		1
CONNECTIVE TISSUE				
STEATITIS	1			
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		2		
ANIMAL MISSING/NO NECROPSY	1			
AUTOLYSIS/NO NECROPSY	1	1	1	

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

TABLE D3.

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

	UNTREATED CONTROL NO. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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. 2	UNTREATED CONTROL NO. 3	UNTREATED CONTROL NO. 1	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 TCDD 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	48	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	48	47
INTEGUMENTARY SYSTEM				
*SKIN	(25)	(50)	(48)	(47)
ULCER, NOS				1 (2%)
HYPERKERATOSIS			1 (2%)	
*SUBCUT TISSUE	(25)	(50)	(48)	(47)
HEMORRHAGE				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
ABSCESS, NOS				1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
FIBROSIS		1 (2%)		
NECROSIS, NOS				2 (4%)
NECROSIS, FOCAL				1 (2%)
RESPIRATORY SYSTEM				
*NASAL CAVITY	(25)	(50)	(48)	(47)
INFLAMMATION, CHRONIC FOCAL		3 (6%)	1 (2%)	
#LUNG/BRONCHUS	(25)	(49)	(48)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR		4 (8%)	26 (54%)	6 (13%)
#LUNG/BRONCHIOLE	(25)	(49)	(48)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
#LUNG	(25)	(49)	(48)	(46)
ATELECTASIS	1 (4%)		1 (2%)	
CONGESTION, NOS		4 (8%)		6 (13%)
EDEMA, NOS		1 (2%)		1 (2%)
HEMORRHAGE	1 (4%)			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	14 (29%)	5 (10%)	10 (22%)
PNEUMONIA INTERSTITIAL CHRONIC				1 (2%)
BRONCHOPNEUMONIA, CHRONIC				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
HYPERPLASIA, ADENOMATOUS	1 (4%)			1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(23)	(50)	(48)	(47)
MYELOFIBROSIS	19 (83%)	40 (80%)	44 (92%)	39 (83%)
#SPLEEN	(23)	(49)	(45)	(43)
CONGESTION, NOS	1 (4%)			
HEMOSIDEROSIS			1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	1 (4%)		1 (2%)	
HEMATOPOIESIS	1 (4%)		2 (4%)	2 (5%)
#LYMPH NODE	(22)	(41)	(39)	(35)
HYPERPLASIA, LYMPHOID	3 (14%)		1 (3%)	2 (6%)
#MANDIBULAR L. NODE	(22)	(41)	(39)	(35)
HYPERPLASIA, NOS				1 (3%)
HYPERPLASIA, LYMPHOID	1 (5%)		1 (3%)	2 (6%)
#BRONCHIAL LYMPH NODE	(22)	(41)	(39)	(35)
HYPERPLASIA, LYMPHOID			1 (3%)	
#MIDCOLIC LYMPH NODE	(22)	(41)	(39)	(35)
INFLAMMATION, FOCAL GRANULOMATOU			1 (3%)	
*ADIPOSE TISSUE	(25)	(50)	(48)	(47)
HISTIOCYTOSIS		1 (2%)		
#LIVER	(24)	(50)	(48)	(47)
HEMATOPOIESIS	2 (8%)	1 (2%)	3 (6%)	2 (4%)
#SMALL INTESTINE	(23)	(49)	(46)	(46)
HYPERPLASIA, LYMPHOID	1 (4%)			
#PEYER'S PATCH	(23)	(49)	(46)	(46)
HYPERPLASIA, LYMPHOID	3 (13%)			
#THYMUS	(21)	(38)	(34)	(29)
HYPERPLASIA, LYMPHOID		1 (3%)		
CIRCULATORY SYSTEM				
#MYOCARDIUM	(25)	(47)	(45)	(45)
INFLAMMATION, CHRONIC			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 FOCAL			1 (2%)	5 (11%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(25)	(48)	(46)	(42)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)	8 (17%)	11 (24%)	5 (12%)
#LIVER	(24)	(50)	(48)	(47)
CONGESTION, NOS		1 (2%)	1 (2%)	1 (2%)
HEMORRHAGIC CYST		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (13%)	10 (20%)	11 (23%)	5 (11%)
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (4%)		1 (2%)	
ADHESION, NOS		1 (2%)		
HEPATITIS, TOXIC		1 (2%)	2 (4%)	34 (72%)
DEGENERATION, NOS				1 (2%)
NECROSIS, NOS		1 (2%)		
NECROSIS, FOCAL		2 (4%)		1 (2%)
METAMORPHOSIS FATTY	2 (8%)	1 (2%)	1 (2%)	1 (2%)
HYPERTROPHY, FOCAL			1 (2%)	
*GALLBLADDER	(25)	(50)	(48)	(47)
INFLAMMATION, CHRONIC		1 (2%)		
#PANCREAS	(23)	(49)	(44)	(43)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (4%)			
FIBROSIS			1 (2%)	
ATROPHY, FOCAL	1 (4%)		1 (2%)	
#STOMACH	(25)	(49)	(47)	(46)
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL				1 (2%)
HYPERKERATOSIS				1 (2%)
ACANTHOSIS				1 (2%)
#DUODENUM	(23)	(49)	(46)	(46)
NODULE				1 (2%)
#COLON	(25)	(48)	(45)	(45)
INFLAMMATION, CHRONIC	1 (4%)			
INFLAMMATION, CHRONIC FOCAL	7 (28%)			
URINARY SYSTEM				
#KIDNEY	(24)	(50)	(47)	(45)
HYDRONEPHROSIS			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
CONGESTION, NOS	1 (4%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	7 (29%)	33 (66%)	37 (79%)	30 (67%)
INFLAMMATION, CHRONIC	1 (4%)	1 (2%)	3 (6%)	
FIBROSIS			1 (2%)	
CALCIFICATION, NOS			1 (2%)	
ATROPHY, FOCAL			1 (2%)	
METAPLASIA, OSSEOUS			1 (2%)	
#KIDNEY/GLOMERULUS	(24)	(50)	(47)	(45)
AMYLOIDOSIS		1 (2%)	1 (2%)	
#URINARY BLADDER	(24)	(46)	(46)	(44)
INFLAMMATION, CHRONIC	1 (4%)	6 (13%)	3 (7%)	
INFLAMMATION, CHRONIC FOCAL	9 (38%)	9 (20%)	7 (15%)	10 (23%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, CYSTIC	1 (4%)			
ENDOCRINE SYSTEM				
#ADRENAL	(24)	(50)	(44)	(43)
CONGESTION, NOS			1 (2%)	
#ADRENAL CORTEX	(24)	(50)	(44)	(43)
METAMORPHOSIS FATTY	1 (4%)		1 (2%)	
HYPERTROPHY, FOCAL				1 (2%)
#ZONA RETICULARIS	(24)	(50)	(44)	(43)
PIGMENTATION, NOS		1 (2%)		
ATROPHY, NOS		2 (4%)		
#THYROID	(25)	(50)	(47)	(46)
CYSTIC FOLLICLES		1 (2%)		
FOLLICULAR CYST, NOS	1 (4%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
HYPERPLASIA, C-CELL				1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	2 (4%)	
#PARATHYROID	(12)	(41)	(30)	(28)
CYST, NOS			1 (3%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(25)	(50)	(48)	(47)
GALACTOCELE		3 (6%)	3 (6%)	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
CYST, NOS		1 (2%)		
HYPERPLASIA, NOS			1 (2%)	
*VAGINA	(25)	(50)	(48)	(47)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
ACANTHOSIS			1 (2%)	
#UTERUS	(25)	(50)	(48)	(46)
CONGESTION, NOS				1 (2%)
HEMORRHAGE			1 (2%)	
HEMORRHAGIC CYST	1 (4%)			
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
#UTERUS/ENDOMETRIUM	(25)	(50)	(48)	(46)
INFLAMMATION, VESICULAR	1 (4%)		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (4%)	1 (2%)	2 (4%)	
INFLAMMATION, CHRONIC SUPPURATIV	1 (4%)			
INFLAMMATION CHRONIC CYSTIC		1 (2%)	3 (6%)	2 (4%)
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, CYSTIC	20 (80%)	31 (62%)	31 (65%)	5 (11%)
#OVARY	(23)	(46)	(48)	(45)
CYST, NOS		1 (2%)	2 (4%)	1 (2%)
MULTIPLE CYSTS	2 (9%)			
HEMORRHAGIC CYST		10 (22%)	5 (10%)	3 (7%)
CALCIFICATION, NOS			1 (2%)	
ATROPHY, NOS	22 (96%)	17 (37%)	20 (42%)	23 (51%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(25)	(50)	(48)	(44)
INFLAMMATION, NOS			1 (2%)	
#BRAIN	(25)	(50)	(48)	(44)
HEMORRHAGE			1 (2%)	
CALCIFICATION, NOS			1 (2%)	
CALCIFICATION, FOCAL		22 (44%)	19 (40%)	16 (36%)
#BASAL GANGLIA	(25)	(50)	(48)	(44)
CALCIFICATION, FOCAL	6 (24%)			
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(25)	(50)	(48)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR			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
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(25)	(50)	(48)	(47)
INFLAMMATION, CHRONIC		1 (2%)		
*EPICARDIUM	(25)	(50)	(48)	(47)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(25)	(50)	(48)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	12 (48%)	6 (12%)	1 (2%)	
ADIPOSE TISSUE				
FIBROSIS				1
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY			2	3

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

APPENDIX E

Preparation of 2,3,7,8-Tetrachlorodibenzo-p-dioxin

APPENDIX E

Preparation of 2,3,7,8-Tetrachlorodibenzo-p-dioxin

This compound was prepared by the condensation of potassium 2,4,5-trichlorophenate in the presence of the Ullmann copper catalyst. Before the reaction, the trichlorophenol was sublimed and recrystallized from petroleum ether (b.p. 60°-70°C). The phenol was then converted to its potassium salt by treatment with potassium hydroxide in toluene. Water was removed by azeotropic distillation on a Buchi apparatus, and the salt residue was treated with additional toluene and then evaporated to dryness.

A 50-g sample of dry potassium 2,4,5-trichlorophenate was dissolved in 150 ml of bis(ethoxyethyl)ether (BEEE) containing 200 mg of Ullmann copper catalyst that had previously been washed with acetone and stored under ethylene diacetate. A lower boiling solvent fraction was removed by distillation, and the mixture was refluxed with stirring in an oil bath set at 210° to 215°C. Since longer reaction times increased the conversion, the reaction was allowed to proceed for a minimum of 24 hours.

A dark brown residue was obtained when the BEEE solvent was removed by distillation at atmospheric pressure. The residue was treated with 200 ml of o-dichlorobenzene and heated to 170°C. The resulting solution was filtered hot through fluted filter paper, and an additional 100 ml of hot o-dichlorobenzene was used to wash the reaction flask and filter. The solvent was removed by filtration after cooling to room temperature. The product was washed with 200 ml of 1% sodium methylate in methanol and 200 ml of chloroform and was then recrystallized from o-dichlorobenzene.

APPENDIX F

Quarterly Analyses of Stock Solutions of 2,3,7,8-Tetrachlorodibenzo-p-dioxin

APPENDIX F

Quarterly Analyses of Stock Solutions of 2,3,7,8-Tetrachlorodibenzo-p-dioxin

Stock solutions 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 an electron capture-gas chromatography system. The column was a 2 m x 1/8 in. Dexsil 300 with a N_2/CH_4 carrier-gas flow rate of 50 ml/min and an oven temperature of 275°C. Quantitation was achieved by manually measuring the area under the resultant peaks with a planimeter. These values were then multiplied by the attenuation of the gas chromatography electrometer and compared with standard curves for internal standards and test compounds. The standard curve was represented by a third order polynomial equation fitting response to amounts. The amount of dioxin in the test sample was corrected for injection errors and any loss on the column by the value obtained for the internal standard.

The theoretical concentration for the stock solution was 10 μg TCDD per milliliter of acetone. The actual concentration, as measured by the above method, varied from 6.9 to 15.7 μg/ml. The mean of 20 determinations was 12.1 ± 3.6 μg/ml.

The corn oil:acetone working solutions of TCDD were not analyzed because efforts to develop a method that would quantitatively separate the dioxins from the corn oil were not successful.

☆U.S. GOVERNMENT PRINTING OFFICE: 1982-361-132/3782

NIH Publication No. 82-1765
February 1982