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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAYS OF DDT, TDE, AND p,p'-DDE FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassays of DDT, TDE, and p,p'-DDE conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. These are three of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemicals are not carcinogens because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemicals are carcinogenic for animals under the conditions of the tests and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: These bioassays of DDT, TDE, and p,p'-DDE were conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

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Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the

statistical analyses were performed by Mr. W. W. Belew (6,9), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (10).

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The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiments, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,11), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,12), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

Bioassays of technical-grade DDT, TDE, and p,p'-DDE for possible carcinogenicity were conducted using Osborne-Mendel rats and B6C3F1 mice. Each compound was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each species and sex were placed on test as controls for the bioassay of each compound. The time-weighted average high and low dietary concentrations of DDT were, respectively, 642 and 321 ppm for male rats, 420 and 210 ppm for female rats, 44 and 22 ppm for male mice, and 175 and 87 ppm for female mice. The time-weighted average high and low dietary concentrations of TDE were, respectively, 3294 and 1647 ppm for male rats, 1700 and 850 ppm for female rats, and 822 and 411 ppm for male and female mice. The time-weighted average high and low dietary concentrations of DDE were, respectively, 839 and 437 ppm for male rats, 462 and 242 ppm for female rats, and 261 and 148 ppm for male and female mice. After the 78-week dosing period there was an additional observation period of up to 35 weeks for rats and 15 weeks for mice.

There were significant positive associations between increased chemical concentration and accelerated mortality in female mice dosed with DDT and in both sexes of rats and in female mice dosed with DDE. This association was not demonstrated in other groups. There was, however, poor survival among control and dosed male mice used in the bioassays of DDT and DDE. In all cases adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

When those male rats receiving TDE and their controls were combined within each group so that the numerators of the tumor incidences represented those animals with either a follicular-cell carcinoma or a follicular-cell adenoma of the thyroid, the incidence in the low dose group was significantly higher than that in the control. There was a significant positive association between the concentration of DDE administered and the incidences of hepatocellular carcinomas in male and female mice. Among dosed rats and mice no other neoplasms occurred in statistically significant incidences when compared to their respective control groups.

Under the conditions of these bioassays there was no evidence for the carcinogenicity of DDT in Osborne-Mendel rats or B6C3F1 mice, of TDE in female Osborne-Mendel rats or B6C3F1 mice of either sex, or of p,p'-DDE in Osborne-Mendel rats, although p,p'-DDE was hepatotoxic in Osborne-Mendel rats. The findings suggest a possible carcinogenic effect of TDE in male Osborne-Mendel rats, based on the induction of

combined follicular-cell carcinomas and follicular-cell adenomas of the thyroid. Because of the variation of these tumors in control male rats in this study, the evidence does not permit a more conclusive interpretation of these lesions. p,p'-DDE was carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes.

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I. INTRODUCTION

DDT (NCI No. C00464) is the common name for the technical product of which p,p'-DDT (Figure 1) is the predominant component. The compound is a synthetic, chlorinated hydrocarbon insecticide which has broad-spectrum insecticidal activity. After being used commercially and in large quantities in the United States for more than two decades, its status as an insecticide began to fade in the mid-1960s when environmentalists detected a possible link between DDT and various ecological disturbances including the decline of selected bird populations and numerous instances of fish kills. The growing realization of its ubiquitous distribution throughout all compartments of the biosphere, its persistence in the environment, and its accumulation in tissues of living organisms eventually resulted in the establishment of stringent regulations governing its use.

Despite the imposition of use restrictions, the probability of continued low-level chronic exposure to DDT among the general population remained substantial. The classification of DDT as tumorigenic by the Secretary's Commission on Pesticides and their Relationship to Environmental Health (U.S. Department of Health, Education, and Welfare, 1969) heightened the need for additional chronic toxicity studies and prompted the inclusion of DDT in the NCI Carcinogenesis Testing Program. TDE (Figure 2) (also known as DDD; NCI No. C00475) and DDE (Figure 3) (NCI No. C00555), structurally related to DDT

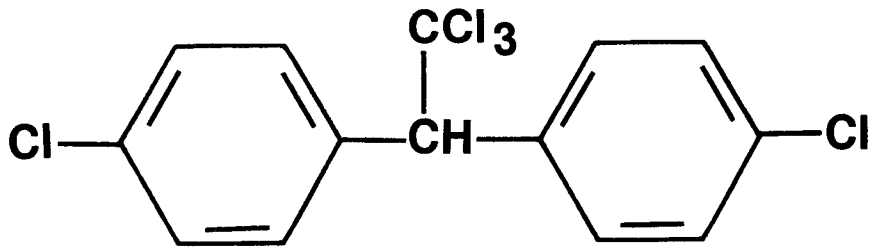

FIGURE 1
CHEMICAL STRUCTURE OF p,p'-DDT

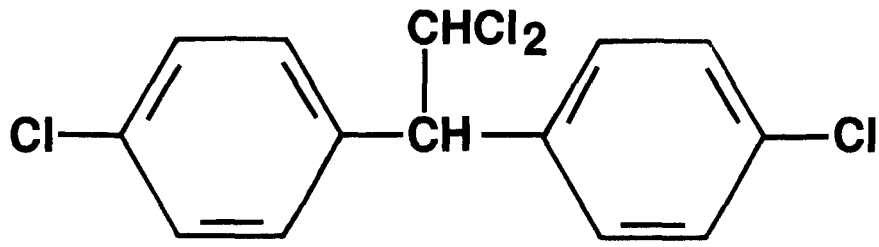

FIGURE 2
CHEMICAL STRUCTURE OF p,p'-TDE

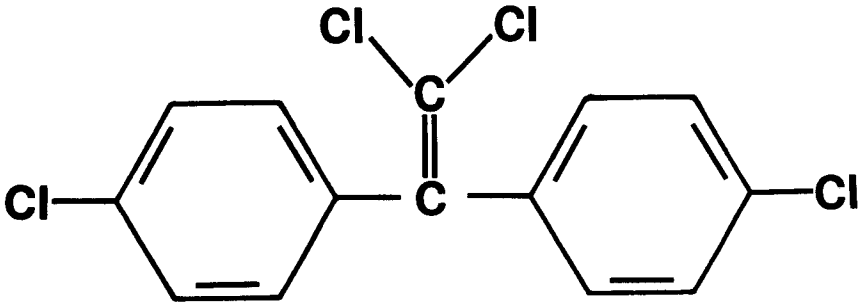

FIGURE 3
CHEMICAL STRUCTURE OF p,p'-DDE

and present as contaminants of the technical-grade compound, were also subjected to bioassay.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for these compounds are 1,1'-(2,2,2-trichloroethylidene) bis(4-chloro)-benzene* for DDT; 1,1'-(2,2-dichloroethylidene) bis (4-chloro)-benzene* for TDE; and 1,1'-(2,2-dichloroethenylidine) bis(4-chloro)-benzene* for DDE. Synonyms include: 1,1,1-trichloro-2,2-bis(p-chlorophenyl)-ethane and p,p'-dichlorodiphenyltrichloroethane for DDT; 1,1-dichloro-2,2-bis(p-chlorophenyl)-ethane and p,p'-dichlorodiphenyldichloroethane for TDE; and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene and p,p'-dichlorodiphenyldichloroethylene for DDE.

DDT has been effective in the past in controlling hundreds of pests attacking vineyard and orchard crops, nursery and greenhouse crops, field crops, vegetables, and forest and shade trees (Andrilenas, 1974; Brooks, 1974; International Agency for Research on Cancer [IARC], 1974). DDT has also profoundly impacted the field of public health where it has played a major role in the control of a large number of insect-borne diseases, most notably malaria. Complete control of mosquito larvae over wide geographical areas as well as long-term protection of dwellings have been achieved, the former through massive aerial spraying programs and the latter through the residual action of

*The CAS registry numbers are: DDT--50-29-3
TDE--72-54-8
DDE--72-55-9

DDT applied as a spray to walls and other home surfaces (Brooks, 1974). Other diseases controlled by DDT include typhus, sleeping sickness, and yellow fever (Brooks, 1974; IARC, 1974). In addition to its agricultural and disease-control applications, DDT has been used against household pests such as houseflies and cockroaches, against pests of livestock (particularly beef and dairy cattle), and as a moth-proofing agent (Brooks, 1974; Andrilenas, 1974; IARC, 1974).

Domestic production of DDT amounted to 123 million pounds in 1969 and declined sharply thereafter (Fowler and Mahan, 1976). The development of widespread resistance to DDT among numerous insect species (Dahlsten et al., 1970) and the corresponding reduction in demand for the pesticide played a significant role in determining production trends; however, the imposition of increasingly stringent use limitations by the U.S. Department of Agriculture (Frost & Sullivan, Inc., 1977), was the major factor in the observed decline in production. By 1972, estimates indicated that as much as 90 percent of DDT consumption in the United States was for use on cotton crops with the remainder used primarily on peanut and soybean crops (IARC, 1974). Following suspension of the pesticide by the U.S. Environmental Protection Agency in 1973, domestic consumption of DDT was restricted to specific public health applications and other minor uses (IARC, 1974).

Although current production statistics are considered proprietary and are therefore not available, it has been estimated that over 70

percent of production in recent years has been for export purposes (Brooks, 1974). Exports in 1975 amounted to 47 million pounds (Fowler and Mahan, 1976). At present, worldwide use of DDT is primarily for prevention of disease, particularly for mosquito abatement in world malaria-control programs (IARC, 1974; Brooks, 1974).

TDE was introduced commercially in the United States in 1945 shortly after the introduction of DDT. Although lacking the broad-spectrum insecticidal activity of DDT, TDE does possess equal or greater potency against the larvae of some mosquitos and lepidoptera (Brooks, 1974). TDE is no longer produced commercially in the United States; however, it was used in the past in this country for protection of a variety of crops including many fruits and vegetables (Farm Chemicals Handbook, 1976). In 1971, 244,000 pounds of TDE were used by farmers in the United States, 67 percent of which were applied to tobacco (Andrilenas, 1974).

The potential for exposure to DDT remains greatest to workers engaged in its manufacture, formulation, or application. During the peak years of DDT usage, estimates of occupational dermal exposure ranged from 84 mg per hour (Hayes, 1959) to 1755 mg per hour (Wolfe et al., 1959; 1967), the latter value experienced by those engaged in indoor spraying operations. Estimates of respiratory exposure during this same period ranged from 0.11 mg per hour (Wolfe et al., 1959) to 14.1 mg per hour (Wolfe and Armstrong, 1971) with formulating plant

workers at highest risk via this route. The average daily intake of DDT by 20 men with high occupational exposure was estimated in 1967 as 17.5 to 18 mg per person or 450 times that of the general population (Laws et al., 1967).

Exposure of the general population to DDT and its metabolites, DDE and TDE, is virtually unavoidable and may occur through inhalation, ingestion, or dermal contact. Exposure via inhalation and dermal contact was probably of greatest concern prior to 1972 in agricultural communities where atmospheric concentrations ranging from 0.1 to 8.0 μg DDT/m^3 were detected during pesticide applications (Tabor, 1966). However, atmospheric transport of these compounds, adsorbed to airborne particulates or in the vapor phase, resulted in their dissemination throughout areas relatively remote from agricultural or other spraying operations. Thus, residents of urban environments also experienced significant levels of exposure. Concentrations of up to 1.14 μg DDT/m^3 air were, for example, noted in Pittsburgh in the early 1960s (Antommaria et al., 1965).

Dermal exposure occurs as a result of contact with contaminated air or with surfaces upon which airborne DDT has alighted. The extent of this type of exposure is illustrated by the fact that DDT, TDE and DDE were all detected in tenths of a microgram quantities in hexane rinses from the hands of several individuals with no history of occupational exposure to DDT or TDE (Kazen et al., 1974).

Although levels of DDT, TDE and DDE in the diet appear to be declining (total dietary intake decreased from 0.9 μg/kg body weight in 1965 to 0.4 μg/kg body weight in 1970; Duggan and Corneliussen, 1972), ingestion of contaminated food (as well as contaminated drinking water) remains a major route of widespread exposure.

Over the years, DDT residues at concentrations of up to 0.51 ppm (Corneliussen, 1972; IARC, 1974) have been detected in a wide variety of fruits and vegetables and will probably continue to be present in agricultural produce indefinitely as a consequence of the persistence of DDT in the soil. Estimates indicate that agricultural soils in the United States contain an average of almost 0.168g DDT/m^2 (Woodwell et al., 1971).

Since DDT is excreted in mammalian milk, ingestion of contaminated feed by lactating cows results in contamination of dairy products. The concentration of total DDT in U.S. dairy products has decreased, however, from a maximum of 0.8 ppm in 1967 to a maximum of 0.3 ppm in 1972 (Duggan et al., 1967; Corneliussen, 1972).

The highest levels of DDT in the diet undoubtedly occur in meat, fish and poultry since DDT and its metabolites are concentrated and stored in animal tissues, particularly in adipose tissues. Once again, concentrations appear to be declining; the maximum value observed in these commodities in 1967 was 3.2 ppm while that observed in 1972 was only 0.9 ppm (Duggan et al., 1967; Corneliussen, 1972).

Ingested DDT is slowly metabolized in humans to TDE and DDE. TDE undergoes further degradation and is eventually excreted in the urine as DDA [2,2-bis(p-chlorophenyl)acetic acid]; DDE, on the other hand, is retained in the adipose tissue along with unmetabolized DDT (IARC, 1974). DDT residues are widely distributed in the adipose tissue of the general population both at home and abroad. The average concentration of total DDT in human fat in the United States was 10.6 ppm in 1966 (Fiserova-Bergerova et al., 1967); averages of 30.2 ppm were reported in India in 1964 (Dale et al., 1965). As is the case for other mammalian species, levels of stored DDT in humans appear to be declining (Fiserova-Bergerova et al., 1967; Morgan and Roan, 1970). DDT and its metabolites are also excreted in human milk (Curley and Kimbrough, 1969; Quinby et al., 1965; Zavon et al., 1969) and may be transported through the placenta (Curley et al., 1969; O'Leary et al., 1970; Zavon et al., 1969).

DDT is generally thought to pose a relatively modest health hazard to warm-blooded animals including man (Farm Chemicals Handbook, 1976; Gosselin et al., 1976). The single oral dose of DDT necessary to produce adverse symptoms in man is 10 mg/kg (Gosselin et al., 1976; Farm Chemicals Handbook, 1976). Human volunteers ingested 35 mg DDT per day, a dose equivalent to 0.5 mg/kg/day, for 21 months without suffering any apparent ill effects (Hayes et al., 1971) and levels of DDT stored in adipose tissue or passed on to breast-fed infants have not been associated with demonstrable toxicity (Gosselin et al.,

1976). TDE is usually considered to be less toxic than DDT (Sax, 1975).

When DDT poisoning does occur, the primary site of action is the central nervous system, particularly the cerebellum and higher motor cortex. Symptoms of acute ingestion include vomiting, malaise, headache, sore throat, fatigue, paresthesias, tremors, and convulsions. Death due to DDT poisoning is extremely rare and is usually attributed to respiratory failure from medullary paralysis. Although no syndrome related to chronic DDT exposure is recognized in humans, evidence indicates that DDT may cause aplastic anemia and thrombocytopenia (Gosselin et al., 1976).

DDT and its metabolites have been tested for mutagenicity in a variety of test systems. DDT and DDE failed to revert histidine-requiring strains of *Salmonella typhimurium* to prototype (The Ames Test using strains TA1535, 1536, 1537, and 1538; Marshall et al., 1976) and, along with DDA (the principal urinary excretion product of DDT in mammals), proved nonmutagenic in host mediated bioassays in mice using *S. typhimurium* G46 His^-, *Serratia marcescens* a21 leu^- and *S. marcescens* a31 His^- as indicator organisms (Buselmaier et al., 1973). DDT and DDA were also negative when tested for mutagenicity in dominant lethal assays in mice (Buselmaier et al., 1973). On the other hand, highly significant increases in back mutation rates were observed in both of the above mentioned strains of *S. marcescens* in the host mediated bioassay with TDE. Spot tests were negative,

suggesting that TDE is activated to a mutagenic agent by the host organism (Buselmaier et al., 1973).

DDA proved positive for mutagenicity in D. melanogaster, inducing sex-linked recessive lethal mutations in male germ cells of that species. DDT itself may be a very weak mutagen in Drosophila (Vogel, 1972).

Lymphocyte cultures from agricultural workers engaged in pesticide application and exposed to a number of insecticides including DDT were examined for chromosomal abberrations during the peak spraying season and again in the wintertime (Yoder et al., 1973). While no appreciable difference in the number of chromatid breaks per person per 25 cells examined was noted at either sampling period among non-exposed controls, a fivefold increase in these lesions was observed among insecticide applicators during the summer months giving rise to the speculation that one or more of the insecticides may be mutagenic in humans (Yoder et al., 1973).

No evidence for carcinogenicity of DDT or its metabolites in humans is available to date. Although increased levels of total DDT have been observed in the adipose tissue of patients with various malignancies when compared to controls (Radomski et al., 1968) and, in one study, concentrations of total DDT-derived materials were higher in malignant breast tissue than in adjacent normal breast tissue or adjacent adipose tissue (Wassermann et al., 1976), these findings are inconclusive as to a causal relationship.

II. MATERIALS AND METHODS

A. Chemicals

Technical-grade DDT containing p,p'-DDT [1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane] as the main component was purchased from Montrose Chemical Corporation and chemical analysis was performed by Hazleton Laboratories America, Inc., Vienna, Virginia. The wide range of the experimentally determined melting point (78° to 102°C) was consistent with the indefinite melting point of the technical product. The major gas-liquid chromatography (GLC) peak represented 70 percent of the total area. This peak was assumed to be the p,p'-DDT isomer. GLC and melting point range analyses performed 12 months later provided similar results and indicated stability of the compound.

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

Technical-grade TDE containing p,p'-TDE [1,1-dichloro-2,2-bis (p-chlorophenyl)-ethane] as the main component was purchased from Rohm and Haas Chemical Company and chemical analysis was performed by Hazleton Laboratories America, Inc. The wide range of the experimentally determined melting point (60° to 103°C) was consistent with the indefinite melting point of the technical material. The major GLC peak represented approximately 60 percent of the total area and was assumed to be the p,p'-TDE isomer. GLC also indicated at least 19 impurities. GLC total-area analysis and melting point range

determination performed 12 months later provided close approximations of the results previously obtained. Therefore, these analyses indicated stability of the compound.

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

Commercially available DDE (dichlorodiphenyl dichloroethylene) was purchased from Aldrich Chemical Company and chemical analysis was performed by Hazleton Laboratories America, Inc. The narrow range of the experimentally determined melting point (87° to 89°C) is consistent with the fact that the commercially available material is the relatively pure p,p'-DDE isomer. GLC utilizing both internal standard and total-area analysis methodologies suggested a purity greater than 95 percent. This was assumed to be the p,p'-DDE isomer. One minor impurity was found to be present.

Throughout this report the term DDE is used to represent the relatively pure p,p'-DDE isomer.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois) plus 2 percent Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) by weight. Fresh mixtures of each chemical in corn oil were prepared weekly and stored in the dark. These mixtures of DDT, TDE, or DDE in corn oil were each incorporated as often as necessary into the appropriate amount of laboratory diet in a twin-shell blender fitted with an accelerator bar.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassays. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

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

D. Animal Maintenance

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

floors. Mice were housed by sex in groups of 10 in solid-bottom polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food and water were available ad libitum.

The rats dosed with DDT or TDE and their respective controls were housed in a room with other rats receiving diets containing* chlorobenzilate (510-15-6) and sulfallate (95-06-7). The rats dosed with DDE and their controls were housed in the same room with rats receiving diets containing methoxychlor (72-43-5) and safrole (94-59-7).

All dosed and control mice used in these bioassays were housed in a room with other mice receiving diets containing chlorobenzilate (510-15-6); dioxathion (78-34-2); sulfallate (95-06-7); mexacarbate (315-18-4); methoxychlor (72-43-5); dicofol (115-32-2); pentachloronitrobenzene (82-68-8); clonitralid (1420-04-8); nitrofen (1836-75-5); endosulfan (115-29-7); trifluralin (1582-09-8); amitrole (61-82-5); acetylaminofluorene (53-96-3); and safrole (94-59-7).

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*CAS registry numbers are given in parentheses.

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of DDT, TDE, or DDE for addition to the diets of dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. For the subchronic study for each of the three chemicals, animals of each species were distributed among six groups, each consisting of five males and five females. DDT, TDE, or DDE was premixed with a small amount of corn oil. The mixture was then incorporated into the laboratory diet and fed *ad libitum* to five of the six rat groups and five of the six mouse groups, for each of these chemicals. The sixth group of each species served as a control group, receiving only the basal diet of corn oil and laboratory meal. The dosed dietary preparations were administered for a period of 6 weeks, followed by a 2-week observation period during which all animals were fed the basal diet.

A concentration inducing no mortality and resulting in a depression in mean group body weight relative to controls was selected as the high concentration for the chronic study. When weight gain criteria were not applicable, mortality data alone were utilized.

1. DDT

Mixtures of DDT in corn oil were incorporated into the basal laboratory diet and fed *ad libitum* to the dosed rat groups at concentrations of 178, 316, 562, 1000, and 1780 ppm. The dosed mouse groups received concentrations of 18, 32, 56, 100, and 178 ppm.

In rats dosed with DDT at 562 ppm, the mean body weight depression relative to controls was 16 percent in male rats and 4 percent in female rats. At a concentration of 1000 ppm the mean body weight depression in male rats was 7 percent and in female rats 45 percent. One female rat receiving 1000 ppm died. The high concentrations of DDT selected for administration in the chronic bioassay were 840 ppm for the male rats and 630 ppm for the female rats.

In the mice dosed with DDT, mean body weight depression was not dose-related in either sex. In the male mice the mean body weight gain, expressed as a percentage of that gained by the controls, was 121 percent at a level of 18 ppm and 147 percent at 32 ppm. One male mouse receiving 32 ppm died during the study. In the female mice, mean body weight gain was 152 percent at 56 ppm, 126 percent at 100 ppm, and 132 percent at 178 ppm. Four female mice receiving 178 ppm died by the end of the 8-week subchronic study. The high concentrations of DDT selected for administration in the chronic study were 20 ppm for the male mice and 100 ppm for the female mice.

2. TDE

Mixtures of TDE in corn oil were incorporated into the basal laboratory diet in concentrations of 562, 1000, 1780, 3160, and 5620 ppm for the dosed rats, and in concentrations of 251, 398, 631, 1000, and 1590 ppm for the dosed mice.

In male rats, at a concentration of 1780 ppm the depression in mean body weight was 9 percent. At 3160 ppm the mean body weight depression was 10 percent. For female rats, the depression in mean body weight was 39 percent at 1000 ppm and 4 percent at 1780 ppm. No deaths were observed at these dosages. The high concentrations of TDE selected for administration in the chronic study were 2800 ppm for the male rats, and 1700 ppm for the female rats.

In the mice, the mean body weight was not clearly affected by compound administration. Mean body weight gain in males and females receiving up to 631 ppm was greater than the mean body weight gain in their respective control groups. Deaths occurred in all male groups, except the controls and the group receiving 631 ppm, and in the female groups receiving 1000 and 1590 ppm. The high concentrati of TDE selected for administration in the chronic mouse bioassay was 630 ppm for both males and females.

3. DDE

Mixtures of DDE in corn oil were incorporated into the basal laboratory diet and administered to the dosed rats in concentrations of 316, 562, 1000, 1780, and 3160 ppm. The dosed mice received DDE in concentrations of 139, 193, 269, 363, and 519 ppm.

In the male rats, mean body weight depression was observed in all dosed groups. At 1000 ppm, the depression in mean group body weight was 11 percent while at 1780 ppm the depression was 22 perce No deaths occurred in the male rats dosed with 1780 ppm or less.

In the female rats, mean body weight depression was not associated with compound administration. At a concentration of 1000 ppm one female rat died and at 1780 and 3160 ppm all female rats were dead by week 6. The high concentrations of DDE selected for administration in the chronic study were 1350 ppm for the male rats and 750 ppm for the female rats.

In either male or female mice, DDE administration was not related to mean body weight depression. One death was observed in the male control group and in the male group receiving 269 ppm. Four deaths in the males and two deaths in the females occurred in the groups receiving 373 ppm of DDE. The high concentration of DDE selected for administration in the chronic study was 250 ppm for both male and female mice.

F. Experimental Design

The experimental design parameters for the chronic bioassays (species, sex, group size, concentrations administered, duration of treated and untreated observation periods, and the time-weighted average concentrations) are summarized in Tables 1 and 2 for DDT, Tables 3 and 4 for TDE, and Tables 5 and 6 for DDE. All concentrations given were administered to the dosed rats and mice during a dosing period of 78 weeks, followed by observation periods of up to 35 weeks for the rats and up to 15 weeks for the mice.

1. DDT

The experimental design parameters for the DDT chronic bioassay are presented in Tables 1 and 2. At the initiation of the study all

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
DDT FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DDT CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		111	0
LOW DOSE	50	420	12		321
		500	14		
		250	52		
		0		32	
HIGH DOSE	50	840	12		642
		1000	14		
		500	52		
		0		33	
FEMALE					
CONTROL	20	0		111	0
LOW DOSE	50	315	26		210
		158	52		
		0		33	
HIGH DOSE	50	630	26		420
		315	52		
		0		33	

[a]Concentrations given in parts per million.

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

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
DDT FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DDT CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		91	0
LOW DOSE	50	10	8		22
		15	6		
		20	14		
		25	50		
		0		14	
HIGH DOSE	50	20	8		44
		30	6		
		40	14		
		50	50		
		0		14	
FEMALE					
CONTROL	20	0		92	0
LOW DOSE	50	50	8		87
		60	6		
		75	14		
		100	50		
		0		15	
HIGH DOSE	50	100	8		175
		120	6		
		150	14		
		200	50		
		0		15	

[a]Concentrations given in parts per million.

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

TABLE 3

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
TDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	TDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		111	0
LOW DOSE	50	1400	23		1647
		1750	55		
		0		34	
HIGH DOSE	50	2800	23		3294
		3500	55		
		0		35	
FEMALE					
CONTROL	20	0		111	0
LOW DOSE	50	850	78		850
		0		35	
HIGH DOSE	50	1700	78		1700
		0		35	

[a]Concentrations given in parts per million.

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

TABLE 4

DESIGN SUMMARY FOR B6C3F1 MICE
TDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	TDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		90	0
LOW DOSE	50	315	5		411
		375	11		
		425	62		
		0		13	
HIGH DOSE	50	630	5		822
		750	11		
		850	62		
		0		14	
FEMALE					
CONTROL	20	0		90	0
LOW DOSE	50	315	5		411
		375	11		
		425	62		
		0		14	
HIGH DOSE	50	630	5		822
		750	11		
		850	62		
		0		15	

[a]Concentrations given in parts per million.

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

TABLE 5

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
DDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
MALE					
CONTROL	20	0		111	0
LOW DOSE	50				437
		675	23		
		338	55		
		0		33	
HIGH DOSE	50	1350	23		839
		675	36		
		675[c]	15	4	
		0		33	
FEMALE					
CONTROL	20	0		111	0
LOW DOSE	50	375	23		242
		187	55		
		0		34	
HIGH DOSE	50	750	23		462
		375	32		
		375[c]	18	5	
		0		34	

[a]Concentrations given in parts per million.

[b]Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

[c]These concentrations were cyclically administered with a pattern of 1 dosage-free week followed by 4 weeks of dosing at the level indicated.

TABLE 6

DESIGN SUMMARY FOR B6C3F1 MICE
DDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
MALE					
CONTROL	20	0		92	0
LOW DOSE	50	125	7		148
		150	71		
		0		14	
HIGH DOSE	50	250	7		261
		300	29		
		300[c]	33	9	
		0		14	
FEMALE					
CONTROL	20	0		92	0
LOW DOSE	50	125	7		148
		150	71		
		0		15	
HIGH DOSE	50	250	7		261
		300	29		
		300[c]	33	9	
		0		15	

[a]Concentrations given in parts per million.

[b]Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

[c]These concentrations were cyclically administered with a pattern of 1 dosage-free week followed by 4 weeks of dosing at the level indicated.

rats were approximately 7 weeks old. The dietary concentrations of DDT initially utilized for male rats were 840 and 420 ppm. Throughout this report those male rats initially receiving the former concentration are referred to as the high dose male rats, while those initially receiving the latter concentration are referred to as the low dose male rats. For female rats, the initial concentrations were 630 and 315 ppm. Throughout this report those female rats initially receiving the former concentration are referred to as the high dose female rats, while those initially receiving the latter concentration are referred to as the low dose female rats. During week 13, the high and low levels administered to the male rats were increased to 1000 and 500 ppm, respectively. During week 27, the administered concentrations were decreased for all of the dosed rats as signs of toxicity at the previous dosages had been observed. The concentrations administered to the high and low dose male rats were decreased to 500 and 250 ppm, respectively, while those administered to the female rats were decreased to 315 and 158 ppm, respectively. These dosages were maintained for the remainder of the dosing period.

At the initiation of the study all mice were approximately 6 weeks old. The dietary concentrations of DDT initially administered to the male mice were 20 and 10 ppm. The dietary concentrations initially administered to the female mice were 100 and 50 ppm. Throughout this report those male mice initially receiving 20 ppm and those female mice initially receiving 100 ppm are referred to as the high

dose groups, while those male mice initially receiving 10 ppm and those female mice initially receiving 50 ppm are referred to as the low dose groups. The concentrations administered to all dosed mice were increased on three separate occasions as tolerance to the previous dosage levels was observed. In week 9, the concentrations administered to the high and low dose groups were increased, respectively, to 30 and 15 ppm for the male mice and to 120 and 60 ppm for the female mice. During week 15, the high and low doses were again increased, this time to 40 and 20 ppm for the high and low dose male mice, respectively. The high and low doses administered to the female mice were raised to 150 and 75 ppm, respectively. In week 29 the doses administered were again increased, to 50 and 25 ppm for the high and low dose male mice, and to 200 and 100 ppm for the high and low dose female mice, respectively. These dosage levels were maintained for the remainder of the dosing period.

2. TDE

The experimental design parameters for the TDE chronic bioassay are presented in Tables 3 and 4. At the initiation of the study all rats were approximately 7 weeks old. The dietary concentrations of TDE initially utilized for male rats were 2800 and 1400 ppm. For female rats the initial dietary concentrations were 1700 and 850 ppm. Throughout this report those male rats initially receiving 2800 ppm and those female rats initially receiving 1700 ppm are referred to as the high dose groups, while those males initially receiving 1400

ppm and those females initially receiving 850 ppm are referred to as the low dose groups. In week 24, the high and low doses administered to the male rats were increased to 3500 and 1750 ppm, respectively, as tolerance to the previous doses was observed. These concentrations were maintained for the remainder of the dosing period.

At the initiation of the study all mice were approximately 6 weeks old. The dietary concentrations initially administered to the male and female mice were 630 and 315 ppm. Throughout this report those mice initially receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. The dosages administered to the mice were increased twice, as tolerance to the previous concentrations was observed. In week 6, the concentration administered to the high dose male and female mice was increased to 750 ppm, and the concentration administered to the low dose male and female mice was increased to 375 ppm. The high and low concentrations administered to the male and female mice were raised again in week 17, to 850 and 425 ppm, respectively. These concentrations were maintained for the remainder of the dosing period.

3. DDE

The experimental design parameters for the DDE chronic bioassay are presented in Tables 5 and 6.

At the initiation of the study all rats were approximately 7 weeks old. The dietary concentrations of DDE initially utilized for

male rats were 1350 and 675 ppm. For female rats, the initial concentrations were 750 and 375 ppm. Throughout this report those male rats initially receiving 1350 ppm and those female rats initially receiving 750 ppm are referred to as the high dose groups, while those male rats initially receiving 675 ppm and those female rats initially receiving 375 ppm are referred to as the low dose groups. During week 24, the concentrations administered to all of the dosed rats were decreased as signs of toxicity were observed. The high and low concentrations administered to the male rats were decreased to 675 and 338 ppm, respectively. The high and low concentrations administered to the female rats were decreased to 375 and 187 ppm, respectively. In week 56, administration of DDE to the high dose female rats ceased for 1 week followed by 4 weeks of feeding at the previous concentration of 375 ppm. This same method of total intake reduction was employed for the high dose male rats beginning with week 60. This pattern of cyclic administration continued for the remainder of the dosing period at the concentrations indicated.

At the initiation of the study all mice were approximately 7 weeks old. The initial dietary concentrations administered to the male and female mice were 250 and 125 ppm. Throughout this report those mice initially receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. In week 8, the dosages administered to all dosed mice were increased as

tolerance to the previous dosages had been observed. The high dose male and female mice received 300 ppm, and the low dose male and female mice received 150 ppm. Administration of DDE to the high dose male and female mice ceased for 1 week in week 37 followed by 4 weeks of feeding at the previous dosage of 300 ppm. This method of total intake reduction was used for the remainder of the dosing period at the concentrations indicated.

G. Clinical and Histopathologic Examinations

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

During the course of these bioassays several pathology protocols were in effect, each for different periods of time. The minimum protocol required that tissues were to be taken and examined histopathologically from all control animals, from any animal in which a tumor was observed during gross examination, and from at least 10 grossly normal males and 10 grossly normal females from each dosed group. Under later protocols, tissues were taken from additional dosed animals. In addition, any tissue from any animal showing gross

abnormalities was to be taken and examined histopathologically. The number of animals in each group from which a particular tissue was examined is indicated in Appendices A through L.

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

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

Slides were prepared from the following tissues from selected animals: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, muscle, tunica vaginalis, uterus, mammary gland, and ovary. Bone samples were not examined in animals dosed with DDE or TDE and the tunica vaginalis was not examined in animals dosed with DDE.

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

H. Data Recording and Statistical Analyses

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

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be

missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When

results for a number of treated groups, k, were compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provided a two-tailed test of departure from linear trend.

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

found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

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

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk

of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

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

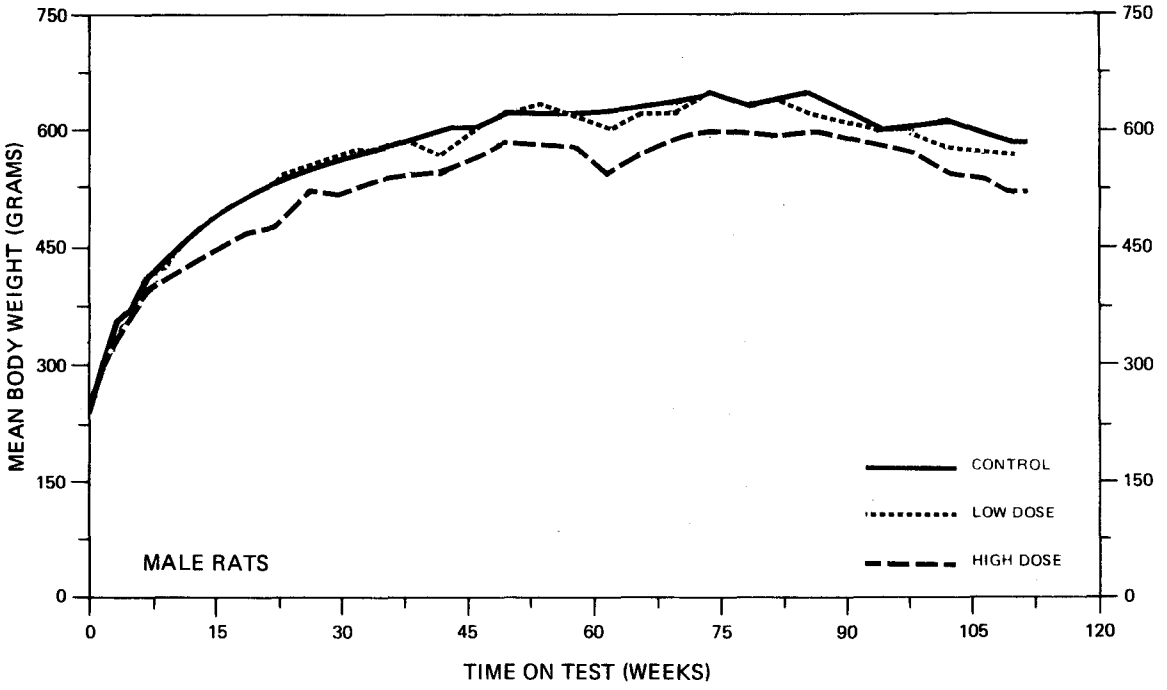
III. CHRONIC TESTING RESULTS: RATS

A. DDT

1. Body Weights and Clinical Observations

Compound-related mean body weight depression was observed in high dose rats of both sexes (Figure 4).

Clinical signs characteristic of central nervous system stimulation were observed in the dosed female rats early in the study. Beginning in week 5, a number of high dose females started to exhibit hyperactivity, body tremors, and a hunched appearance. By the following week about 70 percent of the high dose females appeared hunched, with 50 percent showing concomitant tremors. As the study progressed, a few low dose females and some high dose males started to show tremors and occasional hunched appearance. By week 26, tremors were evident in about 8 percent of the low dose females, 40 percent of the high dose males, and 90 percent of the high dose females. Because of the observed neurotoxicity, the feeding levels of DDT were decreased. Consequently, in week 30 only two high dose females exhibited tremors and in the succeeding weeks (until week 58), none of the dosed rats exhibited this obviously reversible neurotoxic effect. In the following weeks, as compound intake continued with presumed DDT tissue accumulation, tremors were again exhibited by an increasing number of high dose females (30 to 50 percent) and a small number of high dose males and low dose females. By termination of the study (week 111,



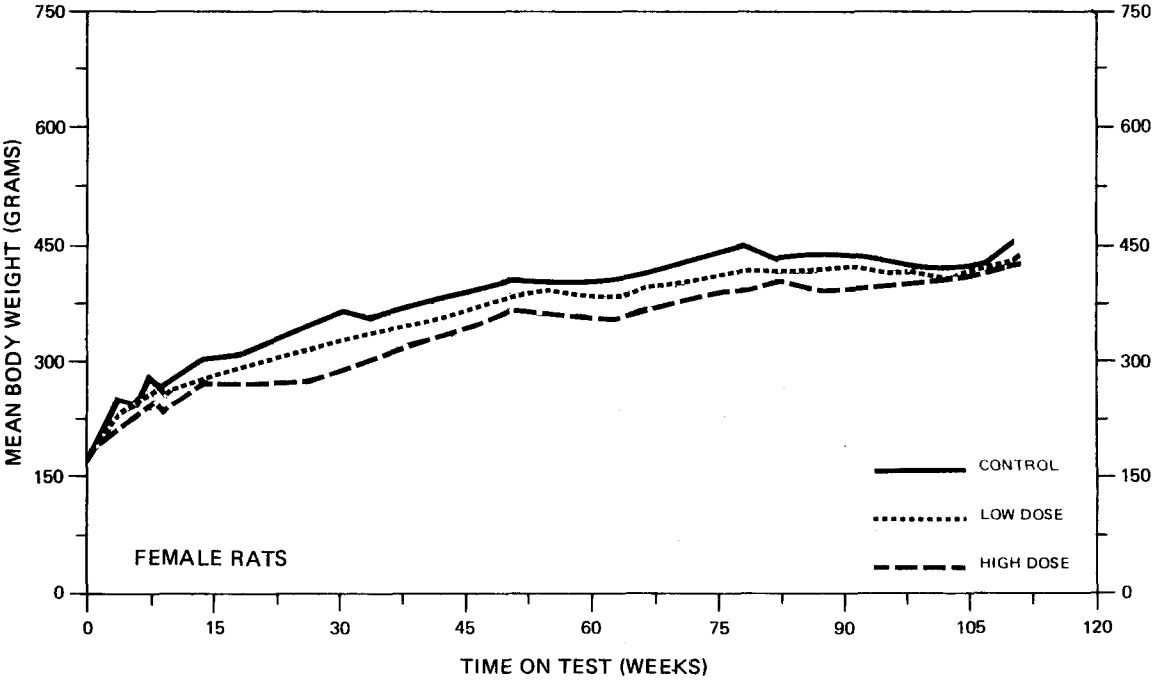


FIGURE 4
GROWTH CURVES FOR DDT CHRONIC STUDY RATS

including 14 to 15 weeks on compound-free diets) tremors had completely subsided in all dosed groups.

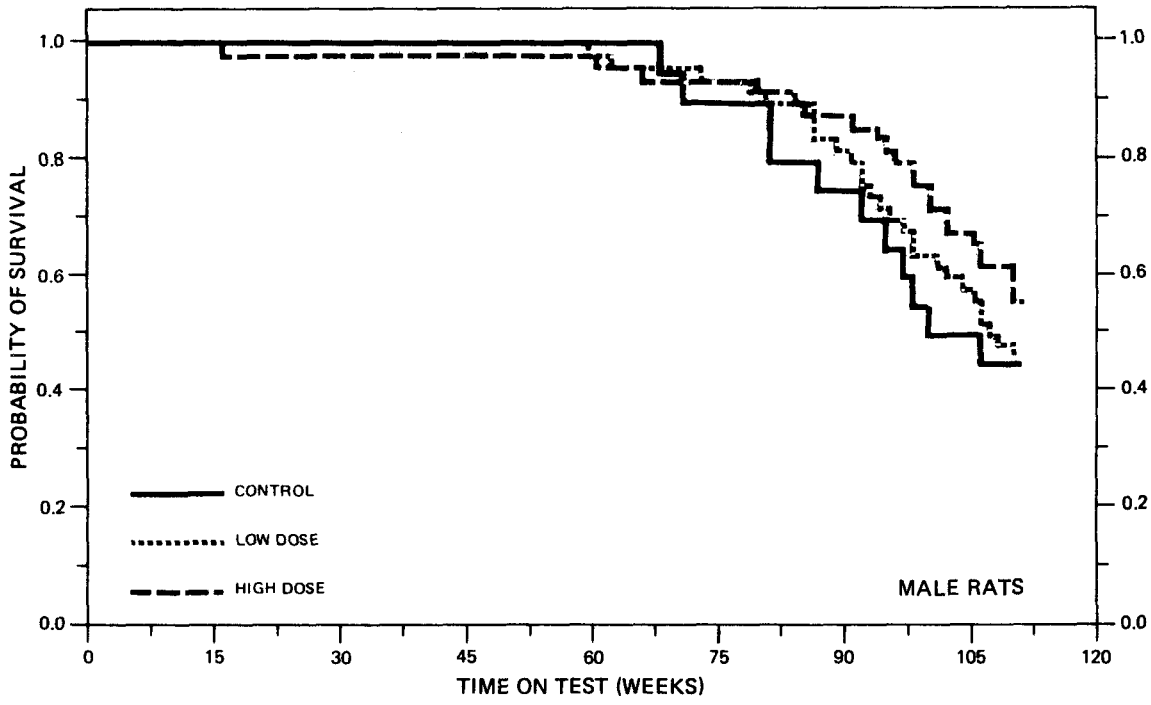
Other clinical signs observed with slightly greater frequency in the dosed groups than in the controls included a hunched appearance and abdominal urine stains. Respiratory signs characterized by labored respiration, wheezing and/or nasal discharge were observed during the second year at a low incidence in all groups including controls. The incidence of this condition increased slightly during the last 4 months of the study.

Signs often associated with aging in Osborne-Mendel rats were observed at a comparable rate in dosed and control animals during the last year. These signs included sores on the body and/or extremities, localized alopecia, reddish crust or discharge around body orifices, palpable tissue masses, and swollen areas of the body or nodules. Isolated observations in one or two dosed rats included head tilt, circling, ataxia, apparent hernia, bloating, and hind-limb paralysis.

2. Survival

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

Adequate numbers of males were at risk from late-developing tumors, as 76 percent (38/50) of the high dose, 64 percent (32/50) of the low dose, and 55 percent (11/20) of the control rats survived on



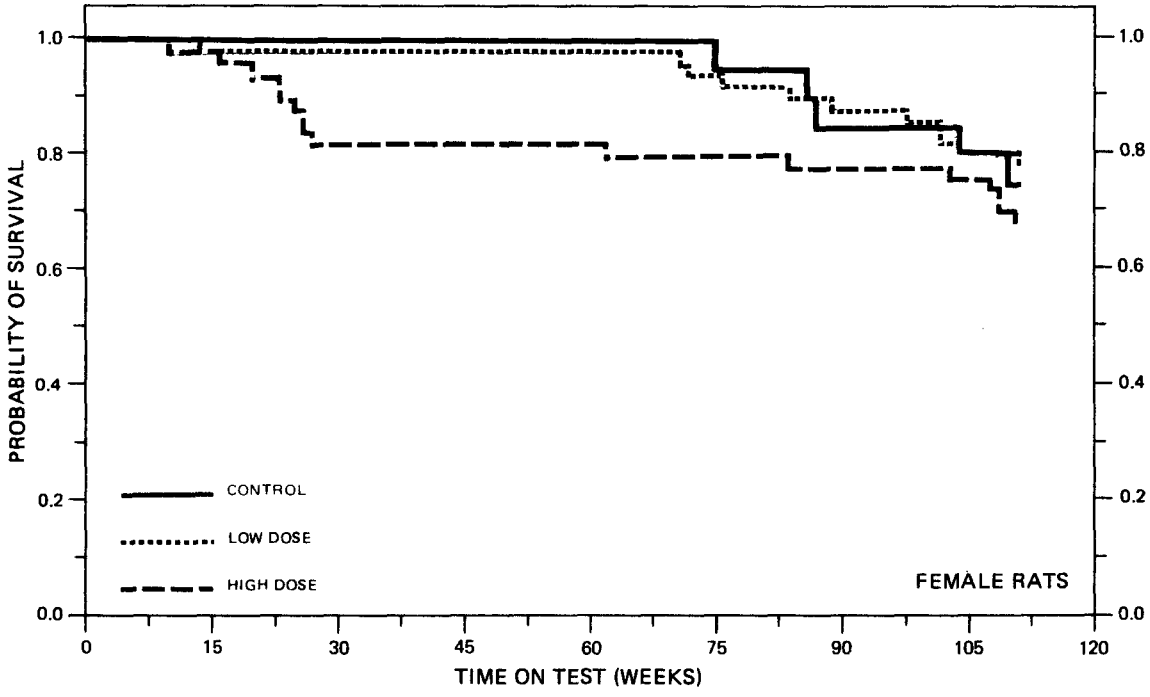


FIGURE 5
SURVIVAL COMPARISONS OF DDT CHRONIC STUDY RATS

test at least 100 weeks. For females the survival was also adequate as 78 percent (39/50) of the high dose, 86 percent (43/50) of the low dose, and 85 percent (17/20) of the control rats survived on test at least 100 weeks.

3. Pathology

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

A variety of neoplasms was observed among both the dosed and control rats. Each of the types of tumors represented has been encountered previously as a spontaneous lesion in the Osborne-Mendel rat.

Neoplasms and hyperplasias of the thyroid gland occurred with a moderate incidence in both dosed and control rats as shown in the following tabulation:

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Animals with Thyroids Examined Histopathologically	(19)	(45)	(49)	(19)	(45)	(43)
Follicular-Cell Carcinoma	1	6	5	0	4	6
Follicular-Cell Adenoma	8	14	17	1	10	5
Follicular-Cell Hyperplasia	0	4	7	1	3	0
C-Cell Carcinoma	0	1	1	1	1	0
C-Cell Adenoma	1	4	2	3	2	0
C-Cell Hyperplasia	3	3	1	2	8	3

The morphology of the thyroid lesions was similar to that described in TDE (pp. 56-57).

The inflammatory, degenerative, and proliferative lesions seen in the control and dosed rats were similar in number and kind to those lesions occurring naturally in aged Osborne-Mendel rats.

In this study, there was no pathologic evidence for the carcinogenicity of DDT in Osborne-Mendel rats.

4. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 7 and 8. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or DDT-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to early deaths in the high dose group, additional time-adjusted analyses were conducted for the female rats; no important differences were observed in the statistical results.

For females the Cochran-Armitage test indicated a significant ($P = 0.031$) positive association between dose and the incidence of adrenal pheochromocytomas. The Fisher exact tests, however, were not significant.

When incidences of follicular-cell adenomas and follicular-cell carcinomas of the thyroid were combined, the Fisher exact test comparing low dose to control had a probability level of $P = 0.032$, a

TABLE 7

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	3/50(0.06)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.250	0.250
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	92	106
Pituitary: Chromophobe Adenoma[b]	3/19(0.16)	4/22(0.18)	3/21(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.152	0.905
Lower Limit	---	0.224	0.137
Upper Limit	---	6.957	5.993
Weeks to First Observed Tumor	106	104	106
Thyroid: Follicular-Cell Carcinoma[b]	1/19(0.05)	6/45(0.13)	5/49(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.533	1.939
Lower Limit	---	0.346	0.243
Upper Limit	---	113.695	89.722
Weeks to First Observed Tumor	111	110	102

TABLE 7 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma or Follicular-Cell Adenoma[b]	9/19(0.47)	19/45(0.42)	22/49(0.45)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.891	0.948
Lower Limit	---	0.497	0.542
Upper Limit	---	1.866	1.953
Weeks to First Observed Tumor	81	62	94
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/19(0.05)	5/45(0.11)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.111	1.163
Lower Limit	---	0.265	0.103
Upper Limit	---	97.475	59.809
Weeks to First Observed Tumor	111	101	110
Brain: Glioma NOS[b]	0/19(0.00)	2/21(0.10)	0/21(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.047	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.278	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	86	---

TABLE 7 (CONCLUDED)

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[a]Treated groups received time-weighted average doses of 321 or 642 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 8

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	6/50(0.12)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.005	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.666	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	76	---
Pituitary: Chromophobe Adenoma[b]	13/19(0.68)	16/39(0.41)	13/27(0.48)
P Values[c]	N.S.	P = 0.046(N)	N.S.
Relative Risk (Control)[d]	---	0.600	0.704
Lower Limit	---	0.383	0.431
Upper Limit	---	1.080	1.265
Weeks to First Observed Tumor	104	71	103
Adrenal: Pheochromocytoma[b]	0/19(0.00)	0/38(0.00)	3/24(0.13)
P Values[c]	P = 0.031	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.498
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	109

TABLE 8 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma[b]	0/19(0.00)	4/45(0.09)	6/43(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.408	0.740
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	109
Thyroid: Follicular-Cell Carcinoma or Follicular-Cell Adenoma[b]	1/19(0.05)	13/45(0.29)	10/43(0.23)
P Values[c]	N.S.	P = 0.032	N.S.
Relative Risk (Control)[d]	---	5.489	4.419
Lower Limit	---	0.942	0.714
Upper Limit	---	226.304	186.157
Weeks to First Observed Tumor	111	111	84
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	4/19(0.21)	3/45(0.07)	0/43(0.00)
P Values[c]	P = 0.004(N)	N.S.	P = 0.007(N)
Relative Risk (Control)[d]	---	0.317	0.000
Lower Limit	---	0.053	0.000
Upper Limit	---	1.722	0.469
Weeks to First Observed Tumor	110	111	---

TABLE 8 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	8/20(0.40)	11/50(0.22)	6/50(0.12)
P Values[c]	P = 0.008(N)	N.S.	P = 0.012(N)
Relative Risk (Control)[d]	---	0.550	0.300
Lower Limit	---	0.249	0.104
Upper Limit	---	1.376	0.871
Weeks to First Observed Tumor	75	111	103
Uterus: Endometrial Stromal Polyp[b]	0/19(0.00)	2/43(0.05)	4/31(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.137	0.594
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	103
Ovary: Granulosa-Cell Tumor[b]	0/19(0.00)	2/37(0.05)	0/24(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.158	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	111	---

TABLE 8 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Kidney: Lipoma or Liposarcoma[b]	0/19(0.00)	2/38(0.05)	1/25(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.154	0.042
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	111

[a]Treated groups received time-weighted average doses of 210 or 420 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

marginal result which was not significant under the Bonferroni criterion.

No other statistical tests for either males or females indicated a positive association between chemical administration and incidence. Based upon these statistical results there was no convincing evidence of the carcinogenicity of DDT in rats.

For females a negative association between administration and incidence was observed both for mammary fibroadenomas and for the combined incidence of C-cell adenomas and C-cell carcinomas of the thyroid. No other tests were significant under the Bonferroni criterion.

The incidence of thyroid follicular-cell neoplasms (9/19 or 47 percent) in control males was somewhat higher than commonly seen. In historical control data collected by this laboratory for the NCI Carcinogenesis Testing Program, these neoplasms were observed in 32/383 (8 percent) of the untreated male Osborne-Mendel rats. With 15 control groups included in this historical data, this DDT control group had 9 of the total of 32 tumors. Excluding the DDT control group, the incidences in the other 14 control groups ranged from 0/50 to 3/20 (15 percent).

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in

Tables 7 and 8, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by DDT that could not be established under the conditions of this test.

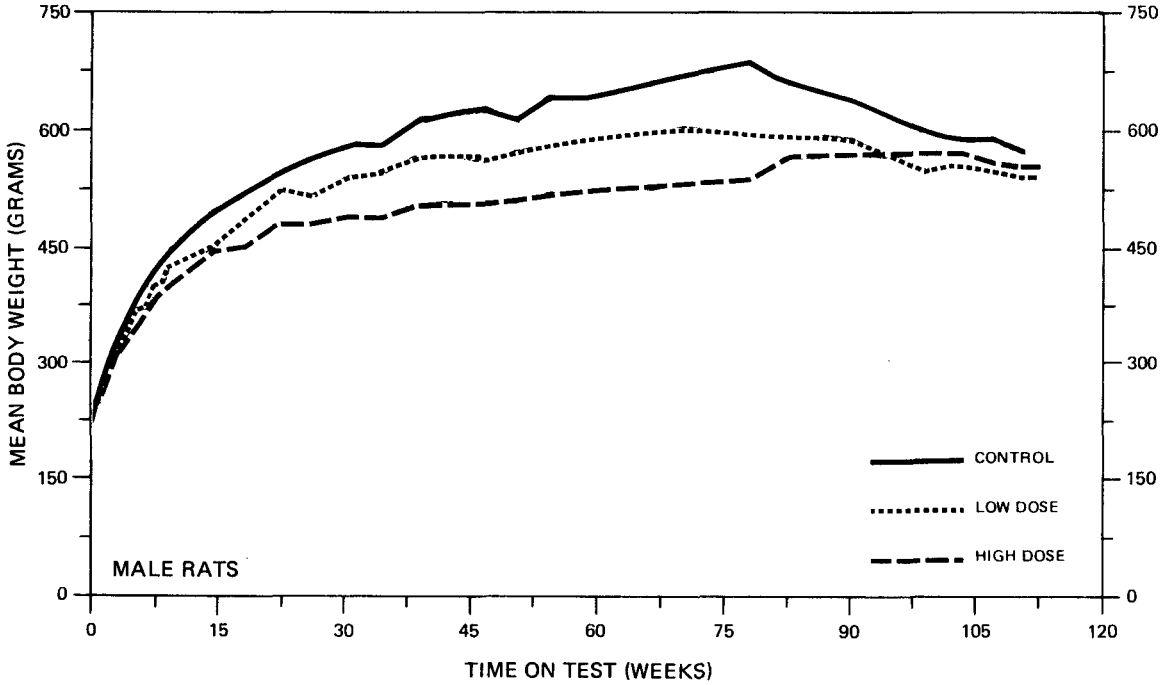
B. TDE

1. Body Weights and Clinical Observations

Distinct dose-related mean body weight depression was evident among both male and female rats (Figure 6).

During the first 6 months of the study, the appearance and behavior of the TDE-dosed rats was generally comparable to that of the controls. From week 30 to cessation of dosing in week 78, clinical signs consisting of a hunched appearance and abdominal urine stains were observed in a slightly greater number of dosed rats than controls. The incidences of these signs were comparable in dosed and control rats during the last 6 months of the study. Respiratory signs were observed at a low incidence in all groups during the second year of the study, increasing slightly during the last 6 months.

Clinical signs commonly associated with aging in the Osborne-Mendel rat were observed at comparable rates in dosed and control rats during the second year. These signs included sores on the body and extremities, localized alopecia, rough or discolored fur, squinted or reddened eyes (often with exudate in the conjunctival sac), palpable



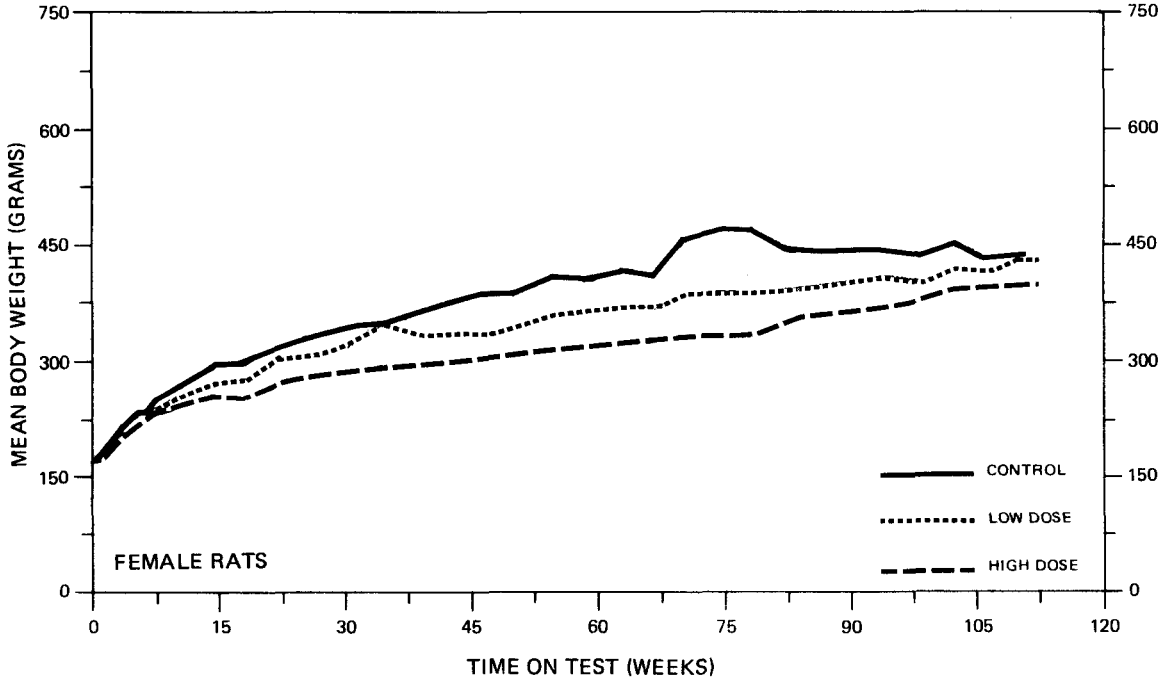


FIGURE 6
GROWTH CURVES FOR TDE CHRONIC STUDY RATS

nodules, and tissue masses or swollen areas of the body. Isolated, apparently spontaneous observations in one or two dosed rats included paralysis of hind limbs, salivation, circling, tremors, ataxia, and testicular atrophy.

2. Survival

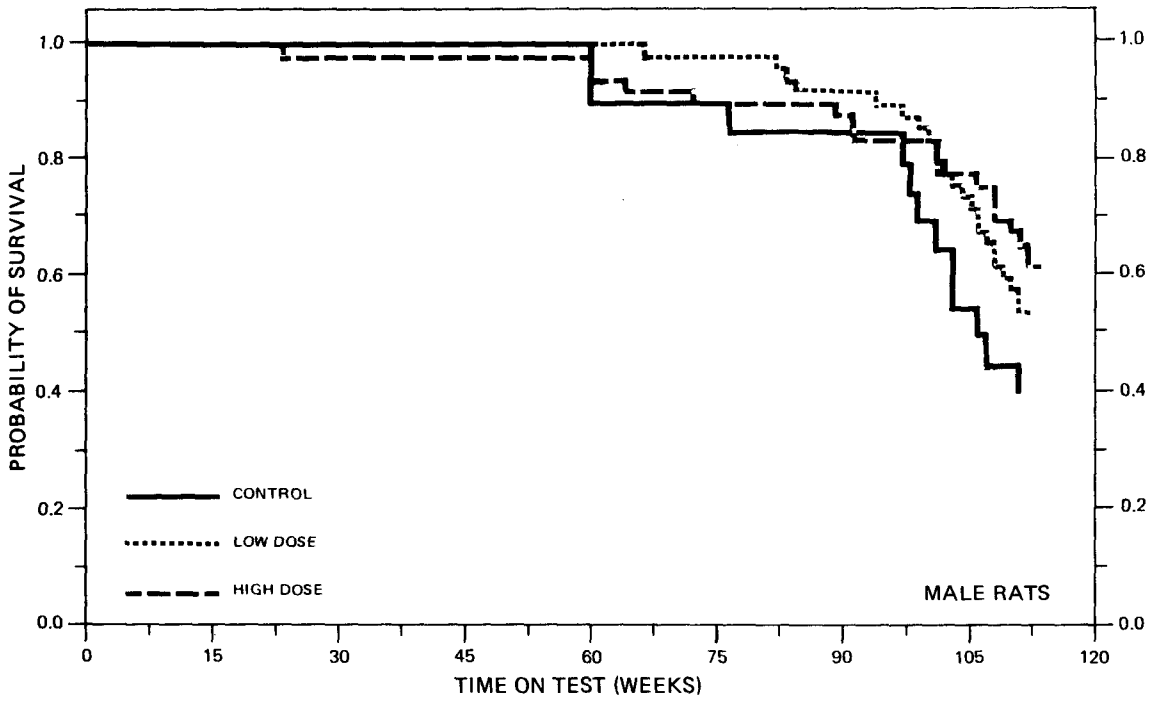
The estimated probabilities of survival for male and female rats in the control and TDE-dosed groups are shown in Figure 7. No significant positive association between dosage and mortality was observed for either male or female rats.

Adequate numbers of males were at risk from late-developing tumors, as 84 percent (42/50) of the high dose, 86 percent (43/50) of the low dose and 70 percent (14/20) of the control rats survived on test for at least 100 weeks. Adequate numbers of females were also at risk, as 84 percent (42/50) of the high dose, 86 percent (43/50) of the low dose, and 75 percent (15/20) of the control rats survived on test for at least 100 weeks.

3. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix E (Tables E1 and E2); findings on nonneoplastic lesions are summarized in Appendix G (Tables G1 and G2).

Neoplasms and hyperplasias of the thyroid gland occurred in both the dosed and control rats as shown in the following tabulation:



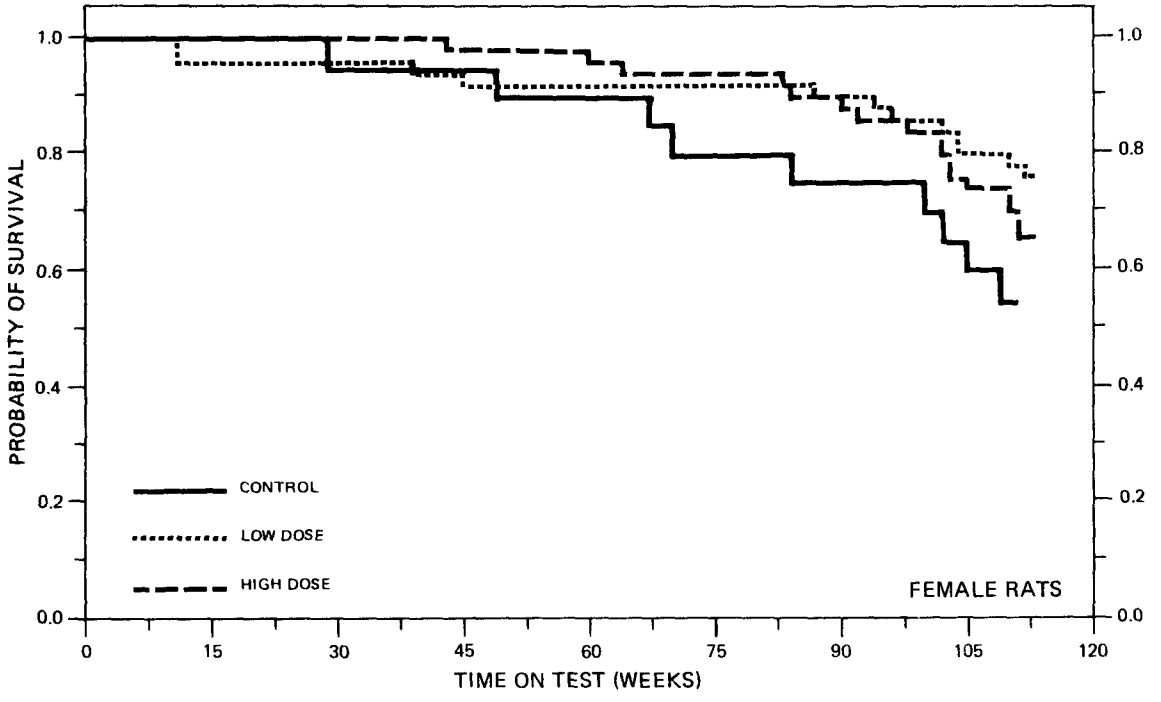


FIGURE 7
SURVIVAL COMPARISONS OF TDE CHRONIC STUDY RATS

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Animals with Thyroid Examined Histopathologically	(19)	(49)	(49)	(19)	(48)	(50)
Follicular-Cell Carcinoma	1	6	3	2	5	1
Follicular-Cell Adenoma	0	11	9	0	6	5
Follicular-Cell Hyperplasia	2	5	6	1	2	3
Follicular Cyst	0	2	4	0	0	1
C-Cell Carcinoma	0	4	2	1	2	4
C-Cell Adenoma	1	4	1	1	2	1
C-Cell Hyperplasia	1	2	2	2	4	5

The morphology of the follicular-cell carcinomas in this study consisted of hyperchromatic anaplastic cuboidal epithelial cells forming irregular-sized follicles, with a piling up of cells around the follicles, papillary projections into the enlarged follicles, and in some areas forming densely cellular sheets. Pale colloid material was present in some of the follicles. The neoplastic cells had central nuclei which were variable and could be small or large, pale or dark, round or bizarre. In some areas the follicular-cell carcinomas approached the spindle-cell form. The neoplastic cells invaded the capsule and adjacent normal tissue.

The follicular-cell adenomas were expansive growths composed of follicles lined by single layers of large basophilic epithelial cells, usually well-demarcated from the adjacent normal thyroid parenchyma. Differentiation of the follicular-cell adenoma from hyperplasia was based largely on compression of the normal thyroid tissue and encapsulation of the adenoma and the degree of differentiation of the follicular cells.

The C-cell adenomas were composed of sheets and compact masses of large pale, irregular cuboidal cells with central nuclei and pale eosinophilic cytoplasm which resembled interfollicular thyroid cells. The C-cell carcinomas were generally composed of less differentiated cells with poor demarcation from the surrounding tissue. C-cell hyperplasias of the thyroid were determined by their architecture, size, and cellular differentiation.

Other proliferative, degenerative, and inflammatory lesions that occurred in the control and dosed rats were similar in number and kind to those lesions occurring naturally in aged Osborne-Mendel rats.

This pathologic evaluation indicated that under the conditions of this bioassay, there was an increased incidence of thyroid follicular-cell tumors in dosed rats of both sexes and a marginal increased incidence of C-cell tumors in dosed males when compared with controls.

4. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 9 and 10. The analysis is included for

TABLE 9

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	4/20(0.20)	2/50(0.04)	0/50(0.00)
P Values[c]	P = 0.002(N)	N.S.	P = 0.005(N)
Relative Risk (Control)[d]	---	0.200	0.000
Lower Limit	---	0.020	0.000
Upper Limit	---	1.297	0.427
Weeks to First Observed Tumor	98	111	---
Pituitary: Chromophobe Adenoma[b]	1/20(0.05)	7/26(0.27)	5/25(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	5.385	4.000
Lower Limit	---	0.786	0.505
Upper Limit	---	230.300	180.057
Weeks to First Observed Tumor	99	84	108
Thyroid: Follicular-Cell Carcinoma[b]	1/19(0.05)	6/49(0.12)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.327	1.163
Lower Limit	---	0.316	0.104
Upper Limit	---	104.667	59.809
Weeks to First Observed Tumor	103	99	112

TABLE 9 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Carcinoma or Follicular-Cell Adenoma[b]	1/19(0.05)	16/49(0.33)	11/49(0.22)
P Values[c]	N.S.	P = 0.016	N.S.
Departure from Linear Trend[e]	P = 0.025	---	---
Relative Risk (Control)[d]	---	6.204	4.265
Lower Limit	---	1.102	0.704
Upper Limit	---	252.587	178.941
Weeks to First Observed Tumor	103	94	60
Thyroid: C-Cell Carcinoma[b]	0/19(0.00)	4/49(0.08)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.374	0.120
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	112
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/19(0.05)	8/49(0.16)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.102	1.163
Lower Limit	---	0.469	0.104
Upper Limit	---	134.437	59.809
Weeks to First Observed Tumor	111	103	112

TABLE 9 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	1/27(0.04)	2/38(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.041	0.161
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	108	112
Spleen: Hemangiosarcoma[b]	0/20(0.00)	4/20(0.21)	0/20(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.004	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.975	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	109	---

[a]Treated groups received time-weighted average doses of 1647 or 3294 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 10

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	2/19(0.11)	0/49(0.00)	0/49(0.00)
P Values[c]	P = 0.023(N)	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.037	---	---
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.303	1.303
Weeks to First Observed Tumor	49	---	---
Subcutaneous Tissue: Lipoma[b]	0/19(0.00)	0/49(0.00)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.243
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	113
Hematopoietic System: Malignant Lymphoma[b]	3/19(0.16)	1/49(0.02)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.129	0.259
Lower Limit	---	0.003	0.024
Upper Limit	---	1.516	2.120
Weeks to First Observed Tumor	29	113	113

TABLE 10 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	4/19(0.21)	14/30(0.47)	12/33(0.36)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.217	1.727
Lower Limit	---	0.849	0.630
Upper Limit	---	7.869	6.427
Weeks to First Observed Tumor	111	102	90
Thyroid: Follicular-Cell Carcinoma[b]	2/19(0.11)	5/48(0.10)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.990	0.190
Lower Limit	---	0.184	0.009
Upper Limit	---	9.980	3.494
Weeks to First Observed Tumor	105	113	113
Thyroid: Follicular-Cell Carcinoma or Follicular-Cell Adenoma[b]	2/19(0.11)	11/48(0.23)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.177	1.140
Lower Limit	---	0.549	0.231
Upper Limit	---	19.100	10.985
Weeks to First Observed Tumor	105	112	92

TABLE 10 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma[b]	1/19(0.05)	2/48(0.04)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.792	1.520
Lower Limit	---	0.045	0.168
Upper Limit	---	45.751	73.309
Weeks to First Observed Tumor	70	113	113
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	2/19(0.11)	4/48(0.08)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.792	0.950
Lower Limit	---	0.127	0.177
Upper Limit	---	8.329	9.498
Weeks to First Observed Tumor	70	113	113
Liver: Hepatocellular Carcinoma[b]	1/19(0.05)	0/32(0.00)	3/40(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	1.425
Lower Limit	---	0.000	0.126
Upper Limit	---	10.977	72.891
Weeks to First Observed Tumor	111	---	90

TABLE 10 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	1/19(0.05)	6/30(0.20)	8/36(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.800	4.222
Lower Limit	---	0.521	0.646
Upper Limit	---	167.766	180.880
Weeks to First Observed Tumor	111	94	92
Mammary Gland: Fibroadenoma[b]	7/19(0.37)	13/49(0.27)	10/49(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.720	0.554
Lower Limit	---	0.332	0.235
Upper Limit	---	1.857	1.504
Weeks to First Observed Tumor	84	104	83

[a]Treated groups received time-weighted average doses of 850 or 1700 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

every type of tumor in either sex where at least two such tumors were observed in at least one of the control or TDE-dosed groups and where such tumors were observed in at least 5 percent of the group.

High incidences of follicular-cell thyroid neoplasms were noted in dosed male rats. When incidences were combined so that the numerator represented males with either a follicular-cell adenoma or a follicular-cell carcinoma of the thyroid, the Fisher exact test comparing the low dose to the control was significant ($P = 0.016$). The first observed thyroid follicular-cell neoplasm was in week 60, 94, and 103 for the high dose, low dose, and control group, respectively. In the historical control data compiled by this laboratory for the NCI Carcinogenesis Testing Program, 32/352 (9 percent) of the untreated male Osborne-Mendel rats had a follicular-cell adenoma or a follicular-cell carcinoma of the thyroid--compared to 1/19 (5 percent), 16/49 (33 percent), or 11/49 (22 percent) for the control, low dose, or high dose group, respectively, in this bioassay.

Based upon these results the statistical conclusion is that the increased incidence of follicular-cell neoplasms of the thyroid in male rats was associated with the administration of TDE. No such association was shown for C-cell neoplasms of the thyroid.

For both male and female rats the incidence of fibromas of the subcutaneous tissue had a significant negative association with the administration of TDE. For the females, however, the Fisher exact tests were not significant.

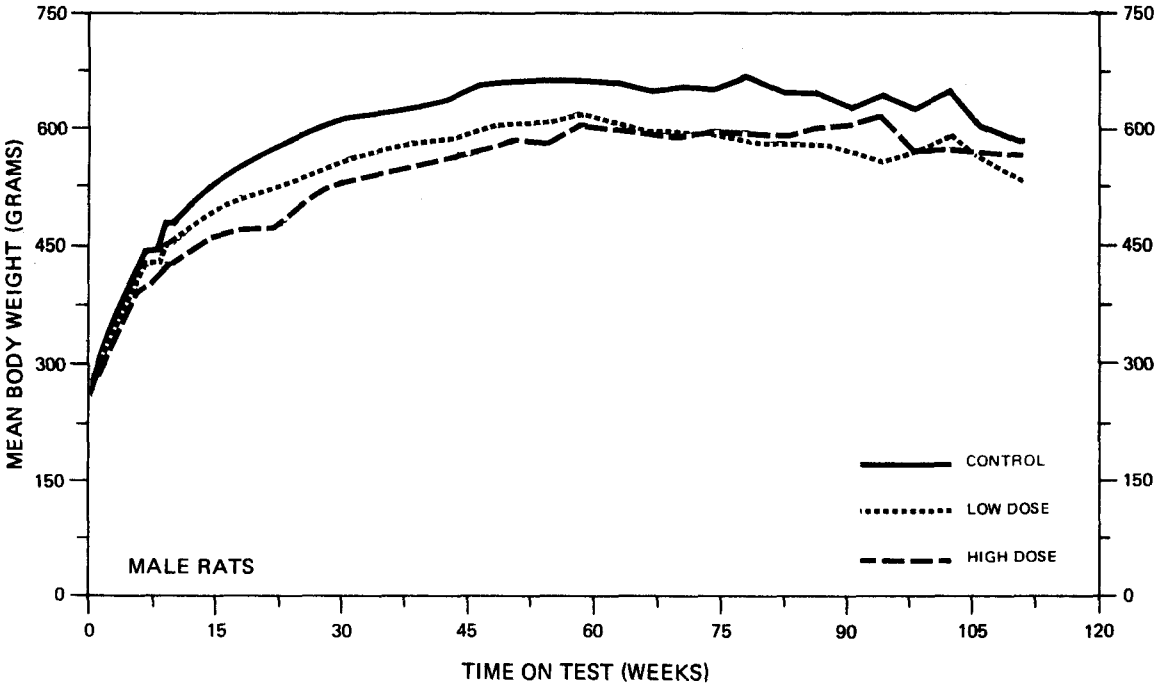
To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 9 and 10, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by TDE that could not be established under the conditions of this test.

C. DDE

1. Body Weights and Clinical Observations

Compound-related mean body weight depression was observed in both male and female rats (Figure 8).

No clinical signs were observed during the first 7 weeks of the study. Beginning in week 8, a few dosed rats started to exhibit a hunched or thin appearance which was observed in increasing numbers of rats, particularly in the high dose males. Following a decrease in dose level in week 24, the incidence of this sign decreased sharply in the dosed groups; however, it was still noted with greater frequency in these groups than in the controls for the duration of the dosing period. From week 78 to termination of the study, comparable numbers of dosed and control rats showed a hunched appearance. Other signs



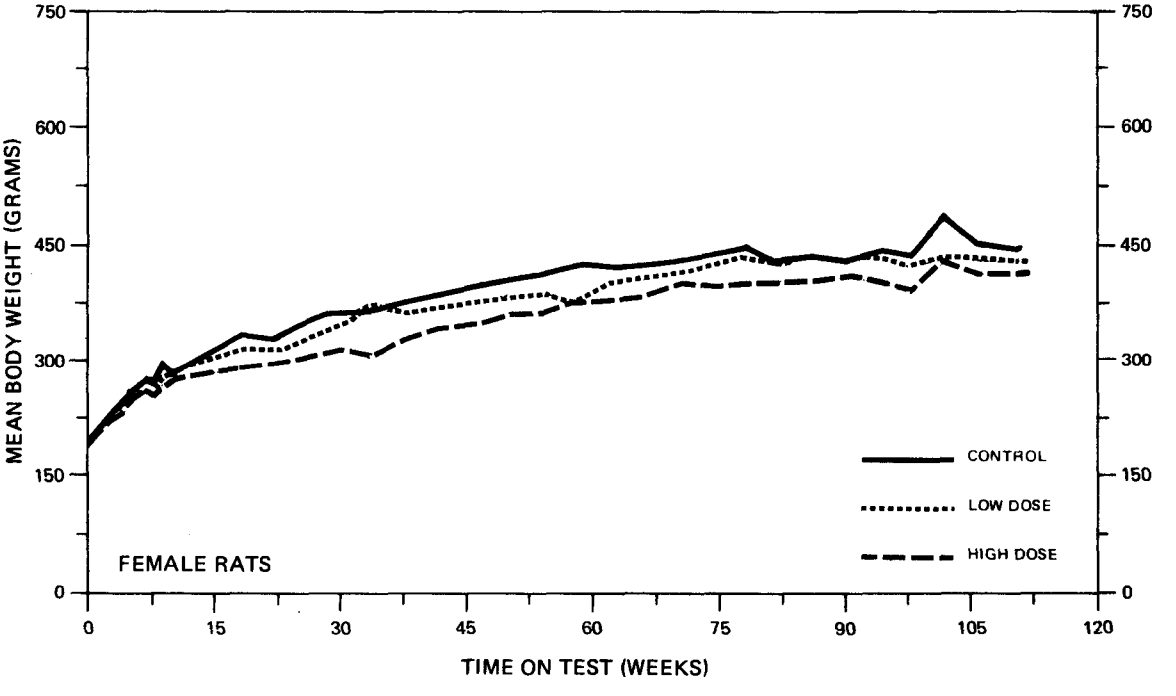


FIGURE 8
GROWTH CURVES FOR DDE CHRONIC STUDY RATS

observed at similar frequency and at a low incidence in dosed and control rats included respiratory signs, abdominal urine stains, squinted or reddened eyes, body sores, alopecia, bloated appearance, and palpable nodules and/or tissue masses. Isolated instances of tremors, ataxia, loss of equilibrium, hyperactivity, and vaginal discharge were observed in one or two dosed rats.

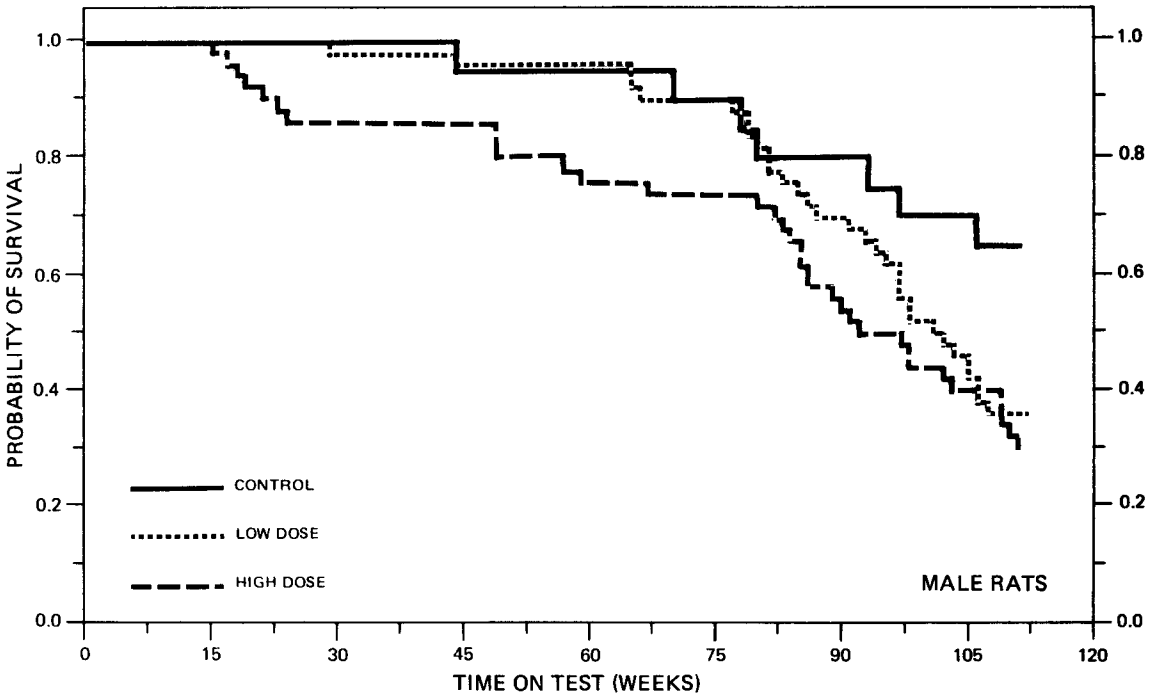
2. Survival

The estimated probabilities of survival for male and female rats in the control and DDE-dosed groups are shown in Figure 9. For both male and female rats the Tarone test indicated a significant ($P < 0.015$) positive association between dosage and mortality.

Adequate numbers of males were at risk from late-developing tumors, as 52 percent (26/50) of the high dose, 68 percent (34/50) of the low dose, and 80 percent (16/20) of the control rats survived on test at least 92 weeks. For females the survival was also adequate as 72 percent (36/50) of the high dose, 84 percent (42/50) of the low dose, and all 20 of the control rats survived on test at least 92 weeks. Of the 14 high dose females that died before week 92, 9 died in weeks 21 through 24; 2 of the 9 were autolyzed.

3. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix I (Tables I1 and I2); findings on nonneoplastic lesions are summarized in Appendix K (Tables K1 and K2).



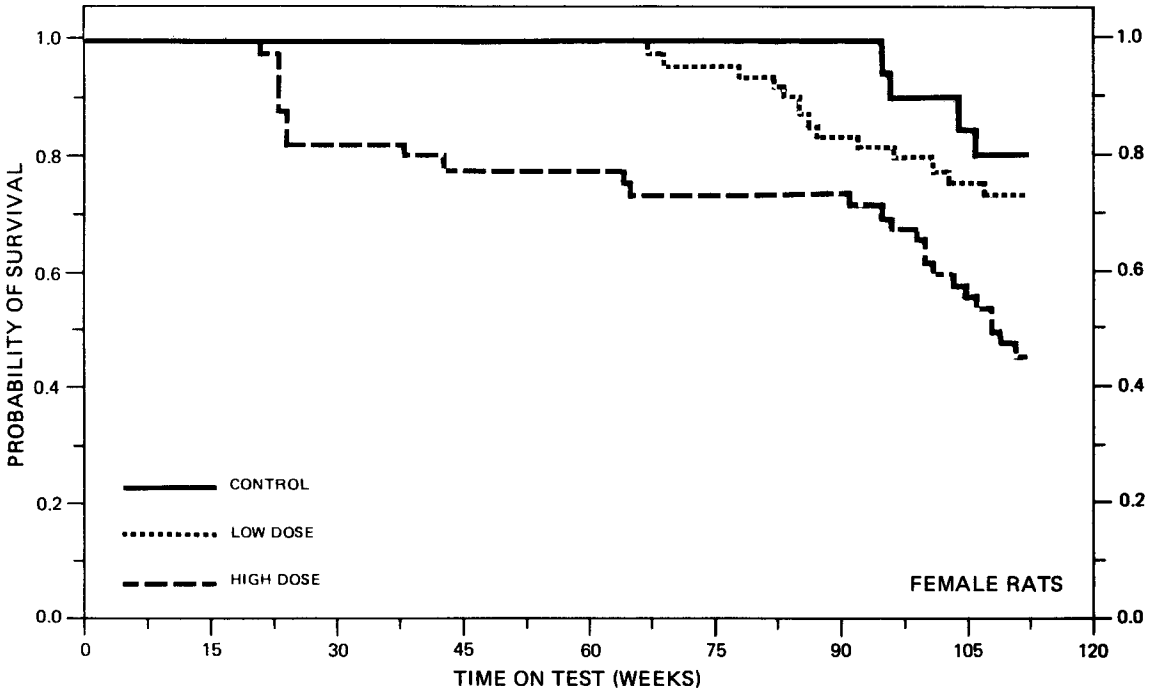


FIGURE 9
SURVIVAL COMPARISONS OF DDE CHRONIC STUDY RATS

Neoplasms and hyperplasias of the thyroid gland occurred in both dosed and control rats as shown in the following tabulation:

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of Animals with Thyroid Examined Histopathologically	(20)	(49)	(47)	(19)	(48)	(48)
Follicular-Cell Adenoma	2	8	8	1	6	8
Follicular-Cell Carcinoma	1	5	2	1	3	4
Follicular-cell Hyperplasia	2	2	4	0	7	4
C-Cell Adenoma	2	1	1	0	5	1
C-Cell Carcinoma	1	1	0	1	3	1
C-Cell Hyperplasia	4	0	1	3	3	2

The morphology of the thyroid lesions observed in this study was similar to that described in TDE (pp. 56-57).

DDE caused a toxic hepatopathy which was manifested by centrilobular necrosis and fatty metamorphosis in the hepatocytes. Centrilobular necrosis occurred in 2/40 low dose males, 3/40 high dose males, 1/20 control females, 7/34 low dose females, and 10/33 high dose females. Fatty metamorphosis in hepatocytes occurred in 2/20 control males, 25/40 low dose males, 20/40 high dose males, 11/20 control females, 3/34 low dose females, and 10/33 high dose females. The livers with centrilobular necrosis had lost many centrilobular

hepatocytes and the adjacent hepatocytes in the lobule contained lipid droplets. In some livers there was an infiltration of lymphocytes.

The numbers and kinds of neoplasms that occurred in dosed rats were similar in frequency to those occurring in the control rats.

In this study pathologic evidence was not provided for the carcinogenicity of DDE in Osborne-Mendel rats, but the compound was toxic to the livers, causing a centrilobular necrosis and fatty metamorphosis in the dosed male and female rats.

4. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 11 and 12. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or DDE-dosed groups and where such tumors were observed in at least 5 percent of the group. Because of the early mortality in the high dose males and females, additional, time-adjusted analyses were conducted based either upon those rats which survived at least 52 weeks or, in the event that the tumor of interest was observed earlier than 52 weeks, upon rats which survived at least until the first tumor of that type was observed. The results of interest for these additional analyses are given in Table 13.

For the time-adjusted analysis, the Cochran-Armitage test indicated a significant ($P = 0.041$) positive association between dosage

TABLE 11

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	4/50(0.08)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.023	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.386	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	29	---
Pituitary: Chromophobe Adenoma[b]	0/18(0.00)	4/18(0.22)	0/19(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.003	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.983	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	101	---
Thyroid: Follicular-Cell Carcinoma[b]	1/20(0.05)	5/49(0.10)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.041	0.851
Lower Limit	---	0.254	0.048
Upper Limit	---	94.440	49.165
Weeks to First Observed Tumor	111	85	111

TABLE 11 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	3/20(0.15)	12/49(0.24)	10/47(0.21)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.633	1.418
Lower Limit	---	0.512	0.424
Upper Limit	---	8.342	7.425
Weeks to First Observed Tumor	111	77	57
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	3/20(0.15)	2/49(0.04)	1/47(0.02)
P Values[c]	P = 0.047(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.272	0.142
Lower Limit	---	0.025	0.003
Upper Limit	---	2.232	1.665
Weeks to First Observed Tumor	111	105	103

[a]Treated groups received time-weighted average doses of 437 or 839 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparision of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 12

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	9/18(0.50)	10/33(0.30)	14/27(0.52)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.606	1.037
Lower Limit	---	0.291	0.558
Upper Limit	---	1.395	2.118
Weeks to First Observed Tumor	96	107	96
Thyroid: Follicular-Cell Carcinoma[b]	1/19(0.05)	3/48(0.06)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.188	1.583
Lower Limit	---	0.106	0.174
Upper Limit	---	61.031	76.296
Weeks to First Observed Tumor	111	112	109
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	2/19(0.11)	9/48(0.19)	12/48(0.25)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.781	2.375
Lower Limit	---	0.425	0.611
Upper Limit	---	16.042	20.621
Weeks to First Observed Tumor	111	101	43

TABLE 12 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma[b]	1/19(0.05)	3/48(0.06)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.188	0.396
Lower Limit	---	0.106	0.005
Upper Limit	---	61.031	30.454
Weeks to First Observed Tumor	111	112	112
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	1/19(0.05)	8/48(0.17)	2/48(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.040	---	---
Relative Risk (Control)[d]	---	3.167	0.792
Lower Limit	---	0.478	0.045
Upper Limit	---	137.163	45.751
Weeks to First Observed Tumor	111	83	112
Mammary Gland: Adenocarcinoma NOS[b]	1/20(0.05)	5/49(0.10)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.041	0.000
Lower Limit	---	0.254	0.000
Upper Limit	---	94.440	7.475
Weeks to First Observed Tumor	111	67	---

TABLE 12 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	5/20(0.25)	5/49(0.10)	7/50(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.408	0.560
Lower Limit	---	0.110	0.179
Upper Limit	---	1.614	2.028
Weeks to First Observed Tumor	104	82	91
Uterus: Endometrial Stromal Polyp[b]	0/19(0.00)	3/33(0.09)	0/23(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.046	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.363	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	111	---

[a]Treated groups received time-weighted average doses of 242 or 462 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 13

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH DDE[a,e]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b,e]	2/19(0.11)	9/48(0.19)	12/38(0.32)
P Values[c]	P = 0.041	N.S.	N.S.
Relative Risk (Control)[d]	---	1.781	3.000
Lower Limit	---	0.424	0.778
Upper Limit	---	16.042	25.661
Weeks to First Observed Tumor	111	101	43

[a]Treated groups received time-weighted average doses of 242 or 462 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[e]These analyses were based solely upon animals surviving at least 43 weeks.

and the combined incidence of follicular-cell adenomas and follicular-cell carcinomas of the thyroid in females. The Fisher exact tests, however, were not significant. The first observed follicular-cell thyroid neoplasm was at week 43, 101, and 111 for the high dose, low dose, and control group, respectively.

No other statistical tests for any site in rats of either sex indicated a significant positive association between the administration of DDE and tumor incidence. Thus, at the dose levels used in this experiment there was no convincing evidence that DDE was a carcinogen in Osborne-Mendel rats.

In male rats the Cochran-Armitage test indicated a significant negative association between dose and the combined incidence of C-cell adenomas and C-cell carcinomas of the thyroid. The Fisher exact tests, however, did not support this finding.

In female rats the incidence of pituitary chromophobe adenomas in the control group (9/18 or 50 percent) was high compared to that observed in the historical controls (130/350 or 37 percent).

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 11, 12, and 13 the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit

greater than one, indicating the theoretical possibility of tumor induction in rats by DDE that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. DDT

1. Body Weights and Clinical Observations

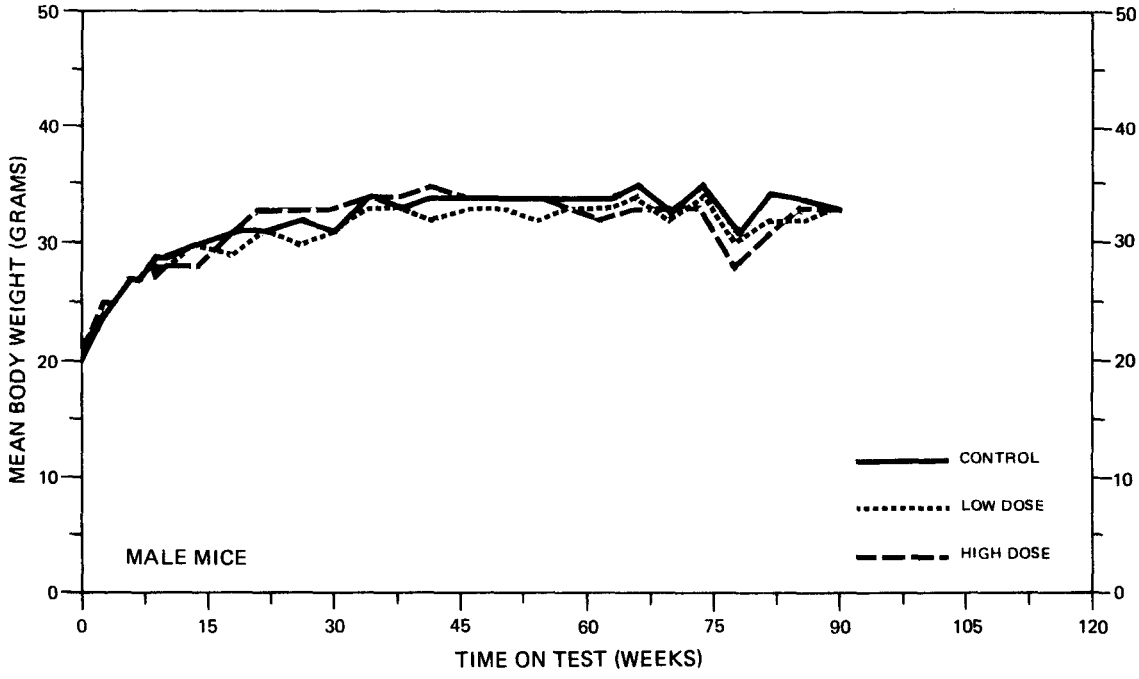
Distinct, dose-related mean body weight depression was not apparent in male or female mice (Figure 10).

Throughout the study, there was no evidence of compound effect with regard to physical appearance and behavior among the mice at any dosage. Clinical signs were observed at similar rates in dosed and control mice. These signs included sores on the body or extremities (more prevalent in the males), localized alopecia, rough or stained fur, external genital irritations with occasional anal prolapse, bloated appearance, palpable nodules, and tissue masses or swollen areas.

2. Survival

The estimated probabilities of survival for male and female mice in the control and DDT-dosed groups are shown in Figure 11. For males no significant positive association between dose and mortality was observed. For females the Tarone test indicated a significant ($P = 0.005$) positive association between dosage and mortality.

There was high mortality among all male groups during the second year of the study--possibly due to fighting. There were, however, adequate numbers of male mice at risk from late developing tumors as 74 percent (37/50) of the high dose, 40 percent (20/50) of the low



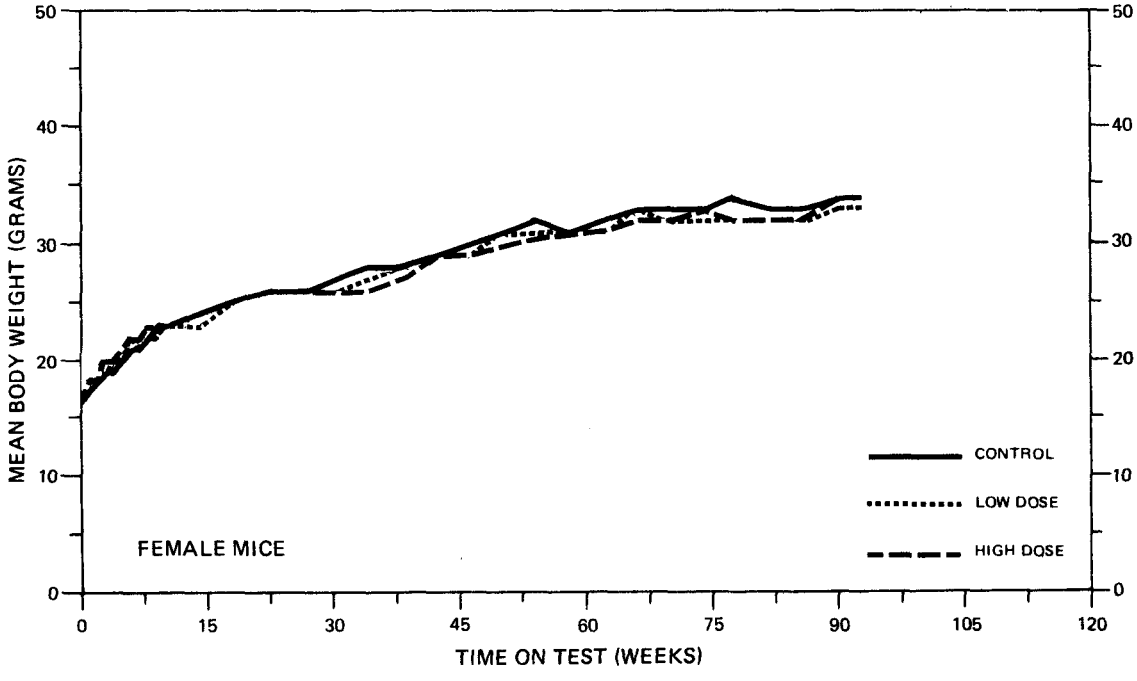


FIGURE 10
GROWTH CURVES FOR DDT CHRONIC STUDY MICE

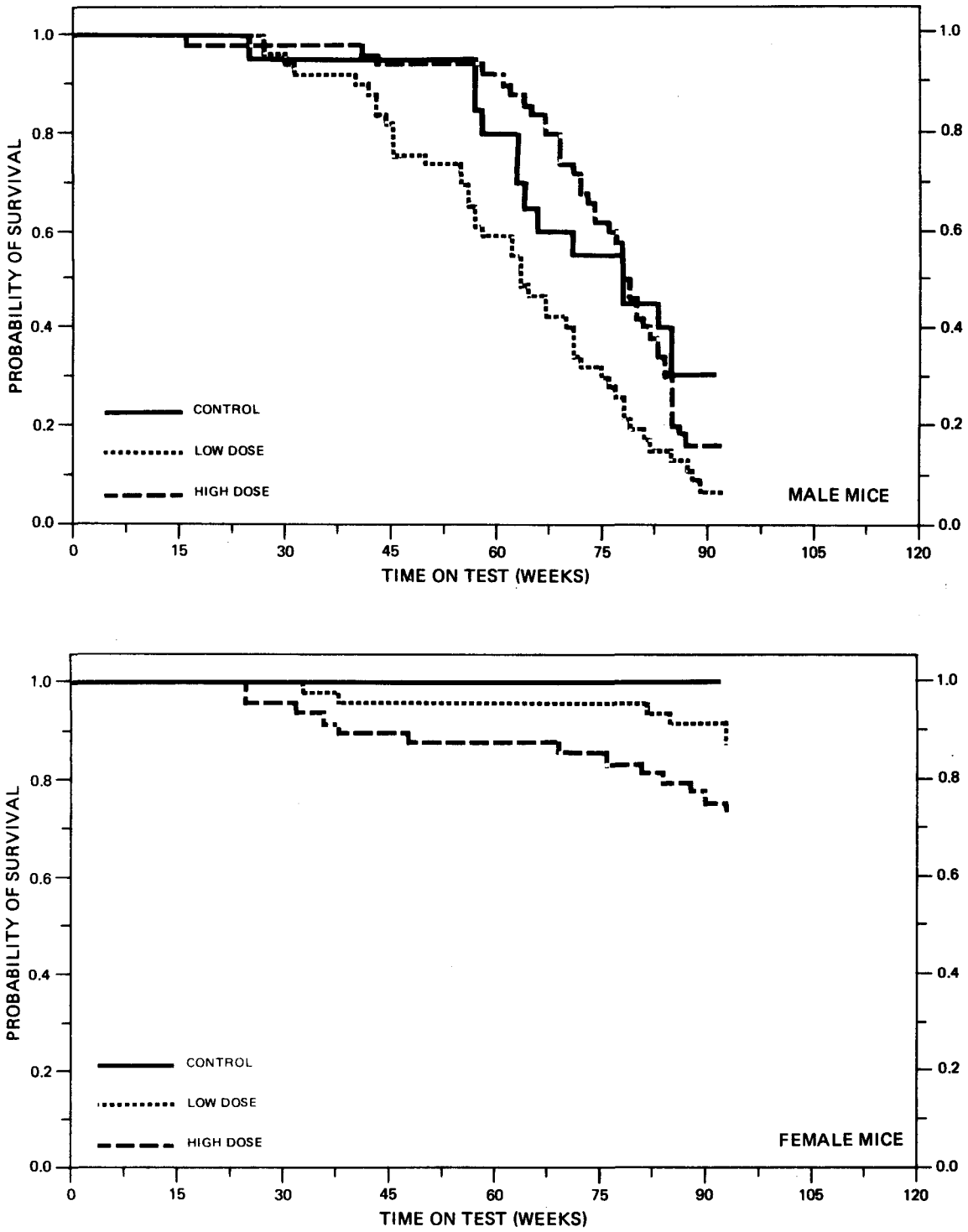


FIGURE 11
SURVIVAL COMPARISONS OF DDT CHRONIC STUDY MICE

dose, and 60 percent (12/20) of the control mice survived on test at least 70 weeks.

For females survival was adequate as 72 percent (36/50) of the high dose, 90 percent (45/50) of the low dose, and all 20 of the control mice survived on test until the end of the experiment.

3. Pathology

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

Hepatocellular carcinomas occurred in 2/19 (11 percent) control males, 1/49 (2 percent) low dose males, 1/48 (2 percent) high dose males, 0/20 control females, 1/22 (5 percent) low dose females, and 3/27 (11 percent) high dose females. The incidence of these tumors in the mice was not considered to have been increased by administration of the chemical.

Other neoplasms that occurred in this bioassay are presented in Appendix B. The inflammatory, degenerative, and proliferative lesions (both neoplastic and nonneoplastic) seen in the control and dosed animals were similar in number and kind to those lesions occurring naturally in aged B6C3F1 mice.

In this study, pathologic evidence was not provided for the carcinogenicity of DDT in B6C3F1 mice.

4. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 14 and 15. The analysis is included

TABLE 14

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	0/19(0.00)	2/49(0.04)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.119	0.021
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	45	71
Liver: Hepatocellular Carcinoma[b]	2/19(0.11)	1/49(0.02)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.194	0.198
Lower Limit	---	0.003	0.004
Upper Limit	---	3.561	3.635
Weeks to First Observed Tumor	91	88	80

[a]Treated groups received time-weighted average doses of 22 or 44 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 15

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	0/20(0.00)	3/49(0.06)	7/46(0.15)
P Values[c]	P = 0.026	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.255	0.880
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	92	76
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	1/22(0.05)	3/27(0.11)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.050	0.465
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	93	93

[a]Treated groups received time-weighted average doses of 87 or 175 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or DDT-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to the poor survival, additional, time-adjusted analyses were conducted; there were no important changes in the statistical results.

For female mice the Cochran-Armitage test indicated a significant ($P = 0.026$) positive association between dosage and the incidence of malignant lymphomas. The Fisher exact tests, however, were not significant.

No other statistical tests were significant for male or female mice. Thus, based upon these statistical results there was no convincing evidence that DDT was a carcinogen in mice under the conditions of this experiment.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 14 and 15, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by DDT that could not be established under the conditions of this test.

B. TDE

1. Body Weights and Clinical Observations

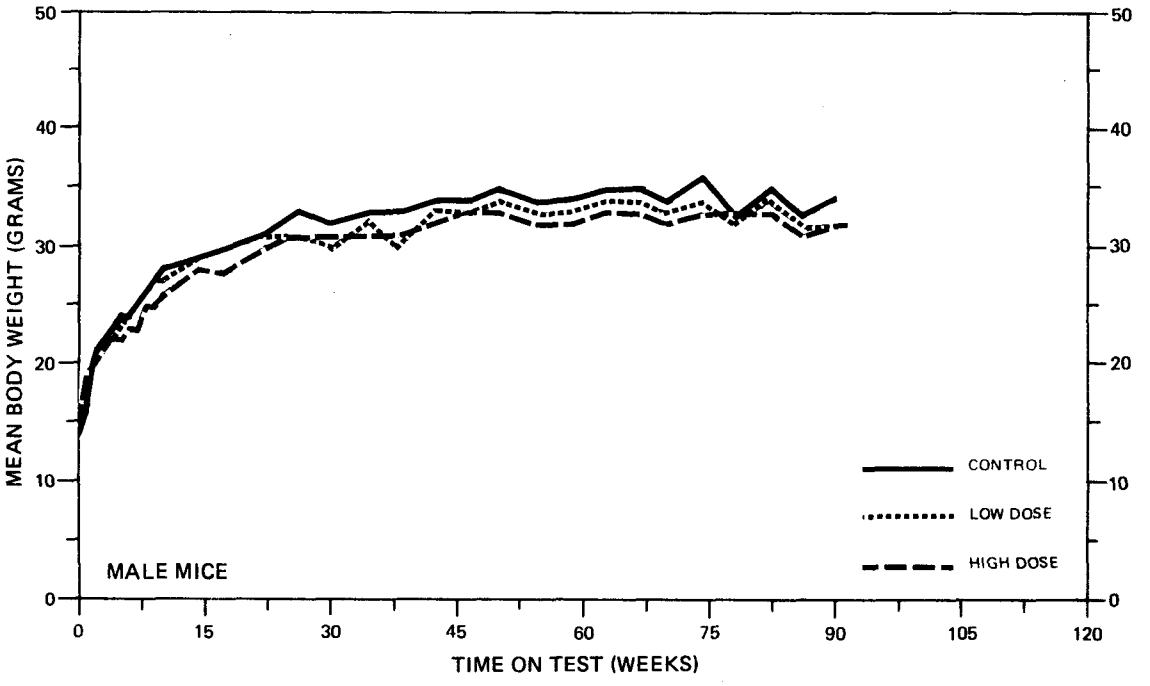
Dose-related mean body weight depression was apparent in females beginning in week 30 and continuing for the remainder of the bioassay. Effect of chemical administration on mean body weight was not readily evident for male mice (Figure 12).

Throughout the study there was no evidence that the compound affected physical appearance or behavior among the dosed mice. Signs often observed in B6C3F1 mice were observed at comparable rates in dosed and control animals. These common signs included body sores (predominantly in the males and attributable to fighting), a hunched appearance, localized alopecia, penile or vulvar irritation, occasional anal prolapse, and rough or stained fur. Palpable nodules, tissue masses, bloating and/or swollen areas on the body were observed at a comparable rate in dosed and control mice, particularly in the females. The incidence of these common signs increased gradually during the last 6 months of the study as the age of the animals increased.

2. Survival

The estimated probabilities of survival for male and female mice in the control and TDE-dosed groups are shown in Figure 13. No significant positive association between dosage and mortality was observed for either sex.

There were adequate numbers of males at risk from late-developing tumors, as 54 percent (27/50) of the high dose, 60 percent (30/50) of



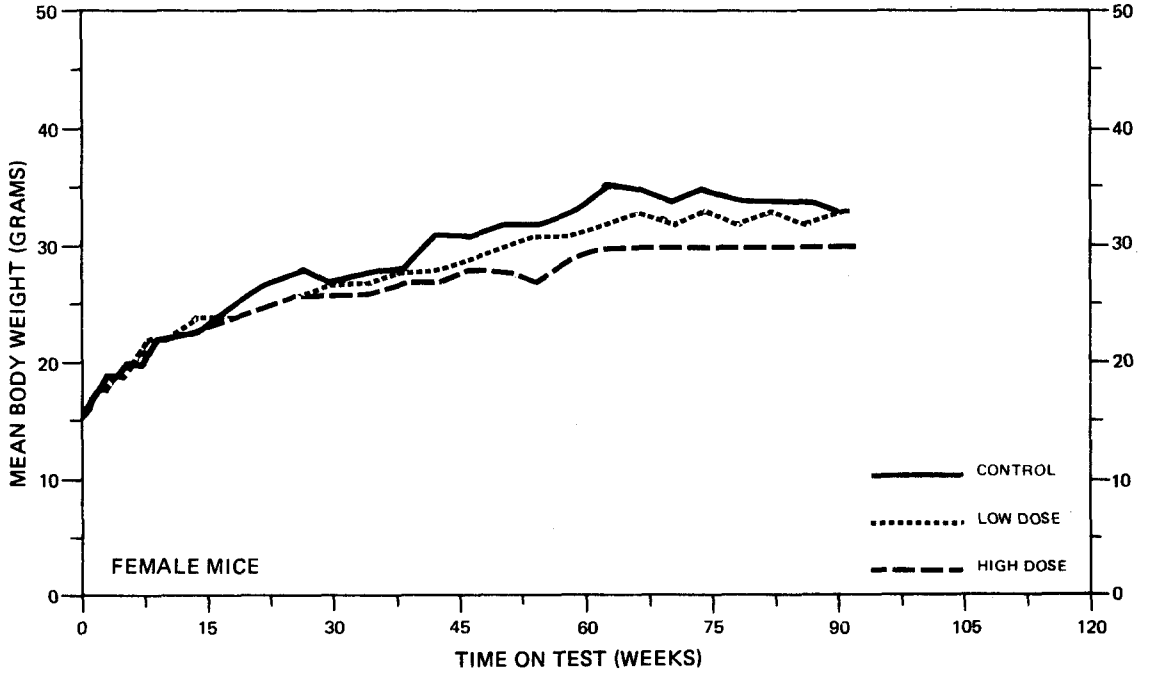
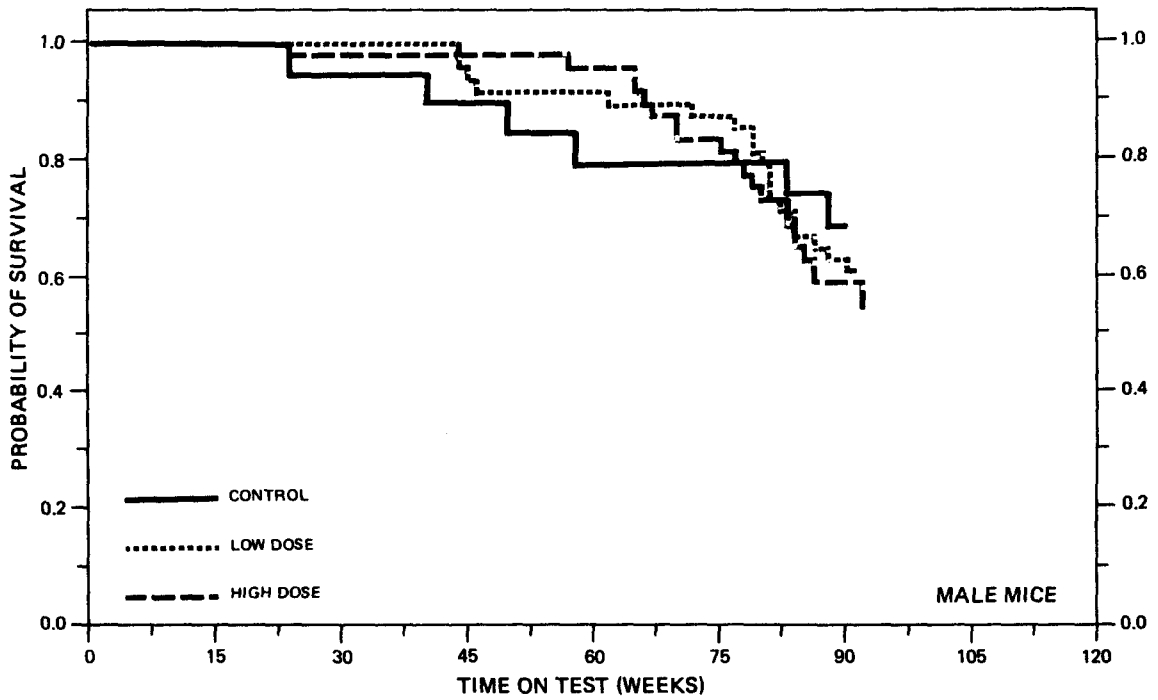


FIGURE 12
GROWTH CURVES FOR TDE CHRONIC STUDY MICE



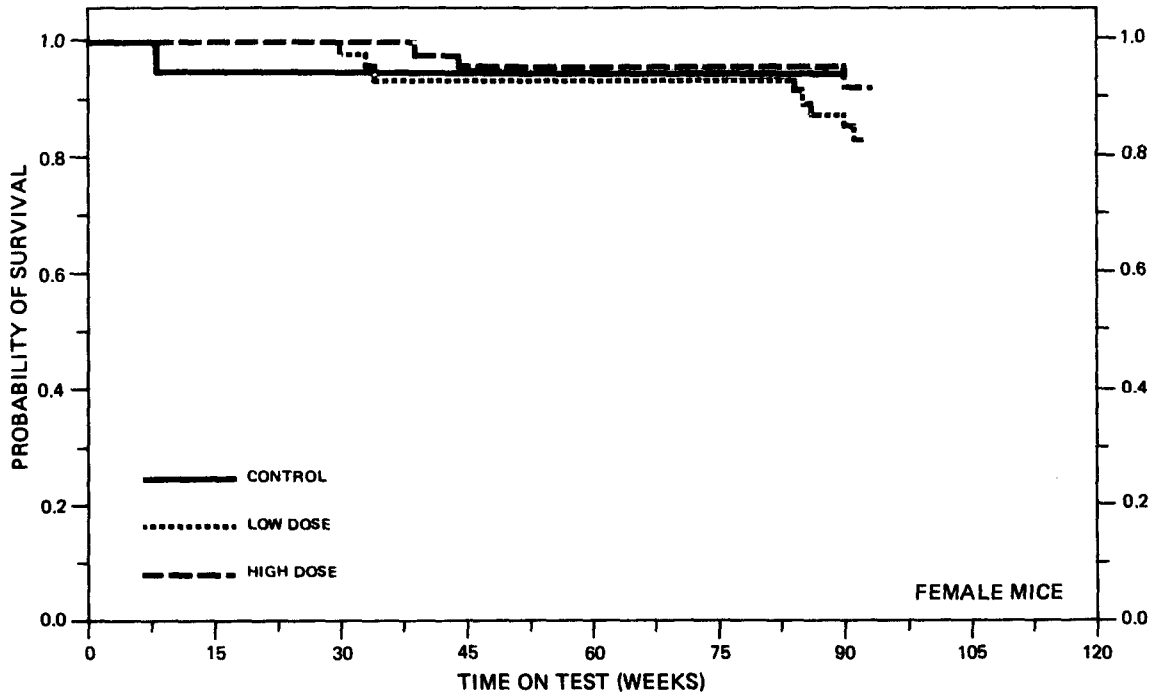


FIGURE 13
SURVIVAL COMPARISONS OF TDE CHRONIC STUDY MICE

the low dose, and 65 percent (13/20) of the control mice survived on test until the end of the study. Survival was also adequate for the females as 88 percent (44/50) of the high dose, 82 percent (41/50) of the low dose, and 90 percent (18/20) of the control mice survived on test until the end of the study.

3. Pathology

Histopathologic findings on neoplasms in mice are summarized in Appendix F (Tables F1 and F2); findings on nonneoplastic lesions are summarized in Appendix H (Tables H1 and H2).

Hepatocellular carcinomas occurred in 2/18 (11 percent) control male, 12/44 (27 percent) low dose male, 14/50 (28 percent) high dose male, 0/20 control female, 2/48 (4 percent) low dose female, and 3/47 (6 percent) high dose female mice. One hepatocellular carcinoma in a low dose male metastasized to the lung.

The hepatocellular carcinomas varied greatly in appearance. Some lesions contained well-differentiated hepatocytes that had relatively uniform arrangement of the cords, and others had very anaplastic liver cells with large hyperchromatic nuclei, often with inclusion bodies and with vacuolated pale cytoplasm. Arrangement of the neoplastic hepatocytes varied from short stubby cords to nests of hepatic cells and occasionally acinar formation. Mitotic figures were often present. Some of the tumors were characterized by foci of anaplastic cells.

The inflammatory, degenerative, and proliferative lesions seen in the control and dosed animals were similar in number and kind to those lesions occurring naturally in aged B6C3F1 mice.

Although there was a higher incidence of hepatocellular carcinomas in TDE-dosed male mice (11 percent in the control group, 27 percent in the low dose group, and 28 percent in the high dose group), these tumors have been observed in as many as 20 percent of the control mice in other studies. Therefore, in the judgment of the pathologist, TDE was not carcinogenic to B6C3F1 mice at the dosages administered in this study.

4. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 16 and 17. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or TDE-dosed groups and where such tumors were observed in at least 5 percent of the group.

No statistical tests for either males or females indicated a significant positive association between chemical administration and tumor incidence. Based upon these results there was no evidence that TDE was a carcinogen in B6C3F1 mice.

A possible negative association between TDE administration and incidence was observed for fibroma of the subcutaneous tissue in males.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in

TABLE 16

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	3/18(0.17)	2/49(0.04)	0/50(0.00)
P Values[c]	P = 0.007(N)	N.S.	P = 0.016(N)
Relative Risk (Control)[d]	---	0.245	0.000
Lower Limit	---	0.023	0.000
Upper Limit	---	2.003	0.592
Weeks to First Observed Tumor	90	91	---
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	1/18(0.06)	4/29(0.14)	2/35(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.483	1.029
Lower Limit	---	0.277	0.058
Upper Limit	---	117.569	58.934
Weeks to First Observed Tumor	90	84	92
Liver: Hepatocellular Carcinoma[b]	2/18(0.11)	12/44(0.27)	14/50(0.28)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.455	2.520
Lower Limit	---	0.638	0.675
Upper Limit	---	21.184	21.536
Weeks to First Observed Tumor	90	83	67

TABLE 16 (CONCLUDED)

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[a]Treated groups received time-weighted average doses of 411 or 822 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 17

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/20(0.00)	4/27(0.15)	1/15(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.718	0.073
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	90
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	2/48(0.04)	3/47(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.128	0.267
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	92
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	0/20(0.00)	2/48(0.04)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.128	0.412
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	91	92

TABLE 17 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	1/20(0.05)	7/49(0.14)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.040(N)	---	---
Relative Risk (Control)[d]	---	2.857	0.426
Lower Limit	---	0.411	0.006
Upper Limit	---	125.834	32.720
Weeks to First Observed Tumor	90	86	93

[a]Treated groups received time-weighted average doses of 411 or 822 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

Tables 16 and 17, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by TDE that could not be established under the conditions of this test.

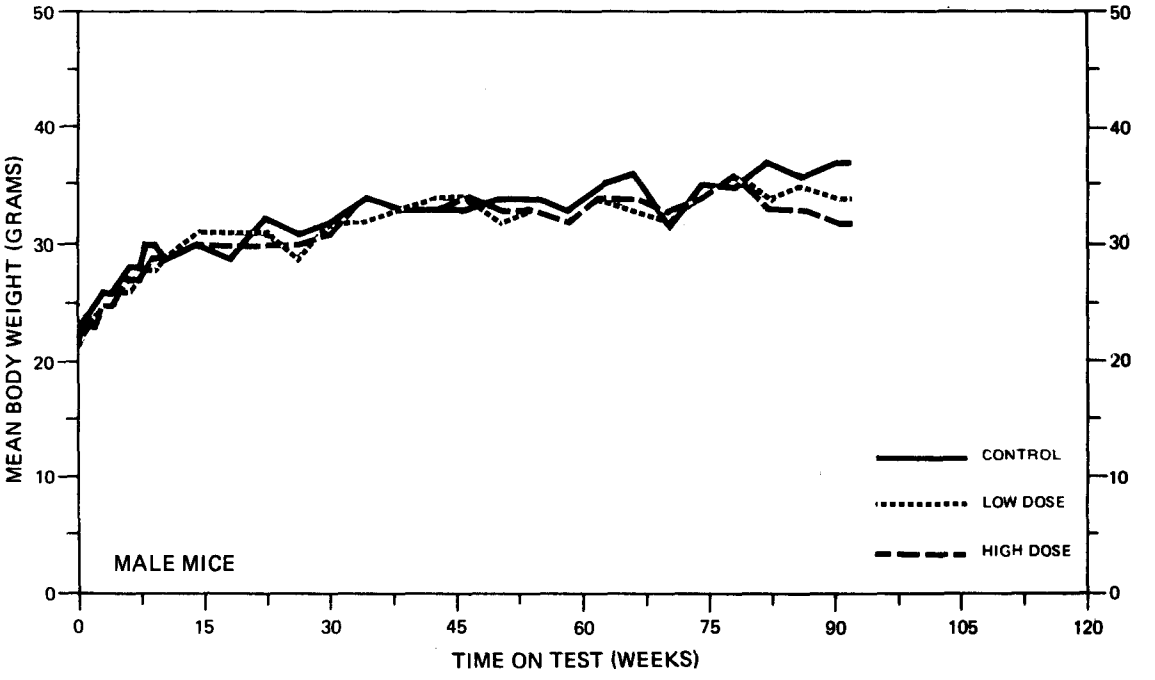
C. DDE

1. Body Weights and Clinical Observations

Dose-related mean body weight depression was evident in female mice as early as week 10. Administration of DDE had no apparent effect on growth of male mice (Figure 14).

During the first 20 weeks of the study, the dosed and control mice exhibited essentially comparable appearance and behavior. Signs often observed in B6C3F1 mice were observed at similar frequencies in all groups. These signs included body sores with localized alopecia, external genital irritation, and abdominal urine stains.

From week 22 to week 34 of the study, 60 to 85 percent of the dosed male mice exhibited a hunched appearance. The incidence of this sign alternately decreased and then increased from week 38 to cessation of dosing in week 78, presumably reflecting the cyclic regimen of compound administration during this period. During the last 12 weeks of the study the signs mentioned above, including palpable tissue masses, were observed at a comparable rate in the surviving dosed and control mice.



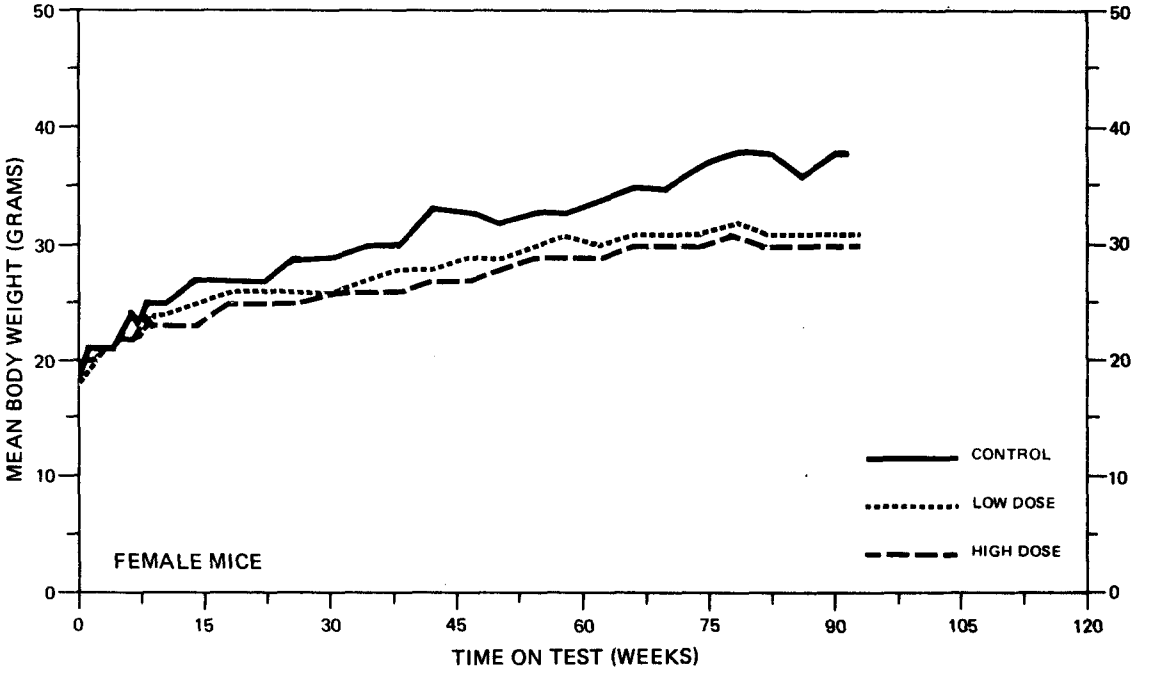


FIGURE 14
GROWTH CURVES FOR DDE CHRONIC STUDY MICE

2. Survival

The estimated probabilities of survival for male and female mice in the control and DDE-dosed groups are shown in Figure 15. For males the Tarone test did not indicate a significant positive association between dosage and mortality. For females a significant ($P < 0.001$) positive association between dosage and mortality was observed.

For males the survival of the control mice was quite low, as 7/20 (35 percent) died in week 40 and only 25 percent (5/20) survived on test at least 70 weeks. Survival was somewhat better in the dosed males as 62 percent (31/50) of the high dose and 70 percent (35/50) of the low dose mice survived on test at least 70 weeks. Amyloidosis of the spleen, kidney, and liver were quite common among the control males and among those low dose males that survived less than 85 weeks.

For females there were adequate numbers of mice at risk from late-developing tumors as 56 percent (28/50) of the high dose, 94 percent (47/50) of the low dose, and 95 percent (19/20) of the control mice survived on test at least 75 weeks.

3. Pathology

Histopathologic findings on neoplasms in mice are summarized in Appendix J (Tables J1 and J2); findings on nonneoplastic lesions are summarized in Appendix L (Tables L1 and L2).

Hepatocellular carcinomas occurred in 7/41 (17 percent) low dose male, 17/47 (36 percent) high dose male, 19/47 (40 percent) low dose

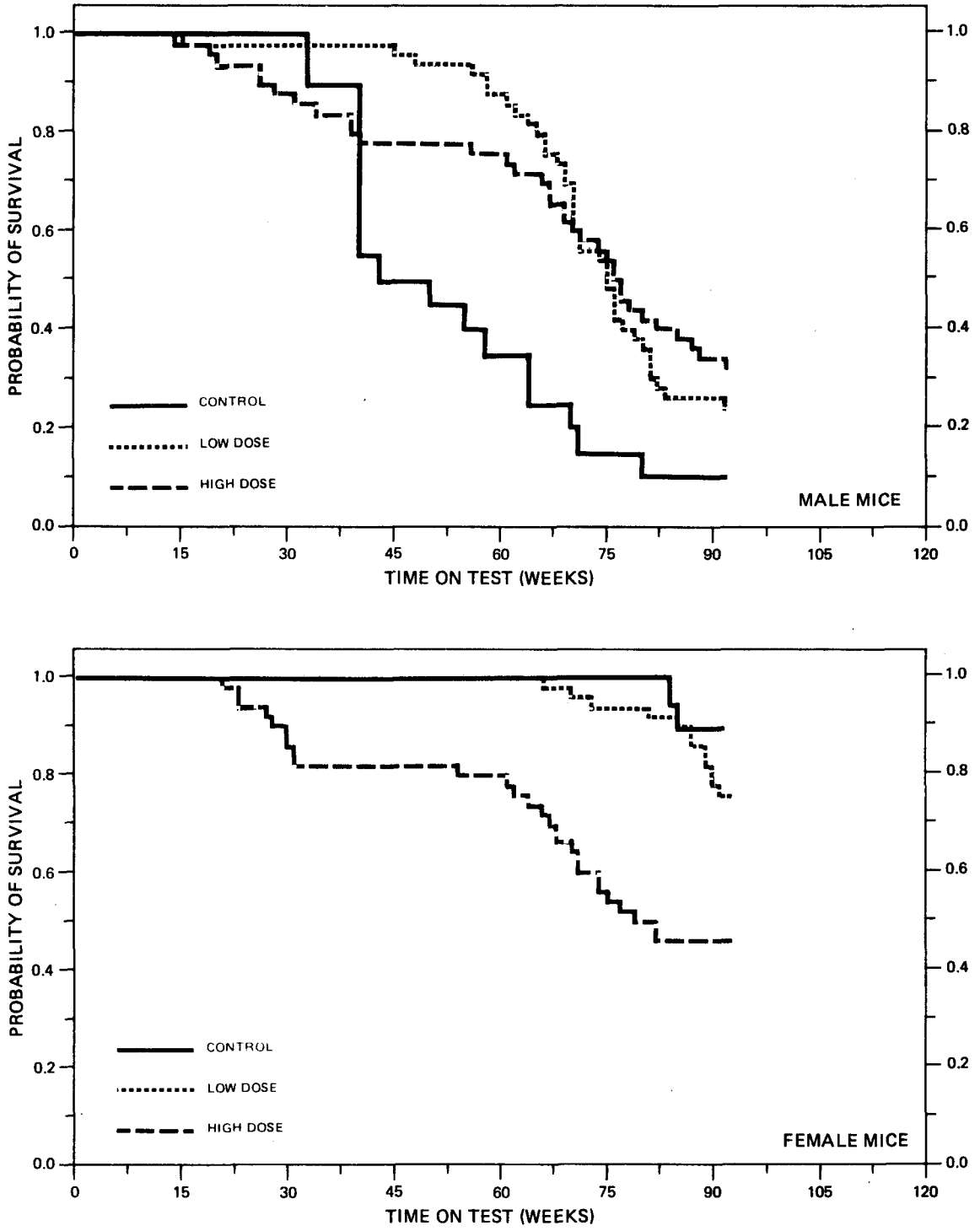


FIGURE 15
SURVIVAL COMPARISONS OF DDE CHRONIC STUDY MICE

female, and 34/48 (71 percent) high dose female mice. None of the male or female controls developed hepatocellular carcinomas. One of the liver tumors in the high dose females metastasized to the lung.

The hepatocellular carcinomas varied greatly in appearance. Some lesions contained well-differentiated hepatocytes that had a relatively uniform arrangement of the cords, and others had anaplastic hepatocytes with large hyperchromatic nuclei, often with inclusion bodies and with vacuolated, pale cytoplasm. Arrangement of the neoplastic hepatocytes varied from short stubby cords to nests of hepatocytes and occasionally acinar formation. Mitotic figures were often present. Some of the tumors were characterized by foci of anaplastic cells.

The number and kind of other neoplasms that occurred in this study were not appreciably different in the control and dosed mice.

Inflammatory, degenerative, and proliferative lesions seen in the control and dosed animals were similar in number and kind to those lesions occurring naturally in aged B6C3F1 mice.

In this study pathologic evidence was provided for the carcinogenicity of DDE in B6C3F1 mice, with a dose-related increase in hepatocellular carcinomas.

4. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 18 and 19. The analysis is included for every type of tumor in either sex where at least two such tumors

TABLE 18

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	0/18(0.00)	1/41(0.02)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.024	0.373
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	92	69
Hematopoietic System: Malignant Lymphoma[b]	0/18(0.00)	4/41(0.10)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.449	0.391
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	70	39
Liver: Hepatocellular Carcinoma[b]	0/19(0.00)	7/41(0.17)	17/47(0.36)
P Values[c]	P = 0.001	N.S.	P = 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.941	2.288
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	71	71

TABLE 18 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hemangioma or Hemangiosarcoma[b]	0/19(0.00)	2/41(0.05)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.143	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	62	---

[a]Treated groups received time-weighted average doses of 148 or 261 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 19

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	2/19(0.11)	4/48(0.08)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.792	0.388
Lower Limit	---	0.127	0.031
Upper Limit	---	8.329	5.109
Weeks to First Observed Tumor	92	66	68
Liver: Hepatocellular Carcinoma[b]	0/19(0.00)	19/47(0.40)	34/48(0.71)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	2.585	4.773
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	87	61
Circulatory System: Hemangioma or Hemangiosarcoma[b]	1/19(0.05)	2/48(0.04)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.792	0.000
Lower Limit	---	0.045	0.000
Upper Limit	---	45.751	7.244
Weeks to First Observed Tumor	84	87	---

TABLE 19 (CONCLUDED)

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[a]Treated groups received time-weighted average doses of 148 or 261 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 20

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF HEPATOCELLULAR CARCINOMAS IN MALE MICE TREATED WITH DDE[a,e]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	0/8(0.00)	7/38(0.18)	17/36(0.47)
P Values[c]	P = 0.002	N.S.	P = 0.013
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.473	1.398
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	71	71

[a]Treated groups received time-weighted average doses of 148 or 261 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]These analyses were based solely upon animals surviving at least 52 weeks, except for sites where the first tumor of interest was observed earlier than 52 weeks, where the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

were observed in at least one of the control or DDE-dosed groups and where such tumors were observed in at least 5 percent of the group.

In both male and female dosed mice significant numbers of hepatocellular carcinomas were observed. For both sexes the Cochran-Armitage test indicated a significant ($P \leq 0.001$) positive association between dosage and incidence. For the males the Fisher exact test comparing high dose to control was significant ($P = 0.001$); for the females both the high dose and the low dose comparisons were significant ($P < 0.001$). In the historical controls for untreated B6C3F1 mice, 68/389 (18 percent) of the males and 8/411 (2 percent) of the females had hepatocellular carcinomas or hepatocellular adenomas, compared to the 17/47 (36 percent) and 34/48 (71 percent) observed in the high dose males and high dose females, respectively.

Because of the unexpectedly low survival in the male control mice an additional, time-adjusted analysis of the incidence of hepatocellular carcinomas was performed (Table 20). This analysis considered only those mice that survived on test for at least 52 weeks. Once again both the Cochran-Armitage test ($P = 0.002$) and the Fisher exact test comparing high dose to control ($P = 0.013$) were significant.

Based upon these results the statistical conclusion is that the administration of DDE was associated with an increased incidence of hepatocellular carcinomas in both male and female B6C3F1 mice.

V. DISCUSSION

Under the conditions of these bioassays there were statistically significant associations between increased concentration and accelerated mortality in female mice dosed with DDT and in both sexes of rats and female mice dosed with DDE. This association was not demonstrated in other groups. There was, however, poor survival among control and dosed male mice used in the bioassays of DDT and DDE. In all cases adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

Hyperplasias and neoplasms of the thyroid were observed in rats dosed with each of the three compounds; however, only for TDE did the pathologists consider that the tumors were related to chemical administration. The percentage of rats in each group having either follicular-cell adenoma or follicular-cell carcinoma of the thyroid is shown in the following table. The percentage of rats with follicular-cell carcinoma is shown in parentheses.

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
DDT	47(5)	42(13)	45(10)	5(0)	29(9)	23(14)
TDE	5(5)	33(12)	22(6)	11(11)	23(10)	12(2)
DDE	15(5)	24(10)	21(4)	11(5)	19(6)	25(8)

When those male rats receiving TDE and their controls were combined within each group so that the numerators of the tumor incidences represented those animals with either a follicular-cell carcinoma or a follicular-cell adenoma of the thyroid the Fisher exact comparison

of the low dose to the control was significant. In historical control data compiled by the laboratory performing these bioassays for the NCI Carcinogenesis Testing Program, 32/352 (9 percent) of the untreated Osborne-Mendel male rats had either a follicular-cell adenoma or a follicular-cell carcinoma of the thyroid. However, because of the high variation (5 to 47 percent) of these lesions in control male rats in these studies, the findings must be considered only as suggestive of a chemical-related effect.

Among dosed rats no other neoplasms occurred in statistically significant incidences when compared to controls.

In mice the only neoplasms occurring in statistically significant incidences were hepatocellular carcinomas among groups receiving DDE. The incidences of hepatocellular carcinoma in DDE-dosed mice were 0/19, 7/41 (17 percent), and 17/47 (36 percent) in control, low dose, and high dose males, respectively, and 0/19, 19/47 (40 percent), and 34/48 (71 percent) in control, low dose, and high dose females, respectively. The Cochran-Armitage tests indicated a significant positive association between dosage and incidence in both sexes. Both Fisher exact comparisons for the females supported the finding as did the high dose to control Fisher exact comparison for the males. Although administration of DDE did not result in significant incidences of liver tumors in rats, the compound was indicated to be hepatotoxic, inducing centrilobular necrosis and fatty metamorphosis.

Long-term ingestion of p,p'-DDT or technical-grade DDT has been found to induce liver tumors in several strains of mice (IARC, 1974).

Administration of technical-grade DDT in the diet at a concentration of 2 ppm resulted in a significant increase in the incidence of tumors observed in male CF-1 mice surviving for more than 60 weeks (Tomatis et al., 1972); a concentration of 250 ppm was, however, necessary to induce a significant number of tumors in BALB/c mice. At this concentration 59 percent of the females and 48 percent of the males developed liver tumors as compared to none of the female controls and 2 percent of the male controls (Terracini et al., 1973). Dietary administration of p,p'-DDT at a concentration of 100 ppm for 110 weeks induced liver tumors in 79 percent of male and 96 percent of female CF-1 mice. Tumors were observed in 24 percent of the male and 23 percent of the female controls, respectively. The ratio of benign tumors to those possessing characteristics associated with malignancy was 1:1 in the dosed mice (Thorpe and Walker, 1973).

Other tumors reported in the literature to have occurred at elevated frequencies in various strains of dosed mice included maligant lymphoma (Innes et al., 1969); lymphoma, carcinoma of the lung, and leukemia (Tarjan and Kemeny, 1969); and adenoma of the lung (Shabad et al., 1973).

Ingestion of technical-grade DDT at a concentration of 500 ppm produced liver cell tumors in 56 percent of surviving female outbred Wistar rats and in 35 percent of surviving males. These tumors were not, however, classified by the authors as hepatocellular carcinomas. No liver cell tumors were observed in controls and no other compound-related tumors were detected (Rossi et al., 1977).

DDT by the oral route did not produce tumors in Syrian golden hamsters in excess of those observed in controls, and feeding studies in dogs, monkeys and rainbow trout were considered inconclusive by the IARC Working Group (IARC, 1974).

Tumor induction has been observed in CF-1 mice following dietary administration of either p,p'-TDE or p,p'-DDE at a concentration of 250 ppm for their lifespan (Tomatis et al., 1974). TDE produced an elevated incidence of hepatomas in males (52 percent versus 34 percent in controls) and lung tumors in males and females (86 percent in males versus 54 percent in controls; 73 percent in females versus 41 percent in controls). DDE produced an elevated incidence of hepatomas in both sexes (74 percent in males versus 34 percent in controls; 98 percent in females versus 1 percent in controls).

The concentration of DDT to male mice may have been set too low because of undue emphasis on a single death during the subchronic test. During the chronic bioassay, no growth retardation or other adverse clinical signs appeared to be associated with administration of DDT to male mice. Survival of DDT-dosed male mice was better than that of controls. No tumors were induced by DDT in male mice although tumor induction by DDT in male mice has been reported in the literature.

Under the conditions of these bioassays there was no evidence for the carcinogenicity of DDT in Osborne-Mendel rats or B6C3F1 mice, of TDE in female Osborne-Mendel rats or B6C3F1 mice of either sex, or

of p,p'-DDE in Osborne-Mendel rats, although p,p'-DDE was hepatotoxic in Osborne-Mendel rats. The findings suggest a possible carcinogenic effect of TDE in male Osborne-Mendel rats, based on the induction of combined follicular-cell carcinomas and follicular-cell adenomas of the thyroid. Because of the variation of these tumors in control male rats in this study, the evidence does not permit a more conclusive interpretation of these lesions. p,p'-DDE was carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH DDT

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

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	46	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROMA		3 (6%)	3 (6%)
FIBROSARCOMA		1 (2%)	
LIPOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA	1 (5%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(24)	(23)
ADENOCARCINOMA, NOS, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND		(1)	(1)
SQUAMOUS CELL CARCINOMA			1 (100%)
#LIVER	(19)	(44)	(41)
FIBROSARCOMA, METASTATIC			1 (2%)
LIPOMA		1 (2%)	

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

TABLE A1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
URINARY SYSTEM			
#KIDNEY	(19)	(28)	(26)
LIPOSARCOMA		1 (4%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(22)	(21)
CHROMOPHOBE ADENOMA	3 (16%)	4 (18%)	3 (14%)
#ADRENAL	(19)	(23)	(21)
PHEOCHROMOCYTOMA		1 (4%)	
#THYROID	(19)	(45)	(49)
FOLLICULAR-CELL ADENOMA	8 (42%)	14 (31%)	17 (35%)
FOLLICULAR-CELL CARCINOMA	1 (5%)	6 (13%)	5 (10%)
C-CELL ADENOMA	1 (5%)	4 (9%)	2 (4%)
C-CELL CARCINOMA		1 (2%)	1 (2%)
#PANCREATIC ISLETS	(18)	(21)	(22)
ISLET-CELL ADENOMA		1 (5%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)		
FIBROADENOMA		1 (2%)	
*EPIDIDYMIS	(20)	(50)	(50)
LIPOMA			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(19)	(21)	(21)
GLIOMA, NOS		2 (10%)	
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF BACK	(20)	(50)	(50)
FIBROSARCOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
LIPOMA			1 (2%)
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS			2 (4%)
ALL OTHER SYSTEMS			
THORACIC CAVITY			
FIBROSARCOMA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	11	24	22
MORIBUND SACRIFICE		3	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	23	28
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	29	32
TOTAL PRIMARY TUMORS	15	42	41
TOTAL ANIMALS WITH BENIGN TUMORS	9	24	24
TOTAL BENIGN TUMORS	12	31	28
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	10	10
TOTAL MALIGNANT TUMORS	3	11	11
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2
TOTAL UNCERTAIN TUMORS			2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	46	44
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA		6 (12%)	
FIBROSARCOMA		1 (2%)	1 (2%)
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(37)	(29)
CARCINOMA, NOS, METASTATIC			1 (3%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(37)	(23)
CARCINOMA, NOS, METASTATIC			1 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(42)	(38)
CARCINOMA, NOS, METASTATIC			1 (3%)
*BILE DUCT	(20)	(50)	(50)
BILE DUCT CARCINOMA		1 (2%)	
#PANCREAS	(19)	(38)	(24)
CARCINOMA, NOS			1 (4%)

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

TABLE A2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
FIBROSARCOMA, METASTATIC		1 (3%)	
#STOMACH	(19)	(38)	(29)
CARCINOMA, NOS, METASTATIC			1 (3%)
URINARY SYSTEM			
#KIDNEY	(19)	(38)	(25)
LIPOMA		2 (5%)	
LIPOSARCOMA			1 (4%)
*URETER	(20)	(50)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(39)	(27)
CHROMOPHOBE ADENOMA	13 (68%)	16 (41%)	13 (48%)
#ADRENAL	(19)	(38)	(24)
CORTICAL ADENOMA		1 (3%)	
PHEOCHROMOCYTOMA			3 (13%)
#THYROID	(19)	(45)	(43)
FOLLICULAR-CELL ADENOMA	1 (5%)	10 (22%)	5 (12%)
FOLLICULAR-CELL CARCINOMA		4 (9%)	6 (14%)
C-CELL ADENOMA	3 (16%)	2 (4%)	
C-CELL CARCINOMA	1 (5%)	1 (2%)	
#PANCREATIC ISLETS	(19)	(38)	(24)
ISLET-CELL ADENOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
FIBROADENOMA	8 (40%)	11 (22%)	6 (12%)
*VAGINA	(20)	(50)	(50)
FIBROSARCOMA		1 (2%)	1 (2%)
#UTERUS	(19)	(43)	(31)
ENDOMETRIAL STROMAL POLYP		2 (5%)	4 (13%)

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

TABLE A2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
#OVARY	(19)	(37)	(24)
CYSTADENOMA, NOS	1 (5%)		1 (4%)
GRANULOSA-CELL TUMOR		2 (5%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*RIB	(20)	(50)	(50)
CHONDROMA		1 (2%)	
BODY CAVITIES			
*ABDOMINAL VISCERA	(20)	(50)	(50)
FIBROSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
OMENTUM			
CARCINOMA, NOS, METASTATIC			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	4	9	12
MORIBUND SACRIFICE	1	2	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	15	39	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	16	38	27
TOTAL PRIMARY TUMORS	28	63	45
TOTAL ANIMALS WITH BENIGN TUMORS	16	35	22
TOTAL BENIGN TUMORS	27	52	33
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	8	9
TOTAL MALIGNANT TUMORS	1	9	12
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	6
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	
TOTAL UNCERTAIN TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH DDT

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

	CONTROL (VEH) 02-M042	LOW DOSE 02-M043	HIGH DOSE 02-M044
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	19	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(49)	(50)
FIBROMA	1 (5%)	1 (2%)	1 (2%)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#KIDNEY	(19)	(49)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(48)
HEPATOCELLULAR CARCINOMA	2 (11%)	1 (2%)	1 (2%)
URINARY SYSTEM			
NONE			

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

TABLE B1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-M042	LOW DOSE 02-M043	HIGH DOSE 02-M044
ENDOCRINE SYSTEM			
#THYROID	(17)	(41)	(45)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
#BRAIN	(19)	(49)	(48)
EPENDYMOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	14	45	42
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		2	
TERMINAL SACRIFICE	6	3	8
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-M042	LOW DOSE 02-M043	HIGH DOSE 02-M044
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	6	4
TOTAL PRIMARY TUMORS	4	6	5
TOTAL ANIMALS WITH BENIGN TUMORS	2	2	2
TOTAL BENIGN TUMORS	2	2	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	4	3
TOTAL MALIGNANT TUMORS	2	4	3
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DDT

	CONTROL(VEH) 02-F042	LOW DOSE 02-F045	HIGH DOSE 02-F046
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	22	27
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(21)	(27)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (5%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(46)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	5 (11%)
#SPLEEN	(20)	(22)	(26)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (4%)
#MESENTERIC L. NODE	(20)	(20)	(24)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (5%)	1 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*LIVER	(20)	(22)	(27)
HEPATOCELLULAR CARCINOMA		1 (5%)	3 (11%)
HEMANGIOSARCOMA		1 (5%)	
URINARY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-F042	LOW DOSE 02-F045	HIGH DOSE 02-F046
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(15)	(25)
CHROMOPHOBE ADENOMA	1 (5%)	1 (7%)	
#THYROID	(20)	(22)	(27)
FOLLICULAR-CELL ADENOMA			1 (4%)
FOLLICULAR-CELL CARCINOMA		1 (5%)	
C-CELL ADENOMA			1 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(46)
ADENOCARCINOMA, NOS	1 (5%)		
#OVARY	(20)	(21)	(27)
CYSTADENOMA, NOS	1 (5%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-F042	LOW DOSE 02-F045	HIGH DOSE 02-F046
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@		5	13
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	20	45	36
ANIMAL MISSING			1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	8	10
TOTAL PRIMARY TUMORS	3	8	12
TOTAL ANIMALS WITH BENIGN TUMORS	2	2	2
TOTAL BENIGN TUMORS	2	2	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	6	9
TOTAL MALIGNANT TUMORS	1	6	10
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH DDT

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

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	19	46	49
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, NOS	1 (5%)		3 (6%)
*SUBCUT TISSUE	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (5%)		2 (4%)
ULCER, NOS			1 (2%)
ABSCESS, NOS	1 (5%)		2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(24)	(23)
PNEUMONIA, CHRONIC MURINE	2 (11%)	5 (21%)	4 (17%)
CALCIUM DEPOSIT	1 (5%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(22)	(22)
HEMORRHAGE		1 (5%)	
ABSCESS, NOS		1 (5%)	
ANGIECTASIS		1 (5%)	
HEMATOPOIESIS	1 (5%)	1 (5%)	4 (18%)
#MESENTERIC L. NODE	(16)	(21)	(19)
CONGESTION, NOS		1 (5%)	
HEMORRHAGE		2 (10%)	
CIRCULATORY SYSTEM			
#HEART	(19)	(24)	(22)
MINERALIZATION		1 (4%)	

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

TABLE C1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
ARTERIOSCLEROSIS, NOS	1 (5%)		
CALCIUM DEPOSIT	2 (11%)	1 (4%)	1 (5%)
CALCIFICATION, NOS		1 (4%)	
#MYOCARDIUM	(19)	(24)	(22)
INFLAMMATION, NOS	7 (37%)		
DEGENERATION, NOS	2 (11%)	4 (17%)	5 (23%)
#ENDOCARDIUM	(19)	(24)	(22)
HYPERPLASIA, NOS	2 (11%)	1 (4%)	1 (5%)
*AORTA	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS	3 (15%)	9 (18%)	2 (4%)
CALCIUM DEPOSIT		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND		(1)	(1)
INFLAMMATION, NOS		1 (100%)	
FIBROSIS		1 (100%)	
#LIVER	(19)	(44)	(41)
CYST, NOS		1 (2%)	1 (2%)
INFLAMMATION, NOS	2 (11%)	11 (25%)	7 (17%)
METAMORPHOSIS FATTY	1 (5%)	20 (45%)	16 (39%)
HYPERPLASIA, NOS		1 (2%)	
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS		3 (6%)	1 (2%)
#PANCREAS	(18)	(21)	(22)
THROMBOSIS, NOS	1 (6%)		
PERIARTERITIS	3 (17%)	1 (5%)	2 (9%)
ARTERIOSCLEROSIS, NOS	1 (6%)		
CALCIUM DEPOSIT		1 (5%)	
#STOMACH	(19)	(25)	(26)
INFLAMMATION, NOS		1 (4%)	
ULCER, FOCAL		2 (8%)	2 (8%)
CALCIUM DEPOSIT	5 (26%)	3 (12%)	3 (12%)
#DUODENUM	(19)	(22)	(22)
INFLAMMATION, NOS		1 (5%)	
#COLON	(19)	(20)	(20)
PARASITISM		2 (10%)	

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

TABLE C1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
URINARY SYSTEM			
#KIDNEY	(19)	(28)	(26)
CYST, NOS			1 (4%)
PYELONEPHRITIS, NOS		1 (4%)	1 (4%)
INFLAMMATION, CHRONIC	17 (89%)	17 (61%)	18 (69%)
CALCIUM DEPOSIT	4 (21%)	4 (14%)	1 (4%)
#URINARY BLADDER	(19)	(22)	(21)
INFLAMMATION, NOS		1 (5%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(22)	(21)
CYST, NOS		2 (9%)	
HYPERPLASIA, NOS	1 (5%)		
#ADRENAL	(19)	(23)	(21)
ANGIECTASIS		3 (13%)	
#THYROID	(19)	(45)	(49)
FOLLICULAR CYST, NOS	1 (5%)	4 (9%)	5 (10%)
HYPERPLASIA, C-CELL	3 (16%)	3 (7%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		4 (9%)	7 (14%)
#PARATHYROID	(19)	(40)	(49)
HYPERPLASIA, NOS	5 (26%)	8 (20%)	5 (10%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
GALACTOCELE			1 (2%)
*SEMINAL VESICLE	(20)	(50)	(50)
DILATATION, NOS		1 (2%)	
INFLAMMATION, NOS	1 (5%)		1 (2%)
ABSCESS, NOS			1 (2%)
#TESTIS	(19)	(20)	(23)
CALCIUM DEPOSIT	2 (11%)	1 (5%)	
ATROPHY, NOS	6 (32%)	8 (40%)	9 (39%)
*EPIDIDYMIS	(20)	(50)	(50)
ATROPHY, NOS	3 (15%)	5 (10%)	7 (14%)

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

TABLE C1 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-M018	LOW DOSE 01-M019	HIGH DOSE 01-M020
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
PANNUS	2 (10%)		
SYNECHIA, ANTERIOR	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
*PERICARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)		
*MESENTERY	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS	2 (10%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	5
NECROPSY PERF/NO HISTO PERFORMED		3	1
AUTO/NECROPSY/NO HISTO	1	1	

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	46	44
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
INFLAMMATION, NOS			2 (4%)
HYPERKERATOSIS			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(19)	(37)	(29)
PNEUMONIA, CHRONIC MURINE	3 (16%)	4 (11%)	4 (14%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(37)	(23)
INFLAMMATION, NOS		1 (3%)	
HEMATOPOIESIS	2 (11%)		1 (4%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(37)	(23)
INFLAMMATION, NOS		1 (3%)	
DEGENERATION, NOS	3 (16%)	5 (14%)	2 (9%)
#ENDOCARDIUM	(19)	(37)	(23)
HYPERPLASIA, NOS			1 (4%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(42)	(38)
CYST, NOS		2 (5%)	7 (18%)

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

TABLE C2 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
INFLAMMATION, NOS	1 (5%)	4 (10%)	2 (5%)
METAMORPHOSIS FATTY			4 (11%)
HYPERPLASIA, NOS		2 (5%)	
*BILE DUCT	(20)	(50)	(50)
DILATATION, NOS	1 (5%)	1 (2%)	
HYPERPLASIA, NOS			1 (2%)
#PANCREAS	(19)	(38)	(24)
PERIARTERITIS			1 (4%)
#STOMACH	(19)	(38)	(29)
ULCER, FOCAL		2 (5%)	4 (14%)
#COLON	(19)	(37)	(23)
PARASITISM	1 (5%)	1 (3%)	1 (4%)
URINARY SYSTEM			
#KIDNEY	(19)	(38)	(25)
INFLAMMATION, CHRONIC	5 (26%)	6 (16%)	6 (24%)
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(38)	(24)
INFLAMMATION, NOS			1 (4%)
ANGIECTASIS	1 (5%)		
#THYROID	(19)	(45)	(43)
FOLLICULAR CYST, NOS		2 (4%)	4 (9%)
HYPERPLASIA, C-CELL	2 (11%)	8 (18%)	3 (7%)
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)	3 (7%)	
#PARATHYROID	(19)	(45)	(43)
HYPERPLASIA, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
GALACTOCELE	1 (5%)	1 (2%)	1 (2%)
*VAGINA	(20)	(50)	(50)
POLYP			1 (2%)

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

TABLE C2 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDT

	CONTROL (VEH) 01-F018	LOW DOSE 01-F021	HIGH DOSE 01-F022
#UTERUS	(19)	(43)	(31)
HYDROMETRA	3 (16%)	4 (9%)	3 (10%)
INFLAMMATION, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(19)	(43)	(31)
HYPERPLASIA, CYSTIC		5 (12%)	5 (16%)
#OVARY	(19)	(37)	(24)
CYST, NOS	2 (11%)		
FOLLICULAR CYST, NOS	1 (5%)		
INFLAMMATION, NOS		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		3	8
NECROPSY PERF/NO HISTO PERFORMED	1	4	4
AUTO/NECROPSY/NO HISTO			2

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH DDT

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

	CONTROL (VEH) 02-M042	LOW DOSE 02-M043	HIGH DOSE 02-M044
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	19	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
CALCIUM DEPOSIT		1 (2%)	
*SUBCUT TISSUE	(19)	(49)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
ULCER, NOS			1 (2%)
ABSCESS, NOS	1 (5%)		1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(47)	(48)
AMYLOIDOSIS	11 (61%)	42 (89%)	38 (79%)
#CERVICAL LYMPH NODE	(16)	(43)	(45)
EDEMA, NOS	1 (6%)		
INFLAMMATION, NOS	1 (6%)		
#MESENTERIC L. NODE	(16)	(43)	(45)
INFLAMMATION, NOS	6 (38%)		4 (9%)
#INGUINAL LYMPH NODE	(16)	(43)	(45)
EDEMA, NOS	1 (6%)		
INFLAMMATION, NOS	1 (6%)		
CIRCULATORY SYSTEM			
#HEART	(19)	(49)	(48)
AMYLOIDOSIS			1 (2%)

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

TABLE D1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-M042	LOW DOSE 02-M043	HIGH DOSE 02-M044
CALCIUM DEPOSIT		3 (6%)	
#MYOCARDIUM	(19)	(49)	(48)
INFLAMMATICN, NOS			1 (2%)
#ENDOCARDIUM	(19)	(49)	(48)
INFLAMMATICN, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(48)
INFLAMMATICN, NOS		1 (2%)	
AMYLOIDOSIS	3 (16%)	20 (41%)	25 (52%)
HYPERPLASIA, NODULAR	2 (11%)		
#STOMACH	(19)	(49)	(50)
CALCIUM DEPOSIT	2 (11%)	3 (6%)	1 (2%)
#COLON	(19)	(49)	(47)
INFLAMMATICN, NOS	1 (5%)		
PARASITISM			1 (2%)
*RECTUM	(19)	(49)	(50)
PROLAPSE	1 (5%)		
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(48)
HYDRONEPHROSIS	2 (11%)		
CYST, NOS		1 (2%)	
PYELONEPHRITIS, NOS		2 (4%)	3 (6%)
INFLAMMATICN, CHRONIC	11 (58%)	28 (57%)	35 (73%)
AMYLOIDOSIS	11 (58%)	37 (76%)	37 (77%)
#URINARY BLADDER	(19)	(47)	(48)
INFLAMMATICN, NOS		1 (2%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#PROSTATE	(18)	(46)	(47)
INFLAMMATICN, NOS	2 (11%)		

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

TABLE D1 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-M042	LOW DOSE 02-M043	HIGH DOSE 02-M044
#TESTIS	(19)	(49)	(47)
ATROPHY, NOS		1 (2%)	
*EPIDIDYMIS	(19)	(49)	(50)
GRANULOMA, SPERMATIC			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	3	3
AUTO/NECROPSY/HISTO PERF	1	1	4
AUTOLYSIS/NO NECROPSY	1	1	

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-F042	LOW DOSE 02-F045	HIGH DOSE 02-F046
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	49	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	22	27
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(22)	(26)
HYPERPLASIA, RETICULUM CELL			1 (4%)
HEMATOPOIESIS			1 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(22)	(27)
HYPERPLASIA, NODULAR		1 (5%)	1 (4%)
ANGIECTASIS		2 (9%)	
#PANCREAS	(19)	(22)	(26)
ATROPHY, NOS	1 (5%)		
#PANCREATIC DUCT	(19)	(22)	(26)
CYST, NOS	1 (5%)		
#STOMACH	(20)	(22)	(26)
ULCER, FOCAL		1 (5%)	

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

TABLE D2 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-F042	LOW DOSE 02-F045	HIGH DOSE 02-F046
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(20)	(22)	(27)
HYPERPLASIA, FOLLICULAR-CELL			1 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(46)
GALACTOCELE	1 (5%)		
#UTERUS	(20)	(22)	(27)
HYDROMETRA	4 (20%)	2 (9%)	1 (4%)
INFLAMMATION, NOS	6 (30%)	2 (9%)	3 (11%)
#UTERUS/ENDOMETRIUM	(20)	(22)	(27)
HYPERPLASIA, CYSTIC	3 (15%)	5 (23%)	6 (22%)
#OVARY/OVIDUCT	(20)	(22)	(27)
INFLAMMATION, NOS			1 (4%)
#OVARY	(20)	(21)	(27)
CYST, NOS	3 (15%)	3 (14%)	3 (11%)
INFLAMMATION, NOS	2 (10%)	2 (10%)	2 (7%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE D2 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DDT

	CONTROL (VEH) 02-F042	LOW DOSE 02-F045	HIGH DOSE 02-F046
BODY CAVITIES			
*PERITONEUM	(20)	(49)	(46)
INFLAMMATION, NOS	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	6	6
ANIMAL MISSING/NO NECROPSY			1
NECROPSY PERF/NO HISTO PERFORMED		27	19
AUTO/NECROPSY/HISTO PERF		1	1
AUTOLYSIS/NO NECROPSY		1	3

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

APPENDIX E

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH TDE

TABLE E1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH TDE

	CONTROL (VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA	4 (20%)	2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(19)	(20)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
*SPLEEN	(20)	(20)	(20)
HEMANGIOSARCOMA		4 (20%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(27)	(38)
HEPATOCELLULAR ADENOMA	1 (5%)		
HEPATOCELLULAR CARCINOMA		1 (4%)	2 (5%)
URINARY SYSTEM			
#KIDNEY	(20)	(20)	(20)
MIXED TUMOR, MALIGNANT			1 (5%)

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

TABLE E1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
HAMARTOMA		2 (10%)	
#URINARY BLADDER	(19)	(20)	(23)
PAPILLOMA, NOS			1 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(26)	(25)
CHROMOPHOBE ADENOMA	1 (5%)	7 (27%)	5 (20%)
GLIOMA, NOS			1 (4%)
#ADRENAL	(20)	(19)	(20)
PHEOCHROMOCYTOMA	1 (5%)		1 (5%)
#THYROID	(19)	(49)	(49)
ADENOMA, NOS			1 (2%)
FOLLICULAR-CELL ADENOMA		11 (22%)	9 (18%)
FOLLICULAR-CELL CARCINOMA	1 (5%)	6 (12%)	3 (6%)
C-CELL ADENOMA	1 (5%)	4 (8%)	1 (2%)
C-CELL CARCINOMA		4 (8%)	2 (4%)
#PANCREATIC ISLETS	(20)	(19)	(22)
ISLET-CELL ADENOMA			1 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(19)	(20)
GLIOMA, NOS		1 (5%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE E1 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH TDE

	CONTROL (VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
BODY CAVITIES			
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	12	23	19
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	8	27	31
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	33	25
TOTAL PRIMARY TUMORS	10	45	30
TOTAL ANIMALS WITH BENIGN TUMORS	7	22	19
TOTAL BENIGN TUMORS	9	27	20
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	14	9
TOTAL MALIGNANT TUMORS	1	18	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE E2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH TDE

	CONTROL (VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	19	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	48	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(49)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
SARCOMA, NOS		1 (2%)	
FIBROMA	2 (11%)		
FIBROSARCOMA	2 (11%)		
LIPOMA			3 (6%)
LIPOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		1 (2%)
*SUBCUT TISSUE/AXILLA	(19)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)		
#PANCREAS	(19)	(25)	(30)
MALIGNANT LYMPHOMA, NOS		1 (4%)	
#KIDNEY	(19)	(25)	(29)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE E2 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
DIGESTIVE SYSTEM			
#LIVER	(19)	(32)	(40)
HEPATOCELLULAR CARCINOMA	1 (5%)		3 (8%)
#PANCREAS	(19)	(25)	(30)
SQUAMOUS CELL CARCINOMA, METASTA		1 (4%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(30)	(33)
CHROMOPHOBE ADENOMA	4 (21%)	14 (47%)	12 (36%)
#ADRENAL	(19)	(27)	(29)
CORTICAL ADENOMA			1 (3%)
CORTICAL CARCINOMA			1 (3%)
PHEOCHROMOCYTOMA		1 (4%)	
#THYROID	(19)	(48)	(50)
FOLLICULAR-CELL ADENOMA		6 (13%)	5 (10%)
FOLLICULAR-CELL CARCINOMA	2 (11%)	5 (10%)	1 (2%)
C-CELL ADENOMA	1 (5%)	2 (4%)	1 (2%)
C-CELL CARCINOMA	1 (5%)	2 (4%)	4 (8%)
#PARATHYROID	(1)	(1)	(1)
ADENOMA, NOS	1 (100%)		
#PANCREATIC ISLETS	(19)	(25)	(30)
ISLET-CELL ADENOMA	2 (11%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(49)	(49)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
FIBROADENOMA	7 (37%)	13 (27%)	10 (20%)
#UTERUS	(19)	(30)	(36)
SQUAMOUS CELL CARCINOMA		1 (3%)	1 (3%)

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

TABLE E2 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
LEIOMYOSARCOMA	1 (5%)		
ENDOMETRIAL STROMAL POLYP	1 (5%)	6 (20%)	8 (22%)
#OVARY	(19)	(26)	(30)
GRANULOSA-CELL TUMOR			1 (3%)
NERVOUS SYSTEM			
#BRAIN	(19)	(26)	(28)
ASTROCYTOMA		1 (4%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL VISCERA	(19)	(49)	(49)
FIBROSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	8	12	16
MORIBUND SACRIFICE	1		1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	38	33
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE E2 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	35	36
TOTAL PRIMARY TUMORS	28	54	57
TOTAL ANIMALS WITH BENIGN TUMORS	13	30	30
TOTAL BENIGN TUMORS	18	42	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	10	12	15
TOTAL MALIGNANT TUMORS	10	12	16
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-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 F

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH TDE

TABLE F1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-M029	LOW DOSE 02-M030	HIGH DOSE 02-M031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	1	
ANIMALS NECROPSIED	18	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(18)	(49)	(50)
SEBACEOUS ADENOMA			1 (2%)
FIBROMA			1 (2%)
FIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(18)	(49)	(50)
SEBACEOUS ADENOMA			1 (2%)
FIBROMA	3 (17%)	2 (4%)	
FIBROSARCOMA	1 (6%)	2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(18)	(29)	(35)
HEPATOCELLULAR CARCINOMA, METAST		1 (3%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (6%)	4 (14%)	1 (3%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (3%)	1 (3%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(18)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
#KIDNEY	(18)	(35)	(40)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(18)	(44)	(50)
HEPATOCELLULAR CARCINOMA	2 (11%)	12 (27%)	14 (28%)

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

TABLE F1. (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH TDE

	CONTROL(VEH) 02-M029	LOW DOSE 02-M030	HIGH DOSE 02-M031
URINARY SYSTEM			
#URINARY BLADDER	(18)	(24)	(22)
PAPILLOMA, NOS	1 (6%)	1 (4%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*EPIDIDYMIS	(18)	(49)	(50)
LIPOMA	1 (6%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(18)	(49)	(50)
FIBROSARCOMA		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE F1 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-M029	LOW DOSE 02-M030	HIGH DOSE 02-M031
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	19	22
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	13	30	27
ANIMAL MISSING	1	1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	8	19	19
TOTAL PRIMARY TUMORS	9	25	22
TOTAL ANIMALS WITH BENIGN TUMORS	6	7	4
TOTAL BENIGN TUMORS	6	7	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	17	17
TOTAL MALIGNANT TUMORS	3	18	18
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE F2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-F029	LOW DOSE 02-F030	HIGH DOSE 02-F031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(27)	(15)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (11%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (4%)	1 (7%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (5%)	2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#LUNG	(20)	(27)	(15)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (4%)	
#LIVER	(20)	(48)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(47)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA		2 (4%)	3 (6%)
URINARY SYSTEM			
NONE			

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

TABLE F2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-F029	LOW DOSE 02-F030	HIGH DOSE 02-F031
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(47)
ADENOCARCINOMA, NOS	1 (5%)		
#UTERUS	(19)	(31)	(23)
ENDOMETRIAL STROMAL POLYP		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE F2 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH TDE

	CONTROL(VEH) 02-F029	LOW DOSE 02-F030	HIGH DOSE 02-F031
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	8	3
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	18	41	44
ANIMAL MISSING		1	3
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	13	6
TOTAL PRIMARY TUMORS	2	14	6
TOTAL ANIMALS WITH BENIGN TUMORS		4	1
TOTAL BENIGN TUMORS		4	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	10	5
TOTAL MALIGNANT TUMORS	2	10	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS

\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX G

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH TDE

TABLE G1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH TDE

	CONTROL (VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	47
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
INFLAMMATION, NOS	1 (5%)	2 (4%)	
GRANULOMA, NOS			1 (2%)
CALCIUM DEPOSIT			1 (2%)
HYPERKERATOSIS			2 (4%)
ACANTHOSIS			2 (4%)
VERRUCA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
#TRACHEA	(20)	(19)	(20)
INFLAMMATION, NOS			1 (5%)
#LUNG	(20)	(19)	(20)
PNEUMONIA, CHRONIC MURINE	5 (25%)	6 (32%)	7 (35%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(20)	(20)
ATROPHY, NOS			1 (5%)
HEMATOPOIESIS	1 (5%)		
CIRCULATORY SYSTEM			
#HEART	(20)	(24)	(22)
CALCIUM DEPOSIT	1 (5%)	2 (8%)	

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

TABLE G1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
#MYOCARDIUM	(20)	(24)	(22)
DEGENERATION, NOS	9 (45%)	3 (13%)	6 (27%)
#ENDOCARDIUM	(20)	(24)	(22)
INFLAMMATION, NOS			1 (5%)
HYPERPLASIA, NOS		1 (4%)	
*AORTA	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ARTERIOSCLEROSIS, NOS	4 (20%)	6 (12%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(27)	(38)
CYST, NOS			2 (5%)
INFLAMMATION, NOS	2 (10%)		
METAMORPHOSIS FATTY	1 (5%)	5 (19%)	4 (11%)
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	1 (2%)
#PANCREAS	(20)	(19)	(22)
PERIARTERITIS	2 (10%)		3 (14%)
#STOMACH	(20)	(27)	(24)
INFLAMMATION, NOS		2 (7%)	
ULCER, FOCAL	1 (5%)	2 (7%)	
CALCIUM DEPOSIT	3 (15%)	5 (19%)	1 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(20)	(20)
CYST, NOS	1 (5%)		
PYELONEPHRITIS, NOS			1 (5%)
INFLAMMATION, CHRONIC	12 (60%)	11 (55%)	12 (60%)
CALCIUM DEPOSIT	2 (10%)		
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(26)	(25)
CYST, NOS		1 (4%)	
#ADRENAL	(20)	(19)	(20)
ANGIECTASIS			1 (5%)

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

TABLE G1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
#THYROID	(19)	(49)	(49)
FOLLICULAR CYST, NOS		2 (4%)	4 (8%)
HYPERPLASIA, C-CELL	1 (5%)	2 (4%)	2 (4%)
HYPERPLASIA, FOLLICULAR-CELL	2 (11%)	5 (10%)	6 (12%)
#PARATHYROID	(7)	(7)	(2)
HYPERPLASIA, NOS	4 (57%)	7 (100%)	1 (50%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(19)	(17)	(20)
HEMORRHAGE			1 (5%)
INFLAMMATION, NOS	1 (5%)		1 (5%)
*SEMINAL VESICLE	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
#TESTIS	(19)	(19)	(23)
INFLAMMATION, NOS			1 (4%)
CALCIUM DEPOSIT	2 (11%)		
ATROPHY, NOS	4 (21%)	7 (37%)	2 (9%)
*EPIDIDYMIS	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		1 (2%)
CALCIUM DEPOSIT	1 (5%)		
ATROPHY, NOS	1 (5%)	1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(19)	(20)
HEMORRHAGE			1 (5%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
PANNUS	1 (5%)		
SYNECHIA, ANTERIOR	1 (5%)		
CATARACT	1 (5%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE G1 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-M033	LOW DOSE 01-M034	HIGH DOSE 01-M035
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
*MESENTERY	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS	4 (20%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		4	6
NECROPSY PERF/NO HISTO PERFORMED			1
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO			2

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

TABLE G2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH TDE

	CONTROL (VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	19	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	48	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(26)	(28)
PNEUMONIA, CHRONIC MURINE	1 (5%)	1 (4%)	4 (14%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(25)	(28)
METAMORPHOSIS FATTY	1 (5%)		
#SPLEEN	(19)	(27)	(30)
HEMORRHAGE			1 (3%)
HEMATOPOIESIS	3 (16%)	1 (4%)	4 (13%)
#CERVICAL LYMPH NODE	(17)	(26)	(27)
INFLAMMATION, NOS		1 (4%)	
#MESENTERIC L. NODE	(17)	(26)	(27)
HEMORRHAGE	1 (6%)		
CIRCULATORY SYSTEM			
#HEART	(19)	(25)	(29)
THROMBOSIS, NOS		1 (4%)	1 (3%)
#MYOCARDIUM	(19)	(25)	(29)
INFLAMMATION, NOS		1 (4%)	
DEGENERATION, NOS		1 (4%)	
#ENDOCARDIUM	(19)	(25)	(29)
HYPERPLASIA, NOS			1 (3%)

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

TABLE G2 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
DIGESTIVE SYSTEM			
#LIVER	(19)	(32)	(40)
CYST, NOS		2 (6%)	1 (3%)
MULTILOCULAR CYST	1 (5%)		2 (5%)
INFLAMMATION, NOS		2 (6%)	
METAMORPHOSIS FATTY		1 (3%)	
#LIVER/CENTRILOBULAR	(19)	(32)	(40)
DEGENERATION, NOS			1 (3%)
*BILE DUCT	(19)	(49)	(49)
DILATATION, NOS			1 (2%)
HYPERPLASIA, NOS		1 (2%)	2 (4%)
#PANCREAS	(19)	(25)	(30)
INFLAMMATION, NOS			1 (3%)
PERIARTERITIS	1 (5%)		
#STOMACH	(19)	(30)	(33)
ULCER, FOCAL	2 (11%)	3 (10%)	2 (6%)
#LARGE INTESTINE	(19)	(25)	(27)
INFLAMMATION, NOS			1 (4%)
#COLON	(19)	(25)	(27)
PARASITISM		3 (12%)	
URINARY SYSTEM			
#KIDNEY	(19)	(25)	(29)
HYDRONEPHROSIS		1 (4%)	
CYST, NOS	1 (5%)		
INFLAMMATION, CHRONIC	4 (21%)	10 (40%)	13 (45%)
CALCIUM DEPOSIT	1 (5%)	1 (4%)	
ENDOCRINE SYSTEM			
#ADRENAL	(19)	(27)	(29)
ANGIECTASIS	2 (11%)	3 (11%)	
#THYROID	(19)	(48)	(50)
FOLLICULAR CYST, NOS			1 (2%)

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

TABLE G2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
HYPERPLASIA, C-CELL	2 (11%)	4 (8%)	5 (10%)
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)	2 (4%)	3 (6%)
#PARATHYROID	(1)	(1)	(1)
HYPERPLASIA, NOS			1 (100%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(49)	(49)
GALACTOCELE		1 (2%)	
*VAGINA	(19)	(49)	(49)
INFLAMMATION, NOS		2 (4%)	2 (4%)
POLYP			2 (4%)
#UTERUS	(19)	(30)	(36)
HYDROMETRA	5 (26%)	1 (3%)	5 (14%)
CYST, NOS			1 (3%)
INFLAMMATION, NOS	1 (5%)	2 (7%)	1 (3%)
#UTERUS/ENDOMETRIUM	(19)	(30)	(36)
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, CYSTIC		3 (10%)	4 (11%)
#OVARY	(19)	(26)	(30)
CYST, NOS			1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			

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

TABLE G2 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH TDE

	CONTROL(VEH) 01-F033	LOW DOSE 01-F036	HIGH DOSE 01-F037
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		7	4
AUTO/NECROPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY	1	1	1

APPENDIX H

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH TDE

TABLE H1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-M029	LOW DOSE 02-M030	HIGH DOSE 02-M031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1	1	
ANIMALS NECROPSIED	18	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(18)	(49)	(50)
INFLAMMATION, NOS	2 (11%)	7 (14%)	3 (6%)
CALCIFICATION, NOS		1 (2%)	
HYPERKERATOSIS	1 (6%)		
ACANTHOSIS	1 (6%)		
RESPIRATORY SYSTEM			
*ACCESSORY SINUS	(18)	(49)	(50)
INFLAMMATION, NOS	1 (6%)		
#LUNG	(18)	(29)	(35)
PNEUMONIA, CHRONIC MURINE		1 (3%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(27)	(26)
AMYLOIDOSIS		1 (4%)	3 (12%)
HEMATOPOIESIS		3 (11%)	2 (8%)
#MESENTERIC L. NODE	(17)	(25)	(23)
INFLAMMATION, NOS			2 (9%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(18)	(24)	(22)
DEGENERATION, NOS	1 (6%)		
DIGESTIVE SYSTEM			
#LIVER	(18)	(44)	(50)
DEGENERATION, NOS	1 (6%)		

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

TABLE H1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH TDE

	CONTROL(VEH) 02-M029	LOW DOSE 02-M030	HIGH DOSE 02-M031
INFARCT, NOS		1 (2%)	
AMYLOIDOSIS		1 (2%)	1 (2%)
CALCIUM DEPOSIT	1 (6%)		
HYPERPLASIA, NODULAR	1 (6%)	2 (5%)	1 (2%)
*RECTUM	(18)	(49)	(50)
PROLAPSE	1 (6%)	14 (29%)	4 (8%)
URINARY SYSTEM			
#KIDNEY	(18)	(35)	(40)
HYDRONEPHROSIS		2 (6%)	
CYST, NOS	1 (6%)		
POLYCYSTIC KIDNEY		1 (3%)	
PYELONEPHRITIS, NOS			1 (3%)
INFLAMMATION, CHRONIC	2 (11%)	12 (34%)	6 (15%)
AMYLOIDOSIS		6 (17%)	
CALCIUM DEPOSIT			1 (3%)
ENDOCRINE SYSTEM			
#ADRENAL	(17)	(24)	(23)
INFLAMMATION, NOS			1 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(18)	(49)	(50)
GALACTOCELE		1 (2%)	
*PREPUCE	(18)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
*PREPUTIAL GLAND	(18)	(49)	(50)
INFLAMMATION, NOS	1 (6%)		
#TESTIS	(18)	(25)	(25)
ATROPHY, NOS			2 (8%)
*EPIDIDYMIS	(18)	(49)	(50)
GRANULOMA, SPERMATIC	1 (6%)		2 (4%)
NERVOUS SYSTEM			
NONE			

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

TABLE H1 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-M029	LOW DOSE 02-M030	HIGH DOSE 02-M031
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*MUSCLE HIP/THIGH	(18)	(49)	(50)
PARASITISM	1 (6%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	7	19
ANIMAL MISSING/NO NECROPSY	1	1	
AUTO/NECROPSY/HISTO PERF	1	1	
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY	1		

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

TABLE H2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH TDE

	CONTROL (VEH) 02-F029	LOW DOSE 02-F030	HIGH DOSE 02-F031
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(21)	(16)
AMYLOIDOSIS		1 (5%)	
HEMATOPOIESIS			3 (19%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SMALL INTESTINE	(20)	(16)	(13)
INFLAMMATION, NOS			1 (8%)
URINARY SYSTEM			
#KIDNEY	(20)	(22)	(14)
HYDRONEPHROSIS	1 (5%)		
AMYLOIDOSIS		11 (50%)	
ENDOCRINE SYSTEM			
NONE			

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

TABLE H2 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH TDE

	CONTROL(VEH) 02-F029	LOW DOSE 02-F030	HIGH DOSE 02-F031
REPRODUCTIVE SYSTEM			
#UTERUS	(19)	(31)	(23)
HYDROMETRA	11 (58%)	16 (52%)	7 (30%)
#UTERUS/ENDOMETRIUM	(19)	(31)	(23)
INFLAMMATION, NOS	1 (5%)	4 (13%)	4 (17%)
HYPERPLASIA, CYSTIC	1 (5%)	4 (13%)	2 (9%)
#OVARY	(19)	(22)	(16)
CYST, NOS	4 (21%)	5 (23%)	4 (25%)
INFLAMMATION, NOS		3 (14%)	2 (13%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(47)
NECROSIS, FAT	1 (5%)	1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	10	23
ANIMAL MISSING/NO NECROPSY		1	3

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

APPENDIX I

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH DDE

TABLE II
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-N028	LOW DOSE 01-N029	HIGH DOSE 01-N030
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	45
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(47)
FIBROMA		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(47)
PAPILLOMA, NOS		1 (2%)	1 (2%)
FIBROMA		4 (8%)	
FIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(21)	(19)
HEMANGIOSARCOMA	1 (5%)		
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(20)	(24)	(25)
SARCOMA, NOS	1 (5%)		
DIGESTIVE SYSTEM			
*BILE DUCT	(20)	(50)	(47)
CYSTADENOMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(20)	(20)
LIPOMA			2 (12%)

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

TABLE I1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
LIPOSARCOMA		1 (5%)	
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(18)	(19)
CARCINOMA, NOS			1 (5%)
CHROMOPHOBE ADENOMA		4 (22%)	
#THYROID	(20)	(49)	(47)
FOLLICULAR-CELL ADENOMA	2 (10%)	8 (16%)	8 (17%)
FOLLICULAR-CELL CARCINOMA	1 (5%)	5 (10%)	2 (4%)
C-CELL ADENOMA	2 (10%)	1 (2%)	1 (2%)
C-CELL CARCINOMA	1 (5%)	1 (2%)	
#PANCREATIC ISLETS	(20)	(20)	(21)
ISLET-CELL ADENOMA		1 (5%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(47)
ADENOMA, NOS	1 (5%)		
FIBROADENOMA			1 (2%)
#PROSTATE	(16)	(13)	(16)
SARCOMA, NOS			1 (6%)
#TESTIS	(18)	(19)	(18)
INTERSTITIAL-CELL TUMOR			1 (6%)
*EPIDIDYMIS	(20)	(50)	(47)
LIPOMA	1 (5%)		
NERVOUS SYSTEM			
#BRAIN	(19)	(19)	(18)
GLIOMA, NOS		1 (5%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE I1 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(47)
FIBROSARCOMA		1 (2%)	
*MESENTERY	(20)	(50)	(47)
HEMANGIOMA	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	7	32	34
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	18	15
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	21	20
TOTAL PRIMARY TUMORS	11	29	20
TOTAL ANIMALS WITH BENIGN TUMORS	5	15	15
TOTAL BENIGN TUMORS	7	20	15
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	9	5
TOTAL MALIGNANT TUMORS	4	9	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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 I2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	47	46
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)	1 (2%)	
SARCOMA, NOS		1 (2%)	
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMANGIOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (10%)	1 (2%)	
*SUBCUT TISSUE/BACK	(20)	(49)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#SPLEEN	(20)	(30)	(22)
HEMANGIOMA		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(20)	(29)	(22)
FIBROSARCOMA		1 (3%)	
*AORTA	(20)	(49)	(50)
FIBROSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
NONE			

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

TABLE I2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
URINARY SYSTEM			
#KIDNEY	(20)	(30)	(23)
PAPILLOMA, NOS	1 (5%)		
TUBULAR-CELL ADENOMA			1 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(33)	(27)
CHROMOPHOBE ADENOMA	9 (50%)	10 (30%)	14 (52%)
#ADRENAL	(19)	(30)	(24)
CORTICAL ADENOMA		1 (3%)	1 (4%)
#THYROID	(19)	(48)	(48)
FOLLICULAR-CELL ADENOMA	1 (5%)	6 (13%)	8 (17%)
FOLLICULAR-CELL CARCINOMA	1 (5%)	3 (6%)	4 (8%)
C-CELL ADENOMA		5 (10%)	1 (2%)
C-CELL CARCINOMA	1 (5%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
ADENOMA, NOS		2 (4%)	1 (2%)
ADENOCARCINOMA, NOS	1 (5%)	5 (10%)	
FIBROADENOMA	5 (25%)	5 (10%)	7 (14%)
*VAGINA	(20)	(49)	(50)
LEIOMYOSARCOMA	1 (5%)		
#UTERUS	(19)	(33)	(23)
SARCOMA, NOS			1 (4%)
LEIOMYOSARCOMA			1 (4%)
ENDOMETRIAL STROMAL POLYP		3 (9%)	
#OVARY	(19)	(30)	(21)
CYSTADENOMA, NOS		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

TABLE I2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
MUSCULOSKELETAL SYSTEM			
*SKULL	(20)	(49)	(50)
OSTEOMA			1 (2%)
*SKELETAL MUSCLE	(20)	(49)	(50)
FIBROSARCOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(50)
FIBROSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	11	24
MORIBUND SACRIFICE	2	2	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	37	23
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE 12 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	16	36	29
TOTAL PRIMARY TUMORS	23	49	45
TOTAL ANIMALS WITH BENIGN TUMORS	14	27	25
TOTAL BENIGN TUMORS	16	34	34
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	14	10
TOTAL MALIGNANT TUMORS	7	15	11
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX J

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH DDE

TABLE J1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-M047	LOW DOSE 02-M048	HIGH DOSE 02-M049
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	18	41	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	41	47
INTEGUMENTARY SYSTEM			
*SKIN	(18)	(41)	(47)
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(18)	(41)	(47)
FIBROSARCOMA		1 (2%)	4 (9%)
RESPIRATORY SYSTEM			
#LUNG	(18)	(41)	(45)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(18)	(41)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (5%)	1 (2%)
#MESENTERIC L. NODE	(12)	(37)	(39)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (5%)
#LIVER	(19)	(41)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(41)	(47)
HEPATOCELLULAR CARCINOMA		7 (17%)	17 (36%)

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

TABLE J1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-M047	LOW DOSE 02-M048	HIGH DOSE 02-M049
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#TESTIS	(17)	(41)	(44)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE J1 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-M047	LOW DOSE 02-M048	HIGH DOSE 02-M049
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	18	38	34
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	2	11	16
ANIMAL MISSING		1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*		15	22
TOTAL PRIMARY TUMORS		18	28
TOTAL ANIMALS WITH BENIGN TUMORS		4	2
TOTAL BENIGN TUMORS		4	2
TOTAL ANIMALS WITH MALIGNANT TUMORS		13	22
TOTAL MALIGNANT TUMORS		14	26
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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 J2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DDE

	CONTROL(VEH) 02-F047	LOW DOSE 02-F050	HIGH DOSE 02-F051
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	48	47
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(48)	(49)
SEBACEOUS ADENOMA	1 (5%)		
*SUBCUT TISSUE	(19)	(48)	(49)
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(33)	(44)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
#SPLEEN	(19)	(33)	(45)
HEMANGIOMA	1 (5%)		
HEMANGIOSARCOMA		1 (3%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#LYMPH NODE	(19)	(32)	(43)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	
#UTERUS	(18)	(33)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)		
CIRCULATORY SYSTEM			
NONE			

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

TABLE J2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-F047	LOW DOSE 02-F050	HIGH DOSE 02-F051
DIGESTIVE SYSTEM			
#LIVER	(19)	(47)	(48)
HEPATOCELLULAR CARCINOMA		19 (40%)	34 (71%)
HEMANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#THYROID	(19)	(33)	(36)
FOLLICULAR-CELL CARCINOMA			1 (3%)
#PANCREATIC ISLETS	(19)	(33)	(45)
ISLET-CELL ADENOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(48)	(49)
ADENOCARCINOMA, NOS		2 (4%)	
FIBROADENOMA	1 (5%)		
#UTERUS	(18)	(33)	(44)
ADENOCARCINOMA, NOS			1 (2%)
ENDOMETRIAL STROMAL POLYP			1 (2%)
HEMANGIOMA	1 (6%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE J2 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-F047	LOW DOSE 02-F050	HIGH DOSE 02-F051
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	11	27
MORIBUND SACRIFICE		1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	16	38	23
ANIMAL MISSING	1		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	25	35
TOTAL PRIMARY TUMORS	6	29	39
TOTAL ANIMALS WITH BENIGN TUMORS	3	1	1
TOTAL BENIGN TUMORS	4	1	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	24	35
TOTAL MALIGNANT TUMORS	2	28	38
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX K

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH DDE

TABLE K1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	45
INTEGUMENTARY SYSTEM			
#SKIN	(20)	(50)	(47)
SEBACEOUS CYST		1 (2%)	
#SUBCUT TISSUE	(20)	(50)	(47)
HEMATOMA, NOS			1 (2%)
ULCER, NOS		3 (6%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(21)	(23)
CONGESTION, NOS			4 (17%)
EDEMA, NOS	1 (5%)		
HEMORRHAGE		3 (14%)	6 (26%)
PNEUMONIA, CHRONIC MURINE	3 (15%)	7 (33%)	8 (35%)
CALCIUM DEPOSIT	1 (5%)	1 (5%)	
HYPERPLASIA, EPITHELIAL			1 (4%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(19)	(19)	(18)
METAMORPHOSIS FATTY		3 (16%)	
#SPLEEN	(19)	(21)	(19)
CONGESTION, NOS			1 (5%)
PERIARTERITIS	1 (5%)		
HEMATOPOIESIS	1 (5%)	5 (24%)	6 (32%)
HYPOPLASIA, LYMPHOID			1 (5%)
#LYMPH NODE	(19)	(19)	(20)
HYPERPLASIA, NOS		1 (5%)	
#MESENTERIC L. NODE	(19)	(19)	(20)
HYPERPLASIA, NOS			2 (10%)

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

TABLE K1 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
CIRCULATORY SYSTEM			
#HEART	(20)	(24)	(25)
ARTERIOSCLEROSIS, NOS		2 (8%)	1 (4%)
CALCIUM DEPOSIT	1 (5%)		3 (12%)
CALCIFICATION, NOS	1 (5%)	1 (4%)	
#MYOCARDIUM	(20)	(24)	(25)
INFLAMMATION, NOS		1 (4%)	1 (4%)
DEGENERATION, NOS	10 (50%)	18 (75%)	21 (84%)
CALCIUM DEPOSIT	1 (5%)		
#ENDOCARDIUM	(20)	(24)	(25)
HYPERPLASIA, NOS	2 (10%)	1 (4%)	2 (8%)
*AORTA	(20)	(50)	(47)
ARTERIOSCLEROSIS, NOS	3 (15%)	10 (20%)	6 (13%)
CALCIFICATION, NOS			1 (2%)
*PULMONARY ARTERY	(20)	(50)	(47)
HYPERTROPHY, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(40)	(40)
CONGESTION, NOS		3 (8%)	5 (13%)
HEMATOMA, ORGANIZED			1 (3%)
FIBROSIS		1 (3%)	
NECROSIS, NOS		2 (5%)	3 (8%)
METAMORPHOSIS FATTY	2 (10%)	25 (63%)	20 (50%)
ANGIECTASIS		7 (18%)	5 (13%)
#LIVER/CENTRILOBULAR	(20)	(40)	(40)
NECROSIS, COAGULATIVE			1 (3%)
*BILE DUCT	(20)	(50)	(47)
DILATATION, NOS			4 (9%)
CYST, NOS			1 (2%)
INFLAMMATION, NOS			1 (2%)
FIBROSIS		1 (2%)	
HYPERPLASIA, NOS	2 (10%)	14 (28%)	9 (19%)
#PANCREAS	(20)	(20)	(21)
FIBROSIS		2 (10%)	1 (5%)

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

TABLE K1 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
PERIARTERITIS	1 (5%)	4 (20%)	1 (5%)
ARTERIOSCLEROSIS, NOS	2 (10%)		1 (5%)
NECROSIS, FOCAL		1 (5%)	2 (10%)
#STOMACH	(19)	(25)	(21)
ULCER, NOS			2 (10%)
ULCER, FOCAL	1 (5%)	5 (20%)	2 (10%)
CALCIUM DEPOSIT	3 (16%)		2 (10%)
CALCIFICATION, NOS		6 (24%)	1 (5%)
HYPERKERATOSIS		1 (4%)	1 (5%)
#GASTRIC MUCOSA	(19)	(25)	(21)
ULCER, NOS			1 (5%)
#PEYERS PATCH	(19)	(19)	(19)
HYPERPLASIA, NOS			1 (5%)
#COLON	(19)	(18)	(17)
NEMATODIASIS			1 (6%)
PARASITISM		1 (6%)	
URINARY SYSTEM			
#KIDNEY	(20)	(20)	(20)
HYDRONEPHROSIS			1 (5%)
CONGESTION, NOS		1 (5%)	
INFLAMMATION, CHRONIC	15 (75%)	18 (90%)	18 (90%)
FIBROSIS			1 (5%)
CALCIUM DEPOSIT	3 (15%)	1 (5%)	2 (10%)
#KIDNEY/PELVIS	(20)	(20)	(20)
INFLAMMATION, NOS		1 (5%)	1 (5%)
*URETER	(20)	(50)	(47)
CALCIUM DEPOSIT		1 (2%)	
#URINARY BLADDER	(19)	(25)	(21)
CYST, NOS		2 (8%)	
INFLAMMATION, NOS		3 (12%)	
ULCER, FOCAL			1 (5%)
HYPERTROPHY, NOS		3 (12%)	
HYPERPLASIA, EPITHELIAL		1 (4%)	3 (14%)
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(18)	(19)
CYST, NOS		1 (6%)	1 (5%)

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

TABLE K1 (CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
CONGESTION, NOS		1 (6%)	
#ADRENAL	(19)	(19)	(19)
CONGESTION, NOS		1 (5%)	1 (5%)
INFLAMMATION, FOCAL		1 (5%)	
DEGENERATION, NOS			1 (5%)
HYPERTROPHY, NOS		1 (5%)	
HYPERPLASIA, NOS			3 (16%)
ANGIECTASIS		1 (5%)	
#ADRENAL CORTEX	(19)	(19)	(19)
CYTOPLASMIC VACUOLIZATION		1 (5%)	
HYPERTROPHY, NOS		2 (11%)	
HYPERPLASIA, NOS		1 (5%)	
#THYROID	(20)	(49)	(47)
CYST, NOS		1 (2%)	
FOLLICULAR CYST, NOS		3 (6%)	6 (13%)
INFLAMMATION, NOS		1 (2%)	
ATROPHY, NOS			1 (2%)
HYPERPLASIA, C-CELL	4 (20%)		1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	2 (10%)	2 (4%)	4 (9%)
#PARATHYROID	(2)	(14)	(13)
FIBROSIS		1 (7%)	
HYPERPLASIA, NOS	2 (100%)	14 (100%)	12 (92%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(16)	(13)	(16)
CYST, NOS		5 (38%)	
INFLAMMATION, NOS	1 (6%)	2 (15%)	2 (13%)
ATROPHY, NOS		1 (8%)	
*SEMINAL VESICLE	(20)	(50)	(47)
INFLAMMATION, NOS		1 (2%)	2 (4%)
INFLAMMATION, CHRONIC		1 (2%)	
#TESTIS	(18)	(19)	(18)
INFLAMMATION, NOS			1 (6%)
CALCIUM DEPOSIT	1 (6%)		
CALCIFICATION, NOS		1 (5%)	
ATROPHY, NOS	6 (33%)	10 (53%)	4 (22%)
*EPIDIDYMIS	(20)	(50)	(47)
ATROPHY, NOS	2 (10%)		1 (2%)

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

TABLE K1 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-M028	LOW DOSE 01-M029	HIGH DOSE 01-M030
NERVOUS SYSTEM			
*BRAIN	(19)	(19)	(18)
HYDROCEPHALUS, NOS			1 (6%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(47)
PANNUS	2 (10%)	1 (2%)	
CATARACT	1 (5%)		
*EYE/CORNEA	(20)	(50)	(47)
ULCER, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(47)
HEMORRHAGE		1 (2%)	
FIBROSIS		1 (2%)	
NECROSIS, FAT		1 (2%)	
*PERITONEUM	(20)	(50)	(47)
INFLAMMATION, NOS			1 (2%)
*MESENTERY	(20)	(50)	(47)
PERIARTERITIS			1 (2%)
ARTERIOSCLEROSIS, NOS	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
NECROPSY PERF/NO HISTO PERFORMED		1	
AUTO/NECROPSY/NO HISTO			2
AUTOLYSIS/NO NECROPSY			3

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

TABLE K2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	47	46
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(50)
ULCER, NOS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(29)	(28)
MINERALIZATION			1 (4%)
CONGESTION, NOS			1 (4%)
EDEMA, NOS		6 (21%)	16 (57%)
HEMORRHAGE	5 (25%)	11 (38%)	5 (18%)
ABSCESS, NOS			1 (4%)
PNEUMONIA, CHRONIC MURINE	4 (20%)	1 (3%)	7 (25%)
GRANULOMA, NOS			1 (4%)
CALCIFICATION, NOS			1 (4%)
HYPERPLASIA, EPITHELIAL	2 (10%)	1 (3%)	4 (14%)
#ALVEOLAR WALL	(20)	(29)	(28)
CALCIFICATION, NOS		1 (3%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(29)	(21)
METAMORPHOSIS FATTY	4 (20%)	1 (3%)	
#SPLEEN	(20)	(30)	(22)
THROMBOSIS, NOS			1 (5%)
CONGESTION, NOS		1 (3%)	
GRANULOMA, NOS			1 (5%)
PIGMENTATION, NOS	5 (25%)		
HYPERPLASIA, RETICULUM CELL	2 (10%)		
HEMATOPOIESIS	4 (20%)	5 (17%)	1 (5%)
#MESENTERIC L. NODE	(18)	(27)	(18)
INFLAMMATION, NOS			1 (6%)

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

TABLE K2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
ARTERIOSCLEROSIS, NOS			1 (6%)
HYPERPLASIA, NOS		1 (4%)	1 (6%)
CIRCULATORY SYSTEM			
#HEART	(20)	(29)	(22)
THROMBOSIS, NOS			1 (5%)
CONGESTION, NOS	1 (5%)		
FIBROSIS	1 (5%)		
ARTERIOSCLEROSIS, NOS		1 (3%)	
#MYOCARDIUM	(20)	(29)	(22)
INFLAMMATION, NOS	2 (10%)	6 (21%)	4 (18%)
INFLAMMATION, FOCAL			1 (5%)
DEGENERATION, NOS	11 (55%)	12 (41%)	8 (36%)
#ENDOCARDIUM	(20)	(29)	(22)
HYPERPLASIA, NOS		1 (3%)	3 (14%)
HYPERPLASIA, FOCAL			1 (5%)
*AORTA	(20)	(49)	(50)
ARTERIOSCLEROSIS, NOS		2 (4%)	2 (4%)
*PULMONARY VEIN	(20)	(49)	(50)
FIBROSIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(34)	(33)
THROMBOSIS, NOS		1 (3%)	1 (3%)
CONGESTION, NOS			4 (12%)
GRANULOMA, NOS	1 (5%)		1 (3%)
NECROSIS, NOS		6 (18%)	9 (27%)
NECROSIS, FOCAL	1 (5%)		1 (3%)
NECROSIS, COAGULATIVE		1 (3%)	
METAMORPHOSIS FATTY	11 (55%)	3 (9%)	10 (30%)
ATROPHY, NOS			1 (3%)
HYPERTROPHY, NOS		2 (6%)	
HYPERTROPHY, FOCAL		2 (6%)	
ANGIECTASIS		3 (9%)	2 (6%)
*BILE DUCT	(20)	(49)	(50)
DILATATION, NOS		3 (6%)	3 (6%)
INFLAMMATION, NOS	1 (5%)	4 (8%)	

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

TABLE K2(CONTINUED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
FIBROSIS	1 (5%)		
DEGENERATION, NOS			1 (2%)
HYPERPLASIA, NOS	9 (45%)	20 (41%)	12 (24%)
#PANCREAS	(20)	(28)	(21)
PERIARTERITIS	1 (5%)	1 (4%)	
ARTERIOSCLEROSIS, NOS			1 (5%)
CALCIFICATION, NOS			1 (5%)
#STOMACH	(20)	(30)	(30)
ULCER, FOCAL		2 (7%)	6 (20%)
ULCER, ACUTE			1 (3%)
GRANULOMA, NOS			1 (3%)
CALCIUM DEPOSIT			1 (3%)
HYPERKERATOSIS		1 (3%)	1 (3%)
ACANTHOSIS		1 (3%)	
#GASTRIC MUCOSA	(20)	(30)	(30)
ULCER, FOCAL	2 (10%)		
#SMALL INTESTINE	(20)	(29)	(20)
HYPERPLASIA, NOS		1 (3%)	
#LARGE INTESTINE	(20)	(29)	(21)
IMPACTION, NOS	1 (5%)		
URINARY SYSTEM			
#KIDNEY	(20)	(30)	(23)
MINERALIZATION	3 (15%)	11 (37%)	6 (26%)
HYDRONEPHROSIS	1 (5%)		
CONGESTION, NOS	2 (10%)	1 (3%)	
INFLAMMATION, CHRONIC	12 (60%)	17 (57%)	12 (52%)
GRANULOMA, NOS			1 (4%)
CALCIFICATION, NOS		1 (3%)	1 (4%)
HYPERPLASIA, NOS	1 (5%)		
HYPERPLASIA, EPITHELIAL		3 (10%)	4 (17%)
#KIDNEY/PELVIS	(20)	(30)	(23)
MINERALIZATION	2 (10%)		
INFLAMMATION, NOS	1 (5%)		
#URINARY BLADDER	(20)	(28)	(21)
HYPERTROPHY, NOS	1 (5%)		

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

TABLE K2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDE

	CONTROL (VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(33)	(27)
CYST, NOS	1 (6%)	1 (3%)	
HYPERTROPHY, NOS			1 (4%)
HYPERPLASIA, NOS		1 (3%)	1 (4%)
HYPERPLASIA, CHROMOPHOBE-CELL		1 (3%)	
#ADRENAL	(19)	(30)	(24)
THROMBOSIS, NOS			1 (4%)
CONGESTION, NOS		1 (3%)	
HEMORRHAGE		1 (3%)	
DEGENERATION, NOS			1 (4%)
CYTOLOGIC DEGENERATION		2 (7%)	
HYPERTROPHY, NOS		1 (3%)	
ANGIECTASIS	15 (79%)	8 (27%)	4 (17%)
#ADRENAL CORTEX	(19)	(30)	(24)
HYPERTROPHY, NOS		7 (23%)	4 (17%)
#THYROID	(19)	(48)	(48)
FOLLICULAR CYST, NOS	2 (11%)	3 (6%)	2 (4%)
DEGENERATION, CYSTIC	1 (5%)	1 (2%)	
HYPERPLASIA, C-CELL	3 (16%)	3 (6%)	2 (4%)
HYPERPLASIA, FOLLICULAR-CELL		7 (15%)	4 (8%)
#PARATHYROID		(2)	(3)
HYPERPLASIA, NOS		2 (100%)	3 (100%)
REPRODUCTIVE SYSTEM			
*VAGINA	(20)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
#UTERUS	(19)	(33)	(23)
HYDROMETRA	3 (16%)	13 (39%)	6 (26%)
GRANULOMA, NOS			1 (4%)
#UTERUS/ENDOMETRIUM	(19)	(33)	(23)
CYST, NOS	1 (5%)		
INFLAMMATION, NOS	1 (5%)	2 (6%)	2 (9%)
HYPERPLASIA, NOS			2 (9%)
HYPERPLASIA, CYSTIC		3 (9%)	1 (4%)
#OVARY	(19)	(30)	(21)
CYST, NOS		2 (7%)	1 (5%)

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

TABLE K2 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DDE

	CONTROL(VEH) 01-F028	LOW DOSE 01-F031	HIGH DOSE 01-F032
FOLLICULAR CYST, NOS			1 (5%)
NERVOUS SYSTEM			
#BRAIN	(20)	(29)	(20)
CYTOPLASMIC VACUOLIZATION			1 (5%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(49)	(50)
CONGENITAL MALFORMATION, NOS		1 (2%)	
EDEMA, NOS		1 (2%)	
CALCIFICATION, NOS		1 (2%)	
*EYE/CORNEA	(20)	(49)	(50)
INFLAMMATION, NOS	1 (5%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE HIP/THIGH	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
ARTERIOSCLEROSIS, NOS			1 (2%)
BODY CAVITIES			
*EPICARDIUM	(20)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED		2	2
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO			2
AUTOLYSIS/NO NECROPSY		1	

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

APPENDIX L

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH DDE

TABLE L1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DDE

	CONTROL(VEH) 02-M047	LOW DOSE 02-M048	HIGH DOSE 02-M049
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	18	41	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	41	47
INTEGUMENTARY SYSTEM			
*SKIN	(18)	(41)	(47)
EPIDERMAL INCLUSION CYST		1 (2%)	
*SUBCUT TISSUE	(18)	(41)	(47)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(18)	(41)	(45)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(41)	(44)
INFLAMMATION, NOS	1 (5%)		
AMYLOIDOSIS	17 (89%)	25 (61%)	13 (30%)
HEMATOPOIESIS		2 (5%)	1 (2%)
#MESENTERIC L. NODE	(12)	(37)	(39)
INFLAMMATION, NOS	1 (8%)	1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(19)	(41)	(45)
THROMBOSIS, NOS		1 (2%)	
#MYOCARDIUM	(19)	(41)	(45)
INFLAMMATION, NOS		2 (5%)	1 (2%)
#ENDOCARDIUM	(19)	(41)	(45)
INFLAMMATION, NOS		1 (2%)	

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

TABLE L1 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-M047	LOW DOSE 02-M048	HIGH DOSE 02-M049
DIGESTIVE SYSTEM			
#LIVER	(19)	(41)	(47)
THROMBOSIS, NOS		1 (2%)	
AMYLOIDOSIS	8 (42%)		1 (2%)
HYPERPLASIA, NODULAR	1 (5%)	2 (5%)	
#COLON	(17)	(41)	(45)
PARASITISM		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(41)	(45)
POLYCYSTIC KIDNEY			1 (2%)
PYELONEPHRITIS, NOS		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	2 (11%)	11 (27%)	16 (36%)
AMYLOIDOSIS	10 (53%)	26 (63%)	12 (27%)
#URINARY BLADDER	(15)	(40)	(44)
INFLAMMATION, NOS			2 (5%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#PROSTATE	(17)	(39)	(42)
INFLAMMATION, NOS			1 (2%)
*SEMINAL VESICLE	(18)	(41)	(47)
INFLAMMATION, NOS	1 (6%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE L1 (CONCLUDED)

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-M047	LOW DOSE 02-M048	HIGH DOSE 02-M049
BODY CAVITIES			
*PERICARDIUM	(18)	(41)	(47)
INFLAMMATION, NOS		2 (5%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		2	14
ANIMAL MISSING/NO NECROPSY		1	
AUTOLYSIS/NO NECROPSY	2	8	3

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

TABLE L2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DDE

	CONTROL(VEH) 02-F047	LOW DOSE 02-F050	HIGH DOSE 02-F051
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	48	47
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(48)	(49)
CYST, NOS		1 (2%)	
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(33)	(44)
PNEUMONIA, CHRONIC MURINE			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(33)	(45)
AMYLOIDOSIS		1 (3%)	
HEMATOPOIESIS		1 (3%)	1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(33)	(44)
INFLAMMATION, NOS		1 (3%)	
DIGESTIVE SYSTEM			
#LIVER	(19)	(47)	(48)
THROMBUS, ORGANIZED			4 (8%)
HYPERPLASIA, NODULAR			1 (2%)
*GALLBLADDER	(19)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
#PANCREAS	(19)	(33)	(45)
CYST, NOS			2 (4%)

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

TABLE L2 (CONTINUED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DDE

	CONTROL (VEH) 02-F047	LOW DOSE 02-F050	HIGH DOSE 02-F051
ATROPHY, NOS			2 (4%)
URINARY SYSTEM			
#KIDNEY	(19)	(33)	(45)
INFLAMMATION, CHRONIC		2 (6%)	
AMYLOIDOSIS		1 (3%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(18)	(33)	(44)
HYDROMETRA	1 (6%)	1 (3%)	1 (2%)
INFLAMMATION, NOS	1 (6%)	8 (24%)	
#UTERUS/ENDOMETRIUM	(18)	(33)	(44)
HYPERPLASIA, CYSTIC	3 (17%)	8 (24%)	6 (14%)
#OVARY/OVIDUCT	(18)	(33)	(44)
INFLAMMATION, NOS	1 (6%)		
#OVARY	(19)	(33)	(44)
CYST, NOS	6 (32%)	4 (12%)	3 (7%)
INFLAMMATION, NOS	1 (5%)	4 (12%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE L2 (CONCLUDED)
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DDE

	CONTROL(VEH) 02-F047	LOW DOSE 02-F050	HIGH DOSE 02-F051
BODY CAVITIES			
*PERITONEUM	(19)	(48)	(49)
INFLAMMATION, NOS	1 (5%)	1 (2%)	
*PERICARDIUM	(19)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	7	14	9
ANIMAL MISSING/NO NECROPSY	1		
NECROPSY PERF/NO HISTO PERFORMED			1
AUTO/NECROPSY/HISTO PERF			2
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY		2	1

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

Review of the Bioassay of DDT, TDE, and *p,p'*-DDE*
for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

June 29, 1978

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

The reviewer agreed that the study did not provide firm evidence for the carcinogenicity of DDT in rats or mice; that TDE may be carcinogenic in the treated rats, as evidenced by an increased incidence of thyroid tumors; and that *p,p'*-DDE was not carcinogenic in treated rats but did appear to be a hepatocarcinogen in mice. The reviewer said that caution should be exercised in interpreting the results in view of the studies' shortcomings. Among the experimental limitations, he noted the small matched control groups, the fact that the study was conducted in a room in which other chemicals were under test, the numerous dosage changes during the course of the chronic study, and the variations in the pathology protocol. The reviewer said that it was not possible to assess human risk based on the results of the study.

A Program staff member noted that other studies have demonstrated the carcinogenicity of some of the test compounds in mice. He said that the data from this study were probably not ambiguous but rather reflected a difference in response that exists between species and strains. It was noted that any consideration to retesting the compounds would be based, in part, on a review of all published studies. The reviewer moved that the report on the bioassay of DDT, TDE, and *p,p'*-DDE be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

REPORT ON BIOASSAY OF DDT,TDE AND P,P'-DDE FOR POSSIBLE CARCINOGENICITY

Availability

DDT, TDE and p,p'-DDE (CAS 50-29-3) have been tested for cancer-causing activity with rats and mice in the Bioassay Program, Division of Cancer Cause and Prevention, National Cancer Institute. A report is available to the public.

Summary: Bioassays of technical-grade DDT, TDE, and p,p'-DDE for possible carcinogenicity were conducted using Osborne-Mendel rats and B6C3F1 mice. TDE and p,p'-DDE are chemicals related to the insecticide DDT. Each compound was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species.

Under the conditions of these bioassays there was no evidence for the carcinogenicity of DDT in Osborne-Mendel rats or B6C3F1 mice, of TDE in female Osborne-Mendel rats or B6C3F1 mice of either sex, or of p,p'-DDE in Osborne-Mendel rats, although p,p'-DDE was hepatotoxic in Osborne-Mendel rats. The findings suggest a possible carcinogenic effect of TDE in male Osborne-Mendel rats, based on the induction of combined follicular-cell carcinomas and follicular-cell adenomas of the thyroid. Because of the variation of these tumors in control male rats in this study, the evidence does not permit a more conclusive interpretation of these

lesions. p,p'-DDE was carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes.

Single copies of the report are available from the Office of Cancer Communications, National Cancer Institute, Building 31, Room 10A21, National Institutes of Health, Bethesda, Maryland 20014.

Dated:
October 10, 1978

Director
National Institutes of Health

(Catalogue of Federal Domestic Assistance Program Number 13.393, Cancer Cause and Prevention Research)

DHEW Publication No. (NIH) 78-1386