NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of *p,p'*-Dichlorodiphenyl Sulfone (CAS No. 80-07-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies)

NTP TR 501

SEPTEMBER 2001

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF *p,p′*-DICHLORODIPHENYL SULFONE

(CAS NO. 80-07-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

September 2001

NTP TR 501

NIH Publication No. 01-4435

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears on the inside back cover.

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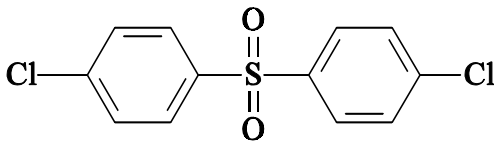
CONTENTS

ABSTRACT



_p,p′_-DICHLORODIPHENYL SULFONE

CAS No. 80-07-9

Chemical Formula: $C_{12}H_8Cl_2O_2S$ Molecular Weight: 287.16

Synonyms: Bis (4-chlorophenyl) sulfone; bis (*p*-chlorophenyl) sulfone; 4-chloro-1-(4-chlorophenylsulfonyl) benzene; 4-chlorophenyl sulfone; *p*-chlorophenyl sulfone; 4,4′-dichlorodiphenyl sulfone; 4,4′-dichlorodiphenyl sulphone; di-4-chlorophenyl sulfone; di-*p*-chlorophenyl sulfone; 1,1′-sulfonylbis (4-chlorobenzene)

p,p′-Dichlorodiphenyl sulfone is used as a starting material in the production of polysulfones and polyethersulfones and as a component in reactive dyes in the textile industry; it is also a by-product of pesticide production. *p,p′*-Dichlorodiphenyl sulfone was nominated for study by the National Cancer Institute because of its history of high production and use, the prospect of increased production and use, and the absence of adequate toxicity testing. Male and female F344/N rats and $B6C3F_1$ mice were exposed to *p,p′*-dichlorodiphenyl sulfone (greater than 99% pure) in feed for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium,* cultured Chinese hamster ovary cells, and mouse bone marrow.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm *p,p′*-dichlorodiphenyl sulfone (equivalent to average daily doses of approximately 2, 6, 19, 65, or 200 mg *p,p′*-dichlorodiphenyl sulfone/kg body weight) for 14 weeks. All rats survived until the end of the study. Mean body weights of groups exposed to 300 ppm or greater were significantly less than those of the controls. Liver weights of groups exposed to 100 ppm or greater and kidney weights of 1,000 and 3,000 ppm male rats were significantly greater than those of the controls. Centrilobular hepatocyte hypertrophy of the liver was observed in most male rats exposed to 100 ppm or greater and in all female rats exposed to 300 ppm or greater, and the severities were increased in 300 ppm males and 1,000 and 3,000 ppm males and females. The incidences of nephropathy in 1,000 and 3,000 ppm female rats were significantly increased. Dose-related increases in severity of nephropathy were observed in male rats.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female $B6C3F_1$ mice were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm *p,p′*-dichlorodiphenyl sulfone (equivalent to average daily doses of approximately 3.5, 15, 50, 165, or 480 mg/kg) for 14 weeks. All mice survived until the end of the study. Mean body weights of groups exposed to 300 ppm or greater were significantly less than those of the controls. Liver weights of groups exposed to 300 ppm or greater were significantly increased. Centrilobular hypertrophy of the liver was observed in most males exposed to 100 ppm or greater and in all females exposed to 1,000 or 3,000 ppm, and the severities generally increased with increasing exposure concentration.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were fed diets containing 0, 10 (males), 30, 100, or 300 (females) ppm *p,p′*-dichlorodiphenyl sulfone for 105 weeks. Dietary concentrations of 10, 30, and 100 ppm resulted in average daily doses of approximately 0.5, 1.5, and 5.0 mg/kg to males. Dietary concentrations of 30, 100, and 300 ppm resulted in average daily doses of approximately 1.6, 5.4, and 17 mg/kg to females. Additional groups of 10 male and 10 female rats were fed the same *p,p′*-dichlorodiphenyl sulfone-containing diets for 18 months and bled for plasma determinations of *p,p′*-dichlorodiphenyl sulfone at approximately 2 weeks and 3, 12, and 18 months.

Survival of all exposed groups of male and female rats was similar to that of the control groups. Mean body weights of 30 and 100 ppm males were generally less than those of the controls during the latter part of the study, and mean body weights of 100 and 300 ppm female rats were less from weeks 30 and 18, respectively. Feed consumption by the exposed groups was similar to that by the controls throughout the study.

The incidences of centrilobular hepatocyte hypertrophy in 100 ppm male and 100 and 300 ppm female rats were significantly greater than those in the controls. The incidences of bile duct hyperplasia and centrilobular degeneration were also significantly increased in 100 and 300 ppm females. No neoplasms were related to chemical exposure.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were fed diets containing 0, 30, 100, or 300 ppm *p,p′*-dichlorodiphenyl sulfone for 105 to 106 weeks. Dietary concentrations of 30, 100, and 300 ppm delivered average daily doses of approximately 4, 13, and 40 mg/kg to males and approximately 3, 10, and 33 mg/kg to females. Additional groups of 10 male and 10 female mice were fed the same *p,p′*-dichlorodiphenyl sulfone-containing diets for up to 12 months; three mice in each group were bled for plasma determinations of *p,p′*-dichloro-diphenyl sulfone at approximately 2 weeks or 3 or 12 months.

Survival of all exposed groups of male and female mice was similar to that of the control groups. Mean body weights of 300 ppm mice were less than those of the controls throughout most of the study. Feed consumption by the exposed groups was similar to that by the controls throughout the study.

The incidences of centrilobular hepatocyte hypertrophy in all exposed groups of male mice and in 100 and 300 ppm females were significantly greater than those in the controls. The incidence of eosinophilic foci in 300 ppm females was significantly increased. No neoplasms were related to chemical exposure.

PHARMACOKINETICS OF *p,p′*-DICHLORODIPHENYL SULFONE

p,p′-Dichlorodiphenyl sulfone is rapidly absorbed from the gut and metabolized by a saturable process. Although some *p,p′*-dichlorodiphenyl sulfone is eliminated unchanged in feces and urine, most of the elimination is via metabolism. Mathematical modeling of the toxicokinetics supports the view that *p,p′*-dichlorodiphenyl sulfone induces enzymes involved in its metabolism.

GENETIC TOXICOLOGY

p,p′-Dichlorodiphenyl sulfone was not mutagenic in any of several strains of *Salmonella typhimurium*, with or without metabolic activation enzymes (S9). Results of the sister chromatid exchange test in cultured Chinese hamster ovary cells were judged to be negative in the presence of S9 and equivocal in the absence of S9, but no induction of chromosomal aberrations was noted, with or without S9. In contrast to the *in vitro* results, positive results were obtained in an acute *in vivo* mouse bone marrow micronucleus assay with *p,p′*-dichlorodiphenyl sulfone administered by intraperitoneal injection three times over a dose range of 200 to 800 mg/kg.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of *p,p′*-dichlorodiphenyl sulfone in male F344/N rats exposed to 10, 30, or 100 ppm or in female F344/N rats exposed to 30, 100, or 300 ppm. There was *no evidence of carcinogenic activity* of *p,p′*-dichlorodiphenyl sulfone in male or female B6C3F_1 mice exposed to 30, 100, or 300 ppm.

Exposure to *p,p′*-dichlorodiphenyl sulfone for 2 years caused increased incidences of nonneoplastic lesions of the liver in male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *p,p′*-Dichlorodiphenyl Sulfone

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in feed	0, 10, 30, or 100 ppm	0, 30, 100, or 300 ppm	0, 30, 100, or 300 ppm	0, 30, 100, or 300 ppm
Body weights	30 and 100 ppm groups less than control group	100 and 300 ppm groups less than control group	300 ppm group less than control group	300 ppm group less than control group
Survival rates	24/50, 30/50, 20/50, 28/50	36/50, 38/50, 35/50, 35/50	40/50, 45/50, 44/50, 42/50	42/50, 40/50, 43/50, 45/50
Nonneoplastic effects	Liver: centrilobular hypertrophy (0/50, 1/50, 3/50, 16/50)	Liver: centrilobular hypertrophy (0/50, 2/50, 24/50, 38/50); bile duct hyperplasia (5/50, 12/50, 21/50, 32/50); centrilobular degeneration (1/50, 5/50, 10/50, 7/50)	Liver: centrilobular hypertrophy (1/50, 24/50, 43/50, 45/50)	Liver: centrilobular hypertrophy (0/50, 0/50, 9/50, 29/50); eosinophilic focus (2/50, 1/50, 4/50, 14/50)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; equivocal without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Micronucleated erythrocytes				
Mouse bone marrow *in vivo*:	Positive when administered by intraperitoneal injection			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *p,p′*-dichlorodiphenyl sulfone on 18 May 2000 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 18 May 2000, the draft Technical Report on the toxicology and carcinogenesis studies of *p,p′*-dichlorodiphenyl sulfone received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenesis studies of *p,p′*-dichloro-diphenyl sulfone by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in male and female rats and mice. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male or female F344/N rats or B6C3F$_1$ mice.

Dr. F.M. Parham, NIEHS, said the objective of the toxicokinetic study was to characterize the absorption, distribution, metabolism, and elimination of *p,p′*-dichlorodiphenyl sulfone in rats and mice under the conditions of the 2-year study. Data sources were time-course data for radiolabeled *p,p′*-dichlorodiphenyl sulfone in tissues and exreta after intravenous injection, similar data after single gavage doses, and plasma concentrations of *p,p′*-dichlorodiphenyl sulfone in rats and mice after 2 weeks and 3, 12, and 18 months of exposure in feed. He said the pharmacokinetic model used was similar to the one used in the naphthalene study reported earlier, and that it demonstrated a nonlinear metabolism of *p,p′*-dichlorodiphenyl sulfone by Michaelis-Menten kinetics in the liver. Conclusions from the toxicokinetic studies were that absorption of *p,p′*-dichlorodiphenyl sulfone was very rapid and first-pass liver extraction was very low, while the amount metabolized within the first day was higher. *p,p′*-Dichlorodiphenyl sulfone induced enzymes involved in its metabolism, and elimination half-lives were higher in rats than in mice. Dr. Medinsky said it would be helpful if the NTP could standardize the presentions. Dr. Christopher Portier, NIEHS, agreed and asked for Dr. Medinsky's input to develop a standard format.

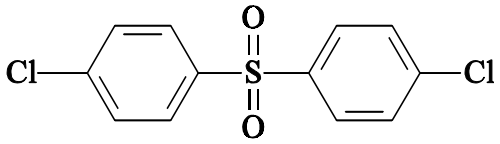
Dr. Hecht, a principal reviewer, agreed with the proposed conclusions.

Dr. Bus, the second principal reviewer, agreed with the proposed conclusions. He questioned the designation of a positive response for the mouse micronucleus test, perhaps because of a low control value in the second replicate, and thought *equivocal evidence of carcinogenic activity* might be more appropriate. Dr. Chhabra responded that he discussed this with a genetic toxicologist and they determined that the finding was inconclusive.

Dr. Drinkwater, the third principal reviewer, agreed with the proposed conclusions. He commented that dose-dependent increases in the incidences of eosinophilic foci in the liver of female mice, along with the ability of *p,p′*-dichlorodiphenyl sulfone to cause microsomal enzyme induction and hepatomegaly, are consistent with activity of the chemical as a weak hepatic tumor promoter, and this should be discussed. Dr. Chhabra agreed and said he would clarify this in the Discussion.

Dr. Drinkwater moved that the Technical Report on *p,p′*-dichlorodiphenyl sulfone be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Cullen seconded the motion, which was accepted unanimously with five votes (Dr. Hecht was absent for the vote).

INTRODUCTION



***p,p′*-DICHLORODIPHENYL SULFONE**

CAS No. 80-07-9

Chemical Formula: $C_{12}H_8Cl_2O_2S$ Molecular Weight: 287.16

Synonyms: Bis (4-chlorophenyl) sulfone; bis (*p*-chlorophenyl) sulfone; 4-chloro-1-(4-chlorophenylsulfonyl) benzene; 4-chlorophenyl sulfone; *p*-chlorophenyl sulfone; 4,4′-dichlorodiphenyl sulfone; 4,4′-dichlorodiphenyl sulphone; di-4-chlorophenyl sulfone; di-*p*-chlorophenyl sulfone; 1,1′-sulfonylbis (4-chlorobenzene)

CHEMICAL AND PHYSICAL PROPERTIES

p,p′-Dichlorodiphenyl sulfone is a white powder with a melting point of 145° to 149° C, a boiling point of 250° C at 10 mm Hg, and a specific gravity of 1.293 (*Aldrich*, 1988; Sloss Industries, 1988). It is insoluble in water and soluble in acetone and olive oil (Domenjoz, 1946). *p,p′*-Dichlorodiphenyl sulfone is combustible and has a flash point above 100° C (Sloss Industries, 1988). When heated to decomposition, it releases toxic chlorine and sulfur oxide fumes (Sax and Lewis, 1989). A log water:octanol partition coefficient of 3.9 has been reported (Olsson and Bergman, 1995).

PRODUCTION, USE, AND HUMAN EXPOSURE

p,p′-Dichlorodiphenyl sulfone is synthesized via a two-step process. Chlorobenzene, sulfur trioxide, and thionyl chloride react to form a mixture of *p*-chlorobenzene sulfonyl chloride and *p,p′*-dichlorodiphenyl sulfone. *p*-Chlorobenzene sulfonyl chloride reacts with chlorobenzene in the presence of ferric chloride, forming additional *p,p′*-dichlorodiphenyl sulfone (Street *et al.*, 1971; Garty *et al.*, 1974). The annual production volume of *p,p′*-dichlorodiphenyl sulfone in the United States was estimated to be between 0.1 and 20 million pounds in 1990 (*Fed. Reg.,* 1991).

p,p′-Dichlorodiphenyl sulfone is used as a starting material in the production of polysulfones and polyethersulfones. Polysulfones and polyethersulfones are a family of thermoplastics known as engineering plastics and are used in high-temperature applications (Garty *et al.*, 1974; Haglund *et al.*, 1998). Polysulfones are used in the manufacture of medical equipment (nebulizers and dialysis components), appliances (coffeemakers, humidifiers, and microwave ovens), automobile parts (steering column lock switches, relay insulators, and pistons), and electronic equipment (television components and capacitor film). *p,p′*-Dichlorodiphenyl sulfone has been shown to be as potent an insecticide as dichlorodiphenyl-trichloroethane (DDT) for the fly *Musca nebulo* (Misra and Asthana, 1957). *p,p′*-Dichlorodiphenyl sulfone was used as a pesticide and is a by-product of pesticide production and may also be used in reactive dyes in the textile industry (Olsson and Bergman, 1995). *p,p′*-Dichlorodiphenyl sulfone has also been identified as a contaminant of 4-chlorobenzene sulfonamide pesticides (Harnagea and Badilescu, 1965).

Although human exposure can be anticipated to occur mainly in the workplace, recent studies of environmental samples suggest the potential for more widespread exposure. No information is available on *p,p′*-dichlorodiphenyl sulfone regarding workplace exposure concentrations or the number of workers potentially exposed to this compound. The concentration of *p,p′*-dichlorodiphenyl sulfone in human liver samples from Germany ranged from 1.5 to 39 ng/g lipid (Ellerichmann *et al.*, 1998). *p,p′*-Dichlorodiphenyl sulfone has been identified in lakes in northern Italy (Como, Garda, and Maggiore), effluents from industrial sites in the Mediterranean, and the river Elbe (Swindlehurst *et al.*, 1995; Müller *et al.*, 1997; Guzella and Sora, 1998); no concentrations were reported. In perch (*Perca fluviatilis*) collected from the Gulf of Riga area along the Latvian coast in 1997, *p,p′*-dichlorodiphenyl sulfone concentrations ranged from 53 to 160 ng/g lipid (Valters *et al.*, 1999). This range is also similar to those of 2,2′,4,4′,-5,5′-hexachlorobiphenyl (22 to 120 ng/g lipid) and the sum of 1,1,1-trichloro-2,2-bis-(4-chlorophenyl)ethane, 1,1-dichloro-2,2-bis-(4-chlorophenyl)ethene, and 1,1-dichloro-2,2-bis-(4-chlorophenyl)ethane (150 to 330 ng/g lipid) (Valters *et al.*, 1999). Concentrations of *p,p′*-dichlorodiphenyl sulfone in perch collected from the same area in 1994 and 1995 ranged from 55 to 82 ng/g lipid (Olsson and Bergman, 1995; Olsson *et al.*, 1996). A white-tailed sea eagle egg and grey seal blubber samples collected in Sweden contained *p,p′*-dichlorodiphenyl sulfone concentrations of 500 and 53 to 88 ng/g lipid, respectively (Olsson and Bergman, 1995). The concentration of *p,p′*-dichlorodiphenyl sulfone in white-tailed sea eagle eggs from Lake Ontario has increased over the last 30 years (K. Ceder, Stockholm University, personal communication). *p,p′*-Dichlorodiphenyl sulfone is taken up by alfalfa, sugar beets, fescue, wheat, and corn (Guenzi *et al.*, 1981). A slow biodegradation was observed in soil, with approximately 20% biodegradation in 160 days (Guenzi and Beard, 1981). The lipophilic *p,p′*-dichlorodiphenyl sulfone has thus been identified at various trophic levels, including in humans.

In the United States, no occupational exposure limits have been established by the American Conference of Governmental Industrial Hygienists, the National Institute of Occupational Safety and Health, or the Occupational Safety and Health Administration.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

p,p′-Dichlorodiphenyl sulfone is well absorbed after oral exposure and is distributed mainly throughout the adipose tissue as the parent compound. Metabolism occurs slowly, with an estimated half-life of 12 days in adipose tissue. *p,p′*-Dichlorodiphenyl sulfone is excreted in urine and feces as metabolites (some are identified) and as the parent compound (Mathews *et al.*, 1996).

p,p′-Dichlorodiphenyl sulfone was readily and almost completely absorbed from the gastrointestinal tract after gavage dosing (10 mg/kg) in male Fischer 344 rats (Mathews *et al.*, 1996). A single gavage dose distributed *p,p′*-dichlorodiphenyl sulfone in percentages similar to those by intravenous injection: radiolabel was found primarily in adipose tissue (41% to 49%), followed by the skin (16% to 18%) and muscle (12%). Identification of the radiolabel indicated that virtually all was unmetabolized *p,p′*-dichlorodiphenyl sulfone. The percentage of the administered dose in adipose tissue, skin, muscle, and liver decreased with increasing gavage doses (10, 100, and 1,000 mg/kg), indicating increased metabolism, as measured by increased excretion of radiolabel in urine.

Repeat gavage dosing for 7 days resulted in a similar distribution of *p,p′*-dichlorodiphenyl sulfone over the various tissues, with adipose tissue again the major storage site (Mathews *et al.*, 1996). A dose-dependent decrease was observed in the percentage of the dose found in all tissues, especially adipose tissue. For example, after a daily dose of 1 mg/kg for 7 days, 41% of the administered dose was found in the adipose tissue, whereas after a daily dose of 100 mg/kg for 7 days, only 22% of the administered dose was found. At the same time, a dose-dependent increase in excretion of radiolabel in urine (from 11% to 22%) and feces (from 20% to 33%) was observed. This indicates an increase in metabolism and a decrease in absorption with dose.

The increase in metabolism was further demonstrated by repeated gavage dosing of male F344 rats with 10 mg/kg per day, 5 days a week for up to 5 weeks (Mathews *et al.*, 1996). After 2 weeks, 20% of the administered dose was found in the adipose tissue, whereas 7% was found after 5 weeks of dosing. The total amount recovered in the tissues decreased from 28% after 2 weeks to 10% after 5 weeks of dosing. However, in these 7-day and 5-week repeated-dose studies, the vehicle used was Emulphor EL-620. Emulphor EL-620 has been shown to double total cytochrome P450 activities (RTI, 1994). Therefore, the increased dose-dependent metabolism may have been due in part to the vehicle.

In a 4-week feed study with *p,p′*-dichlorodiphenyl sulfone in male Sprague-Dawley rats, the distribution was similar to those in gavage and intravenous experiments in male F344 rats; the adipose tissue had the highest concentration, followed by the liver and kidney (muscle and skin were not measured) (Poon *et al.*, 1999). In this feed study, an exposure concentration-dependent decrease (as a percentage of the administered dose) in the concentration of *p,p′*-dichlorodiphenyl sulfone was observed in the adipose tissue.

Mathews *et al.* (1996) estimated a terminal half-life of 12 days for *p,p′*-dichlorodiphenyl sulfone in adipose tissue after a single intravenous dose of 10 mg/kg to male F344 rats. Three metabolites in the urine and feces were observed initially, along with small amounts of unchanged *p,p′*-dichlorodiphenyl sulfone, especially in the urine. The metabolites were identified as a glucuronide, its aglycone, and an unidentified chromatographic peak, which was found to consist of up to five components. The aglycone was characterized as the product of hydroxylation of *p,p′*-dichlorodiphenyl sulfone *meta* to the sulfone group. In the 4-week dosed-feed study in male Sprague-Dawley rats, hepatic microsomal activities of benzyloxyresorufin-*O*-dealkylase and pentoxyresorufin-*O*-dealkylase, markers for cytochrome P4502B catalytic activity, were induced by *p,p′*-dichlorodiphenyl sulfone 67- and 25-fold, respectively, compared to the controls (Poon *et al.*, 1999). No increases occurred in hepatic ethoxyresorufin-*O*-deethylase and methoxyresorufin-*O*-dealkylase activities, markers for CYP1A catalytic activity. In contrast, in the 7-day gavage study in male F344 rats (Mathews *et al.*, 1996), hepatic ethoxyresorufin-*O*-deethylase activity doubled in the group administered 10 mg/kg per day. However, the vehicle, Emulphor EL-620, doubled cytochrome P450 activities (RTI, 1994). In the 7-day study, Mathews *et al.* (1996) measured no increase in hepatic benzphetamine *N*-demethylase (associated with CYP2B). In the 4-week feed study (Poon *et al.*, 1999), hepatic UDP-glucuronyltransferase was induced up to sixfold when 4-nitrophenol was used as the substrate, and a fivefold increase was seen in unspecified microsomal glutathione-S-transferase activity.

As part of the present studies, a physiologically based pharmacokinetic model was developed to represent the absorption, distribution, metabolism, and excretion of *p,p′*-dichlorodiphenyl sulfone in rats and mice. The model included compartments representing blood, gastrointestinal tract tissue, liver, muscle, skin, fat (adipose tissue), kidney, and gastrointestinal tract lumen. When five metabolites of *p,p′*-dichlorodiphenyl sulfone found in tissues and excreta of animals were combined, the model provided a fairly good fit to the data under the assumption of nonlinear (saturable) metabolism. Full data are given in Appendix N.

Humans

No absorption, distribution, metabolism, or excretion studies of *p,p′*-dichlorodiphenyl sulfone in humans were found in a review of the literature. However, Ellerichmann *et al.* (1998) reported concentrations of *p,p′*-dichlorodiphenyl sulfone ranging from 1.5 to 39 ng/g lipid in liver samples collected from people who died in accidents or of heart failure.

TOXICITY

Experimental Animals

The acute oral LD_{50} of *p,p′*-dichlorodiphenyl sulfone has been reported as 24 g/kg and from 5 to 10 g/kg in mice (unspecified strains) (Domenjoz, 1946). In rats (unspecified strain), the oral LD_{50} was reported to range from 5 to 20 g/kg. The dermal LD_{50} has been reported as 1 g/kg in mice (unspecified strain) (Sloss Industries, 1988). The toxic effects observed included tremor, hypermotility, and diarrhea.

No clinical findings of toxicity were observed in male Sprague-Dawley rats administered 10, 100, or

1,000 ppm *p,p′*-dichlorodiphenyl sulfone in feed for 4 weeks (equivalent to 0.8, 8.1, and 76 mg/kg per day) (Poon *et al.*, 1999). The 1,000 ppm group had a slightly lower body weight gain (93% of control value) and had lower feed consumption, especially during the first week. A marked exposure concentration-dependent increase in relative liver weights was observed. In the 100 and 1,000 ppm groups, relative liver weights were 30% and 100% greater than that of the controls. In addition, the relative kidney weight was 20% greater in the 1,000 ppm group than in the controls. Serum cholesterol concentrations were increased threefold above the controls in the 1,000 ppm group. A decrease in lactate dehydrogenase activity was observed in the 100 and 1,000 ppm groups. A 30% increase in platelet counts compared to the controls was observed in the 1,000 ppm group. Hepatic lipid peroxidation, as measured by thiobarbituric acid-reactive substances (TBARS), was increased threefold in the 1,000 ppm group, whereas no alteration was observed in the concentration of TBARS in serum. Excretion of ascorbic acid in urine was up to 23 times greater than that of the controls.

A 260% increase in *O*-ethyl-*O*-(*p*-nitrophenyl)-phenylphosphonothionate oxidation in liver homogenates was seen in female rats exposed to 50 ppm *p,p′*-dichlorodiphenyl sulfone and 1 ppm dieldrin in feed compared to female rats exposed to 1 ppm dieldrin alone (Street *et al.*, 1971). Females exposed to both chemicals also exhibited a 60% decrease in the concentration of dieldrin in the adipose tissue compared to rats exposed to dieldrin alone. In addition, a 60% decrease was observed in hexobarbital sleeping time after coexposure when compared to dieldrin alone.

Humans

No epidemiology studies or reports of health effects related to exposure to *p,p′*-dichlorodiphenyl sulfone were found in the literature.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No studies of the reproductive or developmental effects of *p,p′*-dichlorodiphenyl sulfone in experimental animals or in humans were found in a review of the literature.

CARCINOGENICITY

No carcinogenicity studies of *p,p′*-dichlorodiphenyl sulfone in experimental animals or epidemiology studies in humans were found in the literature.

GENETIC TOXICITY

p,p′-Dichlorodiphenyl sulfone was reported to increase the frequency of genetic recombination in cultured V79 cells that carried duplications (tandem or displaced) of the HPRT gene, leading to production of a nonfunctional HGPRT protein (Helleday *et al.*, 1999). A significant increase in the frequency of cells with functional HGPRT protein was observed at the highest concentration (50 µg/mL) tested, but the effect was small (3.4-fold increase), and no response was observed at lower doses. The authors stated that for this tandem duplication to revert to wild type, homologous recombination had to occur. Negative results were obtained in this assay with cells carrying a duplication that required nonhomologous recombination for reversion to the wild-type phenotype. No other published reports on the genotoxicity of *p,p′*-dichlorodiphenyl sulfone were identified.

STUDY RATIONALE

p,p′-Dichlorodiphenyl sulfone, a structural analogue of 1,1′-(2,2,2-trichloroethylidine)bis[4-chlorobenzene] (DDT), was selected by the NTP for toxicity characterization and carcinogenicity evaluation based on its current high production volume and use, prospects for increased use and production in the future, the potential for more widespread human exposure. Fourteen-week and 2-year studies were performed by administering *p,p′*-dichlorodiphenyl sulfone in the diet of male and female F344/N rats and $B6C3F_1$ mice. The genetic toxicity of *p,p′*-dichlorodiphenyl sulfone was assessed in several strains of *Salmonella typhimurium*, in cultured Chinese hamster ovary cells, and in mouse bone marrow.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *p,p′*-DICHLORODIPHENYL SULFONE

p,p′-Dichlorodiphenyl sulfone was obtained in two lots. Lot AX01 was obtained from TCI America (Portland, OR), and lot P02300 was obtained from Lancaster Synthesis, Inc. (Windham, NH). Identity and purity analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) and the study laboratory (Appendix J). Reports on analyses performed in support of the *p,p′*-dichlorodiphenyl sulfone studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a white powder, were identified as *p,p′*-dichlorodiphenyl sulfone by infrared spectroscopy, and lot P02300 was also identified as *p,p′*-dichlorodiphenyl sulfone by ultraviolet/visible and proton and ^{13}C nuclear magnetic resonance spectroscopy. The melting point of approximately 148.3° C for lot P02300 was consistent with published values.

For lot AX01, the manufacturer indicated that the purity was greater than 99%. For lot P02300, the analytical chemistry laboratory determined that the purity was greater than 99% based on gas chromatography results indicating one major peak and two impurities with areas greater than 0.1% of the major peak area. Elemental analyses for carbon, hydrogen, oxygen, sulfur, and chlorine by the study laboratory were in agreement with the theoretical values for *p,p′*-dichlorodiphenyl sulfone. Karl Fischer water analysis indicated less than 0.04% water. HPLC analysis indicated no impurities with areas greater than 0.1% of the major peak area.

Major peak comparisons of a sample of the batch of lot P02300 analyzed by the study laboratory with a sample of the batch analyzed by the analytical chemistry laboratory indicated that the two batches were identical. Gas chromatography detected one volatile impurity with an area of 0.2% relative to the major peak area in each batch. The overall purity of lot P02300 was determined to be greater than 99%.

Stability studies of lot 00918BF of the bulk chemical (not used in these studies) were performed by Radian Corporation (Austin, TX) using gas chromatography. These studies indicated that *p,p′*-dichlorodiphenyl sulfone was stable as a bulk chemical for at least 14 days when stored in sealed vials with Teflon® septa and no headspace at temperatures up to 62° C. To ensure stability, the bulk chemical was stored at room temperature in amber glass bottles. Stability was monitored by the study laboratory throughout the studies using HPLC. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 5 to 9 days (14-week studies) or every 4 weeks (2-year studies) by mixing *p,p′*-dichlorodiphenyl sulfone with feed (Table J2). Formulations were stored in plastic buckets at approximately −20° C for up to 14 days (14-week studies) or at room temperature for up to 52 days (2-year studies). The study laboratory conducted homogeneity studies of the 30 and 3,000 ppm dose formulations (formulated in NIH-07 feed) for the 14-week studies and the 10 and 300 ppm dose formulations (formulated in nonirradiated NTP-2000 feed up to 28 May 1996, irradiated thereafter) for the 2-year studies using HPLC. The study laboratory also conducted stability studies of the 30 ppm dose formulation for the 14-week studies and the 10 ppm dose formulation for the 2-year rat study using HPLC. For the 14-week study dose formulations, homogeneity was confirmed; stability was confirmed for up to 28 days for dose formulations sealed and protected from light at −20° C, for 7 days for dose formulations sealed at room temperature, and for 4 days for dose formulations exposed to air and light. Samples stored under simulated animal room conditions were

stable for 4 days. Because of the change from NIH-07 diet to irradiated NTP-2000 diet, the formulation studies were repeated. Homogeneity results within acceptable limits were achieved by sieving the chemical prior to blending and increasing the sample size for analysis. The stability of the 10 ppm dose formulation for the 2-year study was confirmed for 53 days for formulations stored in amber glass bottles at up to room temperature; after administration analyses of formulations were usually within 10% of the target concentrations, but were often low for the 10 ppm (male rats) and 30 ppm dose formulations and appeared consistent with contamination by the urine and feces.

Periodic analyses of the dose formulations of *p,p′*-dichlorodiphenyl sulfone were conducted by the study laboratory using HPLC. The dose formulations were analyzed three times during the 14-week studies (Table J3). Of the 13 dose formulations analyzed, 12 were within 10% of the target concentrations. Animal room samples were also analyzed; 6 of 8 for rats and 15 of 21 for mice were within 10% of the target concentrations. During the 2-year studies, the dose formulations were analyzed approximately every 7 to 12 weeks (Table J4). All but one of the 63 dose formulations used were within 10% of the target concentrations. One dose formulation mixed on 5 February 1996 that was 113% of the 30 ppm target concentration was used because there was not enough feed available to formulate a remix. Of the animal room samples analyzed, 17 of 22 for rats and 5 of 18 for mice were within 10% of the target concentrations.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to *p,p′*-dichlorodiphenyl sulfone and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were approximately 6 weeks old. Animals were quarantined for 11 to 15 days and were approximately 8 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. All tests for viral titers in sera from rats and mice were negative.

Groups of 10 male and 10 female rats and mice were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm *p,p′*-dichlorodiphenyl sulfone for 14 weeks. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage, and male mice were housed individually. Clinical findings were recorded and animals were weighed at study initiation, weekly, and at the end of the studies. Feed consumption was recorded weekly. Details of the study design and animal maintenance are summarized in Table 1.

Neurobehavioral evaluations were conducted during week 12 on groups of male and female rats and male mice exposed to 0, 100, 300, or 1,000 ppm and groups of female mice exposed to 0, 300, 1,000, or 3,000 ppm. Body weight was recorded, and functional measurements to assess autonomic, convulsive, excitability, neuromuscular, sensorimotor, and general motor activity domains were taken according to the procedures described by Moser *et al*. (1997).

At the end of the 14-week studies, blood was collected from the retroorbital sinus of all animals under carbon dioxide anesthesia. Blood was collected for hematology and clinical chemistry analyses for rats and hematology analyses for mice. Blood samples for hematology analyses were placed into microcollection tubes containing potassium EDTA (Sarstedt, Inc., Nümbrecht, Germany). Erythrocyte, platelet, and leukocyte counts, hematocrit values, hemoglobin concentration, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using a System 9000® hematology analyzer (Serono-Baker Diagnostics, Allentown, PA). Differential leukocyte counts and erythrocyte morphology were determined microscopically from blood smears stained with a modified Wright-Giemsa stain on a Hema-Tek® slide stainer (Miles Laboratory, Ames Division, Elkhart, IN). A Miller disc was used to determine reticulocyte counts from smears prepared with blood stained with new methylene blue. For clinical chemistry analyses, blood samples from rats were placed into microcollection serum separator tubes (Sarstedt, Inc.), centrifuged, and the serum samples were analyzed using a Hitachi 704® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) with

commercially available reagents. The hematology and clinical chemistry parameters measured are listed in Table 1.

Complete necropsies were performed on all animals. The heart, right kidney, liver, ovary, right testis, thymus, and uterus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all 0 and 3,000 ppm rats and mice. In addition, target tissues were examined in animals in all groups. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were fed diets containing 0, 10 (male rats only), 30, 100, or 300 (except for male rats) ppm *p,p′*-dichlorodiphenyl sulfone for 105 to 106 weeks. Additional groups of 10 male and 10 female rats and mice were fed the same *p,p′*-dichlorodiphenyl sulfone-containing diets (no controls) for up to 18 months and bled for plasma determinations of *p,p′*-dichlorodiphenyl sulfone at approximately 2 weeks and 3, 12, and 18 (rats only) months.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 11 to 15 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Rats were housed two or three (males) or five (females) per cage and mice were housed one (males) or five (females) per cage. Feed and water were available *ad libitum*. Feed consumption of core study animals was measured every 4 weeks by cage. Cages were changed twice weekly (rats and female mice) or once weekly (male mice); racks were changed and rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix L.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights of core study animals were recorded at the beginning of the studies, and clinical findings and body weights of core study animals were subsequently recorded at weeks 1, 2, every 4 weeks, and at the end of the studies.

Blood samples were collected from the retroorbital sinus of special study rats or by cardiac puncture from special study mice at approximately 2 weeks and 3, 12, and 18 (rats only) months for determination of plasma concentrations of *p,p′*-dichlorodiphenyl sulfone. Body weights were recorded for these animals prior to each blood collection. Blood was collected at three time points in rats and one time point in mice, and three animals/gender per group were generally sampled at each time point. Rats were discarded after the final sampling at 18 months; mice were used only once and then discarded. Blood was collected in tubes containing EDTA as an anticoagulant; plasma was prepared by centrifugation and stored at approximately −20° C until analysis. Additional details concerning these studies are presented in Table 1.

Complete necropsies and microscopic examinations were performed on all core study rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were eval-uated by an independent quality assessment laboratory. The individual animal records and tables

were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs including the liver in male and female rats and mice, and the uterus of female mice. In addition, the following organs/tissues were reviewed for specific lesions including the pituitary gland of male and female rats; the lung of male rats; the adrenal gland, mammary gland, spleen, thyroid gland, and uterus of female rats; the spleen of male and female mice; the lung, adrenal gland, oral mucosa, and preputial gland of male mice; and the kidney and pituitary gland of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

14-Week Studies	2-Year Studies
Study Laboratory Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$
Animal Source Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies Rats: 14 (males) or 15 (females) days Mice: 11 (males) or 12 (females) days	Rats: 11 (males) or 12 (females) days Mice: 14 (males) or 15 (females) days
Average Age When Studies Began 8 to 9 weeks	6 weeks
Date of First Exposure Rats: 28 (males) or 29 (females) January 1993 Mice: 25 (males) or 26 (females) January 1993	Rats: 18 (males) or 19 (females) December 1995 Mice: 4 (males) or 5 (females) January1996
Duration of Exposure 14 weeks	Rats: 105 weeks Mice: 105 to 106 weeks
Date of Last Exposure Rats: 29 (males) or 30 (females) April 1993 Mice: 26 (males) or 27 (females) April 1993	Rats: 15-16 (males) or 17-19 (females) December 1997 Mice: 5-7 (males) or 7-9 (females) January 1998
Necropsy Dates Rats: 29 (males) or 30 (females) April 1993 Mice: 26 (males) or 27 (females) April 1993	Rats: 15-16 (males) or 17-19 (females) December 1997 Mice: 5-7 (males) or 7-9 (females) January 1998
Average Age at Necropsy 22 weeks	110 to 111 weeks
Size of Study Groups 10 males and 10 females	50 males and 50 females
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 14-week studies
Animals per Cage Rats: 5 Mice: 1 (male) or 5 (females)	Rats: 2 or 3 (males) or 5 (females) Mice: 1 (male) or 5 (females)
Method of Animal Identification Tail tattoo	Tail tattoo
Diet NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	NTP-2000 meal feed (Zeigler Brothers, Inc., Gardners, PA; nonirradiated up to 28 May 1996, irradiated thereafter), available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

14-Week Studies	2-Year Studies
Water Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 14-week studies
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ) changed twice weekly	Polycarbonate (Lab Products, Inc., Maywood, NJ) changed twice weekly (rats and female mice) or once weekly (male mice)
Bedding Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ) changed at least twice weekly	Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ) changed twice weekly (rats and female mice) or once weekly (male mice)
Cage Filters Dupont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH) changed every 2 weeks	Same as 14-week studies
Racks Stainless steel (Lab Products, Inc., Maywood, NJ) changed and rotated every 2 weeks	Same as 14-week studies
Animal Room Environment Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations 0, 30, 100, 300, 1,000, or 3,000 ppm in feed, available *ad libitum*	Rats: 0, 10 (males), 30, 100, or 300 (females) ppm in feed, available *ad libitum* Mice: 0, 30, 100, or 300 ppm in feed, available *ad libitum*
Type and Frequency of Observation Observed twice daily; clinical findings were recorded and animals were weighed at study initiation, weekly, and at the end of the studies. Feed consumption was recorded weekly.	Observed twice daily; core study animals were weighed at the beginning of the studies, and body weights and clinical findings were subsequently recorded at weeks 1, 2, every 4 weeks, and at the end of the studies. Feed consumption (by cage, core study animals only) was determined over a 7-day period and recorded every 4 weeks, starting during the first week. Special study animals were weighed prior to blood collection at 2 weeks and 3, 12, and 18 months (rats only).
Method of Sacrifice Carbon dioxide asphyxiation	Same as 14-week studies
Necropsy Necropsy was performed on all animals. Organs weighed were heart, right kidney, liver, ovary, right testis, thymus, and uterus.	Necropsy was performed on core study rats and mice.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

14-Week Studies	2-Year Studies
Clinical Pathology Blood was collected from the retroorbital sinus of all rats and mice surviving to the end of the study for hematology and clinical chemistry (rats) determinations. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile salts	None
Histopathology Complete histopathology was performed on all 0 and 3,000 ppm rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, blood vessel, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland with adjacent skin, skeletal muscle (rats only), nose, ovary, pancreas, pancreatic islets, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the liver and kidney of rats and the liver of mice were examined in all groups.	Complete histopathology was performed on all core study animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, blood vessel, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland with adjacent skin (except male mice), nose, oral mucosa (male mice only), ovary, pancreas, pancreatic islets, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.
Neurobehavioral Studies Neurobehavioral evaluations were conducted during week 12 on all male and female rats and male mice exposed to 0, 100, 300, or 1,000 ppm and female mice exposed to 0, 300, 1,000, or 3,000 ppm. In addition to measurement of body weight, functional observational measurements of each animal to assess autonomic, convulsive, excitability, neuromuscular, sensorimotor, and general motor activity domains.	None
Determinations of *p,p′*-Dichlorodiphenyl Sulfone in Plasma None	Blood was collected from special study animals for determinations of plasma concentrations of *p,p′*-dichlorodiphenyl sulfone at approximately 2 weeks and 3, 12, and 18 (rats only) months. Samples were collected from the retroorbital sinus of three male and three female rats exposed to 10 (males), 30, 100, or 300 (females) ppm and via cardiac puncture from three male and three female mice exposed to 30, 100, or 300 ppm *p,p′*-dichlorodiphenyl sulfone. Blood was collected from rats at 0900, 1200, and 1500 hours and from mice at 0900 hours. Generally, three animals/gender per dose group were sampled at each time point.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B4, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions are presented as 1−P with the letter N added (e.g., P=0.99 is presented as P=0.01N). For neoplasms and nonneoplastic lesions detected in the 14-week studies, the Fisher exact test (Gart *et al.*, 1979), a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971,

1972). Hematology, clinical chemistry, neurobehavioral, and plasma concentration data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. Until recently, the NTP historical control database consisted of animals fed NIH-07 diet. In 1995, the NTP changed the diet fed to animals used in toxicity and carcinogenesis studies conducted by the NTP. This new diet (NTP-2000) contains less protein and more fiber and fat than the NIH-07 diet previously used (Rao, 1996, 1997). This dietary change was instituted primarily to increase longevity and decrease the incidence and/or severity of some spontaneous neoplastic and nonneoplastic lesions in the rats and mice used in NTP studies. This study of *p,p′*-dichlorodiphenyl sulfone is one of the first in which the animals on study were fed the NTP-2000 diet. Because the incidence of some neoplastic and nonneoplastic lesions are affected by the dietary change, use of the existing historical control database (NIH-07) diet is not appropriate for all neoplasm types.

Currently, the number of studies in which the NTP-2000 diet was used is limited. This diet was used in four studies (indium phosphide, sodium nitrite, *p,p′*-dichlorophenyl sulfone, and naphthalene) reported at the May 18, 2000, peer review and for two others (methacrylonitrile and *p*-nitrotoluene) reported 3 May 2001. Therefore, a database of incidences of neoplastic lesions was created for this group of six studies. Four routes of administration were used in these six studies: *p*-nitrotoluene and *p,p′*-dichlorophenyl sulfone were administered by dosed feed; sodium nitrite was administered in the drinking water; methacrylonitrile was administered by gavage using deionized water; and naphthalene and indium phosphide were administered via whole body inhalation. Based on the extensive NTP historical database using the NIH-07 diet, incidences of the vast majority of spontaneous neoplasms are not significantly different between control groups irrespective of the route of administration. There is no reason to expect this to be different with the NTP-2000 diet. Clearly, control animals from dosed feed and dosed water studies are treated no differently and no differences in incidence of neoplasms are expected. There are some exceptions, and if comparisons are necessary for these neoplasm types, only studies with similar routes of administration will be used.

The set of six studies using the NTP-2000 diet will be the primary historical control group used for comparison. However, where appropriate, the larger historical database (NIH-07 diet) may be used to augment the smaller NTP-2000 database.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of *p,p′*-dichlorodiphenyl sulfone was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and micronucleated erythrocytes in mouse bone marrow. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of *p,p′*-dichlorodiphenyl sulfone are part of a larger effort by the NTP to develop a comprehensive database that would permit a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). These short-term genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by Miller and Miller (1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens.

For mutagenic carcinogens, the combination of DNA reactivity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in multiple species and genders of rodents and at multiple tissue sites (Ashby and Tennant, 1991). Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no complementarity among the *in vitro* genetic toxicity tests (Tennant *et al*., 1987; Zeiger *et al*., 1990). That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. Although other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity compared with the *Salmonella* test, these other tests can provide useful information on the types of DNA and chromosomal effects induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in the acute *in vivo* bone marrow chromosome aberration test or micronucleus test appears to be less than that in the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests are associated with high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

14-WEEK STUDY

All rats survived to the end of the study (Table 2). Final mean body weights and body weight gains of rats exposed to 300 ppm or greater were significantly less than those of the controls. During the first week of the study, feed consumption by male and female rats exposed to 3,000 ppm was 23% and 39% less than that by the controls, respectively. However, feed consumption by all exposed groups was generally similar to that by the controls at week 13. Dietary concen-trations of 30, 100, 300, 1,000, and 3,000 ppm *p,p′*-dichlorodiphenyl sulfone resulted in average daily doses of approximately 2, 6, 19, 65, and 200 mg/kg to males and females. There were no exposure-related clinical findings.

TABLE 2
Survival, Body Weights, and Feed Consumption of Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	188 ± 2	369 ± 4	181 ± 3		17.2	20.6
30	10/10	190 ± 2	378 ± 7	188 ± 6	102	16.5	17.2
100	10/10	192 ± 1	366 ± 4	175 ± 4	99	17.1	18.3
300	10/10	191 ± 2	350 ± 4*	159 ± 3**	95	16.2	20.1
1,000	10/10	191 ± 2	340 ± 6**	150 ± 6**	92	15.5	19.4
3,000	10/10	190 ± 2	304 ± 8**	115 ± 7**	82	13.3	18.1
Female							
0	10/10	134 ± 1	204 ± 2	70 ± 2		11.7	12.0
30	10/10	133 ± 1	201 ± 2	68 ± 2	99	10.8	11.1
100	10/10	134 ± 1	200 ± 2	66 ± 2	98	10.8	11.0
300	10/10	134 ± 1	196 ± 3*	62 ± 3*	96	10.7	10.6
1,000	10/10	133 ± 1	185 ± 2**	51 ± 3**	91	9.0	10.2
3,000	10/10	134 ± 1	174 ± 3**	39 ± 3**	85	7.1	10.2

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** ($P \leq 0.01$)
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

Rats were examined for neurological effects using a functional observation screening battery of tests. This battery included tests to assess several aspects of neurologic function including autonomic, convulsive, excitability, neuromuscular, sensorimotor, and general motor activity domains. Exposure-related effects were not observed in any of these domains in any of the exposed groups of rats. Evaluation of individual tests within each domain showed a statistically significant decrease in landing hindlimb footsplay of the 1,000 ppm male rats; a similar effect was not evident in female rats (Table F1). No alterations were seen in other tests of neuromuscular functioning such as limb grip strength, gait, motor activity, or pain response. A 15% decrement in mean body weight gain was seen in 1,000 ppm male rats, and this may have influenced the growth and development of the hindlimbs over the 12-week exposure period from 45 days of age to 129 days of age. Because landing footsplay is dependent upon the size of the animal and no exposure-related effects were seen with any other measures of neuromuscular function, this isolated effect in males was not considered to be an adverse neurotoxic effect.

The hematology and clinical chemistry data for rats are presented in Table G1. There was evidence of a minimal treatment-related effect on the erythron. Alteration of the erythron was demonstrated by minimal decreases in the hemoglobin concentrations in the 1,000 and 3,000 ppm male and female rats; erythrocyte counts were minimally decreased in the 1,000 ppm male group.

Additional evidence suggesting a treatment-related erythropoietic effect was demonstrated by decreases in mean cell volume (1,000 and 3,000 ppm females) and mean cell hemoglobin and mean cell hemoglobin concentration (300 and 1,000 ppm females and 3,000 ppm males and females). Also, reticulocyte counts were minimally increased in 3,000 ppm males. A minimal to mild increase in platelet counts occurred in the 1,000 and 3,000 ppm males and females.

The clinical chemistry data demonstrated increased albumin and total protein concentrations in groups exposed to 300 ppm or greater. Alkaline phosphatase activity decreased in an exposure-related manner. There was evidence of a hepatocellular effect demonstrated by increased sorbitol dehydrogenase activity in the 3,000 ppm groups. Alanine amino-transferase activity, another marker of hepatocellular health, was not affected similarly and, in fact, demonstrated decreased activity in the lower exposed groups. Bile acid concentrations were increased in 3,000 ppm males and would support the possibility of a hepatic effect. Minimal increases in urea nitrogen and creatinine concentrations occurred in the 3,000 ppm male and female rats.

Liver weights of male and female rats exposed to 100 ppm or greater were significantly increased compared to the controls (Tables 3 and H1). Kidney and testis weights of 1,000 and 3,000 ppm male rats were also significantly greater than those of the controls. The thymus weights of male rats exposed to 300 ppm or greater were significantly less when compared to controls.

TABLE 3
Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	391 ± 4	387 ± 8	381 ± 5	366 ± 4**	353 ± 6**	313 ± 8**
R. Kidney						
Absolute	1.378 ± 0.028	1.368 ± 0.041	1.424 ± 0.028	1.427 ± 0.035	1.630 ± 0.039**	1.560 ± 0.030**
Relative	0.352 ± 0.005	0.353 ± 0.005	0.374 ± 0.006*	0.389 ± 0.007**	0.462 ± 0.007**	0.500 ± 0.005**
Liver						
Absolute	15.494 ± 0.370	15.596 ± 0.504	18.156 ± 0.478**	20.093 ± 0.362**	24.983 ± 0.599**	26.405 ± 0.458**
Relative	3.960 ± 0.081	4.029 ± 0.070	4.768 ± 0.119**	5.481 ± 0.063**	7.082 ± 0.093**	8.471 ± 0.159**
R. Testis						
Absolute	1.486 ± 0.016	1.484 ± 0.036	1.514 ± 0.022	1.499 ± 0.013	1.565 ± 0.010*	1.537 ± 0.021*
Relative	0.380 ± 0.005	0.384 ± 0.006	0.398 ± 0.008	0.410 ± 0.005**	0.445 ± 0.009**	0.494 ± 0.011**
Thymus						
Absolute	0.345 ± 0.020	0.302 ± 0.016	0.310 ± 0.018	0.275 ± 0.011**	0.247 ± 0.012**	0.226 ± 0.015**
Relative	0.088 ± 0.005	0.078 ± 0.003	0.081 ± 0.005	0.075 ± 0.003*	0.070 ± 0.003**	0.072 ± 0.004**
Female						
Necropsy body wt	213 ± 3	206 ± 2*	206 ± 2*	201 ± 3**	189 ± 2**	177 ± 3**
Liver						
Absolute	7.520 ± 0.168	7.650 ± 0.142	8.186 ± 0.101*	9.293 ± 0.256**	12.229 ± 0.274**	14.670 ± 0.241**
Relative	3.526 ± 0.042	3.719 ± 0.057	3.968 ± 0.036**	4.609 ± 0.078**	6.471 ± 0.118**	8.316 ± 0.147**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

No exposure-related gross lesions were observed. Incidences of centrilobular hepatocyte hypertrophy in male rats exposed to 100 ppm or greater and in female rats exposed to 300 ppm or greater were significantly increased compared to the controls (Table 4). Hypertrophy consisted of minimal to mild increases in the size of hepatocytes surrounding the central veins and was more readily apparent in exposed males than females. The severity of hypertrophy was minimal in 100 ppm males and 300 ppm females and mild in 300, 1,000, and 3,000 ppm males and in 1,000 and 3,000 ppm females. Both cytomegaly and karyomegaly (nuclear enlargement) were evident. Affected hepatocytes had a lightly stained, ground-glass appearance due to numerous intracytoplasmic, small, clear vacuoles. There were significant increases in the incidences of nephropathy in 1,000 and 3,000 ppm female rats. Nephropathy was mild in 300 ppm males, moderate in 1,000 ppm males, and marked in 3,000 ppm males. All lesions in females were of minimal severity.

Nephropathy was characterized by foci of regenerating renal tubules with associated peritubular fibrosis and mononuclear inflammatory cell infiltration into the adjacent interstitium. Minimal nephropathy consisted of a few scattered foci of regenerating tubules with minimal interstitial fibrosis and inflammatory cell infiltrate. Rare tubules contained a small amount of protein. Mild nephropathy consisted of scattered foci

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
Male						
Liver[a]	10	10	10	10	10	10
Centrilobular Hypertrophy[b]	0	0	7** (1.1)[c]	10** (2.0)	10** (2.0)	10** (2.0)
Kidney	10	10	10	10	10	10
Nephropathy	9 (1.0)	10 (1.0)	10 (1.0)	10 (1.8)	10 (2.9)	10 (3.8)
Female						
Liver	10	10	10	10	10	10
Centrilobular Hypertrophy	0	0	0	10** (1.0)	10** (1.9)	10** (1.9)
Kidney	10	10	10	10	10	10
Nephropathy	0	0	1 (1.0)	2 (1.0)	5* (1.0)	10** (1.2)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

of regenerating tubules with minimal interstitial fibrosis and inflammatory cell infiltrate and increased numbers of tubules distended with protein. Moderate nephropathy consisted of frequent foci of regenerating tubules with minimal to mild interstitial fibrosis and inflammatory cell infiltrate. Many prominent tubules were distended with protein. Marked nephropathy consisted of numerous foci of regenerating tubules with mild interstitial fibrosis and inflammatory cell infiltrate.

Exposure Concentration Selection Rationale: Based on lower final mean body weights, organ weight changes, and increased incidences and/or severities of centrilobular hypertrophy in the liver and renal nephropathy at the higher dietary concentration in the 14-week studies, *p,p′*-dichlorodiphenyl sulfone exposure concentrations selected for the 2-year feed study in rats were 10, 30, and 100 ppm for males, and 30, 100, and 300 ppm for females.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 1). Survival of all exposed groups of male and female rats was similar to that of the control groups.

TABLE 5
Survival of Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	19	16	24	15
Natural eaths	7	4	6	7
Animals surviving to study termination	24	30	20	28
Percent probability of survival at end of study[a]	48	60	40	56
Mean survival (days)[b]	659	688	667	683
Survival analysis[c]	P=0.742N	P=0.252N	P=0.649	P=0.516N

	0 ppm	30 ppm	100 ppm	300 ppm
Female				
Animals initially in study	50	50	50	50
Moribund	11	9	12	5
Natural deaths	3	3	3	10
Animals surviving to study termination	36	38	35[d]	35
Percent probability of survival at end of study	72	76	70	70
Mean survival (days)	695	697	705	679
Survival analysis	P=0.646	P=0.809N	P=1.000	P=0.894

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.
[d] Includes one animal that died during the last week of the study

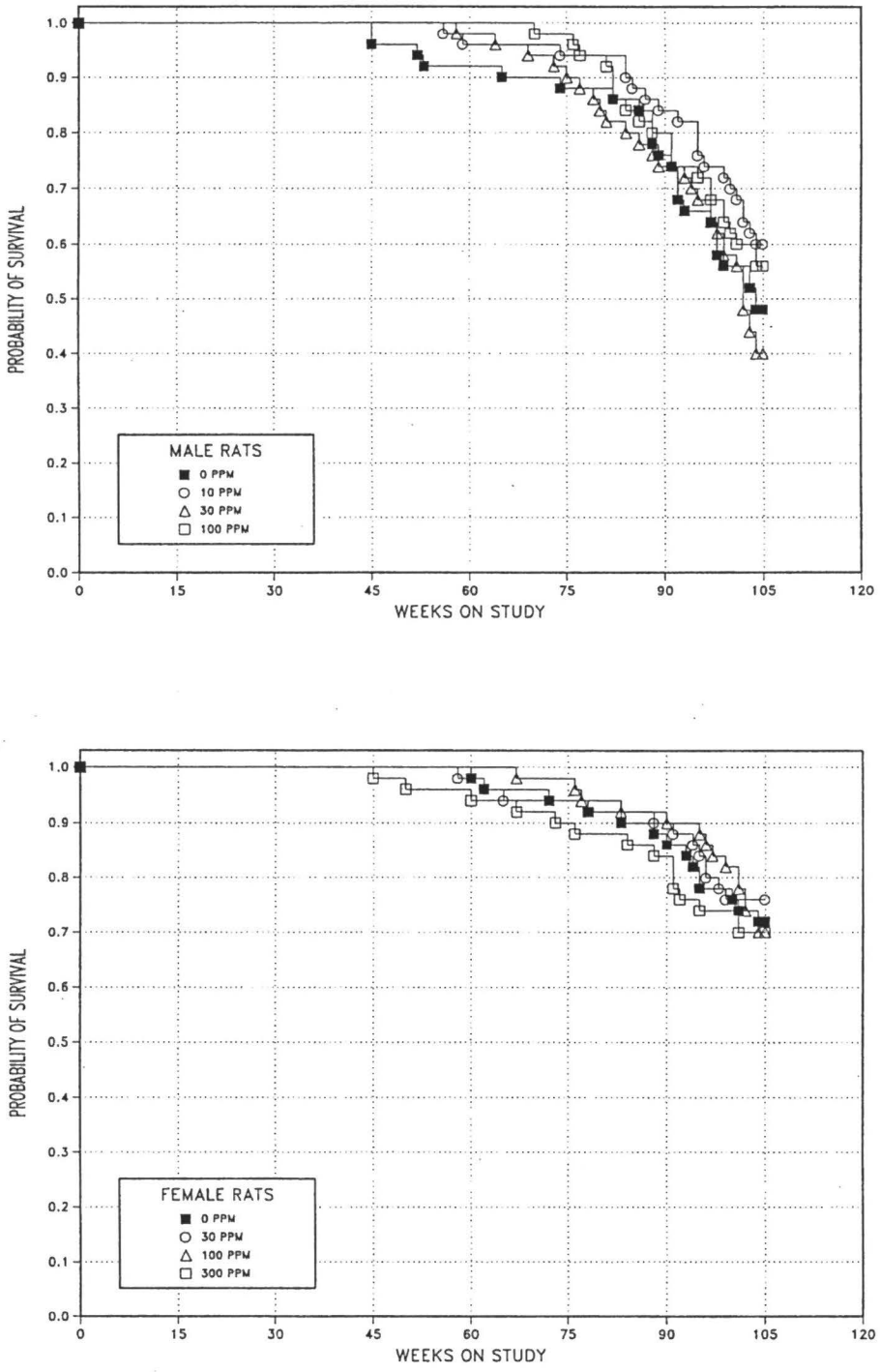


Figure 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to *p,p′*-Dichlorodiphenyl Sulfone in Feed for 2 Years

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 30 and 100 ppm male rats were generally less than those of the controls from week 66 through the end of the study; mean body weights of 300 ppm female rats were less than those of the controls from week 18 (Tables 6 and 7 and Figure 2); mean body weights of females exposed to 100 ppm were also less after week 30. Feed consumption by the exposed groups was similar to that by the controls throughout the study (Tables K1 and K2). Dietary concentrations of 10, 30, and 100 ppm resulted in average daily doses of approximately 0.5, 1.5, and 5.0 mg *p,p′*-dichlorodiphenyl sulfone/kg body weight to males. Dietary concentrations of 30, 100, and 300 ppm resulted in average daily doses of approximately 1.6, 5.4, and 17 mg/kg to females. There were no clinical findings attributed to *p,p′*-dichlorodiphenyl sulfone exposure.

Determinations of p,p′-Dichlorodiphenyl Sulfone in Plasma

Plasma concentrations of *p,p′*-dichlorodiphenyl sulfone were similar at the common exposure concentrations in male and female rats at 2 weeks and 3 months (Table I1). At 12 months and 18 months, however, plasma *p,p′*-dichlorodiphenyl sulfone concentrations were slightly higher in females than in males at the common dosing concentrations. Overall, samples at all time points showed a correlation between exposure concentration and plasma *p,p′*-dichlorodiphenyl sulfone concentration.

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

Weeks on Study	0 ppm		10 ppm			30 ppm			100 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	103	50	103	99	50	102	99	50	103	99	50
2	152	50	148	98	50	147	97	50	150	99	50
6	268	50	257	96	50	256	96	50	260	97	50
10	325	50	318	98	50	313	96	50	316	97	50
14	365	50	357	98	50	354	97	50	354	97	50
18	397	50	385	97	50	383	97	50	387	98	50
22	414	50	407	98	50	400	96	50	398	96	50
26	432	50	424	98	50	415	96	50	412	95	50
30	443	50	433	98	50	427	96	50	427	96	50
34	452	50	445	98	50	439	97	50	433	96	50
38	458	50	451	99	50	442	97	50	440	96	50
42	468	50	460	98	50	452	97	50	455	97	50
46	474	48	466	98	50	454	96	50	453	96	50
50	476	48	469	98	50	461	97	50	458	96	50
54	482	46	473	98	50	466	97	50	461	96	50
58	482	46	474	98	49	464	96	49	459	95	50
62	483	46	476	99	48	467	97	49	461	95	50
66	487	45	473	97	48	465	96	48	455	94	50
70	488	45	477	98	48	469	96	47	456	94	50
74	492	44	473	96	48	467	95	46	459	93	49
78	497	44	483	97	47	471	95	44	461	93	47
82	486	44	478	99	47	468	97	41	461	95	46
86	485	43	475	98	44	459	95	40	452	93	42
89	482	38	471	98	42	458	95	37	448	93	40
94	476	33	462	97	41	446	94	36	442	93	37
98	462	32	462	100	37	444	96	32	440	95	34
102	465	28	451	97	34	425	92	28	434	93	30
Mean for weeks											
1-13	212		207	98		205	97		207	98	
14-52	438		430	98		423	97		422	96	
53-102	482		471	98		459	95		453	94	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

Weeks on Study	0 ppm		30 ppm			100 ppm			300 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	93	50	93	100	50	94	101	50	93	100	50
2	119	50	118	99	50	118	99	50	118	99	50
6	169	50	164	97	50	165	98	50	160	95	50
10	189	50	184	97	50	186	98	50	179	95	50
14	199	50	194	98	50	196	98	50	188	95	50
18	211	50	204	97	50	205	97	50	197	93	50
22	219	50	211	96	50	211	96	50	203	93	50
26	222	50	217	98	50	216	97	50	207	93	50
30	232	50	223	96	50	222	95	50	210	90	50
34	236	50	228	97	50	222	94	50	213	91	50
38	242	50	233	96	50	228	94	50	218	90	50
42	248	50	238	96	50	232	94	50	221	89	50
46	257	50	244	95	50	239	93	50	226	88	49
50	264	50	253	96	50	247	93	50	231	88	49
54	271	50	259	96	50	252	93	50	236	87	48
58	278	50	269	97	50	260	94	50	242	87	48
62	287	49	279	97	49	270	94	50	252	88	47
66	295	48	285	96	47	276	93	50	257	87	47
70	300	48	293	98	47	281	94	49	262	87	46
74	310	47	299	97	47	287	92	49	267	86	45
78	321	47	310	97	47	299	93	47	279	87	44
82	321	46	312	97	46	296	92	47	277	86	44
86	321	45	312	97	46	298	93	46	281	88	43
90	313	44	310	99	45	295	94	46	280	89	42
94	321	42	310	97	44	300	94	45	286	89	38
98	325	39	318	98	39	306	94	42	289	89	37
102	331	37	317	96	38	305	92	39	288	87	35
Mean for weeks											
1-13	143		140	98		141	99		138	97	
14-52	233		225	97		222	95		211	91	
53-102	307		298	97		287	93		269	88	

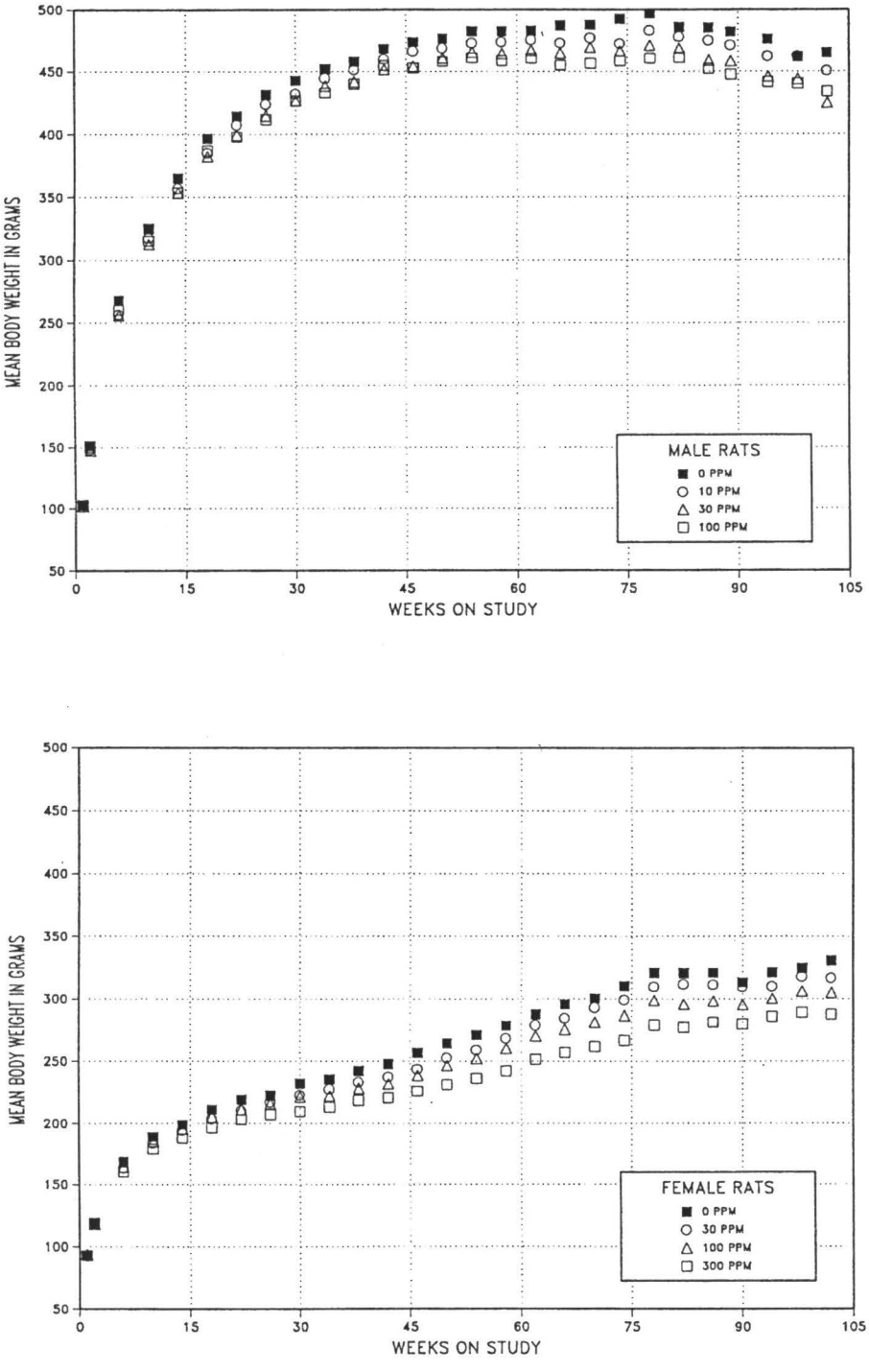


Figure 2
Growth Curves for Male and Female Rats
Exposed to *p,p′*-Dichlorodiphenyl Sulfone in Feed for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant mesothelioma and neoplasms and/or nonneoplastic lesions of the liver and pituitary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats.

Liver: The incidences of several nonneoplastic lesions of the liver in exposed groups were significantly increased compared to those in the controls (Tables 8, A4, and B4). The incidences of centrilobular hepatocyte hypertrophy were increased in 100 ppm males and 100 and 300 ppm females. The incidences of bile duct hyperplasia and centrilobular degeneration were significantly increased in 100 and 300 ppm females.

TABLE 8
Incidences of Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm		10 ppm		30 ppm		100 ppm	
Male								
Number Examined Microscopically	50		50		50		50	
Centrilobular, Hypertrophy[a]	0		1	(1.0)[b]	3	(1.0)	16**	(1.3)
Bile Duct, Hyperplasia	46	(1.7)	47	(1.5)	44	(1.8)	48	(1.9)
Centrilobular, Degeneration	18	(2.0)	15	(2.1)	20	(2.1)	23	(2.2)
	0 ppm		**30 ppm**		**100 ppm**		**300 ppm**	
Female								
Number Examined Microscopically	50		50		50		50	
Centrilobular, Hypertrophy	0		2	(1.5)	24**	(1.3)	38**	(1.7)
Bile Duct, Hyperplasia	5	(1.4)	12	(1.1)	21**	(1.0)	32**	(1.0)
Centrilobular, Degeneration	1	(1.0)	5	(2.0)	10**	(2.2)	7*	(1.7)

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Hepatocyte hypertrophy was a minimal to mild change characterized by increased size of the centrilobular hepatocytes compared to those of the concurrent controls and to the affected animal's midzonal or periportal hepatocytes (Plates 1 and 2). Hypertrophic hepatocytes also had decreased staining intensity due to fine cytoplasmic vacuolization accompanied by eosinophilic or basophilic stippling. Bile duct hyperplasia was of minimal to mild severity and consisted of increased bile duct profiles within the portal areas. Centrilobular degeneration was a minimal to mild change observed only in those animals that had mononuclear cell leukemia in the liver and was most likely a manifestation of anoxia due to large numbers of mononuclear leukemic cells infiltrating the centrilobular sinusoids.

Malignant Mesothelioma: Incidences of malignant mesothelioma in 30 and 100 ppm male rats were slightly increased (0 ppm, 2/50; 10 ppm, 2/50; 30 ppm, 5/50; 100 ppm, 6/50; Table A3). Although not significantly greater than the control incidence, the incidence of malignant mesothelioma in the 100 ppm group exceeded the historical range in controls given NTP-2000 diet [12/299 (4.0% ± 3.8%; range, 0% - 10%)]; the incidences in the 30 and 100 ppm groups exceeded the historical range for feed controls given NIH-07 diet [25/1,004 (2.5% ± 2.0%); range, 0% - 8%]. While the incidences of malignant mesothelioma in this study exceeded the historical ranges for feed studies, as many as six (12%) malignant mesotheliomas have been reported in the control groups of two dermal studies that used rats fed NIH-07 diet. Because of this finding and the fact that the increased incidences were not significant, mesotheliomas were not considered to be related to exposure. Microscopically, the mesotheliomas that were observed in the exposed rats were similar to those seen in the controls from the present and previous 2-year studies. They originated from the tunica vaginalis covering the testes and the epididymis, and they occurred as variably sized, multifocal to coalescing, exophytic nodular, papillary and expansive masses on the surface of the testes and epididymis. Most mesotheliomas were polypoid masses consisting of complex papillary to frond-like structures with a dense fibrovascular core covered by one to several layers of flattened to cuboidal or polygonal cells. The fibrovascular component varied from scant to abundant among the masses. Some masses had solid areas composed of poorly defined tubular structures and clusters of polygonal cells surrounded by stroma. Other mesotheliomas consisted of sheets of haphazardly arranged spindyloid cells with very little stroma.

Pituitary Gland: The incidences of pituitary gland pars distalis adenoma in 30 and 300 ppm female rats were significantly less than that in the controls (0 ppm, 23/50; 30 ppm, 13/49; 100 ppm, 17/50; 300 ppm, 8/50; Table B3). The incidence of adenoma in 300 ppm females was below the historical ranges for this neoplasm in controls given NTP-2000 diet [127/299 (42.5% ± 13.2%); range, 24%-60%], and in untreated feed controls given NIH-07 diet [478/992 (48.1% ± 12.2%); range, 31%-72%]. However, while the incidence of adenoma in the 30 ppm group was within the historical range for controls given NTP-2000 diet, it was below the historical range for controls given NIH-07 diet. Additional information does not support these decreases being exposure related. Pituitary gland pars distalis hyperplasia is generally considered a preneoplastic change; the incidences of this lesion were similar in control and exposed female rats (23/50, 28/49, 23/50, 24/50; Table B4). Because the incidences of adenoma were not clearly related to exposure concentration and the incidences of hyperplasia in exposed female rats were not decreased compared to the controls, it is uncertain if the decreases in pituitary gland pars distalis adenoma in the 30 and 300 ppm groups were related to *p,p′*-dichlorodiphenyl sulfone exposure.

MICE

14-WEEK STUDY

All mice survived to the end of the study (Table 9). Final mean body weights and body weight gains of groups of mice exposed to 300 ppm or greater were significantly less than those of the controls. During the first week of the study, feed consumption by male and female mice exposed to 3,000 ppm was 47% and 52% less than that by the controls, respectively. However, feed consumption by all exposed groups was generally similar to that by the controls at week 13. Dietary concentrations of 30, 100, 300, 1,000, and 3,000 ppm *p,p′*-dichlorodiphenyl sulfone resulted in average daily doses of approximately 3.5, 15, 50, 165, and 480 mg/kg to males and females. There were no exposure-related clinical findings.

TABLE 9
Survival, Body Weights, and Feed Consumption of Mice in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	23.8 ± 0.3	33.7 ± 0.5	9.9 ± 0.5		4.7	4.3
30	10/10	24.1 ± 0.3	36.0 ± 0.5	11.9 ± 0.5	107	4.0	4.5
100	10/10	23.8 ± 0.3	33.5 ± 0.8	9.7 ± 0.6	99	4.0	4.2
300	10/10	23.7 ± 0.3	30.9 ± 0.4**	7.2 ± 0.3**	92	3.5	4.1
1,000	10/10	24.0 ± 0.3	28.9 ± 0.4**	4.8 ± 0.3**	86	3.3	4.4
3,000	10/10	24.1 ± 0.3	28.5 ± 0.3**	4.4 ± 0.2**	85	2.5	4.5
Female							
0	10/10	20.2 ± 0.2	27.7 ± 0.7	7.5 ± 0.5		4.8	3.7
30	10/10	19.7 ± 0.2	29.3 ± 0.8	9.6 ± 0.7	106	4.3	4.4
100	10/10	20.1 ± 0.4	28.5 ± 0.6	8.4 ± 0.5	103	4.5	3.9
300	10/10	19.9 ± 0.2	25.3 ± 0.4**	5.4 ± 0.4**	91	3.4	4.2
1,000	10/10	19.4 ± 0.2	24.1 ± 0.5**	4.8 ± 0.3**	87	3.4	4.1
3,000	10/10	19.9 ± 0.2	23.9 ± 0.2**	4.0 ± 0.3**	86	2.3	3.9

** Significantly different ($P \leq 0.01$) from the control group by Williams' test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

Mice were examined for neurological effects using a functional observation screening battery of tests. This battery included tests to assess several aspects of neurologic function including autonomic, convulsive, excitability, neuromuscular, sensorimotor, and general motor activity domains. Exposure-related effects were not observed in any of these domains in any of the exposed groups of mice compared to the controls. In addition, no exposure-related neurotoxic effects were found when individual tests within each domain were evaluated (Table F2).

The hematology data for mice are presented in Table G2. A minimal to mild increase in platelet counts occurred in all exposed groups of males and in 1,000 and 3,000 ppm females. There was evidence of a minimal decrease in the erythron of the female mice. This was demonstrated by minimal decreases in the erythrocyte counts in 1,000 and 3,000 ppm females and a minimal decrease in hematocrit values in the 3,000 ppm group. The red cell indices (mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration) for the affected female mice demonstrated minimal increases. In general, the altered values for the erythron and red cell indices were within physiological ranges and the severity of these alterations were so minimal that they were not considered biologically significant.

Liver weights of male and female mice exposed to 300 ppm or greater were significantly increased compared to the controls (Tables 10 and H2).

The incidences of centrilobular hypertrophy of the liver in males exposed to 100 ppm or greater and females exposed to 1,000 or 3,000 ppm were significantly greater than those in the controls, and the severities generally increased with increasing exposure concentration (Table 10). Centrilobular hypertrophy in mice was morphologically similar to that observed in rats. The incidences of focal hepatocyte necrosis in 1,000 and 3,000 ppm males were significantly increased. This lesion consisted of multiple, randomly scattered small foci of coagulative necrosis.

Exposure Concentration Selection Rationale: Based on lower mean body weights, increased liver weights, and incidences and severities of hepatocellular lesions in mice exposed to 1,000 or 3,000 ppm, *p,p′*-dichlorodiphenyl sulfone exposure concentrations selected for the 2-year feed study in mice were 30, 100, and 300 ppm.

TABLE 10
Liver Weights and Incidences of Nonneoplastic Lesions of the Liver in Mice in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt[a]	35.3 ± 0.5	37.7 ± 0.5	35.6 ± 0.9	33.0 ± 0.4▲▲	31.2 ± 0.6▲▲	29.8 ± 0.3▲▲
Liver Weight[a]						
Absolute	1.709 ± 0.031	1.855 ± 0.039	1.789 ± 0.052	1.945 ± 0.037▲▲	2.387 ± 0.063▲▲	2.952 ± 0.060▲▲
Relative	4.851 ± 0.089	4.925 ± 0.105	5.020 ± 0.075	5.890 ± 0.098▲▲	7.650 ± 0.103▲▲	9.913 ± 0.167▲▲
Liver						
Centrilobular Hypertrophy[b]	0	0	6** (1.0)[c]	10** (2.0)	10** (3.0)	10** (3.0)
Necrosis	0	0	1 (1.0)	3 (1.0)	7** (1.0)	8** (1.0)
Female						
Necropsy body wt	28.4 ± 0.7	30.1 ± 0.8	28.1 ± 0.6	25.9 ± 0.5▲▲	25.2 ± 0.4▲▲	25.2 ± 0.2▲▲
Liver Weight						
Absolute	1.247 ± 0.036	1.344 ± 0.036	1.335 ± 0.024	1.564 ± 0.047▲▲	1.802 ± 0.049▲▲	2.290 ± 0.036▲▲
Relative	4.385 ± 0.069	4.469 ± 0.077	4.753 ± 0.092▲	6.041 ± 0.130▲▲	7.142 ± 0.118▲▲	9.092 ± 0.102▲▲
Liver						
Centrilobular Hypertrophy	0	0	0	0	10** (1.0)	10** (2.0)
Necrosis	0	0	0	0	1 (1.0)	2 (1.5)

▲ Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
▲▲ P≤0.01
** Significantly different (P≤0.01) from the control group by the Fisher exact test
[a] Liver weights (absolute weights) and body weights are given in grams; liver-weight-to-body-weight ratios (relative weights) are given as g liver weight/g body weight as a percentage (mean ± standard error).
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice are shown in Table 11 and in the Kaplan-Meier survival curves (Figure 3). Survival of all exposed groups of male and female mice was similar to that of the control groups.

TABLE 11
Survival of Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	1	2	2	3
Natural deaths	9	3	4	5
Animals surviving to study termination	40	45	44[c]	42
Percent probability of survival at end of study[a]	80	90	88	84
Mean survival (days)[b]	705	714	699	689
Survival analysis[d]	P=1.000	P=0.254N	P=0.446N	P=0.837N
Female				
Animals initially in study	50	50	50	50
Moribund	3	1	1	1
Natural deaths	5	9	6	4
Animals surviving to study termination	42	40	43	45
Percent probability of survival at end of study	84	80	86	90
Mean survival (days)	717	711	727	729
Survival analysis	P=0.258N	P=0.769	P=0.924N	P=0.507N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] Includes one animal that died during the last week of the study
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.

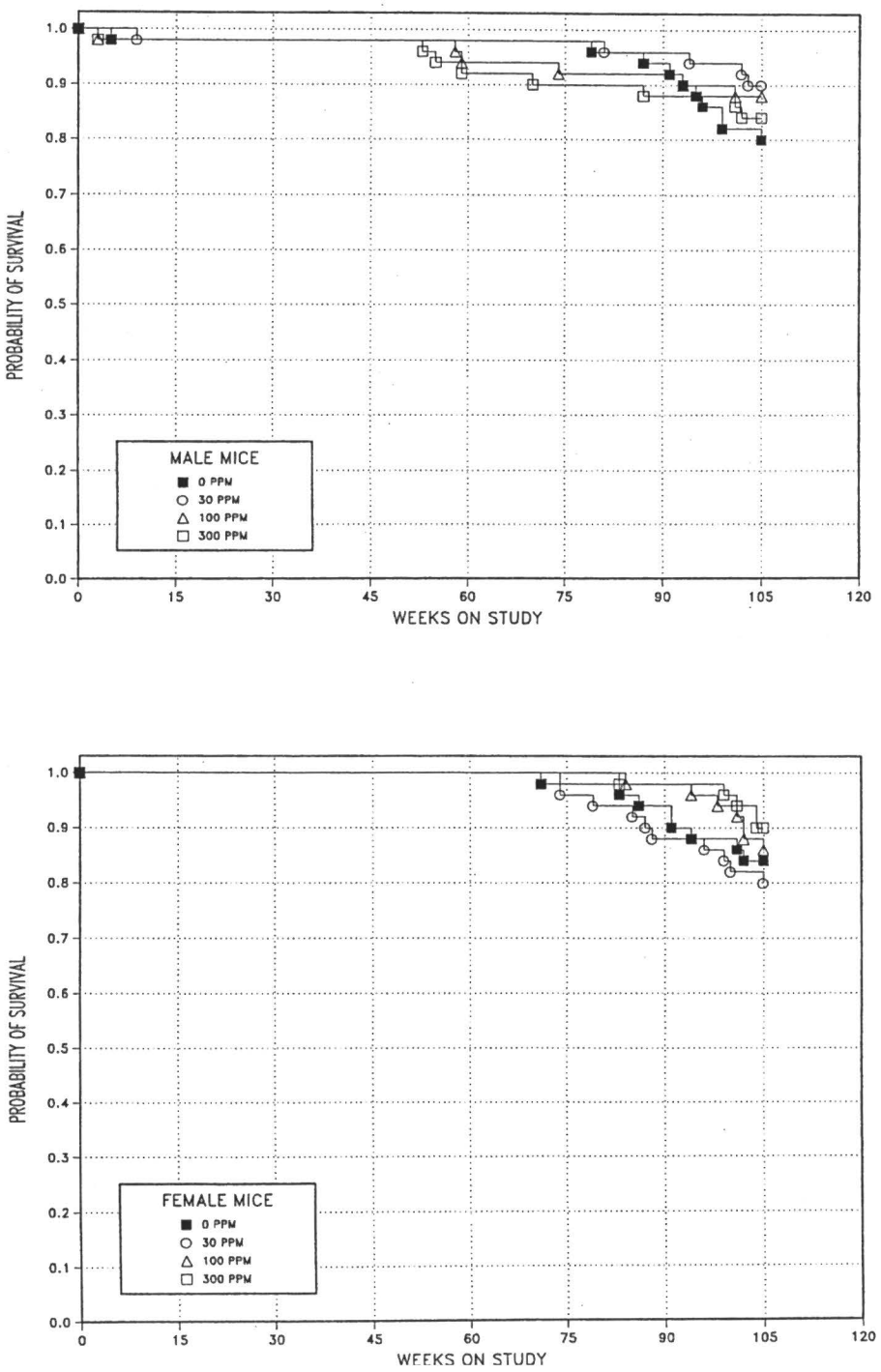


Figure 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to *p,p′*-Dichlorodiphenyl Sulfone in Feed for 2 Years

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 300 ppm mice were less than those of the controls throughout most of the study (Figure 4 and Tables 12 and 13). The mean body weights of mice in the 30 and 100 ppm groups were generally similar to those of the controls. Feed consumption by the exposed groups was similar to that by the controls throughout the study (Tables K3 and K4). Dietary concentrations of 30, 100, and 300 ppm delivered average daily doses of approximately 4, 13, and 40 mg/kg to males and approximately 3, 10, and 33 mg/kg to females. There were no clinical findings attributed to *p,p′*-dichlorodiphenyl sulfone exposure.

Determinations of p,p′-Dichlorodiphenyl Sulfone in Plasma

Plasma concentrations of *p,p′*-dichlorodiphenyl sulfone were consistently higher in all exposed groups of female mice compared to male mice at 2 weeks, 3 months, and 12 months (Table I2). Overall, samples at all time points showed a correlation between the dose administered and plasma *p,p′*-dichlorodiphenyl sulfone concentration, with male mice showing a nearly linear response at 2 weeks.

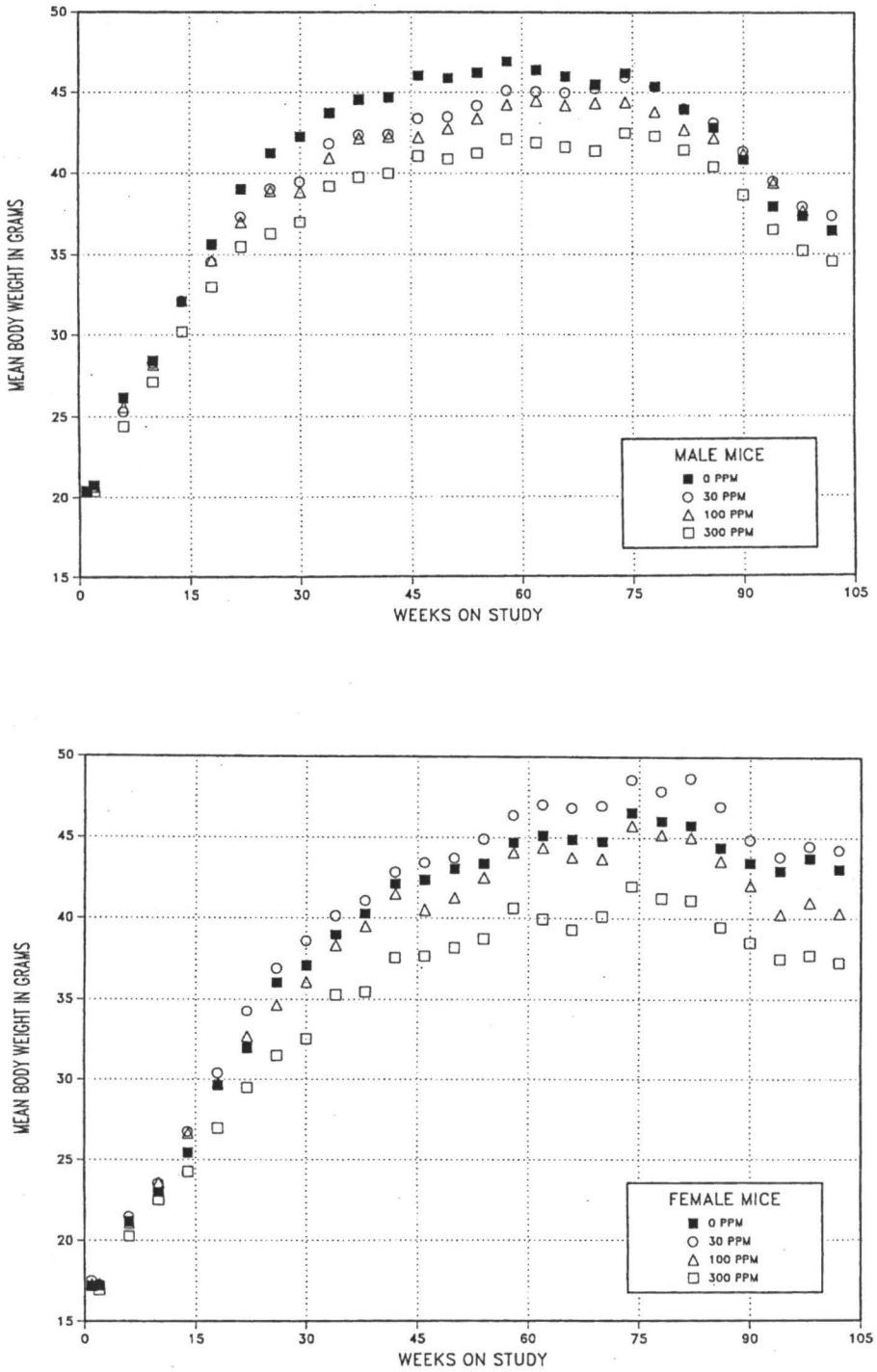


Figure 4
Growth Curves for Male and Female Mice
Exposed to *p,p′*-Dichlorodiphenyl Sulfone in Feed for 2 Years

TABLE 12
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

Weeks on Study	0 ppm		30 ppm			100 ppm			300 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.4	50	20.4	100	50	20.4	100	50	20.4	100	50
2	20.8	50	20.6	99	50	20.7	100	50	20.4	98	50
6	26.2	49	25.3	97	50	25.6	98	49	24.4	93	49
10	28.4	49	28.3	100	49	28.2	99	49	27.1	95	49
14	32.1	49	32.1	100	49	32.1	100	49	30.2	94	49
18	35.6	49	34.6	97	49	34.6	97	49	33.0	93	49
22	39.0	49	37.3	96	49	37.0	95	49	35.5	91	49
26	41.2	49	39.1	95	49	38.9	94	49	36.3	88	49
30	42.3	49	39.5	93	49	38.9	92	49	37.0	88	49
34	43.7	49	41.8	96	49	40.9	94	49	39.2	90	49
38	44.5	49	42.4	95	49	42.1	95	49	39.7	89	49
42	44.7	49	42.4	95	49	42.2	94	49	40.0	90	49
46	46.0	49	43.4	94	49	42.2	92	49	41.1	89	49
50	45.8	49	43.5	95	49	42.8	93	49	40.9	89	49
54	46.2	49	44.2	96	49	43.4	94	49	41.2	89	48
58	46.9	49	45.1	96	49	44.2	94	49	42.1	90	47
62	46.3	49	45.0	97	49	44.5	96	47	41.9	91	46
66	46.0	49	45.0	98	49	44.2	96	47	41.6	90	46
70	45.5	49	45.2	99	49	44.4	98	47	41.4	91	46
74	46.2	49	45.9	99	49	44.4	96	47	42.5	92	45
78	45.3	49	45.3	100	49	43.8	97	46	42.3	93	45
82	44.0	48	44.0	100	48	42.7	97	46	41.4	94	45
86	42.8	48	43.1	101	48	42.2	99	46	40.4	94	45
90	40.9	47	41.4	101	48	41.2	101	46	38.7	95	44
94	37.9	45	39.5	104	47	39.4	104	45	36.5	96	44
98	37.4	43	38.0	102	47	37.7	101	45	35.2	94	44
102	36.5	41	37.4	103	47	36.5	100	44	34.6	95	43
Mean for weeks											
1-13	24.0		23.7	99		23.7	99		23.1	96	
14-52	41.5		39.6	95		39.2	95		37.3	90	
53-102	43.2		43.0	100		42.2	98		40.0	93	

TABLE 13
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

Weeks on Study	0 ppm		30 ppm			100 ppm			300 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.2	50	17.5	102	50	17.3	101	50	17.2	100	50
2	17.2	50	17.3	101	50	17.3	101	50	16.9	98	50
6	21.2	50	21.5	101	50	21.1	100	50	20.3	96	50
10	23.0	50	23.5	102	50	23.6	103	50	22.5	98	50
14	25.5	50	26.8	105	50	26.7	105	50	24.3	95	50
18	29.6	50	30.4	103	50	29.8	101	50	27.0	91	50
22	32.0	50	34.3	107	50	32.7	102	50	29.5	92	50
26	36.0	50	36.9	103	50	34.6	96	50	31.5	88	50
30	37.1	50	38.6	104	50	36.1	97	50	32.5	88	50
34	39.0	50	40.1	103	50	38.3	98	50	35.3	91	50
38	40.3	50	41.1	102	50	39.5	98	50	35.5	88	50
42	42.1	50	42.8	102	50	41.5	99	50	37.6	89	50
46	42.4	50	43.4	102	50	40.5	96	50	37.6	89	50
50	43.0	50	43.7	102	50	41.2	96	50	38.2	89	50
54	43.4	50	44.9	104	50	42.5	98	50	38.7	89	50
58	44.7	50	46.4	104	50	44.1	99	50	40.6	91	50
62	45.1	50	47.0	104	50	44.4	98	50	39.9	89	50
66	44.9	50	46.8	104	50	43.8	98	50	39.3	88	50
70	44.8	50	47.0	105	50	43.7	98	50	40.1	90	50
74	46.5	49	48.6	105	48	45.8	99	50	42.0	90	50
78	46.0	49	47.9	104	48	45.2	98	50	41.2	90	50
82	45.7	49	48.7	107	47	45.0	99	50	41.1	90	50
86	44.4	48	46.9	106	46	43.6	98	49	39.5	89	49
90	43.4	47	44.9	104	44	42.0	97	49	38.5	89	49
94	42.9	45	43.8	102	44	40.2	94	48	37.5	87	49
98	43.7	44	44.5	102	43	41.0	94	48	37.7	86	49
102	43.0	43	44.3	103	41	40.3	94	46	37.3	87	47
Mean for weeks											
1-13	19.7		20.0	102		19.8	101		19.2	97	
14-52	36.7		37.8	103		36.1	98		32.9	90	
53-102	44.5		46.3	104		43.2	97		39.5	89	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Lung: The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 30 ppm females was significantly greater than that in the controls (0 ppm, 0/50; 30 ppm, 6/50; 100 ppm, 3/50; 300 ppm, 3/50), but it was within the historical ranges for controls given NTP-2000 diet and for untreated feed controls given NIH-07 diet (Tables D3 and D4). Furthermore, this is the only study in either database (includes 24 studies) in which no incidence of alveolar bronchiolar adenoma or carcinoma occurred in control female mice. Because the increase occurred only in the low exposure group, was within historical control ranges, and the incidence in the concurrent control group was unusually low, the increase was not considered exposure related.

There was a significant negative trend in the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in male mice (13/50; 11/50; 8/50; 4/50; Table C3). The incidence of these neoplasms in 300 ppm males was significantly less than that in the controls and was below the historical ranges in controls given NTP-2000 diet and in untreated feed controls given NIH-07 diet (Table C4). Other information does not support these decreases being exposure related. Focal alveolar epithelial hyperplasia of the lung is generally considered a preneoplastic lesion; the incidences of this lesion in exposed males (0/50, 2/50, 2/50, 4/50; Table C5) were not decreased compared to controls in this study. However, chemical-induced neoplastic effects in the lungs of mice tend to occur in both genders, and in this study, decreases in the incidences of lung neoplasms were not observed in female mice. It is uncertain if the decrease in lung neoplasms in male mice is related to the administration of *p,p′*-dichlorodiphenyl sulfone.

Liver: The incidences of centrilobular hepatocyte hypertrophy in all exposed groups of males and in 100 and 300 ppm females were significantly greater than those in the controls, and the severity increased with increasing exposure concentration (Tables 14, C5, and D5). Hepatocyte hypertrophy in mice was morphologically similar to that observed in rats (Plates 3 and 4). The incidence of eosinophilic foci in 300 ppm females was significantly increased.

TABLE 14
Incidences of Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Male				
Number Examined Microscopically	50	50	50	50
Centrilobular, Hypertrophy[a]	1 (1.0)[b]	24** (1.0)	43** (1.4)	45** (2.8)
Eosinophilic ocus	5	9	7	8
Female				
Number Examined Microscopically	50	50	50	50
Centrilobular, Hypertrophy	0	0	9** (1.0)	29** (1.4)
Eosinophilic Focus	2	1	4	14**

** Significantly different ($P \leq 0.01$) from the control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICOLOGY

p,p′-Dichlorodiphenyl sulfone (10 to 1,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without induced rat or hamster liver S9 metabolic activation enzymes (Table E1). Tests for induction of sister chromatid exchanges in cultured Chinese hamster ovary cells yielded equivocal results in the absence of S9 and negative results in the single trial conducted with S9 (Table E2). In the sister chromatid exchange test without S9, the first trial was judged to be equivocal, based on the small, dose-related increase in the number of sister chromatid exchanges per cell over the concentration range of 20 to 200 µg/mL; the second trial without S9 produced dose-related increases that were less significant, and the result of the second trial was judged to be negative. Overall, data from the first trial were weighted more than those from the second due to the shorter duration of exposure of the cells to bromodeoxyuridine and the broader concentration range that was tested, and the final call for the sister chromatid exchange test without S9 was equivocal. No significant induction of chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with *p,p′*-dichlorodiphenyl sulfone, with or without S9 (Table E3). In the first trial with S9, increases were noted in the total number of aberrations at the two highest concentrations tested, but the percentage of damaged cells was not particularly high except at the intermediate concentration of 930 µg/mL, and no increases were observed in the second trial conducted with S9. Therefore, the test was concluded to be negative overall. *In vivo*, *p,p′*-dichlorodiphenyl sulfone (200 to 800 mg/kg) induced micronuclei in polychromatic erythrocytes of male mice administered intraperitoneal injections three times at 24-hour intervals (Table E4). In the first trial, the frequency of micronucleated polychromatic erythrocytes in the 400 mg/kg group was significantly increased. Results of the second trial, conducted to clarify the initial response, were positive, with small but significant increases in the frequency of micronucleated polychromatic erythrocytes in the 400 and 800 mg/kg groups. It should be noted that the micronucleus frequency in the corn oil control group in Trial 2 was lower than that in Trial 1; the response in the positive control group in Trial 2 was also decreased compared to Trial 1. Overall, the results of the *in vivo* micronucleus test were positive.

In conclusion, the pattern of mutagenic activity shown by *p,p′*-dichlorodiphenyl sulfone in these four assays is unusual. No clear mutagenic activity in bacterial or mammalian assays designed to detect gene mutation induction or chromosomal damage *in vitro* was observed, but results of the mouse bone marrow micronucleus test indicate a potential for induction of chromosomal damage in the form of breakage or aneuploidy *in vivo*.

DISCUSSION AND CONCLUSIONS

p,p′-Dichlorodiphenyl sulfone, a structural analogue of 1,1′-(2,2,2-trichloroethylidine)bis[4-chlorobenzene] (DDT), was selected by the NTP for toxicity characterization and carcinogenicity evaluation based on its current high production volume and use, prospects for increased use and production in the future, and the potential for more widespread human exposure.

In the 14-week toxicity studies, there were no exposure-related deaths or clinical signs of toxicity related to *p,p′*-dichlorodiphenyl sulfone in rats or mice. Although some exposure concentrations appeared unpalatable during the first week, the animals displayed feed consumption similar to controls during the remainder of the studies.

The liver was the primary organ affected by exposure to *p,p′*-dichlorodiphenyl sulfone in rats and mice. Rats exposed to 100 ppm or greater had exposure concentration-dependent increases in liver weights, up to twice that of the control groups. Also, groups exposed to 100 ppm or greater generally had centrilobular hypertrophy. The severity of this lesion increased in an exposure-related manner. Changes in sorbitol dehydrogenase activity and bile acid concentrations were consistent with the liver lesions observed histopathologically in rats. There were species and sex differences in susceptibility of animals to *p,p′*-dichlorodiphenyl sulfone-induced liver effects. The liver effects in female rats were seen at greater exposure concentrations and were less severe than those in males. Although the patterns of liver toxicity expressed as increases in liver weights accompanied by centrilobular hypertrophy were similar in rats and mice, mice were less sensitive to these effects. Mice required higher exposure concentrations on a body weight basis to display liver effects similar to those in rats (6 to 200 mg/kg in rats versus 15 to 480 mg/kg in male mice and 165 to 480 mg/kg in female mice). These variations could be due to differences in the metabolism/disposition of *p,p′*-dichlorodiphenyl sulfone between males and females and rats and mice. Higher rates of oxidation of foreign chemicals by the mixed-function oxidase system are found in mice than in rats (Parke and Ioannides, 1990).

The increased incidences of hepatocellular hypertrophy and increased liver weights seen in the current studies were most likely due to induction of drug metabolizing enzymes by *p,p′*-dichlorodiphenyl sulfone. In a 4-week study using male Sprague-Dawley rats, hepatic microsomal activities of benzyloxyresorufin-*O*-dealkylase (BROD) and pentoxyresorufin-*O*-dealkylase (PROD) were induced by *p,p′*-dichlorodiphenyl sulfone 67- and 25-fold, respectively, when compared to controls. These changes were accompanied by hepatomegaly. Hepatic UDP-glucoronyltransferase and glutathione S-transferase activities were also induced (Poon *et al*., 1999). BROD and PROD are markers for cytochrome P4502B catalytic activity (Lubet *et al*., 1989). The characteristics of hepatic microsomal enzyme and cytochrome P450 induction by *p,p′*-dichlorodiphenyl sulfone resemble phenobarbitone-type inducers including organohalogen pesticides such as DDT. Treatment of animals with phenobarbitone-type inducers results in marked hepatic hypertrophy, increased concentration of microsomal protein, and proliferation of the smooth endoplasmic reticulum. These changes are accompanied by increases in protein and phospholipid synthesis and selected cytochrome P450 isozymes, and they occur predominantly in the centrilobular region of the liver. The net effect of these changes is increased biotransformation of foreign and endogenous substances. Induction of specific cyto-chrome P450 isozymes by phenobarbitone-type compounds is most likely regulated at the transcriptional level and involves an increase in the mRNAs encoding these enzymes (Sipes and Gandolfi, 1986). Many hepatic cytochrome P450 inducers of the pheno-barbitone type (CYP2B1) have been shown to act as nongenotoxic rodent hepatocarcinogens and/or tumor promoters. The phenobarbitone-type inducers include a diverse group of chemical classes such as chlorinated hydrocarbon pesticides, polyhalogenated biphenyls, hypolipidemic peroxisome proliferating agents, and certain steroids (Lubet *et al*., 1989).

DDT and its metabolites are lipid soluble. Once absorbed, they are readily distributed to all the tissues and stored preferentially in tissues with a high lipid content. The central nervous system, liver, and reproductive systems are major sites of DDT toxicity. Acute oral exposure to DDT has been associated with tremors, hyperexcitability, and convulsions in several species. Oral administration of DDT causes liver tumors including carcinomas in rodents. According to the International Agency for Research on Cancer, DDT is possibly carcinogenic in humans. DDT impairs reproduction and/or development in mice, rats, rabbits, dogs and avian species, is nonmutagenic in bacterial or mammalian test systems, and inhibits cell-cell communication (Flodström *et al*., 1990; IARC, 1991; ATSDR, 1994).

The study of DDT-induced hepatocarcinogenesis has provided insight into the tumor formation process in this organ. The early changes in rat liver produced by short-term treatment with DDT consist of hepatic cellular hyperplasia, hepatomegaly accompanied by induction of the microsomal mixed-function oxidases in rodents (and primates), an increase in the frequency of γ-glutamyltranspeptidase-positive foci, an increase in nuclear DNA synthesis, and a rise in mitotic activity. Hepatocellular proliferation appears to be related to a regenerative liver response. It is believed that in the liver in particular, cell proliferation plays a crucial role in the initiation of carcinogenesis, either by inducing errors in replication or by converting DNA adducts to mutations before DNA repair can occur (Kostka *et al*., 1996).

p,p′-Dichlorodiphenyl sulfone, like DDT, is highly lipid soluble, slowly metabolized, and distributed mainly throughout the adipose tissue as the parent compound with an estimated half-life of 12 days in this compartment (Mathews *et al*., 1996). Although some *p,p′*-dichlorodiphenyl sulfone is eliminated unchanged in the feces and urine, most of the elimination of *p,p′*-dichlorodiphenyl sulfone is via metabolism. Mathematical modeling of the toxicokinetics supports the view that *p,p′*-dichlorodiphenyl sulfone induces enzymes involved in its metabolism (Appendix N). Unlike DDT, *p,p′*-dichlorodiphenyl sulfone is minimally toxic to the liver and central nervous system. Specifically, the liver effects seen in the current studies were limited to hypertrophy (possibly a secondary response to induction of the drug metabolizing enzymes), and central nervous system toxicity was not observed because neither clinical signs of toxicity nor neurobehavioral alterations were observed.

In the current 2-year studies, there were no increases in the incidences of neoplasms in the liver or any other organ in rats or mice related to *p,p′*-dichlorodiphenyl sulfone exposure, nor were there any liver changes indicative of overt toxicity in exposed animals. As in the 14-week studies, liver effects were mostly limited to hepatocyte hypertrophy. Increased incidences of hepatocyte hypertrophy were seen in 30 and 100 ppm male rats and in 100 and 300 ppm female rats and male and female mice. Hepatocyte hypertrophy was a minimal to generally mild change characterized by increased size of centrilobular hepatocytes compared to those of the controls and to the affected animal's midzonal or periportal hepatocytes. In contrast, centrilobular degenerative changes were seen only in 100 and 300 ppm female rats. Overall, these results suggest that even though *p,p′*-dichlorodiphenyl sulfone is struct-urally related to DDT and has some common physical and biochemical properties, it is minimally toxic to rodents or at most a weak tumor promotor in female mice. This diversity in toxicity could be attributed to the structural differences between the compounds. It has been reported that bridged diphenyl acaricides, which are structurally similar to DDT, are generally several times less toxic than DDT (March, 1976). The sulfonyl compound, tetradifon (2,4,5,4′-tetrachloro-diphenyl sulfone), used as an acaricide, has a similar pattern of minimal liver effects as seen for *p,p′*-dichlorodiphenyl sulfone (WHO, 1986). Furthermore, the sulfonated derivatives of DDT were much less toxic to mallard ducks during egg production compared to the parent compound, suggesting sulfonation reduces the toxicity of DDT (Kolaja, 1977). Accordingly, it seems the sulfone moiety in the *p,p′*-dichlorodiphenyl sulfone structure mitigates the expected toxic effects of this organohalogen compound.

Induction of drug-metabolizing enzymes is a reversible event, and withdrawal of an inducing agent returns enzymatic activity to basal levels (Sipes and Gandolfi, 1986). However, highly lipophilic inducing agents such as DDT and *p,p′*-dichlorodiphenyl sulfone may be retained in the body and lead to prolonged induction because of their continued presence. In most instances, liver enlargement in the absence of pathological

changes (such as degenerative lesions, cell proliferation, and necrosis) is considered to be an adaptation to increased function load and thus a physiological rather than toxicological response (Amacher *et al*., 1998). However, adverse effects may possibly arise from increased mixed-function oxidase activities that cause altered sensitivities toward hepatotoxins or carcinogens (Schulte-Hermann, 1974; Parke and Ioannides, 1990). Based on the results of the current 14-week and 2-year studies, a no-observed-adverse-effect level of 30 ppm (1.5 mg/kg) in rats is suggested for both short-and long-term exposures.

Although *p,p′*-dichlorodiphenyl sulfone was not mutagenic in *Salmonella typhimurium*, it was positive in the *in vivo* mouse bone marrow micronucleus test. This test is not a sensitive assay (few chemicals give positive results) but when a positive test result occurs, it is predictive of rodent carcinogenicity 76% of the time (Shelby *et al*., 1993; Shelby and Witt, 1995). In addition, *p,p′*-dichlorodiphenyl sulfone produced a weak response in a mammalian cell chromosomal recombination assay at the highest concentration tested (Helleday *et al*., 1999), and equivocal results were seen in the cultured Chinese hamster ovary cell sister chromatid exchange test in the absence of liver microsomes. Although these mammalian cell cytogenetic data suggest potential *p,p′*-dichlorodiphenyl sulfone-induced chromosomal damage in mammals and hence an increased risk for cancer, no evidence of carcinogenicity was seen in the current studies. *p,p′*-Dichlorodiphenyl sulfone is one of the minority cases were a positive test result in the bone marrow micronucleus test is observed with a chemical that shows no evidence of carcinogenicity in rodents.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of *p,p′*-dichlorodiphenyl sulfone in male F344/N rats exposed to 10, 30, or 100 ppm or in female F344/N rats exposed to 30, 100, or 300 ppm. There was *no evidence of carcinogenic activity* of *p,p′*-dichlorodiphenyl sulfone in male or female B6C3F_1 mice exposed to 30, 100, or 300 ppm.

Exposure to *p,p′*-dichlorodiphenyl sulfone for 2 years caused increased incidences of nonneoplastic lesions of the liver in male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF *p,p′*-DICHLORODIPHENYL SULFONE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	10 ppm	30 ppm	100 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	19	16	24	15
Natural deaths	7	4	6	7
Survivors				
Terminal sacrifice	24	30	20	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Lipoma			1 (2%)	
Polyp adenomatous		1 (2%)		
Intestine large, rectum	(50)	(50)	(50)	(50)
Intestine large, cecum	(49)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Carcinoma			1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Intestine small, ileum	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin	1 (2%)			
Hepatocellular carcinoma	2 (4%)			1 (2%)
Hepatocellular adenoma				2 (4%)
Histiocytic sarcoma		1 (2%)		
Schwannoma malignant, metastatic, skin			1 (2%)	
Mesentery	(7)	(12)	(12)	(14)
Pancreas	(50)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Schwannoma malignant	2 (4%)		1 (2%)	
Schwannoma malignant, metastatic, skin			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, skin	1 (2%)			
Vena cava, pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	2 (4%)		2 (4%)	1 (2%)
Pheochromocytoma malignant, multiple		1 (2%)		
Pheochromocytoma benign	4 (8%)	3 (6%)	7 (14%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma			2 (4%)	
Carcinoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	11 (22%)	13 (26%)	7 (14%)	11 (22%)
Thyroid gland	(50)	(50)	(50)	(50)
Sarcoma, metastatic, skin	1 (2%)			
C-cell, adenoma	7 (14%)	6 (12%)	4 (8%)	7 (14%)
C-cell, adenoma, multiple	1 (2%)	1 (2%)	1 (2%)	1 (2%)
C-cell, carcinoma		1 (2%)	1 (2%)	2 (4%)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma		1 (2%)		
General Body System				
Peritoneum		(1)		(1)
Tissue NOS		(1)		
Thoracic, schwannoma malignant		1 (100%)		
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	3 (6%)	1 (2%)	3 (6%)
Carcinoma		2 (4%)		1 (2%)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Seminoma malignant			1 (2%)	
Interstitial cell, adenoma	2 (4%)	3 (6%)		2 (4%)
Interstitial cell, adenoma, multiple	39 (78%)	43 (86%)	45 (90%)	47 (94%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(15)	(11)	(14)	(14)
Mediastinal, squamous cell carcinoma, metastatic, lung		1 (9%)		
Lymph node, mandibular	(50)	(50)	(49)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Spleen	(50)	(50)	(50)	(50)
Sarcoma NOS				1 (2%)
Thymus	(46)	(47)	(46)	(47)
Squamous cell carcinoma, metastatic, lung		1 (2%)		
Integumentary System				
Mammary gland	(47)	(50)	(48)	(50)
Adenoma				1 (2%)
Fibroadenoma	3 (6%)	6 (12%)	3 (6%)	2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Fibrous histiocytoma	1 (2%)			
Keratoacanthoma	3 (6%)	5 (10%)	2 (4%)	4 (8%)
Squamous cell papilloma	1 (2%)			
Trichoepithelioma	1 (2%)			
Subcutaneous tissue, fibroma	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)		
Subcutaneous tissue, melanoma malignant		1 (2%)		
Subcutaneous tissue, sarcoma NOS	1 (2%)			
Subcutaneous tissue, schwannoma malignant		1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Skeletal muscle	(1)	(2)		(1)
Sarcoma NOS, metastatic, skin	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Ependymoma malignant		1 (2%)		
Glioma malignant	1 (2%)			
Meningioma malignant			1 (2%)	
Oligodendroglioma malignant			2 (4%)	
Spinal cord	(1)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma				1 (2%)
Fibrous histiocytoma, metastatic, liver		1 (2%)		
Fibrous histiocytoma, metastatic, skin	1 (2%)			
Hemangiosarcoma, metastatic, skin	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)	1 (2%)		1 (2%)
Schwannoma malignant, metastatic, skin		1 (2%)	1 (2%)	1 (2%)
Squamous cell carcinoma		1 (2%)		
Squamous cell carcinoma, metastatic, lung		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Sarcoma, metastatic, skin	1 (2%)			
Special Senses System				
Zymbal's gland	(1)	(1)	(1)	(1)
Carcinoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Mesenchymal tumor malignant		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, liver		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia mononuclear	27 (54%)	22 (44%)	25 (50%)	27 (54%)
Mesothelioma malignant	2 (4%)	2 (4%)	5 (10%)	6 (12%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	50	50	50
Total primary neoplasms	122	126	121	127
Total animals with benign neoplasms	42	48	47	50
Total benign neoplasms	81	89	77	84
Total animals with malignant neoplasms	34	33	37	37
Total malignant neoplasms	41	37	44	43
Total animals with metastatic neoplasms	4	4	1	2
Total metastatic neoplasms	9	7	3	2

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	3 1 2	3 1 3	3 6 1	3 6 8	4 5 4	5 1 2	5 6 9	5 9 7	6 1 1	6 1 3	6 1 4	6 1 7	6 3 3	6 4 0	6 4 0	6 4 2	6 4 8	6 7 4	6 8 2	6 8 2	6 8 2	6 8 7	7 1 8	7 1 8	7 2 3
Carcass ID Number	0 0 6	0 5 0	0 2 5	0 0 2	0 3 4	0 1 8	0 3 8	0 1 7	0 4 2	0 3 0	0 4 8	0 1 2	0 0 4	0 1 3	0 4 0	0 2 2	0 2 4	0 4 7	0 0 1	0 0 5	0 2 6	0 4 3	0 1 9	0 2 3	0 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																									
Hepatocellular carcinoma													X												
Mesentery		+							+					+			+					+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																						X			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin																								X	
Vena cava, pheochromocytoma malignant, metastatic, adrenal medulla																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign														X								X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X	X							X			X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																								X	
C-cell, adenoma																				X					
C-cell, adenoma, multiple																									
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	728	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	04 5	00 7	00 8	00 9	01 5	02 0	02 7	02 8	02 9	03 2	03 5	04 4	04 6	03 0	01 0	01 1	01 4	01 6	02 1	03 1	03 6	03 7	03 9	04 1	04 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin	X																									1
Hepatocellular carcinoma												X														2
Mesentery																		+		+						7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant					X																					2
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Vena cava, pheochromocytoma malignant, metastatic, adrenal medulla																					X					1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																			X		X					2
Pheochromocytoma benign	X							X																		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X																					1
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X													X	X			X	X			11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
C-cell, adenoma				X	X	X							X						X		X					7
C-cell, adenoma, multiple												X														1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	3 1 2	3 1 3	3 6 1	3 6 8	4 5 4	5 1 2	5 6 9	5 9 7	6 1 1	6 1 3	6 1 4	6 1 7	6 3 3	6 4 0	6 4 0	6 4 2	6 4 8	6 7 4	6 8 2	6 8 2	6 8 2	6 8 7	7 1 8	7 1 8	7 2 3
Carcass ID Number	0 0 6	0 5 0	0 2 5	0 0 2	0 3 4	0 1 8	0 3 8	0 1 7	0 4 2	0 3 0	0 4 8	0 1 2	0 1 0 4	0 1 1 3	0 1 4 0	0 4 2 2	0 2 2 4	0 4 4 7	0 0 1	0 0 5	0 2 2 6	0 4 4 3	0 1 1 9	0 2 3 3	0 3 3 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma												X								X					
Interstitial cell, adenoma, multiple							X	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+	+			+	+		+				+			+	+	+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroadenoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																X									
Fibrous histiocytoma																									
Keratoacanthoma																									
Squamous cell papilloma																				X					
Trichoepithelioma																									X
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangiosarcoma								X																	
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma NOS																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								+	
Sarcoma NOS, metastatic, skin																								X	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant	X																								
Spinal cord				+																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Fibrous histiocytoma, metastatic, skin																									
Hemangiosarcoma, metastatic, skin								X																	
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	728	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	04 5	00 7	00 8	00 9	01 5	02 0	02 7	02 8	02 9	03 2	03 5	04 4	04 6	04 3	01 0	01 1	01 4	01 6	02 1	03 1	03 6	03 7	03 9	04 1	04 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X			X											3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										2
Interstitial cell, adenoma, multiple	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	39
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+												+	+						+	15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma						X								X												3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Fibrous histiocytoma	X																									1
Keratoacanthoma						X				X									X							3
Squamous cell papilloma																										1
Trichoepithelioma																										1
Subcutaneous tissue, fibroma					X		X																			2
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, lipoma				X																						1
Subcutaneous tissue, sarcoma NOS																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Sarcoma NOS, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									X	2
Fibrous histiocytoma, metastatic, skin	X																									1
Hemangiosarcoma, metastatic, skin																										1
Pheochromocytoma malignant, metastatic, adrenal medulla																					X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	3 1 2	3 1 3	3 6 1	3 6 8	4 5 4	5 1 2	5 6 9	5 9 7	6 1 1	6 1 3	6 1 4	6 1 7	6 3 3	6 4 0	6 4 0	6 4 2	6 4 8	6 7 4	6 8 2	6 8 2	6 8 2	6 8 7	7 1 8	7 1 8	7 2 3
Carcass ID Number	0 0 6	0 5 0	0 2 5	0 0 2	0 3 4	0 1 8	0 3 8	0 1 7	0 4 2	0 3 0	0 4 8	0 1 2	0 0 4	0 1 3	0 4 0	0 2 2	0 2 4	0 4 7	0 0 1	0 0 5	0 2 6	0 4 3	0 1 9	0 2 3	0 3 3
Special Senses System																									
Eye																								+	
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X		X
Mesothelioma malignant																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 5	0 0 7	0 0 8	0 0 9	0 1 5	0 2 0	0 2 7	0 2 8	0 2 9	0 3 2	0 3 5	0 4 4	0 4 6	0 3	0 1 0	0 1 1	0 1 4	0 1 6	0 2 1	0 3 1	0 3 6	0 3 7	0 3 9	0 4 1	0 4 9	Total Tissues/ Tumors	
Special Senses System																											
Eye																										1	
Zymbal's gland																										1	
Carcinoma																										1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear					X	X										X	X	X	X		X				X	27	
Mesothelioma malignant							X																			2	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 10 ppm

Number of Days on Study	3 8 6	4 1 0	5 1 2	5 8 5	5 8 5	5 9 2	6 0 3	6 1 7	6 3 9	6 5 9	6 6 3	6 6 3	6 6 9	6 8 7	6 9 6	7 0 1	7 0 8	7 0 9	7 1 8	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 8 9	0 8 4	0 8 7	0 7 8	0 8 5	0 8 8	0 7 4	0 5 1	0 9 8	0 5 5	0 8 6	0 9 0	0 6 9	0 9 3	0 5 2	0 6 3	0 5 8	0 7 1	0 9 2	0 8 2	0 5 3	0 5 4	0 5 9	0 6 1	0 6 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																					X				
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mesentery				+	+	+					+								+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, multiple																									
Pheochromocytoma benign							X																	X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis adenoma												X		X	X		X		X		X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma	X																				X				
C-cell, adenoma, multiple																									
C-cell, carcinoma																							X		
Follicular cell, adenoma																				X					
Follicular cell, carcinoma								X																	
General Body System																									
Peritoneum						+																			
Tissue NOS																					+				
Thoracic, schwannoma malignant																					X				
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma							X						X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma			X																			X			X
Interstitial cell, adenoma, multiple				X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 10 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	00770	00776	00777	00881	00883	00891	00994	00996	00999	01000	00556	00557	00760	00962	00964	00966	00967	00968	00972	00973	00975	00979	00980	00995	00997	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																			X							1
Mesentery	+							+		+			+			+				+	+					12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, multiple			X																							1
Pheochromocytoma benign														X												3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X		X	X												X					X	13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X				X								X		X					6
C-cell, adenoma, multiple																									X	1
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
Follicular cell, carcinoma																										1
General Body System																										
Peritoneum																										1
Tissue NOS																										1
Thoracic, schwannoma malignant																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X											X											3
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										3
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 10 ppm

Number of Days on Study	3 8 6	4 1 0	5 1 2	5 8 5	5 8 5	5 9 2	6 0 3	6 1 7	6 3 9	6 5 9	6 6 3	6 6 3	6 6 9	6 8 7	6 9 6	7 0 1	7 0 8	7 0 9	7 1 8	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 8 9	0 8 4	0 8 7	0 7 8	0 8 5	0 8 8	0 7 4	0 5 1	0 9 8	0 5 5	0 8 6	0 9 0	0 6 9	0 9 3	0 5 2	0 6 3	0 5 8	0 7 1	0 9 2	0 8 2	0 5 3	0 5 4	0 5 9	0 6 1	0 6 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+			+	+	+	+	+							+		+					
Mediastinal, squamous cell carcinoma, metastatic, lung		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									X
Keratoacanthoma																			X						
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, melanoma malignant															X										
Subcutaneous tissue, schwannoma malignant																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+		+																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ependymoma malignant			X																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, liver																									
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Schwannoma malignant, metastatic, skin																	X								
Squamous cell carcinoma		X																							
Squamous cell carcinoma, metastatic, lung		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland	+																								
Carcinoma	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 10 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	00770	00776	00777	00881	00883	00991	00994	00996	00999	01000	00556	00557	00560	00662	00664	00666	00667	00668	00772	00773	00775	00779	00880	00995	00997	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+									+				11
Mediastinal, squamous cell carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma				X				X							X					X	X					6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma			X												X		X						X			5
Subcutaneous tissue, fibroma												X					X									2
Subcutaneous tissue, lipoma				X																						1
Subcutaneous tissue, melanoma malignant																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ependymoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, liver																			X							1
Pheochromocytoma malignant, metastatic, adrenal medulla			X																							1
Schwannoma malignant, metastatic, skin																										1
Squamous cell carcinoma																										1
Squamous cell carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 10 ppm

Number of Days on Study	3 8 6	4 1 0	5 1 2	5 8 5	5 8 5	5 9 2	6 0 3	6 1 7	6 3 9	6 5 9	6 6 3	6 6 3	6 6 9	6 8 7	6 9 6	7 0 1	7 0 8	7 0 9	7 1 8	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 8 9	0 8 4	0 8 7	0 7 8	0 8 5	0 8 8	0 7 4	0 5 1	0 9 8	0 5 5	0 8 6	0 9 0	0 6 9	0 9 3	0 5 2	0 6 3	0 5 8	0 7 1	0 9 2	0 8 2	0 5 3	0 5 4	0 5 9	0 6 1	0 6 5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenchymal tumor malignant																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, liver																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear					X			X	X	X	X	X	X	X		X	X			X			X		X
Mesothelioma malignant				X		X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 10 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 7 0	0 7 6	0 7 7	0 8 1	0 8 3	0 9 1	0 9 4	0 9 6	0 9 9	0 9 9	1 0 0	0 5 6	0 5 7	0 6 0	0 6 2	0 6 4	0 6 6	0 6 7	0 6 8	0 7 2	0 7 3	0 7 5	0 7 9	0 8 0	0 9 5	0 9 7	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesenchymal tumor malignant																	X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, liver																				X							1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X							1
Leukemia mononuclear	X	X				X			X			X		X					X	X				X			22
Mesothelioma malignant																											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	4 0 0	4 4 4	4 8 2	5 0 8	5 2 3	5 3 7	5 4 9	5 5 7	5 6 2	5 8 5	6 0 2	6 1 4	6 2 1	6 4 6	6 5 3	6 6 3	6 7 5	7 7 6	6 8 2	6 9 1	6 9 1	7 0 1	7 0 8	7 0 8	7 0 8
Carcass ID Number	1 1 4	1 4 9	1 4 7	1 0 8	1 2 0	1 3 5	1 4 5	1 0 1	1 2 6	1 1 8	1 4 8	1 0 1	1 2 1	1 3 2	1 3 4	1 4 4	1 3 9	1 4 6	1 3 6	1 0 9	1 2 4	1 4 2	1 3 7	1 4 0	1 5 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																							X		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin																						X			
Mesentery	+	+		+		+				+	+														
Oral mucosa																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant							X																		
Schwannoma malignant, metastatic, skin																						X			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																						+			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant	X																								
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant							X											X							
Pheochromocytoma benign												X								X		X		X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X						X			X						X		X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X																		
C-cell, adenoma, multiple																									
C-cell, carcinoma																							X		
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 1 2	7 1 5	7 2 1	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 3 1	1 0 6	1 2 2	1 0 2	1 2 3	1 0 4	1 0 7	1 1 1	1 1 2	1 1 7	1 2 5	1 2 8	1 3 3	1 4 3	1 0 3	1 0 5	1 1 3	1 1 5	1 1 6	1 1 9	1 2 7	1 2 9	1 3 0	1 3 8	1 4 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																									1
Mesentery			+						+				+	+					+				+		12
Oral mucosa																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																									1
Schwannoma malignant, metastatic, skin																									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma										X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																									1
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																									2
Pheochromocytoma benign							X													X	X				7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X		X							2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma						X																			7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X			X						X									4
C-cell, adenoma, multiple																								X	1
C-cell, carcinoma																									1
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	4 0 0	4 4 4	4 8 2	5 0 8	5 2 3	5 3 7	5 4 9	5 5 7	5 6 2	5 8 5	6 0 2	6 1 4	6 2 1	6 4 6	6 5 3	6 6 3	6 7 5	7 7 6	7 8 2	7 9 1	7 9 1	7 0 1	7 0 8	7 0 8	7 0 8
Carcass ID Number	1 1 4	1 4 9	1 4 7	1 0 8	1 2 0	1 3 5	1 4 5	1 0 1	1 2 6	1 1 8	1 4 8	1 1 0	1 1 1	1 2 2	1 3 4	1 3 4	1 4 4	1 3 9	1 4 6	1 3 6	1 0 9	1 2 4	1 4 2	1 3 7	1 4 0	1 5 0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminoma malignant																									
Interstitial cell, adenoma, multiple		X	X		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+		+	+	+	+	+	+			+									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								X	
Keratoacanthoma																									X
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, schwannoma malignant																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant			X																						
Oligodendroglioma malignant							X				X														
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Schwannoma malignant, metastatic, skin																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland					+																				
Carcinoma					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 1 2	7 1 5	7 2 1	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 3 1	1 0 6	1 2 2	1 0 2	1 2 3	1 0 4	1 0 7	1 1 1	1 1 2	1 1 7	1 2 5	1 2 8	1 3 3	1 4 3	1 0 3	1 0 5	1 1 3	1 1 5	1 1 6	1 1 9	1 2 7	1 2 9	1 3 0	1 3 8	1 4 1	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminoma malignant																				X						1
Interstitial cell adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	45
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+								+			+					+					+				14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma		X					X																			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma																X										2
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma malignant																										1
Oligodendroglioma malignant																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																				X	2
Schwannoma malignant, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+															1
Zymbal's gland																										1
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	4 0 0	4 4 4	4 8 2	5 0 8	5 2 3	5 3 7	5 4 9	5 5 7	5 6 2	5 8 5	6 0 2	6 1 4	6 2 1	6 4 6	6 5 3	6 6 3	6 7 5	7 7 6	6 8 2	6 9 1	6 9 1	7 0 1	7 0 8	7 0 8	7 0 8
Carcass ID Number	1 1 4	1 4 9	1 4 7	1 0 8	1 2 0	1 3 5	1 4 5	1 0 1	1 2 6	1 1 8	1 4 8	1 1 0	1 2 1	1 3 2	1 3 4	1 4 4	1 3 9	1 4 6	1 3 6	1 0 9	1 2 4	1 4 2	1 3 7	1 4 0	1 5 0
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X							X	X	X	X	X	X	X	X	X		X			X	X	X	X
Mesothelioma malignant						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 1 2	7 1 5	7 2 1	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 3 1	1 0 6	1 2 2	1 0 2	1 2 3	1 0 4	1 0 7	1 1 1	1 1 2	1 1 7	1 2 5	1 2 8	1 3 3	1 4 3	1 0 3	1 0 5	1 1 3	1 1 5	1 1 6	1 1 9	1 2 7	1 2 9	1 3 0	1 3 8	1 4 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra						+																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X				X				X					X					X	X		X	25
Mesothelioma malignant				X									X	X					X							5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	490	529	537	562	569	569	569	585	602	610	632	633	634	659	676	677	690	691	699	701	722	723	729	729	729
Carcass ID Number	17505	18807	18508	18601	18700	18802	18900	19064	19283	19366	19568	19684	19769	19865	19963	19985	19990	19992	19996	19974	19977	19971	19951	19952	19953
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																				X					
Hepatocellular adenoma																X									
Mesentery			+				+		+			+			+		+			+		+			+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X	X		X								X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X	X														
C-cell, adenoma, multiple						X																			
C-cell, carcinoma													X												
General Body System																									
Peritoneum							+																		
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma				X																					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma	X																					X			
Interstitial cell, adenoma, multiple		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	15 54	15 57	16 62	17 22	17 76	18 00	18 81	18 86	19 00	19 05	19 06	19 99	19 99	15 99	16 00	16 67	17 33	17 78	17 79	18 88	18 89	19 01	19 03	19 04	19 07	19 08	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																											1
Hepatocellular adenoma	X																										2
Mesentery					+	+						+					+									+	14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X																				1
Pheochromocytoma benign																			X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X					X						X	X								X			X		X	11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X					X		X									X		X								7
C-cell, adenoma, multiple																											1
C-cell, carcinoma				X																							2
General Body System																											
Peritoneum																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X	X				3
Carcinoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																											2
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	47

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	490	529	537	562	569	569	569	585	602	610	632	633	634	659	676	677	690	691	699	701	722	723	729	729	729
Carcass ID Number	17505	18807	15808	16101	17010	18202	19200	16404	18303	16606	16808	18404	16909	16505	16303	18505	15505	19252	15696	17404	17707	17711	15911	16252	15653
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+			+	+	+	+			+		+			+	+	+		+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS	X																								
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma															X										
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma			X																						
Subcutaneous tissue, schwannoma malignant														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Schwannoma malignant, metastatic, skin														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+																	
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X		X	X	X	X	X	X		X	X	X	X	X		X	X			X
Mesothelioma malignant						X	X		X											X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	15 54	15 57	16 62	17 22	17 76	18 80	18 81	18 86	19 00	19 05	19 06	19 99	19 99	15 59	16 60	16 67	17 73	17 78	17 79	18 88	18 89	19 01	19 03	19 04	19 07	19 08	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+													+						14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																			1
Fibroadenoma	X																							X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma												X															1
Keratoacanthoma			X									X								X							4
Subcutaneous tissue, fibroma							X																				1
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, schwannoma malignant																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																						1
Alveolar/bronchiolar carcinoma														X													1
Pheochromocytoma malignant, metastatic, adrenal medulla							X																				1
Schwannoma malignant, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X		X			X		X					X	X					X				X	X	27
Mesothelioma malignant						X																				X	6

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/50 (8%)	3/50 (6%)	7/50 (14%)	1/50 (2%)
Adjusted rate[b]	9.9%	6.8%	17.1%	2.4%
Terminal rate[c]	1/24 (4%)	2/30 (7%)	3/20 (15%)	1/28 (4%)
First incidence (days)	640	603	614	729 (T)
Poly-3 test[d]	P=0.143N	P=0.453N	P=0.266	P=0.162N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	6/50 (12%)	4/50 (8%)	9/50 (18%)	2/50 (4%)
Adjusted rate	14.9%	9.1%	21.6%	4.7%
Terminal rate	3/24 (13%)	3/30 (10%)	3/20 (15%)	2/28 (7%)
First incidence (days)	640	603	549	729 (T)
Poly-3 test	P=0.122N	P=0.315N	P=0.308	P=0.115N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	5.0%	0.0%	0.0%	7.0%
Terminal rate	1/24 (4%)	0/30 (0%)	0/20 (0%)	1/28 (4%)
First incidence (days)	633	—[e]	—	677
Poly-3 test	P=0.145	P=0.219N	P=0.236N	P=0.528
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	7.5%	13.8%	7.4%	4.7%
Terminal rate	2/24 (8%)	5/30 (17%)	1/20 (5%)	2/28 (7%)
First incidence (days)	640	723	621	729 (T)
Poly-3 test	P=0.208N	P=0.282	P=0.658N	P=0.475N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	3/50 (6%)	6/50 (12%)	3/50 (6%)	3/50 (6%)
Adjusted rate	7.5%	13.8%	7.4%	7.1%
Terminal rate	2/24 (8%)	5/30 (17%)	1/20 (5%)	3/28 (11%)
First incidence (days)	640	723	621	729 (T)
Poly-3 test	P=0.368N	P=0.282	P=0.658N	P=0.637N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	11/50 (22%)	13/50 (26%)	7/50 (14%)	11/50 (22%)
Adjusted rate	26.9%	29.5%	16.4%	25.4%
Terminal rate	7/24 (29%)	8/30 (27%)	1/20 (5%)	8/28 (29%)
First incidence (days)	614	663	482	633
Poly-3 test	P=0.482N	P=0.491	P=0.182N	P=0.539N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	7.5%	6.9%	2.5%	7.1%
Terminal rate	2/24 (8%)	2/30 (7%)	0/20 (0%)	2/28 (7%)
First incidence (days)	611	709	725	699
Poly-3 test	P=0.594	P=0.625N	P=0.305N	P=0.637N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	1/50 (2%)	4/50 (8%)
Adjusted rate	7.5%	11.3%	2.5%	9.3%
Terminal rate	2/24 (8%)	2/30 (7%)	0/20 (0%)	2/28 (7%)
First incidence (days)	611	603	725	562
Poly-3 test	P=0.555	P=0.410	P=0.305N	P=0.537
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	4/50 (8%)
Adjusted rate	7.5%	11.5%	5.0%	9.4%
Terminal rate	3/24 (13%)	4/30 (13%)	1/20 (5%)	3/28 (11%)
First incidence (days)	729 (T)	718	708	676
Poly-3 test	P=0.569	P=0.406	P=0.495N	P=0.537
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/50 (8%)	5/50 (10%)	2/50 (4%)	4/50 (8%)
Adjusted rate	10.0%	11.5%	5.0%	9.4%
Terminal rate	3/24 (13%)	4/30 (13%)	1/20 (5%)	3/28 (11%)
First incidence (days)	682	718	708	676
Poly-3 test	P=0.535N	P=0.554	P=0.333N	P=0.609N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	6/50 (12%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
Adjusted rate	14.9%	13.8%	7.4%	9.4%
Terminal rate	3/24 (13%)	5/30 (17%)	1/20 (5%)	3/28 (11%)
First incidence (days)	642	718	708	676
Poly-3 test	P=0.294N	P=0.566N	P=0.239N	P=0.334N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma NOS				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	7.5%	4.6%	4.9%	4.7%
Terminal rate	2/24 (8%)	2/30 (7%)	0/20 (0%)	1/28 (4%)
First incidence (days)	728	729 (T)	557	537
Poly-3 test	P=0.487N	P=0.459N	P=0.488N	P=0.465N
Testes: Adenoma				
Overall rate	41/50 (82%)	46/50 (92%)	45/50 (90%)	49/50 (98%)
Adjusted rate	91.5%	95.5%	94.7%	98.0%
Terminal rate	22/24 (92%)	29/30 (97%)	19/20 (95%)	27/28 (96%)
First incidence (days)	569	512	444	490
Poly-3 test	P=0.148	P=0.345	P=0.415	P=0.143
Thyroid Gland (C-cell): Adenoma				
Overall rate	8/50 (16%)	7/50 (14%)	5/50 (10%)	8/50 (16%)
Adjusted rate	20.0%	15.8%	12.3%	18.3%
Terminal rate	7/24 (29%)	6/30 (20%)	4/20 (20%)	5/28 (18%)
First incidence (days)	682	386	549	569
Poly-3 test	P=0.526	P=0.412N	P=0.259N	P=0.532N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	8/50 (16%)	6/50 (12%)	10/50 (20%)
Adjusted rate	20.0%	18.1%	14.7%	22.7%
Terminal rate	7/24 (29%)	7/30 (23%)	4/20 (20%)	6/28 (21%)
First incidence (days)	682	386	549	569
Poly-3 test	P=0.345	P=0.519N	P=0.368N	P=0.486
All Organs: Malignant Mesothelioma				
Overall rate	2/50 (4%)	2/50 (4%)	5/50 (10%)	6/50 (12%)
Adjusted rate	5.0%	4.5%	12.3%	13.7%
Terminal rate	1/24 (4%)	0/30 (0%)	3/20 (15%)	2/28 (7%)
First incidence (days)	687	585	537	569
Poly-3 test	P=0.086	P=0.655N	P=0.222	P=0.165
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/50 (54%)	22/50 (44%)	25/50 (50%)	27/50 (54%)
Adjusted rate	57.2%	47.8%	55.7%	57.1%
Terminal rate	8/24 (33%)	11/30 (37%)	6/20 (30%)	11/28 (39%)
First incidence (days)	313	585	444	529
Poly-3 test	P=0.389	P=0.239N	P=0.524N	P=0.579N
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	48/50 (96%)	47/50 (94%)	50/50 (100%)
Adjusted rate	93.8%	97.6%	97.5%	100.0%
Terminal rate	23/24 (96%)	29/30 (97%)	20/20 (100%)	28/28 (100%)
First incidence (days)	569	386	444	490
Poly-3 test	P=0.081	P=0.319	P=0.315	P=0.073
All Organs: Malignant Neoplasms				
Overall rate	34/50 (68%)	33/50 (66%)	37/50 (74%)	36/50 (72%)
Adjusted rate	69.1%	66.2%	75.5%	73.0%
Terminal rate	10/24 (42%)	15/30 (50%)	11/20 (55%)	15/28 (54%)
First incidence (days)	312	386	400	529
Poly-3 test	P=0.326	P=0.461N	P=0.315	P=0.419
All Organs: Benign or Malignant Neoplasms				
Overall	49/50 (98%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	98.0%	100.0%	100.0%	100.0%
Terminal rate	23/24 (96%)	30/30 (100%)	20/20 (100%)	28/28 (100%)
First incidence (days)	312	386	400	490
Poly-3 test	P=0.500	P=0.500	P=0.500	P=0.500

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	10 ppm	30 ppm	100 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	19	16	24	15
Natural deaths	7	4	6	7
Survivors				
Terminal sacrifice	24	30	20	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)	4 (8%)	1 (2%)	2 (4%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Inflammation			2 (4%)	
Parasite metazoan	3 (6%)	6 (12%)	8 (16%)	7 (14%)
Ulcer				1 (2%)
Intestine large, cecum	(49)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Inflammation				1 (2%)
Ulcer			1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			
Intestine small, ileum	(50)	(50)	(50)	(50)
Inflammation			1 (2%)	1 (2%)
Parasite metazoan		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Basophilic focus	30 (60%)	29 (58%)	26 (52%)	27 (54%)
Clear cell focus	6 (12%)	11 (22%)	2 (4%)	4 (8%)
Degeneration, cystic	5 (10%)	4 (8%)	4 (8%)	6 (12%)
Eosinophilic focus	6 (12%)	8 (16%)	6 (12%)	8 (16%)
Fibrosis			1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	7 (14%)	5 (10%)	10 (20%)	4 (8%)
Inflammation	18 (36%)	27 (54%)	19 (38%)	21 (42%)
Mixed cell focus	7 (14%)	17 (34%)	8 (16%)	11 (22%)
Necrosis	4 (8%)	1 (2%)	3 (6%)	4 (8%)
Pigmentation	2 (4%)			
Thrombosis		1 (2%)	2 (4%)	
Vacuolization cytoplasmic	9 (18%)	4 (8%)	2 (4%)	5 (10%)
Bile duct, hyperplasia	46 (92%)	47 (94%)	44 (88%)	48 (96%)
Centrilobular, degeneration	18 (36%)	15 (30%)	20 (40%)	23 (46%)
Centrilobular, hypertrophy		1 (2%)	3 (6%)	16 (32%)
Centrilobular, necrosis	1 (2%)	1 (2%)	1 (2%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Alimentary System (continued)				
Mesentery	(7)	(12)	(12)	(14)
Hemorrhage		1 (8%)	1 (8%)	
Inflammation		1 (8%)	1 (8%)	
Necrosis	1 (14%)			
Fat, inflammation	1 (14%)	1 (8%)		2 (14%)
Fat, necrosis	3 (43%)	7 (58%)	8 (67%)	7 (50%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	14 (28%)	14 (28%)	13 (26%)	12 (24%)
Cytoplasmic alteration	2 (4%)	2 (4%)		1 (2%)
Hyperplasia	3 (6%)	2 (4%)		2 (4%)
Inflammation	1 (2%)	4 (8%)	4 (8%)	2 (4%)
Necrosis			1 (2%)	
Thrombosis			1 (2%)	
Artery, inflammation			2 (4%)	
Duct, cyst			1 (2%)	1 (2%)
Duct, hyperplasia		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	
Cytoplasmic alteration	1 (2%)			2 (4%)
Duct, hyperplasia	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Inflammation	1 (2%)	1 (2%)		
Ulcer	2 (4%)		3 (6%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)
Edema		1 (2%)		
Erosion	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Hyperplasia	1 (2%)			
Mineralization			1 (2%)	1 (2%)
Necrosis				1 (2%)
Ulcer	2 (4%)	2 (4%)	4 (8%)	2 (4%)
Tooth	(1)		(1)	
Gingiva, inflammation			1 (100%)	
Periodontal tissue, inflammation	1 (100%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Inflammation	1 (2%)			
Aorta, inflammation				1 (2%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	39 (78%)	46 (92%)	43 (86%)	43 (86%)
Inflammation	1 (2%)			
Thrombosis	1 (2%)	5 (10%)	5 (10%)	2 (4%)
Artery, inflammation			1 (2%)	
Endocardium, degeneration			1 (2%)	
Epicardium, hyperplasia		1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Atrophy			1 (2%)	
Degeneration, cystic	1 (2%)			1 (2%)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	11 (22%)	13 (26%)	8 (16%)	9 (18%)
Hypertrophy	3 (6%)	7 (14%)	3 (6%)	2 (4%)
Necrosis	2 (4%)			
Vacuolization cytoplasmic	8 (16%)	6 (12%)	4 (8%)	3 (6%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Hyperplasia	14 (28%)	10 (20%)	15 (30%)	12 (24%)
Infiltration cellular, lymphocyte		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		
Parathyroid gland	(46)	(48)	(47)	(46)
Hyperplasia, focal		1 (2%)		
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	7 (14%)	6 (12%)	6 (12%)	3 (6%)
Cyst	2 (4%)	8 (16%)	10 (20%)	6 (12%)
Hemorrhage	1 (2%)		2 (4%)	
Pars distalis, hyperplasia	15 (30%)	17 (34%)	21 (42%)	15 (30%)
Pars distalis, pseudocyst	6 (12%)			1 (2%)
Pars intermedia, cyst	1 (2%)			
Pars intermedia, hyperplasia		1 (2%)		
Pars intermedia, pseudocyst	3 (6%)			
Thyroid gland	(50)	(50)	(50)	(50)
Inflammation	1 (2%)			
C-cell, hyperplasia	19 (38%)	30 (60%)	26 (52%)	20 (40%)
Follicular cell, hyperplasia			3 (6%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		
Inflammation	1 (2%)		1 (2%)	
Mesothelium, hyperplasia		1 (2%)	1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)
Hyperplasia			4 (8%)	2 (4%)
Inflammation	46 (92%)	45 (90%)	48 (96%)	48 (96%)
Duct, cyst		3 (6%)	2 (4%)	2 (4%)
Prostate	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Inflammation	27 (54%)	38 (76%)	31 (62%)	29 (58%)
Dorsal, cyst, mucous		1 (2%)	1 (2%)	1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Inflammation	1 (2%)		1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Genital System (continued)				
Testes	(50)	(50)	(50)	(50)
Atrophy	5 (10%)	7 (14%)	3 (6%)	6 (12%)
Cyst		1 (2%)		
Hyperplasia	1 (2%)			
Artery, inflammation	1 (2%)			
Interstitial cell, hyperplasia	28 (56%)	37 (74%)	28 (56%)	24 (48%)
Mesothelium, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	18 (36%)	18 (36%)	16 (32%)	20 (40%)
Inflammation, granulomatous			1 (2%)	
Myelofibrosis	4 (8%)	2 (4%)	1 (2%)	2 (4%)
Necrosis	1 (2%)		1 (2%)	
Lymph node	(15)	(11)	(14)	(14)
Inguinal, hyperplasia, plasma cell		1 (9%)		
Mediastinal, atrophy		1 (9%)		
Mediastinal, ectasia		1 (9%)		
Mediastinal, hemorrhage				1 (7%)
Mediastinal, necrosis	1 (7%)			
Mediastinal, pigmentation	4 (27%)	1 (9%)	4 (29%)	3 (21%)
Pancreatic, necrosis		1 (9%)		
Renal, hyperplasia, plasma cell	1 (7%)			
Renal, necrosis	1 (7%)			
Lymph node, mandibular	(50)	(50)	(49)	(50)
Ectasia	3 (6%)	5 (10%)	3 (6%)	2 (4%)
Hyperplasia, plasma cell	4 (8%)	1 (2%)		
Necrosis	1 (2%)	1 (2%)		
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Atrophy	1 (2%)			1 (2%)
Ectasia		1 (2%)		1 (2%)
Hyperplasia, reticulum cell		2 (4%)		
Necrosis	1 (2%)	1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	1 (2%)	1 (2%)		2 (4%)
Fibrosis	2 (4%)	4 (8%)	4 (8%)	5 (10%)
Hematopoietic cell proliferation	4 (8%)	5 (10%)	3 (6%)	5 (10%)
Hyperplasia, lymphoid		1 (2%)		
Hyperplasia, reticulum cell		1 (2%)	1 (2%)	
Hyperplasia, stromal	1 (2%)			
Infarct		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, lipocyte			1 (2%)	
Necrosis	1 (2%)			1 (2%)
Pigmentation	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Lymphoid follicle, atrophy	2 (4%)		3 (6%)	2 (4%)
Thymus	(46)	(47)	(46)	(47)
Atrophy	44 (96%)	45 (96%)	40 (87%)	43 (91%)
Artery, inflammation		1 (2%)		
Epithelial cell, hyperplasia			1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Integumentary System				
Mammary gland	(47)	(50)	(48)	(50)
Cyst	1 (2%)		1 (2%)	
Galactocele				2 (4%)
Hyperplasia	2 (4%)	8 (16%)	9 (19%)	6 (12%)
Inflammation	1 (2%)		1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		
Edema			1 (2%)	
Fibrosis				1 (2%)
Hyperkeratosis		1 (2%)		1 (2%)
Hyperplasia	1 (2%)	1 (2%)		
Inflammation		1 (2%)	1 (2%)	1 (2%)
Ulcer	1 (2%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	1 (2%)	1 (2%)		1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Gliosis			1 (2%)	1 (2%)
Hemorrhage	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Necrosis	1 (2%)		4 (8%)	
Thrombosis			1 (2%)	
Spinal cord	(1)			
Hemorrhage	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Edema			1 (2%)	1 (2%)
Foreign body	1 (2%)		1 (2%)	1 (2%)
Hemorrhage	2 (4%)		3 (6%)	4 (8%)
Inflammation	11 (22%)	16 (32%)	14 (28%)	18 (36%)
Inflammation, granulomatous	1 (2%)			
Necrosis	1 (2%)	1 (2%)		
Pigmentation	1 (2%)			
Thrombosis	1 (2%)	1 (2%)	2 (4%)	
Alveolar epithelium, hyperplasia	9 (18%)	7 (14%)	2 (4%)	5 (10%)
Nose	(50)	(50)	(50)	(50)
Foreign body	5 (10%)	6 (12%)	3 (6%)	5 (10%)
Inflammation	12 (24%)	9 (18%)	6 (12%)	8 (16%)
Trachea	(50)	(50)	(50)	(50)
Inflammation		1 (2%)	1 (2%)	1 (2%)
Special Senses System				
Eye	(1)		(1)	(1)
Cataract			1 (100%)	1 (100%)
Retina, degeneration			1 (100%)	1 (100%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	10 ppm	30 ppm	100 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Inflammation		2 (4%)		
Necrosis			2 (4%)	
Nephropathy	42 (84%)	48 (96%)	41 (82%)	44 (88%)
Pigmentation	13 (26%)	4 (8%)	15 (30%)	19 (38%)
Thrombosis			1 (2%)	
Artery, inflammation	1 (2%)			
Pelvis, inflammation			1 (2%)	
Renal tubule, degeneration	1 (2%)			
Urethra			(1)	
Inflammation			1 (100%)	
Urinary bladder	(50)	(50)	(50)	(50)
Inflammation			2 (4%)	
Transitional epithelium, hyperplasia			2 (4%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF *p,p′*-DICHLORODIPHENYL SULFONE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	9	12	5
Natural deaths	3	3	3	10
Survivors				
Died last week of study			1	
Terminal sacrifice	36	38	34	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(50)	(50)	(50)	(49)
Liver	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, spleen				1 (2%)
Schwannoma malignant, metastatic, heart		1 (2%)		
Mesentery	(7)	(8)	(4)	(4)
Sarcoma NOS, metastatic, uterus	1 (14%)			
Pancreas	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Sarcoma NOS, metastatic, uterus	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Adenocarcinoma	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue		(2)		(1)
Squamous cell carcinoma		1 (50%)		1 (100%)
Squamous cell papilloma		1 (50%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant		1 (2%)	2 (4%)	2 (4%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	2 (4%)	1 (2%)	
Sarcoma NOS, metastatic, uterus	1 (2%)			
Adrenal medulla	(50)	(49)	(50)	(50)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign	2 (4%)			
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma			1 (2%)	
Pituitary gland	(50)	(49)	(50)	(50)
Schwannoma malignant, metastatic, peripheral nerve			1 (2%)	
Pars distalis, adenoma	23 (46%)	13 (27%)	17 (34%)	8 (16%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	8 (16%)	6 (12%)	2 (4%)
C-cell, adenoma, multiple	2 (4%)			
C-cell, carcinoma	2 (4%)			1 (2%)
Follicular cell, adenoma	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
General Body System				
Tissue NOS		(1)		
Leiomyoma		1 (100%)		
Genital System				
Clitoral gland	(47)	(50)	(50)	(48)
Adenoma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Carcinoma			1 (2%)	1 (2%)
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor malignant				1 (2%)
Granulosa cell tumor benign				1 (2%)
Sarcoma NOS, metastatic, uterus	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Polyp stromal	10 (20%)	8 (16%)	5 (10%)	5 (10%)
Sarcoma NOS	1 (2%)			
Sarcoma stromal	1 (2%)			2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(27)	(23)	(28)	(28)
Lumbar, carcinoma, metastatic, clitoral gland				1 (4%)
Lymph node, mandibular	(49)	(50)	(48)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
Thymus	(46)	(48)	(50)	(48)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma	1 (2%)	1 (2%)	2 (4%)	
Carcinoma, multiple				1 (2%)
Fibroadenoma	12 (24%)	18 (36%)	19 (38%)	8 (16%)
Fibroadenoma, multiple	3 (6%)	2 (4%)	1 (2%)	
Myoepithelioma	1 (2%)			
Skin	(50)	(50)	(50)	(49)
Pinna, melanoma malignant		1 (2%)		
Subcutaneous tissue, fibroma		2 (4%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)		
Musculoskeletal System				
Skeletal muscle		(1)	(1)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)	1 (2%)		1 (2%)
Oligodendroglioma malignant				1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Nervous System (continued)				
Peripheral nerve	(1)		(1)	
Trigeminal, schwannoma malignant			1 (100%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)	
Carcinoma, metastatic, clitoral gland				1 (2%)
Osteosarcoma, metastatic, spleen				1 (2%)
Sarcoma NOS, metastatic, uterus	1 (2%)			
Mediastinum, sarcoma NOS, metastatic, uterus	1 (2%)			
Trachea	(50)	(50)	(50)	(50)
Sarcoma NOS				1 (2%)
Special Senses System				
Zymbal's gland				(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Sarcoma NOS, metastatic, uterus	1 (2%)			
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Sarcoma NOS, metastatic, uterus	1 (2%)			
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	8 (16%)	7 (14%)	14 (28%)	14 (28%)
Lymphoma malignant		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	40	42	36
Total primary neoplasms	79	74	73	57
Total animals with benign neoplasms	37	35	35	20
Total benign neoplasms	63	59	52	28
Total animals with malignant neoplasms	16	14	20	25
Total malignant neoplasms	16	15	21	29
Total animals with metastatic neoplasms	2	1	1	2
Total metastatic neoplasms	9	1	1	4

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	4 1 4	4 2 9	5 0 1	5 4 3	5 7 5	6 1 3	6 2 5	6 4 5	6 5 6	6 6 0	6 6 5	6 9 4	7 0 1	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 4 2	2 2 2	2 0 5	2 1 5	2 3 4	2 4 9	2 2 5	2 2 7	2 1 4	2 4 5	2 1 3	2 2 1	2 4 6	2 0 8	2 0 1	2 0 3	2 0 6	2 0 7	2 1 7	2 1 9	2 2 6	2 2 8	2 3 0	2 3 1	2 3 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+							+											+		
Sarcoma NOS, metastatic, uterus												X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uterus												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus								X																	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Sarcoma NOS, metastatic, uterus												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X		X	X		X		X	X	X	X	X	X	X		X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X												
C-cell, adenoma, multiple																					X				
C-cell, carcinoma																									
Follicular cell, adenoma														X											
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	235	243	248	202	216	218	229	233	236	238	240	244	247	250	204	209	210	211	212	220	223	224	237	239	241	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+				+				+		+						7
Sarcoma NOS, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																						X				1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						2
Sarcoma NOS, metastatic, uterus																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X				X															2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X			X		X	X							X			X					X	23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X							X											3
C-cell, adenoma, multiple	X																									2
C-cell, carcinoma		X																						X		2
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	4 1 4	4 2 9	5 0 1	5 4 3	5 7 5	6 1 3	6 2 5	6 4 5	6 5 6	6 6 0	6 6 5	6 9 4	7 0 1	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 4 2	2 2 2	2 0 5	2 1 5	2 3 4	2 4 9	2 2 5	2 2 7	2 1 4	2 4 5	2 1 3	2 2 1	2 4 6	2 0 8	2 0 1	2 0 3	2 0 6	2 0 7	2 1 7	2 1 9	2 2 6	2 2 8	2 3 0	2 3 1	2 3 2
Genital System																									
Clitoral gland	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uterus												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X									X		X							X	X		
Sarcoma NOS												X													
Sarcoma stromal								X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+	+	+	+	+	+		+	+					+			+			+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma						X																			
Fibroadenoma						X		X		X							X		X				X		
Fibroadenoma, multiple														X											X
Myoepithelioma		X																							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, lipoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Peripheral nerve									+																
Spinal cord									+																
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uterus												X													
Mediastinum, sarcoma NOS, metastatic, uterus												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+																	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	23 5	24 3	24 8	20 2	21 6	21 8	22 9	23 3	23 6	23 8	24 0	24 4	24 7	25 0	20 4	20 9	21 0	21 1	21 2	22 0	22 3	22 4	23 7	23 9	24 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma		X																								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS, metastatic, uterus																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal									X			X			X			X		X						10
Sarcoma NOS																										1
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+						+		+		+		+		+	+			+	+	+	+	+	27
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Carcinoma																										1
Fibroadenoma			X				X				X			X	X						X					12
Fibroadenoma, multiple	X																									3
Myoepithelioma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS, metastatic, uterus																										1
Mediastinum, sarcoma NOS, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+																	+								3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	4 1 4	4 2 9	5 0 1	5 4 3	5 7 5	6 1 3	6 2 5	6 4 5	6 5 6	6 6 0	6 6 5	6 9 4	7 0 1	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 4 2	2 2 2	2 0 5	2 1 5	2 3 4	2 4 9	2 2 5	2 2 7	2 1 4	2 4 5	2 1 3	2 2 1	2 4 6	2 0 8	2 0 1	2 0 3	2 0 6	2 0 7	2 1 7	2 1 9	2 2 6	2 2 8	2 3 0	2 3 1	2 3 2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uterus												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS, metastatic, uterus												X													
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X									X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 3 5	2 4 3	2 4 8	2 0 2	2 1 6	2 1 8	2 2 9	2 3 3	2 3 6	2 3 8	2 4 0	2 4 4	2 4 7	2 5 0	2 0 4	2 0 9	2 1 0	2 1 1	2 1 2	2 2 0	2 2 3	2 2 4	2 3 7	2 3 9	2 4 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS, metastatic, uterus																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS, metastatic, uterus																										1
Transitional epithelium, papilloma																									X	1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X								X					X				X	X							8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	4 0 3	4 2 9	4 5 1	5 4 0	6 1 6	6 3 3	6 5 2	6 5 9	6 6 6	6 6 6	6 8 0	6 9 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 7 6	2 7 7	2 7 3	2 9 0	2 9 8	2 7 4	2 9 4	2 6 1	2 6 8	2 9 5	2 6 6	2 7 2	2 5 3	2 5 5	2 5 8	2 6 0	2 6 7	2 8 5	2 8 6	2 9 2	2 9 6	3 0 0	2 5 2	2 5 6	2 5 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart																									
Mesentery			+		+		+						+			+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue											+														
Squamous cell carcinoma											X														
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Adrenal medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X											X	X				X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X			X	X
General Body System																									
Tissue NOS																	+								
Leiomyoma																	X								
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X							X	X													X		
Vagina	+								+																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	26 4	26 9	27 8	27 9	28 0	28 1	28 4	28 7	29 3	29 7	25 1	25 4	25 9	26 2	26 3	26 5	27 0	27 1	27 5	28 2	28 3	28 8	28 9	29 1	29 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, heart		X																								1
Mesentery							+							+										+		8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue					+																					2
Squamous cell carcinoma																										1
Squamous cell papilloma					X																					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant		X																								1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	50
Adenoma																X										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant											X															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X				X				X								X	X				13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X	X		X					X		X													8
General Body System																										
Tissue NOS																										1
Leiomyoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X	X															3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X							X												X			X			8
Vagina																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	4 0 3	4 2 9	4 5 1	5 4 0	6 1 6	6 3 3	6 5 2	6 5 9	6 6 6	6 6 6	6 8 0	6 9 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 7 6	2 7 7	2 7 3	2 9 0	2 9 8	2 7 4	2 9 4	2 6 1	2 6 8	2 9 5	2 6 6	2 7 2	2 5 3	2 5 5	2 5 8	2 6 0	2 6 7	2 8 5	2 8 6	2 9 2	2 9 6	3 0 0	2 5 2	2 5 6	2 5 7
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+	+		+		+	+	+		+	+			+		+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Fibroadenoma						X		X	X						X	X		X				X		
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, melanoma malignant		X																						
Subcutaneous tissue, fibroma		X																						
Subcutaneous tissue, lipoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+															
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																				X				
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																	+							+
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma												X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemian ononuclear								X		X		X		X		X								
Lymphoma malignant									X															

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	26 4	26 9	27 8	27 9	28 0	28 1	28 4	28 7	29 3	29 7	25 1	25 4	25 9	26 2	26 3	26 5	27 0	27 1	27 5	28 2	28 3	28 8	28 9	29 1	29 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+	+				+	+			+				+		+	+		+	+	+		+	23
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																						X				1
Fibroadenoma			X				X	X		X		X	X			X			X	X			X		X	18
Fibroadenoma, multiple									X												X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, melanoma malignant																										1
Subcutaneous tissue, fibroma				X																						2
Subcutaneous tissue, lipoma																									X	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X										X													7
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	468	526	536	575	625	662	667	676	687	701	703	708	714	723	725	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	303	301	302	225	234	206	240	214	227	218	219	241	311	324	212	204	207	208	211	216	222	230	233	236	237
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																			+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																X									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, peripheral nerve																									
Pars distalis, adenoma	X	X				X	X			X		X	X						X					X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X							
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																X				X			X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+	+		+			+					+	+	+		+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	
Carcass ID Number	34343	34646	34848	34949	35005	35313	35717	36020	36221	36423	36629	36932	37038	37239	37442	37545	37809	37910	37915	38226	38428	38535	38644	38747	38850	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery											+									+	+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant		X																								2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, peripheral nerve																							X			1
Pars distalis, adenoma		X		X	X							X		X	X	X							X			17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X				X			X					X									X			6
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal															X						X					5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+		+		+		+	+	+	+		+			+		+	+		+	+	+	28
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	4 6 8	5 2 6	5 3 6	5 7 5	6 2 5	6 6 2	6 6 7	6 7 6	6 8 7	7 0 1	7 0 3	7 0 8	7 1 4	7 2 3	7 2 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 0 3	3 0 1	3 0 2	3 2 5	3 3 4	3 0 6	3 4 0	3 1 4	3 2 7	3 1 8	3 1 9	3 4 1	3 3 1	3 2 4	3 1 2	3 0 4	3 0 7	3 0 8	3 1 1	3 1 6	3 2 2	3 3 0	3 3 3	3 3 6	3 3 7
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																	X	
Fibroadenoma			X								X	X	X	X				X	X	X	X				
Fibroadenoma, multiple																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Trigeminal, schwannoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X	X	X	X	X						X	X							X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	
Carcass ID Number	34343	34646	34848	34949	30505	31113	31117	32020	32201	32303	32909	33202	33808	33909	34202	34505	34609	35010	35115	35226	35428	35535	35644	35747	35850	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										2
Fibroadenoma				X	X	X					X		X		X	X	X	X	X							19
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																							+			1
Trigeminal, schwannoma malignant																							X			1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X	X		X								X				14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	309	347	414	465	511	531	584	614	631	633	637	639	659	701	707	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	379	363	585	544	667	555	699	885	556	776	881	892	722	995	999	551	552	553	662	663	670	673	675	680	684
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen																								X	
Mesentery																						+	+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue					+																				
Squamous cell carcinoma					X																				
Tooth													+							+					
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X												X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X				X				
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma														X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal											X							X							
Sarcoma stromal												X						X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 9 4	4 0 0	3 5 7	3 6 4	3 7 1	3 7 4	3 7 8	3 8 6	3 8 7	3 8 8	3 9 0	3 9 3	3 9 6	3 9 8	3 5 9	3 6 0	3 6 1	3 6 5	3 6 8	3 7 7	3 8 2	3 8 3	3 8 9	3 9 1	3 9 7	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Mesentery															+											4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Tooth								+									+									4
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant								X																X		2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	M	+	+	M	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X			X		X								X					X				8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										2
C-cell, carcinoma					X																					1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X				X																			3
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant							X																			1
Granulosa cell tumor benign												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																							X			1
Polyp stromal							X			X								X								5
Sarcoma stromal																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	309	347	414	465	511	531	584	644	631	633	637	639	659	701	707	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	379	363	585	544	667	555	689	855	656	676	681	892	722	795	991	951	952	953	962	966	970	973	975	980	984
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+								+	+	+		+	+		+		+		+		+	+	+	+
Lumbar, carcinoma, metastatic, clitoral gland														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								X	
Thymus	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, multiple																									
Fibroadenoma										X								X			X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant								X																	
Oligodendroglioma malignant		X																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, clitoral gland														X											
Osteosarcoma, metastatic, spleen																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma NOS																									
Special Senses System																									
Eye																+									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X					X			X	X	X	X			X		X					X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 9 4	4 0 0	3 5 7	3 6 4	3 7 1	3 7 4	3 7 8	3 8 6	3 8 7	3 8 8	3 9 0	3 9 3	3 9 6	3 9 8	3 5 9	3 6 0	3 6 1	3 6 5	3 6 8	3 7 7	3 8 2	3 8 3	3 8 9	3 9 1	3 9 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+			+		+	+	+			+		+	+	+			+	+	+			28
Lumbar, carcinoma, metastatic, clitoral gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, multiple	X																									1
Fibroadenoma	X	X							X					X			X									8
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Oligodendroglioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, clitoral gland																										1
Osteosarcoma, metastatic, spleen																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma NOS							X																			1
Special Senses System																										
Eye								+			+												+			4
Zymbal's gland																+										1
Carcinoma																X										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X			X	X				X						14

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Clitoral Gland: Adenoma				
Overall rate[a]	1/47 (2%)	3/50 (6%)	1/50 (2%)	3/48 (6%)
Adjusted rate[b]	2.3%	6.7%	2.2%	7.3%
Terminal rate[c]	1/36 (3%)	3/38 (8%)	1/35 (3%)	2/34 (6%)
First incidence (days)	730 (T)	730 (T)	730 (T)	633
Poly-3 test[d]	P=0.317	P=0.321	P=0.746N	P=0.291
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	1/47 (2%)	3/50 (6%)	2/50 (4%)	4/48 (8%)
Adjusted rate	2.3%	6.7%	4.4%	9.7%
Terminal rate	1/36 (3%)	3/38 (8%)	1/35 (3%)	2/34 (6%)
First incidence (days)	730 (T)	730 (T)	714	633
Poly-3 test	P=0.168	P=0.321	P=0.523	P=0.167
Mammary Gland: Fibroadenoma				
Overall rate	15/50 (30%)	20/50 (40%)	20/50 (40%)	8/50 (16%)
Adjusted rate	33.0%	43.7%	42.8%	18.6%
Terminal rate	11/36 (31%)	17/38 (45%)	15/35 (43%)	7/35 (20%)
First incidence (days)	613	633	536	633
Poly-3 test	P=0.022N	P=0.199	P=0.224	P=0.095N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	16/50 (32%)	20/50 (40%)	20/50 (40%)	8/50 (16%)
Adjusted rate	35.2%	43.7%	42.8%	18.6%
Terminal rate	12/36 (33%)	17/38 (45%)	15/35 (43%)	7/35 (20%)
First incidence (days)	613	633	536	633
Poly-3 test	P=0.015N	P=0.267	P=0.296	P=0.062N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	16/50 (32%)	21/50 (42%)	22/50 (44%)	8/50 (16%)
Adjusted rate	35.2%	45.9%	46.8%	18.6%
Terminal rate	12/36 (33%)	18/38 (47%)	16/35 (46%)	7/35 (20%)
First incidence (days)	613	633	536	633
Poly-3 test	P=0.012N	P=0.201	P=0.175	P=0.062N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/50 (46%)	13/49 (27%)	17/50 (34%)	8/50 (16%)
Adjusted rate	49.6%	29.0%	35.4%	18.6%
Terminal rate	16/36 (44%)	11/37 (30%)	10/35 (29%)	7/35 (20%)
First incidence (days)	575	540	468	631
Poly-3 test	P=0.007N	P=0.033N	P=0.115N	P<0.001N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/50 (10%)	8/50 (16%)	6/50 (12%)	2/50 (4%)
Adjusted rate	11.2%	17.8%	13.1%	4.7%
Terminal rate	4/36 (11%)	8/38 (21%)	6/35 (17%)	2/35 (6%)
First incidence (days)	701	730 (T)	730 (T)	730 (T)
Poly-3 test	P=0.091N	P=0.279	P=0.520	P=0.234N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/50 (14%)	8/50 (16%)	6/50 (12%)	3/50 (6%)
Adjusted rate	15.7%	17.8%	13.1%	7.0%
Terminal rate	6/36 (17%)	8/38 (21%)	6/35 (17%)	3/35 (9%)
First incidence (days)	701	730 (T)	730 (T)	730 (T)
Poly-3 test	P=0.099N	P=0.506	P=0.478N	P=0.175N
Uterus: Stromal Polyp				
Overall rate	10/50 (20%)	8/50 (16%)	5/50 (10%)	5/50 (10%)
Adjusted rate	22.1%	17.3%	10.9%	11.6%
Terminal rate	8/36 (22%)	5/38 (13%)	5/35 (14%)	4/35 (11%)
First incidence (days)	543	429	730 (T)	637
Poly-3 test	P=0.145N	P=0.377N	P=0.121N	P=0.151N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	11/50 (22%)	8/50 (16%)	5/50 (10%)	6/50 (12%)
Adjusted rate	24.2%	17.3%	10.9%	13.9%
Terminal rate	8/36 (22%)	5/38 (13%)	5/35 (14%)	4/35 (11%)
First incidence (days)	543	429	730 (T)	637
Poly-3 test	P=0.188N	P=0.291N	P=0.080N	P=0.166N
All Organs: Mononuclear Cell Leukemia				
Overall rate	8/50 (16%)	7/50 (14%)	14/50 (28%)	14/50 (28%)
Adjusted rate	17.5%	15.4%	29.4%	30.7%
Terminal rate	5/36 (14%)	4/38 (11%)	7/35 (20%)	7/35 (20%)
First incidence (days)	501	659	575	309
Poly-3 test	P=0.050	P=0.505N	P=0.131	P=0.107
All Organs: Benign Neoplasms				
Overall rate	37/50 (74%)	35/50 (70%)	35/50 (70%)	20/50 (40%)
Adjusted rate	77.1%	73.3%	71.8%	45.8%
Terminal rate	27/36 (75%)	28/38 (74%)	25/35 (71%)	17/35 (49%)
First incidence (days)	429	429	468	631
Poly-3 test	P<0.001N	P=0.421N	P=0.357N	P<0.001N
All Organs: Malignant Neoplasms				
Overall rate	15/50 (30%)	14/50 (28%)	20/50 (40%)	25/50 (50%)
Adjusted rate	31.5%	29.9%	41.8%	52.4%
Terminal rate	8/36 (22%)	8/38 (21%)	11/35 (31%)	14/35 (40%)
First incidence (days)	414	429	575	309
Poly-3 test	P=0.009	P=0.523N	P=0.201	P=0.029

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	40/50 (80%)	42/50 (84%)	36/50 (72%)
Adjusted rate	84.9%	83.1%	84.0%	75.5%
Terminal rate	30/36 (83%)	31/38 (82%)	27/35 (77%)	25/35 (71%)
First incidence (days)	414	429	468	309
Poly-3 test	P=0.129N	P=0.517N	P=0.562N	P=0.177N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	9	12	5
Natural deaths	3	3	3	10
Survivors				
Died last week of study			1	
Terminal sacrifice	36	38	34	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	8 (16%)	4 (8%)	3 (6%)	4 (8%)
Intestine large, cecum	(50)	(49)	(50)	(50)
Inflammation		1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)	1 (2%)	2 (4%)
Basophilic focus	47 (94%)	48 (96%)	43 (86%)	36 (72%)
Clear cell focus	2 (4%)	5 (10%)	1 (2%)	2 (4%)
Eosinophilic focus	9 (18%)	10 (20%)	14 (28%)	7 (14%)
Fatty change	1 (2%)			
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	9 (18%)	11 (22%)	12 (24%)	14 (28%)
Inflammation	43 (86%)	44 (88%)	39 (78%)	30 (60%)
Mixed cell focus	8 (16%)	19 (38%)	7 (14%)	9 (18%)
Necrosis	3 (6%)		1 (2%)	4 (8%)
Pigmentation			1 (2%)	
Vacuolization cytoplasmic	7 (14%)	11 (22%)	9 (18%)	9 (18%)
Bile duct, hyperplasia	5 (10%)	12 (24%)	21 (42%)	32 (64%)
Centrilobular, degeneration	1 (2%)	5 (10%)	10 (20%)	7 (14%)
Centrilobular, hypertrophy		2 (4%)	24 (48%)	38 (76%)
Mesentery	(7)	(8)	(4)	(4)
Inflammation		2 (25%)		
Artery, inflammation		1 (13%)		1 (25%)
Fat, necrosis	6 (86%)	6 (75%)	4 (100%)	3 (75%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Atrophy	10 (20%)	8 (16%)	8 (16%)	8 (16%)
Cytoplasmic alteration			1 (2%)	1 (2%)
Hyperplasia		1 (2%)		1 (2%)
Inflammation	5 (10%)	2 (4%)	7 (14%)	3 (6%)
Metaplasia, hepatocyte				1 (2%)
Thrombosis		1 (2%)		
Artery, inflammation		1 (2%)		1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	2 (4%)	
Cytoplasmic alteration	1 (2%)	1 (2%)	1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema			1 (2%)	
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation	1 (2%)		1 (2%)	
Ulcer			2 (4%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	2 (4%)	1 (2%)		3 (6%)
Inflammation	1 (2%)	1 (2%)		
Mineralization			1 (2%)	1 (2%)
Ulcer	3 (6%)	1 (2%)	3 (6%)	
Tooth				(4)
Inflammation				1 (25%)
Periodontal tissue, inflammation				3 (75%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		
Aorta, inflammation				1 (2%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	30 (60%)	23 (46%)	23 (46%)	27 (54%)
Inflammation	5 (10%)	4 (8%)		1 (2%)
Thrombosis		1 (2%)	1 (2%)	
Valve, inflammation			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule				1 (2%)
Angiectasis	27 (54%)	21 (42%)	26 (52%)	26 (52%)
Degeneration, cystic	3 (6%)	1 (2%)	2 (4%)	
Hyperplasia	14 (28%)	11 (22%)	19 (38%)	18 (36%)
Hypertrophy	4 (8%)	4 (8%)	5 (10%)	3 (6%)
Inflammation			1 (2%)	
Necrosis			1 (2%)	2 (4%)
Vacuolization cytoplasmic	3 (6%)	6 (12%)	5 (10%)	1 (2%)
Adrenal medulla	(50)	(49)	(50)	(50)
Angiectasis			2 (4%)	
Hyperplasia	4 (8%)	8 (16%)	3 (6%)	1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(49)	(50)	(50)
Angiectasis	19 (38%)	17 (35%)	23 (46%)	21 (42%)
Cyst	4 (8%)	4 (8%)		3 (6%)
Pars distalis, hyperplasia	23 (46%)	28 (57%)	23 (46%)	24 (48%)
Pars intermedia, hyperplasia			1 (2%)	
Pars nervosa, hyperplasia			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Cyst	1 (2%)			
C-cell, hyperplasia	35 (70%)	38 (76%)	34 (68%)	23 (46%)
Follicular cell, hyperplasia	1 (2%)	1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(47)	(50)	(50)	(48)
Hyperplasia	6 (13%)	6 (12%)	6 (12%)	3 (6%)
Inflammation	16 (34%)	17 (34%)	21 (42%)	18 (38%)
Duct, cyst	3 (6%)	5 (10%)	2 (4%)	3 (6%)
Ovary	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)	1 (2%)	
Cyst	3 (6%)	7 (14%)	3 (6%)	2 (4%)
Infiltration cellular, histiocyte		2 (4%)	3 (6%)	1 (2%)
Inflammation	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Dilatation				1 (2%)
Hemorrhage			1 (2%)	
Hydrometra	2 (4%)		4 (8%)	
Hyperplasia				1 (2%)
Inflammation		1 (2%)		1 (2%)
Cervix, cyst, squamous			1 (2%)	1 (2%)
Cervix, hydrometra			1 (2%)	
Cervix, hyperplasia, squamous			1 (2%)	
Cervix, inflammation	1 (2%)		1 (2%)	2 (4%)
Endometrium, adenomyosis				1 (2%)
Endometrium, hyperplasia, cystic	3 (6%)	7 (14%)	7 (14%)	6 (12%)
Vagina		(2)		
Hyperplasia		1 (50%)		
Inflammation		2 (100%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Hyperplasia	9 (18%)	12 (24%)	8 (16%)	12 (24%)
Inflammation, granulomatous			2 (4%)	
Myelofibrosis	1 (2%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Hematopoietic System (continued)				
Lymph node	(27)	(23)	(28)	(28)
Mediastinal, congestion				1 (4%)
Mediastinal, ectasia				1 (4%)
Mediastinal, hyperplasia, plasma cell		1 (4%)		
Mediastinal, pigmentation	26 (96%)	19 (83%)	26 (93%)	24 (86%)
Lymph node, mandibular	(49)	(50)	(48)	(50)
Ectasia	1 (2%)	8 (16%)	5 (10%)	5 (10%)
Hyperplasia, plasma cell		4 (8%)	1 (2%)	5 (10%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, plasma cell		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Accessory spleen			1 (2%)	
Fibrosis			2 (4%)	1 (2%)
Hematopoietic cell proliferation	3 (6%)	4 (8%)	7 (14%)	2 (4%)
Infarct			1 (2%)	
Pigmentation	25 (50%)	26 (52%)	28 (56%)	32 (64%)
Capsule, fibrosis		1 (2%)		
Lymphoid follicle, atrophy		1 (2%)	1 (2%)	3 (6%)
Thymus	(46)	(48)	(50)	(48)
Atrophy	46 (100%)	46 (96%)	47 (94%)	48 (100%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Cyst			1 (2%)	1 (2%)
Dilatation	2 (4%)			
Galactocele	1 (2%)		6 (12%)	1 (2%)
Hyperplasia	14 (28%)	19 (38%)	20 (40%)	10 (20%)
Skin	(50)	(50)	(50)	(49)
Inflammation				1 (2%)
Ulcer				2 (4%)
Subcutaneous tissue, inflammation		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	2 (4%)	2 (4%)	6 (12%)	4 (8%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)		1 (2%)	
Inflammation				1 (2%)
Necrosis				1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Edema				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation	23 (46%)	21 (42%)	23 (46%)	31 (62%)
Necrosis				2 (4%)
Pigmentation	40 (80%)	40 (80%)	42 (84%)	35 (70%)
Thrombosis		1 (2%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	8 (16%)	7 (14%)	9 (18%)	9 (18%)
Bronchiole, hyperplasia		1 (2%)		
Mediastinum, thrombosis				1 (2%)
Serosa, inflammation				1 (2%)
Nose	(50)	(50)	(50)	(50)
Foreign body	2 (4%)		1 (2%)	
Inflammation	3 (6%)	2 (4%)	4 (8%)	4 (8%)
Nasolacrimal duct, inflammation				1 (2%)
Trachea	(50)	(50)	(50)	(50)
Inflammation	1 (2%)	1 (2%)		1 (2%)
Special Senses System				
Eye	(3)	(2)		(4)
Atrophy				1 (25%)
Cataract	1 (33%)	2 (100%)		3 (75%)
Hemorrhage	1 (33%)			1 (25%)
Cornea, edema				1 (25%)
Retina, degeneration	1 (33%)	2 (100%)		3 (75%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Glomerulosclerosis		1 (2%)		
Hydronephrosis	1 (2%)			1 (2%)
Infarct			1 (2%)	
Inflammation	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Nephropathy	39 (78%)	43 (86%)	42 (84%)	42 (84%)
Pigmentation	5 (10%)	2 (4%)	9 (18%)	9 (18%)
Vacuolization cytoplasmic		1 (2%)		
Pelvis, inflammation	2 (4%)	1 (2%)		
Renal tubule, hyperplasia		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Calculus, gross observation				1 (2%)
Calculus, microscopic observation only	1 (2%)			
Serosa, fibrosis		1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)			1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF *p,p′*-DICHLORODIPHENYL SULFONE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	1	2	2	3
Natural deaths	9	3	4	5
Survivors				
Died last week of study			1	
Terminal sacrifice	40	45	43	42
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Intestine small, duodenum	(50)	(50)	(49)	(50)
Polyp adenomatous		1 (2%)		2 (4%)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)			1 (2%)
Hepatocellular carcinoma	8 (16%)	2 (4%)	4 (8%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)		1 (2%)
Hepatocellular adenoma	4 (8%)	8 (16%)	4 (8%)	9 (18%)
Hepatocellular adenoma, multiple	2 (4%)	1 (2%)	1 (2%)	
Histiocytic sarcoma			1 (2%)	
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Oral mucosa	(50)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Tongue			(1)	
Squamous cell carcinoma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Adenoma		1 (2%)		
Adrenal medulla	(49)	(50)	(50)	(50)
Islets, pancreatic	(50)	(49)	(49)	(49)
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(49)
Follicular cell, adenoma	1 (2%)		1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Prostate	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangioma		1 (2%)		
Hemangiosarcoma			1 (2%)	
Mast cell tumor malignant	1 (2%)	1 (2%)		1 (2%)
Lymph node	(2)	(1)	(1)	(1)
Lymph node, mandibular	(46)	(49)	(48)	(50)
Lymph node, mesenteric	(48)	(45)	(47)	(46)
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Spleen	(50)	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma			1 (2%)	
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			
Thymus	(45)	(47)	(39)	(44)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, mast cell tumor malignant	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meninges, meningioma malignant			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	3 (6%)	
Alveolar/bronchiolar adenoma, multiple	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	7 (14%)	5 (10%)	4 (8%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Carcinoma, metastatic, harderian gland		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	6 (12%)		1 (2%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow		1 (2%)		
Special Senses System				
Harderian gland	(5)	(2)	(2)	(1)
Adenoma	4 (80%)	1 (50%)	2 (100%)	1 (100%)
Carcinoma		1 (50%)		
Bilateral, adenoma	1 (20%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Mast cell tumor malignant, metastatic, bone marrow	1 (2%)			1 (2%)
Renal tubule, adenoma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	32	28	22	21
Total primary neoplasms	43	37	29	27
Total animals with benign neoplasms	16	18	11	12
Total benign neoplasms	19	21	13	14
Total animals with malignant neoplasms	21	16	12	11
Total malignant neoplasms	24	16	16	13
Total animals with metastatic neoplasms	7	2	1	2
Total metastatic neoplasms	15	2	1	3

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	0 3 0	5 5 0	6 0 3	6 3 1	6 4 9	6 6 1	6 6 6	6 9 1	6 9 3	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4
Carcass ID Number	0 0 3	0 3 9	0 2 3	0 1 3	0 2 4	0 5 0	0 4 3	0 1 2	0 1 6	0 3 1	0 0 6	0 0 7	0 0 9	0 1 5	0 1 7	0 1 8	0 1 9	0 2 7	0 2 9	0 3 4	0 3 6	0 4 1	0 4 4	0 4 8	0 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Hepatocellular carcinoma					X			X	X					X		X									
Hepatocellular carcinoma, multiple				X																					
Hepatocellular adenoma																	X								
Hepatocellular adenoma, multiple																					X				
Mast cell tumor malignant, metastatic, bone marrow																									
Mesentery			+																						
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Parathyroid gland	+	M	+	M	M	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma															X										

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 0 2	0 0 8	0 0 1 0	0 2 0	0 2 1	0 2 6	0 2 8	0 3 0	0 3 2	0 3 3	0 3 5	0 3 7	0 3 8	0 4 2	0 4 7	0 4 9	0 4 4	0 5 5	0 1 1	0 1 4	0 2 2	0 2 5	0 4 0	0 4 5	0 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													2
Hepatocellular carcinoma					X				X										X							8
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma																	X	X							X	4
Hepatocellular adenoma, multiple								X																		2
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Mesentery							+		+																	3
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	M	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	0 3 0	5 5 0	6 0 3	6 3 1	6 4 9	6 6 1	6 6 6	6 9 1	6 9 3	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4
Carcass ID Number	0 0 3	0 3 9	0 2 3	0 1 3	0 2 4	0 5 0	0 4 3	0 1 2	0 1 6	0 3 1	0 0 6	0 0 7	0 0 9	0 1 5	0 1 7	0 1 8	0 1 9	0 2 7	0 2 9	0 3 4	0 3 6	0 4 1	0 4 4	0 4 8	0 4 1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Lymph node		+																			+				
Lymph node, mandibular	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Mast cell tumor malignant, metastatic, bone marrow																									
Thymus	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, mast cell tumor malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma						X					X			X											
Hepatocellular carcinoma, metastatic, liver				X				X	X					X		X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	73 34	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 55	73 55	73 55	73 55	73 55	73 55	73 55	73 55	73 55	
Carcass ID Number	00 02	00 08	00 10	00 20	00 21	00 26	00 28	00 30	00 32	00 33	00 35	00 37	00 38	00 42	00 47	00 49	00 04	00 05	00 11	00 14	00 22	00 25	00 40	00 45	00 46	Total Tissues/ Tumors	
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Interstitial cell, adenoma			X																							1	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Mast cell tumor malignant		X																								1	
Lymph node																										2	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46	
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Mast cell tumor malignant, metastatic, bone marrow		X																								1	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hemangiosarcoma																										1	
Mast cell tumor malignant, metastatic, bone marrow		X																								1	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45	
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Subcutaneous tissue, mast cell tumor malignant		X																								1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma														X											X	3	
Alveolar/bronchiolar adenoma, multiple								X														X	X			3	
Alveolar/bronchiolar carcinoma			X								X										X			X		7	
Hepatocellular carcinoma, metastatic, liver																			X							6	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	0 3 0	5 5 0	6 0 3	6 3 1	6 4 9	6 6 1	6 6 6	6 9 1	6 9 3	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4
Carcass ID Number	0 0 3	0 3 9	0 2 3	0 1 3	0 2 4	0 5 0	0 4 3	0 1 2	0 1 6	0 3 1	0 0 6	0 0 7	0 0 9	0 1 5	0 1 7	0 1 8	0 1 9	0 2 7	0 2 9	0 3 4	0 3 6	0 4 1	0 4 4	0 4 8	0 4 1
Special Senses System																									
Harderian gland																								+	
Adenoma																								X	
Bilateral, adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																									
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant		X			X																X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 0 2	0 0 8	0 1 0	0 2 0	0 2 1	0 2 6	0 2 8	0 3 0	0 3 2	0 3 3	0 3 5	0 3 7	0 3 8	0 4 2	0 4 7	0 4 9	0 0 4	0 0 5	0 1 1	0 1 4	0 2 2	0 2 5	0 4 0	0 4 5	0 4 6	Total Tissues/ Tumors
Special Senses System																										
Harderian gland	+	+																	+						+	5
Adenoma	X	X																	X							4
Bilateral, adenoma																									X	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow		X																								1
Ureter							+																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	0 6 1	5 6 5	6 5 2	7 1 2	7 1 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4
Carcass ID Number	0 0 9 3	0 0 9 4	0 0 9 2	0 0 6 3	0 0 6 9	0 0 5 6	0 0 6 0	0 0 6 4	0 0 7 1	0 0 7 5	0 0 7 9	0 0 8 0	0 0 8 1	0 0 8 2	0 0 8 3	0 0 8 4	0 0 8 5	0 0 8 7	0 0 9 0	0 0 9 8	0 0 9 9	0 1 0 0	0 0 5 1	0 0 5 4	0 0 5 7
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous				X																						
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X																	
Hepatocellular carcinoma, multiple																						X				
Hepatocellular adenoma		X																			X		X			
Hepatocellular adenoma, multiple																										
Mesentery												+														+
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 5 8	0 5 9	0 6 2	0 6 5	0 6 6	0 7 0	0 7 2	0 7 3	0 7 6	0 7 7	0 7 8	0 8 8	0 8 9	0 9 1	0 9 6	0 9 7	0 5 2	0 5 3	0 5 5	0 6 1	0 6 7	0 6 8	0 7 4	0 8 6	0 9 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X								1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																			X							2
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X				X			X	X								X							8
Hepatocellular adenoma, multiple													X													1
Mesentery																										2
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma											X															1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	0 6 1	5 6 5	6 5 2	7 1 2	7 1 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 3 4
Carcass ID Number	0 0 9 3	0 0 9 4	0 0 9 2	0 0 6 3	0 0 6 9	0 0 5 6	0 0 6 0	0 0 6 4	0 0 7 1	0 0 7 5	0 0 7 9	0 0 8 0	0 0 8 1	0 0 8 2	0 0 8 3	0 0 8 4	0 0 8 5	0 0 8 7	0 0 9 0	0 0 9 8	0 0 9 9	0 1 0 0	0 0 5 1	0 0 5 4	0 0 5 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Mast cell tumor malignant				X																					
Lymph node																					+				
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							X
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma					X											X									
Alveolar/bronchiolar carcinoma, multiple																	X								
Carcinoma, metastatic, harderian gland			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																						
Harderian gland			+																						
Adenoma																									
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																				X	X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 5 8	0 5 9	0 6 2	0 6 5	0 6 6	0 7 0	0 7 2	0 7 3	0 7 6	0 7 7	0 7 8	0 8 8	0 8 9	0 9 1	0 9 6	0 9 7	0 5 2	0 5 3	0 5 5	0 6 1	0 6 7	0 6 8	0 7 4	0 8 6	0 9 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma	X																									1
Mast cell tumor malignant																										1
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Thymus	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X																X					5
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma													X				X				X					5
Alveolar/bronchiolar carcinoma, multiple																										1
Carcinoma, metastatic, harderian gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland				+																						2
Adenoma				X																						1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																						X				3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	0 1 5	4 0 6	4 1 3	5 1 3	6 4 9	7 0 5	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 1 5	1 0 2	1 4 9	1 3 2	1 2 9	1 3 6	1 0 1	1 0 3	1 0 4	1 0 6	1 0 9	1 1 0	1 1 2	1 1 3	1 1 4	1 1 7	1 2 0	1 2 1	1 2 2	1 2 5	1 2 8	1 3 1	1 3 3	1 3 8	1 3 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X															X						
Hepatocellular adenoma													X			X									
Hepatocellular adenoma, multiple									X																
Histiocytic sarcoma					X																				
Mesentery							+																		
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma									X																
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma									X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 4 2	1 5 0	1 0 5	1 0 8	1 1 1	1 1 6	1 1 8	1 2 7	1 3 0	1 3 4	1 3 5	1 3 7	1 4 0	1 4 3	1 4 4	1 4 5	1 4 6	1 4 8	1 0 7	1 1 9	1 2 3	1 2 4	1 2 6	1 4 1	1 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X								X													4
Hepatocellular adenoma				X													X									4
Hepatocellular adenoma, multiple																										1
Histiocytic sarcoma																										1
Mesentery																										1
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																									+	1
Squamous cell carcinoma																									X	1
Tooth															+											1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	0 1 5	4 0 6	4 1 3	5 1 3	6 4 9	7 0 5	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 1 5	1 0 2	1 4 9	1 3 2	1 2 9	1 3 6	1 0 1	1 0 3	1 0 4	1 0 6	1 0 9	1 1 0	1 1 2	1 1 3	1 1 4	1 1 7	1 2 0	1 2 1	1 2 2	1 2 5	1 2 8	1 3 1	1 3 3	1 3 8	1 3 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Histiocytic sarcoma					X																				
Thymus	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, meningioma malignant			X																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple							X																		
Alveolar/bronchiolar carcinoma															X										
Hepatocellular carcinoma, metastatic, liver				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland														+						+					
Adenoma														X						X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymphoma malignant						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 4 2	1 5 0	1 0 5	1 0 8	1 1 1	1 1 6	1 1 8	1 2 7	1 3 0	1 3 4	1 3 5	1 3 7	1 4 0	1 4 3	1 4 4	1 4 5	1 4 6	1 4 8	1 0 7	1 1 9	1 2 3	1 2 4	1 2 6	1 4 1	1 4 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																						+				1
Lymph node, mandibular	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	M	M	+	M	+	+	+	+	39
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, meningioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X									X			X							3
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma		X																				X			X	4
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																						X				2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	0 1 6	3 6 9	3 7 9	4 0 7	4 8 5	6 0 9	7 0 2	7 1 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 5 7	1 6 5	1 7 4	1 8 3	1 8 1	1 6 1	1 5 6	1 9 1	1 5 2	1 5 3	1 5 4	1 6 3	1 6 4	1 6 6	1 7 1	1 7 2	1 7 5	1 7 7	1 7 8	1 7 9	1 8 2	1 8 6	1 9 0	1 9 3	1 9 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous										X															
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Hepatocellular carcinoma							X																	X	
Hepatocellular carcinoma, multiple				X																					
Hepatocellular adenoma		X							X	X				X			X								
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+															
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	M	+	M	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	
Carcass ID Number	15 1	15 5	15 9	16 0	16 2	17 0	17 6	18 0	18 4	18 5	18 7	18 9	19 2	19 4	19 6	19 8	20 8	16 7	16 8	16 9	17 3	18 8	19 5	19 7	20 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous			X																							2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma							X		X																	4
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X						X										X				X					9
Oral mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	0 1 6	3 6 9	3 7 9	4 0 7	4 8 5	6 0 9	7 0 2	7 1 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 5 7	1 6 5	1 7 4	1 8 3	1 8 1	1 6 1	1 5 6	1 9 1	1 5 2	1 5 3	1 5 4	1 6 3	1 6 4	1 6 6	1 7 1	1 7 2	1 7 5	1 7 7	1 7 8	1 7 9	1 8 2	1 8 6	1 9 0	1 9 3	1 9 9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																		X								
Lymph node																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X												
Thymus	+	+	+	+	M	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																				
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+																				
Spinal cord						+																				
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple						X																				
Alveolar/bronchiolar carcinoma								X												X						
Hepatocellular carcinoma, metastatic, liver																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X												
Mast cell tumor malignant, metastatic, bone marrow																		X								
Urinary Bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 5 1	1 5 5	1 5 9	1 6 0	1 6 2	1 7 0	1 7 6	1 8 0	1 8 4	1 8 5	1 8 7	1 8 9	1 9 2	1 9 4	1 9 6	1 9 8	1 5 8	1 6 7	1 6 8	1 6 9	1 7 3	1 8 8	1 9 5	1 9 7	2 0 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
Lymph node								+																		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma, multiple																							X			2
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver							X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland																							+			1
Adenoma																							X			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Mast cell tumor malignant, metastatic, bone marrow																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant								X																		1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Harderian Gland: Adenoma				
Overall rate[a]	5/50 (10%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate[b]	10.8%	2.1%	4.3%	2.2%
Terminal rate[c]	5/40 (13%)	1/45 (2%)	2/44 (5%)	1/42 (2%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)
Poly-3 test[d]	P=0.176N	P=0.094N	P=0.218N	P=0.109N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate	10.8%	4.1%	4.3%	2.2%
Terminal rate	5/40 (13%)	1/45 (2%)	2/44 (5%)	1/42 (2%)
First incidence (days)	733 (T)	652	733 (T)	733 (T)
Poly-3 test	P=0.138N	P=0.201N	P=0.218N	P=0.109N
Liver: Hepatocellular Adenoma				
Overall rate	6/50 (12%)	9/50 (18%)	5/50 (10%)	9/50 (18%)
Adjusted rate	12.9%	18.5%	10.8%	19.6%
Terminal rate	6/40 (15%)	8/45 (18%)	5/44 (11%)	8/42 (19%)
First incidence (days)	733 (T)	565	733 (T)	369
Poly-3 test	P=0.312	P=0.320	P=0.503N	P=0.279
Liver: Hepatocellular Carcinoma				
Overall rate	9/50 (18%)	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted rate	19.0%	6.2%	8.5%	10.9%
Terminal rate	5/40 (13%)	3/45 (7%)	3/44 (7%)	3/42 (7%)
First incidence (days)	631	733 (T)	513	407
Poly-3 test	P=0.394N	P=0.057N	P=0.120N	P=0.210N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	15/50 (30%)	11/50 (22%)	9/50 (18%)	13/50 (26%)
Adjusted rate	31.6%	22.7%	19.2%	27.7%
Terminal rate	11/40 (28%)	10/45 (22%)	8/44 (18%)	10/42 (24%)
First incidence (days)	631	565	513	369
Poly-3 test	P=0.547	P=0.225N	P=0.124N	P=0.425N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	6/50 (12%)	4/50 (8%)	2/50 (4%)
Adjusted rate	12.8%	12.4%	8.6%	4.4%
Terminal rate	5/40 (13%)	5/45 (11%)	4/44 (9%)	1/42 (2%)
First incidence (days)	631	565	733 (T)	609
Poly-3 test	P=0.095N	P=0.595N	P=0.377N	P=0.142N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	7/50 (14%)	6/50 (12%)	4/50 (8%)	2/50 (4%)
Adjusted rate	15.0%	12.5%	8.6%	4.4%
Terminal rate	6/40 (15%)	5/45 (11%)	4/44 (9%)	1/42 (2%)
First incidence (days)	661	718	733 (T)	712
Poly-3 test	P=0.067N	P=0.478N	P=0.267N	P=0.087N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/50 (26%)	11/50 (22%)	8/50 (16%)	4/50 (8%)
Adjusted rate	27.6%	22.6%	17.3%	8.8%
Terminal rate	11/40 (28%)	9/45 (20%)	8/44 (18%)	2/42 (5%)
First incidence (days)	631	565	733 (T)	609
Poly-3 test	P=0.015N	P=0.373N	P=0.172N	P=0.017N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.4%	2.1%	2.2%	2.2%
Terminal rate	2/40 (5%)	1/45 (2%)	1/44 (2%)	1/42 (2%)
First incidence (days)	603	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.358N	P=0.297N	P=0.310N	P=0.320N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.4%	4.2%	2.2%	2.2%
Terminal rate	2/40 (5%)	2/45 (4%)	1/44 (2%)	1/42 (2%)
First incidence (days)	603	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.278N	P=0.489N	P=0.310N	P=0.320N
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.3%	6.2%	4.3%	2.2%
Terminal rate	1/40 (3%)	3/45 (7%)	1/44 (2%)	1/42 (2%)
First incidence (days)	550	733 (T)	705	733 (T)
Poly-3 test	P=0.228N	P=0.656N	P=0.509N	P=0.323N
All Organs: Benign Neoplasms				
Overall rate	16/50 (32%)	18/50 (36%)	11/50 (22%)	12/50 (24%)
Adjusted rate	34.2%	37.0%	23.8%	25.9%
Terminal rate	15/40 (38%)	15/45 (33%)	11/44 (25%)	10/42 (24%)
First incidence (days)	631	565	733 (T)	369
Poly-3 test	P=0.162N	P=0.472	P=0.190N	P=0.259N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	16/50 (32%)	12/50 (24%)	11/50 (22%)
Adjusted rate	43.1%	33.0%	24.9%	23.8%
Terminal rate	14/40 (35%)	13/45 (29%)	8/44 (18%)	8/42 (19%)
First incidence (days)	550	652	413	407
Poly-3 test	P=0.049N	P=0.209N	P=0.046N	P=0.037N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	32/50 (64%)	28/50 (56%)	22/50 (44%)	21/50 (42%)
Adjusted rate	65.6%	57.1%	45.7%	44.3%
Terminal rate	25/40 (63%)	24/45 (53%)	18/44 (41%)	16/42 (38%)
First incidence (days)	550	565	413	369
Poly-3 test	P=0.032N	P=0.257N	P=0.036N	P=0.027N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.

TABLE C4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Male B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	6/50	7/50	13/50
Indium phosphide (inhalation)	13/50	6/50	18/50
Methacrylonitrile (gavage)	2/49	4/49	6/49
p-Nitrotoluene (feed)	6/50	2/50	8/50
Sodium nitrite (drinking water)	10/50	4/50	13/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	37/249 (14.9%)	23/249 (9.2%)	58/249 (23.3%)
Mean ± standard deviation	14.8% ± 8.4%	9.2% ± 3.9%	23.3% ± 9.4%
Range	4%-26%	4%-14%	12%-36%
Historical Incidence in Feed Controls Given NIH-07 Diet at Battelle Columbus Laboratory[b]			
Anthraquinone	6/50	3/50	8/50
4,4′-Thiobis-(6-*t*-butyl-*m*-cresol)	11/50	8/50	17/50
Manganese (II) sulfate monohydrate	7/50	5/50	12/50
Oxazepam	11/50	2/50	13/50
Primidone	7/50	4/50	11/50
Triamterene	3/50	6/50	9/50
Triamterene	6/50	7/50	13/50
Tricresyl phosphate	7/52	1/52	8/52
Overall Historical Incidence in Feed Controls Given NIH-07 Diet			
Total (%)	172/952 (18.1%)	72/952 (7.6%)	236/952 (24.8%)
Mean ± standard deviation	18.1% ± 6.7%	7.6% ± 5.2%	24.8% ± 7.0%
Range	6%-30%	2%-20%	12%-36%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	1	2	2	3
Natural deaths	9	3	4	5
Survivors				
Died last week of study			1	
Terminal sacrifice	40	45	43	42
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(50)	(50)	(49)	(50)
Epithelium, necrosis	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Congestion		1 (2%)		1 (2%)
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	3 (6%)	4 (8%)	1 (2%)	
Clear cell focus	4 (8%)	6 (12%)	3 (6%)	4 (8%)
Clear cell focus, multiple	1 (2%)			
Eosinophilic focus	2 (4%)	8 (16%)	6 (12%)	6 (12%)
Eosinophilic focus, multiple	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Fatty change, diffuse				2 (4%)
Fatty change, focal			1 (2%)	
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule			1 (2%)	
Infarct	1 (2%)			
Inflammation, focal, suppurative	4 (8%)			
Inflammation, granulomatous	1 (2%)		1 (2%)	
Mixed cell focus	1 (2%)	3 (6%)		3 (6%)
Mixed cell focus, multiple		1 (2%)		
Necrosis, focal	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Tension lipidosis	4 (8%)	1 (2%)	3 (6%)	1 (2%)
Vacuolization cytoplasmic		1 (2%)	1 (2%)	
Vacuolization cytoplasmic, focal		1 (2%)		
Bile duct, cyst		1 (2%)		
Centrilobular, degeneration				1 (2%)
Centrilobular, hypertrophy	1 (2%)	24 (48%)	43 (86%)	45 (90%)
Centrilobular, necrosis	2 (4%)			
Vein, congestion				1 (2%)
Mesentery	(3)	(2)	(1)	
Inflammation, granulomatous	1 (33%)			
Fat, necrosis	2 (67%)	2 (100%)	1 (100%)	
Oral mucosa	(50)	(50)	(50)	(50)
Ulcer	23 (46%)	27 (54%)	25 (50%)	18 (36%)
Gingival, inflammation, chronic	37 (74%)	36 (72%)	34 (68%)	33 (66%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Alimentary System (continued)				
Pancreas	(50)	(49)	(50)	(49)
Inflammation, chronic		3 (6%)	1 (2%)	1 (2%)
Acinus, atrophy				1 (2%)
Acinus, hypertrophy, focal	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, diffuse				1 (2%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Ulcer	1 (2%)			
Epithelium, hyperplasia, focal			2 (4%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion			1 (2%)	
Ulcer	1 (2%)			
Epithelium, hypertrophy				1 (2%)
Tooth			(1)	(1)
Inflammation, suppurative			1 (100%)	
Malformation				1 (100%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, mineralization				1 (2%)
Heart	(50)	(50)	(50)	(50)
Infiltration cellular, focal, lymphocyte			1 (2%)	
Artery, inflammation, chronic		1 (2%)	1 (2%)	4 (8%)
Artery, coronary artery, thrombosis		1 (2%)		
Atrium, thrombosis	1 (2%)			
Myocardium, degeneration		3 (6%)	1 (2%)	1 (2%)
Myocardium, mineralization	3 (6%)			
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Atrophy		1 (2%)		
Cytoplasmic alteration, focal	10 (20%)	13 (26%)	11 (22%)	7 (14%)
Hyperplasia, focal	3 (6%)	4 (8%)	1 (2%)	3 (6%)
Hypertrophy, focal	14 (29%)	16 (32%)	21 (42%)	15 (30%)
Subcapsular, hyperplasia	40 (82%)	42 (84%)	41 (82%)	44 (88%)
Islets, pancreatic	(50)	(49)	(49)	(49)
Hyperplasia	13 (26%)	13 (27%)	7 (14%)	9 (18%)
Parathyroid gland	(39)	(40)	(42)	(39)
Cyst		1 (3%)	1 (2%)	
Pituitary gland	(49)	(50)	(49)	(50)
Cyst		2 (4%)	1 (2%)	
Pars distalis, hyperplasia, focal		1 (2%)	1 (2%)	
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	2 (4%)		2 (4%)	2 (4%)
Hemorrhage			1 (2%)	1 (2%)
Preputial gland	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Cyst	26 (52%)	23 (46%)	25 (50%)	11 (22%)
Inflammation, chronic active	31 (62%)	29 (58%)	23 (46%)	14 (28%)
Inflammation, suppurative	6 (12%)	3 (6%)		2 (4%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)		
Artery, inflammation, chronic				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Fibrosis, chronic				1 (2%)
Inflammation, suppurative				1 (2%)
Artery, inflammation, chronic				1 (2%)
Testes	(50)	(50)	(50)	(50)
Fibrosis, focal		1 (2%)		
Germinal epithelium, atrophy	1 (2%)	1 (2%)	3 (6%)	4 (8%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Necrosis	1 (2%)			
Lymph node, mandibular	(46)	(49)	(48)	(50)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	6 (12%)	4 (8%)	
Hyperplasia, plasma cell	1 (2%)			
Lymph node, mesenteric	(48)	(45)	(47)	(46)
Angiectasis				1 (2%)
Ectasia	1 (2%)			1 (2%)
Erythrophagocytosis	1 (2%)			2 (4%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	4 (9%)	
Vein, ectasia	1 (2%)			
Spleen	(50)	(50)	(50)	(49)
Hematopoietic cell proliferation	17 (34%)	12 (24%)	9 (18%)	13 (27%)
Capsule, inflammation, acute			1 (2%)	
Lymphoid follicle, atrophy	8 (16%)	2 (4%)	3 (6%)	8 (16%)
Lymphoid follicle, hyperplasia	1 (2%)	5 (10%)	7 (14%)	2 (4%)
Thymus	(45)	(47)	(39)	(44)
Atrophy	25 (56%)	35 (74%)	25 (64%)	20 (45%)
Cyst	4 (9%)	6 (13%)	6 (15%)	5 (11%)
Hyperplasia		1 (2%)		1 (2%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			
Sebaceous gland, hyperplasia	1 (2%)			
Subcutaneous tissue, edema	1 (2%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosis		1 (2%)		2 (4%)
Skeletal muscle				(1)
Degeneration, focal				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Cerebrum, necrosis				1 (2%)
Peripheral nerve				(1)
Axon, degeneration				1 (100%)
Spinal cord				(1)
Axon, degeneration				1 (100%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Erythrophagocytosis, focal			1 (2%)	
Hematopoietic cell proliferation				1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Inflammation, chronic, focal	1 (2%)		1 (2%)	
Inflammation, granulomatous		2 (4%)		1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia, focal		2 (4%)	2 (4%)	4 (8%)
Bronchus, foreign body				1 (2%)
Bronchus, inflammation, suppurative			1 (2%)	
Serosa, inflammation, chronic, focal		1 (2%)		
Vein, mineralization	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Sinus, inflammation, chronic		1 (2%)		
Sinus, inflammation, suppurative	2 (4%)			
Turbinate, inflammation, suppurative	3 (6%)	2 (4%)	1 (2%)	
Special Senses System				
Eye		(1)		
Degeneration		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct		1 (2%)	2 (4%)	1 (2%)
Metaplasia, osseous	1 (2%)			
Nephropathy	36 (72%)	44 (88%)	42 (84%)	36 (72%)
Artery, inflammation, chronic				1 (2%)
Pelvis, inflammation, chronic active		1 (2%)		
Pelvis, transitional epithelium, mineralization				1 (2%)
Renal tubule, cyst	1 (2%)	3 (6%)		1 (2%)
Renal tubule, necrosis, acute				3 (6%)
Ureter	(1)			
Cyst	1 (100%)			

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF *p,p′*-DICHLORODIPHENYL SULFONE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	1	1	1
Natural deaths	5	9	6	4
Survivors				
Terminal sacrifice	42	40	43	45
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(49)	(50)	(50)
Squamous cell papilloma				1 (2%)
Gallbladder	(49)	(49)	(50)	(49)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Leiomyosarcoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Hemangioma			1 (2%)	
Hepatocellular carcinoma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hepatocellular adenoma	4 (8%)	4 (8%)	6 (12%)	7 (14%)
Hepatocellular adenoma, multiple				1 (2%)
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Sarcoma, metastatic, skin				1 (2%)
Mesentery	(5)	(2)	(5)	(5)
Sarcoma NOS			1 (20%)	1 (20%)
Pancreas	(50)	(49)	(50)	(50)
Salivary glands	(49)	(48)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)	
Tongue				(1)
Epithelium, squamous cell carcinoma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Adrenal medulla	(50)	(49)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Pituitary gland	(48)	(46)	(48)	(48)
Pars distalis, adenoma	3 (6%)	2 (4%)	6 (13%)	6 (13%)
Pars intermedia, adenoma	1 (2%)		1 (2%)	1 (2%)
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, adenoma	2 (4%)	1 (2%)		1 (2%)
General Body System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Genital System				
Ovary	(50)	(48)	(49)	(48)
Cystadenoma	2 (4%)	4 (8%)		2 (4%)
Granulosa cell tumor benign	1 (2%)			
Histiocytic sarcoma		1 (2%)		2 (4%)
Bilateral, cystadenoma			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		2 (4%)
Polyp stromal	1 (2%)	1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma				2 (4%)
Lymph node	(3)	(6)	(4)	(4)
Bronchial, histiocytic sarcoma		1 (17%)		
Mediastinal, carcinoma, metastatic, islets, pancreatic	1 (33%)			
Mediastinal, histiocytic sarcoma		1 (17%)		
Renal, histiocytic sarcoma		1 (17%)		
Lymph node, mandibular	(47)	(47)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymph node, mesenteric	(50)	(46)	(49)	(46)
Histiocytic sarcoma		1 (2%)		
Spleen	(49)	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Thymus	(49)	(48)	(50)	(50)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, myxosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma NOS				3 (6%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			
Nervous System				
Brain	(50)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Cranial nerve, schwannoma malignant		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		4 (8%)	1 (2%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma		2 (4%)	1 (2%)	2 (4%)
Carcinoma, metastatic, islets, pancreatic	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal cortex	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(1)	(3)	(3)	(1)
Harderian gland	(3)	(2)	(2)	(2)
Adenoma	3 (100%)	2 (100%)	2 (100%)	1 (50%)
Carcinoma				1 (50%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant	6 (12%)	10 (20%)	5 (10%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	23	28	20	26
Total primary neoplasms	30	39	30	38
Total animals with benign neoplasms	15	15	15	16
Total benign neoplasms	17	18	20	23
Total animals with malignant neoplasms	12	18	9	14
Total malignant neoplasms	13	21	10	15
Total animals with metastatic neoplasms	3	1		1
Total metastatic neoplasms	4	1		1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	4 9 1	5 8 0	6 0 0	6 3 1	6 3 6	6 5 7	7 0 5	7 1 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 4 6	2 3 2	2 3 4	2 2 2	2 3 5	2 4 9	2 2 3	2 3 1	2 0 2	2 0 7	2 4 0	2 4 8	2 0 1	2 0 4	2 0 6	2 0 9	2 1 3	2 1 5	2 1 6	2 1 8	2 1 9	2 2 0	2 2 5	2 2 6	2 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X			X																		
Hepatocellular adenoma																									
Mesentery						+													+						
Oral mucosa						+			+	+	+	+			+		+	+	+	+	+	+	+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																						
Parathyroid gland	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	M	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X																			
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma									X																
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma												X													
Granulosa cell tumor benign					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									X

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	23 6	23 8	24 1	24 4	24 5	24 7	25 0	00 3	00 5	00 8	01 0	01 1	01 2	01 4	01 7	02 1	02 4	02 7	02 8	02 9	03 0	03 7	03 9	04 2	04 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																							X			3
Hepatocellular adenoma								X				X							X				X			4
Mesentery			+					+					+													5
Oral mucosa	+	+	+			+	+		+	+		+	+	+	+	+	+	+		+	+		+			31
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																				X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	M	+	+	M	M	34
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X																						X		3
Pars intermedia, adenoma																X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X														2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																								X		2
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	4 9 1	5 8 0	6 0 0	6 3 1	6 3 6	6 5 7	7 0 5	7 1 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 4 6	2 3 2	2 3 4	2 2 2	2 3 5	2 4 9	2 2 3	2 3 1	2 0 2	2 0 7	2 4 0	2 4 8	2 0 1	2 0 4	2 0 6	2 0 9	2 1 3	2 1 5	2 1 6	2 1 8	2 1 9	2 2 0	2 2 5	2 2 6	2 3 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+			+																	+		
Mediastinal, carcinoma, metastatic, islets, pancreatic			X																						
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, myxosarcoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic			X																						
Osteosarcoma, metastatic, bone					X																				
Pheochromocytoma malignant, metastatic, adrenal cortex																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+																	
Harderian gland																							+		
Adenoma																							X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X					X	X									X							X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 0 ppm

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 3 6	2 3 8	2 4 1	2 4 4	2 4 5	2 4 7	2 5 0	2 0 3	2 0 5	2 0 8	2 1 0	2 1 1	2 1 2	2 1 4	2 1 7	2 2 1	2 2 4	2 2 7	2 2 8	2 2 9	2 3 0	2 3 7	2 3 9	2 4 2	2 4 3	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Mediastinal, carcinoma, metastatic, islets, pancreatic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, myxosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Osteosarcoma, metastatic, bone																										1
Pheochromocytoma malignant, metastatic, adrenal cortex																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland			+						+																	3
Adenoma			X						X																	3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																		X								6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	5 1 2	5 1 2	5 5 0	5 9 2	6 0 5	6 1 6	6 6 7	6 9 0	6 9 4	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 9 0	2 9 8	3 0 0	2 5 2	2 5 9	2 6 5	2 7 2	2 9 4	2 8 2	2 8 1	2 6 2	2 6 6	2 7 3	2 7 9	2 8 3	2 9 3	2 9 6	2 5 8	2 6 0	2 6 1	2 6 3	2 6 4	2 7 1	2 7 8	2 8 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X																	
Hepatocellular adenoma													X												
Histiocytic sarcoma	X	X																							
Mesentery																									
Oral mucosa											+								+		+	+	+	+	
Pancreas	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X								X														
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma									X		X		X												
Histiocytic sarcoma		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Polyp stromal																							X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 8 5	2 8 7	2 8 9	2 9 1	2 9 5	2 9 7	2 9 9	2 5 1	2 5 3	2 5 4	2 5 5	2 5 6	2 5 7	2 6 7	2 6 8	2 6 9	2 7 0	2 7 4	2 7 5	2 7 6	2 7 7	2 8 0	2 8 6	2 8 8	2 9 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma									X																	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma												X			X		X									4
Histiocytic sarcoma																										2
Mesentery						+						+														2
Oral mucosa	+	+	+	+		+	+	+					+	+	+	+		+		+				+	+	21
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	M	M	+	+	+	+	M	M	+	+	M	M	+	M	+	+	+	+	+	+	M	M	35
Pituitary gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma											X															1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma										X																4
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Polyp stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	5 1 2	5 1 2	5 5 0	5 9 2	6 0 5	6 1 6	6 6 7	6 9 0	6 9 4	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 9 0	2 9 8	3 0 0	2 5 2	2 5 9	2 6 5	2 6 7	2 9 4	2 8 2	2 8 1	2 6 2	2 6 6	2 7 3	2 7 9	2 8 3	2 9 3	2 9 6	2 5 8	2 6 0	2 6 1	2 6 3	2 6 4	2 7 1	2 7 8	2 8 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Lymph node		+																		+				+	
Bronchial, histiocytic sarcoma		X																							
Mediastinal, histiocytic sarcoma		X																							
Renal, histiocytic sarcoma		X																							
Lymph node, mandibular	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymph node, mesenteric	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma		X																							
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Cranial nerve, schwannoma malignant	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X				X																	
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver								X																	
Histiocytic sarcoma		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																			+						+
Harderian gland																					+		+		
Adenoma																					X		X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	73 35	73 55	73 55	73 55	73 55	73 55	73 55	73 36	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	73 66	
Carcass ID Number	28 85	28 87	28 89	29 01	29 05	29 07	29 09	29 51	55 13	55 14	55 55	55 56	55 57	56 67	56 68	56 69	57 00	57 04	57 45	57 46	57 47	58 00	58 06	58 08	58 92	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+			+		+																				6
Bronchial, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X																						1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																						X				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Cranial nerve, schwannoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X	X																						4
Alveolar/bronchiolar carcinoma																		X			X					2
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																							3
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	5 1 2	5 1 2	5 5 0	5 9 2	6 0 5	6 1 6	6 6 7	6 9 0	6 9 4	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 9 0	2 9 8	3 0 0	2 5 2	2 5 9	2 6 5	2 7 2	2 9 4	2 8 2	2 8 1	2 6 2	2 6 6	2 7 3	2 7 9	2 8 3	2 9 3	2 9 6	2 5 8	2 6 0	2 6 1	2 6 3	2 6 4	2 7 1	2 7 8	2 8 4
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X	X																								
Lymphoma malignant									X									X		X				X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 30 ppm

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 8 5	2 8 7	2 8 9	2 9 1	2 9 5	2 9 7	2 9 9	2 5 1	2 5 3	2 5 4	2 5 5	2 5 6	2 5 7	2 6 7	2 6 8	2 6 9	2 7 0	2 7 4	2 7 5	2 7 6	2 7 7	2 8 0	2 8 6	2 8 8	2 9 2	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant	X			X		X						X		X					X							10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	5 8 6	6 5 2	6 8 3	7 0 2	7 0 9	7 1 1	7 3 2	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 1 9	3 4 7	3 1 0	3 0 2	3 1 8	3 2 9	3 3 7	3 0 4	3 0 9	3 1 2	3 1 5	3 1 7	3 2 1	3 2 3	3 2 4	3 2 6	3 3 1	3 3 2	3 3 6	3 3 8	3 4 5	3 0 1	3 0 7	3 1 1	3 1 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma				X																		X			
Histiocytic sarcoma							X																		
Mesentery	+				+					+		+											+		
Sarcoma NOS										X															
Oral mucosa			+	+		+		+	+	+	+	+		+		+		+		+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	M	M	+	+	+	+	+	M	M	+	M	+	M	M	M	M	M	+	+	+	M
Pituitary gland	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X	X					X			
Pars intermedia, adenoma		X																							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Bilateral, cystadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	31 6	32 0	33 0	33 5	33 9	34 0	44 1	44 2	44 3	44 4	44 6	44 8	44 9	50 3	00 5	00 6	00 8	11 3	22 2	22 5	22 7	22 8	33 3	33 4	35 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																							X			1
Hepatocellular carcinoma																X							X			2
Hepatocellular adenoma								X								X					X		X			6
Histiocytic sarcoma																										1
Mesentery																										5
Sarcoma NOS																										1
Oral mucosa	+	+	+				+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	37
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma											X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	M	M	+	+	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	M	M	24
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X						X			X															6
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, cystadenoma																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	5 8 6	6 5 2	6 8 3	7 0 2	7 0 9	7 1 1	7 3 2	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 1 9	3 4 7	3 1 0	3 0 2	3 1 8	3 2 9	3 3 7	3 0 4	3 0 9	3 1 2	3 1 5	3 1 7	3 2 1	3 2 3	3 2 4	3 2 6	3 3 1	3 3 2	3 3 6	3 3 8	3 4 5	3 0 1	3 0 7	3 1 1	3 1 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+																			+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar adenoma, multiple																								X	
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																+									
Harderian gland										+		+													
Adenoma										X		X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymphoma malignant	X			X						X													X		X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 100 ppm

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	31 6	32 0	33 0	33 5	33 9	34 0	44 1	44 2	44 3	44 4	44 6	44 8	44 9	00 3	00 5	00 6	00 8	11 3	22 2	22 5	22 7	22 8	33 3	33 4	35 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+																+									4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+										+				3
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																										5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	578	690	701	723	726	734	734	734	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	3999	3655	3678	3754	3756	3759	3761	3764	3770	3780	3782	3792	3796	3800	3852	3855	3857	3860	3863	3868	3871	3876	3877	3886	3887
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																		X	X						
Hepatocellular adenoma, multiple									X																
Histiocytic sarcoma				X																					
Sarcoma, metastatic, skin			X																						
Mesentery																								+	
Sarcoma NOS																									
Oral mucosa				+		+	+	+	+	+	+	+	+		+	+		+			+	+		+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue		+																							
Epithelium, squamous cell carcinoma		X																							
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X	X							X						X		
Pars intermedia, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma												X													
Histiocytic sarcoma				X																					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	389	390	393	394	395	397	398	511	533	588	622	666	667	669	672	673	674	675	679	681	683	684	685	688	691	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma								X																		1
Hepatocellular adenoma				X				X		X		X									X					7
Hepatocellular adenoma, multiple																										1
Histiocytic sarcoma									X																	2
Sarcoma, metastatic, skin																										1
Mesentery		+											+				+		+							5
Sarcoma NOS													X													1
Oral mucosa	+	+	+			+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	37
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Epithelium, squamous cell carcinoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	M	+	+	+	+	M	+	+	M	+	+	+	M	+	M	M	+	M	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma								X				X														6
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma					X																					1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma																				X						2
Histiocytic sarcoma									X																	2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	5 7 8	6 9 0	7 0 1	7 2 3	7 2 6	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 9 9	3 6 5	3 7 8	3 5 4	3 5 6	3 5 9	3 6 1	3 6 4	3 7 0	3 8 0	3 8 2	3 9 2	3 9 6	4 0 0	3 5 2	3 5 5	3 5 7	3 6 0	3 6 3	3 6 8	3 7 1	3 7 6	3 7 7	3 8 6	3 8 7
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node					+																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma NOS			X													X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma																									X
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																									
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymphoma malignant																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone: 300 ppm

Number of Days on Study	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	38989	39090	39393	39944	39955	39967	39988	40511	40553	40588	40662	40666	40667	40669	40672	40673	40674	40675	40679	40681	40683	40684	40685	40688	40691	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	2
Lymph node		+															+	+								4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma NOS											X															3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+															2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					2
Alveolar/bronchiolar carcinoma																					X					2
Histiocytic sarcoma									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																			+							1
Harderian gland										+										+						2
Adenoma																				X						1
Carcinoma										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	2
Lymphoma malignant		X								X							X									3

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate[b]	6.4%	4.3%	4.1%	2.0%
Terminal rate[c]	3/42 (7%)	2/40 (5%)	2/43 (5%)	1/45 (2%)
First incidence (days)	734 (T)	734 (T)	734 (T)	734 (T)
Poly-3 test[d]	P=0.253N	P=0.509N	P=0.485N	P=0.291N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.4%	4.3%	4.1%	4.1%
Terminal rate	3/42 (7%)	2/40 (5%)	2/43 (5%)	2/45 (4%)
First incidence (days)	734 (T)	734 (T)	734 (T)	734 (T)
Poly-3 test	P=0.470N	P=0.509N	P=0.485N	P=0.481N
Liver: Hepatocellular Adenoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	8/50 (16%)
Adjusted rate	8.5%	8.7%	12.3%	16.3%
Terminal rate	4/42 (10%)	4/40 (10%)	5/43 (12%)	8/45 (18%)
First incidence (days)	734 (T)	734 (T)	702	734 (T)
Poly-3 test	P=0.123	P=0.632	P=0.392	P=0.198
Liver: Hepatocellular Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.3%	2.2%	4.1%	2.0%
Terminal rate	1/42 (2%)	0/40 (0%)	2/43 (5%)	1/45 (2%)
First incidence (days)	631	690	734 (T)	734 (T)
Poly-3 test	P=0.327N	P=0.315N	P=0.490N	P=0.295N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	6/50 (12%)	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted rate	12.6%	10.8%	12.3%	16.3%
Terminal rate	4/42 (10%)	4/40 (10%)	5/43 (12%)	8/45 (18%)
First incidence (days)	631	690	702	734 (T)
Poly-3 test	P=0.285	P=0.519N	P=0.603N	P=0.411
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	0.0%	8.5%	4.1%	4.1%
Terminal rate	0/42 (0%)	2/40 (5%)	2/43 (5%)	2/45 (4%)
First incidence (days)	—[e]	592	734 (T)	734 (T)
Poly-3 test	P=0.571	P=0.060	P=0.245	P=0.247
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	0/50 (0%)	6/50 (12%)	3/50 (6%)	3/50 (6%)
Adjusted rate	0.0%	12.8%	6.2%	6.1%
Terminal rate	0/42 (0%)	4/40 (10%)	3/43 (7%)	3/45 (7%)
First incidence (days)	—	592	734 (T)	734 (T)
Poly-3 test	P=0.537	P=0.015	P=0.125	P=0.127
Ovary: Cystadenoma				
Overall rate	2/50 (4%)	4/48 (8%)	1/49 (2%)	2/48 (4%)
Adjusted rate	4.2%	9.0%	2.1%	4.2%
Terminal rate	2/42 (5%)	3/39 (8%)	1/42 (2%)	2/44 (5%)
First incidence (days)	734 (T)	694	734 (T)	734 (T)
Poly-3 test	P=0.440N	P=0.312	P=0.496N	P=0.693N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	3/48 (6%)	2/46 (4%)	6/48 (13%)	6/48 (13%)
Adjusted rate	6.5%	4.6%	12.7%	12.6%
Terminal rate	2/41 (5%)	1/38 (3%)	6/43 (14%)	6/44 (14%)
First incidence (days)	657	550	734 (T)	734 (T)
Poly-3 test	P=0.150	P=0.526N	P=0.258	P=0.261
Skin (Subcutaneous Tissue): Sarcoma NOS				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	6.1%
Terminal rate	0/42 (0%)	0/40 (0%)	0/43 (0%)	2/45 (4%)
First incidence (days)	—	—[f]	—	701
Poly-3 test	P=0.009	—	—	P=0.127
All Organs: Malignant Lymphoma				
Overall rate	6/50 (12%)	10/50 (20%)	5/50 (10%)	3/50 (6%)
Adjusted rate	12.4%	21.6%	10.1%	6.1%
Terminal rate	3/42 (7%)	9/40 (23%)	3/43 (7%)	3/45 (7%)
First incidence (days)	491	694	586	734 (T)
Poly-3 test	P=0.065N	P=0.181	P=0.485N	P=0.234N
All Organs: Benign Neoplasms				
Overall rate	15/50 (30%)	15/50 (30%)	15/50 (30%)	16/50 (32%)
Adjusted rate	31.4%	31.5%	30.5%	32.6%
Terminal rate	13/42 (31%)	11/40 (28%)	13/43 (30%)	16/45 (36%)
First incidence (days)	636	550	652	734 (T)
Poly-3 test	P=0.495	P=0.581	P=0.551N	P=0.537
All Organs: Malignant Neoplasms				
Overall rate	12/50 (24%)	18/50 (36%)	9/50 (18%)	11/50 (22%)
Adjusted rate	24.3%	37.3%	18.2%	22.2%
Terminal rate	6/42 (14%)	13/40 (33%)	6/43 (14%)	8/45 (18%)
First incidence (days)	491	512	586	690
Poly-3 test	P=0.219N	P=0.120	P=0.314N	P=0.499N
All Organs: Benign or Malignant Neoplasms				
Overall rate	23/50 (46%)	28/50 (56%)	20/50 (40%)	23/50 (46%)
Adjusted rate	46.6%	57.3%	40.3%	46.5%
Terminal rate	17/42 (41%)	22/40 (55%)	16/43 (37%)	20/45 (44%)
First incidence (days)	491	512	586	690
Poly-3 test	P=0.364N	P=0.194	P=0.337N	P=0.577N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, and pituitary gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE D4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female B6C3F$_1$ Mice

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Controls Given NTP-2000 Diet[a]			
p,p′-Dichlorodiphenyl sulfone (feed)	0/50	0/50	0/50
Indium phosphide (inhalation)	3/50	1/50	4/50
Methacrylonitrile (gavage)	6/50	1/50	6/50
p-Nitrotoluene (feed)	5/50	1/50	6/50
Sodium nitrite (drinking water)	1/50	0/50	1/50
Overall Historical Incidence in Controls Given NTP-2000 Diet			
Total (%)	15/250 (6.0%)	3/250 (1.2%)	17/250 (6.8%)
Mean ± standard deviation	6.0% ± 5.1%	1.2% ± 1.1%	6.8% ± 5.6%
Range	0%-12%	0%-2%	0%-12%
Historical Incidence in Feed Controls Given NIH-07 Diet at Battelle Columbus Laboratory[b]			
Anthraquinone	1/50	3/50	4/50
4,4′-Thiobis-(6-*t*-butyl-*m*-cresol)	2/51	0/51	2/51
Manganese (II) sulfate monohydrate	2/51	4/51	6/51
Oxazepam	4/50	1/50	5/50
Primidone	4/50	4/50	7/50
Triamterene	4/50	0/50	4/50
Triamterene	2/50	1/50	3/50
Tricresyl phosphate	2/50	4/50	5/50
Overall Historical Incidence in Feed Controls Given NIH-07 Diet			
Total (%)	53/952 (5.6%)	31/952 (3.3%)	81/952 (8.5%)
Mean ± standard deviation	5.6% ± 2.6%	3.2% ± 3.1%	8.5% ± 3.6%
Range	2%-10%	0%-8%	2%-14%

[a] Data as of 14 March 2000
[b] Data as of 23 December 1999

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	1	1	1
Natural deaths	5	9	6	4
Survivors				
Terminal sacrifice	42	40	43	45
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Lymphoid tissue, hyperplasia, lymphoid	1 (2%)			
Serosa, inflammation, chronic	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid	2 (4%)			4 (8%)
Liver	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Basophilic focus		1 (2%)		2 (4%)
Clear cell focus	2 (4%)	1 (2%)		1 (2%)
Eosinophilic focus	2 (4%)	1 (2%)	4 (8%)	11 (22%)
Eosinophilic focus, multiple				3 (6%)
Fatty change, diffuse		3 (6%)		1 (2%)
Infiltration cellular, mononuclear cell	8 (16%)	9 (18%)	12 (24%)	10 (20%)
Inflammation, chronic active	4 (8%)	6 (12%)	3 (6%)	9 (18%)
Inflammation, granulomatous			1 (2%)	
Mixed cell focus	1 (2%)	1 (2%)		2 (4%)
Mixed cell focus, multiple			1 (2%)	
Necrosis			1 (2%)	
Necrosis, focal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Tension lipidosis	4 (8%)	1 (2%)		
Vacuolization cytoplasmic, focal	1 (2%)	1 (2%)	2 (4%)	
Bile duct, cyst				1 (2%)
Centrilobular, fatty change		1 (2%)		
Centrilobular, hypertrophy			9 (18%)	29 (58%)
Oval cell, hyperplasia		1 (2%)		
Periportal, degeneration		1 (2%)		
Periportal, fibrosis		1 (2%)		
Periportal, hyperplasia, lymphoid		1 (2%)		
Serosa, hyperplasia, lymphoid	1 (2%)			
Mesentery	(5)	(2)	(5)	(5)
Fat, necrosis	4 (80%)	1 (50%)	3 (60%)	4 (80%)
Oral mucosa	(31)	(21)	(37)	(37)
Ulcer	14 (45%)	7 (33%)	17 (46%)	18 (49%)
Gingival, inflammation, chronic	31 (100%)	21 (100%)	37 (100%)	36 (97%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Alimentary System (continued)				
Pancreas	(50)	(49)	(50)	(50)
Amyloid deposition	1 (2%)			
Hypertrophy, focal				1 (2%)
Inflammation, chronic	2 (4%)		1 (2%)	
Acinus, atrophy		1 (2%)	1 (2%)	
Duct, cyst			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Hyperkeratosis, focal			1 (2%)	
Mineralization			1 (2%)	
Epithelium, hyperplasia, focal	2 (4%)			
Muscularis, hyperplasia, focal		1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			
Epithelium, cyst				2 (4%)
Epithelium, hyperplasia, focal	1 (2%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, inflammation, chronic	1 (2%)			
Aorta, mineralization			1 (2%)	
Pulmonary vein, inflammation, chronic	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Artery, inflammation, chronic	1 (2%)			2 (4%)
Epicardium, inflammation, chronic		1 (2%)		
Myocardium, degeneration	1 (2%)		1 (2%)	2 (4%)
Myocardium, mineralization		1 (2%)		
Nerve, inflammation, chronic	1 (2%)			
Valve, inflammation	1 (2%)	1 (2%)	1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Cytoplasmic alteration, focal	1 (2%)			
Hyperplasia, focal	1 (2%)	1 (2%)		
Hypertrophy, diffuse			1 (2%)	1 (2%)
Hypertrophy, focal	2 (4%)			3 (6%)
Subcapsular, hyperplasia	47 (94%)	47 (96%)	50 (100%)	47 (94%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Pituitary gland	(48)	(46)	(48)	(48)
Inflammation, suppurative			1 (2%)	
Pars distalis, hemorrhage				1 (2%)
Pars distalis, hyperplasia, focal	5 (10%)	6 (13%)	7 (15%)	11 (23%)
Pars distalis, vacuolization cytoplasmic	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(50)
Hyperplasia, focal				1 (2%)
General Body System				
None				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Atrophy			1 (2%)	
Cyst		1 (2%)	3 (6%)	1 (2%)
Ovary	(50)	(48)	(49)	(48)
Angiectasis	2 (4%)	7 (15%)	2 (4%)	1 (2%)
Cyst	15 (30%)	11 (23%)	16 (33%)	9 (19%)
Hemorrhage	7 (14%)		4 (8%)	
Inflammation, granulomatous				1 (2%)
Inflammation, suppurative			1 (2%)	2 (4%)
Thrombosis	1 (2%)	4 (8%)		1 (2%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)		
Inflammation, granulomatous				2 (4%)
Inflammation, suppurative	3 (6%)	2 (4%)	7 (14%)	11 (22%)
Thrombosis				1 (2%)
Ulcer	1 (2%)		1 (2%)	1 (2%)
Endometrium, hyperplasia, cystic	41 (82%)	44 (88%)	48 (96%)	47 (94%)
Epithelium, metaplasia, squamous				1 (2%)
Serosa, cyst	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Necrosis		1 (2%)		
Lymph node	(3)	(6)	(4)	(4)
Lumbar, hyperplasia, lymphoid		1 (17%)	2 (50%)	1 (25%)
Renal, hyperplasia, lymphoid		1 (17%)	1 (25%)	2 (50%)
Lymph node, mandibular	(47)	(47)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)		
Lymph node, mesenteric	(50)	(46)	(49)	(46)
Erythrophagocytosis	1 (2%)			1 (2%)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	3 (6%)	1 (2%)
Infiltration cellular, plasma cell	1 (2%)			
Infiltration cellular, histiocyte			1 (2%)	
Vein, ectasia			1 (2%)	
Spleen	(49)	(49)	(50)	(50)
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	11 (22%)	15 (31%)	11 (22%)	21 (42%)
Lymphoid follicle, atrophy	5 (10%)	7 (14%)	4 (8%)	2 (4%)
Lymphoid follicle, hyperplasia	10 (20%)	9 (18%)	11 (22%)	8 (16%)
Thymus	(49)	(48)	(50)	(50)
Atrophy	28 (57%)	25 (52%)	26 (52%)	33 (66%)
Cyst	4 (8%)	4 (8%)	4 (8%)	7 (14%)
Hyperplasia, lymphoid				2 (4%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Infiltration cellular, mast cell				1 (2%)
Subcutaneous tissue, edema			1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrosis	10 (20%)	4 (8%)	12 (24%)	15 (30%)
Nervous System				
Brain	(50)	(49)	(50)	(50)
Hypothalamus, degeneration	1 (2%)		1 (2%)	
Thalamus, necrosis, focal				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia		1 (2%)		
Infiltration cellular, histiocyte	2 (4%)		1 (2%)	
Inflammation, chronic, focal				2 (4%)
Inflammation, granulomatous		1 (2%)		
Alveolar epithelium, hyperplasia				1 (2%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (2%)		2 (4%)
Bronchiole, hyperplasia				1 (2%)
Serosa, fibrosis				1 (2%)
Nose	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)			
Inflammation, granulomatous				1 (2%)
Respiratory epithelium, cytoplasmic alteration				1 (2%)
Turbinate, inflammation, suppurative	1 (2%)		1 (2%)	
Special Senses System				
Eye	(1)	(3)	(3)	(1)
Atrophy		2 (67%)	1 (33%)	
Degeneration		1 (33%)	2 (67%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Glomerulosclerosis		1 (2%)		
Hydronephrosis	1 (2%)	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Infarct	3 (6%)	2 (4%)	2 (4%)	
Inflammation, chronic, focal		1 (2%)		1 (2%)
Inflammation, focal, suppurative		1 (2%)		
Renal tubule, accumulation, hyaline droplet	1 (2%)			
Renal tubule, casts protein	32 (64%)	30 (60%)	31 (62%)	38 (76%)
Renal tubule, hyperplasia, focal	2 (4%)			
Renal tubule, necrosis, acute	1 (2%)			
Renal tubule, regeneration	1 (2%)	1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)			
Serosa, inflammation, granulomatous	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). *p,p′*-Dichlorodiphenyl sulfone was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of *p,p′*-dichlorodiphenyl sulfone. The high dose was limited by solubility. All trials without S9 were repeated. Trials initially performed with 10% S9 were repeated with 30% S9.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). *p,p′*-Dichlorodiphenyl sulfone was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of *p,p′*-dichlorodiphenyl sulfone; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with *p,p′*-dichlorodiphenyl sulfone in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing *p,p′*-dichlorodiphenyl sulfone was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with *p,p′*-dichlorodiphenyl sulfone, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no *p,p′*-dichlorodiphenyl sulfone. Incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time for cells in Trial 2 without S9 was lengthened to 33 hours (31 hours in BrdU) to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with *p,p′*-dichlorodiphenyl sulfone for 13.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with *p,p′*-dichlorodiphenyl sulfone and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by *p,p′*-dichlorodiphenyl sulfone exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male $B6C3F_1$ mice were injected intraperitoneally [three times at 24-hour intervals] with *p,p′*-dichlorodiphenyl sulfone dissolved in corn oil. Solvent control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of four or five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose

groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgment of the overall evidence for activity of the chemical in an assay.

RESULTS

p,p′-Dichlorodiphenyl sulfone (10 to 1,000 µg/plate) was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, with or without induced rat or hamster liver S9 metabolic activation enzymes (Table E1). Tests for induction of SCEs in cultured CHO cells yielded equivocal results in the absence of S9 and negative results in the single trial conducted with S9 (Table E2). In the SCE test without S9, the first trial was judged to be equivocal, based on the small, dose-related increase in the number of SCEs/cell over the concentration range of 20 to 200 µg/mL; the second trial without S9 produced dose-related increases that were less significant, and the result of the second trial was judged to be negative. Overall, data from the first trial were weighted more than those from the second due to the shorter duration of exposure of the cells to BrdU and the broader concentration range that was tested, and the final call for the SCE test without S9 was equivocal. No significant induction of Abs was observed in cultured CHO cells treated with *p,p′*-dichlorodiphenyl sulfone, with or without S9 (Table E3). In the first trial with S9, increases were noted in the total number of aberrations at the two highest concentrations tested, but the percentage of damaged cells was not particularly high except at the intermediate concentration of 930 µg/mL, and no increases were observed in the second trial conducted with S9. Therefore, the test was concluded to be negative overall. *In vivo*, *p,p′*-dichlorodiphenyl sulfone (200 to 800 mg/kg) induced micronuclei in PCEs of male mice administered intraperitoneal injections three times at 24-hour intervals (Table E4). In the first trial, the frequency of micronucleated polychromatic erythrocytes in the 400 mg/kg group was significantly increased. Results of the second trial, conducted to clarify the initial response, were positive, with small but significant increases in the frequency of micronucleated polychromatic erythrocytes in the 400 and 800 mg/kg groups. It should be noted that the micronucleus frequency in the corn oil control group in Trial 2 was lower than that in Trial 1; the response in the positive control group in Trial 2 was also decreased compared to Trial 1. Overall, the results of the *in vivo* micronucleus test were positive.

In conclusion, the pattern of mutagenic activity shown by *p,p′*-dichlorodiphenyl sulfone in these four assays is interesting. No clear mutagenic activity in bacterial or mammalian assays designed to detect gene mutation induction or chromosomal damage *in vitro* was observed, but results of the mouse bone marrow micronucleus test indicate a potential for induction of chromosomal damage in the form of breakage or aneuploidy *in vivo*.

TABLE E1
Mutagenicity of *p,p′*-Dichlorodiphenyl Sulfone in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b]					
		-S9		+hamster S9		+rat S9	
		Trial 1	Trial 2	10%	30%	10%	30%
TA100	0	127 ± 15.1	110 ± 7.1	123 ± 8.0	161 ± 11.9	135 ± 7.2	159 ± 2.3
	10	121 ± 2.1	116 ± 8.2	134 ± 8.8	156 ± 9.4	118 ± 11.9	152 ± 2.1
	33	130 ± 3.8	90 ± 5.3	130 ± 8.3	143 ± 1.5	128 ± 10.2	171 ± 4.4
	100[c]	104 ± 8.3	124 ± 0.6	155 ± 2.8	148 ± 7.4	121 ± 10.2	139 ± 4.1
	333[c]	131 ± 0.9	105 ± 5.5	131 ± 7.3	158 ± 9.3	109 ± 7.2	164 ± 7.3
	1,000[c]	137 ± 3.0	128 ± 14.4	131 ± 4.7	149 ± 5.4	119 ± 5.9	165 ± 9.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		561 ± 9.5	573 ± 13.5	479 ± 10.0	471 ± 15.7	1,525 ± 64.2	491 ± 20.5
TA1535	0	8 ± 1.7	10 ± 0.6	11 ± 2.4	10 ± 1.5	8[e]	12 ± 1.7
	10	8 ± 0.9	9 ± 1.2	12 ± 2.3	13 ± 0.9	9 ± 1.2	12 ± 1.7
	33	9 ± 0.7	9 ± 0.9	9 ± 0.6	11 ± 0.3	8 ± 1.2	12 ± 1.2
	100[c]	7 ± 0.7	12 ± 2.4	10 ± 1.8	11 ± 2.6	7 ± 1.5	13 ± 2.0
	333[c]	9 ± 1.0	9 ± 1.2	7 ± 0.9	9 ± 2.2	9 ± 1.5	12 ± 1.3
	1,000[c]	11 ± 0.7	9 ± 1.7	7 ± 1.0	13 ± 2.3	6 ± 2.0	11 ± 2.4
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		159 ± 15.4	371 ± 22.0	50 ± 8.6	66 ± 4.9	158 ± 6.2	140 ± 9.1
TA97	0	134 ± 5.3	151 ± 4.2	164 ± 5.8	138 ± 4.3	159 ± 4.7	188 ± 3.2
	10	127 ± 0.9	161 ± 8.0	157 ± 3.8	145 ± 6.4	133 ± 4.0	187 ± 5.5
	33	140 ± 5.2	158 ± 7.5	128 ± 5.9	149 ± 5.1	160 ± 5.4	193 ± 12.9
	100[c]	125 ± 7.5	142 ± 7.3	161 ± 3.2	160 ± 8.1	166 ± 9.5	189 ± 5.6
	333[c]	139 ± 16.8	141 ± 9.2	154 ± 6.9	158 ± 7.4	149 ± 19.0	180 ± 3.1
	1,000[c]	127 ± 8.1	125 ± 2.9	151 ± 8.4	171 ± 2.4	108 ± 5.9	185 ± 4.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		353 ± 9.8	347 ± 9.6	992 ± 8.1	661 ± 5.2	1,719 ± 31.5	561 ± 39.8
TA98	0	16 ± 1.5	15 ± 2.6	15 ± 1.3	25 ± 5.2	19 ± 0.9	24 ± 1.2
	10	10 ± 0.9	15 ± 2.7	20 ± 0.9	27 ± 3.9	18 ± 1.5	24 ± 2.7
	33	13 ± 2.0	11 ± 3.1	20 ± 2.2	31 ± 1.0	21 ± 2.0	27 ± 0.9
	100[c]	13 ± 3.7	15 ± 1.9	18 ± 0.7	22 ± 4.4	18 ± 1.2	25 ± 1.2
	333[c]	11 ± 1.5	16 ± 1.9	21 ± 2.8	18 ± 1.9	19 ± 0.3	26 ± 1.9
	1,000[c]	17 ± 1.8	11 ± 0.6	17 ± 2.6	31 ± 5.4	23 ± 1.7	33 ± 2.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		286 ± 17.5	278 ± 3.8	419 ± 33.2	465 ± 20.7	458 ± 23.7	239 ± 8.1

[a] Study was performed at Microbiological Associates. The detailed protocol is presented by Zeiger *et al.* (1992). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Precipitate on all plates
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[e] Results available from a single plate only

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p,p′*-Dichlorodiphenyl Sulfone[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
−S9								
Trial 1								
Summary: Equivocal								
Dimethylsulfoxide[c]		50	1,050	364	0.35	7.3	26.0	
Mitomycin-C[d]	0.001	50	1,050	484	0.46	9.7	26.0	32.97*
	0.004	10	208	240	1.15	24.0	26.0	232.84*
p,p′-Dichlorodiphenyl sulfone	20	50	1,049	367	0.35	7.3	26.0	0.92
	67	50	1,048	393	0.38	7.9	26.0	8.18
	200	50	1,046	432	0.41	8.6	26.0	19.14
	667	Toxic						
					P=0.004[e]			
Trial 2								
Summary: Negative								
Dimethylsulfoxide		50	1,050	404	0.38	8.1	31.0[f]	
Mitomycin-C	0.001	50	1,049	522	0.50	10.4	26.0	29.33*
	0.004	10	210	256	1.22	25.6	26.0	216.83*
p,p′-Dichlorodiphenyl sulfone	200	50	1,049	418	0.40	8.4	31.0[f]	3.56
	250	50	1,050	444	0.42	8.9	31.0[f]	9.90
	300	50	1,045	468	0.45	9.4	31.0[f]	16.39
					P=0.008			
+S9								
Summary: Negative								
Dimethylsulfoxide		50	1,051	357	0.34	7.1	26.0	
Cyclophosphamide[d]	0.125	50	1,048	551	0.53	11.0	26.0	54.79*
	0.500	10	210	188	0.90	18.8	26.0	163.56*
p,p′-Dichlorodiphenyl sulfone	6.7	50	1,050	364	0.35	7.3	26.0	2.06
	20	50	1,044	365	0.35	7.3	26.0	2.93
	667	50	1,050	383	0.36	7.7	26.0	7.39
	2,000	50	1,049	416	0.40	8.3	26.0	16.75
					P=0.013			

* Positive response (≥20% increase over solvent control)
[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose
[f] Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *p,p′*-Dichlorodiphenyl Sulfone[a]

Compound	Dose (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
-S9					
Harvest time: 15.5 hours					
Summary: Negative					
Dimethylsulfoxide[b]		200	0	0.00	0.0
p,p′-Dichlorodiphenyl sulfone	94	200	1	0.01	0.5
	201	200	2	0.01	1.0
	432	200	2	0.01	1.0
					P=0.080[c]
Mitomycin-C[d]	0.4	25	28	1.12	48.0*
+S9					
Trial 1					
Harvest time: 13.0 hours					
Summary: Negative					
Dimethylsulfoxide		200	0	0.00	0.0
p,p′-Dichlorodiphenyl sulfone	9.4	200	0	0.00	0.0
	20	200	7	0.04	0.5
	930	200	12	0.06	3.5*
	2,000	200	11	0.06	1.0
					P=0.001
Cyclophosphamide[d]	20	25	35	1.40	48.0*
Trial 2					
Harvest time: 13.0 hours					
Summary: Negative					
Dimethylsulfoxide		200	0	0.00	0.0
p,p′-Dichlorodiphenyl sulfone	750	200	4	0.02	2.0
	1,000	200	2	0.01	1.0
	1,250	200	2	0.01	1.0
	1,500	200	1	0.01	0.5
	2,000	200	3	0.02	1.5
					P=0.292
Cyclophosphamide	20	25	11	0.44	36.0*

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al*. (1987).
[b] Solvent control
[c] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[d] Positive control

TABLE E4
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with *p,p′*-Dichlorodiphenyl Sulfone by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]
Trial 1				
Corn oil[d]		5	1.20 ± 0.41	
p,p′-Dichlorodiphenyl sulfone	200	5	2.20 ± 0.51	0.1079
	400	5	3.80 ± 1.29	0.0040
	600	5	2.90 ± 0.58	0.0276
	800	5	1.60 ± 0.48	0.2927
			P=0.239[e]	
Cyclophosphamide[f]	25	5	22.40 ± 1.85	0.0000
Trial 2				
Corn oil		4	0.50 ± 0.35	
p,p′-Dichlorodiphenyl sulfone	200	5	2.20 ± 0.89	0.0215
	400	4	3.25 ± 1.05	0.0032
	600	4	2.88 ± 0.85	0.0065
	800	5	3.30 ± 0.44	0.0026
			P=0.007	
Cyclophosphamide	25	5	11.30 ± 1.35	0.0000

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al.* (1993).
[b] PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control. Exposed group values are significant at P≤0.006; positive control values are significant at P≤0.05 (ILS, 1990)
[e] Vehicle control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
Positive control

APPENDIX F
FUNCTIONAL OBSERVATION BATTERY DATA

TABLE F1
Functional Observation Data for Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	100 ppm	300 ppm	1,000 ppm
n	10	10	10	10
Male				
Body weight (g)	371 ± 4	368 ± 4	352 ± 4**	342 ± 7**
Body temperature (° C)	36.370 ± 0.154	36.460 ± 0.145	36.090 ± 0.170	36.200 ± 0.212
Forelimb grip strength (kg)	1.642 ± 0.040	1.613 ± 0.034	1.563 ± 0.030	1.556 ± 0.037
Hindlimb grip strength (kg)	0.658 ± 0.015	0.662 ± 0.014	0.645 ± 0.015	0.678 ± 0.020
Hindlimb footsplay (cm)	7.040 ± 0.226	6.770 ± 0.390	6.675 ± 0.251	6.000 ± 0.146**
Female				
Body weight (g)	206 ± 2	201 ± 2	197 ± 3*	187 ± 3**
Body temperature (° C)	37.240 ± 0.156	37.060 ± 0.173	37.120 ± 0.136	36.940 ± 0.145
Forelimb grip strength (kg)	1.039 ± 0.035	1.066 ± 0.022	1.045 ± 0.028	0.992 ± 0.023
Hindlimb grip strength (kg)	0.506 ± 0.022	0.521 ± 0.023	0.531 ± 0.016	0.518 ± 0.012
Hindlimb footsplay (cm)	5.265 ± 0.242	5.570 ± 0.223	5.125 ± 0.343	5.355 ± 0.134

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test (body weights) or Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE F2
Functional Observation Data for Mice in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
Male					
n	10	10	10	10	0[b]
Body weight (g)	33.9 ± 0.5	33.7 ± 0.8	31.0 ± 0.4**	28.9 ± 0.4**	
Body temperature (° C)	36.070 ± 0.296	35.730 ± 0.370	35.920 ± 0.327	35.980 ± 0.391	
Forelimb grip strength (kg)	0.118 ± 0.005	—	0.119 ± 0.003	0.115 ± 0.005	
Hindlimb grip strength (kg)	0.067 ± 0.002	0.059 ± 0.001*	0.066 ± 0.002	0.062 ± 0.002	
Hindlimb footsplay (cm)	4.885 ± 0.213	4.680 ± 0.115	4.915 ± 0.105	4.840 ± 0.123	
Female					
n	10	0[b]	10	10	10
Body weight (g)	28.1 ± 0.7		25.6 ± 0.4**	24.4 ± 0.5**	24.2 ± 0.2**
Body temperature (° C)	37.290 ± 0.133		37.060 ± 0.208	37.280 ± 0.220	37.250 ± 0.259
Forelimb grip strength (kg)	0.118 ± 0.005		0.119 ± 0.003	0.115 ± 0.005	0.123 ± 0.004
Hindlimb grip strength (kg)	0.049 ± 0.003		0.048 ± 0.001	0.046 ± 0.002	0.046 ± 0.001
Hindlimb footsplay (cm)	4.335 ± 0.108		4.535 ± 0.108	4.620 ± 0.115	4.565 ± 0.135

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's (body weights) or Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not examined for this exposure group

APPENDIX G
CLINICAL PATHOLOGY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Male						
Hematology						
Hematocrit (%)	48.6 ± 0.7	48.8 ± 0.4	47.7 ± 0.7	47.9 ± 0.9	46.6 ± 0.4	48.5 ± 0.9
Hemoglobin (g/dL)	16.5 ± 0.2	16.6 ± 0.1	16.2 ± 0.2	16.3 ± 0.2	15.6 ± 0.1**	15.8 ± 0.2**
Erythrocytes (10^6/μL)	9.48 ± 0.10	9.33 ± 0.09	9.19 ± 0.15	9.28 ± 0.16	9.03 ± 0.10*	9.36 ± 0.17
Reticulocytes (10^6/μL)	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.14 ± 0.01	0.15 ± 0.02*
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	51.3 ± 0.3	52.3 ± 0.1**	51.9 ± 0.3	51.6 ± 0.2	51.6 ± 0.2	51.8 ± 0.2
Mean cell hemoglobin (pg)	17.4 ± 0.1	17.8 ± 0.1	17.6 ± 0.1	17.6 ± 0.1	17.3 ± 0.1	16.9 ± 0.3*
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.2	34.0 ± 0.1	33.9 ± 0.2	34.0 ± 0.2	33.5 ± 0.2	32.6 ± 0.3**
Platelets (10^3/μL)	754.7 ± 15.0	793.6 ± 56.5	769.1 ± 22.8	761.1 ± 13.3	837.8 ± 20.4**	948.8 ± 21.0**
Leukocytes (10^3/μL)	12.32 ± 0.47	14.48 ± 1.21	13.10 ± 0.56	13.12 ± 0.61	12.61 ± 0.50	13.08 ± 0.33
Segmented neutrophils (10^3/μL)	1.94 ± 0.25	2.92 ± 0.78	1.78 ± 0.31	1.93 ± 0.34	2.00 ± 0.29	2.10 ± 0.23
Lymphocytes (10^3/μL)	10.21 ± 0.49	11.18 ± 0.50	11.10 ± 0.36	10.88 ± 0.50	10.36 ± 0.37	10.75 ± 0.43
Monocytes (10^3/μL)	0.12 ± 0.03	0.29 ± 0.19	0.14 ± 0.06	0.21 ± 0.08	0.21 ± 0.10	0.17 ± 0.05
Eosinophils (10^3/μL)	0.05 ± 0.02	0.09 ± 0.04	0.06 ± 0.02	0.11 ± 0.03	0.05 ± 0.02	0.06 ± 0.02
Clinical Chemistry						
Urea nitrogen (mg/dL)	20.5 ± 0.3	18.2 ± 0.5	19.8 ± 0.4	21.0 ± 0.3	21.0 ± 0.3	24.0 ± 0.3**
Creatinine (mg/dL)	0.68 ± 0.01	0.70 ± 0.02	0.69 ± 0.01	0.69 ± 0.01	0.71 ± 0.02	0.76 ± 0.02**
Total protein (g/dL)	7.4 ± 0.1	7.4 ± 0.2	7.7 ± 0.1	8.2 ± 0.1**	8.2 ± 0.1**	8.6 ± 0.1**
Albumin (g/dL)	4.9 ± 0.1	4.9 ± 0.1	5.1 ± 0.1	5.4 ± 0.1**	5.1 ± 0.0**	5.3 ± 0.1**
Alanine aminotransferase (IU/L)	73 ± 6	53 ± 4*	50 ± 3**	61 ± 6	63 ± 5	73 ± 6
Alkaline phosphatase (IU/L)	602 ± 11	509 ± 27**	460 ± 7**	474 ± 9**	402 ± 8**	421 ± 8**
Creatine kinase (IU/L)	166 ± 16	275 ± 62	295 ± 45	224 ± 72	163 ± 23	174 ± 20
Sorbitol dehydrogenase (IU/L)	23 ± 2	24 ± 2	20 ± 1	23 ± 3	27 ± 2	42 ± 4**
Bile salts (μmol/L)	25.2 ± 2.4	23.6 ± 1.4	27.8 ± 2.9	25.0 ± 0.8	26.2 ± 0.5	32.0 ± 1.3**

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Female						
Hematology						
Hematocrit (%)	45.5 ± 0.6	46.6 ± 0.5	45.5 ± 0.6	46.1 ± 0.8	45.4 ± 0.7	45.0 ± 0.7
Hemoglobin (g/dL)	15.8 ± 0.2	16.1 ± 0.1	15.7 ± 0.1	15.6 ± 0.2	15.0 ± 0.2**	14.8 ± 0.2**
Erythrocytes (10^6/μL)	8.23 ± 0.12	8.33 ± 0.08	8.19 ± 0.09	8.36 ± 0.14	8.36 ± 0.13	8.32 ± 0.11
Reticulocytes (10^6/μL)	0.09 ± 0.01	0.10 ± 0.01	0.11 ± 0.02	0.10 ± 0.01	0.11 ± 0.01	0.12 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.04 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)	55.2 ± 0.2	55.9 ± 0.2	55.6 ± 0.2	55.1 ± 0.2	54.4 ± 0.2*	54.1 ± 0.4**
Mean cell hemoglobin (pg)	19.2 ± 0.1	19.4 ± 0.1	19.2 ± 0.1	18.7 ± 0.1**	17.9 ± 0.1**	17.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.9 ± 0.2	34.6 ± 0.2	34.5 ± 0.3	33.9 ± 0.3*	32.9 ± 0.2**	32.8 ± 0.2**
Platelets (10^3/μL)	736.4 ± 11.5	783.9 ± 14.9*	772.7 ± 23.2	790.4 ± 12.4*	843.9 ± 14.3**	826.9 ± 16.8**
Leukocytes (10^3/μL)	10.89 ± 0.43	10.91 ± 0.46	10.82 ± 0.28	11.09 ± 0.34	11.40 ± 0.52	10.52 ± 0.42
Segmented neutrophils (10^3/μL)	1.72 ± 0.22	1.73 ± 0.20	1.60 ± 0.22	1.39 ± 0.13	1.49 ± 0.22	1.47 ± 0.16
Lymphocytes (10^3/μL)	8.96 ± 0.41	8.98 ± 0.37	9.06 ± 0.32	9.42 ± 0.29	9.79 ± 0.35	8.81 ± 0.39
Monocytes (10^3/μL)	0.13 ± 0.03	0.05 ± 0.02	0.09 ± 0.04	0.17 ± 0.03	0.08 ± 0.02	0.17 ± 0.05
Eosinophils (10^3/μL)	0.08 ± 0.03	0.14 ± 0.05	0.07 ± 0.02	0.11 ± 0.03	0.05 ± 0.02	0.07 ± 0.03
Clinical Chemistry						
Urea nitrogen (mg/dL)	19.3 ± 0.6	18.7 ± 0.8	18.2 ± 0.5	19.6 ± 1.0	18.6 ± 0.5	21.8 ± 0.6
Creatinine (mg/dL)	0.67 ± 0.02	0.71 ± 0.02	0.68 ± 0.01	0.68 ± 0.01	0.68 ± 0.01	0.73 ± 0.02*
Total protein (g/dL)	7.2 ± 0.1	7.6 ± 0.1**	7.5 ± 0.1**	8.0 ± 0.1**	9.1 ± 0.1**	9.5 ± 0.2**
Albumin (g/dL)	5.1 ± 0.1	5.3 ± 0.1*	5.1 ± 0.1	5.4 ± 0.1**	6.0 ± 0.1**	6.1 ± 0.1**
Alanine aminotransferase (IU/L)	52 ± 3	44 ± 1	41 ± 2*	40 ± 1*	48 ± 6	47 ± 4
Alkaline phosphatase (IU/L)	447 ± 16	432 ± 125	368 ± 14**	339 ± 15**	225 ± 8**	243 ± 9**
Creatine kinase (IU/L)	229 ± 37	255 ± 62	274 ± 61	240 ± 64	193 ± 49	180 ± 22
Sorbitol dehydrogenase (IU/L)	20 ± 2	20 ± 1	20 ± 2	21 ± 1	27 ± 4	29 ± 4*
Bile salts (μmol/L)	48.5 ± 5.3	54.2 ± 6.1	59.1 ± 5.1	72.0 ± 10.3	42.2 ± 2.4	49.4 ± 5.8

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE G2
Hematology Data for Mice in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Male						
Hematocrit (%)	47.8 ± 0.5	49.4 ± 0.2	47.8 ± 0.6	48.0 ± 0.4	48.0 ± 0.5	47.2 ± 0.5
Hemoglobin (g/dL)	16.6 ± 0.1	16.9 ± 0.1	16.6 ± 0.1	16.8 ± 0.1	16.7 ± 0.1	16.7 ± 0.1
Erythrocytes (10^6/µL)	10.17 ± 0.12	10.44 ± 0.06	10.12 ± 0.14	10.06 ± 0.13	9.91 ± 0.10	9.82 ± 0.11
Reticulocytes (10^6/µL)	0.13 ± 0.01	0.12 ± 0.02	0.11 ± 0.01	0.11 ± 0.02	0.10 ± 0.01	0.12 ± 0.01
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.1 ± 0.2	47.3 ± 0.3	47.3 ± 0.2	47.8 ±+ 0.3	48.4 ± 0.2**	48.1 ± 0.4**
Mean cell hemoglobin (pg)	16.3 ± 0.1	16.2 ± 0.1	16.4 ± 0.1	16.6 ± 0.2	16.9 ± 0.1**	17.1 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	34.7 ± 0.2	34.3 ± 0.2	34.7 ± 0.2	34.9 ± 0.2	34.9 ± 0.2	35.5 ± 0.3
Platelets (10^3/µL)	924.5 ± 14.7	1,056.4 ± 11.9**	976.2 ± 24.3**	1,074.3 ± 25.3**	1,142.9 ± 36.6**	1,210.1 ± 27.8**
Leukocytes (10^3/µL)	5.91 ± 0.46	5.24 ± 0.49	4.94 ± 0.78	5.76 ± 0.63	4.40 ± 0.59	5.18 ± 0.56
Segmented neutrophils (10^3/µL)	0.94 ± 0.10	1.13 ± 0.13	1.06 ± 0.20	1.21 ± 0.14	1.00 ± 0.14	1.51 ± 0.12*
Lymphocytes (10^3/µL)	4.86 ± 0.42	4.07 ± 0.51	3.82 ± 0.62	4.49 ± 0.52	3.35 ± 0.53	3.65 ± 0.54
Monocytes (10^3/µL)	0.01 ± 0.01	0.01 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.02	0.02 ± 0.01
Eosinophils (10^3/µL)	0.10 ± 0.03	0.03 ± 0.02	0.06 ± 0.03	0.04 ± 0.02	0.03 ± 0.02	0.00 ± 0.00**
Female						
Hematocrit (%)	47.9 ± 0.4	48.7 ± 0.4	47.3 ± 0.3	46.9 ± 0.5	46.8 ± 0.3	46.6 ± 0.4*
Hemoglobin (g/dL)	16.8 ± 0.1	16.8 ± 0.1	16.8 ± 0.1	16.7 ± 0.1	16.8 ± 0.1	16.6 ± 0.1
Erythrocytes (10^6/µL)	10.05 ± 0.08	10.29 ± 0.09	9.99 ± 0.07	9.78 ± 0.11	9.55 ± 0.09**	9.50 ± 0.09**
Reticulocytes (10^6/µL)	0.10 ± 0.02	0.12 ± 0.01	0.12 ± 0.01	0.11 ± 0.02	0.09 ± 0.01	0.09 ± 0.01
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.7 ± 0.2	47.3 ± 0.1	47.4 ± 0.1	48.0 ± 0.1	49.0 ± 0.2**	49.0 ± 0.2**
Mean cell hemoglobin (pg)	16.7 ± 0.1	16.4 ± 0.1	16.8 ± 0.1	17.1 ± 0.1	17.6 ± 0.1**	17.5 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	35.1 ± 0.2	34.6 ± 0.2	35.4 ± 0.2	35.6 ± 0.2	35.9 ± 0.2*	35.7 ± 0.2*
Platelets (10^3/µL)	952.6 ± 21.2	1,000.8 ± 15.2	967.0 ± 15.7	995.6 ± 11.4	1,013.2 ± 17.2*	1,018.7 ± 14.7*
Leukocytes (10^3/µL)	6.44 ± 0.36	5.54 ± 0.49	6.16 ± 0.68	5.30 ± 0.26	6.63 ± 0.96	5.19 ± 0.46
Segmented neutrophils (10^3/µL)	1.14 ± 0.14	0.77 ± 0.13	1.21 ± 0.20	1.08 ± 0.11	1.25 ± 0.22	0.81 ± 0.08
Lymphocytes (10^3/µL)	5.19 ± 0.30	4.65 ± 0.36	4.87 ± 0.58	4.13 ± 0.26	5.29 ± 0.81	4.35 ± 0.43
Monocytes (10^3/µL)	0.05 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.02	0.07 ± 0.03	0.03 ± 0.02
Eosinophils (10^3/µL)	0.07 ± 0.02	0.10 ± 0.03	0.04 ± 0.01	0.05 ± 0.02	0.03 ± 0.02	0.02 ± 0.01*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

APPENDIX H
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	391 ± 4	387 ± 8	381 ± 5	366 ± 4**	353 ± 6**	313 ± 8**
Heart						
Absolute	1.116 ± 0.024	1.101 ± 0.042	1.144 ± 0.022	1.080 ± 0.016	1.103 ± 0.021	0.982 ± 0.018**
Relative	0.285 ± 0.006	0.285 ± 0.009	0.300 ± 0.005	0.295 ± 0.005	0.313 ± 0.004**	0.315 ± 0.007**
R. Kidney						
Absolute	1.378 ± 0.028	1.368 ± 0.041	1.424 ± 0.028	1.427 ± 0.035	1.630 ± 0.039**	1.560 ± 0.030**
Relative	0.352 ± 0.005	0.353 ± 0.005	0.374 ± 0.006*	0.389 ± 0.007**	0.462 ± 0.007**	0.500 ± 0.005**
Liver						
Absolute	15.494 ± 0.370	15.596 ± 0.504	18.156 ± 0.478**	20.093 ± 0.362**	24.983 ± 0.599**	26.405 ± 0.458**
Relative	3.960 ± 0.081	4.029 ± 0.070	4.768 ± 0.119**	5.481 ± 0.063**	7.082 ± 0.093**	8.471 ± 0.159**
R. Testis						
Absolute	1.486 ± 0.016	1.484 ± 0.036	1.514 ± 0.022	1.499 ± 0.013	1.565 ± 0.010*	1.537 ± 0.021*
Relative	0.380 ± 0.005	0.384 ± 0.006	0.398 ± 0.008	0.410 ± 0.005**	0.445 ± 0.009**	0.494 ± 0.011**
Thymus						
Absolute	0.345 ± 0.020	0.302 ± 0.016	0.310 ± 0.018	0.275 ± 0.011**	0.247 ± 0.012**	0.226 ± 0.015**
Relative	0.088 ± 0.005	0.078 ± 0.003	0.081 ± 0.005	0.075 ± 0.003*	0.070 ± 0.003**	0.072 ± 0.004**
Female						
Necropsy body wt	213 ± 3	206 ± 2*	206 ± 2*	201 ± 3**	189 ± 2**	177 ± 3**
Heart						
Absolute	0.695 ± 0.011	0.675 ± 0.010	0.678 ± 0.008	0.686 ± 0.025	0.713 ± 0.012	0.692 ± 0.015
Relative	0.327 ± 0.007	0.328 ± 0.004	0.329 ± 0.004	0.340 ± 0.009	0.377 ± 0.005**	0.392 ± 0.009**
R. Kidney						
Absolute	0.754 ± 0.016	0.762 ± 0.012	0.765 ± 0.013	0.738 ± 0.019	0.788 ± 0.012	0.781 ± 0.018
Relative	0.354 ± 0.006	0.370 ± 0.005	0.371 ± 0.006	0.366 ± 0.006	0.417 ± 0.004**	0.442 ± 0.007**
Liver						
Absolute	7.520 ± 0.168	7.650 ± 0.142	8.186 ± 0.101*	9.293 ± 0.256**	12.229 ± 0.274**	14.670 ± 0.241**
Relative	3.526 ± 0.042	3.719 ± 0.057	3.968 ± 0.036**	4.609 ± 0.078**	6.471 ± 0.118**	8.316 ± 0.147**
Ovaries						
Absolute	0.117 ± 0.009	0.115 ± 0.004	0.112 ± 0.003	0.122 ± 0.004	0.112 ± 0.006	0.105 ± 0.002
Relative	0.055 ± 0.004	0.056 ± 0.002	0.054 ± 0.001	0.061 ± 0.002	0.059 ± 0.003	0.060 ± 0.001
Thymus						
Absolute	0.250 ± 0.012	0.247 ± 0.009	0.258 ± 0.011	0.255 ± 0.007	0.201 ± 0.009**	0.192 ± 0.008**
Relative	0.117 ± 0.004	0.120 ± 0.004	0.125 ± 0.005	0.127 ± 0.004	0.107 ± 0.005	0.109 ± 0.006
Uterus						
Absolute	0.610 ± 0.066	0.656 ± 0.074	0.687 ± 0.099	0.508 ± 0.028	0.568 ± 0.042	0.532 ± 0.048
Relative	0.288 ± 0.033	0.319 ± 0.035	0.332 ± 0.047	0.253 ± 0.016	0.300 ± 0.021	0.302 ± 0.028

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	0 ppm	30 ppm	100 ppm	300 ppm	1,000 ppm	3,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	35.3 ± 0.5	37.7 ± 0.5	35.6 ± 0.9	33.0 ± 0.4**	31.2 ± 0.6**	29.8 ± 0.3**
Heart						
Absolute	0.171 ± 0.009	0.183 ± 0.009	0.162 ± 0.006	0.169 ± 0.008	0.163 ± 0.007	0.169 ± 0.004
Relative	0.486 ± 0.026	0.485 ± 0.021	0.456 ± 0.011	0.513 ± 0.024	0.523 ± 0.018	0.569 ± 0.017**
R. Kidney						
Absolute	0.303 ± 0.007	0.308 ± 0.009	0.302 ± 0.008	0.292 ± 0.007	0.290 ± 0.007	0.291 ± 0.009
Relative	0.862 ± 0.026	0.817 ± 0.019	0.849 ± 0.019	0.885 ± 0.020	0.930 ± 0.018*	0.980 ± 0.032**
Liver						
Absolute	1.709 ± 0.031	1.855 ± 0.039	1.789 ± 0.052	1.945 ± 0.037**	2.387 ± 0.063**	2.952 ± 0.060**
Relative	4.851 ± 0.089	4.925 ± 0.105	5.020 ± 0.075	5.890 ± 0.098**	7.650 ± 0.103**	9.913 ± 0.167**
R. Testis						
Absolute	0.122 ± 0.002	0.120 ± 0.003	0.121 ± 0.003	0.119 ± 0.002	0.117 ± 0.003	0.121 ± 0.003
Relative	0.346 ± 0.005	0.318 ± 0.005	0.340 ± 0.005	0.361 ± 0.005	0.378 ± 0.012**	0.407 ± 0.008**
Thymus						
Absolute	0.042 ± 0.002	0.046 ± 0.002	0.044 ± 0.005	0.040 ± 0.003	0.037 ± 0.002	0.041 ± 0.003
Relative	0.118 ± 0.006	0.122 ± 0.004	0.122 ± 0.011	0.121 ± 0.009	0.120 ± 0.006	0.138 ± 0.010
Female						
Necropsy body wt	28.4 ± 0.7	30.1 ± 0.8	28.1 ± 0.6	25.9 ± 0.5**	25.2 ± 0.4**	25.2 ± 0.2**
Heart						
Absolute	0.132 ± 0.003	0.135 ± 0.005	0.131 ± 0.004	0.136 ± 0.005	0.128 ± 0.004	0.123 ± 0.002
Relative	0.464 ± 0.009	0.450 ± 0.019	0.467 ± 0.020	0.525 ± 0.018*	0.508 ± 0.014	0.489 ± 0.009
R. Kidney						
Absolute	0.191 ± 0.004	0.189 ± 0.005	0.194 ± 0.004	0.189 ± 0.004	0.193 ± 0.007	0.196 ± 0.004
Relative	0.674 ± 0.017	0.627 ± 0.011	0.691 ± 0.018	0.732 ± 0.014*	0.765 ± 0.022**	0.779 ± 0.014**
Liver						
Absolute	1.247 ± 0.036	1.344 ± 0.036	1.335 ± 0.024	1.564 ± 0.047**	1.802 ± 0.049**	2.290 ± 0.036**
Relative	4.385 ± 0.069	4.469 ± 0.077	4.753 ± 0.092*	6.041 ± 0.130**	7.142 ± 0.118**	9.092 ± 0.102**
Ovaries						
Absolute	0.025 ± 0.001	0.025 ± 0.001	0.027 ± 0.001	0.027 ± 0.001	0.027 ± 0.001	0.025 ± 0.001
Relative	0.089 ± 0.004	0.084 ± 0.005	0.095 ± 0.005	0.104 ± 0.004*	0.106 ± 0.003*	0.101 ± 0.003*
Thymus						
Absolute	0.044 ± 0.002	0.048 ± 0.001	0.043 ± 0.002	0.043 ± 0.002	0.040 ± 0.002	0.035 ± 0.002**
Relative	0.156 ± 0.007	0.160 ± 0.005	0.152 ± 0.009	0.167 ± 0.005	0.157 ± 0.008	0.140 ± 0.009
Uterus						
Absolute	0.097 ± 0.008	0.103 ± 0.008	0.118 ± 0.010	0.114 ± 0.011	0.126 ± 0.011	0.120 ± 0.010
Relative	0.342 ± 0.026	0.340 ± 0.024	0.423 ± 0.040	0.440 ± 0.040	0.503 ± 0.045**	0.480 ± 0.040**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as g organ weight/g body weight as a percentage (mean ± standard error).

APPENDIX I
DETERMINATIONS
OF *p,p′*-DICHLORODIPHENYL SULFONE
IN PLASMA

TABLE I1
Plasma Concentrations of *p,p′*-Dichlorodiphenyl Sulfone in Rats at 2 Weeks and 3, 12, and 18 Months in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	10 ppm	30 ppm	100 ppm
n	9	9	9
Male			
2 Weeks	0.625 ± 0.022	1.494 ± 0.086	4.046 ± 0.236
3 Months	0.456 ± 0.020	1.150 ± 0.052	2.613 ± 0.058
12 Months	0.511 ± 0.043[b]	1.272 ± 0.049	2.492 ± 0.116
18 Months	0.495 ± 0.029	1.201 ± 0.049	2.766 ± 0.072
	30 ppm	**100 ppm**	**300 ppm**
Female			
2 Weeks	1.086 ± 0.039	3.139 ± 0.102	6.004 ± 0.463
3 Months	1.296 ± 0.054	2.741 ± 0.113	5.019 ± 0.118
12 Months	1.416 ± 0.077	3.409 ± 0.157	6.377 ± 0.235
18 Months	1.704 ± 0.071	3.668 ± 0.167	7.274 ± 0.223

[a] Data are given in µg/mL as mean ± standard error.
[b] n=8

TABLE I2
Plasma Concentrations of *p,p′*-Dichlorodiphenyl Sulfone in Mice at 2 Weeks and 3 and 12 Months in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	30 ppm	100 ppm	300 ppm
n	3	3	3
Male			
2 Weeks	1.350 ± 0.098	4.403 ± 0.273	16.50 ± 1.06
3 Months	2.167 ± 0.120	3.470 ± 0.287	9.577 ± 0.158
12 Months	2.040 ± 0.168	7.220 ± 0.140[b]	12.72 ± 2.99
Female			
2 Weeks	2.040 ± 0.293	5.570 ± 0.490	18.43 ± 1.83
3 Months	2.997 ± 0.222	4.330 ± 0.490	12.00 ± 0.46
12 Months	2.987 ± 0.073	7.877 ± 1.028	20.10 ± 0.40

[a] Data are given in µg/mL as mean ± standard error.
[b] n=2

APPENDIX J
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF *p,p′*-DICHLORODIPHENYL SULFONE

p,p′-Dichlorodiphenyl sulfone was obtained in two lots. Lot AX01, obtained from TCI America (Portland, OR), was used during the 14-week studies and lot P02300, obtained from Lancaster Synthesis, Inc. (Windham, NH), was used during the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) and the study laboratory. Reports on analyses performed in support of the *p,p′*-dichlorodiphenyl sulfone studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a white powder, were identified as *p,p′*-dichlorodiphenyl sulfone by infrared spectroscopy, and lot P02300 was also identified as *p,p′*-dichlorodiphenyl sulfone by ultraviolet/visible and proton and ^{13}C nuclear magnetic resonance spectroscopy. Infrared spectra for lots AX01 and P02300 were consistent with the literature spectra (*Aldrich*, 1981) of *p,p′*-dichlorodiphenyl sulfone. Additionally, for lot P02300, NMR and UV spectra were consistent with the literature (*Handbook of Proton NMR Spectra and Data*, 1985; Radian Corporation, 1985). The infrared and nuclear magnetic resonance spectra are presented in Figures J1 and J2. The melting point of approximately 148.3° C determined by Galbraith Laboratories, Inc. (Knoxville, TN), for lot P02300 was consistent with theoretical values.

The purity of lot AX01 was provided by the manufacturer. For lot P02300, purity was determined by elemental analyses, Karl Fischer water analysis, gas chromatography, and high-performance liquid chromatography (HPLC). Elemental analyses and Karl Fischer water analysis were preformed by Galbraith Laboratories, Inc. The analytical chemistry laboratory conducted gas chromatography analyses using system A (Table J1). The study laboratory analyzed lot P02300 using gas chromatography (system B) (Table J1). HPLC was performed with two systems:

1) Hypersil® Phenyl reverse-phase 250 mm × 4.6 mm, 5 µm column (Thermoquest, Hypersil Division, Cheshire, United Kingdom) with ultraviolet photodiode array detection at 246 nm and a solvent system of Milli-Q® water:acetonitrile (30:70) at an isocratic flow rate of 0.5 mL/minute, and

2) Phenomenex Ultracarb ODS reverse-phase 150 mm × 4.6 mm, 5 µm column (Phenomenex, Torrance, CA) with ultraviolet detection at 246 nm and a solvent system of water:acetonitrile (30:70) at an isocratic flow rate of 0.5 mL/minute; benzophenone was added as an internal standard.

For lot AX01, the manufacturer indicated that the purity was greater than 99%. For lot P02300, the analytical chemistry laboratory determined that the purity was greater than 99% based on gas chromatography results indicating one major peak and two impurities with areas greater than 0.1% of the major peak area. Elemental analyses for carbon, hydrogen, oxygen, sulfur, and chlorine were in agreement with the theoretical values for *p,p′*-dichlorodiphenyl sulfone. Karl Fischer water analysis indicated less than 0.04% water. HPLC analysis by system 1 indicated no impurities with areas greater than 0.1% of the major peak area. Major peak comparisons of a sample of the batch of lot P02300 analyzed by the study laboratory with a sample of the batch analyzed by the analytical chemistry laboratory indicated that the two batches were identical. Gas chromatography by system B detected one volatile impurity with an area of 0.2% relative to the major peak area in each batch. The overall purity of lot P02300 was determined to be greater than 99%.

Stability studies of lot 00918BF of the bulk chemical at least (not used in these studies) were performed by Radian Corporation (Austin, TX) using gas chromatography (system C). These studies indicated that *p,p′*-dichlorodiphenyl sulfone was stable as a bulk chemical for at least 14 days when stored in sealed vials with Teflon® septa and no headspace at temperatures up to 62° C. To ensure stability, the bulk chemical was stored at room temperature in amber glass bottles. Stability was monitored by the study laboratory throughout the studies using HPLC by system 2. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared every 5 to 9 days (14-week studies) or every 4 weeks (2-year studies) by mixing *p,p′*-dichlorodiphenyl sulfone with feed (Table J2). The test article was ground and sieved to ensure consistent particle size. A premix of *p,p′*-dichlorodiphenyl sulfone and feed was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for 15 minutes. Formulations were stored in plastic buckets at approximately –20° C for up to 14 days (14-week studies) or at room temperature for up to 52 days (2-year studies).

The study laboratory conducted homogeneity studies of the 30 and 3,000 ppm dose formulations (formulated in NIH-07 feed) for the 14-week studies using HPLC by system 2 and the 10 and 300 ppm dose formulations (formulated in nonirradiated NTP-2000 feed) for the 2-year studies using HPLC by system 1. The study laboratory also conducted stability studies of the 30 ppm dose formulation for the 14-week studies using HPLC by system 2 and the 10 ppm dose formulation for the 2-year rat study using HPLC by system 1. For the 14-week study dose formulations, homogeneity was confirmed; stability was confirmed for up to 28 days for dose formulations stored sealed and protected from light at –20° C, for 7 days for dose formulations stored sealed at room temperature, and for 4 days for dose formulations exposed to air and light. Samples stored under simulated animal room conditions were stable for 4 days. Because of the change from NIH-07 diet to irradiated NTP-2000 diet, the formulation studies were repeated. Homogeneity results within acceptable limits were achieved by sieving the chemical prior to blending and increasing the sample size for analysis. The stability of the 10 ppm dose formulation for the 2-year study was confirmed for 53 days for formulations stored in amber glass bottles at up to room temperature. Analyses of formulations after administration were usually within 10% of the target concentrations, but were often low for the 10 ppm (male rats) and 30 ppm dose formulations and appeared consistent with contamination by the urine and feces.

Periodic analyses of the dose formulations of *p,p′*-dichlorodiphenyl sulfone were conducted by the study laboratory using HPLC by system 2 (14-week studies) or system 1 (2-year studies). The dose formulations were analyzed three times during the 14-week studies (Table J3). Of the dose formulations analyzed, 12 of 13 were within 10% of the target concentrations. Animal room samples were also analyzed, revealing a continuing problem, particularly with mice, of degradation due to contamination of the feed with urine and feces; six of eight for rats and 15 of 21 for mice were within 10% of the target concentrations. During the 2-year studies, the dose formulations were analyzed approximately every 7 to 12 weeks (Table J4). Of the dose formulations used, 62 of 63 were within 10% of the target concentrations, with no value greater than 113% of the target concentration. One dose formulation mixed on 5 February 1996 that was 113% of the 30 ppm target concentration was used because there was not enough feed available to formulate a remix. The out-of-range 100 ppm formulation mixed on 29 April 1996 was remixed and found to be within the target range. Initial analyses of the two 30 ppm dose formulations mixed on 18 August 1997 indicated that these dose formulations were out of range; however, analyses of frozen archive samples of these formulations showed that the initial analyses were in error, and the formulations were within the acceptable range. Of the animal room samples analyzed, 17 of 22 for rats and 5 of 18 for mice were within 10% of the target concentrations.

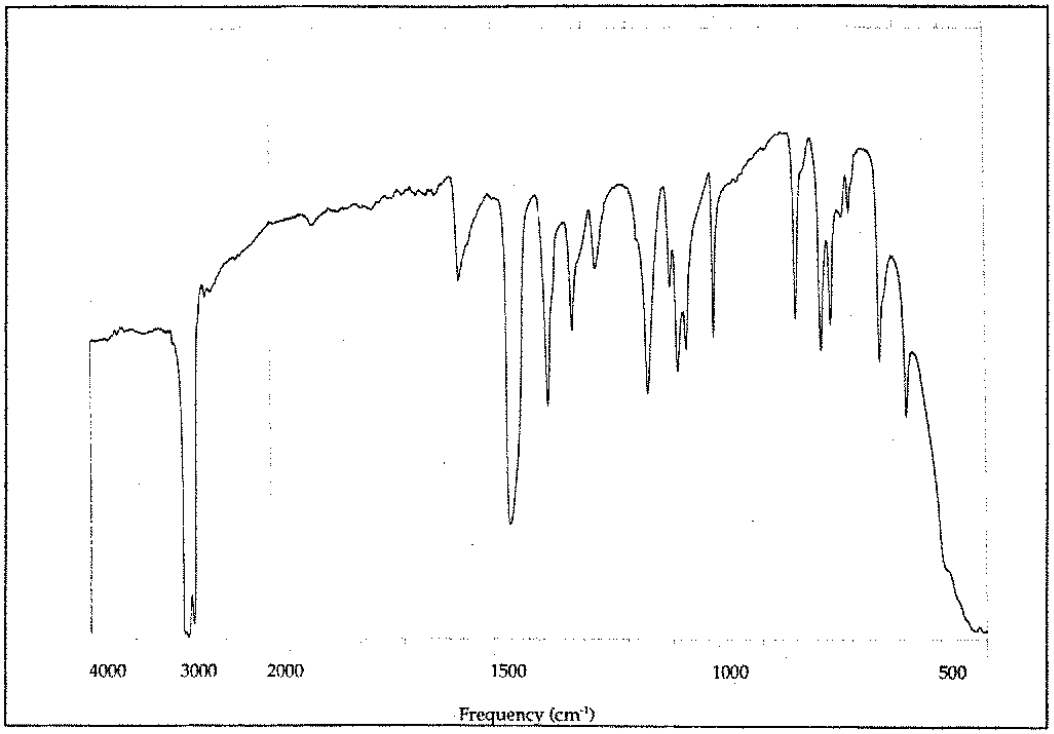
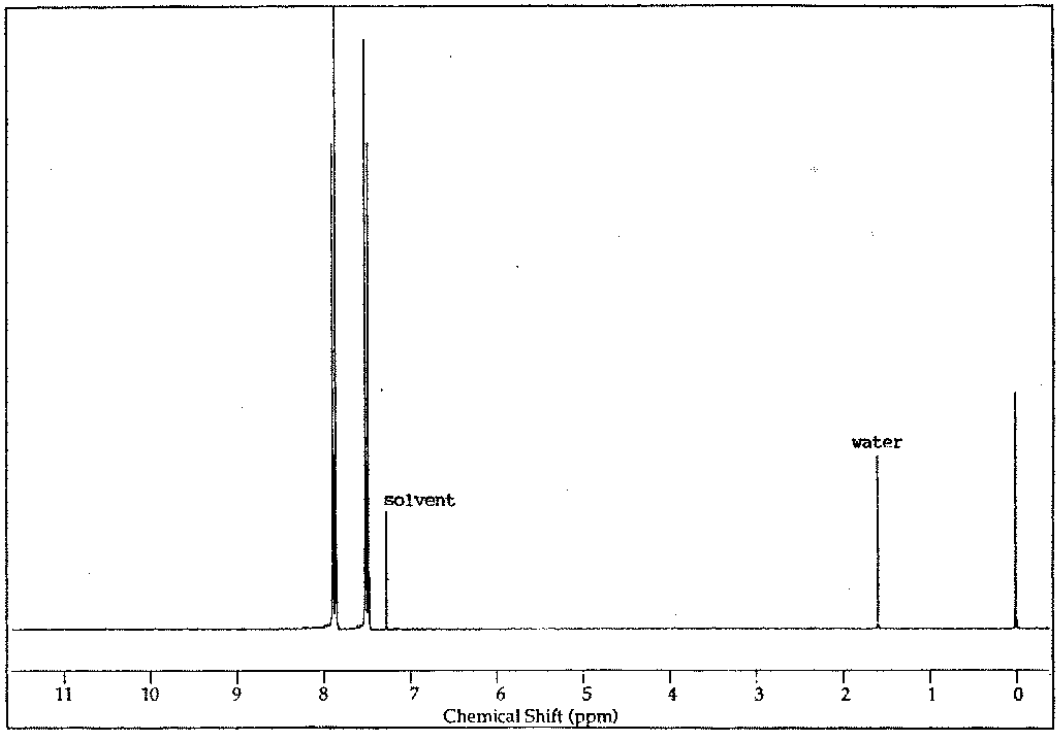


FIGURE J1
Infrared Absorption Spectrum of *p,p′*-Dichlorodiphenyl Sulfone



NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4,4'-DICHLORODIPHENYLSULFONE (K51)

Instrument: Bruker AM-250 NMR Spectrometer
Nucleus: ^1H
Solvent: $CDCl_3$
Reference: TMS
Sweep Frequency: 250 MHz

FIGURE J2
Nuclear Magnetic Resonance Spectrum of *p,p′*-Dichlorodiphenyl Sulfone

TABLE J1
Gas Chromatography Systems Used in the Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Flame ionization	DB-17, 30 m × 0.25 mm, 0.25 µm film (J&W Scientific, Folsom, CA)	Nitrogen at 1 mL/minute	75° C for 5 minutes, then 20° C/minute to 250° C, held for 26 minutes
System B			
Flame ionization	DB-17, 30 m × 0.25 mm, 0.15 µm film (J&W Scientific)	Helium at 3.4 mL/minute	75° C for 5 minutes, then 20° C/minute to 250° C, held for 11 minutes
System C			
Flame ionization	DB-1, 30 m × 0.53 mm, 1.5 µm film (J&W Scientific)	Helium at 6.6 mL/minute	210° C for 25 minutes, then 30° C/minute to 250° C, held for 20 minutes

[a] The gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA) (systems A and B) and Varian, Inc. (Palo Alto, CA) (system C).

TABLE J2
Preparation and Storage of Dose Formulations in the Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

	14-Week Studies	2-Year Studies
Preparation	*p,p′*-Dichlorodiphenyl sulfone was ground with a mortar and pestle and passed through a 100-mesh sieve (30 and 100 ppm formulations) or an 80-mesh sieve (300, 1,000, and 3,000 ppm formulations). A premix of NIH-07 feed and *p,p′*-dichlorodiphenyl sulfone was prepared by hand, then layered with the remaining feed in a Patterson-Kelly twin-shell blender and blended for 15 minutes with the intensifier bar on for the first 5 minutes. Doses were prepared every 5 to 9 days.	*p,p′*-Dichlorodiphenyl sulfone was ground with a mortar and pestle and passed through a 100-mesh sieve beginning 4 March 1996 (10 and 30 ppm formulations) or through an 80-mesh sieve beginning 30 April 1996 (100 and 300 ppm formulations). A premix of NIH-07 or NTP-2000 feed (irradiated or nonirradiated) and *p,p′*-dichlorodiphenyl sulfone was prepared, then layered with the remaining feed in a Patterson-Kelly twin-shell blender and blended for 15 minutes with the intensifier bar on for the first 5 minutes (10-ft^3 blender) or for the mixing period (3-ft^3 blender). Doses were prepared every 4 weeks.
Chemical Lot Number	AX01	P02300
Maximum Storage Time	14 days	52 days
Storage Conditions	Stored in sealed plastic buckets at approximately –20° C	Stored in sealed plastic buckets at room temperature
Study Laboratory	Battelle Columbus Laboratories (Columbus, OH)	Battelle Columbus Laboratories (Columbus, OH)

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
18 January 1993	19-21 January 1993	30	3.5[b]	−88
		100	95.1	−5
		300	280	−7
		1,000	987	−1
		3,000	2,910	−3
21 January 1993	21 January 1993	30	28.2[c]	−6
10 February 1993	19-21 February 1993[d]	30	30.7	+2
		300	301	0
		3,000	3,120	+4
	19-21 February 1993[e]	30	26.4	−12
		300	309	+3
		3,000	3,120	+4
1 March 1993	3-5 March 1993	30	26.9	−10
		100	104	+4
		300	289	−4
		1,000	946	−5
		3,000	2,790	−7
	18-19 March 1993[e]	30	26.5	−12
		100	103	+3
		300	287	−4
		1,000	903	−10
		3,000	2,730	−9
Mice				
18 January 1993	19-21 January 1993	30	3.5[b]	−88
		100	95.1	−5
		300	280	−7
		1,000	987	−1
		3,000	2,910	−3
21 January 1993	21 January 1993	30	28.2[d]	−6
18 and 21 January 1993	2-3 February 1993[f]	30	24.3	−19
		100	69.3	−31
		300	219	−27
		1,000	747	−25
		3,000	2,910	−3

TABLE J3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
10 February 1993	19-21 February 1993[d]	30	30.7	+2
		300	301	0
		3,000	3,120	+4
	19-21 February 1993[g]	30	28.0	−7
		300	321	+7
		3,000	2,970	−1
	19-21 February 1993[f]	30	28.7	−4
		300	330	+10
		3,000	3,170	+6
1 March 1993	3-5 March 1993	30	26.9	−10
		100	104	+4
		300	289	−4
		1,000	946	−5
		3,000	2,790	−7
	18-19 March 1993[g]	30	29.5	−2
		100	97.2	−3
		300	282	−6
		1,000	960	−4
		3,000	2,890	−4
	18-19 March 1993[f]	30	28.8	−4
		100	95.7	−4
		300	264	−12
		1,000	917	−8
		3,000	2,680	−11

[a] Results of duplicate analyses
[b] Remixed; not used in study
[c] Results of remix
[d] Results of analyses of frozen archive samples
[e] Animal room samples
[f] Animal room samples for females
[g] Animal room samples for males

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
11 December 1995	12-15 December 1995	10	11.0	+10
		30	27.6	−8
		100	97.4	−3
		300	287	−4
	14-15 January 1996[b]	10	9.94	−1
		30	25.6	−15
		100	87.0	−13
		300	294	−2
5 February 1996	7-8 February 1996	10	9.87	−1
		30	33.9	+13
		30	29.4	−2
		100	95.5	−4
		100	103	+3
		300	272	−9
29 April 1996	29-30 April 1996	10	10.2	+2
		30	29.3	−2
		30	29.1	−3
		100	136[c]	+36
		100	96.6	−3
		300	304	+1
30 April 1996	30 April 1996	100	101[d]	+1
24 June 1996	26 June 1996	10	9.29	−7
		30	27.6	−8
		30	28.0	−7
		100	99.1	−1
		100	98.6	−1
		300	297	−1
	31 July 1996[b]	10	8.99	−10
		30	27.1	−10
		30	26.7	−11
		100	93.6	−6
		100	92.1	−8
		300	278	−7
16 September 1996	17 September 1996	10	10.3	+3
		30	27.1	−10
		30	27.7	−8
		100	93.0	−7
		100	92.7	−7
		300	285	−5

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
11 November 1996	12 November 1996	10	10.2	+2
		30	30.5	+2
		30	31.6	+5
		100	105	+5
		100	103	+3
		300	311	+4
3 February 1997	4 February 1997	10	9.75	−2
		30	28.2	−6
		30	28.6	−5
		100	94.6	−5
		100	93.5	−6
		300	284	−5
	19-20 March 1997[b]	10	6.25	−37
		30	26.6	−11
		30	29.5	−2
		100	94.0	−6
		100	94.1	−6
		300	284	−5
31 March 1997	1 April 1997	10	10.2	+2
		30	29.8	−1
		30	30.0	0
		100	105	+5
		100	102	+2
		300	311	+4
23 June 1997	25 June 1997	10	10.9	+9
		30	28.9	−4
		30	30.3	+1
		100	98.3	−2
		100	97.3	−3
		300	290	−3

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
18 August 1997	19 August 1997	10	10.1	+1
		30	33.7	+12
		30	35.1	+17
		100	98.2	−2
		100	109	+9
		300	308	+3
	4 October 1997[e]	30	29.1	−3
		30	28.9	−4
	4 October 1997[b]	10	10.3	+3
		30	28.1	−6
		30	28.5	−5
		100	95.2	−5
		100	93.2	−7
		300	280	−7
10 November 1997	12 November 1997	10	9.03	−10
		30	30.6	+2
		30	30.1	0
		100	107	+7
		100	101	+1
		300	310	+3
Mice				
11 December 1995	12-15 December 1995	30	27.6	−8
		100	97.4	−3
		300	287	−4
	14-15 January 1996[b]	30	24.0	−20
		100	70.5	−29
		300	207	−31
5 February 1996	7-8 February 1996	30	33.9	+13
		30	29.4	−2
		100	95.5	−4
		100	103	+3
		300	272	−9
29 April 1996	29-30 April 1996	30	29.3	−2
		30	29.1	−3
		100	136[c]	+36
		100	96.6	−3
		300	304	+1
30 April 1996	30 April 1996	100	101[d]	+1

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
24 June 1996	26 June 1996	30	27.6	−8
		30	28.0	−7
		100	99.1	−1
		100	98.6	−1
		300	297	−1
	31 July 1996[b]	30	27.4	−9
		30	25.8	−14
		100	95.2	−5
		100	94.2	−6
		300	240	−20
16 September 1996	17 September 1996	30	27.1	−10
		30	27.7	−8
		100	93.0	−7
		100	92.7	−7
		300	285	−5
11 November 1996	12 November 1996	30	30.5	+2
		30	31.6	+5
		100	105	+5
		100	103	+3
		300	311	+4
3 February 1997	4 February 1997	30	28.2	−6
		30	28.6	−5
		100	94.6	−5
		100	93.5	−6
		300	284	−5
	19-20 March 1997[b]	30	23.0	−23
		30	24.2	−19
		100	92.4	−8
		100	89.7	−10
		300	266	−11
31 March 1997	1 April 1997	30	29.8	−1
		30	30.0	0
		100	105	+5
		100	102	+2
		300	311	+4
23 June 1997	25 June 1997	30	28.9	−4
		30	30.3	+1
		100	98.3	−2
		100	97.3	−3
		300	290	−3

TABLE J4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p,p′*-Dichlorodiphenyl Sulfone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
18 August 1997	19 August 1997	30	33.7	+12
		30	35.1	+17
		100	98.2	−2
		100	109	+9
		300	308	+3
	4 October 1997[e]	30	29.1	−3
		30	28.9	−4
	4 October 1997[b]	30	20.5	−32
		30	25.7	−14
		100	83.1	−17
		100	86.2	−14
		300	214	−29
10 November 1997	12 November 1997	30	30.6	+2
		30	30.1	0
		100	107	+7
		100	101	+1
		300	310	+3

[a] Results of duplicate analyses
[b] Animal room samples
[c] Remixed; not used in study
[d] Results of remix
[e] Results of analyses of frozen archive samples

APPENDIX K
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF *p,p′*-DICHLORODIPHENYL SULFONE

TABLE K1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm		10 ppm			30 ppm			100 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	18.2	103	17.8	103	1.7	16.7	102	4.9	17.7	103	17.2
2	18.0	152	18.3	148	1.2	17.3	147	3.5	17.3	150	11.5
6	19.0	268	19.0	257	0.7	18.8	256	2.2	19.6	260	7.5
10	18.6	325	18.6	318	0.6	18.3	313	1.8	18.7	316	5.9
14	17.6	365	17.9	357	0.5	18.0	354	1.5	18.7	354	5.3
18	19.5	397	18.4	385	0.5	18.9	383	1.5	19.5	387	5.0
22	18.3	414	18.7	407	0.5	18.0	400	1.4	18.1	398	4.5
26	18.9	432	18.6	424	0.4	18.8	415	1.4	19.0	412	4.6
30	19.0	443	18.5	433	0.4	19.8	427	1.4	19.2	427	4.5
34	20.2	452	19.8	445	0.4	19.8	439	1.4	20.3	433	4.7
38	18.7	458	18.7	451	0.4	18.3	442	1.2	19.7	440	4.5
42	18.4	468	18.8	460	0.4	19.1	452	1.3	19.2	455	4.2
46	18.3	474	18.5	466	0.4	19.0	454	1.3	18.8	453	4.2
50	20.0	476	20.6	469	0.4	21.4	461	1.4	21.3	458	4.6
54	18.4	482	17.1	473	0.4	18.2	466	1.2	19.1	461	4.1
58	18.8	482	18.1	474	0.4	18.2	464	1.2	18.4	459	4.0
62	19.0	483	19.0	476	0.4	18.9	467	1.2	19.0	461	4.1
66	18.5	487	17.9	473	0.4	18.7	465	1.2	18.4	455	4.0
70	20.1	488	19.9	477	0.4	19.3	469	1.2	19.8	456	4.3
74	18.0	492	18.3	473	0.4	17.8	467	1.1	18.0	459	3.9
78	18.8	497	18.6	483	0.4	17.9	471	1.1	17.4	461	3.8
82	17.8	486	16.7	478	0.4	17.1	468	1.1	17.4	461	3.8
86	17.3	485	17.5	475	0.4	17.6	459	1.2	17.1	452	3.8
89	18.1	482	17.2	471	0.4	18.3	458	1.2	18.2	448	4.1
94	18.6	476	17.8	462	0.4	17.5	446	1.2	17.6	442	4.0
98	18.2	462	18.0	462	0.4	18.9	444	1.3	18.6	440	4.2
102	17.9	465	17.8	451	0.4	18.5	425	1.3	17.3	434	4.0
Mean for weeks											
1-13	18.4	212	18.4	206	1.1	17.8	205	3.1	18.3	207	10.5
14-52	18.9	438	18.8	430	0.4	19.1	423	1.4	19.4	422	4.6
53-102	18.4	482	18.0	471	0.4	18.2	459	1.2	18.2	453	4.0

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p,p′*-dichlorodiphenyl sulfone consumed per kilogram body weight per day

TABLE K2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm		30 ppm			100 ppm			300 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	13.0	93	13.0	93	4.2	13.0	94	13.8	12.8	93	41.2
2	12.4	119	12.3	118	3.1	11.7	118	10.0	12.0	118	30.4
6	12.7	169	12.2	164	2.2	12.2	165	7.4	12.0	160	22.5
10	11.2	189	11.1	184	1.8	11.7	186	6.3	11.3	179	18.9
14	10.8	199	10.3	194	1.6	10.8	196	5.5	10.3	188	16.4
18	11.4	211	10.5	204	1.5	10.7	205	5.2	10.5	197	16.0
22	11.3	219	10.6	211	1.5	10.8	211	5.1	10.7	203	15.7
26	11.0	222	10.9	217	1.5	11.1	216	5.1	11.0	207	15.9
30	11.3	232	11.1	223	1.5	11.0	222	5.0	10.7	210	15.4
34	12.7	236	12.3	228	1.6	12.7	222	5.7	12.2	213	17.1
38	12.5	242	11.6	233	1.5	12.5	228	5.5	11.7	218	16.1
42	11.8	248	11.0	238	1.4	11.6	232	5.0	10.8	221	14.7
46	12.5	257	11.8	244	1.5	11.9	239	5.0	11.5	226	15.3
50	12.7	264	11.8	253	1.4	11.8	247	4.8	11.5	231	14.9
54	12.8	271	12.2	259	1.4	12.0	252	4.8	12.1	236	15.3
58	12.5	278	12.0	269	1.3	12.5	260	4.8	11.8	242	14.6
62	12.8	287	12.9	279	1.4	13.3	270	4.9	12.3	252	14.6
66	12.8	295	12.7	285	1.3	12.4	276	4.5	12.4	257	14.5
70	13.1	300	13.2	293	1.4	12.7	281	4.5	12.7	262	14.5
74	13.6	310	13.5	299	1.4	13.2	287	4.6	12.3	267	13.8
78	13.1	321	12.8	310	1.2	12.6	299	4.2	12.6	279	13.5
82	13.4	321	12.7	312	1.2	12.4	296	4.2	12.2	277	13.2
86	13.2	321	12.1	312	1.2	12.2	298	4.1	12.3	281	13.2
90	12.9	313	13.0	310	1.3	12.4	295	4.2	12.4	280	13.3
94	14.0	321	13.1	310	1.3	12.9	300	4.3	13.7	286	14.4
98	14.1	325	13.5	318	1.3	14.2	306	4.6	14.0	289	14.5
102	14.5	331	13.5	317	1.3	13.6	305	4.5	13.4	288	14.0
Mean for weeks											
1-13	12.4	143	12.1	140	2.8	12.2	140	9.4	12.0	138	28.2
14-52	11.8	233	11.2	224	1.5	11.5	222	5.2	11.1	211	15.8
52-102	13.3	307	12.9	298	1.3	12.8	287	4.5	12.6	269	14.1

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p,p′*-dichlorodiphenyl sulfone consumed per kilogram body weight per day

TABLE K3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm		30 ppm			100 ppm			300 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
2	2.9	20.8	2.9	20.6	4.2	2.9	20.7	13.8	2.9	20.4	42.3
6	3.8	26.2	3.8	25.3	4.5	3.6	25.6	14.1	3.6	24.4	44.1
10	4.2	28.4	3.9	28.3	4.2	4.1	28.2	14.6	3.6	27.1	39.8
14	4.3	32.1	4.6	32.1	4.3	4.7	32.1	14.8	4.4	30.2	43.6
18	4.7	35.6	4.5	34.6	3.9	4.5	34.6	12.9	4.4	33.0	40.1
22	5.2	39.0	5.2	37.3	4.2	5.3	37.0	14.3	5.1	35.5	43.1
26	4.7	41.2	4.6	39.1	3.5	4.7	38.9	12.1	4.6	36.3	38.0
30	5.3	42.3	5.3	39.5	4.0	5.4	38.9	13.9	5.4	37.0	43.9
34	5.1	43.7	5.3	41.8	3.8	5.0	40.9	12.2	5.1	39.2	39.2
38	4.7	44.5	4.8	42.4	3.4	4.8	42.1	11.3	4.7	39.7	35.6
42	4.6	44.7	4.6	42.4	3.3	4.5	42.2	10.7	4.9	40.0	36.8
46	5.3	46.0	5.3	43.4	3.7	5.3	42.2	12.7	5.5	41.1	40.4
50	5.2	45.8	4.9	43.5	3.4	5.1	42.8	11.8	5.1	40.9	37.2
54	5.4	46.2	5.1	44.2	3.5	5.1	43.4	11.7	5.3	41.2	38.8
58	5.3	46.9	5.2	45.1	3.5	5.1	44.2	11.5	5.3	42.1	38.0
62	5.1	46.3	4.9	45.0	3.2	4.7	44.5	10.7	4.9	41.9	34.9
66	5.4	46.0	5.3	45.0	3.5	5.3	44.2	11.9	5.3	41.6	37.9
70	5.7	45.5	5.4	45.2	3.6	5.2	44.4	11.8	5.4	41.4	39.2
74	5.3	46.2	4.6	45.9	3.0	4.5	44.4	10.1	4.8	42.5	34.1
78	5.5	45.3	5.1	45.3	3.4	5.0	43.8	11.5	5.5	42.3	38.7
82	5.2	44.0	5.0	44.0	3.4	5.2	42.7	12.2	5.4	41.4	38.9
86	5.9	42.8	5.6	43.1	3.9	5.7	42.2	13.4	5.8	40.4	43.4
90	5.8	40.9	5.5	41.4	4.0	5.4	41.2	13.2	5.6	38.7	43.4
94	5.4	37.9	4.9	39.5	3.7	4.8	39.4	12.2	5.4	36.5	44.1
98	5.8	37.4	5.5	38.0	4.3	5.6	37.7	14.8	5.4	35.2	46.2
102	5.7	36.5	5.5	37.4	4.4	5.6	36.5	15.3	5.5	34.6	47.3
Mean for weeks											
1-13	3.6	25.1	3.5	24.8	4.3	3.5	24.8	14.2	3.4	24.0	42.0
14-52	4.9	41.5	4.9	39.6	3.7	4.9	39.2	12.7	4.9	37.3	39.8
53-102	5.5	43.2	5.2	43.0	3.7	5.2	42.2	12.3	5.4	40.0	40.4

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p,p′*-dichlorodiphenyl sulfone consumed per kilogram body weight per day

TABLE K4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone

	0 ppm		30 ppm			100 ppm			300 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	1.4	17.2	1.4	17.5	2.5	1.4	17.3	8.1	1.2	17.2	21.4
2	2.0	17.2	1.8	17.3	3.1	2.1	17.3	12.0	1.8	16.9	32.4
6	2.5	21.2	2.3	21.5	3.2	2.3	21.1	11.1	2.2	20.3	32.2
10	2.6	23.0	2.6	23.5	3.4	2.3	23.6	9.6	1.9	22.5	25.5
14	2.8	25.5	2.3	26.8	2.6	2.5	26.7	9.5	2.3	24.3	28.8
18	2.7	29.6	2.1	30.4	2.1	2.5	29.8	8.4	2.2	27.0	24.9
22	3.5	32.0	3.0	34.3	2.6	3.1	32.7	9.5	3.2	29.5	32.8
26	4.2	36.0	3.8	36.9	3.1	3.7	34.6	10.7	3.9	31.5	36.9
30	4.0	37.1	3.5	38.6	2.7	3.7	36.1	10.3	3.1	32.5	28.3
34	4.4	39.0	4.4	40.1	3.3	4.3	38.3	11.2	4.3	35.3	36.5
38	3.9	40.3	4.3	41.1	3.1	3.8	39.5	9.7	4.2	35.5	35.8
42	4.0	42.1	3.6	42.8	2.5	4.0	41.5	9.7	4.3	37.6	34.0
46	4.5	42.4	4.1	43.4	2.8	4.4	40.5	11.0	4.5	37.6	36.3
50	4.4	43.0	3.8	43.7	2.6	4.1	41.2	10.0	4.4	38.2	34.9
54	4.5	43.4	4.2	44.9	2.8	4.5	42.5	10.5	4.6	38.7	35.9
58	4.5	44.7	4.1	46.4	2.7	4.5	44.1	10.3	4.7	40.6	34.6
62	4.4	45.1	4.1	47.0	2.6	4.3	44.4	9.7	4.2	39.9	31.8
66	4.4	44.9	4.1	46.8	2.6	4.1	43.8	9.4	4.5	39.3	34.2
70	4.0	44.8	4.0	47.0	2.6	4.2	43.7	9.7	4.4	40.1	33.2
74	4.3	46.5	4.0	48.6	2.5	4.4	45.8	9.7	4.5	42.0	31.8
78	4.2	46.0	3.6	47.9	2.2	3.8	45.2	8.4	3.9	41.2	28.4
82	4.6	45.7	4.4	48.7	2.7	4.7	45.0	10.5	5.0	41.1	36.2
86	5.0	44.4	4.5	46.9	2.9	4.7	43.6	10.7	5.1	39.5	38.5
90	4.3	43.4	4.4	44.9	3.0	4.4	42.0	10.5	4.4	38.5	34.4
94	4.5	42.9	4.2	43.8	2.9	4.0	40.2	9.9	4.3	37.5	34.6
98	4.8	43.7	4.6	44.5	3.1	4.6	41.0	11.3	4.5	37.7	35.5
102	4.7	43.0	4.4	44.3	3.0	4.7	40.3	11.6	5.0	37.3	40.2
Mean for weeks											
1-13	2.1	19.6	2.0	20.0	3.0	2.0	19.8	10.2	1.8	19.2	27.9
14-52	3.8	36.7	3.5	37.8	2.8	3.6	36.1	10.0	3.6	32.9	32.9
53-102	4.5	44.5	4.2	46.3	2.7	4.4	43.2	10.2	4.5	39.5	34.6

[a] Grams of feed consumed per animal per day
[b] Milligrams of *p,p′*-dichlorodiphenyl sulfone consumed per kilogram body weight per day

APPENDIX L
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE L1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE L2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

TABLE L3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.8 ± 0.76	12.6 – 16.2	23
Crude fat (% by weight)	8.1 ± 0.34	7.5 – 9.0	23
Crude fiber (% by weight)	9.6 ± 0.76	7.8 – 11.1	23
Ash (% by weight)	5.1 ± 0.27	4.7 – 5.9	23
Amino Acids (% of total diet)			
Arginine	0.732 ± 0.050	0.670 – 0.800	6
Cystine	0.220 ± 0.011	0.210 – 0.240	6
Glycine	0.683 ± 0.048	0.620 – 0.740	6
Histidine	0.333 ± 0.020	0.310 – 0.350	6
Isoleucine	0.522 ± 0.054	0.430 – 0.590	6
Leucine	1.065 ± 0.070	0.960 – 1.130	6
Lysine	0.705 ± 0.066	0.620 – 0.790	6
Methionine	0.402 ± 0.042	0.350 – 0.460	6
Phenylalanine	0.600 ± 0.042	0.540 – 0.640	6
Threonine	0.512 ± 0.056	0.430 – 0.590	6
Tryptophan	0.125 ± 0.015	0.110 – 0.150	6
Tyrosine	0.410 ± 0.037	0.360 – 0.460	6
Valine	0.628 ± 0.052	0.550 – 0.690	6
Essential Fatty Acids (% of total diet)			
Linoleic	3.98 ± 0.325	3.59 – 4.54	6
Linolenic	0.30 ± 0.048	0.21 – 0.35	6
Vitamins			
Vitamin A (IU/kg)	4,941 ± 1,494	2,570 – 8,140	23
Vitamin D (IU/kg)[a]	1,000	–	
α-Tocopherol (ppm)	77.2 ± 10.94	62.2 – 87.1	6
Thiamine (ppm)[b]	9.3 ± 1.92	7.0 – 15.0	23
Riboflavin (ppm)	5.6 ± 1.24	4.20 – 7.70	6
Niacin (ppm)	73.1 ± 4.13	66.4 – 78.8	6
Pantothenic acid (ppm)	24.2 ± 2.92	21.4 – 29.1	6
Pyridoxine (ppm)[b]	9.37 ± 2.50	6.7 – 12.4	6
Folic acid (ppm)	1.70 ± 0.43	1.26 – 2.32	6
Biotin (ppm)	0.349 ± 0.18	0.225 – 0.704	6
Vitamin B_{12} (ppb)	83.4 ± 67.1	30.0 – 174.0	6
Choline (ppm)	3,082 ± 232	2,700 – 3,400	6
Minerals			
Calcium (%)	0.992 ± 0.049	0.884 – 1.080	23
Phosphorus (%)	0.582 ± 0.025	0.548 – 0.640	23
Potassium (%)	0.660 ± 0.026	0.627 – 0.691	6
Chloride (%)	0.356 ± 0.031	0.300 – 0.392	6
Sodium (%)	0.193 ± 0.020	0.160 – 0.212	6
Magnesium (%)	0.197 ± 0.010	0.185 – 0.213	6
Sulfur (%)	0.182 ± 0.023	0.153 – 0.209	6
Iron (ppm)	158 ± 15.2	135 – 173	6
Manganese (ppm)	51.8 ± 4.05	46.2 – 56.0	6
Zinc (ppm)	53.2 ± 5.68	45.0 – 61.1	6
Copper (ppm)	6.49 ± 0.786	5.38 – 7.59	6
Iodine (ppm)	0.487 ± 0.204	0.233 – 0.843	6
Chromium (ppm)	0.763 ± 0.620	0.330 – 2.000	6
Cobalt (ppm)	0.53 ± 0.720	0.20 – 2.0	6

[a] From formulation
[b] As hydrochloride

TABLE L4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.25 ± 0.103	0.10 – 0.50	23
Cadmium (ppm)	0.05 ± 0.011	0.04 – 0.09	23
Lead (ppm)	0.13 ± 0.099	0.06 – 0.40	23
Mercury (ppm)	< 0.02		23
Selenium (ppm)	0.17 ± 0.033	0.12 – 0.24	23
Aflatoxins (ppb)	< 5.00		23
Nitrate nitrogen (ppm)[c]	13.2 ± 3.92	6.5 – 22.7	23
Nitrite nitrogen (ppm)[c]	0.82 ± 0.66	0.30 – 3.20	23
BHA (ppm)[d]	1.2 ± 0.75	0.01 – 3.50	23
BHT (ppm)[d]	1.0 ± 0.41	0.01 – 2.30	23
Aerobic plate count (CFU/g)[e]	241,571 ± 194,051	46,000 – 590,000	7
Coliform (MPN/g)[e]	119 ± 176	9 – 510	7
Escherichia coli (MPN/g)	< 10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[f]	5.6 ± 2.48	2.7 – 12.6	23
N-Nitrosodimethylamine (ppb)[f]	2.7 ± 1.80	0.9 – 6.6	23
N-Nitrosopyrrolidine (ppb)[f]	2.9 ± 1.74	1.1 – 8.7	23
Pesticides (ppm)			
α-BHC	< 0.01		23
β-BHC	< 0.02		23
γ-BHC	< 0.01		23
δ-BHC	< 0.01		23
Heptachlor	< 0.01		23
Aldrin	< 0.01		23
Heptachlor epoxide	< 0.01		23
DDE	< 0.01		23
DDD	< 0.01		23
DDT	< 0.01		23
HCB	< 0.01		23
Mirex	< 0.01		23
Methoxychlor	< 0.05		23
Dieldrin	< 0.01		23
Endrin	< 0.01		23
Telodrin	< 0.01		23
Chlordane	< 0.05		23
Toxaphene	< 0.10		23
Estimated PCBs	< 0.20		23
Ronnel	< 0.01		23
Ethion	< 0.02		23
Trithion	< 0.05		23
Diazinon	< 0.10		23
Methyl chlorpyrifos	0.079 ± 0.087	0.010 – 0.300	19
Methyl parathion	< 0.02		23
Ethyl parathion	< 0.02		23
Malathion	0.145 ± 0.149	0.020 – 0.600	23
Endosulfan I	< 0.01		23
Endosulfan II	< 0.01		23
Endosulfan sulfate	< 0.03		23

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] Nonirradiated samples. Microbial counts for irradiated samples were below the detection limit.
[f] All values were corrected for percent recovery.

APPENDIX M
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc., or MA Bioservices, Inc. (Rockville, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed. At 18 months, live mice were shipped to the serology laboratory for evaluation of bacterial profile and viral serology according to NIEHS Advisory Number 19.

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	1, 6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Helicobacter hepaticus	12 months
Mycoplasma arthritidis	Study termination
Parvovirus	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	1, 6, 12, and 18 months
KRV (Kilham rat virus)	1, 6, 12, and 18 months

Method and Test	Time of Analysis
MICE	
Bacterial Assays	
Enterococcus faecium	18 months
Enterococcus faecalis	18 months
Streptococcus lactis	18 months
Pseudomonas aeruginosa	18 months
H. hepaticus	18 months
ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	1, 6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	1, 6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	1, 6, 12, and 18 months, study termination
M. arthritidis	18 months, study termination
M. pulmonis	18 months, study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
GDVII	18 months
H. hepaticus	12 months
LCM	6 and 18 months
Mouse adenoma virus-FL	18 months
MCMV (mouse cytomegalovirus)	18 months, study termination
M. arthritidis	Study termination
Parvovirus	Study termination
Hemagglutination Inhibition	
K (papovavirus)	1, 6, 12, and 18 months
MVM (minute virus of mice)	1, 6, 12, and 18 months
Polyoma virus	1, 6, 12, and 18 months

RESULTS

For the 2-year study in rats, all serology tests were negative. Bacterial profiles of sentinel mice at 18 months indicated *E. faecalis* in 10 mice, *P. aeruginosa* in one mouse, *S. lactis* in one mouse, and *E. faecium* in two mice. These had no impact on the study results. One mouse had a positive titer for *M. arthritidis* at 18 months. Further evaluation of the sample positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titer may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in the animal with the positive titer. Accordingly, the *M. arthritidis*-positive titer was considered a false positive.

APPENDIX N
PHARMACOKINETIC MODEL

PHARMACOKINETIC MODEL

INTRODUCTION

A physiologically based pharmacokinetic model was developed to represent the pharmacokinetics of *p,p′*-dichlorodiphenyl sulfone in rats and mice. This model is based on that of Lutz *et al*. (1977). The blood, gastrointestinal tract tissue, liver, muscle, skin, fat (adipose), and kidneys are represented as flow-limited compartments. Equations describing the model represent the concentrations of the parent compound (*p,p′*-dichlorodiphenyl sulfone) in each compartment. Excretion and absorption are modeled using a gut compartment with separate subcompartments for the stomach, duodenum, jejunum, and colon. Data used with the model come from single-dose studies (radiolabeled *p,p′*-dichlorodiphenyl sulfone administered intravenously or by gavage; Mathews *et al*., 1996) described below and the 2-year rat and mouse feed studies reported in this Technical Report.

MATERIALS AND METHODS

For the three single-dose studies, *p,p′*-dichlorodiphenyl sulfone (98% pure) was supplied by Aldrich Chemical Company, Inc. (Milwaukee, WI). Uniformly labeled [^{14}C]*p,p′*-dichlorodiphenyl sulfone (6.75 mCi/mmol) was prepared by NEN Research Products (Boston, MA). The radiochemical purity of [^{14}C]*p,p′*-dichlorodiphenyl sulfone was determined by reverse-phase high-performance liquid chromatography (HPLC) to be 96%.

Adult male F344 rats were purchased from Charles River Laboratories, Inc. (Raleigh, NC) and were given Purina Rodent Chow and water *ad libitum*. Gavage formulations contained 23 to 29 μCi radiolabel, an appropriate amount of unlabeled *p,p′*-dichlorodiphenyl sulfone, and Emulphor EL-620 (GAF Corporation, New York, NY) in a single-dose volume of 5 mL/kg body weight. A mixture of 20% Emulphor EL-620 in F344 rat plasma (total volume = 1 mL/kg) was injected into a lateral tail vein for intravenous administration.

In one single-dose study, three to five male rats were injected intravenously with 10 mg *p,p′*-dichlorodiphenyl sulfone/kg body weight. The following data were collected: (1) total cumulative radioactivity in feces and urine for the 7 consecutive days after dosing and amounts of *p,p′*-dichlorodiphenyl sulfone and metabolites in feces at 1, 2, and 3 days; (2) total radioactivity in the blood, liver, muscle, skin, adipose, and kidney at 0.5 (except kidney), 4, and 8 hours and 1, 3, 7, and 21 days after dosing; and (3) amounts of *p,p′*-dichlorodiphenyl sulfone and its metabolites in the blood and liver 3 days after dosing.

In the other two single-dose studies, three to five male rats were given a single oral gavage dose of either 10 or 100 mg *p,p′*-dichlorodiphenyl sulfone/kg body weight. The rats were sacrificed 3 days after dosing. The following data were collected: (1) total cumulative radioactivity in urine at 6 hours and 1, 2, and 3 days after dosing and concentrations of *p,p′*-dichlorodiphenyl sulfone and metabolites in feces at 1, 2, and 3 days; and (2) total radioactivity in the skin, adipose, kidney, and gut and concentrations of *p,p′*-dichlorodiphenyl sulfone and its metabolites in the blood, liver, and muscle 3 days after dosing.

After dosing, rats were housed in glass metabolism cages that provided for separate collection of urine and feces into round-bottomed flasks cooled with dry ice. At the end of the studies, rats were anesthetized with ketamine and xylazine, exsanguinated, and killed with an intracardiac injection of sodium pentobarbital. Required tissues were removed and assayed for radiochemical content. Aliquots of urine were added directly to vials containing scintillation cocktail. Samples of tissues, feces, and blood were digested in Soluene-350 overnight. After digestion, samples that required bleaching were decolorized with perchloric acid and hydrogen peroxide before addition of the scintillation cocktail. Radioactivity in each sample was determined using a Packard Tricarb 1500 liquid scintillation analyzer (Packard Instrument Company, Downers Grove, IL).

For metabolite measurements, urine was filtered through a 0.45 µm Millex filter before analysis by HPLC. Feces samples (~2 to 3 grams from each 0- to 72-hour collection) were pooled and extracted with acetone. Extracts were centrifuged and concentrated under a stream of nitrogen to about one-half of the original volume before analysis by HPLC. Samples of tissues were collected 72 hours after dosing and were homogenized in normal saline, extracted with acetone, and centrifuged. The supernatants were removed, combined, and concentrated under a stream of nitrogen before analysis by HPLC.

p,p′-Dichlorodiphenyl sulfone-derived metabolites were separated using a Zorbax ODS analytical column (4.6 × 250 mm, 5 µm) with an isocratic mobile phase of acetonitrile/1% aqueous triethylammonium acetate [pH 4.1, 60:40]; the flow rate was 1 mL/minute. The column effluent was monitored by an Applied Biosystems 759a absorbance detector (PE Biosystems) at a wavelength of 254 nm and by a Ramona-5-LS radioactivity detector equipped with a 500-µL solid scintillate flow cell.

Plasma concentrations of *p,p′*-dichlorodiphenyl sulfone were measured in 2-year rats at 2 weeks and 3, 12, and 18 months. At each collection period, concentrations were measured at 0900, 1200, and 1500 hours. Data were available for male rats fed 10, 30, or 100 ppm and female rats fed 30, 100, or 300 ppm *p,p′*-dichlorodiphenyl sulfone. Plasma concentrations of *p,p′*-dichlorodiphenyl sulfone were measured in 2-year mice at 0900 hours at 2 weeks and 3 and 12 months. Data were available for male and female mice fed 30, 100, or 300 ppm *p,p′*-dichlorodiphenyl sulfone. For purposes of model fitting, the concentration in whole blood was assumed to be equal to the concentration in plasma.

MODEL DEVELOPMENT

p,p′-Dichlorodiphenyl sulfone has several identified metabolites (Mathews *et al*., 1996); five major metabolites have been found in the tissues and excreta of experimental animals. Only two of these metabolites were definitely identified in these experiments: *m*-hydroxy-dichlorodiphenyl sulfone and its glucuronide. *m*-Hydroxy-*p,p′*-dichlorodiphenyl sulfone was the only metabolite that occurred in measurable quantities in the liver in all of the single-dose studies. Other metabolites appeared in measurable concentrations in various tissues, but not in the liver in all of the single-dose studies. To limit the number of variables, all of the metabolites were combined. Variables representing the total concentration of metabolites in the muscle, liver, and blood were used in the model. (The variables were actually dose equivalents; if the variable representing the concentration of metabolite in the liver had a value of 1 mg/mL, it meant that the concentration of radioactivity in the liver due to metabolite was the same as would be produced by 1 mg/mL *p,p′*-dichloro-diphenyl sulfone.) The concentrations of total metabolites in the skin and fat were negligible and were not included. Accordingly, the model included equations for the amount of metabolites in the blood, liver, muscle, and kidney. Metabolism of *p,p′*-dichlorodiphenyl sulfone was assumed to occur in the liver following nonlinear Michaelis-Menten kinetics.

In the model, excretion of metabolites in urine occurred at a rate proportional to their concentration in the blood. Excretion of *p,p′*-dichlorodiphenyl sulfone in the urine was found to be minimal compared to that of its metabolites and was not included in the model. Excretion of *p,p′*-dichlorodiphenyl sulfone and its metabolites from the liver into the gut via bile was modeled as proportional to the concentration in the liver. Absorption of *p,p′*-dichlorodiphenyl sulfone from the gut was modeled using Michaelis-Menten kinetics. The model was originally constructed to include absorption of metabolites from the gut, but this effect was found to be negligible and was not included in the final version.

The model used several parameters with predetermined values. Volumes of the various compartments, rates of blood flow, and gastrointestinal tract transit times were taken from the literature. Volumes and flow rates depend on the body weight of the rats; body weights were measured during the single-dose and 2-year studies, as was feed consumption in the 2-year study.

Other parameters included the metabolism constants, the clearance rates for bile and urine, the constants for absorption from the gut, a tissue-to-capillary permeability constant for *p,p′*-dichlorodiphenyl sulfone, and the tissue:blood partition coefficients for *p,p′*-dichlorodiphenyl sulfone and the metabolites. These parameters were calculated by a multistep procedure. In the first step, values for all parameters were determined by weighted least-squares fitting of the model results to the data from the single-dose studies in male rats. Data from the 2-year feed studies in male and female rats and mice were used in the second step. In this second step, the model was initially fitted to the results of all studies in male rats. Parameter values found in this initial step were used as a starting point for subsequent fitting, and an additional parameter was added to represent the difference in absorption rates between the single-dose gavage and 2-year feed studies. In the final steps, the model was fitted to the 2-year studies for female rats and male and female mice. In these steps, most of the model parameters were held constant, with the remaining parameters found by least-squares fitting. Fitted parameters in the second step included the absorption parameter GV_{max} for dosed feed (for mice), the induction constants K_{ind} and K_v (for all data sets), and the maximum metabolic rate V_{max} (for all data sets).

The physiologically based pharmacokinetic model for the absorption, distribution, metabolism, and excretion of *p,p′*-dichlorodiphenyl sulfone consists of the following differential equations. The defined abbreviations and parameter values for rats are also given.

Differential Equations

1) Distribution in tissues other than blood and liver (adipose, gastrointestinal tract, kidney, muscle, and skin for *p,p'*-dichlorodiphenyl sulfone; kidney and muscle for metabolites):

p,p'-Dichlorodiphenyl sulfone:

$$P'_{XT} = Perm \cdot Q_X\left(CP_{XC} - {CP_{XT}}/{R_{PX}}\right)$$

$$P'_{XC} = -Perm \cdot Q_X\left(CP_{XC} - {CP_{XT}}/{R_{PX}}\right) + Q_T(CP_B - CP_{XC})$$

Metabolites:

$$M'_X = Q_X\left(CM_B - {CM_X}/{R_{MX}}\right)$$

2) Distribution in blood:

$$P'_B = -Q_A(CP_B - CP_{AC}) - Q_K(CP_B - CP_{KC}) - (Q_L + Q_G)\left(CP_B - {CP_L}/{R_{PL}}\right)$$
$$-Q_M(CP_B - CP_{MC}) - Q_S(CP_B - CP_{SC})$$

$$M'_B = -Q_K\left(CM_B - {CM_K}/{R_{MK}}\right) - Q_L\left(CM_B - {CM_L}/{R_{ML}}\right) - Q_M\left(CM_B - {CM_M}/{R_{MM}}\right) - K_K M_B$$

3) Distribution in liver:

$$P'_L = Q_L\left(CP_B - {CP_L}/{R_{PL}}\right) + Q_G\left(CP_{GC} - {CP_L}/{R_{PL}}\right) + G_{ABS} - K_{BP}P_L - \frac{P_L \cdot V_{max\,IND}}{K_M + C_{PL}}$$

$$M'_L = Q_L\left(CM_B - {CM_L}/{R_{ML}}\right) - K_{BM}M_L + \frac{P_L \cdot V_{max\,IND}}{K_M + C_{PL}}$$

4) Transport through gut:

$$GP_S' = Feed - T_S \cdot GP_S - \frac{GV_{MAX} \cdot GP_S}{GK_M + GC_S}$$

$$GP_D' = T_S \cdot GP_S - T_D \cdot GP_D - \frac{GV_{MAX} \cdot GP_D}{GK_M + GC_D} + K_{BP} P_L$$

$$GP_J' = T_D \cdot GP_D - T_J \cdot GP_J - \frac{GV_{MAX} \cdot GP_J}{GK_M + GC_J}$$

$$G_{ABS} = \frac{GV_{MAX} \cdot GP_S}{GK_M + GC_S} + \frac{GV_{MAX} \cdot GP_D}{GK_M + GC_D} + \frac{GV_{MAX} \cdot GP_J}{GK_M + GC_J}$$

$$GP_C' = T_J \cdot GP_J - T_C \cdot GP_C$$

$$GM_D' = -T_D \cdot GM_D + K_{BM} M_L$$

$$GM_J' = T_D \cdot GM_D - T_J \cdot GM_J$$

$$GM_C' = T_J \cdot GM_J - T_C \cdot GM_C$$

5) Excretion:

$$U' = K_K M_B$$

$$F_P' = T_C GP_C$$

$$F_M' = T_C GM_C$$

6) Induction of metabolic rate:

$$V_{MAXIND}' = K_{IND} CP_L - K_V (V_{MAXIND} - V_{MAX})$$

Initial conditions

$P_B(0)$	IV dose
$GP_S(0)$	gavage dose
$V_{MAXIND}(0)$	VMAX
All other variables	0 at time 0

Definitions of Abbreviations

Subscripts for tissues:

A	Adipose
B	Blood
G	Gastrointestinal tract
K	Kidney
L	Liver
M	Muscle
S	Skin

Subscripts for gastrointestinal tract lumen segments:

S	Stomach
D	Duodenum
J	Jejunum
C	Colon

Parameters:

V_{XC}	volume of capillary space of tissue
V_{XT}	volume of tissue space of tissue
Q_X	rate of blood flow to tissue
Perm	capillary permeability parameter
T_X	transit rate out of gastrointestinal tract segment
V_{max}	maximum metabolic rate in absence of induction of metabolism
K_m	Michaelis-Menten parameter for metabolism
GV_{max}	maximum rate of absorption from gut
GK_m	Michaelis-Menten parameter for absorption from gut
K_{IND}	constant for induction of metabolism
K_V	constant for return of induced metabolic rate to base value
R_{PX}	tissue:blood partition coefficient for *p,p′*-dichlorodiphenyl sulfone in tissue
R_{MX}	tissue:blood partition coefficient for metabolites in tissue

Variables:

Amounts in tissues [tissues with equations for parent compound are adipose, blood, kidney, liver, muscle, and skin; tissues with equations for metabolites are (with the same subscripts), blood, kidney, muscle, and liver]:

P_{XC}	Amount of parent compound in tissue's capillary space
P_{XT}	Amount of parent compound in tissue's tissue space
P_X	Amount of parent compound in tissue
M_X	Amount of metabolites in tissue

Amounts in gut lumen:

GP_X	Amount of parent compound in gastrointestinal tract segment
GM_X	Amount of metabolites in gastrointestinal tract segment
G_{ABS}	Rate of absorption from gut

Concentrations in the tissues and gut lumen (the concentration in a compartment is equal to the amount in that compartment divided by the volume of the compartment):

CP_{XC}	Concentration of parent compound in tissue's capillary space
CP_{XT}	Concentration of parent compound in tissue's tissue space
CP_X	Concentration of parent compound in tissue
CM_X	Concentration of metabolites in tissue
GCP_X	Concentration of parent compound in gastrointestinal tract segment
GCM_X	Concentration of metabolites in gastrointestinal tract segment

Amounts in the excreta:

U	Cumulative amount of metabolites excreted in urine
F_P	Cumulative amount of parent compound excreted in feces
F_M	Cumulative amount of metabolites excreted in feces

Induced metabolic rate:

V_{maxIND}	Maximum metabolic rate of *p,p′*-dichlorodiphenyl sulfone

Parameter Values for Rats

Physiological values:

Body weight (BW)	from 2-year studies; in kg
Feed consumption	from 2-year studies

Volumes in liters (tissue space + capillary space, where applicable):

Blood	0.052 × BW
Adipose	(0.021 + 0.3 × BW) × BW
Kidney	0.00848 × BW
Liver	$0.0088471 \times (\text{age in months})^{0.1482}$ for males;
	0.045 × BW for females
Muscle	0.01 × BW × [45.4 – 0.1593(W – 10)] for W>10;
	0.01 × BW× [32.6 + 2.56(W – 5)] for W<10, where W is age in weeks
Skin	0.17 × BW

Volume [fraction as capillary space (i.e., ratio $V_{XC}/(V_{XC} + V_{XT})$)]:

Adipose	0.02
Kidney	0.16
Muscle	0.16
Skin	0.16

Gastrointestinal tract volumes, in liters:

V_{GI} (total lumen vol.)	$0.056 \times BW$
Duodenum	$0.06 \times V_{GI}$
Jejunum	$0.486 \times V_{GI}$
Colon	$0.292 \times V_{GI}$
Stomach	$0.162 \times V_{GI}$

Flow rates [blood flow rates (Q_X) as a fraction of Q_T, in L/hr]:

Q_T (total flow)	$14.7 \times BW^{0.7}$
Adipose	0.065
Kidney	0.13
Liver	0.15
Muscle	0.2608
Skin	0.05465

GI tract transit rates [multiplied by $(0.197/BW)^{0.67}$]:

Stomach	1/3.94
Duodenum	1/2.53
Jejunum	1/2.53
Colon	1/13.5

Parameters Derived by Fitting to Male Rat Data

Partition coefficients:

Tissue:blood partition coefficients for p,p′-dichlorodiphenyl sulfone (R_{PX})

Adipose	71.09
Kidney	2.27
Liver	3.94
Muscle	2.41
Skin	11.49

Tissue:blood partition coefficients for metabolites (RMX)

Kidney	14.98
Liver	4.42
Muscle	0.96

Metabolic parameters:

V_{MAX}	570.04 mg/(L·hr)
K_M	5,206.7 mg/L
K_{IND}	0.4914 hr^{-2}
K_V	0.001811 hr^{-1}

Other parameters:

GV_{MAX}	50,556 mg/(L·hr) for fit to intravenous injection and single-dose gavage data only 0.2681 × 50,556 mg/(L·hr) for fit to 2-year data
GK_M	5,443.9 mg/L
Perm	0.5537

Parameters Derived by Fitting to Female Rat Data

V_{MAX}	227 mg/(L·hr)
K_{IND}	1.54 hr^{-2}
K_V	0.209 hr^{-1}
GV_{MAX}	n/a (not applicable)

Parameters Derived by Fitting to Male Mouse Data

V_{MAX}	445 mg/(L·hr)
K_{IND}	0.585 hr^{-2}
K_V	0.0353 hr^{-1}
GV_{MAX}	0.996 (as a multiple of male rat gavage value)

Parameters Derived by Fitting to Female Mouse Data

V_{MAX}	0.857 mg/(L·hr)
K_{IND}	0.358 hr^{-2}
K_V	0.105 hr^{-1}
GV_{MAX}	0.996 (as a multiple of male rat gavage value)

RESULTS

The model is shown in Figure N1. Model results and the corresponding data for the intravenous injection study in male rats are given in Tables N1 through N4. Table N1 gives the concentration of *p,p′*-dichlorodiphenyl sulfone-derived radioactivity in the blood, liver, muscle, kidney, skin, and adipose. Initially, all of the radioactivity was in the blood. By 0.5 hours after injection (the first time point measured), the muscle had the largest amount of radioactivity (though not the greatest concentration). One day after dosing, the largest amount of radioactivity was in the adipose. The model reproduced this behavior well. Data on the amounts of *p,p′*-dichlorodiphenyl sulfone and its metabolites were available at only one time point, 72 hours after dosing. Table N2 shows the concentrations of *p,p′*-dichlorodiphenyl sulfone and its metabolites as observed and as predicted by the model in the blood and liver. The concentration of *p,p′*-dichlorodiphenyl sulfone was much greater than that of the metabolites. Tables N3 and N4 show the amounts of *p,p′*-dichlorodiphenyl sulfone-derived radioactivity in feces and urine. Again, the model fit most of the data well.

Figures N2 through N4 and Tables N5 and N6 compare the data from the single-dose gavage studies in male rats to the model results. Figures N2 through N4 show the amount of *p,p′*-dichlorodiphenyl sulfone-derived radioactivity in excreta of rats administered a single 10 or 100 mg/kg gavage dose of *p,p′*-dichlorodiphenyl sulfone. The model overestimated the amount of metabolites in urine for the 100 mg/kg dose but otherwise fit the data well. Tables N5 and N6 give results for *p,p′*-dichlorodiphenyl sulfone and its metabolites in tissues 3 days after administration. The model fit the 10 mg/kg data better than the 100 mg/kg data. Neither the data nor the model results are 10-fold greater for 100 mg/kg than for 10 mg/kg; this is due to nonlinear metabolism.

It should also be noted that the model gave very similar results for intravenous and oral doses of 10 mg/kg; this was consistent with the data.

Tables N7 and N8 present data and model results for the 2-year feed studies in rats and mice, respectively. For male rats, the model tended to underestimate blood concentrations somewhat for the 2-week data, and overestimate them at 3, 12, and 18 months. The quality of the fit of the model to the female rat and male and female mice data sets varied. The model results for female rats show decreasing concentration with time, in contrast to the observed data. The data for 300 ppm mice at 2 weeks are underpredicted. With the available data, it is unclear how to change the model to improve the fit.

DISCUSSION

In the model, the absorption of *p,p′*-dichlorodiphenyl sulfone from the gut was assumed to be nonlinear; however, with the parameter values found by fitting to the data, the absorption was nearly linear for the exposure concentrations used in the 2-year studies. The absorption was very rapid (~0.1 hours for single gavage doses, 0.4 hours for 2-year feed exposures), so nearly all of the administered *p,p′*-dichlorodiphenyl sulfone was absorbed rather than passed through the gut and eliminated in the feces. *p,p′*-Dichlorodiphenyl sulfone was distributed to the tissues; of the tissues considered in the pharmacokinetic model, the highest measured concentration was found in the adipose and the second highest was in the skin. In the data from single-dose intravenous injections, the tissue:blood concentration ratios of *p,p′*-dichlorodiphenyl sulfone appeared to reach a more or less steady state by 24 hours after injection. Metabolism of *p,p′*-dichlorodiphenyl sulfone was nonlinear, as seen in comparison of blood concentrations of *p,p′*-dichlorodiphenyl sulfone in 2-year studies with different doses. For example, the blood concentration in the 100 ppm male rat 2-year feed study was less than 10 times the concentration in the 10 ppm study. The fit of the model to the data was greatly improved by including the induction by *p,p′*-dichlorodiphenyl sulfone of its own metabolism. Nevertheless, because of the lack of extensive data on *p,p′*-dichlorodiphenyl sulfone metabolites, the representation of metabolism in the model was not very detailed and the model should not be used to draw detailed conclusions on the induction of metabolizing enzymes. The data from the single-dose studies (intravenous and gavage exposures) showed some excretion of *p,p′*-dichlorodiphenyl sulfone in the urine, but this was ignored in the model because it was negligible compared to the excretion of *p,p′*-dichlorodiphenyl sulfone in the feces and the excretion of metabolites in the urine and feces. At the doses used in the model, most of the excretion of *p,p′*-dichlorodiphenyl sulfone-derived compound in the feces was in the form of metabolites of *p,p′*-dichlorodiphenyl sulfone; this was related to the rapid absorption noted above.

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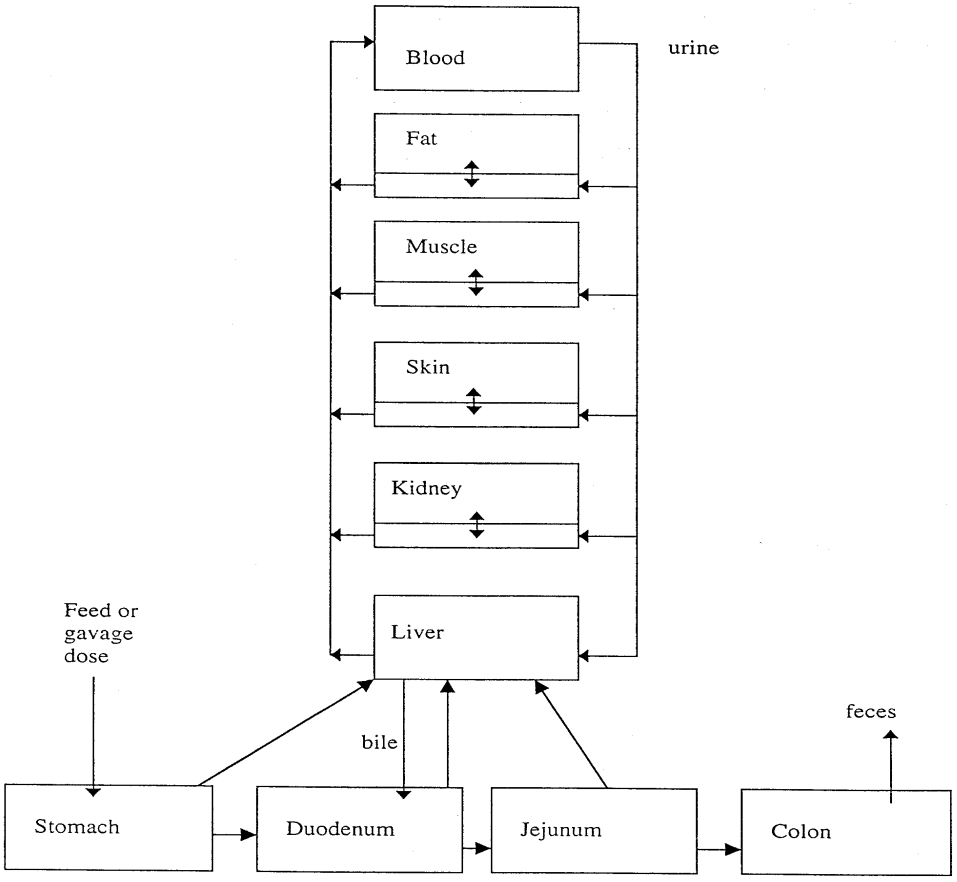

FIGURE N1
Diagram of the Physiologically Based Pharmacokinetic Model for *p,p′*-Dichlorodiphenyl Sulfone
Each compartment except for adipose and skin has both parent compound and metabolites. Metabolism occurs in the liver. Adipose, kidney, muscle, and skin are divided into tissue and capillary space. (Tissue is the large space, capillary is the small space connected to the blood.)

TABLE N1
Concentrations of Equivalent *p,p′*-Dichlorodiphenyl Sulfone-Derived Compound in Male Rats after a Single Intravenous Injection of 10 mg/kg *p,p′*-Dichlorodiphenyl Sulfone[a]

Tissue	Observed Concentration	Concentration Predicted by Model
Blood		
Time after dosing (hours)		
0.5	4.37 ± 0.15	3.99
4	1.37 ± 0.071	1.51
8	1.07 ± 0.078	1.18
24	0.864 ± 0.083	1.00
72	0.729 ± 0.17	0.892
168	0.383 ± 0.047	0.699
504	0.232 ± 0.034	0.257
Liver		
Time after dosing (hours)		
0.5	14.9 ± 0.59	17.2
4	6.01 ± 0.20	6.02
8	4.76 ± 0.67	4.67
24	4.6 ± 0.24	3.95
72	3.72 ± 0.31	3.52
168	3.01 ± 0.36	2.76
504	1.15 ± 0.22	1.01
Muscle		
Time after dosing (hours)		
0.5	6.04 ± 0.57	11.3
4	4.01 ± 0.16	3.81
8	3.99 ± 0.40	2.83
24	3.91 ± 0.49	2.37
72	2.68 ± 0.49	2.10
168	1.87 ± 0.24	1.64
504	0.725 ± 0.18	0.601
Kidney		
Time after dosing (hours)		
0.5	7.91 ± 0.61	10.1
4	3.83 ± 0.35	4.29
8	3.43 ± 0.10	3.25
24	3.61 ± 0.43	2.74
72	2.41 ± 0.42	2.49
168	1.87 ± 0.22	2.0
504	0.795 ± 0.13	0.752

TABLE N1
Concentrations of Equivalent *p,p′*-Dichlorodiphenyl Sulfone-Derived Compound in Male Rats after a Single Intravenous Injection of 10 mg/kg *p,p′*-Dichlorodiphenyl Sulfone

Tissue	Observed Concentration	Concentration Predicted by Model
Skin		
Time after dosing (hours)		
0.5	15.5 ± 1.5	11.9
4	21.2 ± 3.7	18.9
8	15.6 ± 1.0	15.7
24	10.7 ± 1.9	11.4
72	10.2 ± 0.52	9.93
168	6.67 ± 2.0	7.73
504	2.81 ± 0.53	2.83
Adipose		
Time after dosing (hours)		
0.5	23.4 ± 1.5	23.5
4	59.6 ± 8.8	54.5
8	63.9 ± 6.1	63.6
24	79.5 ± 4.9	69.3
72	63.2 ± 3.3	62.7
168	51.7 ± 2.5	49.1
504	19.6 ± 2.1	18.0

[a] Observed concentrations are given in mg/L as mean ± standard deviation; model-predicted values are given in mg/L as the mean; n=3 to 5 animals per group.

TABLE N2
Concentrations of *p,p′*-Dichlorodiphenyl Sulfone and Its Metabolites in Male Rats 3 Days after a Single Intravenous Injection of 10 mg/kg *p,p′*-Dichlorodiphenyl Sulfone[a]

Tissue	Type	Observed Concentration	Concentration Predicted by Model
Blood	*p,p′*-Dichlorodiphenyl sulfone	0.65969	0.82944
Blood	Metabolites	0.069315	0.038463
Liver	*p,p′*-Dichlorodiphenyl sulfone	3.5277	3.2456
Liver	Metabolites	0.19229	0.1777

[a] Data are given in mg/L; n=3 to 5 animals per group

TABLE N3
Cumulative Excretion of Equivalent *p,p′*-Dichlorodiphenyl Sulfone-Derived Compound in Feces of Male Rats after a Single Intravenous Injection of 10 mg/kg *p,p′*-Dichlorodiphenyl Sulfone[a]

	Observed Compound	Compound Predicted by Model
Time after Dosing (hours)		
24	0.0490 ± 0.0049	0.0416
48	0.135 ± 0.0074	0.117
72	0.221 ± 0.0074	0.197
96	0.316 ± 0.012	0.277
120	0.407 ± 0.020	0.356
144	0.468 ± 0.020	0.433
168	0.527 ± 0.029	0.508

[a] Observed values are given in mg as mean ± standard deviation; model-predicted values are given in mg as the mean; n=3 to 5 animals per group.

TABLE N4
Cumulative Excretion of *p,p′*-Dichlorodiphenyl Sulfone Metabolites in Feces and Urine of Male Rats after a Single Intravenous Injection of 10 mg/kg *p,p′*-Dichlorodiphenyl Sulfone[a]

	Observed Compound	Compound Predicted by Model
Feces		
Time after Dosing (hours)		
24	0.0376	0.0372
48	0.105	0.108
72	0.181	0.182
Urine		
Time after Dosing (hours)		
6	0.0417 ± 0.0025	0.0187
24	0.0539 ± 0.0025	0.0495
48	0.0736 ± 0.0049	0.0875
72	0.0907 ± 0.0074	0.125
96	0.105 ± 0.0098	0.163
120	0.120 ± 0.0098	0.200
144	0.132 ± 0.0147	0.235
168	0.159 ± 0.0319	0.270

[a] Observed values are given in mg as mean (feces) or mean ± standard deviation (urine); model-predicted values are given in mg as the mean; n=3 to 5 animals per group.

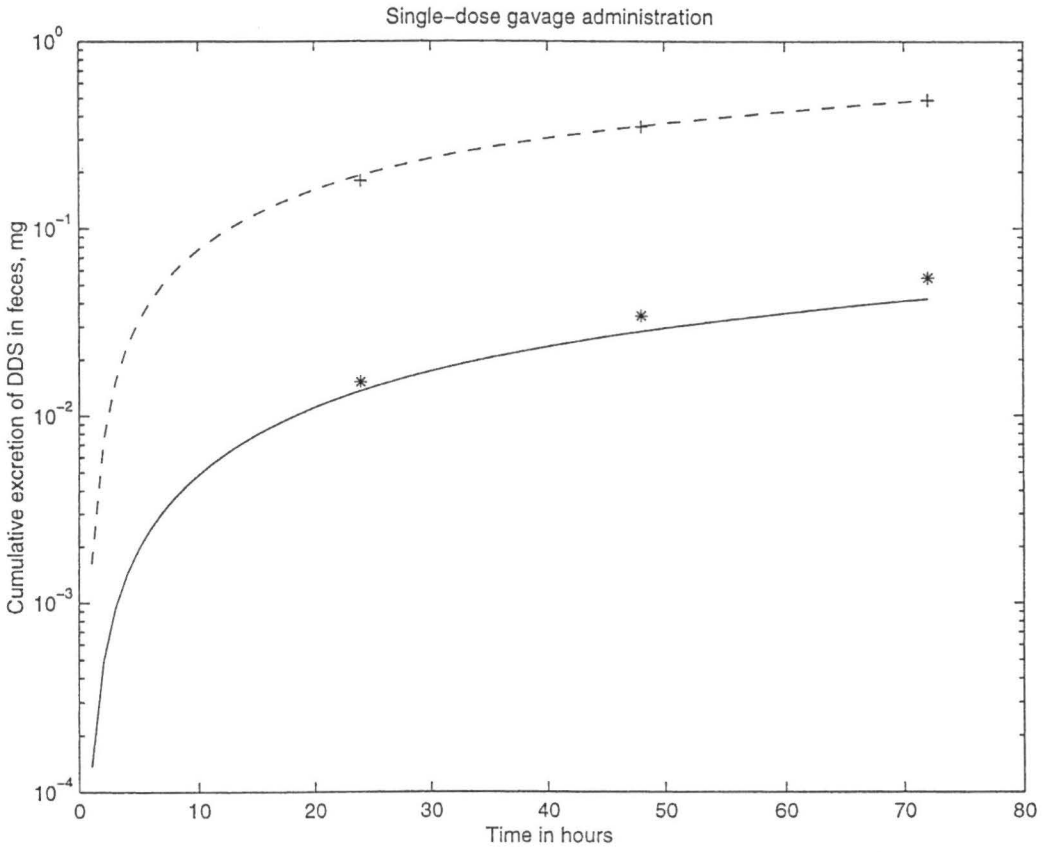

Figure N2
Cumulative Excretion of *p,p′*-Dichlorodiphenyl Sulfone in Feces of Male Rats Given a Single Gavage Dose: Model vs. Data. Solid line and * represent the 10 mg/dose; dashed line and + represent the 100 mg/kg dose.

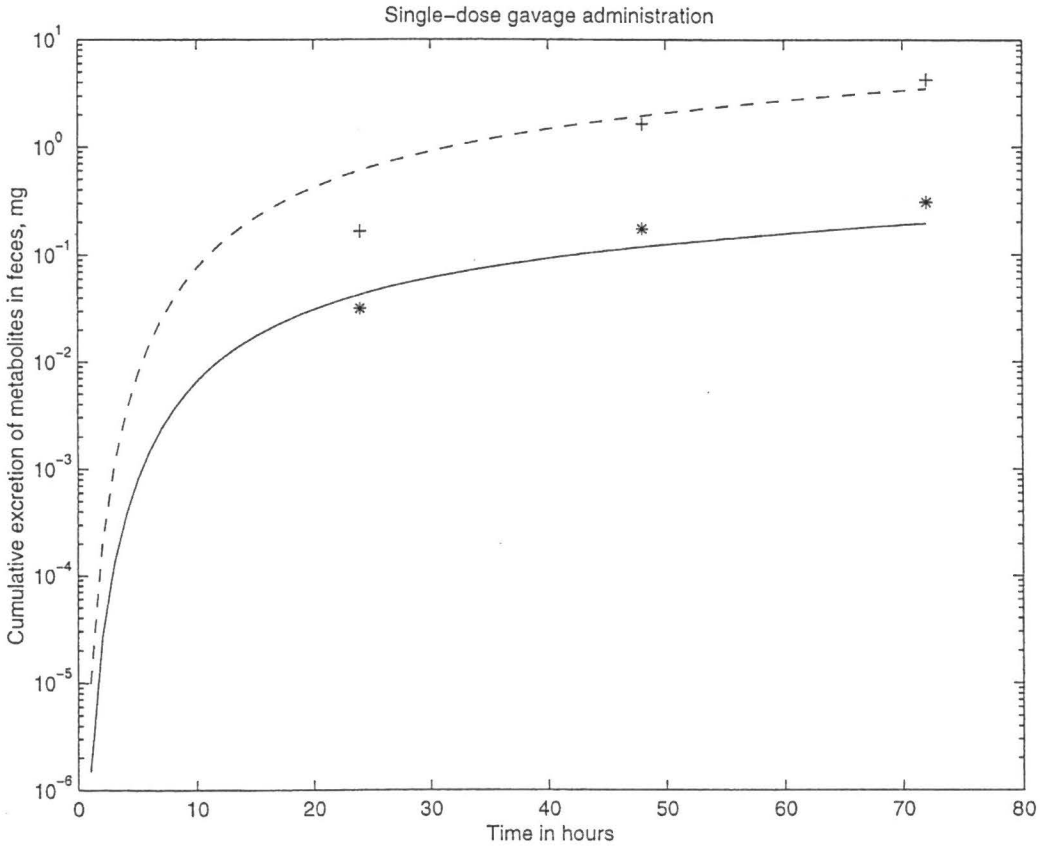

Figure N3
Cumulative Excretion of *p,p′*-Dichlorodiphenyl Sulfone-Derived Metabolites in Feces of Male Rats Given a Single Gavage Dose: Model vs. Data. Solid line and * represent the 10 mg/dose; dashed line and + represent the 100 mg/kg dose.

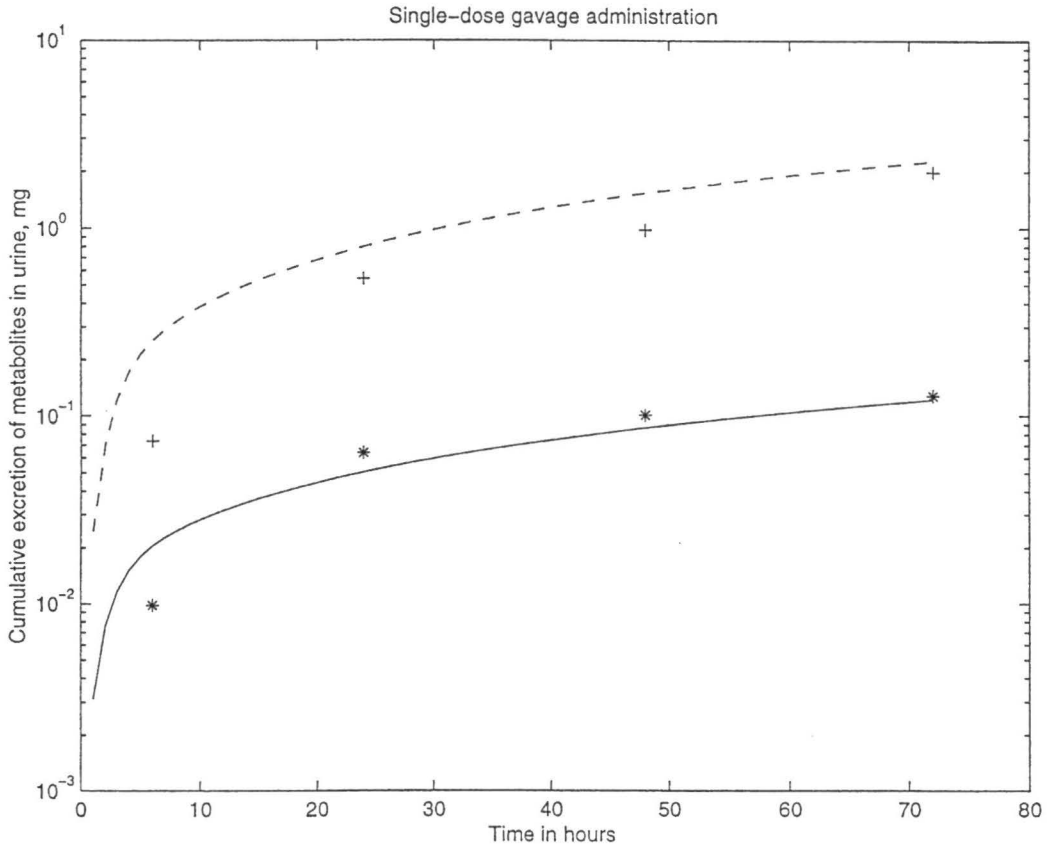

Figure N4
Cumulative Excretion of *p,p′*-Dichlorodiphenyl Sulfone-Derived Metabolites in Urine of Male Rats Given a Single Gavage Dose: Model vs. Data. Solid line and * represent the 10 mg/dose; dashed line and + represent the 100 mg/kg dose.

TABLE N5
Concentrations of *p,p′*-Dichlorodiphenyl Sulfone and Its Metabolites in Male Rats 3 Days after a Single Gavage Dose of 10 mg/kg *p,p′*-Dichlorodiphenyl Sulfone[a]

Tissue	Type	Observed Concentration	Concentration Predicted by Model
Blood	*p,p′*-Dichlorodiphenyl sulfone	0.60232	0.82503
Blood	Metabolites	0.028682	0.03831
Liver	*p,p′*-Dichlorodiphenyl sulfone	4.1019	3.2284
Liver	Metabolites	0.14812	0.177
Muscle	*p,p′*-Dichlorodiphenyl sulfone	2.5199	1.992
Muscle	Metabolites	0.062054	0.036828
Skin	*p,p′*-Dichlorodiphenyl sulfone	11	9.5753
Adipose	*p,p′*-Dichlorodiphenyl sulfone	73.8	60.5847
Gut	Total radioactivity	0.12515	0.12294

[a] Data are given in mg/L except for amount in gut, which is in mg; n=3 to 5 animals per group.

TABLE N6
Concentrations of *p,p′*-Dichlorodiphenyl Sulfone and Its Metabolites in Male Rats 3 Days after a Single Gavage Dose of 100 mg/kg *p,p′*-Dichlorodiphenyl Sulfone[a]

Tissue	Type	Observed Concentration	Concentration Predicted by Model
Blood	*p,p′*-Dichlorodiphenyl sulfone	5.1649	6.6125
Blood	Metabolites	2.7151	0.77838
Liver	*p,p′*-Dichlorodiphenyl sulfone	33.8929	25.6199
Liver	Metabolites	3.8071	3.5949
Muscle	Total radioactivity	12.5	16.7382
Skin	*p,p′*-Dichlorodiphenyl sulfone	57.5	77.7323
Adipose	*p,p′*-Dichlorodiphenyl sulfone	615	506.9466
Gut	Total radioactivity	2.7365	1.8658

[a] Data are given in mg/L except for amount in gut, which is in mg; n=3 to 5 animals per group.

TABLE N7
Observed and Model-Predicted Plasma Concentrations of *p,p′*-Dichlorodiphenyl Sulfone in Rats at 2 Weeks and 3, 12, and 18 Months in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	10 ppm		30 ppm		100 ppm	
Exposure	**Observed**	**Predicted**	**Observed**	**Predicted**	**Observed**	**Predicted**
Male						
2 Weeks	0.625 ± 0.066	0.57061	1.494 ± 0.257	1.392	4.046 ± 0.709	3.1584
3 Months	0.456 ± 0.059	0.58418	1.150 ± 0.155	1.2271	2.613 ± 0.176	2.532
12 Months	0.511 ± 0.121	0.55117	1.272 ± 0.147	1.1241	2.492 ± 0.348	2.2818
18 Months	0.495 ± 0.087	0.51531	1.201 ± 0.148	1.0573	2.766 ± 0.216	2.15
	30 ppm		**100 ppm**		**300 ppm**	
Female						
2 Weeks	1.0864 ± 0.1175	1.8686	3.1389 ± 0.3051	3.8706	6.0044 ± 1.3899	7.16
3 Months	1.2956 ± 0.1614	1.4833	2.7411 ± 0.3380	3.153	5.0189 ± 0.3549	5.7218
12 Months	1.4156 ± 0.2311	1.3831	3.4089 ± 0.4696	3.8894	6.3767 ± 0.7044	5.3925
18 Months	1.7044 ± 0.2136	1.3304	3.6678 ± 0.5024	3.753	7.2744 ± 0.6692	5.1206

[a] Observed concentrations are given in µg/mL as mean ± standard deviation; predicted values are given in µg/mL as the mean.

TABLE N8
Observed and Model-Predicted Plasma Concentrations of *p,p′*-Dichlorodiphenyl Sulfone in Mice at 2 Weeks and 3 and 12 Months in the 2-Year Feed Study of *p,p′*-Dichlorodiphenyl Sulfone[a]

	30 ppm		100 ppm		300 ppm	
Exposure	**Observed**	**Predicted**	**Observed**	**Predicted**	**Observed**	**Predicted**
Male						
2 Weeks	1.35 ± 0.17	1.4825	4.4033 ± 0.4725	4.3508	16.5 ± 1.8	10.4487
3 Months	2.1667 ± 0.2079	1.9246	3.47 ± 0.50	5.5086	9.5767 ± 0.2730	11.9227
12 Months	2.04 ± 0.29	1.9425	7.22 ± 0.20	5.4293	12.7167 ± 5.1827	12.2276
Female						
2 Weeks	2.04 ± 0.51	1.2153	5.57 ± 0.85	4.3218	18.433 ± 3.166	10.3649
3 Months	2.9967 ± 0.3842	1.8039	4.33 ± 0.85	5.5401	12 ± 1	12.9361
12 Months	2.9867 ± 0.1266	3.0001	7.88 ± 1.78	9.016	20.1 ± 0.7	21.7291

[a] Observed concentrations are given in µg/mL as mean ± standard deviation; predicted values are given in µg/mL as the mean.

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