NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF 2,2′,4,4′,5,5′-HEXACHLOROBIPHENYL (PCB 153)

(CAS NO. 35065-27-1)

IN FEMALE HARLAN SPRAGUE-DAWLEY RATS

(GAVAGE STUDIES)

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

May 2006

NTP TR 529

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

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CONTENTS

ABSTRACT 5

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 10

TECHNICAL REPORTS REVIEW SUBCOMMITTEE 11

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS 12

OVERVIEW 13

INTRODUCTION 19

MATERIALS AND METHODS 23

RESULTS 31

DISCUSSION AND CONCLUSIONS 47

REFERENCES 51

APPENDIX A Summary of Lesions in Female Rats in the 2-Year Gavage Study of PCB 153 61

APPENDIX B Organ Weights and Organ-Weight-to-Body-Weight Ratios 131

APPENDIX C Chemical Characterization and Dose Formulation Studies 135

APPENDIX D Ingredients, Nutrient Composition, and Contaminant Levels in NTP-2000 Rat and Mouse Ration 145

APPENDIX E Sentinel Animal Program 153

APPENDIX F Physiologically Based Pharmacokinetic Model 155

APPENDIX G Associated Publications 167

SUMMARY

Background
2,2′4,4′,5,5′-Hexachlorobiphenyl (PCB 153) is one of a large family of hydrocarbons called polychlorinated biphenyls (PCBs) that are similar in structure to dioxins. Some dioxins or dioxin-like compounds are highly toxic and cause cancer, and usually contaminated sites contain many different varieties of these dioxin-like compounds. The National Toxicology Program conducted a series of studies to try to gauge the relative toxicity of some of the more prevalent of these compounds both alone and in mixtures. PCB 153 does not exhibit dioxin-like activity but is the PCB that occurs at the highest concentration in human tissue samples. This study evaluated the effects of PCB 153 on female rats for comparison with the potency of other chemicals in that family.

Methods
We exposed groups of 50 female rats by depositing solutions of PCB 153 dissolved in corn oil through a tube directly into their stomachs five days a week for two years. Daily doses of PCB 153 were 10, 100, 300, 1,000 or 3,000 micrograms (µg) per kilogram of body weight. Tissues from more than 40 sites were examined for every animal.

Results
Exposure to PCB 153 caused a variety of diseases in several organs, including hypertrophy and hyperplasia of the liver, follicular cell hypertrophy of the thyroid gland, and inflammation of the ovary, oviduct, and uterus. Four exposed animals developed rare cholangiomas of the liver.

Conclusions
We conclude that PCB 153 caused toxic effects at several sites in female rats and was possibly associated with cholangioma of the liver.

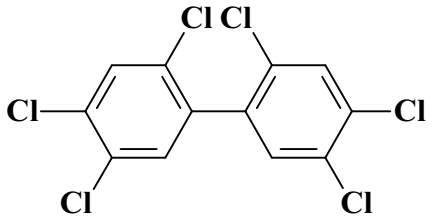
ABSTRACT

Dioxin Toxic Equivalency Factor Evaluation Overview

Polyhalogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) have the ability to bind to and activate the ligand-activated transcription factor, the aryl hydrocarbon receptor (AhR). Structurally related compounds with similar physiochemical properties that bind to the AhR and exhibit biological actions similar to TCDD are commonly referred to as "dioxin-like compounds" (DLCs). Additional compounds not structurally or physiochemically related to TCDD have been identified as AhR ligands and include some of the carotinoids, indoles, flavinoids, isoflavones, and arachidonic acid metabolites (Amakura *et al.*, 2003; Denison and Nagy, 2003; Zhang *et al.*, 2003). Ambient human exposure to DLCs occurs through the ingestion of foods containing residues of DLCs that bioconcentrate through the food chain. Due to their lipophilicity and persistence, once internalized they accumulate in body tissues, mainly adipose tissue, resulting in chronic lifetime human exposure.

Since human exposure to DLCs always involves as a complex mixture, the toxic equivalency factor (TEF) methodology has been developed as a mathematical tool to assess the health risk posed by complex mixtures of these compounds. The TEF methodology is a relative potency scheme that ranks the dioxin-like activity of a compound relative to TCDD, the most potent congener. This allows for the estimation of the potential total dioxin-like activity of a mixture of chemicals, based on a common mechanism of action involving an initial binding of DLCs to the AhR.

The toxic equivalency of DLCs was nominated for evaluation because of the widespread human exposure to DLCs and the lack of data on the adequacy of the TEF methodology for predicting relative potency for cancer risk. To address this, the National Toxicology Program conducted a series of 2-year bioassays in female Harlan Sprague-Dawley rats to evaluate the chronic toxicity and carcinogenicity of DLCs and structurally related polychlorinated biphenyls (PCBs) and mixtures of these compounds.



2,2′,4,4′,5,5′-Hexachlorobiphenyl
(PCB 153)

CAS No. 35065-27-1

Chemical Formula: $C_{12}H_4Cl_6$ Molecular Weight: 360.88

Synonym: 1,1′-Biphenyl, 2,2′,4,4′,5,5′-hexachloro-(9CI)

2,2′,4,4′,5,5′-Hexachlorobiphenyl (PCB 153) was produced as a component of some commercial PCB mixtures before 1977 for the electric industry as a dielectric insulating fluid for transformers and capacitors. Manufacture and use of the chemical was stopped due to increased PCB residues in the environment, but it continues to be released into the environment through the use and disposal of products containing PCBs, as byproducts during the manufacture of certain organic chemicals, and during the combustion and biodegradation of some waste materials. Bioaccumulation of PCB 153 results in persistent levels in animal and human tissues. PCB 153 was selected for study by the National Toxicology Program as a part of the dioxin TEF evaluation to assess the cancer risk posed by complex mixtures of polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs). The dioxin TEF evaluation includes conducting multiple 2-year rat bioassays to evaluate the relative chronic toxicity and carcinogenicity of DLCs, structurally related PCBs, and mixtures of these compounds. PCB 153 was included since it is present at the highest PCB concentrations in human samples on a molar basis. PCB 153 was also included in a mixture study with PCB 126, since previous studies have demonstrated interactions between PCB 153 and DLCs on pharmacokinetic and biological effects. While one of the aims of this study was a comparative analysis of effects seen with PCB 126 and the mixture of PCB 126 and PCB 153, in this Technical Report only the results of the present study of PCB 153 are presented and discussed.

2-Year Study

Female Harlan Sprague-Dawley rats were administered PCB 153 (greater than 99% pure) in corn oil:acetone (99:1) by gavage for 14, 31, or 53 weeks or 2 years. Groups of 80 (3,000 µg PCB 153/kg body weight), 81 (100, 300, and 1,000 µg/kg), or 82 (10 µg/kg) female rats received PCB 153 in corn oil:acetone (99:1) by gavage at doses of 10, 100, 300, 1,000, or 3,000 µg/kg 5 days per week for up to 105 weeks; a group of 81 female rats received the corn oil:acetone (99:1) vehicle alone. A stop-exposure group of 50 female rats was administered 3,000 µg/kg for 30 weeks and then the vehicle for the remainder of the study.

Dose selection for the PCB 153 study was based on the range of PCB 153 doses used in the mixture study of PCB 126 and PCB 153 (10 to 3,000 µg/kg).

Survival of dosed groups was similar to that of the vehicle control group. Mean body weights of 3,000 µg/kg core study rats were less than those of the vehicle controls after week 69 of the study.

Thyroid Hormone Concentrations

Serum total thyroxine (T_4), free T_4, and total triiodothyronine (T_3) concentrations in the 3,000 µg/kg group were significantly lower than those in the vehicle controls at the 14-week interim evaluation. At the 31-week interim evaluation, no significant differences were observed in serum total T_4, free T_4, T_3, or thyroid stimulating hormone concentrations. At the 53-week interim evaluation, serum total T_4 and free T_4 concentrations in the 3,000 µg/kg group were significantly lower than in the vehicle controls.

Hepatic Cell Proliferation Data

No significant differences in hepatocellular labeling index were observed between the vehicle control and dosed groups at any of the interim evaluations.

Cytochrome P450 Enzyme Activities

Hepatic pentoxyresorufin-*O*-deethylase activities were highly and significantly elevated relative to the vehicle control groups. Maximum increases over controls at 14, 31, and 53 weeks were 136-, 140-, and 40-fold, respectively. Hepatic 7-ethoxyresorufin-*O*-deethylase (EROD) and acetanilide-4-hydroxylase (A4H) activities were significantly elevated over controls at 14 and 31 weeks; increases were less than twofold. At 14 weeks, EROD activities in the lung were dose-dependently reduced compared to vehicle controls.

Determinations of PCB 153 Concentrations in Tissues

In the fat from vehicle controls, detectable levels of PCB 153 were observed at 14, 31, and 53 weeks and at the end of the 2-year study. Fat concentrations of PCB 153 increased with increasing doses of PCB 153 and tended to increase with the longer exposure durations. In the fat of the 3,000 µg/kg stop-exposure group, PCB 153 concentrations were between the levels observed in the 300 and 1,000 µg/kg groups. In the liver of vehicle controls, no measurable concentrations of PCB 153 were observed at any time point. In dosed groups, hepatic concentrations of PCB 153 increased with increasing dose and longer exposure duration. Measurable concentrations of PCB 153 were observed in the lungs of vehicle control rats at 31 and 53 weeks and at 2 years. At all time points, PCB 153 lung and blood concentrations increased with increasing dose, and blood concentrations increased with duration of exposure. In liver, lung, and blood of rats from the 3,000 µg/kg stop-exposure group, PCB 153 concentrations were slightly above or below the levels observed in the 1,000 µg/kg group.

Organ Weights

Absolute liver weights of 1,000 µg/kg rats and absolute and relative liver weights of 3,000 µg/kg rats were significantly greater than those of vehicle controls at week 14. At week 31, relative liver weights of 1,000 µg/kg rats and absolute and relative liver weights of 3,000 µg/kg rats were significantly greater than those of vehicle controls. At week 53, absolute and relative liver weights were significantly greater in rats administered 100 µg/kg or greater compared to vehicle controls. Absolute kidney weights of all exposed groups and the relative kidney weight of 3,000 µg/kg rats were significantly increased at week 53.

Pathology and Statistical Analyses

The incidences of hepatocyte hypertrophy were significantly increased in the 1,000 and 3,000 µg/kg groups at 14 weeks and in all groups administered 300 µg/kg or greater at 31 and 53 weeks.

At 2 years, the incidences of hepatocyte hypertrophy were significantly increased in all dosed groups. The incidences of diffuse fatty change in the 300 µg/kg or greater groups and bile duct hyperplasia of the liver in 300 µg/kg and 3,000 µg/kg (core and stop-exposure) groups were significantly increased. The incidences of oval cell hyperplasia and pigmentation of the liver were significantly increased in the 3,000 µg/kg core study group. At 2 years, two cholangiomas were seen in the 1,000 µg/kg group and two cholangiomas were seen in the 3,000 µg/kg stop-exposure group. A single hepatocellular adenoma was observed in the 3,000 µg/kg core study group.

At 53 weeks, sporadic incidences of minimal to mild follicular cell hypertrophy of the thyroid gland occurred in all groups (except 10 µg/kg). At 2 years, the incidences of minimal to mild follicular cell hypertrophy were significantly increased in the 300 µg/kg and 3,000 µg/kg (core and stop-exposure) groups.

At 2 years, significantly increased incidences of chronic active inflammation in the ovary and oviduct occurred in the 1,000 and 3,000 µg/kg core study groups. Incidences of suppurative inflammation of the uterus in the 1,000 µg/kg group and chronic active inflammation in the 3,000 µg/kg core study group were significantly greater than those in the vehicle control group.

Conclusions

Under the conditions of this 2-year gavage study there was *equivocal evidence of carcinogenic activity** of PCB 153 in female Harlan Sprague-Dawley rats based on the occurrences of cholangioma of the liver.

PCB 153 administration caused increased incidences of nonneoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus in female rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis Study of PCB 153 in Female Sprague-Dawley Rats

Doses in corn oil/acetone by gavage
0, 10, 100, 300, 1,000, 3,000 µg/kg, and 3,000 µg/kg (stop-exposure)

Body weights
3,000 µg/kg core study group less than the vehicle control group

Survival rates
24/53, 16/54, 28/53, 21/53, 20/53, 21/51, 20/50

Nonneoplastic effects
Liver:
hepatocyte hypertrophy (0/53, 5/54, 5/53, 24/53, 39/53, 41/51, 32/50);
diffuse fatty change (3/53, 7/54, 2/53, 11/53, 21/53, 17/51, 15/50);
bile duct hyperplasia (5/53, 3/54, 2/53, 14/53, 10/53, 17/51, 12/50);
oval cell hyperplasia (0/53, 0/54, 0/53, 1/53, 0/53, 4/51, 2/50);
pigmentation (1/53, 1/54, 2/53, 5/53, 5/53, 9/51, 3/50)
Thyroid Gland:
follicular cell hypertrophy (5/51, 9/52, 9/53, 12/53, 10/53, 17/51, 12/49)
Ovary:
chronic active inflammation (0/53, 0/53, 2/53, 1/53, 5/53, 7/50, 0/49)
Oviduct:
chronic active inflammation (1/50, 0/38, 2/44, 1/35, 5/39, 7/45, 2/46)
Uterus:
suppurative inflammation (5/53, 6/54, 6/53, 2/53, 16/53, 8/50, 9/49);
chronic active inflammation (2/53, 1/54, 5/53, 4/53, 2/53, 8/50, 1/49)

Neoplastic effects
None

Equivocal findings
Liver:
cholangioma (0/53, 0/54, 0/53, 0/53, 2/53, 0/51, 2/50)

Level of evidence of carcinogenic activity
Equivocal evidence

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.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as “were also related” to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as “may have been” related to chemical exposure.

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 PCB 153 on December 9, 2004, 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 December 9, 2004, the draft Technical Report on the toxicology and carcinogenesis studies of 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB 153) 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 (NIEHS), Research Triangle Park, NC.

Dr. N.J. Walker, NIEHS, presented the background, design, and goals of the NTP study series on the toxic equivalency factor (TEF) evaluations of mixtures of dioxin-like compounds (dioxins, PCBs, furans). Four reports in the TEF evaluation series (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, 3,3′,4,4′,5-pentachlorobiphenyl, 2,3,4,7,8-pentachlorodibenzofuran, and a mixture of the three compounds) were presented at the previous peer review meeting held on February 17, 2004. Dr. N.J. Walker summarized the design and results of these four studies. He described development of dose-response models for various endpoints using these results.

Dr. N.J. Walker introduced the toxicology and carcinogenesis studies of PCB 153 by noting that it is the most prevalent PCB congener in human tissues and that the TEF evaluation series also included studies of PCB 126 and a mixture of PCB 126 and PCB 153 to evaluate potential interactions. He described the study design, the biochemical responses to the chemical, and the occurrences of a few cholangiomas in exposed animals. The proposed conclusions were *equivocal evidence of carcinogenic activity* of PCB 153 in female Harlan Sprague-Dawley rats based on the occurrences of cholangiomas of the liver. PCB 153 administration caused increased incidences of nonneoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus in female Harlan Sprague-Dawley female rats.

Dr. Klaunig, the first principal reviewer, said the conduct and interpretation of the study were proper. He inquired if cholangiofibrosis might be a possible precursor lesion for the cholangiomas.

Dr. Gasiewicz, the second principal reviewer, agreed with the proposed conclusions. He noted that cholangic rather than hepatocellular lesions were the predominant liver effect in this set of studies.

Dr. C.L. Walker, the third principal reviewer, said the report was well written. She inquired if the changes in hepatic cell proliferation were significant.

Dr. N.J. Walker replied that the measures of cell proliferation often give skewed results but that overall no significant effects were noted. He agreed that a number of cholangiomas were seen in this series of studies and speculated that different strains of Sprague-Dawley rats might have different responses. He added that cholangiofibrosis was not a precursor lesion to cholangioma.

Dr. Klaunig moved that the conclusions be accepted as written. Dr. Gasiewicz seconded the motion, which was approved unanimously with nine votes.

OVERVIEW

Dioxin Toxic Equivalency Factor Evaluation

Polyhalogenated Aromatic Hydrocarbons and Human Exposure

Polyhalogenated aromatic hydrocarbons (PHAHs) comprise a large class of compounds including polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), polychlorinated naphthalenes (PCNs), and polybrominated diphenyl ethers (PBDEs).

PCDDs and PCDFs were not manufactured for commercial purposes. They are unwanted by-products of many anthropogenic activities, including combustion processes such as forest and backyard trash fires and manufacturing processes for herbicides and paper. PCB mixtures were commercially produced and used in the electric power industry as dielectric insulating fluids in transformers and capacitors and used in hydraulic fluids, plastics, and paints. PCNs were produced and used as dielectric fluids in capacitors, transformers, and cables. PBDEs are flame retardants, used in the manufacture of items including paints, foams, textiles, furniture, and household plastics (USEPA, 2000a).

Because these compounds are resistant to degradation and persistent in the environment, they have the ability to bioaccumulate and become more concentrated. Ambient human exposure to PHAHs occurs through the ingestion of foods containing PHAH residues. Due to their persistence and lipophilicity, once internalized, they accumulate in body tissues, mainly adipose tissue, resulting in chronic lifetime human exposure (Schecter *et al*., 1994a).

Dioxin-like Compounds

Depending on the location and type of the halogenation, some PHAHs, most notably certain PCDDs, PCDFs, and PCBs have the ability to bind to a cytosolic receptor known as the aryl hydrocarbon receptor (AhR) (Safe, 1990; Whitlock, 1990). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), commonly referred to as "dioxin," is the most well-characterized member of these structurally related compounds and exhibits the highest potency of binding to the AhR. Depending upon the number and position of the substitutions, there are potentially 75 PCDDs, 135 PCDFs, and 209 PCBs. Structurally related compounds that bind to the AhR and exhibit biological actions similar to TCDD are commonly referred to as dioxin-like compounds (DLCs). There are seven PCDDs, 10 PCDFs, and 13 PCBs that exhibit such dioxin-like activity (USEPA, 2000b). In addition to the persistent DLCs, there are a wide variety of other compounds that can also bind to the AhR, including polycyclic aromatic hydrocarbons, (e.g., benzo(*a*)pyrene found in cigarette smoke), dietary indoles (e.g., indole-3-carbinol found in cruciferous vegetables), dietary flavonoids (e.g., quercetin, kaempferol), and heme degradation products (e.g., bilirubin/biliverdin).

The persistent PHAHs and DLCs have been the subject of an extensive amount of research regarding environmental levels, transport, and fate; human exposure; mechanisms of action; and toxicity that is beyond the scope of this report. The extensive body of knowledge on TCDD and related compounds has been fully reviewed by the International Agency for Research on Cancer (1997), the Agency for Toxic Substances and Disease Registry (1998, 2000), and by the United States Environmental Protection Agency (2000a,b,c); therefore, it will not be re-reviewed in depth in this Technical Report.

Mechanism of Action via the Aryl Hydrocarbon Receptor

Based on the extensive body of research on the induction of the cytochrome P450 1A1 (CYP1A1) gene by TCDD, the primary mechanism of action of DLCs involves initial binding to the AhR (Schmidt and Bradfield, 1996). The AhR is a protein found as a multimeric complex in the cytosol of all vertebrate species and acts as a ligand-activated transcription factor. Initial binding of ligand to the receptor disrupts the receptor complex leading to receptor activation and translocation into the nucleus where it heterodimerizes with the AhR nuclear translocator protein (ARNT) (Gu *et al*., 2000). The AhR-ARNT heterodimer binds to specific cognate DNA

sequence elements known as dioxin/xenobiotic response elements (DRE/XRE) present in the regulatory region of specific genes such as CYP1A1. Binding of the AhR-ARNT heterodimer to these elements leads to increased transcription of the specific gene. The hallmark response to TCDD is the transcriptional induction of CYP1A1, which is mediated by binding of the heterodimer to DREs present in the 5′ flanking region of the gene. The AhR is expressed in all tissues with a definite tissue specificity in terms of level of expression and diversity of response. TCDD has been shown to modulate numerous growth factor, cytokine, hormone, and metabolic pathways in animals and experimental systems. Many, if not all, are parts of pathways involved in cellular proliferation and differentiation and, taken together, they provide a plausible mechanism for toxicity and carcinogenicity. Most of the molecular details for induction of gene expression via the AhR have been characterized for the transcriptional activation of the CYP1A1 gene. The expression of many genes has been shown to be affected by TCDD (Puga *et al.,* 2000; Frueh *et al.*, 2001; Martinez *et al.,* 2002), yet there is evidence for direct transcriptional activation through the AhR for only a few of these (Sutter and Greenlee, 1992).

Toxicity of Dioxin-like Compounds

High doses and/or continuous exposure to dioxins lead to a broad spectrum of toxic responses including death, immunosuppression, carcinogenicity, and impaired reproduction and development (Whitlock, 1990; ATSDR, 1998; Grassman *et al.,* 1998; USEPA, 2000c). The type of toxicity is dependent on the magnitude of dose, duration and pattern of exposure, timing of exposure, species, and gender. A generalized mode of action for toxicity induced by dioxins is one that involves initial binding of the compounds to the AhR. Subsequent alterations in expression of specific genes and alterations in biological signal transduction pathways lead to an alteration in growth regulation and differentiation that leads to pathology and toxicity.

The broad spectrum of DLC effects on hormone and growth factor systems, cytokines, and signal transduction pathways indicate they are powerful growth dysregulators. The effect of DLCs on growth regulation may be manifested through alterations in genes involved in cellular growth and homeostasis. Although the relationship between these effects and carcinogenesis can only be inferred, all of these effects are involved in cellular growth and differentiation; disruption of normal cellular processes could be a risk factor for carcinogenicity.

The initial involvement of the AhR in initiating this cascade of events is supported by studies showing the lower potency of structurally related compounds with lower affinity for the AhR, reduction of effects in rodents with lower AhR affinities (Pohjanvirta *et al.,* 1993; Birnbaum, 1994), and the lack of effects using transgenic mice that lack AhR functionality (Gonzalez *et al.,* 1996; Gonzalez and Fernandez-Salguero, 1998; Gonzalez, 2001; Vorderstrasse *et al.,* 2001). These data indicate that the AhR is necessary, but may not be sufficient, for mediating the toxic action of DLCs.

Polyhalogenated Aromatic Hydrocarbon Mixtures and Toxic Equivalency Factors

PHAHs always exist in the environment as complex mixtures; therefore, normal background human exposure to PHAHs always occurs as a complex mixture. The toxic equivalency factor (TEF) approach has been developed to assess risk posed by complex mixtures of PCDDs, PCDFs, and PCBs (Ahlborg *et al.,* 1992; Van den Berg *et al.,* 1998; USEPA, 2000c). The TEF methodology is a relative potency scheme to estimate the total exposure and dioxin-like effects of a mixture of chemicals based on a common mechanism of action involving an initial binding of the compound to the AhR. The TEF methodology is currently the most feasible interim approach for assessing and managing the risk posed by these mixtures, and has been formally adopted by a number of countries including Canada, Germany, Italy, the Netherlands, Sweden, the United Kingdom, and the United States. The method is also used by the International Programme on Chemical Safety and the World Health Organization. Criteria for inclusion of a compound in the TEF methodology are structural relationship to PCDD/PCDFs, binding to the AhR, elicitation of AhR-mediated biochemical and toxic responses, and persistence and accumulation in the food chain.

The current World Health Organization (WHO) TEFs are based on a subjective evaluation of individual studies that examined the relative potency of a given chemical to the reference compound, TCDD, which is assigned a potency of 1. TEF values are an order of magnitude *estimate* of the overall "toxic potency" of a given compound and therefore do not specifically refer to the potency from any single study with a particular endpoint. By comparison, a relative potency factor is determined for a specific chemical in a single study relative to a specific endpoint. Therefore, a single TEF is based on an evaluation of multiple relative potency factors. The TEF determination is a subjective assessment because

the relative potency factors are derived from the literature and there is considerable variability in the types of studies, endpoints analyzed, and quality of procedures. Types of procedures for calculation of relative potency factors vary from a comparative dose response assessment (e.g., rate of ED_{50} or EC_{50}) to a simple administered dose ratio calculation. In evaluating different studies and endpoints, more weight is given to *in vivo* studies than to *in vitro* studies, chronic studies are weighted more than acute studies, and toxic responses are weighted more than simple biochemical responses.

An implicit assumption of the TEF methodology is that the combined effects of the different congeners are dose additive, which is supported by *in vivo* studies with mixtures of PCDDs and PCDFs, mixtures of PCDFs, and mixtures of PCBs and TCDD and by *in vitro* studies with mixtures of PCBs and PCDFs (Birnbaum *et al.,* 1987; Schrenk *et al.*, 1991, 1994; Birnbaum and DeVito, 1995; USEPA, 2000c). Therefore, the total toxic equivalents (TEQs) for the AhR-mediated toxic potency of a mixture of PCDDs, PCDFs, and PCBs may be estimated by the summation of the mass of each congener in the mixture after adjustment for its potency. Currently only PCDDs, PCDFs, and certain PCBs are included in this TEF scheme.

$$TEQ = \sum_{ni} (PCDD_i \times TEF_i)_n + \sum_{ni} (PCDF_i \times TEF_i)_n + \sum_{ni}(PCB_i \times TEF_i)_n,$$

where i = the individual congeners and respective TEF, and n = all congeners within each class of DLCs

Uncertainties in the Use of Toxic Equivalency Factors

While TEFs were developed initially as an interim approach to facilitate exposure assessment and hazard identification, there has been an increasing use of this scheme to determine TEQs in human tissues for dose-response assessment of effects in human populations (Flesch-Janys *et al.,* 1998). While the database for development of TEFs for DLCs is extensive, these data are for dioxin-regulated noncancer endpoints that often reflect simply the activation of the AhR. No mammalian studies have formally evaluated relative potency factors for a neoplastic endpoint. The mechanism by which activation of the AhR and subsequent changes in dioxin-responsive events leads to cancer is not known, and the validity of current TEFs for predicting cancer risk has not been evaluated.

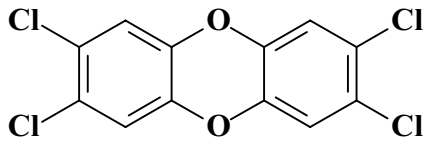
One of the implicit assumptions in the use of TEFs is that the TEQ for different compounds is dose additive. While dose additivity is supported for certain mixtures, for some biological endpoints in some models, this may not be true. As outlined by Van den Berg *et al.* (1998), the TEF methodology is likely valid for biological responses that are clearly AhR dependent, but may not be true for more complex biological responses such as neoplasia.

The Dioxin Toxic Equivalency Factor Evaluation Studies

To test the validity of the TEF approach for the prediction of cancer risk, the National Toxicology Program (NTP) has conducted multiple 2-year bioassays in female Sprague-Dawley rats to evaluate the chronic toxicity and carcinogenicity of DLCs, structurally related PCBs, and mixtures of these compounds. Specific hypotheses to be tested by these studies are:

1. TEFs for PCDDs, PCDFs, and PCBs can predict the relative carcinogenic potency of single congeners in female Sprague-Dawley rats.
2. TEFs for PCDDs, PCDFs, and planar PCBs can predict the relative carcinogenic potency of an environmentally relevant mixture of these chemicals in the female Sprague-Dawley rat.
3. The carcinogenicity of a dioxin-like, non-*ortho*-substituted PCB is not altered by the presence of a mono-*ortho* or di-*ortho*-substituted PCB.
4. Relative potencies for DLCs are dose additive.
5. The relative potencies for activation of biochemical endpoints, such as CYP1A1 induction, in the 2-year studies are equivalent to the relative potency for induction of carcinogenesis when estimated based on administered dose.
6. The relative potencies for activation of biochemical endpoints, such as CYP1A1 induction, in the 2-year studies are equivalent to the relative potency for induction of carcinogenesis when estimated based on target tissue dose.
7. The relative potencies for alteration of a given response are the same, regardless of the dose metric used (e.g., administered dose, serum or whole blood concentrations, or tissue dose).

Individual Compounds, Mixtures, and Rationale for Choice

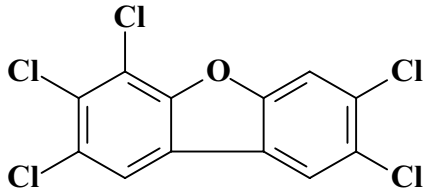


2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
(TCDD)

CAS No. 1746-01-6

Chemical Formula: $C_{12}H_4Cl_4O_2$
Molecular weight: 321.98

TCDD is the most potent DLC and the reference compound to which all DLCs are compared in the TEF methodology. As such it has a TEF value of 1. TCDD is classified as a known human carcinogen by the NTP and the International Agency for Research on Cancer.

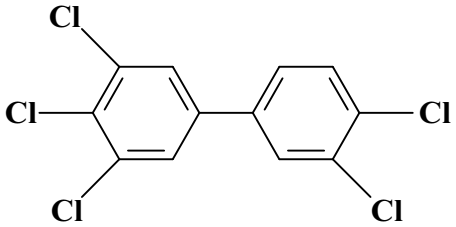


2,3,4,7,8-Pentachlorodibenzofuran
(PeCDF)

CAS No. 57117-31-4

Chemical Formula: $C_{12}H_3Cl_5O$
Molecular weight: 340.4

PeCDF is a dioxin-like PHAH with high bioaccumulation in the food chain and a TEF value of 0.5. This compound represents the most potent PCDF present in human tissues.

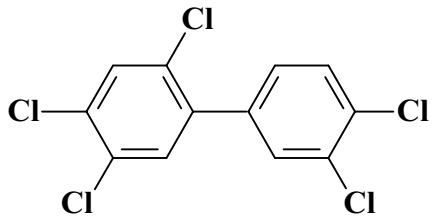


3,3′,4,4′,5-Pentachlorobiphenyl
(PCB 126)

CAS No. 57465-28-8

Chemical Formula: $C_{12}H_5Cl_5$
Molecular weight: 326.42

PCB 126 is a non-*ortho*-substituted PCB with high bioaccumulation in the food chain and a TEF value of 0.1. PCB 126 is considered the most potent dioxin-like PCB congener present in the environment and accounts for 40% to 90% of the total toxic potency of PCBs having a "dioxin-like" activity.

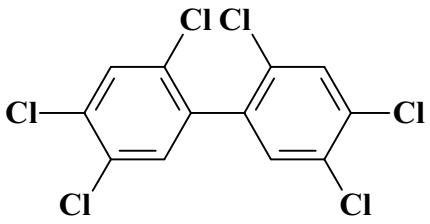


2,3′,4,4′,5-Pentachlorobiphenyl
(PCB 118)

CAS No. 31508-00-6

Chemical Formula: $C_{12}H_5Cl_5$
Molecular weight: 326.43

PCB 118 is a mono-*ortho*-substituted PCB that has partial dioxin-like activity. A tentative TEF value of 0.0001 has been assigned although there is controversy over whether mono-*ortho*-substituted PCBs should be included in the TEF methodology.



2,2′,4,4′,5,5′-Hexachlorobiphenyl
PCB 153

CAS No. 35065-27-1

Chemical Formula: $C_{12}H_4Cl_6$
Molecular weight: 360.88

PCB 153 is a di-*ortho*-substituted nonplanar PCB and is present at the highest concentrations in human samples on a molar basis. Nonplanar PCBs do not have dioxin-like activity and are not included in the TEF methodology; therefore, PCB 153 has no TEF value. Some studies have shown that nondioxin PCBs such as PCB 153 can antagonize the effects of DLCs.

Mixture Studies

Several mixture studies were conducted to assess the dose additivity of DLCs and interactions of PCBs.

Mixture of TCDD, PeCDF, and PCB 126

This mixture was designed to test for dose-additivity of the highest potency DLCs in each of the three classes of PHAHs covered by the TEF methodology. The mixture was composed of equal TEQ ratios (1:1:1) of TCDD, PeCDF, and PCB 126. Total TEQ dosages ranged from 10 to 100 ng TEQ/kg per day. These compounds were chosen because they are the most potent members of the PCDDs, PCDFs, and coplanar PCBs. Based on average human tissue levels of these compounds, they represent approximately 48% of the human tissue burden of dioxin TEQs.

Binary mixture study of PCB 126 and PCB 153

Several studies have indicated an antagonism of the effects of DLCs by di-*ortho*-substituted PCBs such as PCB 153. This binary mixture study consisted of two parts:

1. PCB 126 and PCB 153 at the environmentally relevant ratio of 1:1,000. The dosage levels of PCB 126 were chosen to span the range used in the individual dose-response study of PCB 126.
2. Varying ratios of PCB 153 at the mid-dose of PCB 126 (300 ng/kg per day)

Binary mixture study of PCB 118 and PCB 126

This binary mixture was not designed *a priori* as part of the dioxin TEF evaluation. While the individual PCB 118 study was at the in-life phase, it was found that the PCB 118 compound being used contained not only PCB 118 but also 0.622% PCB 126 (PCB 118:PCB 126 of 161:1). Given the large TEF difference between PCB 118 (0.0001) and PCB 126 (0.1), this resulted in a TEQ ratio for PCB 126:PCB 118 of 6:1. As such, the effects of the compound would be expected to be due mainly to dioxin-like effects of PCB 126 rather than effects of PCB 118. In human tissues, the ratio of PCB 126:PCB 118, on a TEQ basis, ranges from 0.9:1 in blood, 3.9:1 in breast milk, and 15:1 in adipose tissue (USEPA, 2000b). The mass ratio of PCB 118:PCB 126 is on average 135:1 in beef fat and 190:1 in milk. Consequently, the PCB 118:PCB 126 ratio in this compound (161:1) represented an environmentally relevant mixture of PCBs on both a mass and TEQ basis. Since PCB 126 was already being studied, and the PCB 118 study was already in life, the PCB 118 study was continued to test for the effect of a mono-*ortho*-substituted PCB on a coplanar PCB at an environmentally relevant ratio. The PCB 118 was resynthesized to a purity of greater than 99% and checked for the absence of high TEQ contributing compounds, and a new study was started.

Study Design, Species, and Dose Selection Rationale

These studies were conducted in female Harlan Sprague-Dawley rats based on the prior observations by Kociba *et al*. (1978) of the carcinogenicity of TCDD in Spartan Sprague-Dawley rats. Female rats were chosen based on the high potency of hepatocarcinogenicity in females in this strain. Male rats were not studied due to the lack of induction of liver and lung neoplasms in the previous studies of Sprague-Dawley rats with TCDD. Animals were dosed by oral gavage because the majority of human exposure is oral.

Dose selection for TCDD of 3 to 100 ng/kg per day was based on the range used in the Kociba *et al.* (1978) study and on the demonstrated induction of liver tumor incidence over this dose range. Dosage levels for other compounds were based on the TCDD dosage range after adjustment for the current TEF values or relative potency values (Table 1). These studies were designed to examine dose additivity rather than response additivity, and dose spacing was weighted in the 10 to 100 ng/kg range to increase dose density in the region where an increase in liver tumors was expected. Doses higher than 100 ng/kg were not used in order to limit the known effects on body weight and liver toxicity seen with TCDD at this dose level. Prior studies of TCDD suggest that this dose is at or near the predicted maximum tolerated dose.

Interim necropsies at 14, 31, and 53 weeks were incorporated into the studies for the examination of mechanistically based biomarkers of AhR- or PCB-mediated effects. These endpoints included alterations in cytochromes P450 1A1, 1A2, and 2B; thyroid hormone levels; and hepatocyte replication. Tissue analyses of the parent compound in the liver, lung, blood, and adipose were included at each interim necropsy and at terminal necropsy for dose response analysis using both administered dose, total body burden, and target tissue dose as the dose metric.

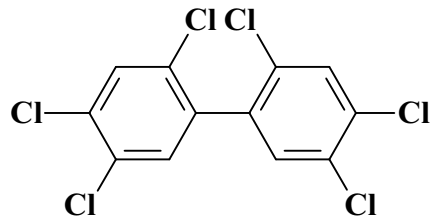
Additional "special study" animals were included at each interim necropsy. Tissues from these animals were provided to specific extramural grantees to facilitate the conduct of additional mechanistic studies. These animals were not evaluated as part of the core study.

TABLE 1
Compounds and Associated Doses Used in the Dioxin TEF Evaluation Studies

Compound	TEF[a]	Core Study	Stop-Exposure Study
TCDD	1	3, 10, 22, 46, 100 ng/kg	100 ng/kg
PCB 126	0.1	10[b], 30, 100, 175, 300, 550, 1,000 ng/kg	1,000 ng/kg
PeCDF	0.5	6, 20, 44, 92, 200 ng/kg	200 ng/kg
TEF Mixture[c]		10 ng TEQ/kg (3.3 ng/kg TCDD, 6.6 ng/kg PeCDF, 33.3 ng/kg PCB 126) 22 ng TEQ/kg (7.3 ng/kg TCDD, 14.5 ng/kg PeCDF, 73.3 ng/kg PCB 126) 46 ng TEQ/kg (15.2 ng/kg TCDD, 30.4 ng/kg PeCDF, 153 ng/kg PCB 126) 100 ng TEQ/kg (33 ng/kg TCDD, 66 ng/kg PeCDF, 333 ng/kg PCB 126)	None
PCB 153	None	10, 100, 300, 1,000, 3,000 µg/kg	3,000 µg/kg
PCB 126/PCB 153[d]		10/10, 100/100, 300/100, 300/300, 300/3,000, 1,000/1,000	None
PCB 126/PCB 118[e]		7 ng TEQ/kg (62 ng/kg PCB 126, 10 µg/kg PCB 118) 22 ng TEQ/kg (187 ng/kg PCB 126, 30 µg/kg PCB 118) 72 ng TEQ/kg (622 ng/kg PCB 126, 100 µg/kg PCB 118) 216 ng TEQ/kg (1,866 ng/kg PCB 126, 300 µg/kg PCB 118) 360 ng TEQ/kg (3,110 ng/kg PCB 126, 500 µg/kg PCB 118)	360 ng TEQ/kg
PCB 118	0.0001	10[b], 30[b], 100, 220, 460, 1,000, 4,600 µg/kg	4,600 µg/kg

[a] Van den Berg *et al.* (1998)
[b] 14-, 31-, and 53-week scheduled sacrifices only
[c] 10, 22, 46, 100 ng TEQ/kg (TCDD:PeCDF:PCB 126, 1:2:10)
[d] PCB 126 dose units are ng/kg, PCB 153 units are µg/kg.
[e] PCB 126 dose units are ng/kg, PCB 118 units are µg/kg. Doses are based on PCB 126 levels that are 0.622% of the administered PCB 118 bulk.

INTRODUCTION



2,2′,4,4′,5,5′-Hexachlorobiphenyl
(PCB 153)

CAS No. 35065-27-1

Chemical Formula: $C_{12}H_4Cl_6$ Molecular Weight: 360.88

Synonym: 1,1′-Biphenyl, 2,2′,4,4′,5,5′-hexachloro-(9CI)

Chemical and Physical Properties

PCB 153 is a di-*ortho*-substituted nonplanar PCB that was commercially produced as a component of technical grade polychlorinated biphenyl (PCB) mixtures, including Aroclors 1242, 1248, 1254, 1260, and 1262 (Frame *et al.*, 1996; ATSDR, 2000). PCB 153 is a crystalline powder. Aroclor mixtures containing PCB 153 are colorless mobile oils (Aroclor 1242 and 1248), viscous liquids (Aroclor 1254) or sticky resins (Aroclors 1260 and 1262) (ATSDR, 2000). PCB 153 has a melting point of 102° C, a vapor pressure of 1.2×10^{-4} (solid) and 7.0×10^{-4} (liquid) at 25° C, and a log octanol:water partition coefficient of 6.9 (Hansen, 1999).

Production, Use, and Human Exposure

PCB mixtures, including PCB 153, were commercially produced between 1929 and 1977 for the electric industry as dielectric insulating fluids for transformers and capacitors. PCBs were also produced for use in hydraulic fluids, solvents, plastics, and paints. The manufacture and use of PCBs in the United States was stopped in 1977 after PCB residues increased in the environment in the 1960s and 1970s. However, PCBs continue to be released into the environment through the use and disposal of products containing PCBs, as by-products during the manufacture of certain organic chemicals, and during combustion of some waste materials (USEPA, 2000a).

Due to their lipophilic nature (log octanol:water partition coefficient of 6.5 to 7.71) and resistance to biodegradation, specific PCBs have the ability to bioaccumulate and bioconcentrate. PCBs are widespread in their distribution and are found in virtually all media, including air, soil, water, sediment, and biota (USEPA, 2000b).

The majority of ambient human exposure to PCBs occurs through the ingestion of food containing PCB residues. PCB-contaminated fish, milk and dairy products, vegetables, and meat and animal fat are estimated to account for a majority of the exposure (Duarte-Davidson and Jones, 1994). The environmental occurrence of PCB 153 is widespread, and it is relatively

abundant in food (Jones, 1988; McFarland and Clarke, 1989). Of all the PCBs, PCB 153 is present at the highest concentrations in human tissue samples on a molar basis (McFarland and Clarke, 1989; Schecter *et al.*, 1994b; Heudorf *et al.*, 2002; Ayotte *et al.*, 2003; Chu *et al.*, 2003). Bioaccumulation of PCB 153 results in persistent levels of PCB 153 in human tissues.

TOXICOKINETICS

There is an extensive body of literature examining the toxicokinetics of mixtures and some individual congeners of PCBs (ATSDR, 2000). In the gastrointestinal tract, PCBs are well absorbed by passive diffusion. Following absorption, PCB 153 is initially distributed to the liver and muscle, and then redistributed into the adipose tissue and skin (Matthews and Tuey, 1980; Birnbaum, 1983). PCB 153 is not metabolized well, and it is excreted primarily as the parent compound in the feces (Kato *et al.*, 1980; Muhlebach and Bickel, 1981). Muhlebach and Bickel (1981) demonstrated that 40 weeks after a single dose of PCB 153 in rats, 16% of the dose was excreted in feces and less than 1% in urine. Approximately 75% of the dose was sequestered in adipose tissue and the excretion half-life for terminal elimination was 100 days. The distribution and elimination of PCB 153 in nonhuman primates is similar to rats, but PCB 153 is readily eliminated in dogs (Sipes *et al.*, 1982).

There are limited data available on the distribution and excretion of PCBs in humans. However, in humans, PCBs are found at the highest concentrations in adipose tissue and they tend to accumulate to a lesser extent in other lipid-rich tissues such as liver, skin, and breast milk (ATSDR, 2000). PCB concentrations of 0.5 to 10 ppm have been reported for human adipose tissue and 0.5 to 4 ppm for human milk fat (Jensen, 1987). Human metabolism of PCB 153 to 3-hydroxy-2,2′,4,4′,5,5′-hexachlorobiphenyl is mediated by cytochrome P450 (CYP) 2B6 (Ariyoshi *et al.*, 1995). However, CYP2B6 is expressed only at low levels, accounting for only 1% to 2% of the total CYP enzymes in the human liver. Reported estimates for the apparent half-life of PCB 153 in humans range from 3.8 to 47 years (Chen *et al.*, 1982; Brown *et al.*, 1989; Ryan *et al.*, 1993).

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and some dioxin-like compounds (DLCs) induce and bind to hepatic CYP1A2 resulting in hepatic sequestration. Unlike TCDD and dioxin-like PCBs, hepatic retention of PCB 153 in rats is low (Diliberto *et al.*, 1997; van der Plas *et al.*, 1998). Studies in CYP1A2 knockout mice demonstrate that PCB 153 is not sequestered in the liver by CYP1A2 like TCDD and DLCs (Diliberto *et al.*, 1997, 1999). However, coadministration of PCB 153 and TCDD results in an interactive effect resulting in higher concentrations of both compounds in the liver and lower concentrations of TCDD in other tissues (van Birgelen *et al.*, 1996). Interactions between DLCs and nondioxin-like PCBs may influence the toxicity of mixtures of these compounds.

PCB 153 Toxic Equivalency Factor

PCB 153 is a di-*ortho*-substituted nonplanar PCB. Nonplanar PCBs do not have dioxin-like activity and are not included in the toxic equivalence factor (TEF) methodology; therefore, PCB 153 has no TEF value.

TOXICITY

Some non-*ortho*-substituted coplanar PCB congeners (PCB 126 for example) interact with the aryl hydrocarbon receptor (AhR) and elicit dioxin-like effects presumably via similar mechanisms of action (Schmidt and Bradfield, 1996). PCB 153 is a di-*ortho*-substituted nonplanar PCB. Nonplanar PCB congeners with two or more chlorines in the *ortho* position do not have dioxin-like activity and exhibit toxicity profiles that are different than those of the dioxin-like coplanar PCB congeners (Fischer *et al.*, 1998).

PCB 153 is a phenobarbital-like inducer of hepatic cytochrome P450 (Denomme *et al.*, 1983). Exposure to PCB 153 induces hepatic lipid peroxidation (Fadhel *et al.*, 2002) and increases glutathione-*S*-transferase activity (Lamartiniere *et al.*, 1979). In Sprague-Dawley rats, subchronic exposure to PCB 153 reduces hepatic and pulmonary vitamin A, induces histological changes in the thyroid gland and liver, and decreases dopamine and its metabolites in the brain (Chu *et al.*, 1996). In tumor promotion studies, PCB 153 induces preneoplastic altered hepatocellular foci (Bager *et al.*, 1995; van der Plas *et al.*, 2000; Dean *et al.*, 2002). In male Sprague-Dawley rats, PCB 153 induces hepatocyte proliferation and activation of the NF-κB transcription factor (Lu *et al.*, 2003). NF-κB regulates expression of cell proliferation and apoptosis-related genes; thus it may play a critical role in tumor promotion and carcinogenesis.

Several studies have investigated the interaction between PCB 153 and dioxin-like congeners on tumor promotion. These studies demonstrate that coexposure of female Sprague-Dawley rats to PCB 153 and PCB 126 antagonizes the formation and development of altered hepatocellular foci expressing the placental form of glutathione-*S*-transferase (Haag-Gronlund *et al.*, 1998; Dean *et al.*, 2002). PCB 153-mediated antagonism of PCB 77-induced altered hepatocellular foci has also been reported (Berberian *et al.*, 1995). PCB 153 antagonizes the promoting effect of TCDD on malignant transformation (Wolfle, 1998). The antagonistic interaction of PCB 153 with TCDD and other dioxin-like PCB congeners may occur via interference with the AhR. Although it does not elicit dioxin-like biological effects, PCB 153 binds the AhR with a binding affinity relative to TCDD of 3×10^{-5} (Schneider *et al.*, 1995). PCB 153 has also been demonstrated to antagonize TCDD-mediated cleft palate, hydronephrosis, and immunotoxicity in mice (Biegel *et al.*, 1989; Morrissey *et al.*, 1992). Although antagonism has been well established, Bager *et al.* (1995) demonstrated that coexposure of female Sprague-Dawley rats to PCB 153 and PCB 126 induced a synergistic effect on the development of altered hepatocellular foci expressing γ-glutamyltranspeptidase.

Nonplanar *ortho*-substituted PCBs have been shown to induce neurobehavioral toxicity, neurotoxicity, and endocrine alterations (Fischer *et al.*, 1998; Giesy and Kannan, 1998). Decreased dopamine concentrations in the caudate, putamen, substantia nigra, and hypothalamus regions of the brain are associated with measurable concentrations of the *ortho*-substituted nonplanar PCB congeners 28, 47, and 52 in monkeys exposed to Aroclor 1016 (Seegal *et al.*, 1990). Aroclor 1254 and *ortho*-substituted PCB congeners 4, 52, 88, 95, 103, 104, and 153 disrupt Ca^{2+} transport in central neurons by direct interaction with ryanodine receptors in specific regions of the central nervous system and may contribute mechanistically to the neurotoxicity of these compounds (Wong *et al.*, 1997). PCB 153 decreases neuronal cell viability and induces apoptosis *in vitro* (Sanchez-Alonso *et al.*, 2003). PCB 153 and Aroclors 1242 and 1254, which contain relatively low concentrations of dioxin-like PCB congeners, also induce death in cultured cerebellar granule cells and formation of reactive oxygen species (Mariussen *et al.*, 2002).

CARCINOGENICITY

Experimental Animals

There is an extensive body of literature examining the carcinogenicity of mixtures of PCBs in rodents (Silberhorn *et al.*, 1990). In general, these studies indicate that PCB mixtures have the potential to be carcinogenic, mainly within the liver (hepatocellular neoplasms). Mixtures of PCBs contain both dioxin-like coplanar PCBs as well as non-dioxin-like PCBs, which may elicit responses via different mechanisms. While these mixtures of PCBs have been shown to be carcinogenic in rats and mice (Nagasaki *et al.*, 1972; Ito *et al.*, 1973; Kimbrough *et al.*, 1975; Mayes *et al.*, 1998), there have been no studies on the carcinogenicity of PCB 153 alone. No epidemiology studies of PCB 153 were found in a review of the literature. As part of the dioxin TEF evaluation, the carcinogenicity of the individual dioxin-like PCB congener, PCB 126, was evaluated for carcinogenicity. In that study, administration of PCB 126 significantly increased the incidences of hepatocellular adenoma and cholangiocarcinoma of the liver, cystic keratinizing epithelioma of the lung, and gingival squamous cell carcinoma of the oral mucosa, (NTP, 2006a). There have been no other published studies examining the carcinogenicity of an individual PCB congener.

A study of PCB mixtures, conducted by Mayes *et al.* (1998), examined the comparative carcinogenicity of Aroclors 1016, 1242, 1254, and 1260 in male and female Sprague-Dawley rats. Increased incidences of hepatocellular adenoma, hepatocellular carcinoma, hepatocholangioma, hepatocholangiocarcinoma, and follicular cell adenoma of the thyroid gland were seen in this study. The incidences of hepatocellular neoplasms were significantly increased in female rats by PCB exposure, with the rank order of Aroclor 1254 > Aroclor 1260 > Aroclor 1242 > Aroclor 1016. In males, thyroid gland tumors were induced by exposure to Aroclors 1242, 1254, and 1260, and liver tumors were induced by Aroclor 1260. Within this context, compared to the other PCB mixtures, Aroclor 1254 has the highest dioxin-like activity, measured on a toxic equivalent (TEQ) basis, due to the presence of specific potent coplanar PCBs, PCDDs, and PCDFs in the mixture. Aroclors 1254 and 1260 are composed of 5.6% and 12.2% PCB 153 by weight, respectively (Frame *et al.*,

1996). The incidences of liver tumors in rats were greater in females than in males. Female tumor incidences were dependent on hepatic TEQ levels of dioxin-like congeners of PCB (Silkworth *et al.*, 1997). The carcinogenicity of these PCB mixtures in females may entirely or in part be attributed to the dioxin-like components. Based on similar AhR-mediated mechanisms for dioxin-like PCBs and TCDD, it is expected that the carcinogenicity of dioxin-like PCBs in Aroclor mixtures may be similar to the carcinogenicity of TCDD.

The carcinogenicity of TCDD has been clearly established in rodents by the dermal, dosed feed, and gavage routes of administration (Kociba *et al.*, 1978; Toth *et al.*, 1979; NTP, 1982a,b; Della Porta *et al.*, 1987; Rao *et al.*, 1988; IARC, 1997; USEPA, 2000c; NTP, 2006b). In a previous NTP study, TCDD administered by gavage significantly increased the incidences of thyroid gland follicular cell adenoma in male and female Osborne-Mendel rats and female $B6C3F_1$ mice, neoplastic liver nodules in female mice, and hepatocellular carcinoma in male and female mice (NTP, 1982a). TCDD administered by dermal application caused an increased incidence of fibrosarcoma of the integumentary system in female Swiss-Webster mice (but equivocal evidence in male mice) (NTP, 1982b). In the TCDD study as part of this TEF evaluation, TCDD administered by gavage significantly increased the incidences of hepatocellular adenoma and cholangiocarcinoma of the liver, cystic keratinizing epithelioma of the lung, and gingival squamous cell carcinoma (NTP, 2006b).

Humans

Humans have not been exposed to significant amounts of PCB 153 alone. Exposures to PCB 153 occur in mixtures, combined with other structurally related PCBs and compounds such as PCDDs and PCDFs.

Two accidental poisoning incidents in Japan and Taiwan resulted from exposures to cooking oils that were highly contaminated with PCDFs and PCBs (Masuda, 1985). In addition to extensive reproductive and developmental effects in these populations, early follow-up studies indicated increased mortality from liver disease and cancer, particularly liver cancer (IARC, 1997). Although recent follow-up studies do not show increased mortality from cancer, mortality from liver disease was still elevated (Yu *et al.*, 1997). However, it is difficult to determine which contaminants are responsible for these effects.

There have been several studies examining cancer incidence and mortality in workers exposed to PCBs, although the small cohort sizes in these studies limit the ability to draw any meaningful conclusions (Silberhorn *et al.*, 1990).

Study Design Overview

The design of these studies on PCB 153 should be considered within the context of the dioxin TEF evaluation. The aim of these studies was to evaluate the carcinogenicity of DLCs and mixtures of PCBs relative to the most potent dioxin, TCDD, rather than to completely evaluate the carcinogenicity of each respective compound/mixture in a standard NTP two-sex, two-species carcinogenicity testing paradigm. Consequently, many of the design rationales are based on the prior observations of the carcinogenicity of TCDD. PCB 153, which is not a DLC, was included in the TEF evaluation to address previous observations demonstrating interactions between PCB 153 and other di-*ortho*-substituted PCBs on dioxin-induced biochemical and toxicological effects.

This 2-year study of PCB 153 in female Harlan Sprague-Dawley rats is one in a series of studies carried out as part of a NTP initiative examining the relative chronic toxicity and carcinogenicity of DLCs and structurally related PCBs (see Overview section). One of the primary aims of the dioxin TEF evaluation was an analysis of the comparative carcinogenicity of TCDD, PeCDF, PCB 126, and mixtures of DLCs and PCBs. This Technical Report describes only the results of the PCB 153 toxicology and carcinogenesis study. A quantitative analysis of the effects observed in this study to responses observed with other compounds studied as part of the dioxin TEF evaluation will be presented elsewhere.

Study Design, Species, and Dose Selection Rationale

PCB 153 is a di-*ortho*-substituted nonplanar PCB that does not demonstrate dioxin-like activity, and therefore, has no TEF value. PCB 153 is the most abundant PCB in human tissues on a mass basis. The dosages of PCB 153 were selected based on those previously used in tumor promotion studies, and fall within the range of the 1:1,000 ratio of a PCB 126:PCB 153 mixture used in another study as part of the dioxin TEF evaluation. The Sprague-Dawley female rat was used for the dioxin TEF evaluation studies based upon the prior observation of high hepatocarcinogenic potency of TCDD within this strain and the extensive literature on the effects of TCDD and related compounds in this model.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PCB 153

PCB 153 was obtained from Radian International LLC (Austin, TX) by Midwest Research Institute (Kansas City, MO) and provided to the study laboratory (Battelle Columbus Operations, Columbus, OH) in one lot (31532-78) that was used in the 2-year study. One additional lot (RAC-29699-67) was procured by the analytical chemistry laboratory (Battelle Columbus Operations, Chemistry Support Services, Columbus, OH) from Radian International LLC solely for dose formulation stability studies and was not used in the 2-year animal study. Identity and purity analyses were conducted by the analytical chemistry laboratory and the study laboratory. Reports on analyses performed in support of the PCB 153 study are on file at the National Institute of Environmental Health Sciences.

Lot 31532-78 of the chemical, a white powder, was identified as PCB 153 by the analytical chemistry laboratory using proton and carbon-13 nuclear magnetic resonance (NMR) spectroscopy. In addition, identity analysis was conducted by the study laboratory using proton NMR; spectra of a purity analysis sample and a frozen reference sample were compared to each other and to the spectrum of the same lot previously reported by the analytical chemistry laboratory. All spectra were consistent with the structure of PCB 153.

The purity of lot 31532-78 was determined by the analytical chemistry laboratory to be approximately 99.8% using gas chromatography (GC) coupled with high resolution mass spectrometry (MS). The purity profile detected two significant impurities: 0.21% of the test article was identified as a pentachlorobiphenyl and 0.002% of the test article was identified as a heptachlorobiphenyl. Standards of the possible impurities were obtained by the analytical chemistry laboratory from Cambridge Isotope Laboratories (Andover, MA) and analyzed using GC/MS; the pentachlorobiphenyl impurity was identified as 2,2′,4,5,5′-pentachlorobiphenyl (PCB 101), and the heptachlorobiphenyl impurity was identified as 2,2′,3,4,4′,5,5′-heptachlorobiphenyl (PCB 180). These impurities are di-*ortho*-substituted, nondioxin-like PCBs, and therefore have no toxic equivalence factors (TEFs).

Additional evaluations of the purity of lot 31532-78 were performed by the study laboratory. A frozen reference sample of the same lot was obtained from the analytical chemistry laboratory and comparative purity analysis using GC indicated that the relative purity of the test article was 101.1%. Subsequent analyses of these samples using GC/MS detected a single impurity in each sample with a peak area of 0.5% relative to the major peak area. The overall purity of lot 31532-78 was determined to be greater than 99%.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The 4 µg/mL dose formulation was prepared from a working stock of PCB 153 dissolved in acetone (8 mg/mL). An aliquot of this working stock was diluted with corn oil and additional acetone to yield the dose formulation containing 4 µg PCB 153/mL of a 1% solution of acetone in corn oil. The 40, 120, 400, and 1,200 µg/mL dose formulations were prepared by dissolving neat PCB 153 in a 1% solution of acetone in corn oil. All dose formulations were stored at room temperature in amber glass bottles with minimal headspace, sealed with Teflon®-lined lids, for up to 35 days.

Homogeneity of 4 and 1,200 µg/mL dose formulations and gavagability of a 1,200 µg/mL dose formulation were confirmed by the study laboratory using GC. Stability studies of a 4 µg/mL formulation of lot RAC 29699-67 were conducted by the analytical chemistry laboratory using GC; stability was confirmed for at least 35 days for the dose formulation stored in amber glass bottles with minimal headspace, sealed with Teflon®-lined lids at –20° C, 5° C, and room temperature (approximately 25° C), and for 3 hours under simulated animal room conditions.

Periodic analyses of the dose formulations of PCB 153 were conducted by the study laboratory using GC. During the 2-year study, the dose formulations were

analyzed at least every 3 months. Of the dose formulations analyzed and used, 59 of 60 were within 10% of the target concentrations and one other was within 14% of target. Twenty-two of 23 animal room samples were within 10% of the target concentrations and one other was within 12% of target.

2-Year Study

Study Design

Groups of 80 (3,000 µg PCB 153/kg body weight), 81 (100, 300, or 1,000 µg/kg), or 82 (10 µg/kg) female rats received PCB 153 in corn oil:acetone (99:1) by gavage at doses of 10, 100, 300, 1,000, or 3,000 µg/kg 5 days per week for up to 105 weeks; a group of 81 female rats received the corn oil:acetone (99:1) vehicle alone. Up to 10 rats per group were evaluated at 14, 31, or 53 weeks. For stop-exposure evaluation, a group of 50 female rats was administered 3,000 µg/kg for 30 weeks then the vehicle for the remainder of the study.

Additional "special study" animals were included at each interim evaluation. Tissues from these animals were provided to specific extramural grantees to facilitate the conduct of additional mechanistic studies. These animals were not evaluated as part of the core study.

Source and Specification of Animals

Male and female Harlan Sprague-Dawley rats were obtained from Harlan Sprague-Dawley, Inc. (Indianapolis, IN), for use in the 2-year study. Sufficient male rats were included in this study to ensure normal estrous cycling of the female rats. Male rats were not administered test compound. Rats were quarantined for 11 days before and were approximately 8 weeks old at the beginning of the study. Rats were evaluated for parasites and gross observation of disease, and the health of the rats was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix E). Sentinel rats included five males and five females at 1 month, five males at 6, 12, and 18 months, and five 3,000 µg/kg females at the end of the study.

Animal Maintenance

Male rats were housed three per cage and female rats were housed five per cage. Feed and water were available *ad libitum*. Cages were changed twice weekly; racks were changed and rotated every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix D.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded on day 29, every 4 weeks thereafter, and at the end of the study. Body weights were recorded on the first day of the study, weekly for 13 weeks, every 4 weeks thereafter, and at the end of the study.

At 14, 31, and 53 weeks, blood was taken from the retroorbital sinus of up to 10 female rats per group (except stop-exposure) and processed into serum for thyroid hormone determinations. Radioimmunoassays were performed for thyroid stimulating hormone (TSH), total triiodothyronine (T_3), and free thyroxine (T_4) using a Packard Cobra II gamma counter (Packard Instrument Company, Meriden, CT). The assay for total T_4 was performed on a Hitachi 911® chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using a Boehringer Mannheim® enzyme immunoassay test system. Thyroid hormone data were summarized using the XYBION system (XYBION Medical Systems Corporation, Cedar Knolls, NJ).

For cell proliferation analysis at 14, 31, and 53 weeks, up to 10 female rats per group (except stop-exposure) received drinking water containing 40 mg BrdU/100 mL Milli-Q water for 5 days. BrdU solutions were administered in amber glass water bottles (Allentown Caging Equipment Company, Inc., Allentown, NJ) equipped with Teflon®-lined lids and stainless steel sipper tubes. BrdU solutions were changed after 3 days, and water consumption was measured daily for 5 days. Cell turnover rate in the liver of dosed female rats was compared to the turnover rate in the vehicle control rats by determining the incorporation of BrdU into hepatocytes. A sample of duodenum (positive control) and liver was fixed in 10% neutral buffered formalin for 18 to 24 hours then transferred to 70% ethanol. Representative sections of the duodenum and liver were trimmed and embedded, and two sections were cut. One of these sections was stained with hematoxylin and eosin and the other with anti-BrdU antibody complexed with avidin and biotin. At the 14-week interim evaluation, potential interlobular variation was determined in the vehicle control and 3,000 µg/kg groups by counting stained cells in the left lobe and right median lobe. Interlobular variation greater than 25% was considered significant. For the remaining rats, stained cells were counted only in the left lobe. At least 2,000 labeled or unlabeled hepatocyte

nuclei were counted using a 20× objective and ocular grid. The labeling index is expressed as the percentage of total nuclei that were labeled with BrdU.

For determination of cytochrome P450 activities, liver and lung tissue samples were collected from up to 10 female rats per group (except stop-exposure) at 14, 31, and 53 weeks and stored frozen at –70° C. Microsomal suspensions were prepared using the Pearce Method (Pearce *et al.*, 1996). The concentration of protein in each suspension was determined using the microtiter plate method of the Coomassie® Plus Protein Assay (Pierce Chemical Co., Rockford, IL) with bovine serum albumin as the standard. Cytochrome P450 1A1 (CYP1A1)-associated 7-ethoxyresorufin-*O*-deethylase (EROD), CYP1A2-associated acetanilide-4-hydroxylase (A4H), and CYP2B-associated pentoxyresorufin-*O*-deethylase (PROD) activities were determined in microsomal proteins and isolated from frozen liver or lung tissue according to established procedures. Data are shown as pmol/minute per mg (EROD and PROD) or nmol/minute per mg (A4H) microsomal protein.

For analysis of tissue concentrations of PCB 153, samples of fat, liver, lung, and blood were taken from up to 10 female rats per dose group at 14, 31, and 53 weeks and at 2 years. Tissue sample preparation included overnight saponification with ethanolic potassium hydroxide, addition of an internal standard (3,3′,4,4′,5-pentachlorobiphenyl; PCB 126), extraction of the saponificate with hexanes, sample extract clean up on columns using silica gel with hexanes elution by automated solid phase extraction, nitrogen dry down, and reconstitution in nonane. Concentrations of PCB 153 in the reconstituted samples were measured by gas chromatography with electron capture detection.

Complete necropsies and microscopic examinations were performed on all rats. At the interim evaluations, the left kidney, liver, lung, left ovary, spleen, thymus (14 weeks only), and thyroid gland were weighed. 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 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, left ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 2.

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 evaluated 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. A quality assessment pathologist evaluated slides from all tumors and all organs with potential chemical-related changes, which included the adrenal cortex, bone marrow, kidney, liver, lung, mammary gland, nose, ovary, oviduct, pancreas, skin, thyroid gland, urinary bladder, and uterus.

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 study laboratory pathologist, 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).

To maintain consistency of diagnoses within and between all the studies on DLCs conducted as part of the dioxin TEF evaluation, the same pathologists were involved in all phases of the pathology evaluation including the initial examination and the pathology peer review. Because of a need for a consistent diagnostic

approach across all studies and the unusual nature of some of the lesions, this study of PCB 153, along with four other studies (PCB 126, TCDD, PeCDF, and the TEF mixture; NTP, 2006a,b,c,d) were subjected to additional PWG reviews. Within many of these studies, there were hepatocellular proliferative lesions for which the criteria used for common diagnoses did not appear to fit. Furthermore, classification was sometimes confounded by significant liver damage (toxic hepatopathy) that was present in many animals from these studies. With the consecutive pathology peer review of each of these studies, the morphological spectrum of proliferative lesions became more apparent to those involved and the diagnostic criteria for the proliferative lesions further refined. Therefore, a PWG was held to ensure that these important proliferative lesions were sufficiently and consistently categorized across all five studies for which data are to be compared. PWG participants for this review were primarily those involved in previous PWGs. Additionally, a different group of pathologists was convened to provided additional guidance on the most appropriate classification of the hepatocellular proliferative lesions from these studies of DLCs. Participants included: Drs. Jerrold Ward, Ernest McConnell, James Swenberg, Michael Elwell, Peter Bannasch, Douglas Wolf, John Cullen, and Rick Hailey. Final diagnoses for the hepatocellular proliferative lesions reflect the consensus of this complete review process.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Gavage Study of PCB 153

Study Laboratory
Battelle Columbus Operations (Columbus, OH)

Strain and Species
Harlan Sprague-Dawley rats; Hsd:Sprague-Dawley SD™

Animal Source
Harlan Sprague-Dawley, Inc. (Indianapolis, IN; Madison, WI, breeding site)

Time Held Before Study
11 days

Average Age When Study Began
8 weeks

Date of First Dose (female rats only)
August 24, 1998

Duration of Dosing
5 days/week for 14, 31, or 53 (interim evaluation), 30 (stop-exposure), or 105 weeks (core study)

Date of Last Dose
August 23-25, 2000 (core study)
March 22, 1999 (stop-exposure)

Necropsy Dates
August 23-25, 2000

Average Age at Necropsy
112 to 113 weeks

Size of Study Groups
80 (3,000 µg/kg), 81 (vehicle control, 100, 300, 1,000 µg/kg), 82 (10 µg/kg), or 50 (3,000 µg/kg stop-exposure)

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Gavage Study of PCB 153

Animals per Cage
Male rats: 3
Female rats: 5

Method of Animal Identification
Tail tattoo

Diet
Irradiated NTP-2000 wafer diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*

Water
Tap water (Columbus municipal supply) via automatic watering system, except via amber glass bottles during BrdU administration, available *ad libitum*

Cages
Solid polycarbonate (Labs Products, Inc., Seaford, DE), changed twice weekly

Bedding
Irradiated Sani-Chips® hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly

Cage Filters
Dupont 2024 spun-bonded polyester sheets (Snow Filtration Co., Cincinnati, OH), changed every 2 weeks

Racks
Stainless steel (Lab Products, Inc., Sanford, DE), changed and rotated every 2 weeks

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Doses
0, 10, 100, 300, 1,000, and 3,000 µg/kg

Type and Frequency of Observation
Observed twice daily; animals were weighed initially, weekly for 13 weeks, at 4-week intervals thereafter, and at the end of the study. Clinical findings were recorded on day 29, at 4-week intervals thereafter, and at the end of the study.

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsy was performed on all rats. At 14, 31, and 53 weeks, the left kidney, liver, lung, left ovary, spleen, and thymus (14 weeks only), and thyroid gland were weighed.

Thyroid Hormone Analysis
At 14, 31, and 53 weeks, blood was collected from the retroorbital sinus of up to ten rats per group for thyroid stimulating hormone, total triiodothyronine, and total and free thyroxine determinations.

Cell Proliferation
At 14, 31, and 53 weeks, up to 10 rats per group received BrdU in drinking water for 5 days. Samples from the liver and duodenum were measured for BrdU labeling.

Cytochrome P450 Activities
At 14, 31, and 53 weeks, tissue samples from the liver were taken from up to ten rats per group for 7-ethoxyresorufin-*O*-deethylase, 7-pentoxyresorufin-*O*-deethylase, and acetanilide-4-hydroxylase activities. Lung samples from these rats were analyzed for 7-ethoxyresorufin-*O*-deethylase activity.

TABLE 2
Experimental Design and Materials and Methods in the 2-Year Gavage Study of PCB 153

Tissue Concentration Analysis
At 14, 31, and 53 weeks and 2 years, samples of fat, liver, lung, and blood were taken from up to 10 rats per group for analysis of PCB 153 concentrations.

Histopathology
Complete histopathology was performed on all core study and stop-exposure rats at 2 years. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eye, harderian gland, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung with mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, salivary gland, skin, spleen, stomach (forestomach and glandular), thymus, thyroid gland, trachea, urinary bladder, and uterus. The adrenal gland, liver, lung, mammary gland, ovary, pancreas, pituitary gland, spleen, stomach (forestomach and glandular), thymus, thyroid gland, uterus, and vagina of vehicle control and 3,000 µg/kg rats were examined at 14, 31, and 53 weeks. In the remaining dose groups, the following tissues were examined: the liver at 14, 31, and 53 weeks and the thymus at 31 weeks.

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 A1a, A1b, A5a, and A5b 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 A3a and A3b) 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 A3a and A3b 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, only to site-specific, lesion-free 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 dosed group with controls and a test for an overall dose-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 is represented 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 at the interim evaluations, 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 dosed 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). Thyroid hormone, cell proliferation, and cytochrome P450 data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) (as modified by Williams, 1986) 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 (1957) 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. For female Sprague-Dawley rats, the NTP historical database is limited to the seven available gavage studies conducted as part of the dioxin TEF evaluation (the current PCB 153 study, PCB 126, TCDD, PeCDF, the TEF mixture, the binary mixture of PCB 126 and PCB 153, and the binary mixture of PCB 126 and PCB 118; NTP, 2006a,b,c,d,e,f).

Quality Assurance Methods

The 2-year study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was 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.

RESULTS

2-Year Study

Survival

Estimates of 2-year survival probabilities for female rats are shown in Table 3 and in the Kaplan-Meier survival curves (Figure 1). Survival of the dosed groups was similar to that of the vehicle control group.

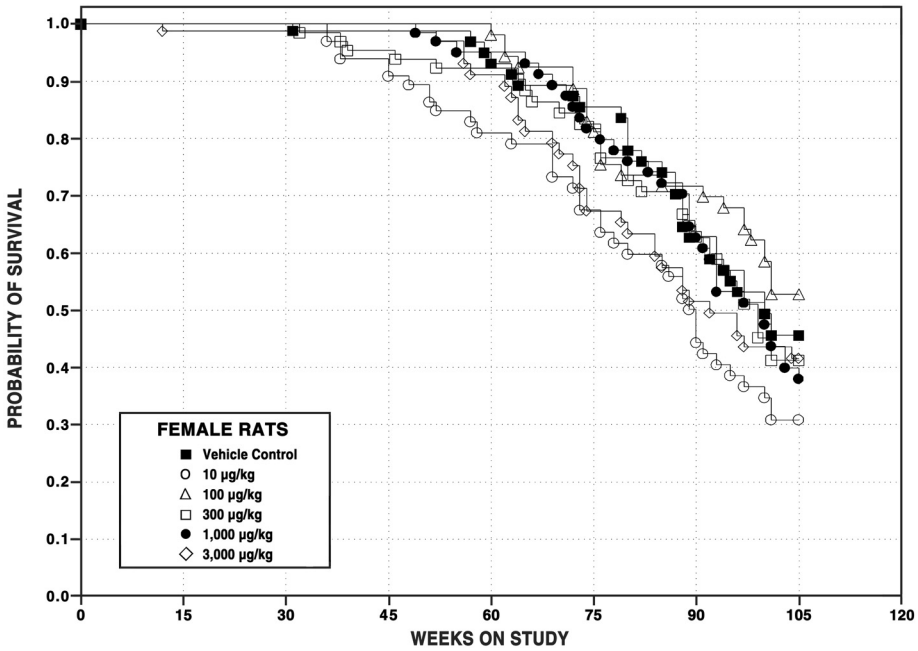
Body Weights and Clinical Findings

Mean body weights of 10, 100, 300, and 1,000 µg/kg core study and 3,000 µg/kg stop-exposure rats were similar to those of the vehicle controls throughout the study; mean body weights of 3,000 µg/kg core study rats were less than those of the vehicle controls after week 69 of the study (Figure 2 and Table 4).

Table 3
Survival of Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Animals initially in study	81	82	81	81	81	80	50
14-Week interim evaluation[a]	10	10	10	10	10	10	0
31-Week interim evaluation[a]	10	10	10	10	10	10	0
53-Week interim evaluation[a]	8	8	8	8	8	9	0
Accidental death[a]	0	0	0	1	0	0	0
Moribund	18	23	17	22	18	19	16
Natural deaths	11	15	8	9	15	11	14
Animals surviving to study termination	24	16	28	21[b]	20	21	20
Percent probability of survival at end of study[c]	45	30	53	40	38	41	40
Mean survival (days)[d]	641	569	657	611	639	603	630
Survival analysis[e]	P=0.701	P=0.051	P=0.518N	P=0.715	P=0.658	P=0.469	P=0.825

[a] Censored from survival analyses
[b] One animal died last week of study
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A lower mortality in a dosed group is indicated by N. The trend test does not include the 3,000 µg/kg stop-exposure group.



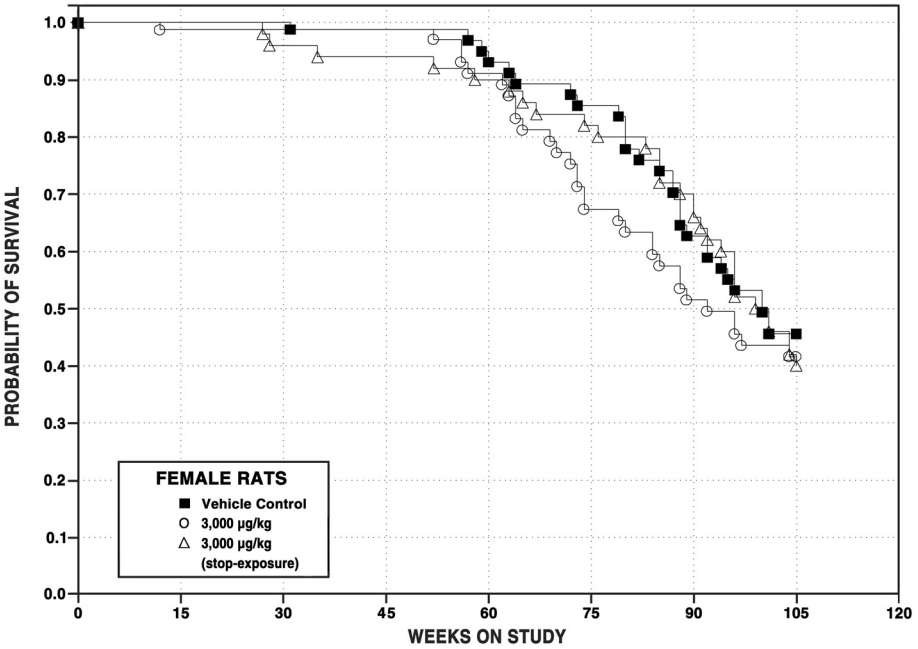
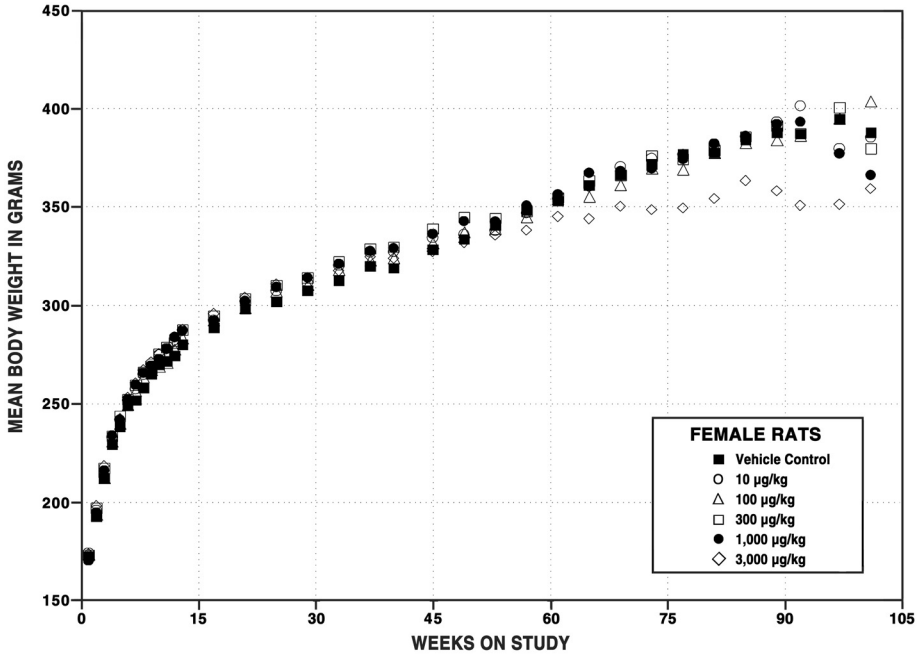


FIGURE 1
Kaplan-Meier Survival Curves for Female Rats Administered PCB 153 by Gavage for 2 Years



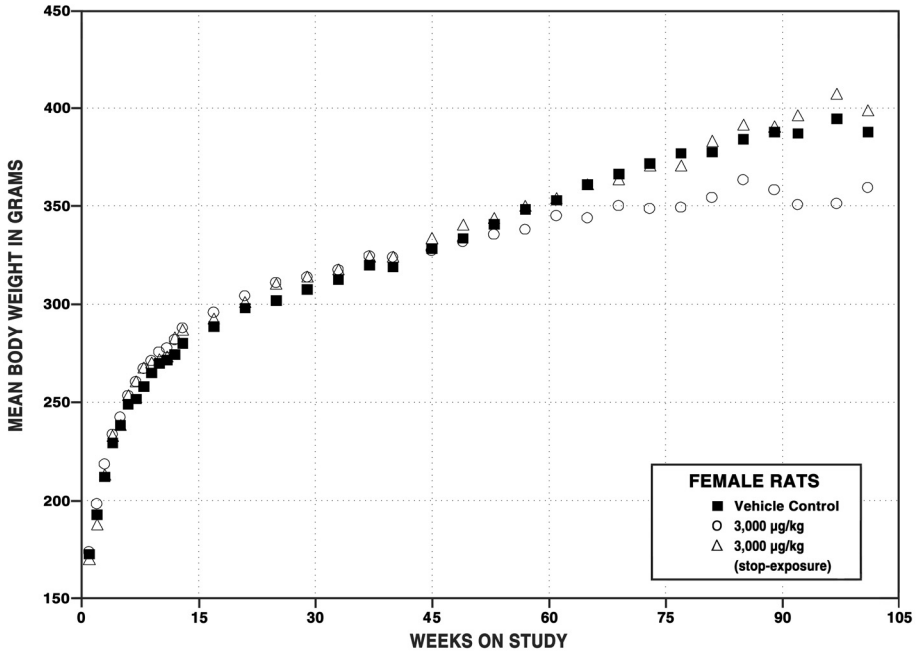


FIGURE 2
Growth Curves for Female Rats Administered PCB 153 by Gavage for 2 Years

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of PCB 153

Weeks on Study	Vehicle Control		10 µg/kg			100 µg/kg			300 µg/kg		
	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	173	98	174	101	86	174	101	98	173	100	98
2	193	98	196	102	86	194	101	98	197	102	98
3	212	98	214	101	86	212	100	98	217	103	98
4	229	98	233	102	86	231	101	98	234	102	98
5	238	98	242	102	86	240	101	98	244	102	98
6	249	98	252	101	86	250	100	98	252	101	98
7	252	98	258	102	86	257	102	98	260	103	98
8	258	98	265	103	86	264	102	98	266	103	98
9	265	98	271	102	86	267	101	98	268	101	98
10	270	98	275	102	86	269	100	98	276	102	97
11	272	98	278	102	86	271	100	98	279	103	97
12	275	98	282	103	86	278	101	98	281	102	97
13	280	98	288	103	86	284	101	98	287	103	97
17[a]	289	82	293	101	76	292	101	82	295	102	81
21	298	82	302	101	76	299	100	82	303	102	81
25	302	82	308	102	76	307	102	82	310	103	81
29	308	82	312	101	76	310	101	82	314	102	81
33[a]	313	65	321	103	66	318	102	66	322	103	64
37	320	65	327	102	64	323	101	66	329	103	64
40	319	65	327	103	62	324	102	66	330	103	62
45	328	65	335	102	62	332	101	66	339	103	62
49	334	65	336	101	59	337	101	66	345	103	61
53[a]	341	57	338	99	48	339	100	58	344	101	52
57	348	52	347	100	43	345	99	53	348	100	47
61	353	49	354	100	42	354	100	52	355	101	47
65	361	47	361	100	41	355	98	49	363	101	46
69	366	47	371	101	41	361	99	49	366	100	44
73	372	46	375	101	37	370	100	47	376	101	43
77	377	45	377	100	33	369	98	40	374	99	39
81	378	41	382	101	31	378	100	39	379	100	37
85	384	40	386	101	31	383	100	39	386	100	36
89	388	34	393	101	27	384	99	38	391	101	34
92	387	32	402	104	22	386	100	37	387	100	32
97	395	28	380	96	20	395	100	36	400	102	29
101	388	24	386	100	16	404	104	28	380	98	23
Mean for weeks											
1-13	244		248	102		245	100		249	102	
14-52	312		318	102		316	101		321	103	
53-101	372		373	100		371	100		373	100	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of PCB 153

Weeks on Study	1,000 µg/kg Av. Wt. (g)	1,000 µg/kg Wt. (% of controls	1,000 µg/kg No. of Survivors	3,000 µg/kg Av. Wt. (g)	3,000 µg/kg Wt. (% of controls)	3,000 µg/kg No. of Survivors	3,000 µg/kg (Stop-Exposure) Av. Wt. (g)	3,000 µg/kg (Stop-Exposure) Wt. (% of controls)	3,000 µg/kg (Stop-Exposure) No. of Survivors
1	171	99	98	174	101	80	170	99	50
2	195	101	98	198	103	80	188	98	50
3	216	102	98	219	103	80	213	101	50
4	234	102	98	234	102	80	233	102	50
5	242	102	98	243	102	80	239	100	50
6	252	101	98	254	102	80	254	102	50
7	260	103	98	261	104	80	261	104	50
8	266	103	98	267	104	80	268	104	50
9	270	102	98	272	103	80	270	102	50
10	273	101	98	276	102	80	272	101	50
11	278	102	98	278	102	80	274	101	50
12	284	104	98	282	103	80	283	103	50
13	287	103	98	288	103	79	287	102	50
17[a]	292	101	82	296	103	69	293	101	50
21	303	102	82	304	102	69	301	101	50
25	309	103	82	311	103	69	311	103	50
29	314	102	82	314	102	69	314	102	48
33[a]	321	103	66	318	102	59	318	102	48
37	328	103	66	325	102	59	324	101	47
40	329	103	66	324	102	59	324	102	47
45	336	103	66	328	100	59	334	102	47
49	343	103	66	332	100	59	341	102	47
53[a]	343	101	56	336	99	49	344	101	46
57	351	101	50	338	97	46	350	101	46
61	357	101	50	345	98	46	354	100	45
65	368	102	50	344	95	42	361	100	44
69	368	101	48	350	96	41	364	99	42
73	370	100	45	349	94	37	371	100	42
77	375	99	42	350	93	34	371	98	40
81	382	101	40	354	94	32	383	102	40
85	386	101	39	364	95	30	392	102	39
89	392	101	36	358	92	27	391	101	35
92	394	102	31	351	91	25	396	102	31
97	377	96	28	351	89	23	407	103	26
101	366	95	25	360	93	22	399	103	23
Mean for weeks									
1-13	248	102		250	102		247	101	
14-52	319	102		317	102		318	102	
53-101	371	100		350	94		376	101	

[a] Interim evaluation occurred during weeks 14, 31, and 53; number of survivors includes 4 (10 µg/kg) or 17 special study animals (except stop-exposure group).

Thyroid Hormone Concentrations

Assays for thyroid stimulating hormone (TSH), total triiodothyronine (T_3), total thyroxine (T_4), and free T_4 were conducted at the 14-, 31-, and 53-week interim evaluations (Table 5). At 14 weeks, serum total T_4, free T_4, and T_3 concentrations in the 3,000 µg/kg group were significantly lower than those in the vehicle controls by 23.5%, 25.9%, and 29.9%, respectively. No significant differences were observed in TSH at 14 weeks in any of the dosed groups.

At the 31-week interim evaluation, no statistically significant differences were observed in serum total T_4, free T_4, T_3, or TSH concentrations compared to vehicle controls. However, total T_4 concentrations in the 3,000 µg/kg group was 24.4% lower than that in the vehicle controls. Serum free T_4 concentrations in the 3,000 µg/kg group were 18.8% lower than vehicle controls. Serum TSH concentrations were 8.1%, 10.6%, and 17.4% higher in the 100, 300, and 3,000 µg/kg groups, respectively, compared to vehicle controls.

At the 53-week interim evaluation, serum total T_4 and free T_4 concentrations in the 3,000 µg/kg group were significantly lower (36.7% and 28.8%, respectively) than in the vehicle control group. Serum total T_4 and free T_4 concentrations were also lower in the 1,000 µg/kg group, but these differences were not significant. Serum T_3 concentrations were lower in all dosed groups, but not significantly different compared to vehicle controls. No significant differences were observed in TSH at 53 weeks in any dosed group.

TABLE 5
Serum Concentrations of Thyroid Hormones in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
Week 14						
n	10	10	10	10	10	10
Total T_4 (µg/dL)	6.040 ± 0.359	6.100 ± 0.257	6.180 ± 0.307	6.170 ± 0.274	5.860 ± 0.294	4.620 ± 0.278*
Free T_4 (ng/dL)	2.403 ± 0.139	2.489 ± 0.156	2.449 ± 0.143	2.347 ± 0.142	2.442 ± 0.134	1.780 ± 0.115*
Total T_3 (ng/dL)	163.3 ± 8.8	146.8 ± 8.9	150.9 ± 9.9	150.4 ± 12.4	144.7 ± 4.0	114.5 ± 5.5**
TSH (ng/mL)	15.64 ± 0.75	15.35 ± 1.14	14.38 ± 0.85	14.08 ± 1.35	17.20 ± 1.66	13.32 ± 1.03
Week 31						
n	10	10	10	10	10	10
Total T_4 (µg/dL)	3.610 ± 0.314	3.560 ± 0.192	3.930 ± 0.199	3.690 ± 0.220	3.390 ± 0.283	2.730 ± 0.252
Free T_4 (ng/dL)	1.975 ± 0.123	1.986 ± 0.108	2.092 ± 0.096	1.973 ± 0.114	2.062 ± 0.089	1.604 ± 0.101
Total T_3 (ng/dL)	143.8 ± 4.6	139.0 ± 6.8	150.3 ± 5.2	138.5 ± 4.0	149.3 ± 7.9	133.0 ± 2.9
TSH (ng/mL)	15.37 ± 0.98	15.37 ± 1.47	16.61 ± 2.02	17.00 ± 1.48	15.10 ± 1.12	18.04 ± 1.28
Week 53						
n	8	8	8	8	8	9
Total T_4 (µg/dL)	3.350 ± 0.098	3.500 ± 0.143	2.963 ± 0.377	3.913 ± 0.214	2.675 ± 0.200	2.122 ± 0.190**
Free T_4 (ng/dL)	2.063 ± 0.116	2.191 ± 0.102	1.969 ± 0.209	2.296 ± 0.143	1.843 ± 0.096	1.469 ± 0.085**
Total T_3 (ng/dL)	133.2 ± 5.1	128.6 ± 4.8	130.7 ± 5.9	125.5 ± 4.6	122.0 ± 5.1	121.4 ± 4.5
TSH (ng/mL)	17.62 ± 1.89	14.97 ± 1.66	18.88 ± 0.73	21.28 ± 1.68	18.82 ± 1.78	18.00 ± 1.87

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error. Statistical tests were performed on unrounded data.
T_4 =thyroxine; T_3=triiodothyronine; TSH=thyroid stimulating hormone

Hepatic Cell Proliferation Data

Hepatic cell proliferation data at the 14-, 31-, and 53-week interim evaluations are presented in Table 6. Consumption of the BrdU drinking water solutions prior to each interim evaluation was similar across groups (data not shown). No significant differences in labeling index were observed between the vehicle control and dosed groups at any of the interim evaluations; however, at 53 weeks, the labeling index was elevated in all dosed groups.

TABLE 6
Hepatic Cell Proliferation Data for Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
n						
Week 14	10	10	10	10	10	10
Week 31	10	10	10	10	10	10
Week 53	8	8	8	8	8	9
Labeling index (%)						
Week 14	1.138 ± 0.172	1.446 ± 0.258	1.655 ± 0.302	0.967 ± 0.132	1.543 ± 0.209	1.694 ± 0.230
Week 31	1.213 ± 0.167	0.922 ± 0.077	1.178 ± 0.241	1.233 ± 0.194	1.437 ± 0.231	1.344 ± 0.336
Week 53	0.563 ± 0.108	1.327 ± 0.294	1.322 ± 0.320	1.556 ± 0.431	0.800 ± 0.087	0.957 ± 0.136

[a] Data are presented as mean ± standard error.

Cytochrome P450 Enzyme Activities

At each interim evaluation, liver and lung samples were collected for determinations of P450 enzyme activity (Table 7). Microsomal suspensions were prepared from liver samples and were assayed for 7-ethoxyresorufin-*O*-deethylase (EROD) activity (a marker for CYP1A1 activity), 7-pentoxyresorufin-*O*-deethylase (PROD) activity (a marker for CYP2B activity), and acetanilide-4-hydroxylase (A4H) activity (a marker for CYP1A2 activity). Microsomal samples from lung were analyzed for EROD activity only.

Hepatic EROD activity generally increased with dose at 14 and 31 weeks. Significant induction of hepatic EROD was observed at 300 µg/kg or greater at 14 weeks and in all dosed groups at 31 weeks. At both the 14- and 31-week interim evaluations, hepatic EROD activity was maximally induced in the 1,000 µg/kg group. At 53 weeks, hepatic EROD activity was elevated in the 300 and 1,000 µg/kg groups and decreased in the 10 and 3,000 µg/kg groups, but these values were not significantly different from the activity in the vehicle controls. Hepatic A4H activity was significantly higher in 300 µg/kg or greater groups at 14 weeks and in 100 µg/kg or greater groups at 31 weeks. Hepatic A4H activity tended to increase with dose and maximal activity occurred in the 1,000 µg/kg group at both 14 and 31 weeks. The maximum degree of induction relative to the vehicle controls was approximately 1.6- and 1.9-fold at the 14- and 31-week interim evaluations, respectively. Similar to hepatic EROD activity at 53 weeks, hepatic A4H activities in the dosed groups at 53 weeks were not significantly different from that in the vehicle controls. There was a significant increasing trend in hepatic PROD activity with increasing doses of PCB 153 at all three interim evaluations, and the increases were significant in the 100 µg/kg or greater groups relative to the vehicle controls. Maximum induction of hepatic PROD activity was observed in the 3,000 µg/kg group with induction relative to vehicle controls of approximately 136-, 140-, and 40-fold for the 14-, 31-, and 53-week interim evaluations, respectively.

EROD activities in the lung were lower in all dosed groups compared to vehicle controls at 14 weeks. Significant reduction of pulmonary EROD activity was observed in the 300, 1,000, and 3,000 µg/kg groups. At 31 and 53 weeks, no significant differences were observed in pulmonary EROD activity between the treated and vehicle control groups.

TABLE 7
Liver and Lung Cytochrome P450 Data for Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
n						
Week 14	10	10	10	10	10	10
Week 31	10	10	10	10	10	10
Week 53	8	8	8	8	8	9
Liver Microsomes						
Acetanilide-4-hydroxylase (A4H) (nmol/minute per mg microsomal protein)						
Week 14	0.490 ± 0.014	0.460 ± 0.018	0.522 ± 0.030	0.651 ± 0.038**	0.744 ± 0.041**	0.569 ± 0.028**
Week 31	0.382 ± 0.020	0.448 ± 0.023	0.470 ± 0.030*	0.533 ± 0.051**	0.709 ± 0.034**	0.564 ± 0.042**
Week 53	0.550 ± 0.030	0.491 ± 0.054	0.633 ± 0.073	0.696 ± 0.071	0.592 ± 0.035	0.457 ± 0.049
7-Ethoxyresorufin-*O*-deethylase (EROD) (pmol/minute per mg microsomal protein)						
Week 14	64.99 ± 4.25	61.36 ± 2.95	65.37 ± 3.83	88.60 ± 3.61**	101.08 ± 4.94**	75.55 ± 3.34**
Week 31	58.50 ± 2.42	69.69 ± 3.89*	76.73 ± 5.61**	93.87 ± 7.79**	98.25 ± 3.84**	75.65 ± 5.49**
Week 53	85.55 ± 4.04	71.16 ± 5.80	96.35 ± 9.73	116.59 ± 10.50	102.84 ± 3.31	74.41 ± 5.95
7-Pentoxyresorufin-*O*-deethylase (PROD) (pmol/minute per mg microsomal protein)						
Week 14	3.234 ± 0.138	3.274 ± 0.105	6.901 ± 0.725**	32.003 ± 3.292**	216.888 ± 28.888**	440.000 ± 37.993**
Week 31	2.954 ± 0.190	3.285 ± 0.205	13.455 ± 1.849**	66.124 ± 6.123**	270.657 ± 24.076**	412.684 ± 45.487**
Week 53	3.791 ± 0.131	3.008 ± 0.169	25.244 ± 7.221*	77.511 ± 11.336**	136.704 ± 5.896**	150.765 ± 2.716**[b]
Lung Microsomes						
7-Ethoxyresorufin-*O*-deethylase (EROD) (pmol/minute per mg microsomal protein)						
Week 14	2.896 ± 0.562	1.991 ± 0.276	1.567 ± 0.255	0.704 ± 0.139**	1.186 ± 0.242**[c]	1.118 ± 0.188**
Week 31	2.185 ± 0.209	2.226 ± 0.259	2.022 ± 0.265	2.204 ± 0.200	2.640 ± 0.680	2.335 ± 0.416
Week 53	1.006 ± 0.177	1.130 ± 0.155	0.939 ± 0.063	1.034 ± 0.069	1.205 ± 0.089	1.089 ± 0.058

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=9

Determinations of PCB 153 Concentrations in Tissues

Concentrations of PCB 153 were determined in fat, liver, lung, and blood at the 14-, 31-, and 53-week interim evaluations and at the end of the 2-year study (Table 8). The highest concentrations of PCB 153 were observed in the fat. In fat of vehicle controls, mean concentrations of PCB 153 were 571, 701, 1,301, and 436 ng/g at 14, 31, 53, and 105 weeks, respectively. In dosed groups, concentrations of PCB 153 in fat increased with increasing doses of PCB 153, and concentrations in fat tended to increase with the longer duration of exposure. In the 3,000 µg/kg stop-exposure group, the PCB 153 concentration in fat at 2 years was 1,142,517 ng/g, which was between the levels observed in the 300 and 1,000 µg/kg groups.

In the liver of vehicle controls, no measurable concentrations of PCB 153 were observed in rats at any time point. In dosed groups, hepatic concentrations of PCB 153 increased with increasing dose and with longer exposure duration. The highest concentrations were observed in the 3,000 µg/kg core study group. In liver tissue of the 3,000 µg/kg stop-exposure group at 2 years, the PCB 153 concentration was 48,651 ng/g, which was slightly higher than the level observed in the 1,000 µg/kg group (42,664 ng/g).

No measurable concentrations of PCB 153 were observed in the lungs from the vehicle controls at the 14-week interim evaluation. PCB 153 concentrations of 158, 145, and 62 ng/g were observed in the lungs of the vehicle controls at 31, 53, and 105 weeks, respectively. In treated groups, PCB 153 lung concentrations increased with increasing dose. The highest concentrations at each time point were observed in the 3,000 µg/kg core study group. The PCB 153 concentration in the lung of the 3,000 µg/kg stop-exposure group was similar to that observed in the 1,000 µg/kg group at 2 years.

No measurable concentrations of PCB 153 were observed in the blood from vehicle controls at the 14- and 53-week interim evaluations or at the end of the study. At 31 weeks, the mean PCB 153 concentration in blood from the vehicle control was 5.51 ng/g. In dosed groups, blood concentrations of PCB 153 increased with increasing dose and longer exposure duration. At each time point, the highest concentrations were observed in the 3,000 µg/kg core study group, and that of the 3,000 µg/kg stop-exposure group was slightly lower than that of the 1,000 µg/kg dose group at 2 years.

TABLE 8
Tissue Concentrations of PCB 153 in Female Rats in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
n							
Week 14	10	10	10	10	10	10	
Week 31	10	10	10	10	10	10	
Week 53	8	8	8	8	8	9	
Week 105	10	10	10	10	10	10	10
Fat							
Week 14	571 ± 218	4,361 ± 291	35,987 ± 2,391	109,453 ± 4,869	319,142 ± 14,868	1,086,152 ± 55,219	
Week 31	701 ± 262	7,790 ± 409	75,839 ± 4,335	212,643 ± 8,893	673,480 ± 61,285	2,297,492 ± 124,742	
Week 53	1,301 ± 510	8,880 ± 829	100,427 ± 16,701	191,195 ± 15,300	687,658 ± 76,289	2,308,494 ± 97,888	
Week 105	436 ± 59	20,059 ± 3,142	158,434 ± 21,088	519,002 ± 60,709	1,556,558 ± 152,803	4,291,837 ± 607,590	1,142,517 ± 191,436
Liver							
Week 14	BLOQ	91 ± 5[b]	985 ± 79	3,425 ± 140	9,250 ± 652	32,838 ± 2,455	
Week 31	BLOQ	195 ± 33	1,550 ± 90	4,892 ± 363	13,012 ± 486	42,111 ± 2,912	
Week 53	BLOQ	218 ± 46[c]	1,709 ± 215	5,572 ± 541	16,728 ± 1,943	68,905 ± 10,493	
Week 105	BLOQ	480 ± 63	3,699 ± 290	13,940 ± 1,365	42,664 ± 4,921	114,516 ± 9,326	48,651 ± 18,871
Lung							
Week 14	BLOQ	112 ± 7	1,003 ± 74	1,878 ± 69	8,610 ± 2,669	15,015 ± 1,717	
Week 31	158 ± 13[d]	345 ± 26	2,980 ± 288	7,038 ± 670	20,513 ± 1,627	60,487 ± 5,738	
Week 53	145 ± 20[e]	314 ± 34	1,700 ± 271	3,664 ± 252	11,016 ± 1,319	40,528 ± 9,302	
Week 105	62[f]	1,283 ± 580	3,541 ± 452	19,622 ± 7,645	34,264 ± 3,491	238,836 ± 73,509	34,798 ± 10,610
Blood							
Week 14	BLOQ	6.32 ± 0.40[g]	53.37 ± 3.51	170.44 ± 4.95	442.05 ± 31.76	1,447.20 ± 105.74	
Week 31	5.51 ± 0.55[d]	12.39 ± 1.46	112.74 ± 7.83	342.35 ± 25.92	957.98 ± 88.06	2,852.00 ± 233.13	
Week 53	BLOQ	17.41 ± 1.81	166.71 ± 31.42	342.00 ± 30.25	1,335.66 ± 207.35	4,433.11 ± 358.84	
Week 105	BLOQ	52.83 ± 9.89	368.65 ± 65.41	1,202.84 ± 196.47	3,738.60 ± 477.08	9,866.70 ± 1,320.57	3,166.10 ± 815.46

[a] Data are given in ng/g tissue (fat, liver, lung) or ng/mL (blood) as the mean ± standard error. Mean values do not include values that were below the experimental limit of quantitation. BLOQ=below the limit of quantitation; LOQ_{fat}=25 ng/g, LOQ_{liver}=75 ng/g, LOQ_{lung}=25 ng/g, LOQ_{blood}=2 ng/mL
[b] n=7
[c] n=6
[d] n=3
[e] n=5
[f] n=1
[g] n=8

Organ Weights

Absolute liver weights of 1,000 µg/kg rats and absolute and relative liver weights of 3,000 µg/kg rats were significantly greater than those of vehicle controls at week 14 (Table B1). At week 31, relative liver weights of 1,000 µg/kg rats and absolute and relative liver weights of 3,000 µg/kg rats were significantly greater than those of vehicle controls. Absolute and relative liver weights were significantly greater in rats administered 100 µg/kg and above compared to vehicle controls at week 53. Absolute kidney weights of all dosed groups and the relative kidney weights of 3,000 µg/kg rats were significantly increased at week 53.

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 liver, thyroid gland, ovary and oviduct, uterus, bone marrow, and lung. 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 A.

Liver: The incidences of hepatocyte hypertrophy were significantly increased in the 1,000 and 3,000 µg/kg groups at 14 weeks and in all groups administered 300 µg/kg or greater at 31 and 53 weeks (Tables 9 and A5a). The severity of this lesion was increased in the 1,000 and 3,000 µg/kg groups at 53 weeks when compared to the vehicle controls.

At 2 years, two cholangiomas were seen in the 1,000 µg/kg group and two cholangiomas occurred in the 3,000 µg/kg stop-exposure group (Tables 10 and A1b). No cholangiomas have occurred in the historical vehicle controls (Tables 10 and A4a).

Cholangioma was a well-demarcated mass consisting of multiple, densely packed, irregular, bile duct structures, some of which were moderately dilated, within a small amount of fibrous stroma (Plates 1 and 2). The bile duct structures were composed of a single layer of densely packed, columnar, somewhat pleomorphic bile duct epithelial cells.

Dose-related increased incidences and average severities of hepatocytic hypertrophy were seen in all groups at 2 years. Significantly increased incidences of diffuse fatty change occurred in all groups administered

TABLE 9
Incidences of Nonneoplastic Lesions of the Liver in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
14-Week Interim Evaluation						
Number Examined Microscopically	10	10	10	10	10	10
Hepatocyte, Hypertrophy[a]	0	0	0	0	9**(1.2)[b]	10**(1.8)
31-Week Interim Evaluation						
Number Examined Microscopically	10	10	10	10	10	10
Hepatocyte, Hypertrophy	1 (2.0)	1 (2.0)	0	7**(1.1)	9**(2.2)	10**(2.3)
53-Week Interim Evaluation						
Number Examined Microscopically	8	8	8	8	8	9
Hepatocyte, Hypertrophy	1 (1.0)	0	3 (1.0)	7**(1.1)	8**(1.8)	9**(2.4)

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

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Number Examined							
Microscopically	53	54	53	53	53	51	50
Hepatocyte, Hypertrophy[a]	0	5* (1.2)[b]	5* (1.4)	24** (1.4)	39** (2.0)	41** (2.3)	32** (1.8)
Fatty Change, Diffuse	3 (1.0)	7 (1.4)	2 (1.0)	11* (1.0)	21** (1.3)	17** (1.2)	15** (1.1)
Bile Duct, Hyperplasia	5 (1.8)	3 (2.0)	2 (1.0)	14** (1.6)	10 (1.6)	17** (1.6)	12* (1.7)
Oval Cell, Hyperplasia	0	0	0	1 (1.0)	0	4* (1.3)	2 (1.0)
Pigmentation	1 (1.0)	1 (1.0)	2 (1.5)	5 (1.6)	5 (1.2)	9** (1.0)	3▲ (1.3)
Hyperplasia, Nodular	0	0	0	0	1	0	1
Cholangiofibrosis	0	0	0	0	1 (2.0)	0	0
Cholangioma, Multiple	0	0	0	0	0	0	1
Cholangioma (includes multiple)[c]	0	0	0	0	2	0	2
Hepatocellular Adenoma[d]	0	0	0	0	0	1	0

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤0.01
▲ Significantly different (P≤0.05) from the 3,000 µg/kg core study 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
[c] Historical incidence for 2-year gavage studies with Sprague-Dawley vehicle control groups: 0/371
[d] Historical incidence (mean ± standard deviation): 4/371 (1.1% ± 1.5%), range 0%-4%

300 µg/kg or greater including the 3,000 µg/kg stop-exposure group. Increased incidences of bile duct hyperplasia occurred in the 300 µg/kg or greater groups, and the increases were significant in all but the 1,000 µg/kg group. Oval cell hyperplasia was seen in a few animals in the 300 and 3,000 µg/kg core study groups and in the 3,000 µg/kg stop-exposure group. Pigmentation was significantly increased in the 3,000 µg/kg core study group compared to the vehicle control group. A single incidence of nodular hyperplasia was seen in the 1,000 µg/kg group and in the 3,000 µg/kg stop-exposure group. Cholangiofibrosis was seen in one rat in the 1,000 µg/kg group.

Hepatocytic hypertrophy was characterized by hepatocytes that were enlarged with increased amounts of eosinophilic cytoplasm (Plate 3). Minimal hypertrophy affected periportal hepatocytes and as severity increased, hepatocytes in other areas of the hepatic lobule were also affected. The hypertrophy usually was not confined to periportal hepatocytes, and therefore the general diagnosis of hepatocytic hypertrophy was used.

The morphological characteristics of the two cases of nodular hyperplasia that were observed in the 1,000 ng/kg and 3,000 ng/kg stop-exposure groups were consistent with those observed in the other dioxin TEF evaluation studies.

Diffuse fatty change was generally a minor change consisting of discrete clear vacuoles (consistent with lipid) in the cytoplasm of hepatocytes and scattered diffusely throughout the liver. Bile duct hyperplasia consisted of increased numbers of portal bile ducts (Plate 4). Oval cell hyperplasia consisted of small ovoid cells with basophilic cytoplasm and round to ovoid nuclei arranged in single or double rows and located predominantly in the portal areas.

Pigmentation consisted of light brown to golden pigment present within macrophages and occasionally hepatocytes. The pigmented macrophages were often seen in portal areas but were also seen scattered randomly within the liver. The pigment was shown to stain positive for iron with Perl's stain.

Cholangiofibrosis appeared relatively small in size and well demarcated lesion, which did not show evidence of localized invasion.

Thyroid Gland: At 53 weeks, sporadic incidences of minimal to mild follicular cell hypertrophy occurred in all groups (except 10 µg/kg) (Tables 11 and A5a). Single occurrences of C-cell adenoma were observed in rats in the 1,000 µg/kg and 3,000 µg/kg groups, and there was a single occurrence of follicular cell adenoma in the 100 µg/kg group (Tables 11 and A1a). At 2 years, incidences of minimal to mild follicular cell hypertrophy were significantly increased at 300 µg/kg and 3,000 µg/kg (core and stop-exposure). Two 3,000 µg/kg stop-exposure rats had follicular cell adenomas; the incidence of this lesion slightly exceeded the historical controls range (Tables 11, A1b, A4a, and A5b).

Follicular cell hypertrophy was a localized to diffuse change, characterized by follicles that were decreased in size and contained decreased amounts of colloid in which aggregates of amphophilic, flocculant appearing material were often present (Plates 5 and 6). The affected follicles were lined by large, prominent cuboidal follicular epithelial cells that were approximately two to three times normal size, usually with abundant pale cytoplasm sometimes containing small, clear, resorption vacuoles. Since some degree of this change can occur spontaneously, the severity grade of minimal was recorded when 50% to 60% of the follicles were involved, mild severity when 60% to 75% of the follicles were involved, moderate when 75% to 90% of the follicles were involved, and marked when over 90% of the follicles were involved.

The incidence of C-cell adenoma or carcinoma (combined) in the 3,000 µg/kg core study group was significantly decreased compared to the vehicle controls and below the historical vehicle control range (Tables 11, A3a, and A4b). The incidence of C-cell adenoma in the 3,000 µg/kg stop-exposure group was significantly greater than that in the 3,000 µg/kg core study group and similar to that of the vehicle controls (Tables 11 and A3b).

Ovary and Oviduct: At 2 years, significantly increased incidences of chronic active inflammation in the ovary and oviduct related to PCB 153 treatment was seen in the 1,000 and 3,000 µg/kg core study groups (Tables 12 and A5b). Those ovaries affected by chronic active inflammation were nearly or completely replaced by large aggregates of neutrophils and debris surrounded by a layer of fibrous tissue that was infiltrated with macrophages (Plates 7 and 8). Thus, chronic active inflammation of the ovary essentially consisted of an encapsulated abscess. In the oviduct, chronic active inflammation had a similar microscopic appearance and often accompanied inflammation of the ovary, suggesting it may have been an extension of the ovarian lesion. Milder cases of oviduct chronic active inflammation consisted of accumulation of small to moderate numbers of mixed inflammatory cells, generally macrophages and neutrophils, within the oviduct lumen. More severe cases consisted of marked accumulation of inflammatory cells and debris that completely filled and sometimes dilated the oviduct lumen and was accompanied by loss of the oviduct epithelium with inflammatory cellular infiltration within smooth muscle of the oviduct wall (Plates 9 and 10).

Uterus: At 2 years, incidences of suppurative inflammation in the 1,000 µg/kg group and chronic active inflammation in the 3,000 µg/kg core study group were significantly greater than those in the vehicle control group (Tables 12 and A5b). Suppurative inflammation consisted of accumulation of small to moderate numbers of neutrophils, usually mixed with varying amounts of keratin, within the uterine lumen accompanied by a diffuse infiltrate of small numbers of eosinophils within the myometrium. The keratin was considered to have sloughed off from areas of squamous metaplasia of the endometrium. The microscopic appearance of the change was similar to that seen normally during estrus and suggested the possibility of an endocrine influence of the chemical on the uterus. Chronic active inflammation, in contrast to the suppurative inflammation consisting of neutrophilic infiltrate, consisted of an accumulation of a mixture of varying numbers of neutrophils and macrophages within the uterine lumen and extending into the underlying myometrium.

Bone Marrow: In the 2-year study, the incidence of hyperplasia was significantly increased in the 3,000 µg/kg core study group (Tables 12 and A5b). The hyperplasia was graded as marked when the entire marrow cavity was filled with dense marrow, moderate when marrow elements comprised about 90% of the cavity (the remaining 10% was fat), and mild when marrow elements comprised approximately 60% to 90% of the marrow cavity. Minimal was rarely recorded because of the normal variation in the amount of bone

TABLE 11
Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
53-Week Interim Evaluation							
Number Examined							
Microscopically	8	8	8	8	8	9	—[c]
Follicular Cell,							
Hypertrophy[a]	1 (1.0)[b]	0	2 (1.5)	1 (1.0)	1 (1.0)	3 (1.0)	
Follicular Cell, Adenoma	0	0	1	0	0	0	—
C-Cell, Adenoma	0	0	0	0	1	1	—
2-Year Evaluation							
Number Examined							
Microscopically	51	52	53	53	53	51	49
Follicular Cell,							
Hypertrophy	5 (2.0)	9 (1.7)	9 (1.9)	12* (1.7)	10 (2.1)	17** (1.8)	12* (1.8)
Follicular Cell, Adenoma[d]	0	0	0	0	0	0	2
C-Cell, Adenoma, Multiple	0	0	0	1	0	1	0
C-Cell Adenoma, (includes multiple)[e]							
Overall rate[f]	16/51 (31%)	13/52 (25%)	17/53 (32%)	12/53 (23%)	22/53 (42%)	7/51 (14%)	18/49 (37%)
Adjusted rate[g]	40.0%	40.5%	39.4%	31.5%	54.5%	21.0%	47.7%
Terminal rate[h]	10/24 (42%)	10/16 (63%)	11/28 (39%)	7/21 (33%)	15/20 (75%)	6/21 (29%)	11/20 (55%)
First incidence (days)	555	438	443	528	555	668	437
Poly-3 test[i]	P=0.090N	P=0.581	P=0.569N	P=0.285N	P=0.129	P=0.062N	P=0.323
Poly-3 test[j]							P=0.014
C-Cell, Carcinoma	2	2	1	1	2	0	3
C-Cell Adenoma or Carcinoma[k]							
Overall rate	18/51 (35%)	15/52 (29%)	18/53 (34%)	13/53 (25%)	23/53 (43%)	7/51 (14%)	19/49 (39%)
Adjusted rate	45.0%	46.8%	41.8%	33.8%	57.0%	21.0%	50.1%
Terminal rate	12/24 (50%)	12/16 (75%)	12/28 (43%)	7/21 (33%)	16/20 (80%)	6/21 (29%)	11/20 (55%)
First incidence (days)	555	438	443	528	555	668	437
Poly-3 test	P=0.038N	P=0.538	P=0.468N	P=0.209N	P=0.185	P=0.023N	P=0.410
Poly-3 test							P=0.008

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤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
[c] Not applicable
[d] Historical incidence for 2-year gavage studies with Sprague-Dawley vehicle control groups (mean ± standard deviation): 1/367 (0.3% ± 0.7%), range 0%-2%
[e] Historical incidence: 100/367 (27.3% ± 7.7%), range 17%-38%
[f] Number of animals with neoplasm per number of animals with thyroid gland examined microscopically
[g] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[h] Observed incidence at terminal kill
[i] Beneath the vehicle control incidence is the P value associated with the trend test; the stop-exposure group is excluded from the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed 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 a dosed group is indicated by **N**.
[j] Pairwise comparison between the 3,000 µg/kg core and stop-exposure groups.
[k] Historical incidence: 113/367 (30.8% ± 5.9%), range 25%-40%

TABLE 12
Incidences of Selected Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control		10 µg/kg		100 µg/kg		300 µg/kg		1,000 µg/kg		3,000 µg/kg		3,000 µg/kg (Stop-Exposure)	
Ovary[a]	53		53		53		53		53		50		49	
Inflammation, Chronic Active[b]	0		0		2	(3.5)[c]	1	(2.0)	5*	(3.0)	7**	(3.6)	0▲▲	
Oviduct	50		38		44		35		39		45		46	
Inflammation, Chronic Active	1	(3.0)	0		2	(2.5)	1	(3.0)	5*	(3.2)	7*	(3.3)	2	(3.0)
Uterus	53		54		53		53		53		50		49	
Inflammation, Suppurative	5	(1.6)	6	(1.8)	6	(1.8)	2	(1.0)	16**	(2.0)	8	(1.6)	9	(2.2)
Inflammation, Chronic Active	2	(3.0)	1	(3.0)	5	(2.4)	4	(2.8)	2	(3.0)	8*	(3.0)	1▲	(3.0)
Bone Marrow	53		54		53		53		53		51		50	
Hyperplasia	34	(2.9)	41	(3.3)	40	(3.0)	38	(3.1)	42	(3.2)	46**	(2.9)	40	(3.1)
Lung	52		54		53		53		53		51		50	
Alveolar Epithelium, Hyperplasia	20	(1.1)	21	(1.4)	16	(1.3)	11	(1.2)	9*	(1.1)	6**	(1.0)	4**	(1.3)
Infiltration Cellular, Histiocyte	45	(1.6)	40	(1.6)	40	(1.8)	40	(1.4)	27**	(1.4)	28**	(1.3)	37	(1.3)
Squamous Metaplasia	0		0		0		1	(1.0)	1	(2.0)	1	(2.0)	0	

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
** $P \leq 0.01$
▲ Significantly different ($P \leq 0.05$) from the 3,000 µg/kg core study group by the Poly-3 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

marrow. Bone marrow was considered normal when the distal end of the femur section contained 20% to 60% marrow.

Lung: At 2 years, the incidences of alveolar epithelium hyperplasia decreased with increasing dose, and the differences at 1,000 µg/kg or greater were significant (Tables 12 and A5b). Also, significantly decreased incidences of histiocytic cellular infiltration characterized by aggregates of large, clear alveolar histiocytes were seen in the 1,000 and 3,000 µg/kg core study groups. A single occurrence of minimal to mild squamous metaplasia was seen in each of the 300, 1,000, and 3,000 µg/kg core study groups. In the alveolar epithelial hyperplasia, alveoli were lined by cuboidal to columnar epithelium, usually associated with prominent inflammatory cell infiltrate, consisting of large aggregates of alveolar macrophages commonly mixed with focal aggregates of neutrophils. Squamous metaplasia of the aveolar epithelium was generally a minor change consisting of one or more small irregular foci of keratinizing stratified squamous epithelium that had replaced the normal alveolar epithelium.

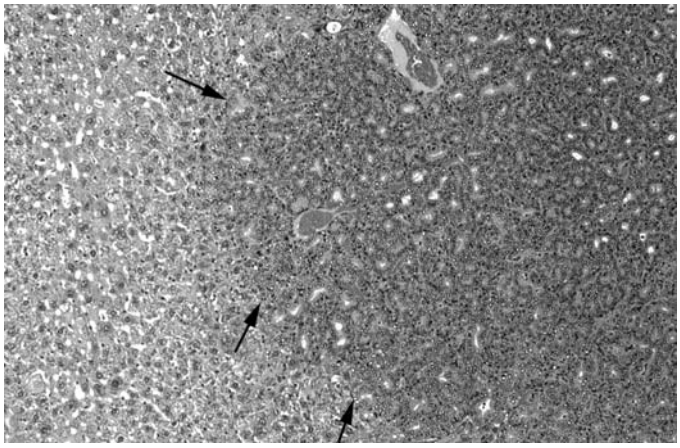


PLATE 1
Cholangioma (arrows) in the liver of a female rat administered 1,000 µg/kg PCB 153 by gavage for 2 years. The neoplasm is well circumscribed, composed of multiple, densely packed, irregular bile duct structures. H&E; 25×

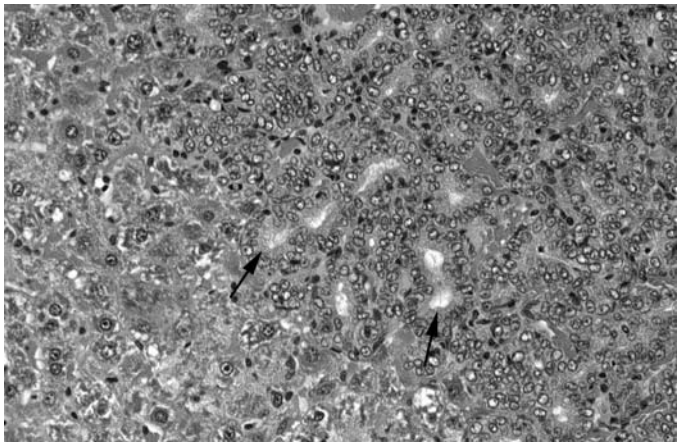


PLATE 2
Higher magnification of Plate 1. The neoplastic bile duct structures (arrows) are composed of a single layer of densely packed, columnar, somewhat pleomorphic bile duct epithelial cells. H&E; 66×

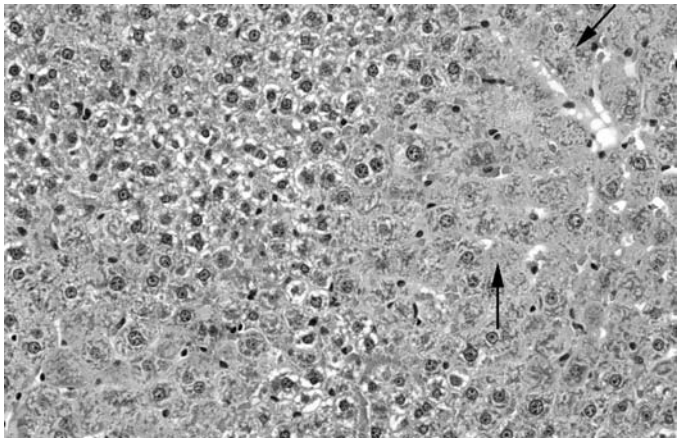


PLATE 3
Periportal hepatocyte hypertrophy (arrows) in the liver of a female rat administered 3,000 µg/kg PCB 153 by gavage for 2 years. Note that the hepatocytes are enlarged and have increased amounts of cytoplasm. H&E; 66×

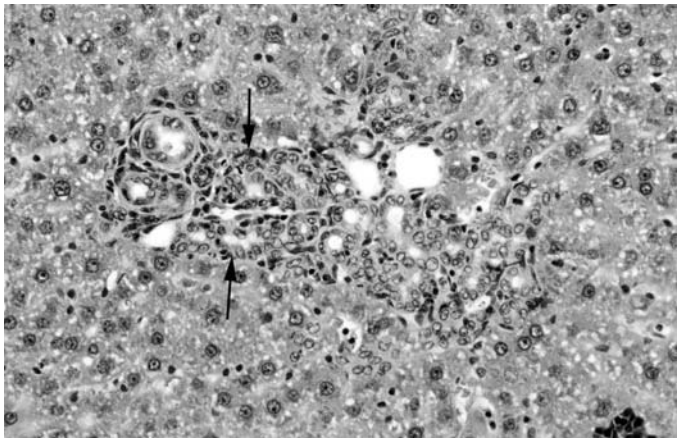


PLATE 4
Bile duct hyperplasia (arrows) in the liver of a female rat administered 3,000 µg/kg PCB 153 by gavage for 2 years. Note the increased number of portal bile ducts. H&E; 66×

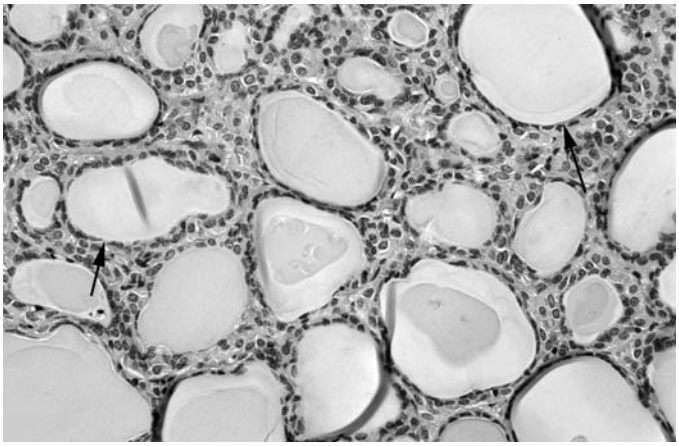


PLATE 5
Thyroid follicles of a vehicle control female rat from the 2-year gavage study of PCB 153. Note that most follicles are lined by flattened epithelium (arrows). H&E; 66×

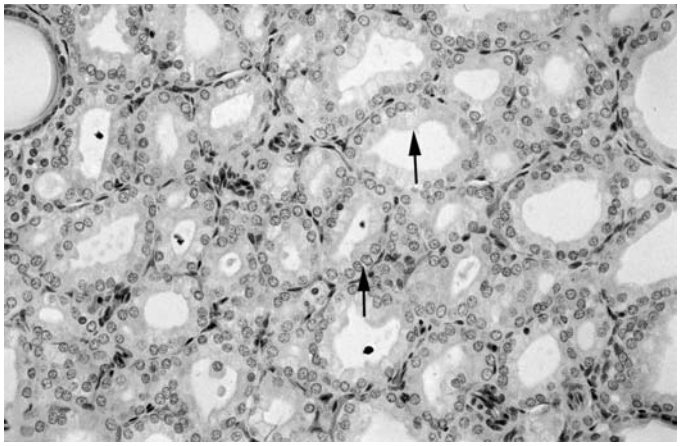


PLATE 6
Follicular hypertrophy in the thyroid gland of a female rat administered 3,000 µg/kg PCB 153 for 2 years. Note that most follicles are lined by cuboidal epithelium (arrows). Compare to Plate 5. H&E; 66×

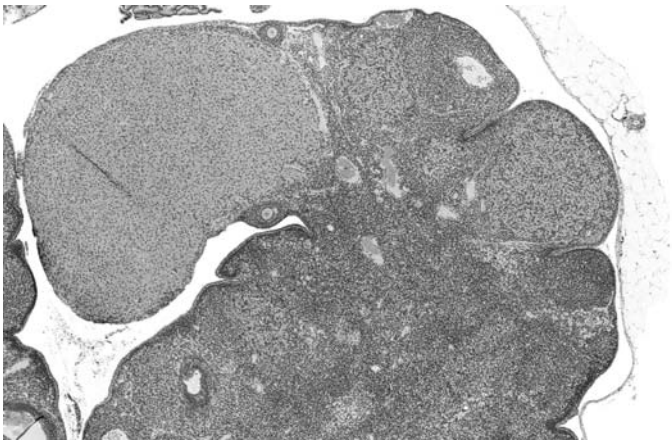


PLATE 7
Ovary of a vehicle control female rat from the 2-year gavage study of PCB 153. H&E; 10×

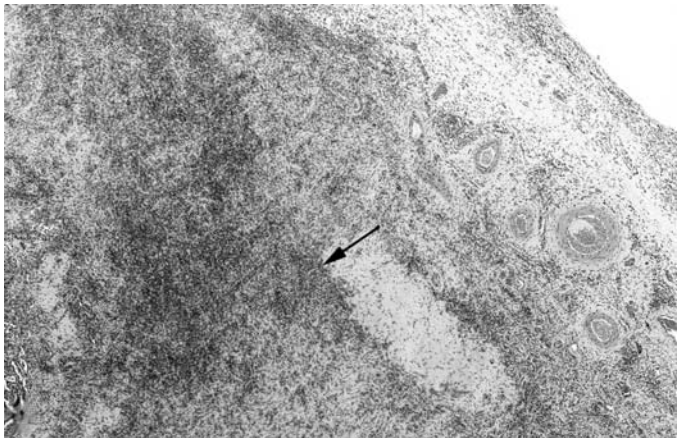


PLATE 8
Chronic active inflammation in the ovary of a female rat administered 3,000 µg/kg PCB 153 by gavage for 2 years. Note that the ovary is diffusely infiltrated by mixed inflammatory cells (arrow). Compare to Plate 7. H&E; 10×

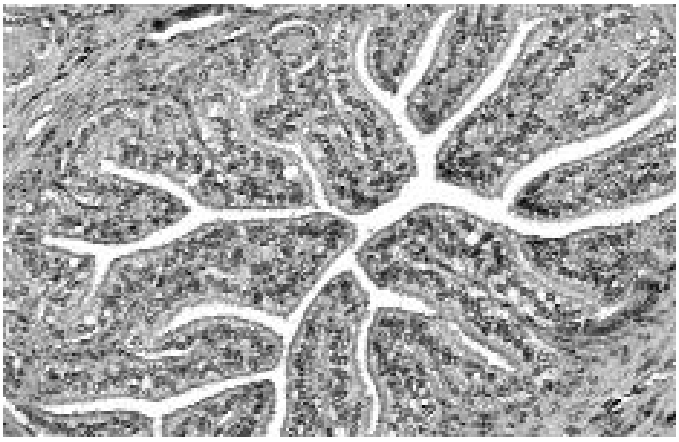


PLATE 9
Oviduct of a vehicle control female rat from the 2-year gavage study of PCB 153. H&E; 66×

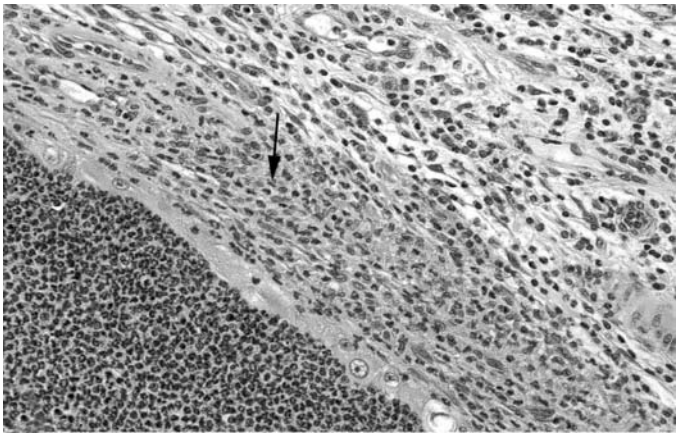


PLATE 10
Chronic active inflammation in the oviduct of a female rat administered 3,000 µg/kg PCB 153 by gavage for 2 years. Note that the lumen and wall (arrow) are diffusely infiltrated by neutrophils. Compare to Plate 9. H&E; 66×

DISCUSSION AND CONCLUSIONS

PCB 153, a di-*ortho*-substituted nonplanar PCB, is the most abundant PCB in human tissue samples on a molar basis (McFarland and Clarke, 1989; Schecter *et al.*, 1994b; Heudorf *et al.*, 2002; Ayotte *et al.*, 2003; Chu *et al.*, 2003). As a di-*ortho*-substituted nonplanar PCB, PCB 153 lacks dioxin-like activity and therefore has no toxic equivalence factor (TEF). Several studies have demonstrated an interaction between exposure to PCB 153 or other di-*ortho*-substituted PCBs on tissue concentrations and biochemical and biological effects induced by dioxin-like compounds (DLCs). The inclusion of PCB 153, a non-DLC, in the dioxin TEF evaluation provided the opportunity to investigate both the carcinogenicity of a di-*ortho*-substituted nonplanar PCB and the effects of a di-*ortho*-substituted nonplanar PCB on DLC-induced carcinogenicity. The PCB 153 doses selected for this study were based on those previously used in tumor promotion studies and are similar to those used in another study of a mixture of PCB 153 and PCB 126, the results of which are reported in a separate Technical Report (NTP, 2006e). While one of the aims of this study was a comparative analysis of effects seen with PCB 126 and the mixture of PCB 126 and PCB 153, in this Technical Report only the results of the present study of PCB 153 are presented and discussed.

In the current study, exposure to PCB 153 had no effect on survival and only a minor effect on body weight gain in the 3,000 µg/kg core study group. Body weights of the 3,000 µg/kg core study group were maximally reduced to 89% of the vehicle control group body weight, but were 93% of the vehicle control body weight at the end of the study.

The principal findings in this study were significant increases in the incidences of nonneoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus. Cholangioma of the liver, which is a rare tumor type in the Harlan Sprague-Dawley rat, was also observed in several treated animals.

Administration for 2 years resulted in accumulation of PCB 153 in liver, lung, blood, and fat. The most significant accumulation occurred in the fat, which is consistent with the lipophilic nature of this compound. Previous studies of DLCs indicate that the liver and fat are the main depots in rodents and together contribute approximately 70% to 80% of the total body burden in rodents (DeVito *et al.*, 1995). For DLCs, the levels in liver are generally higher than those in fat due to their hepatic sequestration as a result of binding to DLC-inducible CYP1A2 in the liver (Kedderis *et al.*, 1993; Diliberto *et al.*, 1997). PCB 153 does not bind CYP1A2 and therefore does not sequester in the liver (van Birgelen *et al.*, 1996).

Concentrations of PCB 153 in fat tended to increase with longer exposure duration. The relationship between PCB 153 intake and concentrations in fat was linear. These results are also reflected in previous tumor promotion studies in which the accumulation of PCB 153 in adipose tissue was linear with respect to administered dose (Dean *et al.*, 2002).

Cessation of daily treatment with PCB 153 in the 3,000 µg/kg stop-exposure group led to lower concentrations of PCB 153 in all tissues examined compared to those of the 3,000 µg/kg core study group at 2 years. Concentrations of PCB 153 in fat from the 3,000 µg/kg stop-exposure group were less than in the 1,000 µg/kg group. Liver, lung, and blood concentrations of PCB 153 in the 3,000 µg/kg stop-exposure group were similar to those of the 1,000 µg/kg group at 2 years. Therefore, interpretation of the pathology results in the stop-exposure animals should consider that although administration ceased and tissue levels declined significantly over the remainder of the study, animals were continually exposed to PCB 153 throughout the 2-year study.

In vehicle control rats, there was measurable PCB 153 in the fat at all time points and in lung tissue after longer durations of exposure. Measurable levels of PCB 153 have been observed in tissues from vehicle control animals and may be attributed to the ingestion of very low levels of PCB 153 normally present in rodent chow (Luotamo *et al.*, 1991; Chu *et al.*, 1996; Feeley and Jordan, 1998; Jordan and Feeley, 1999). PCB 153 levels

of 0.15 ppb (ng/g feed) have been reported in rat feed (Jordan and Feeley, 1999). Levels of PCB 153 in samples of irradiated NTP-2000 feed were 0.59 ng/g (Table D5). This level of PCB 153 (for a 200 gram rat ingesting 10 grams of feed per day) would result in a mean daily intake of approximately 29.5 ng/kg per day (range 1.7 to 257 ng/kg). Therefore all experimental treatments are made in addition to a background exposure to PCB 153 normally present in feed and, therefore, the vehicle control group exposure is not zero. However, the background intake is one to three orders of magnitude lower than the lowest dose in the study. Consequently, the additional contribution of this background exposure rate to the observed increases in treatment-related lesions to administered PCB 153 is negligible.

Nonplanar PCB congeners are typically similar to phenobarbital in their ability to induce specific isozymes of cytochrome P450, including CYP2B (Safe 1984; Waxman and Azaroff, 1992). Previous studies in rodents have demonstrated that 7-pentoxyresorufin-*O*-deethylase (PROD) activity, a measure of CYP2B expression, is induced by PCB 153 (Luotamo *et al.*, 1991; Li *et al.*, 1994; Bouwman *et al.*, 1999; Craft *et al.*, 2002). In the current study, administration of 100 µg/kg or greater dose-dependently induced hepatic CYP2B (PROD) activity at all time points. Dioxin-like PCB congeners and other DLCs are associated with the induction of CYP1A1 (7-ethoxyresorufin-*O*-deethylase, EROD) and CYP1A2 (acetanilide-4-hydroxylase, A4H) activities. In the current study, EROD and A4H activities were significantly induced following PCB 153 exposure for 14 or 31 weeks. Although EROD and A4H activities were significantly higher than vehicle controls in the current study, the level of induction by PCB 153 was less than twofold over vehicle controls. This level of induction is significantly lower than that observed in the study of the dioxin-like congener, PCB 126, as part of the TEF evaluation (NTP, 2006a) in which hepatic EROD activity was induced 50- to 100-fold and A4H was induced approximately 5-fold. Additionally, no effect on EROD or A4H was observed at 53 weeks in the present study. Previously, it has been demonstrated that a single administration of PCB 153 significantly induces EROD and A4H activities and CYP1A2 enzyme expression in C57BL/6J mice (De Jongh *et al.*, 1995) and subchronic (90-day) exposure increases hepatic EROD activity in male and female Sprague-Dawley rats (Chu *et al.*, 1996). However, EROD activity is not induced following 1, 2, or 3 weeks of exposure to PCB 153 in Sprague-Dawley rats (Twaroski *et al.*, 2001). The mechanisms for the temporal differences in the induction of hepatic EROD and A4H activities are currently unclear.

Decreased pulmonary EROD activity was observed at 14 weeks, but not at 31 or 53 weeks. There are no previous reports regarding the effect of PCB 153 on pulmonary EROD activity. Pulmonary EROD activity is increased by dioxin-like PCBs, including PCB 126 (NTP, 2006a).

Although liver is a principal target organ for PCB-induced toxicity, di-*ortho*-substituted PCB congeners are not as hepatotoxic as the coplanar, dioxin-like congeners (Safe, 1994). In the current study, hepatocyte hypertrophy was the only hepatotoxic effect observed at the 14-, 31-, and 53-week interim evaluations. These results are consistent with previous observations that administration of PCB 153 induces hepatocyte hypertrophy in Sprague-Dawley rats and male mice (Biocca *et al.*, 1981; Chu *et al.*, 1996; Peng *et al.*, 1997). A dose-dependent increase in the incidence and severity of hepatocyte hypertrophy was also observed at 2 years. Hepatic toxicity at 2 years was also characterized by diffuse fatty change, bile duct hyperplasia, and increased oval cell hyperplasia and pigmentation in the highest dose group. A single incidence of well-demarcated cholangiofibrosis was also observed in the 1,000 µg/kg group at 2 years. In other studies of DLCs as part of the dioxin TEF evaluation, the diagnosis of toxic hepatopathy was used as a comparative indicator of overall hepatotoxicity (Hailey *et al.*, 2005, NTP, 2006a,b,c,d). Toxic hepatopathy was not indicated in the current study.

There are a limited number of studies of the effects of PCB 153 alone and not in combination as mixtures with other PCB congeners. However, some of the effects observed in initiation-promotion studies where PCB 153 was administered as a promoting agent are consistent with those observed in the current study. In initiation-promotion studies, PCB 153 induces hepatic EROD and PROD activities (Bager *et al.*, 1995) and hepatocyte hypertrophy (Hemming *et al.*, 1993). Similar to the current study, PCB 153 does not affect hepatocyte proliferation (Tharappel *et al.*, 2002).

Two cholangiomas were observed in the 1,000 µg/kg group and in the 3,000 µg/kg stop-exposure group at 2 years. Cholangiomas are rarely occurring neoplasms in Harlan Sprague-Dawley rats. No cholangiomas have occurred in the vehicle controls from any of the seven

studies as part of the dioxin TEF evaluation (NTP, 2006a,b,c,d,e,f). These neoplasms are characterized by multiple, densely-packed, irregular bile duct structures within a small amount of fibrous stroma. The pathogenesis of the cholangioma and its relationship to PCB 153 treatment is not clear. There was an effect of PCB 153 treatment on the bile duct epithelium. PCB 153 increased the incidences of bile duct hyperplasia at 300 µg/kg or greater, including the stop-exposure group, and of oval cell hyperplasia in the 3,000 µg/kg core study group. These effects on the biliary epithelium and oval cells could contribute to the development of cholangioma and, therefore, it was concluded that the few cases of cholangioma observed may have been related to treatment, especially given that these neoplasms had not been seen in any historical control animals.

Several initiation-promotion studies have demonstrated that PCB 153 promotes the development of preneoplastic altered hepatocellular foci (AHF) expressing gamma-glutamyltranspeptidase (GGT-positive) and the placental form of glutathione-*S*-transferase (PGST-positive) (Hemming *et al.*, 1993; Bager *et al.*, 1995; Tharappel *et al.*, 2002). PCB 153 also promotes the development of ATPase-deficient AHF in diethylnitrosamine-initiated Wistar rats (Buchmann *et al.*, 1986). PCB 153 decreases apoptosis in focal hepatocytes, but does not induce cell proliferation (Tharappel *et al.*, 2002). Therefore, the induction of AHF by PCB 153 may occur via the inhibition of apoptosis allowing a selective growth advantage to a subset of initiated cells. Preneoplastic AHF are believed to progress and develop into hepatocyte-derived neoplastic lesions. A significant increase in hepatocellular neoplasms was not observed following administration of PCB 153 for 2 years. It may be possible that, in addition to inhibited apoptosis, a continuous increase in hepatocyte proliferation, which is not induced by PCB 153, is required for the progression of AHF to hepatocellular adenomas and carcinomas. Since PCBs are nongenotoxic, the development of AHF and hepatocyte-derived neoplastic lesions may require an initiating event at a rate that exceeds spontaneous mutation rates.

Decreases in thyroxine (T_4) levels observed in the 3,000 µg/kg group at weeks 14 and 53 are consistent with previously observed effects on serum thyroid hormones (Ness *et al.*, 1993; Morse *et al.*, 1996). Alteration in thyroid hormone homeostasis by DLCs, including dioxin-like PCBs, may be due to increased T_4 glucuronidation as a result of increased UDP-GT expression (Van Birgelen *et al.*, 1994, 1995; Schmidt *et al.*, 2003). Subsequently, a decreased negative feedback inhibition of the thyroid gland may lead to overexpression of thyroid stimulating hormone (TSH) (Curran and DeGroot, 1991). It has been hypothesized that overstimulation of the thyroid gland by TSH may be involved in the mechanism of follicular cell carcinogenesis (Hill *et al.*, 1989). In the present PCB 153 study, the decrease in T_4 at weeks 14 and 53 was not accompanied by an increase in TSH. There were, however, one follicular thyroid gland cell adenoma each in the 1,000 and 3,000 µg/kg core study groups at 53 weeks and two follicular cell adenomas in the 3,000 µg/kg stop-exposure group at 2 years. Since TSH levels were not evaluated in the 3,000 µg/kg stop-exposure group, it is difficult to determine if a sustained increase of TSH following cessation of the PCB 153 administration might have promoted the follicular cell neoplasm. There was a significant increase in the incidence of thyroid gland follicular cell hypertrophy in the 3,000 µg/kg stop-exposure group; significant increases were also observed in the 300 and 3,000 µg/kg groups. The incidences of follicular cell adenoma of the thyroid gland in all dosed groups, except the 3,000 µg/kg stop-exposure group, were similar to the incidences observed in vehicle controls from the seven studies as part of the dioxin TEF evaluation and, therefore, were not considered to be treatment related.

In the current study, there were significant increases in inflammation of the ovary, oviduct, and uterus in the 1,000 and 3,000 µg/kg core study groups at 2 years. These effects have not been reported in previous studies of PCB 153. Similar effects such as inflammation of the oviducts and uterine pyometra may be estrogenic effects and have been observed following exposure to the synthetic estrogen diethylstilbesterol (McLachlan *et al.*, 1980; Newbold 1995). Several studies suggest that PCB 153 possesses estrogenic properties and competes with estrogen at the estrogen receptor (Desaulniers *et al.*, 1999; Bonefeld-Jorgensen *et al.*, 2001; Wojtowicz *et al.*, 2001). The estrogenic potential of PCB 153 may contribute to the induction of these effects.

Conclusions

Under the conditions of this 2-year gavage study there was *equivocal evidence of carcinogenic activity** of PCB 153 in female Harlan Sprague-Dawley rats based on the occurrences of cholangioma of the liver.

PCB 153 administration caused increased incidences of nonneoplastic lesions of the liver, thyroid gland, ovary, oviduct, and uterus in female rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF PCB 153

TABLE A1a Summary of the Incidence of Neoplasms in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153 62

TABLE A1b Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153 64

TABLE A2 Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153 70

TABLE A3a Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153 112

TABLE A3b Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 153 115

TABLE A4a Historical Incidence of Liver Neoplasms in Vehicle Control Female Sprague-Dawley Rats 118

TABLE A4b Historical Incidence of Thyroid Gland Neoplasms in Vehicle Control Female Sprague-Dawley Rats 118

TABLE A5a Summary of the Incidence of Nonneoplastic Lesions in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153 119

TABLE A5b Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153 123

Table A1a
Summary of the Incidence of Neoplasms in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
Disposition Summary						
Animals initially in study	28	28	28	28	28	29
14-Week interim evaluation	10	10	10	10	10	10
31-Week interim evaluation	10	10	10	10	10	10
53-Week interim evaluation	8	8	8	8	8	9
Animals examined microscopically	28	28	28	28	28	29
Systems Examined at 14 Weeks with No Neoplasms Observed						
Alimentary System						
Cardiovascular System						
Endocrine System						
General Body System						
Genital System						
Hematopoietic System						
Integumentary System						
Musculoskeletal System						
Nervous System						
Respiratory System						
Special Senses System						
Urinary System						
31-Week Interim Evaluation						
Integumentary System						
Mammary gland	(10)		(2)			(10)
Fibroadenoma			2 (100%)			
Urinary System						
Kidney			(2)			
Nephroblastoma			1 (50%)			
Systems Examined at 31 Weeks with No Neoplasms Observed						
Alimentary System						
Cardiovascular System						
Endocrine System						
General Body System						
Genital System						
Hematopoietic System						
Musculoskeletal System						
Nervous System						
Respiratory System						
Special Senses System						

TABLE A1a
Summary of the Incidence of Neoplasms in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
53-Week Interim Evaluation						
Endocrine System						
Thyroid gland	(8)	(8)	(8)	(8)	(8)	(9)
C-cell, adenoma					1 (13%)	1 (11%)
Follicle, adenoma			1 (13%)			
Genital System						
Clitoral gland	(1)					
Carcinoma	1 (100%)					
Ovary	(8)	(1)		(1)	(1)	(9)
Sertoli cell tumor malignant		1 (100%)				
Integumentary System						
Mammary gland	(8)	(2)	(2)	(2)		(9)
Fibroadenoma		2 (100%)	2 (100%)	2 (100%)		2 (22%)
Systems Examined at 53 Weeks with No Neoplasms Observed						
Alimentary System						
Cardiovascular System						
General Body System						
Hematopoietic System						
Musculoskeletal System						
Nervous System						
Respiratory System						
Special Senses System						
Urinary System						
Neoplasm Summary						
Total animals with primary neoplasms[b]						
31-Week interim evaluation			2			
53-Week interim evaluation	1	3	3	2	1	2
Total primary neoplasms						
31-Week interim evaluation			3			
53-Week interim evaluation	1	3	3	2	1	3
Total animals with benign neoplasms						
31-Week interim evaluation			2			
53-Week interim evaluation		2	3	2	1	2
Total benign neoplasms						
31-Week interim evaluation			2			
53-Week interim evaluation		2	3	2	1	3
Total animals with malignant neoplasms						
31-Week interim evaluation			1			
53-Week interim evaluation	1	1				
Total malignant neoplasms						
31-Week interim evaluation			1			
53-Week interim evaluation	1	1				

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

Table A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Disposition Summary							
Animals initially in study	53	54	53	53	53	51	50
Early deaths							
Accidental death				1			
Moribund	18	23	17	22	18	19	16
Natural deaths	11	15	8	9	15	11	14
Survivors							
Died last week of study				1			
Terminal sacrifice	24	16	28	20	20	21	20
Animals examined microscopically	53	54	53	53	53	51	50
Alimentary System							
Intestine large, colon	(53)	(54)	(53)	(53)	(53)	(50)	(49)
Intestine large, rectum	(53)	(54)	(53)	(53)	(53)	(50)	(50)
Intestine large, cecum	(53)	(54)	(53)	(53)	(53)	(50)	(48)
Leiomyoma	1 (2%)						
Intestine small, duodenum	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Intestine small, jejunum	(53)	(54)	(53)	(53)	(53)	(50)	(49)
Fibrosarcoma							1 (2%)
Liver	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Carcinoma, metastatic, uterus					1 (2%)		
Cholangioma					2 (4%)		1 (2%)
Cholangioma, multiple							1 (2%)
Hepatocellular adenoma						1 (2%)	
Histiocytic sarcoma				1 (2%)			
Mesentery			(1)		(1)		
Carcinoma, metastatic, uterus					1 (100%)		
Oral mucosa	(21)	(12)	(16)	(12)	(16)	(25)	(15)
Gingival, squamous cell carcinoma		2 (17%)		1 (8%)		1 (4%)	
Pancreas	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Acinus, adenoma							1 (2%)
Salivary glands	(51)	(52)	(53)	(52)	(53)	(51)	(48)
Stomach, forestomach	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Histiocytic sarcoma				1 (2%)			
Stomach, glandular	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Histiocytic sarcoma				1 (2%)			
Tooth	(34)	(13)	(19)	(22)	(23)	(35)	(27)
Peridontal tissue, neurofibrosarcoma	1 (3%)						

Table A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Cardiovascular System							
Blood vessel	(52)	(54)	(53)	(53)	(53)	(51)	(50)
Aorta, hemangiosarcoma, metastatic, heart	1 (2%)						
Heart	(52)	(54)	(53)	(53)	(53)	(51)	(50)
Fibrous histiocytoma, metastatic, skin							1 (2%)
Hemangiosarcoma	1 (2%)						
Histiocytic sarcoma				1 (2%)			
Schwannoma malignant		1 (2%)		1 (2%)	1 (2%)	1 (2%)	
Endocrine System							
Adrenal cortex	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Adenoma				1 (2%)			
Adrenal medulla	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)					
Pheochromocytoma benign	2 (4%)	1 (2%)	4 (8%)	4 (8%)	2 (4%)	2 (4%)	6 (12%)
Bilateral, pheochromocytoma benign						1 (2%)	
Islets, pancreatic	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Adenoma	1 (2%)						1 (2%)
Carcinoma			1 (2%)				1 (2%)
Parathyroid gland	(49)	(46)	(50)	(47)	(46)	(48)	(45)
Adenoma					2 (4%)		1 (2%)
Pituitary gland	(53)	(54)	(53)	(53)	(53)	(50)	(50)
Carcinoma, metastatic, oral mucosa		1 (2%)					
Neurofibrosarcoma, metastatic, tooth	1 (2%)						
Pars distalis, adenoma	18 (34%)	19 (35%)	19 (36%)	19 (36%)	24 (45%)	11 (22%)	23 (46%)
Pars distalis, carcinoma						1 (2%)	1 (2%)
Thyroid gland	(51)	(52)	(53)	(53)	(53)	(51)	(49)
Bilateral, C-cell, adenoma	2 (4%)	4 (8%)			5 (9%)		
C-cell, adenoma	14 (27%)	9 (17%)	17 (32%)	11 (21%)	17 (32%)	6 (12%)	18 (37%)
C-cell, adenoma, multiple				1 (2%)		1 (2%)	
C-cell, carcinoma	2 (4%)	2 (4%)	1 (2%)	1 (2%)	2 (4%)		3 (6%)
Follicular cell, adenoma							2 (4%)
General Body System							
None							

Table A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Genital System							
Clitoral gland	(53)	(51)	(52)	(53)	(51)	(50)	(48)
Carcinoma		1 (2%)					
Carcinoma, metastatic, mammary gland			1 (2%)				
Ovary	(53)	(53)	(53)	(53)	(53)	(50)	(49)
Cystadenoma	1 (2%)						1 (2%)
Granulosa cell tumor malignant				1 (2%)			
Granulosa cell tumor benign			1 (2%)				
Granulosa-theca tumor benign			1 (2%)				1 (2%)
Schwannoma malignant			1 (2%)				
Uterus	(53)	(54)	(53)	(53)	(53)	(50)	(49)
Carcinoma		1 (2%)	1 (2%)		1 (2%)		1 (2%)
Leiomyosarcoma				3 (6%)			
Polyp stromal	6 (11%)	9 (17%)	4 (8%)	6 (11%)	3 (6%)	2 (4%)	4 (8%)
Polyp stromal, multiple	1 (2%)						
Schwannoma malignant		1 (2%)		1 (2%)			
Squamous cell carcinoma			2 (4%)				
Cervix, carcinoma			1 (2%)				
Cervix, schwannoma malignant			1 (2%)				1 (2%)
Cervix, schwannoma malignant, metastatic, vagina						1 (2%)	
Cervix, squamous cell carcinoma		1 (2%)					
Vagina	(1)	(3)	(2)	(1)	(1)	(3)	(1)
Fibrosarcoma		2 (67%)					
Fibrous histiocytoma, metastatic, skin					1 (100%)		
Sarcoma		1 (33%)					
Schwannoma malignant	1 (100%)					3 (100%)	
Squamous cell carcinoma			1 (50%)	1 (100%)			
Hematopoietic System							
Bone marrow	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Histiocytic sarcoma				1 (2%)			
Lipoma	1 (2%)						
Lymph node	(3)	(3)	(3)	(2)	(5)	(6)	(1)
Deep cervical, carcinoma, metastatic, thyroid gland					1 (20%)		
Mediastinal, carcinoma, metastatic, uterus					1 (20%)		
Mediastinal, histiocytic sarcoma				1 (50%)			
Lymph node, mandibular	(51)	(52)	(53)	(51)	(53)	(51)	(48)
Lymph node, mesenteric	(52)	(54)	(53)	(53)	(53)	(51)	(49)
Carcinoma, metastatic, uterus					1 (2%)		
Histiocytic sarcoma				1 (2%)			
Spleen	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Histiocytic sarcoma				1 (2%)			
Thymus	(48)	(53)	(52)	(53)	(53)	(47)	(49)
Hemangiosarcoma, metastatic, heart	1 (2%)						
Histiocytic sarcoma				1 (2%)			

Table A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Integumentary System							
Mammary gland	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)	3 (6%)	2 (4%)	
Adenoma, multiple	1 (2%)						
Carcinoma	8 (15%)	6 (11%)	7 (13%)	4 (8%)	6 (11%)	2 (4%)	10 (20%)
Carcinoma, multiple				1 (2%)			
Fibroadenoma	22 (42%)	21 (39%)	22 (42%)	22 (42%)	27 (51%)	24 (47%)	16 (32%)
Fibroadenoma, multiple	19 (36%)	13 (24%)	14 (26%)	13 (25%)	12 (23%)	8 (16%)	14 (28%)
Skin	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Basal cell adenoma					1 (2%)		
Basal cell carcinoma		1 (2%)				1 (2%)	1 (2%)
Fibroma			2 (4%)	1 (2%)	1 (2%)		2 (4%)
Fibrosarcoma		1 (2%)			1 (2%)		4 (8%)
Fibrous histiocytoma			1 (2%)		1 (2%)		1 (2%)
Histiocytic sarcoma				1 (2%)			
Keratoacanthoma		1 (2%)		1 (2%)			
Lipoma			1 (2%)				
Sarcoma		1 (2%)					
Schwannoma malignant						1 (2%)	1 (2%)
Schwannoma malignant, metastatic, vagina	1 (2%)						
Squamous cell papilloma					1 (2%)		
Subcutaneous tissue, sarcoma			1 (2%)				
Musculoskeletal System							
Bone	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Schwannoma malignant, metastatic, skin							1 (2%)
Nervous System							
Brain	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Astrocytoma malignant				1 (2%)			
Carcinoma, metastatic, pituitary gland						1 (2%)	1 (2%)
Carcinoma, metastatic, oral mucosa		1 (2%)					
Meninges, sarcoma							1 (2%)
Meninges, schwannoma malignant, metastatic, skin							1 (2%)
Neurofibrosarcoma, metastatic, tooth	1 (2%)						

Table A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Respiratory System							
Lung	(52)	(54)	(53)	(53)	(53)	(51)	(50)
Alveolar/bronchiolar adenoma	1 (2%)				2 (4%)		
Basal cell carcinoma, metastatic, skin						1 (2%)	
Carcinoma, metastatic, mammary gland		1 (2%)			1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, uterus					1 (2%)		
Carcinoma, metastatic, oral mucosa		1 (2%)					
Fibrous histiocytoma, metastatic, skin			1 (2%)				1 (2%)
Histiocytic sarcoma				1 (2%)			
Mediastinum, hemangiosarcoma, metastatic, heart	1 (2%)						
Nose	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Basal cell carcinoma, metastatic, skin							1 (2%)
Trachea	(52)	(54)	(53)	(53)	(53)	(51)	(49)
Special Senses System							
Eye	(53)	(54)	(53)	(53)	(52)	(51)	(50)
Neurofibrosarcoma, metastatic, tooth	1 (2%)						
Optic nerve, schwannoma malignant, metastatic, skin							1 (2%)
Harderian gland	(53)	(54)	(53)	(53)	(53)	(49)	(50)
Carcinoma, metastatic, oral mucosa		1 (2%)					
Neurofibrosarcoma, metastatic, tooth	1 (2%)						
Schwannoma malignant, metastatic, skin							1 (2%)
Urinary System							
Kidney	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Carcinoma, metastatic, mammary gland						1 (2%)	
Fibrous histiocytoma, metastatic, skin							1 (2%)
Histiocytic sarcoma				1 (2%)			
Nephroblastoma				1 (2%)			
Stromal nephroma		1 (2%)				1 (2%)	1 (2%)
Bilateral, renal tubule, carcinoma						1 (2%)	
Renal tubule, adenoma			1 (2%)				
Urinary bladder	(53)	(53)	(53)	(53)	(53)	(50)	(49)

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Systemic Lesions							
Multiple organs[b]	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Histiocytic sarcoma				1 (2%)			
Leukemia mononuclear	1 (2%)						
Lymphoma malignant	2 (4%)				3 (6%)		
Neoplasm Summary							
Total animals with primary neoplasms[c]	52	51	49	48	51	48	49
Total primary neoplasms	108	100	105	97	117	70	119
Total animals with benign neoplasms	50	41	45	46	49	40	44
Total benign neoplasms	91	77	87	80	102	58	92
Total animals with malignant neoplasms	12	20	16	14	14	11	23
Total malignant neoplasms	17	23	18	17	15	12	27
Total animals with metastatic neoplasms	3	2	2	0	4	4	5
Total metastatic neoplasms	8	5	2	0	8	5	10

[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 Female Rats in the 2-Year Gavage Study of PCB 153: Vehicle Control

Number of Days on Study	211	399	410	418	437	442	502	507	551	555	555	557	571	590	603	608	613	613	613	621	641	644	656	664	672
Carcass ID Number	078	004	065	044	034	080	011	063	024	022	077	064	014	067	073	003	021	059	091	085	083	033	058	093	032
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oral mucosa	+			+			+		+			+		+	+							+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+			+			+	+	+		+	+		+	+		+	+		+	+	+	+	+	+
Peridontal tissue, neurofibrosarcoma												X													
Cardiovascular System																									
Blood vessel	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aorta, hemangiosarcoma, metastatic, heart						X																			
Heart	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																X									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, metastatic, tooth												X													
Pars distalis, adenoma	X														X						X		X	X	X
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma										X				X							X		X		
C-cell, carcinoma																									
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 Female Rats in the 2-Year Gavage Study of PCB 153: Vehicle Control

Numbers of Days on Study	696	696	701	701	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	041	071	012	045	001	005	042	052	055	057	061	070	076	095	002	015	025	031	060	066	074	081	097	035	051	054	072	075	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leiomyoma											X																		1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Oral mucosa	+	+						+	+	+		+			+		+	+							+	+	+		21
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth	+	+		+				+	+	+		+		+	+	+	+	+		+	+	+				+	+		34
Peridontal tissue, neurofibrosarcoma																													1
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Aorta, hemangiosarcoma, metastatic, heart																													1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																													1
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant																													1
Pheochromocytoma benign			X												X														2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma					X																								1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Neurofibrosarcoma, metastatic, tooth																													1
Pars distalis, adenoma		X		X	X		X			X	X					X	X	X					X				X	X	18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, C-cell, adenoma																		X										X	2
C-cell, adenoma			X	X			X			X		X			X		X						X	X					14
C-cell, carcinoma																			X	X						X			2
General Body System																													
None																													

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: Vehicle Control

Number of Days on Study	211	399	410	418	437	442	502	507	551	555	555	557	571	590	603	608	613	613	613	621	641	644	656	664	672
Carcass ID Number	078	004	065	044	034	080	011	063	024	022	077	064	014	067	073	003	021	059	091	085	083	033	058	093	032
Genital System																										
Clitoral Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Oviduct	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	M
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal														X											
Polyp stromal, multiple																									
Vagina																									
Schwannoma malignant																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Lymph node		+		+					+																
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, heart						X																			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																									
Carcinoma																X									
Fibroadenoma		X	X	X		X	X			X	X					X			X	X		X			
Fibroadenoma, multiple								X	X					X			X	X					X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, vagina																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, metastatic, tooth												X													

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: Vehicle Control

Numbers of Days on Study	696	696	701	701	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	733	733	733	733	733		
Carcass ID Number	041	071	012	045	001	005	042	052	055	057	061	070	076	095	002	015	025	031	060	066	074	081	097	035	051	054	072	075		Total Tissues/ Tumors
Genital System																														
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Cystadenoma																			X											1
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Polyp stromal		X		X				X										X							X					6
Polyp stromal, multiple									X																					1
Vagina		+																												1
Schwannoma malignant		X																												1
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Lipoma							X																							1
Lymph node																														3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		48
Hemangiosarcoma, metastatic, heart																														1
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Adenoma								X																						1
Adenoma, multiple												X																		1
Carcinoma		X					X			X		X			X					X			X							8
Fibroadenoma				X			X	X		X			X	X						X	X	X	X			X				22
Fibroadenoma, multiple	X		X		X	X						X				X	X	X						X	X			X		19
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Schwannoma malignant, metastatic, vagina		X																												1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Neurofibrosarcoma, metastatic, tooth																														1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: Vehicle Control

Number of Days on Study	211	399	410	418	437	442	502	507	551	555	555	557	571	590	603	608	613	613	613	621	641	644	656	664	672
Carcass ID Number	078	004	065	044	034	080	011	063	024	022	077	064	014	067	073	003	021	059	091	085	083	033	058	093	032
Respiratory System																									
Lung	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Mediastinum, hemangiosarcoma, metastatic, heart						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, metastatic, tooth												X													
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, metastatic, tooth												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymphoma malignant													X												

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: Vehicle Control

Numbers of Days on Study	696	696	701	701	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	733	733	733	733	733		
Carcass ID Number	041	071	012	045	001	005	042	052	055	057	061	070	076	095	002	015	025	031	060	066	074	081	097	035	051	054	072	075		Total Tissues/ Tumors
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		52
Alveolar/bronchiolar adenoma			X																											1
Mediastinum, hemangiosarcoma, metastatic, heart																														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		52
Special Senses System																														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Neurofibrosarcoma, metastatic, tooth																														1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Neurofibrosarcoma, metastatic, tooth																														1
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Leukemia mononuclear												X																		1
Lymphoma malignant												X																		2

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 10 µg/kg

Number of Days on Study	250	250	261	261	310	310	331	352	352	360	393	405	438	479	479	479	502	506	507	527	528	545	557	590	600
Carcass ID Number	116	166	118	185	114	179	177	106	184	131	129	133	180	122	123	186	109	182	119	105	140	178	150	183	155
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oral mucosa						+		+					+		+		+						+		
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+			+							+		+		+						+		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, oral mucosa																									
Pars distalis, adenoma																	X						X		X
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma													X							X					
C-cell, carcinoma																									
General Body System																									
Tissue NOS																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 10 µg/kg

Number of Days on Study	613	616	622	624	624	624	637	647	663	675	696	701	701	731	731	731	731	731	731	731	731	731	731	732	732	733	733	733	733	
Carcass ID Number	104	117	139	107	110	126	108	134	102	149	103	146	176	124	125	127	130	132	147	148	152	153	154	121	135	101	128	138	181	Total Tissues/ Tumors
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Oral mucosa		+						+				+		+		+						+								12
Gingival, squamous cell carcinoma		X												X																2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Tooth		+						+				+		+		+				+		+								13
Cardiovascular System																														
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Schwannoma malignant															X															1
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Pheochromocytoma malignant																											X			1
Pheochromocytoma benign																		X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Parathyroid gland	+	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma, metastatic, oral mucosa		X																												1
Pars distalis, adenoma	X		X		X			X				X	X			X	X	X	X	X	X			X		X		X	X	19
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, C-cell, adenoma						X								X		X							X							4
C-cell, adenoma															X		X	X	X			X					X		X	9
C-cell, carcinoma																									X	X				2
General Body System																														
Tissue NOS																				+										1

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 10 µg/kg

Number of Days on Study	250	250	261	261	310	310	331	352	352	360	393	405	438	479	479	479	502	506	507	527	528	545	557	590	600
Carcass ID Number	116	166	118	185	114	179	177	106	184	131	129	133	180	122	123	186	109	182	119	105	140	178	150	183	155
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct	+	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal																								X	X
Schwannoma malignant																	X								
Cervix, squamous cell carcinoma																									
Vagina			+																						
Fibrosarcoma			X																						
Sarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+										+		+				
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X						X	X												X		X		
Fibroadenoma					X		X			X	X		X	X						X	X	X	X		X
Fibroadenoma, multiple						X													X					X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Fibrosarcoma					X																				
Keratoacanthoma																									
Sarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, oral mucosa																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 10 µg/kg

Number of Days on Study	613	616	622	624	624	624	637	647	663	675	696	701	701	731	731	731	731	731	731	731	731	731	731	732	733	733	733	733	733	
Carcass ID Number	104	117	139	107	110	126	108	134	102	149	103	146	176	124	125	127	130	132	147	148	152	153	154	121	135	101	128	138	181	Total Tissues/ Tumors
Genital System																														
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	51
Carcinoma																														1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Oviduct	M	+	M	M	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	38
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma											X																			1
Polyp stromal	X						X									X	X					X			X				X	9
Schwannoma malignant																														1
Cervix, squamous cell carcinoma										X																				1
Vagina										+																+				3
Fibrosarcoma																										X				2
Sarcoma										X																				1
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Lymph node																														3
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma																X														6
Fibroadenoma			X			X		X							X		X	X	X			X			X			X		21
Fibroadenoma, multiple	X			X					X			X		X		X				X	X		X	X						13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Basal cell carcinoma											X																			1
Fibrosarcoma																														1
Keratoacanthoma																X														1
Sarcoma																														1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma, metastatic, oral mucosa		X																												1

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 10 µg/kg

Number of Days on Study	250	250	261	261	310	310	331	352	352	360	393	405	438	479	479	479	502	506	507	527	528	545	557	590	600
Carcass ID Number	116	166	118	185	114	179	177	106	184	131	129	123	180	122	123	186	109	182	119	105	140	178	150	183	155
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland								X																		
Carcinoma, metastatic, oral mucosa																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, oral mucosa																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stromal nephroma																X										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 10 µg/kg

Number of Days on Study	613	616	622	624	624	624	637	647	663	675	696	701	701	731	731	731	731	731	731	731	731	731	732	732	733	733	733	733		
Carcass ID Number	104	117	139	107	110	126	108	134	102	149	103	146	176	124	125	127	130	132	147	148	152	153	154	121	135	101	128	138	181	Total Tissues/ Tumors
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma, metastatic, mammary gland																														1
Carcinoma, metastatic, oral mucosa		X																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Special Senses System																														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Carcinoma, metastatic, oral mucosa		X																												1
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stromal nephroma																														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 100 µg/kg

Number of Days on Study	418	429	429	443	501	501	514	514	514	522	527	530	530	553	591	636	665	674	674	683	696	700	701	701	701
Carcass ID Number	220	273	278	212	223	261	205	238	267	251	288	211	284	218	230	282	216	219	280	213	253	227	224	287	296
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Oral mucosa	+					+	+		+					+			+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+						+		+			+		+						+	+				
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X														X		X		X		X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X							X							X			X		X		X
C-cell, carcinoma																									
General Body System																									
None																									

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 100 µg/kg

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	733	733	733	733	733	733	733	733	
Carcass ID Number	215	225	263	266	268	269	275	279	285	290	202	203	204	217	221	229	236	262	270	286	201	222	228	254	271	274	277	298	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesentery																+													1
Oral mucosa	+	+	+	+	+	+																+	+			+	+		16
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth	+	+	+		+	+		+							+	+						+	+			+	+		19
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign																	X			X					X		X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																X													1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma			X			X		X	X	X				X				X	X		X		X	X		X	X		19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma			X	X						X					X	X	X	X	X			X		X			X		17
C-cell, carcinoma	X																												1
General Body System																													
None																													

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 100 µg/kg

Number of Days on Study	418	429	429	443	501	501	514	514	514	522	527	530	530	553	591	636	656	674	674	683	696	700	701	701	701
Carcass ID Number	220	273	278	212	223	261	205	238	267	251	288	211	284	218	230	282	216	219	280	213	253	227	224	287	296
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland				X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Granulosa-theca tumor benign																									
Schwannoma malignant																							X		
Oviduct	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Polyp stromal												X													
Squamous cell carcinoma																									
Cervix, carcinoma											X														
Cervix, schwannoma malignant																									X
Vagina						+																			
Squamous cell carcinoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+								+										+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X		X					X		X							X					
Fibroadenoma	X	X	X		X		X		X			X					X			X	X			X	
Fibroadenoma, multiple								X								X							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X										
Fibrous histiocytoma																	X								
Lipoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 100 µg/kg

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	733	733	733	733	733	733	733	733	
Carcass ID Number	215	225	263	266	268	269	275	279	285	290	202	203	204	217	221	229	236	262	270	286	201	222	228	254	271	274	277	298	Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, mammary gland																													1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa cell tumor benign																					X								1
Granulosa-theca tumor benign																		X											1
Schwannoma malignant																													1
Oviduct	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	44
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																													1
Polyp stromal	X														X												X		4
Squamous cell carcinoma												X													X				2
Cervix, carcinoma																													1
Cervix, schwannoma malignant																													1
Vagina								+																					2
Squamous cell carcinoma								X																					1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node																													3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	52
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma			X																										1
Carcinoma									X									X											7
Fibroadenoma	X			X				X	X				X		X		X			X		X	X		X				22
Fibroadenoma, multiple			X		X		X			X	X					X		X	X		X			X		X			14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroma																									X				2
Fibrous histiocytoma																													1
Lipoma																			X										1
Subcutaneous tissue, sarcoma																									X				1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 100 µg/kg

Number of Days on Study	418	429	429	443	501	501	514	514	514	522	527	530	530	553	591	636	656	674	674	683	696	700	701	701	701
Carcass ID Number	220	273	278	212	223	261	205	238	267	251	288	211	284	218	230	282	216	219	280	213	253	227	224	287	296
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X			
Ureter											+														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 100 µg/kg

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733		
Carcass ID Number	215	225	263	266	268	269	275	279	285	290	202	203	204	217	221	229	236	262	270	286	201	222	228	254	271	274	277	298		Total Tissues/ Tumors
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Fibrous histiocytoma, metastatic, skin																														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Special Senses System																														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Renal tubule, adenoma																														1
Ureter																														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		53

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 300 µg/kg

Number of Days on Study	059	022	263	269	322	360	443	452	457	486	507	526	528	530	555	556	568	610	613	621	624	647	647	656	675
Carcass ID Number	349	377	371	397	359	323	315	392	358	333	342	395	332	312	301	307	306	302	309	329	298	373	379	374	334
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Oral mucosa													+												+
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Tooth		+					+						+		+					+	+				+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X					X						X	X		X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X	X											
C-cell, adenoma, multiple																									
C-cell, carcinoma																						X			
General Body System																									
Tissue NOS																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 300 µg/kg

Number of Days on Study	675	675	691	691	693	703	703	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733
Carcass ID Number	341	384	313	376	381	346	350	304	324	325	330	343	344	372	378	380	391	396	311	321	331	345	360	385	303	328	393	394	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Oral mucosa					+		+		+	+	+	+				+					+		+				+		12
Gingival, squamous cell carcinoma										X																			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Tooth		+	+		+	+	+	+	+		+	+				+	+			+	+		+				+		22
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Schwannoma malignant																	X												1
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma			X																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign												X						X		X	X								4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M				47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma				X		X	X				X	X	X			X	X		X	X				X		X			19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma	X	X		X					X	X	X						X		X								X		11
C-cell, adenoma, multiple															X														1
C-cell, carcinoma																													1
General Body System																													
Tissue NOS									+																				1

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 300 µg/kg

Number of Days on Study	059	022	263	269	322	360	443	452	457	486	507	526	528	530	555	555	568	610	613	621	624	647	647	656	675
Carcass ID Number	349	377	371	397	359	323	315	392	358	333	342	395	332	312	301	307	306	302	309	329	398	373	379	374	334
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Oviduct	+	+	M	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M		+	M	+	M
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Polyp stromal																						X	X		
Schwannoma malignant																						X			
Vagina																						+			
Squamous cell carcinoma																						X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X	
Lymph node																								+	
Mediastinal, histiocytic sarcoma																								X	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma			X														X								
Carcinoma, multiple																									
Fibroadenoma				X		X		X	X					X	X	X	X	X	X	X					X
Fibroadenoma, multiple											X		X								X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Histiocytic sarcoma																							X		
Keratoacanthoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 300 µg/kg

Number of Days on Study	675	675	691	691	693	703	703	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733
Carcass ID Number	341	384	313	376	381	346	350	304	324	325	330	343	344	372	378	380	391	396	311	321	331	345	360	385	303	328	393	394	Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa cell tumor malignant			X																										1
Oviduct	+	+	+	+	+	+	+	+	M	M	M	M	+	M	+	+	+	+	+	M	+	M	+	+	M	M	+	+	35
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leiomyosarcoma								X	X																		X		3
Polyp stromal				X					X										X					X					6
Schwannoma malignant																													1
Vagina																													1
Squamous cell carcinoma																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Lymph node	+																												2
Mediastinal, histiocytic sarcoma																													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma													X																1
Carcinoma							X						X																4
Carcinoma, multiple						X																							1
Fibroadenoma			X		X		X	X						X		X				X	X			X		X			22
Fibroadenoma, multiple	X	X		X						X	X				X		X					X	X				X		13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroma			X																										1
Histiocytic sarcoma																													1
Keratoacanthoma																	X												1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant								X																					1

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 300 µg/kg

Number of Days on Study	059	022	263	269	322	360	443	452	457	486	507	526	228	230	255	255	568	610	613	621	624	647	644	656	675
Carcass ID Number	349	377	371	397	359	323	315	392	358	333	342	395	332	312	301	307	306	302	309	329	298	373	379	374	334
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Nephroblastoma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 300 µg/kg

Number of Days on Study	675	675	691	691	693	703	703	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	341	384	313	376	381	346	350	304	324	325	330	343	344	372	378	380	391	396	311	321	331	345	360	385	303	328	393	394	Total Tissues/ Tumors
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Nephroblastoma																													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 1,000 µg/kg

Number of Days on Study	341	360	383	452	467	479	497	502	510	514	529	541	555	579	590	613	617	621	621	625	636	639	647	447	649
Carcass ID Number	479	426	497	427	491	444	434	489	449	416	470	453	442	498	420	409	435	422	424	487	493	417	410	432	423
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																									
Cholangioma																									
Mesentery																									
Carcinoma, metastatic, uterus																									
Oral mucosa			+	+				+									+		+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+	+			+	+			+	+	+				+		+				+		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma														X											
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X		X	X		X	X	X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma													X												
C-cell, adenoma																X				X		X			
C-cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 1,000 µg/kg

Number of Days on Study	675	696	696	702	706	715	715	729	731	731	731	731	731	731	731	731	731	732	732	732	733	733	733	733	733	733	733		
Carcass ID Number	481	431	452	421	454	419	451	467	428	429	430	448	466	468	478	480	483	485	406	484	488	425	441	446	447	455	469	490	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, uterus								X																					1
Cholangioma				X							X																		2
Mesentery								+																					1
Carcinoma, metastatic, uterus								X																					1
Oral mucosa			+				+	+	+				+				+	+	+	+						+	+		16
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth	+		+				+		+	+		+	+				+	+	+	+						+	+		23
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Schwannoma malignant											X																		1
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign											X																X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	46
Adenoma										X																			2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma				X	X	X	X	X	X		X	X	X					X	X	X		X		X	X	X	X		24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Bilateral, C-cell, adenoma																X			X		X	X							5
C-cell, adenoma	X				X	X				X	X	X			X		X	X		X				X	X	X		X	17
C-cell, carcinoma													X					X											2
General Body System																													
None																													

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 1,000 µg/kg

Number of Days on Study	341	360	383	452	467	479	497	502	510	514	529	541	555	579	590	613	617	621	622	625	636	639	647	647	649
Carcass ID Number	479	426	497	427	491	444	434	489	449	416	470	453	452	498	420	409	435	422	424	487	493	417	410	432	423
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct	+	+	M	+	M	+	+	+	M	+	+		+	+	+	+	+	M	+	M	+	+	+	+	M
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal					X																	X			
Vagina									+																
Fibrous histiocytoma, metastatic, skin									X																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+						+																		
Deep cervical, carcinoma, metastatic, thyroid gland																									
Mediastinal, carcinoma, metastatic, uterus																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X	X																				
Fibroadenoma	X	X		X		X		X		X	X			X	X	X			X		X			X	
Fibroadenoma, multiple												X	X					X				X	X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma															X										
Fibroma																									
Fibrosarcoma																									
Fibrous histiocytoma									X																
Squamous cell papilloma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 1,000 µg/kg

Number of Days on Study	675	696	696	702	706	715	715	729	731	731	731	731	731	731	731	731	731	732	732	732	733	733	733	733	733	733	733		
Carcass ID Number	481	431	452	421	454	419	451	467	428	429	430	448	466	468	478	480	483	485	406	484	488	425	441	446	447	455	469	490	Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Oviduct	+	M	+	+		+	+	M	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	39
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma								X																					1
Polyp stromal																	X												3
Vagina																													1
Fibrous histiocytoma, metastatic, skin																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node								+										+								+			5
Deep cervical, carcinoma, metastatic, thyroid gland																		X											1
Mediastinal, carcinoma, metastatic, uterus								X																					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, uterus								X																					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma									X		X				X														3
Carcinoma											X				X	X				X									6
Fibroadenoma		X		X				X			X		X	X		X	X	X		X		X		X	X			X	27
Fibroadenoma, multiple	X		X			X	X			X																X			12
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Basal cell adenoma																													1
Fibroma																													1
Fibrosarcoma																	X												1
Fibrous histiocytoma						X																							1
Squamous cell papilloma																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 1,000 µg/kg

Number of Days on Study	341	360	383	452	467	479	497	502	510	514	529	541	555	579	590	613	617	621	621	625	636	639	647	647	649
Carcass ID Number	479	426	497	427	491	444	434	489	449	416	470	453	442	498	420	409	435	422	424	487	493	417	410	432	423
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Carcinoma, metastatic, mammary gland					X																					
Carcinoma, metastatic, uterus																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X					X													

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 1,000 µg/kg

Number of Days on Study	675	696	696	702	706	715	715	729	731	731	731	731	731	731	731	731	731	732	732	732	733	733	733	733	733	733	733		
Carcass ID Number	481	431	452	421	454	419	451	467	428	429	430	448	466	468	478	480	483	485	406	484	488	425	441	446	447	455	469	490	Total Tissues/ Tumors
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma																				X						X			2
Carcinoma, metastatic, mammary gland																													1
Carcinoma, metastatic, uterus								X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymphoma malignant							X																						3

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg

Number of Days on Study	079	360	387	387	393	432	438	442	443	452	479	486	501	505	509	514	514	548	557	583	586	591	612	613	621
Carcass ID Number	511	532	531	534	503	525	522	603	505	502	529	506	543	537	509	612	614	507	510	530	508	527	523	611	536
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Oral mucosa		+			+			+			+	+			+	+		+	+		+			+	+
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth		+						+	+		+	+	+		+	+	+	+	+	+	+	+		+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																							X		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X				
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X									X				
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, adenoma, multiple																									
General Body System																									
None																									

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg

Number of Days on Study	641	668	672	675	723	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	733	733	733	733	733	733	733
Carcass ID Number	604	542	620	615	544	504	524	528	538	540	602	605	617	618	619	521	533	535	539	616	501	526	541	545	601	613	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma											X																1
Oral mucosa			+			+	+	+	+	+	+	+				+	+			+		+	+				25
Gingival, squamous cell carcinoma																X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth		+	+			+	+	+	+	+	+	+	+			+	+	+		+	+	+	+	+		+	35
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Schwannoma malignant																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign									X																		2
Bilateral, pheochromocytoma benign				X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X	X	X						X					X		X	X	X					11
Pars distalis, carcinoma			X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma						X									X		X	X						X		X	6
C-cell, adenoma, multiple		X																									1
General Body System																											
None																											

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg

Number of Days on Study	079	360	387	387	393	432	438	442	443	452	479	486	501	505	509	514	514	548	557	583	586	591	612	613	621
Carcass ID Number	511	532	531	534	503	525	522	603	505	502	529	506	543	537	509	612	614	507	510	530	508	527	523	611	536
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Uterus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Cervix, schwannoma malignant, metastatic, vagina															X										
Vagina								+							+										
Schwannoma malignant								X							X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+									+		+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma	X																						X		
Fibroadenoma		X	X			X	X			X	X	X					X	X	X			X	X		
Fibroadenoma, multiple				X									X			X								X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma									X																
Schwannoma malignant																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg

Number of Days on Study	641	668	672	675	723	731	731	731	731	731	731	731	731	731	731	732	732	732	732	733	733	733	733	733	733	733	
Carcass ID Number	604	542	620	615	544	504	524	528	538	540	602	605	617	618	619	521	533	535	539	616	501	526	541	545	601	613	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oviduct	+		+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	45
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																	X									X	2
Cervix, schwannoma malignant, metastatic, vagina																											1
Vagina																			+								3
Schwannoma malignant																			X								3
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node						+													+				+				6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma						X																					2
Carcinoma																											2
Fibroadenoma											X	X		X	X		X	X	X		X	X	X	X	X		24
Fibroadenoma, multiple	X				X																					X	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell carcinoma																											1
Schwannoma malignant																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, pituitary gland			X																								1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg

Number of Days on Study	079	360	387	387	393	432	438	442	443	452	479	486	501	505	509	514	514	548	557	583	586	591	612	613	621
Carcass ID Number	511	532	531	534	503	525	522	603	505	502	529	506	543	537	509	612	614	507	510	530	508	527	523	611	536
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin									X																
Carcinoma, metastatic, mammary gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Stromal nephroma					X																				
Bilateral, renal tubule, carcinoma																				X					
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg

Number of Days on Study	641	668	672	675	723	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	604	542	620	615	544	504	524	528	538	540	602	605	617	618	619	521	533	535	539	616	501	526	541	545	601	613	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell carcinoma, metastatic, skin																											1
Carcinoma, metastatic, mammary gland														X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, mammary gland														X													1
Stromal nephroma																											1
Bilateral, renal tubule, carcinoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg (Stop-Exposure)

Number of Days on Study	183	191	245	360	400	437	452	467	514	528	575	590	591	591	611	624	627	637	639	656	668	669	670	671	691
Carcass ID Number	599	578	552	559	585	563	576	579	558	565	573	557	554	561	582	600	567	595	596	574	580	588	591	566	569
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangioma																									
Cholangioma, multiple																									
Oral mucosa				+			+							+			+							+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+	+	+	+			+			+	+		+	+	+					+		+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																			X						
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X		X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																				X					
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X									X	X	X		X				X	
Pars distalis, carcinoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
C-cell, adenoma						X						X									X	X	X		
C-cell, carcinoma																						X			X
Follicular cell, adenoma																									
General Body System																									
None																									

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg (Stop-Exposure)

Number of Days on Study	701	701	722	728	730	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	572	594	562	590	568	553	555	560	570	581	584	586	587	597	598	551	575	577	589	593	556	564	571	583	592	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma														X												1
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangioma																X										1
Cholangioma, multiple														X												1
Oral mucosa			+	+			+		+	+						+	+						+		+	15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma								X																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+		+	+	+		+		+	+	+	+				+	+			+			+	+	+	27
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X			X									X	X												6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Carcinoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma													X													1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X		X	X		X		X	X	X	X		X			X	X	X	X	X	X		23
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma			X		X		X			X		X	X	X	X	X	X				X			X	X	18
C-cell, carcinoma														X												3
Follicular cell, adenoma						X																	X			2
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg (Stop-Exposure)

Number of Days on Study	183	191	245	360	400	437	452	467	514	528	575	590	591	591	611	624	627	637	639	656	668	669	670	671	691
Carcass ID Number	599	578	552	559	585	563	576	579	558	565	573	575	554	561	582	600	567	595	596	574	580	588	591	566	569
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa-theca tumor benign																									
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal																X	X								
Cervix, schwannoma malignant																					X				
Vagina																								+	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X												X		X								X
Fibroadenoma				X				X	X	X		X						X	X		X	X			
Fibroadenoma, multiple													X	X						X			X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Fibroma							X																		
Fibrosarcoma	X														X										
Fibrous histiocytoma																			X						
Schwannoma malignant					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin					X																				

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg (Stop-Exposure)

Number of Days on Study	701	701	722	728	730	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	572	594	562	590	568	553	555	560	570	581	584	586	587	597	598	551	575	577	589	593	556	564	571	583	592	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma									X																	1
Granulosa-theca tumor benign								X																		1
Oviduct	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Uterus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma		X																								1
Polyp stromal			X						X																	4
Cervix, schwannoma malignant																										1
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X		X						X		X					X							X		10
Fibroadenoma					X	X	X						X		X				X				X			16
Fibroadenoma, multiple	X	X	X					X	X			X								X	X					14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma							X																			1
Fibroma											X															2
Fibrosarcoma					X											X										4
Fibrous histiocytoma																										1
Schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg (Stop-Exposure)

Number of Days on Study	183	191	245	360	400	437	452	467	514	528	575	590	591	591	611	624	627	637	639	656	668	669	670	671	691
Carcass ID Number	599	578	552	559	585	563	576	579	558	565	573	557	554	561	582	600	567	595	596	574	580	588	591	566	569
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland											X														
Meninges, sarcoma						X																			
Meninges, schwannoma malignant, metastatic, skin					X																				
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland			X																						
Fibrous histiocytoma, metastatic, skin																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Optic nerve, schwannoma malignant, metastatic, skin					X																				
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																			X						
Stromal nephroma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 153: 3,000 µg/kg (Stop-Exposure)

Number of Days on Study	701	701	722	728	730	731	731	731	731	731	731	731	731	731	731	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	572	594	562	590	568	553	555	560	570	581	584	586	587	597	598	551	575	577	589	593	556	564	571	583	592	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Meninges, sarcoma																										1
Meninges, schwannoma malignant, metastatic, skin																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Fibrous histiocytoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma, metastatic, skin							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Optic nerve, schwannoma malignant, metastatic, skin																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Stromal nephroma																										1
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
Adrenal Medulla: Benign Pheochromocytoma						
Overall rate[a]	2/53 (4%)	1/54 (2%)	4/53 (8%)	4/53 (8%)	2/53 (4%)	3/51 (6%)
Adjusted rate[b]	5.1%	3.2%	9.7%	11.0%	5.2%	8.9%
Terminal rate[c]	1/24 (4%)	1/16 (6%)	4/28 (14%)	4/21 (19%)	2/20 (10%)	1/21 (5%)
First incidence (days)	701	731 (T)	731 (T)	731 (T)	731 (T)	586
Poly-3 test[d]	P=0.486	P=0.580N	P=0.359	P=0.301	P=0.688	P=0.433
Adrenal Medulla: Benign or Malignant Pheochromocytoma						
Overall rate	3/53 (6%)	2/54 (4%)	4/53 (8%)	4/53 (8%)	2/53 (4%)	3/51 (6%)
Adjusted rate	7.6%	6.5%	9.7%	11.0%	5.2%	8.9%
Terminal rate	1/24 (4%)	2/16 (13%)	4/28 (14%)	4/21 (19%)	2/20 (10%)	1/21 (5%)
First incidence (days)	608	731 (T)	731 (T)	731 (T)	731 (T)	586
Poly-3 test	P=0.572N	P=0.609N	P=0.521	P=0.453	P=0.514N	P=0.589
Mammary Gland: Fibroadenoma						
Overall rate	41/53 (77%)	34/54 (63%)	36/53 (68%)	35/53 (66%)	39/53 (74%)	32/51 (63%)
Adjusted rate	83.2%	78.7%	75.1%	76.0%	79.3%	71.7%
Terminal rate	19/24 (79%)	13/16 (81%)	22/28 (79%)	14/21 (67%)	13/20 (65%)	13/21 (62%)
First incidence (days)	399	310	418	269	341	360
Poly-3 test	P=0.190N	P=0.377N	P=0.214N	P=0.255N	P=0.399N	P=0.123N
Mammary Gland: Adenoma						
Overall rate	2/53 (4%)	0/54 (0%)	1/53 (2%)	1/53 (2%)	3/53 (6%)	2/51 (4%)
Adjusted rate	5.1%	0.0%	2.4%	2.8%	7.8%	6.0%
Terminal rate	2/24 (8%)	0/16 (0%)	1/28 (4%)	1/21 (5%)	3/20 (15%)	1/21 (5%)
First incidence (days)	731 (T)	—[e]	731 (T)	731 (T)	731 (T)	612
Poly-3 test	P=0.255	P=0.291N	P=0.482N	P=0.525N	P=0.492	P=0.639
Mammary Gland: Fibroadenoma or Adenoma						
Overall rate	41/53 (77%)	34/54 (63%)	36/53 (68%)	36/53 (68%)	41/53 (77%)	33/51 (65%)
Adjusted rate	83.2%	78.7%	75.1%	78.2%	83.4%	74.0%
Terminal rate	19/24 (79%)	13/16 (81%)	22/28 (79%)	15/21 (71%)	15/20 (75%)	14/21 (67%)
First incidence (days)	399	310	418	269	341	360
Poly-3 test	P=0.294N	P=0.377N	P=0.214N	P=0.349N	P=0.607	P=0.184N
Mammary Gland: Carcinoma						
Overall rate	8/53 (15%)	6/54 (11%)	7/53 (13%)	5/53 (9%)	6/53 (11%)	2/51 (4%)
Adjusted rate	20.2%	17.2%	15.9%	13.1%	15.1%	5.8%
Terminal rate	6/24 (25%)	1/16 (6%)	2/28 (7%)	1/21 (5%)	4/20 (20%)	0/21 (0%)
First incidence (days)	608	250	443	263	452	79
Poly-3 test	P=0.072N	P=0.485N	P=0.410N	P=0.297N	P=0.378N	P=0.068N
Mammary Gland: Adenoma or Carcinoma						
Overall rate	9/53 (17%)	6/54 (11%)	8/53 (15%)	5/53 (9%)	7/53 (13%)	3/51 (6%)
Adjusted rate	22.8%	17.2%	18.2%	13.1%	17.6%	8.7%
Terminal rate	7/24 (29%)	1/16 (6%)	3/28 (11%)	1/21 (5%)	5/20 (25%)	1/21 (5%)
First incidence (days)	608	250	443	263	452	79
Poly-3 test	P=0.118N	P=0.378N	P=0.403N	P=0.208N	P=0.383N	P=0.090N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma						
Overall rate	43/53 (81%)	37/54 (69%)	40/53 (75%)	38/53 (72%)	42/53 (79%)	34/51 (67%)
Adjusted rate	87.1%	80.6%	79.0%	80.7%	84.1%	74.5%
Terminal rate	20/24 (83%)	13/16 (81%)	22/28 (79%)	15/21 (71%)	15/20 (75%)	14/21 (67%)
First incidence (days)	399	250	418	263	341	79
Poly-3 test	P=0.158N	P=0.260N	P=0.195N	P=0.268N	P=0.445N	P=0.081N

Table A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
Pituitary Gland (Pars Distalis): Adenoma						
Overall rate	18/53 (34%)	19/54 (35%)	19/53 (36%)	19/53 (36%)	24/53 (45%)	11/50 (22%)
Adjusted rate	43.1%	55.2%	44.3%	47.6%	57.9%	32.0%
Terminal rate	10/24 (42%)	10/16 (63%)	13/28 (46%)	9/21 (43%)	12/20 (60%)	7/21 (33%)
First incidence (days)	211	502	429	443	579	486
Poly-3 test	P=0.120N	P=0.195	P=0.545	P=0.425	P=0.116	P=0.218N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma						
Overall rate	18/53 (34%)	19/54 (35%)	19/53 (36%)	19/53 (36%)	24/53 (45%)	12/50 (24%)
Adjusted rate	43.1%	55.2%	44.3%	47.6%	57.9%	34.7%
Terminal rate	10/24 (42%)	10/16 (63%)	13/28 (46%)	9/21 (43%)	12/20 (60%)	7/21 (33%)
First incidence (days)	211	502	429	443	579	486
Poly-3 test	P=0.182N	P=0.195	P=0.545	P=0.425	P=0.116	P=0.298N
Skin: Fibroma, Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma						
Overall rate	0/53 (0%)	2/54 (4%)	3/53 (6%)	1/53 (2%)	3/53 (6%)	0/51 (0%)
Adjusted rate	0.0%	6.1%	7.2%	2.7%	7.7%	0.0%
Terminal rate	0/24 (0%)	0/16 (0%)	1/28 (4%)	0/21 (0%)	1/20 (5%)	0/21 (0%)
First incidence (days)	—	261	591	691	510	—[f]
Poly-3 test	P=0.312N	P=0.201	P=0.131	P=0.487	P=0.118	—
Thyroid Gland (C-Cell): Adenoma						
Overall rate	16/51 (31%)	13/52 (25%)	17/53 (32%)	12/53 (23%)	22/53 (42%)	7/51 (14%)
Adjusted rate	40.0%	40.5%	39.4%	31.5%	54.5%	21.0%
Terminal rate	10/24 (42%)	10/16 (63%)	11/28 (39%)	7/21 (33%)	15/20 (75%)	6/21 (29%)
First incidence (days)	555	438	443	528	555	668
Poly-3 test	P=0.090N	P=0.581	P=0.569N	P=0.285N	P=0.129	P=0.062N
Thyroid Gland (C-Cell): Adenoma or Carcinoma						
Overall rate	18/51 (35%)	15/52 (29%)	18/53 (34%)	13/53 (25%)	23/53 (43%)	7/51 (14%)
Adjusted rate	45.0%	46.8%	41.8%	33.8%	57.0%	21.0%
Terminal rate	12/24 (50%)	12/16 (75%)	12/28 (43%)	7/21 (33%)	16/20 (80%)	6/21 (29%)
First incidence (days)	555	438	443	528	555	668
Poly-3 test	P=0.038N	P=0.538	P=0.468N	P=0.209N	P=0.185	P=0.023N
Uterus: Leiomyosarcoma						
Overall rate	0/53 (0%)	0/54 (0%)	0/53 (0%)	3/53 (6%)	0/53 (0%)	0/51 (0%)
Adjusted rate	0.0%	0.0%	0.0%	8.3%	0.0%	0.0%
Terminal rate	0/24 (0%)	0/16 (0%)	0/28 (0%)	3/21 (14%)	0/20 (0%)	0/21 (0%)
First incidence (days)	—	—	—	731 (T)	—	—
Poly-3 test	P=0.454N	—	—	P=0.105	—	—
Uterus: Stromal Polyp						
Overall rate	7/53 (13%)	9/54 (17%)	4/53 (8%)	6/53 (11%)	3/53 (6%)	2/51 (4%)
Adjusted rate	17.6%	27.5%	9.6%	16.2%	7.6%	6.0%
Terminal rate	4/24 (17%)	5/16 (31%)	3/28 (11%)	3/21 (14%)	1/20 (5%)	2/21 (10%)
First incidence (days)	590	590	530	647	467	731 (T)
Poly-3 test	P=0.051N	P=0.232	P=0.230N	P=0.554N	P=0.156N	P=0.126N
Vagina: Malignant Schwannoma						
Overall rate	1/53 (2%)	0/54 (0%)	0/53 (0%)	0/53 (0%)	0/53 (0%)	3/51 (6%)
Adjusted rate	2.6%	0.0%	0.0%	0.0%	0.0%	8.7%
Terminal rate	0/24 (0%)	0/16 (0%)	0/28 (0%)	0/21 (0%)	0/20 (0%)	1/21 (5%)
First incidence (days)	696	—	—	—	—	442
Poly-3 test	P=0.007	P=0.546N	P=0.490N	P=0.515N	P=0.504N	P=0.260

Table A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
All Organs: Malignant Lymphoma						
Overall rate	2/53 (4%)	0/54 (0%)	0/53 (0%)	0/53 (0%)	3/53 (6%)	0/51 (0%)
Adjusted rate	5.1%	0.0%	0.0%	0.0%	7.6%	0.0%
Terminal rate	1/24 (4%)	0/16 (0%)	0/28 (0%)	0/21 (0%)	0/20 (0%)	0/21 (0%)
First incidence (days)	571	—	—	—	497	—
Poly-3 test	P=0.591N	P=0.295N	P=0.228N	P=0.256N	P=0.502	P=0.278N
All Organs: Benign Neoplasms						
Overall rate	50/53 (94%)	41/54 (76%)	45/53 (85%)	46/53 (87%)	49/53 (92%)	40/51 (78%)
Adjusted rate	97.8%	91.7%	89.5%	94.9%	96.5%	87.8%
Terminal rate	24/24 (100%)	16/16 (100%)	25/28 (89%)	19/21 (91%)	19/20 (95%)	18/21 (86%)
First incidence (days)	211	310	418	269	341	360
Poly-3 test	P=0.118N	P=0.114N	P=0.063N	P=0.396N	P=0.598N	P=0.034N
All Organs: Malignant Neoplasms						
Overall rate	12/53 (23%)	20/54 (37%)	16/53 (30%)	14/53 (26%)	14/53 (26%)	12/51 (24%)
Adjusted rate	29.0%	49.2%	35.8%	35.2%	33.4%	30.9%
Terminal rate	7/24 (29%)	6/16 (38%)	7/28 (25%)	6/21 (29%)	6/20 (30%)	3/21 (14%)
First incidence (days)	442	250	443	222	452	79
Poly-3 test	P=0.248N	P=0.042	P=0.327	P=0.356	P=0.419	P=0.523
All Organs: Benign or Malignant Neoplasms						
Overall rate	52/53 (98%)	51/54 (94%)	49/53 (92%)	48/53 (91%)	51/53 (96%)	48/51 (94%)
Adjusted rate	99.6%	99.0%	94.6%	95.3%	97.8%	95.4%
Terminal rate	24/24 (100%)	16/16 (100%)	26/28 (93%)	19/21 (91%)	19/20 (95%)	19/21 (91%)
First incidence (days)	211	250	418	222	341	79
Poly-3 test	P=0.327N	P=0.936N	P=0.146N	P=0.201N	P=0.527N	P=0.211N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal medulla, 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 vehicle control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 153

	Vehicle Control	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate[a]	2/53 (4%)	3/51 (6%)	6/50 (12%)
Adjusted rate[b]	5.1%	8.9%	16.0%
Terminal rate[c]	1/24 (4%)	1/21 (5%)	2/20 (10%)
First incidence (days)	701	586	591
Poly-3 test[d]		P=0.433	P=0.117
Poly-3 test[e]			P=0.297
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rate	3/53 (6%)	3/51 (6%)	6/50 (12%)
Adjusted rate	7.6%	8.9%	16.0%
Terminal rate	1/24 (4%)	1/21 (5%)	2/20 (10%)
First incidence (days)	608	586	591
Poly-3 test		P=0.589	P=0.214
Poly-3 test			P=0.297
Mammary Gland: Fibroadenoma			
Overall rate	41/53 (77%)	32/51 (63%)	30/50 (60%)
Adjusted rate	83.2%	71.7%	69.8%
Terminal rate	19/24 (79%)	13/21 (62%)	11/20 (55%)
First incidence (days)	399	360	360
Poly-3 test		P=0.123N	P=0.091N
Poly-3 test			P=0.513N
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	41/53 (77%)	33/51 (65%)	30/50 (60%)
Adjusted rate	83.2%	74.0%	69.8%
Terminal rate	19/24 (79%)	14/21 (67%)	11/20 (55%)
First incidence (days)	399	360	360
Poly-3 test		P=0.184N	P=0.091N
Poly-3 test			P=0.416N
Mammary Gland: Carcinoma			
Overall rate	8/53 (15%)	2/51 (4%)	10/50 (20%)
Adjusted rate	20.2%	5.8%	26.0%
Terminal rate	6/24 (25%)	0/21 (0%)	4/20 (20%)
First incidence (days)	608	79	245
Poly-3 test		P=0.068N	P=0.367
Poly-3 test			P=0.020
Mammary Gland: Adenoma or Carcinoma			
Overall rate	9/53 (17%)	3/51 (6%)	10/50 (20%)
Adjusted rate	22.8%	8.7%	26.0%
Terminal rate	7/24 (29%)	1/21 (5%)	4/20 (20%)
First incidence (days)	608	79	245
Poly-3 test		P=0.090N	P=0.472
Poly-3 test			P=0.051
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	43/53 (81%)	34/51 (67%)	37/50 (74%)
Adjusted rate	87.1%	74.5%	82.7%
Terminal rate	20/24 (83%)	14/21 (67%)	14/20 (70%)
First incidence (days)	399	79	245
Poly-3 test		P=0.081N	P=0.378N
Poly-3 test			P=0.233

Table A3b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 153

	Vehicle Control	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	18/53 (34%)	11/50 (22%)	23/50 (46%)
Adjusted rate	43.1%	32.0%	58.0%
Terminal rate	10/24 (42%)	7/21 (33%)	14/20 (70%)
First incidence (days)	211	486	437
Poly-3 test		P=0.218N	P=0.120
Poly-3 test			P=0.017
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	18/53 (34%)	12/50 (24%)	24/50 (48%)
Adjusted rate	43.1%	34.7%	59.8%
Terminal rate	10/24 (42%)	7/21 (33%)	14/20 (70%)
First incidence (days)	211	486	437
Poly-3 test		P=0.298N	P=0.088
Poly-3 test			P=0.021
Skin: Fibrosarcoma			
Overall rate	0/53 (0%)	0/51 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	10.6%
Terminal rate	0/24 (0%)	0/21 (0%)	1/20 (5%)
First incidence (days)	—[f]	—	183
Poly-3 test		—[g]	P=0.056
Poly-3 test			P=0.083
Skin: Fibroma, Fibrous Histiocytoma or Fibrosarcoma			
Overall rate	0/53 (0%)	0/51 (0%)	7/50 (14%)
Adjusted rate	0.0%	0.0%	18.0%
Terminal rate	0/24 (0%)	0/21 (0%)	2/20 (10%)
First incidence (days)	—	—	183
Poly-3 test		—	P=0.007
Poly-3 test			P=0.014
Thyroid Gland (C-Cell): Adenoma			
Overall rate	16/51 (31%)	7/51 (14%)	18/49 (37%)
Adjusted rate	40.0%	21.0%	47.7%
Terminal rate	10/24 (42%)	6/21 (29%)	11/20 (55%)
First incidence (days)	555	668	437
Poly-3 test		P=0.062N	P=0.323
Poly-3 test			P=0.014
Thyroid Gland (C-Cell): Carcinoma			
Overall rate	2/51 (4%)	0/51 (0%)	3/49 (6%)
Adjusted rate	5.3%	0.0%	8.3%
Terminal rate	2/24 (8%)	0/21 (0%)	1/20 (5%)
First incidence (days)	731 (T)	—	669
Poly-3 test		P=0.269N	P=0.480
Poly-3 test			P=0.140
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rate	18/51 (35%)	7/51 (14%)	19/49 (39%)
Adjusted rate	45.0%	21.0%	50.1%
Terminal rate	12/24 (50%)	6/21 (29%)	11/20 (55%)
First incidence (days)	555	668	437
Poly-3 test		P=0.023N	P=0.410
Poly-3 test			P=0.008

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 153

	Vehicle Control	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Uterus: Stromal Polyp			
Overall rate	7/53 (13%)	2/51 (4%)	4/50 (8%)
Adjusted rate	17.6%	6.0%	10.8%
Terminal rate	4/24 (17%)	2/21 (10%)	1/20 (5%)
First incidence (days)	590	731 (T)	624
Poly-3 test		P=0.126N	P=0.301N
Poly-3 test			P=0.401
All Organs: Benign Neoplasms			
Overall rate	50/53 (94%)	40/51 (78%)	44/50 (88%)
Adjusted rate	97.8%	87.8%	96.2%
Terminal rate	24/24 (100%)	18/21 (86%)	19/20 (95%)
First incidence (days)	211	360	360
Poly-3 test		P=0.034N	P=0.593N
Poly-3 test			P=0.105
All Organs: Malignant Neoplasms			
Overall rate	12/53 (23%)	12/51 (24%)	23/50 (46%)
Adjusted rate	29.0%	30.9%	52.8%
Terminal rate	7/24 (29%)	3/21 (14%)	7/20 (35%)
First incidence (days)	442	79	183
Poly-3 test		P=0.523	P=0.018
Poly-3 test			P=0.033
All Organs: Benign or Malignant Neoplasms			
Overall rate	52/53 (98%)	48/51 (94%)	49/50 (98%)
Adjusted rate	99.6%	95.4%	98.0%
Terminal rate	24/24 (100%)	19/21 (91%)	19/20 (95%)
First incidence (days)	211	79	183
Poly-3 test		P=0.211N	P=0.581N
Poly-3 test			P=0.427

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal medulla, 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 dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group.
[e] The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A lower incidence in a dosed group is indicated by **N**.
[f] Pairwise comparison between the 3,000 µg/kg core and stop-exposure groups. A lower incidence in the stop-exposure group is indicated by **N**.
[g] Not applicable; no neoplasms in animal group
Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Liver Neoplasms in Vehicle Control Female Sprague-Dawley Rats[a]

Study	Incidence in Controls	
	Cholangioma	Hepatocellular Adenoma
Historical Incidence		
PCB 126	0/53	1/53
TCDD	0/53	0/53
PeCDF	0/53	1/53
TEF Mixture	0/53	0/53
PCB 153	0/53	0/53
PCB 126/PCB 153 Binary Mixture	0/53	0/53
PCB 126/PCB 118 Mixture	0/53	2/53
Overall Historical Incidence		
Total (%)	0/371	4/371 (1.1%)
Mean ± standard deviation		1.1% ± 1.5%
Range		0%-4%

[a] Data as of May 5, 2004

TABLE A4b
Historical Incidence of Thyroid Gland Neoplasms in Vehicle Control Female Sprague-Dawley Rats[a]

Study	Incidence in Controls			
	Follicular Cell Adenoma	C-Cell Adenoma	C-Cell Carcinoma	C-Cell Adenoma or Carcinoma
Historical Incidence				
PCB 126	0/52	15/52	0/52	15/52
TCDD	1/52	20/52	1/52	21/52
PeCDF	0/53	13/53	2/53	15/53
TEF Mixture	0/53	17/53	2/53	18/53
PCB 153	0/51	16/51	2/51	18/51
PCB 126/PCB 153 Binary Mixture	0/53	10/53	4/53	13/53
PCB 126/PCB 118 Mixture	0/53	9/53	4/53	13/53
Overall Historical Incidence				
Total (%)	1/367 (0.3%)	100/367 (27.3%)	15/367 (4.1%)	113/367 (30.8%)
Mean ± standard deviation	0.3% ± 0.7%	27.3% ± 7.7%	4.1% ± 2.8%	30.8% ± 5.9%
Range	0%-2%	17%-38%	0%-8%	25%-40%

[a] Data as of May 5, 2004

TABLE A5a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
Disposition Summary						
Animals initially in study	28	28	28	28	28	29
14-Week interim evaluation	10	10	10	10	10	10
31-Week interim evaluation	10	10	10	10	10	10
53-Week interim evaluation	8	8	8	8	8	9
Animals examined microscopically	28	28	28	28	28	29
14-Week Interim Evaluation						
Alimentary System						
Liver	(10)	(10)	(10)	(10)	(10)	(10)
Inflammation	10 (100%)	10 (100%)	10 (100%)	9 (90%)	10 (100%)	10 (100%)
Mixed cell focus						1 (10%)
Hepatocyte, hypertrophy					9 (90%)	10 (100%)
Pancreas	(10)					(10)
Inflammation, chronic active						1 (10%)
Acinus, atrophy						1 (10%)
Endocrine System						
Thyroid gland	(10)	(10)	(10)	(10)	(10)	(10)
Follicular cell, hypertrophy	2 (20%)	3 (30%)	1 (10%)	1 (10%)		4 (40%)
Genital System						
Ovary	(10)					(10)
Atrophy	1 (10%)					1 (10%)
Uterus	(10)					(10)
Metaplasia, squamous	1 (10%)					
Endometrium, hyperplasia, cystic	5 (50%)					2 (20%)
Hematopoietic System						
Spleen	(10)					(10)
Pigmentation	10 (100%)					10 (100%)
Respiratory System						
Lung	(10)	(10)	(10)	(10)	(10)	(10)
Infiltration cellular, histiocyte						1 (10%)
Systems Examined at 14 Weeks with No Neoplasms Observed						
Cardiovascular System						
General Body System						
Integumentary System						
Musculoskeletal System						
Nervous System						
Special Senses System						
Urinary System						

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

Table A5a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
31-Week Interim Evaluation						
Alimentary System						
Liver	(10)	(10)	(10)	(10)	(10)	(10)
Eosinophilic focus	1 (10%)					1 (10%)
Inflammation	9 (90%)	10 (100%)	10 (100%)	9 (90%)	10 (100%)	10 (100%)
Mixed cell focus	1 (10%)	1 (10%)	4 (40%)	2 (20%)	2 (20%)	
Mixed cell focus, multiple	1 (10%)					1 (10%)
Bile duct, hyperplasia						1 (10%)
Hepatocyte, hypertrophy	1 (10%)	1 (10%)		7 (70%)	9 (90%)	10 (100%)
Pancreas	(10)					(10)
Inflammation, chronic active	1 (10%)					
Acinus, atrophy	1 (10%)					
Stomach, glandular	(10)					(10)
Dysplasia						1 (10%)
Endocrine System						
Adrenal cortex	(10)					(10)
Hypertrophy	3 (30%)					2 (20%)
Vacuolization cytoplasmic	1 (10%)					3 (30%)
Thyroid gland	(10)	(10)	(10)	(10)	(10)	(10)
Follicular cell, hypertrophy	2 (20%)	1 (10%)	1 (10%)	2 (20%)		1 (10%)
Genital System						
Ovary	(10)					(10)
Atrophy	7 (70%)					7 (70%)
Uterus	(10)			(1)		(10)
Inflammation, suppurative	1 (10%)			1 (100%)		3 (30%)
Metaplasia, squamous	7 (70%)			1 (100%)		5 (50%)
Endometrium, hyperplasia, cystic	2 (20%)			1 (100%)		1 (10%)
Hematopoietic System						
Spleen	(10)					(10)
Pigmentation	10 (100%)					10 (100%)
Thymus	(10)	(10)	(10)	(10)	(10)	(10)
Atrophy	1 (10%)	2 (20%)		1 (10%)		
Respiratory System						
Lung	(10)	(10)	(10)	(10)	(10)	(10)
Infiltration cellular, histiocyte		1 (10%)				
Alveolar epithelium, hyperplasia				1 (10%)		
Systems Examined at 31 Weeks with No Neoplasms Observed						
Cardiovascular System						
General Body System						
Integumentary System						
Musculoskeletal System						
Nervous System						
Special Senses System						
Urinary System						

Table A5a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
53-Week Interim Evaluation						
Alimentary System						
Liver	(8)	(8)	(8)	(8)	(8)	(9)
Basophilic focus	1 (13%)	1 (13%)				
Clear cell focus	1 (13%)			1 (13%)		
Eosinophilic focus	1 (13%)		1 (13%)			
Fatty change, diffuse					2 (25%)	1 (11%)
Hematopoietic cell proliferation			1 (13%)			
Inflammation	7 (88%)	6 (75%)	8 (100%)	7 (88%)	8 (100%)	8 (89%)
Mixed cell focus	2 (25%)	2 (25%)	3 (38%)	1 (13%)	1 (13%)	2 (22%)
Mixed cell focus, multiple	4 (50%)	5 (63%)	1 (13%)	4 (50%)		
Bile duct, fibrosis	1 (13%)					
Hepatocyte, hypertrophy	1 (13%)		3 (38%)	7 (88%)	8 (100%)	9 (100%)
Serosa, pigmentation					1 (13%)	
Stomach, glandular	(8)					(9)
Erosion	1 (13%)					
Glands, cyst						1 (11%)
Endocrine System						
Adrenal cortex	(8)					(9)
Hyperplasia	1 (13%)					
Hypertrophy	4 (50%)					4 (44%)
Vacuolization cytoplasmic	1 (13%)					1 (11%)
Pituitary gland	(8)					(9)
Cyst						1 (11%)
Thyroid gland	(8)	(8)	(8)	(8)	(8)	(9)
C-cell, hyperplasia	3 (38%)					2 (22%)
Follicular cell, hypertrophy	1 (13%)		2 (25%)	1 (13%)	1 (13%)	3 (33%)
Genital System						
Ovary	(8)	(1)		(1)	(1)	(9)
Atrophy	8 (100%)					7 (78%)
Cyst	1 (13%)			1 (100%)	1 (100%)	
Uterus	(8)					(9)
Inflammation, chronic active						1 (11%)
Inflammation, suppurative	2 (25%)					1 (11%)
Metaplasia, squamous	5 (63%)					6 (67%)
Endometrium, hyperplasia, cystic	5 (63%)					1 (11%)
Hematopoietic System						
Lymph node		(1)				
Mediastinal, hemorrhage		1 (100%)				
Mediastinal, hyperplasia, plasma cell		1 (100%)				
Spleen	(8)					(9)
Hematopoietic cell proliferation	1 (13%)					
Pigmentation	7 (88%)					9 (100%)
Thymus	(8)					(9)
Atrophy	2 (25%)					1 (11%)

Table A5a
Summary of the Incidence of Nonneoplastic Lesions in Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
Respiratory System						
Lung	(8)	(8)	(8)	(8)	(8)	(9)
Infiltration cellular, histiocyte	3 (38%)					1 (11%)
Inflammation				1 (13%)		
Inflammation, chronic	1 (13%)					
Alveolar epithelium, hyperplasia		1 (13%)		1 (13%)		

Systems Examined at 53 Weeks with No Neoplasms Observed
Cardiovascular System
General Body System
Integumentary System
Musculoskeletal System
Nervous System
Special Senses System
Urinary System

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Disposition Summary							
Animals initially in study	53	54	53	53	53	51	50
Early deaths							
Accidental death				1			
Moribund	18	23	17	22	18	19	16
Natural deaths	11	15	8	9	15	11	14
Survivors							
Died last week of study				1			
Terminal sacrifice	24	16	28	20	20	21	20
Animals examined microscopically	53	54	53	53	53	51	50
Alimentary System							
Esophagus	(53)	(54)	(53)	(53)	(53)	(51)	(49)
Muscularis, inflammation		3 (6%)		1 (2%)	2 (4%)	1 (2%)	3 (6%)
Periesophageal tissue, hemorrhage				1 (2%)			
Periesophageal tissue, inflammation				1 (2%)			
Intestine large, colon	(53)	(54)	(53)	(53)	(53)	(50)	(49)
Inflammation, chronic active						1 (2%)	
Parasite metazoan		1 (2%)	1 (2%)		1 (2%)	2 (4%)	
Intestine large, rectum	(53)	(54)	(53)	(53)	(53)	(50)	(50)
Inflammation, chronic active						1 (2%)	
Parasite metazoan	1 (2%)	2 (4%)	3 (6%)	7 (13%)	5 (9%)	5 (10%)	3 (6%)
Intestine large, cecum	(53)	(54)	(53)	(53)	(53)	(50)	(48)
Inflammation							1 (2%)
Inflammation, chronic active						1 (2%)	
Ulcer							1 (2%)
Intestine small, duodenum	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Parasite metazoan						1 (2%)	
Intestine small, jejunum	(53)	(54)	(53)	(53)	(53)	(50)	(49)
Peyer's patch, hyperplasia, lymphoid	1 (2%)					1 (2%)	
Intestine small, ileum	(52)	(54)	(53)	(53)	(53)	(50)	(48)
Hyperplasia, lymphoid	1 (2%)						
Liver	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Angiectasis	5 (9%)	2 (4%)	2 (4%)	1 (2%)	8 (15%)	4 (8%)	8 (16%)
Basophilic focus	8 (15%)	5 (9%)	16 (30%)	6 (11%)	3 (6%)	8 (16%)	8 (16%)
Basophilic focus, multiple	8 (15%)	12 (22%)	9 (17%)	7 (13%)	7 (13%)	2 (4%)	2 (4%)
Cholangiofibrosis					1 (2%)		
Clear cell focus	3 (6%)	3 (6%)	4 (8%)			2 (4%)	1 (2%)
Clear cell focus, multiple	3 (6%)	2 (4%)	1 (2%)				
Degeneration, cystic							1 (2%)
Eosinophilic focus	5 (9%)	1 (2%)	8 (15%)	7 (13%)	14 (26%)	6 (12%)	4 (8%)
Eosinophilic focus, multiple	7 (13%)	1 (2%)	8 (15%)	12 (23%)	9 (17%)	12 (24%)	10 (20%)
Fatty change, diffuse	3 (6%)	7 (13%)	2 (4%)	11 (21%)	21 (40%)	17 (33%)	15 (30%)
Fatty change, focal	4 (8%)		3 (6%)	5 (9%)	4 (8%)	1 (2%)	6 (12%)
Hematopoietic cell proliferation	20 (38%)	22 (41%)	13 (25%)	18 (34%)	16 (30%)	14 (27%)	17 (34%)
Hepatodiaphragmatic nodule					1 (2%)	1 (2%)	2 (4%)

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

Table A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Alimentary System (continued)							
Liver (continued)	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Hyperplasia, histiocytic							1 (2%)
Hyperplasia, nodular					1 (2%)		1 (2%)
Inflammation	44 (83%)	39 (72%)	44 (83%)	47 (89%)	48 (91%)	45 (88%)	44 (88%)
Mixed cell focus	8 (15%)	3 (6%)	7 (13%)	6 (11%)	5 (9%)	3 (6%)	7 (14%)
Mixed cell focus, multiple	21 (40%)	16 (30%)	22 (42%)	19 (36%)	19 (36%)	12 (24%)	13 (26%)
Necrosis	7 (13%)	7 (13%)	7 (13%)	5 (9%)	12 (23%)	10 (20%)	9 (18%)
Pigmentation	1 (2%)	1 (2%)	2 (4%)	5 (9%)	5 (9%)	9 (18%)	3 (6%)
Bile duct, cyst	3 (6%)	2 (4%)	2 (4%)	3 (6%)	5 (9%)	2 (4%)	3 (6%)
Bile duct, fibrosis	2 (4%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)	3 (6%)	5 (10%)
Bile duct, hyperplasia	5 (9%)	3 (6%)	2 (4%)	14 (26%)	10 (19%)	17 (33%)	12 (24%)
Centrilobular, degeneration	2 (4%)	10 (19%)	4 (8%)	2 (4%)	2 (4%)	5 (10%)	5 (10%)
Hepatocyte, hypertrophy		5 (9%)	5 (9%)	24 (45%)	39 (74%)	41 (80%)	32 (64%)
Oval cell, hyperplasia				1 (2%)		4 (8%)	2 (4%)
Serosa, fibrosis						1 (2%)	
Serosa, inflammation			2 (4%)				
Mesentery			(1)		(1)		
Fat, inflammation, chronic active			1 (100%)				
Oral mucosa	(21)	(12)	(16)	(12)	(16)	(25)	(15)
Gingival, hyperplasia, squamous	21 (100%)	10 (83%)	16 (100%)	11 (92%)	16 (100%)	25 (100%)	15 (100%)
Pancreas	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Cyst			1 (2%)				
Degeneration		1 (2%)					
Inflammation, chronic active	2 (4%)		1 (2%)	1 (2%)		2 (4%)	2 (4%)
Acinus, atrophy	1 (2%)		1 (2%)	1 (2%)		2 (4%)	3 (6%)
Acinus, hyperplasia	3 (6%)						2 (4%)
Acinus, vacuolization cytoplasmic				1 (2%)	1 (2%)	2 (4%)	1 (2%)
Salivary glands	(51)	(52)	(53)	(52)	(53)	(51)	(48)
Ectopic tissue				1 (2%)			
Inflammation, chronic active							1 (2%)
Stomach, forestomach	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Hyperkeratosis		1 (2%)			1 (2%)	2 (4%)	2 (4%)
Hyperplasia, squamous	3 (6%)	4 (7%)	2 (4%)	6 (11%)	4 (8%)	4 (8%)	5 (10%)
Inflammation				3 (6%)	3 (6%)	2 (4%)	4 (8%)
Mineralization		1 (2%)		2 (4%)	2 (4%)		3 (6%)
Ulcer				2 (4%)	3 (6%)	1 (2%)	
Serosa, inflammation, chronic active			1 (2%)				
Stomach, glandular	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Erosion	1 (2%)		1 (2%)	2 (4%)			
Inflammation				2 (4%)			1 (2%)
Mineralization	5 (9%)	8 (15%)	8 (15%)	10 (19%)	10 (19%)	2 (4%)	3 (6%)
Ulcer							1 (2%)
Serosa, inflammation							1 (2%)
Tooth	(34)	(13)	(19)	(22)	(23)	(35)	(27)
Degeneration	1 (3%)						
Peridontal tissue, inflammation	33 (97%)	13 (100%)	19 (100%)	21 (95%)	23 (100%)	35 (100%)	27 (100%)

Table A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Cardiovascular System							
Blood vessel	(52)	(54)	(53)	(53)	(53)	(51)	(50)
Aorta, mineralization	2 (4%)	1 (2%)		1 (2%)	1 (2%)		
Heart	(52)	(54)	(53)	(53)	(53)	(51)	(50)
Cardiomyopathy	22 (42%)	18 (33%)	19 (36%)	19 (36%)	23 (43%)	24 (47%)	15 (30%)
Inflammation		2 (4%)		1 (2%)		1 (2%)	
Mineralization	1 (2%)			1 (2%)			
Necrosis		1 (2%)					
Thrombosis		2 (4%)					
Epicardium, inflammation							1 (2%)
Endocrine System							
Adrenal cortex	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Angiectasis	21 (40%)	23 (43%)	34 (64%)	25 (47%)	29 (55%)	21 (41%)	20 (40%)
Atrophy				1 (2%)	2 (4%)		
Degeneration, cystic	9 (17%)	12 (22%)	15 (28%)	13 (25%)	12 (23%)	13 (25%)	7 (14%)
Hematopoietic cell proliferation		1 (2%)		1 (2%)		3 (6%)	2 (4%)
Hyperplasia	18 (34%)	24 (44%)	27 (51%)	27 (51%)	28 (53%)	11 (22%)	18 (36%)
Hypertrophy	48 (91%)	35 (65%)	45 (85%)	35 (66%)	42 (79%)	41 (80%)	35 (70%)
Inflammation				1 (2%)		1 (2%)	
Mineralization				2 (4%)	1 (2%)		
Necrosis	1 (2%)	2 (4%)	1 (2%)	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Vacuolization cytoplasmic	10 (19%)	8 (15%)	14 (26%)	16 (30%)	12 (23%)	14 (27%)	12 (24%)
Adrenal medulla	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Angiectasis			1 (2%)	1 (2%)			1 (2%)
Hyperplasia	18 (34%)	14 (26%)	19 (36%)	14 (26%)	20 (38%)	12 (24%)	19 (38%)
Islets, pancreatic	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Hyperplasia	1 (2%)		1 (2%)	1 (2%)			
Parathyroid gland	(49)	(46)	(50)	(47)	(46)	(48)	(45)
Angiectasis				1 (2%)			
Cyst	1 (2%)						
Fibrosis		1 (2%)					
Hyperplasia	2 (4%)			1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(53)	(54)	(53)	(53)	(53)	(50)	(50)
Angiectasis	15 (28%)	16 (30%)	20 (38%)	26 (49%)	28 (53%)	14 (28%)	24 (48%)
Atypia cellular				1 (2%)			
Cyst			1 (2%)			1 (2%)	
Cytoplasmic alteration	2 (4%)		1 (2%)		1 (2%)		
Vacuolization cytoplasmic					1 (2%)		
Pars distalis, hyperplasia	23 (43%)	18 (33%)	22 (42%)	16 (30%)	23 (43%)	25 (50%)	18 (36%)
Rathke's cleft, pars nervosa, cyst							1 (2%)
Thyroid gland	(51)	(52)	(53)	(53)	(53)	(51)	(49)
Angiectasis		1 (2%)			1 (2%)		
C-cell, hyperplasia	19 (37%)	17 (33%)	23 (43%)	17 (32%)	19 (36%)	16 (31%)	13 (27%)
Follicular cell, hyperplasia	1 (2%)				2 (4%)	2 (4%)	
Follicular cell, hypertrophy	5 (10%)	9 (17%)	9 (17%)	12 (23%)	10 (19%)	17 (33%)	12 (24%)

Table A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
General Body System							
None							
Genital System							
Clitoral gland	(53)	(51)	(52)	(53)	(51)	(50)	(48)
Atrophy				1 (2%)			
Inflammation	52 (98%)	45 (88%)	41 (79%)	48 (91%)	48 (94%)	46 (92%)	44 (92%)
Inflammation, chronic active						1 (2%)	
Duct, cyst	49 (92%)	40 (78%)	36 (69%)	43 (81%)	45 (88%)	41 (82%)	41 (85%)
Ovary	(53)	(53)	(53)	(53)	(53)	(50)	(49)
Atrophy	47 (89%)	43 (81%)	42 (79%)	38 (72%)	44 (83%)	39 (78%)	41 (84%)
Cyst	14 (26%)	7 (13%)	17 (32%)	17 (32%)	16 (30%)	17 (34%)	16 (33%)
Inflammation, chronic active			2 (4%)	1 (2%)	5 (9%)	7 (14%)	
Necrosis			1 (2%)				
Interstitial cell, hyperplasia	1 (2%)					1 (2%)	
Oviduct	(50)	(38)	(44)	(35)	(39)	(45)	(46)
Cyst		1 (3%)	2 (5%)	1 (3%)	1 (3%)		
Dilatation			1 (2%)			1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		2 (5%)	1 (3%)	5 (13%)	7 (16%)	2 (4%)
Uterus	(53)	(54)	(53)	(53)	(53)	(50)	(49)
Adenomyosis	2 (4%)	1 (2%)		1 (2%)		1 (2%)	
Angiectasis		1 (2%)			1 (2%)		
Congestion				1 (2%)			
Cyst			1 (2%)	1 (2%)			1 (2%)
Hemorrhage		2 (4%)					
Inflammation, chronic active	2 (4%)	1 (2%)	5 (9%)	4 (8%)	2 (4%)	8 (16%)	1 (2%)
Inflammation, suppurative	5 (9%)	6 (11%)	6 (11%)	2 (4%)	16 (30%)	8 (16%)	9 (18%)
Metaplasia, squamous	23 (43%)	29 (54%)	27 (51%)	17 (32%)	27 (51%)	32 (64%)	24 (49%)
Thrombosis				1 (2%)	2 (4%)		
Ulcer		1 (2%)					
Cervix, cyst							1 (2%)
Cervix, hyperplasia, stromal	1 (2%)				2 (4%)		2 (4%)
Cervix, inflammation, suppurative	1 (2%)						
Endometrium, hyperplasia, cystic	37 (70%)	29 (54%)	32 (60%)	28 (53%)	25 (47%)	21 (42%)	23 (47%)
Endometrium, hyperplasia, stromal					1 (2%)		
Vagina	(1)	(3)	(2)	(1)	(1)	(3)	(1)
Inflammation			1 (50%)				
Inflammation, chronic active							1 (100%)
Hematopoietic System							
Bone marrow	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Hyperplasia	34 (64%)	41 (76%)	40 (75%)	38 (72%)	42 (79%)	46 (90%)	40 (80%)
Lymph node	(3)	(3)	(3)	(2)	(5)	(6)	(1)
Hemorrhage			1 (33%)				
Hyperplasia, lymphoid			1 (33%)				
Hyperplasia, plasma cell		1 (33%)	1 (33%)				
Iliac, ectasia					1 (20%)		
Iliac, hyperplasia, plasma cell					1 (20%)		
Lumbar, ectasia		1 (33%)	2 (67%)			2 (33%)	
Lumbar, hemorrhage			1 (33%)			1 (17%)	
Lumbar, hyperplasia, histiocytic					1 (20%)		
Lumbar, hyperplasia, plasma cell					1 (20%)	2 (33%)	

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Hematopoietic System (continued)							
Lymph node (continued)	(3)	(3)	(3)	(2)	(5)	(6)	(1)
Mediastinal, congestion	3 (100%)						
Mediastinal, ectasia						2 (33%)	
Mediastinal, hemorrhage							1 (100%)
Mediastinal, hyperplasia, histiocytic	1 (33%)						
Mediastinal, hyperplasia, lymphoid	1 (33%)	1 (33%)					
Mediastinal, hyperplasia, plasma cell	1 (33%)	1 (33%)					
Renal, ectasia						2 (33%)	
Renal, hyperplasia, plasma cell						1 (17%)	
Renal, inflammation, chronic active				1 (50%)			
Lymph node, mandibular	(51)	(52)	(53)	(51)	(53)	(51)	(48)
Congestion					1 (2%)		
Ectasia			1 (2%)		1 (2%)	1 (2%)	1 (2%)
Hemorrhage			1 (2%)				
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, plasma cell	37 (73%)	36 (69%)	30 (57%)	33 (65%)	37 (70%)	38 (75%)	37 (77%)
Inflammation						1 (2%)	1 (2%)
Lymph node, mesenteric	(52)	(54)	(53)	(53)	(53)	(51)	(49)
Ectasia		1 (2%)					
Hemorrhage	1 (2%)						
Hyperplasia, plasma cell						1 (2%)	
Inflammation, chronic active						1 (2%)	
Spleen	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Accessory spleen							1 (2%)
Congestion							1 (2%)
Hematopoietic cell proliferation	46 (87%)	48 (89%)	52 (98%)	48 (91%)	46 (87%)	47 (92%)	44 (88%)
Hemorrhage						1 (2%)	1 (2%)
Infarct						1 (2%)	
Necrosis		1 (2%)	1 (2%)			1 (2%)	
Pigmentation	47 (89%)	42 (78%)	47 (89%)	49 (92%)	49 (92%)	46 (90%)	50 (100%)
Lymphoid follicle, atrophy	1 (2%)	6 (11%)	2 (4%)	3 (6%)	3 (6%)	3 (6%)	4 (8%)
Red pulp, atrophy				2 (4%)			
Thymus	(48)	(53)	(52)	(53)	(53)	(47)	(49)
Atrophy	38 (79%)	38 (72%)	37 (71%)	35 (66%)	41 (77%)	30 (64%)	29 (59%)
Cyst		1 (2%)				1 (2%)	
Hemorrhage		3 (6%)					1 (2%)
Inflammation							1 (2%)
Necrosis, lymphoid							1 (2%)
Integumentary System							
Mammary gland	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Cyst	2 (4%)	1 (2%)		2 (4%)	1 (2%)	3 (6%)	3 (6%)
Cyst, multiple							1 (2%)
Hyperplasia	22 (42%)	23 (43%)	32 (60%)	27 (51%)	32 (60%)	22 (43%)	27 (54%)
Inflammation, chronic active			1 (2%)				
Inflammation, granulomatous		2 (4%)	2 (4%)	3 (6%)		1 (2%)	2 (4%)
Skin	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Cyst						1 (2%)	
Cyst epithelial inclusion		1 (2%)			1 (2%)		
Inflammation					1 (2%)		
Ulcer							1 (2%)

Table A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Musculoskeletal System							
None							
Nervous System							
Brain	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Hemorrhage	1 (2%)		1 (2%)	1 (2%)	2 (4%)		
Hydrocephalus				2 (4%)	1 (2%)		
Hyperplasia, histiocytic				1 (2%)			
Mineralization				1 (2%)			
Necrosis	1 (2%)			1 (2%)			
Vacuolization cytoplasmic						1 (2%)	
Glial cell, hyperplasia		1 (2%)					
Respiratory System							
Lung	(52)	(54)	(53)	(53)	(53)	(51)	(50)
Congestion					1 (2%)		
Hemorrhage	1 (2%)					1 (2%)	1 (2%)
Infiltration cellular, histiocyte	45 (87%)	40 (74%)	40 (75%)	40 (75%)	27 (51%)	28 (55%)	37 (74%)
Inflammation	6 (12%)	7 (13%)	2 (4%)	6 (11%)	7 (13%)	9 (18%)	9 (18%)
Metaplasia, squamous				1 (2%)	1 (2%)	1 (2%)	
Mineralization				1 (2%)	1 (2%)		
Alveolar epithelium, hyperplasia	20 (38%)	21 (39%)	16 (30%)	11 (21%)	9 (17%)	6 (12%)	4 (8%)
Mediastinum, hemorrhage				1 (2%)			
Serosa, inflammation, chronic active				1 (2%)			
Nose	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Cyst		1 (2%)					
Inflammation	1 (2%)	6 (11%)	3 (6%)	6 (11%)	6 (11%)	3 (6%)	2 (4%)
Goblet cell, hyperplasia			2 (4%)	1 (2%)	2 (4%)		
Nasolacrimal duct, inflammation	2 (4%)					2 (4%)	
Respiratory epithelium, hyperplasia			2 (4%)		1 (2%)		
Respiratory epithelium, mineralization		1 (2%)					
Septum, inflammation	4 (8%)	3 (6%)	5 (9%)	3 (6%)	7 (13%)	6 (12%)	4 (8%)
Squamous epithelium, hyperplasia		1 (2%)					
Turbinate, inflammation	8 (15%)	3 (6%)	5 (9%)	9 (17%)	10 (19%)	10 (20%)	5 (10%)
Trachea	(52)	(54)	(53)	(53)	(53)	(51)	(49)
Inflammation						1 (2%)	
Special Senses System							
Eye	(53)	(54)	(53)	(53)	(52)	(51)	(50)
Degeneration	1 (2%)						
Anterior chamber, exudate					1 (2%)		
Lens, degeneration				1 (2%)			
Retina, atrophy	2 (4%)		1 (2%)		1 (2%)		2 (4%)
Harderian gland	(53)	(54)	(53)	(53)	(53)	(49)	(50)
Atrophy		1 (2%)					
Inflammation	20 (38%)	9 (17%)	13 (25%)	16 (30%)	16 (30%)	16 (33%)	15 (30%)

Table A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg	3,000 µg/kg (Stop-Exposure)
Urinary System							
Kidney	(53)	(54)	(53)	(53)	(53)	(51)	(50)
Accumulation, hyaline droplet		3 (6%)	1 (2%)			1 (2%)	
Calculus microscopic observation only	3 (6%)	5 (9%)	4 (8%)	7 (13%)	5 (9%)	1 (2%)	
Casts protein	3 (6%)	2 (4%)	2 (4%)	1 (2%)		1 (2%)	4 (8%)
Cyst	1 (2%)			1 (2%)			1 (2%)
Degeneration			1 (2%)				
Fibrosis							1 (2%)
Hydronephrosis			1 (2%)		1 (2%)		
Infarct	1 (2%)		1 (2%)	2 (4%)			
Inflammation, chronic active		2 (4%)			3 (6%)	1 (2%)	3 (6%)
Inflammation, suppurative	1 (2%)	2 (4%)	3 (6%)	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Mineralization	40 (75%)	42 (78%)	41 (77%)	39 (74%)	40 (75%)	41 (80%)	38 (76%)
Necrosis		1 (2%)					
Nephropathy	34 (64%)	23 (43%)	24 (45%)	33 (62%)	28 (53%)	34 (67%)	22 (44%)
Pelvis, dilatation		2 (4%)					
Pelvis, inflammation	1 (2%)	4 (7%)	2 (4%)	4 (8%)	5 (9%)	4 (8%)	3 (6%)
Renal tubule, degeneration			1 (2%)			1 (2%)	
Renal tubule, hyperplasia		1 (2%)					
Transitional epithelium, hyperplasia	1 (2%)	5 (9%)	2 (4%)	4 (8%)	6 (11%)	4 (8%)	4 (8%)
Ureter			(1)				
Cyst			1 (100%)				
Urinary bladder	(53)	(53)	(53)	(53)	(53)	(50)	(49)
Calculus microscopic observation only		1 (2%)					
Inflammation	8 (15%)	11 (21%)	6 (11%)	8 (15%)	13 (25%)	9 (18%)	10 (20%)
Transitional epithelium, hyperplasia		3 (6%)	2 (4%)	3 (6%)	2 (4%)	3 (6%)	3 (6%)

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

TABLE B1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153 132

TABLE B1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153[a]

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
n						
Week 14	10	10	10	10	10	10
Week 31	10	10	10	10	10	10
Week 53	8	8	8	8	8	9
Necropsy body wt						
Week 14	271 ± 4	286 ± 8	275 ± 5	284 ± 5	290 ± 3*	282 ± 5
Week 31	310 ± 11	305 ± 8	306 ± 5	305 ± 3	304 ± 8	311 ± 8
Week 53	320 ± 9	345 ± 19	364 ± 26	369 ± 18	345 ± 15	322 ± 10
L. Kidney						
Week 14						
Absolute	0.778 ± 0.018	0.832 ± 0.018	0.782 ± 0.018	0.787 ± 0.015	0.831 ± 0.019	0.818 ± 0.016
Relative	2.876 ± 0.053	2.916 ± 0.037	2.846 ± 0.074	2.778 ± 0.047	2.862 ± 0.049	2.902 ± 0.040
Week 31						
Absolute	0.858 ± 0.020	0.895 ± 0.022	0.885 ± 0.028	0.866 ± 0.014	0.888 ± 0.019	0.912 ± 0.019
Relative	2.778 ± 0.062	2.946 ± 0.104	2.895 ± 0.096	2.836 ± 0.034	2.926 ± 0.053	2.947 ± 0.073
Week 53						
Absolute	0.883 ± 0.026	1.011 ± 0.050**	1.011 ± 0.025**	1.014 ± 0.032**	1.042 ± 0.032**	1.036 ± 0.021**
Relative	2.776 ± 0.108	2.938 ± 0.071	2.881 ± 0.221	2.771 ± 0.100	3.062 ± 0.168	3.233 ± 0.058*
Liver						
Week 14						
Absolute	8.926 ± 0.264	10.021 ± 0.315	8.549 ± 0.185	9.191 ± 0.242	10.147 ± 0.333**	10.295 ± 0.228**
Relative	32.978 ± 0.863	35.034 ± 0.589	31.073 ± 0.515	32.389 ± 0.573	34.931 ± 1.028	36.481 ± 0.413**
Week 31						
Absolute	9.966 ± 0.537	10.704 ± 0.373	9.884 ± 0.207	10.017 ± 0.264	10.775 ± 0.264	11.597 ± 0.341**
Relative	31.998 ± 0.960	35.031 ± 0.795	32.288 ± 0.513	32.820 ± 0.757	35.489 ± 0.649**	37.365 ± 0.733**
Week 53						
Absolute	9.854 ± 0.286	10.968 ± 0.694	12.869 ± 1.237*	12.571 ± 0.780*	11.924 ± 0.284*	12.675 ± 0.648**
Relative	30.861 ± 0.714	31.688 ± 0.515	35.191 ± 1.446*	34.007 ± 1.301*	34.856 ± 1.317*	39.436 ± 1.548**
Lung						
Week 14						
Absolute	1.805 ± 0.090	1.915 ± 0.075	1.746 ± 0.050	1.916 ± 0.070	1.872 ± 0.072	1.824 ± 0.059
Relative	6.665 ± 0.304	6.718 ± 0.272	6.350 ± 0.178	6.749 ± 0.208	6.440 ± 0.211	6.483 ± 0.239
Week 31						
Absolute	1.943 ± 0.054	2.051 ± 0.065	1.755 ± 0.039	1.743 ± 0.033*	1.925 ± 0.065	1.806 ± 0.057
Relative	6.340 ± 0.303	6.740 ± 0.233	5.736 ± 0.122	5.722 ± 0.138	6.370 ± 0.291	5.829 ± 0.170
Week 53						
Absolute	2.034± 0.065	2.241 ± 0.053	2.062 ± 0.084	1.941 ± 0.056	1.973 ± 0.041	1.982 ± 0.057
Relative	6.376 ± 0.195	6.602 ± 0.341	5.854 ± 0.428	5.307 ± 0.190*	5.765 ± 0.192	6.188 ± 0.174
L. Ovary						
Week 14						
Absolute	0.056 ± 0.003	0.065 ± 0.003	0.060 ± 0.003	0.063 ± 0.003	0.071 ± 0.006*	0.064 ± 0.003
Relative	0.207 ± 0.010	0.225 ± 0.009	0.218 ± 0.009	0.223 ± 0.010	0.243 ± 0.020	0.228 ± 0.009
Week 31						
Absolute	0.057 ± 0.004	0.056 ± 0.004	0.053 ± 0.001	0.052 ± 0.003	0.054 ± 0.003	0.056 ± 0.005
Relative	0.182 ± 0.009	0.183 ± 0.010	0.173 ± 0.004	0.169 ± 0.010	0.176 ± 0.008	0.182 ± 0.015
Week 53						
Absolute	0.052 ± 0.002	0.058 ± 0.002[b]	0.063 ± 0.006	0.077 ± 0.009*	0.065 ± 0.006	0.062 ± 0.005
Relative	0.163 ± 0.007	0.180 ± 0.010[b]	0.178 ± 0.016	0.206 ± 0.019	0.189 ± 0.017	0.193 ± 0.013

Table B1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Female Rats at the 14-, 31-, and 53-Week Interim Evaluations in the 2-Year Gavage Study of PCB 153

	Vehicle Control	10 µg/kg	100 µg/kg	300 µg/kg	1,000 µg/kg	3,000 µg/kg
n						
Week 14	10	10	10	10	10	10
Week 31	10	10	10	10	10	10
Week 53	8	8	8	8	8	9
Necropsy body wt						
Week 14	271 ± 4	286 ± 8	275 ± 5	284 ± 5	290 ± 3*	282 ± 5
Week 31	310 ± 11	305 ± 8	306 ± 5	305 ± 3	304 ± 8	311 ± 8
Week 53	320 ± 9	345 ± 19	364 ± 26	369 ± 18	345 ± 15	322 ± 10
Spleen						
Week 14						
Absolute	0.593 ± 0.015	0.629 ± 0.018	0.588 ± 0.009	0.628 ± 0.024	0.606 ± 0.024	0.581 ± 0.020
Relative	2.190 ± 0.054	2.199 ± 0.042	2.139 ± 0.033	2.213 ± 0.066	2.089 ± 0.083	2.066 ± 0.081
Week 31						
Absolute	0.526 ± 0.025	0.563 ± 0.019	0.590 ± 0.027	0.555 ± 0.023	0.531 ± 0.024	0.535 ± 0.017
Relative	1.691 ± 0.042	1.854 ± 0.079	1.931 ± 0.089*	1.818 ± 0.065	1.745 ± 0.060	1.722 ± 0.027
Week 53						
Absolute	0.538 ± 0.013[c]	0.585 ± 0.034	0.638 ± 0.042	0.560 ± 0.019	0.564 ± 0.038	0.547 ± 0.014
Relative	1.663 ± 0.035[c]	1.697 ± 0.056	1.765 ± 0.063	1.526 ± 0.035	1.635 ± 0.092	1.708 ± 0.040
Thymus						
Week 14						
Absolute	0.249 ± 0.025	0.255 ± 0.019	0.266 ± 0.016	0.246 ± 0.019	0.245 ± 0.013	0.266 ± 0.017
Relative	0.922 ± 0.093	0.897 ± 0.073	0.968 ± 0.063	0.868 ± 0.067	0.844 ± 0.046	0.941 ± 0.052
Thyroid gland						
Week 14						
Absolute	0.027 ± 0.002	0.025 ± 0.002	0.029 ± 0.002	0.030 ± 0.002	0.031 ± 0.002	0.026 ± 0.001
Relative	0.102 ± 0.007	0.088 ± 0.006	0.104 ± 0.007	0.105 ± 0.006	0.108 ± 0.006	0.093 ± 0.005
Week 31						
Absolute	0.025 ± 0.001	0.025 ± 0.001	0.027 ± 0.002	0.025 ± 0.002	0.026 ± 0.001	0.029 ± 0.003
Relative	0.079 ± 0.004	0.082 ± 0.005	0.089 ± 0.006	0.082 ± 0.005	0.087 ± 0.004	0.091 ± 0.007
Week 53						
Absolute	0.025 ± 0.001	0.026 ± 0.002	0.025 ± 0.002	0.030 ± 0.002	0.028 ± 0.001	0.024 ± 0.001
Relative	0.077 ± 0.003	0.076 ± 0.008	0.068 ± 0.003	0.081 ± 0.006	0.083 ± 0.005	0.073 ± 0.003

* Significantly different ($P \leq 0.05$) from the vehicle 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 mg organ weight/g body weight (mean ± standard error).
[b] n=6
[c] n=7

APPENDIX C
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION 136
PREPARATION AND ANALYSIS OF DOSE FORMULATIONS 137
FIGURE C1 Proton Nuclear Magnetic Resonance Spectrum of PCB 153 138
FIGURE C2 Expanded Carbon-13 Nuclear Magnetic Resonance Spectrum of PCB 153 139
TABLE C1 Gas Chromatography Systems Used in the 2-Year Gavage Study of PCB 153 140
TABLE C2 Preparation and Storage of Dose Formulations in the 2-Year Gavage Study of PCB 153 140
TABLE C3 Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of PCB 153 141

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization

PCB 153

PCB 153 was obtained from Radian International LLC (Austin, TX) by Midwest Research Institute (Kansas City, MO) and provided to the study laboratory (Battelle Columbus Operations, Columbus, OH) in one lot (31532-78) that was used in the 2-year study. One additional lot (RAC-29699-67) was procured by the analytical chemistry laboratory (Battelle Columbus Operations, Chemistry Support Services, Columbus, OH) from Radian International LLC solely for dose formulation stability studies and was not used in the 2-year animal study. Identity and purity analyses were conducted by the analytical chemistry laboratory and the study laboratory. Reports on analyses performed in support of the PCB 153 study are on file at the National Institute of Environmental Health Sciences.

Lot 31532-78 of the chemical, a white powder, was identified as PCB 153 by the analytical chemistry laboratory using proton and carbon-13 nuclear magnetic resonance (NMR) spectroscopy. In addition, identity analysis was conducted by the study laboratory using proton NMR; spectra of a purity analysis sample and a frozen reference sample were compared to each other and to the spectrum of the same lot previously reported by the analytical chemistry laboratory. All spectra were consistent with the structure of PCB 153. The NMR spectra are presented in Figures C1 and C2.

The purity of lot 31532-78 was determined by the analytical chemistry laboratory to be approximately 99.8% using gas chromatography (GC) high resolution mass spectrometry (MS) system A (Table C1). The purity profile detected two significant impurities: 0.21% of the test article was identified as a pentachlorobiphenyl and 0.002% of the test article was identified as a heptachlorobiphenyl. Standards of the possible impurities were obtained by the analytical chemistry laboratory from Cambridge Isotope Laboratories (Andover, MA) and analyzed using GC/MS system A; the pentachlorobiphenyl impurity was identified as 2,2′,4,5,5′-pentachlorobiphenyl (PCB 101), and the heptachlorobiphenyl impurity was identified as 2,2′,3,4,4′,5,5′,-heptachlorobiphenyl (PCB 180). These impurities are di-*ortho*-substituted, nondioxin-like PCBs, and therefore have no dioxin toxic equivalency factors (TEFs).

Additional evaluations of the purity of lot 31532-78 were performed by the study laboratory. A frozen reference sample of the same lot was obtained from the analytical chemistry laboratory and comparative purity analysis using GC system B indicated that the relative purity of the test article was 101.1%. Subsequent analyses of these samples using GC/MS system A detected a single impurity in each sample with a peak area of 0.5% relative to the major peak area. The overall purity of lot 31532-78 was determined to be greater than 99%.

Formulation Materials

USP-grade acetone was obtained from Spectrum Quality Products (Gardena, CA) in five lots and was used with corn oil (Spectrum Quality Products) as the vehicle in the 2-year gavage study. The identity of each lot of acetone was confirmed by the study laboratory using infrared spectroscopy prior to its use. The purity of each lot was determined by the study laboratory using GC system C prior to initial use and at intervals of no more than 6 months thereafter. All acetone lots showed a purity of at least 99.9% except one that had a single impurity of 0.125%. Periodic analyses of the corn oil vehicle performed by the study laboratory using potentiometric titration demonstrated peroxide concentrations below the acceptable limit of 3 mEq/kg.

Preparation and Analysis of Dose Formulations

The 4 µg/mL dose formulation was prepared from a working stock of PCB 153 dissolved in acetone (8 mg/mL) (Table C2). An aliquot of this working stock was diluted with corn oil and additional acetone to yield the dose formulation containing 4 µg PCB 153/mL of a 1% solution of acetone in corn oil. The 40, 120, 400, and 1,200 µg/mL dose formulations were prepared by dissolving neat PCB 153 in a 1% solution of acetone in corn oil. All dose formulations were stored at room temperature in amber glass bottles with minimal headspace, sealed with Teflon®-lined lids, for up to 35 days.

Homogeneity of 4 and 1,200 µg/mL dose formulations and gavagability of a 1,200 µg/mL dose formulation were confirmed by the study laboratory using GC system D. Stability studies of a 4 µg/mL formulation of lot RAC 29699-67 were conducted by the analytical chemistry laboratory using GC system D. Stability was confirmed for at least 35 days for the dose formulation stored in amber glass bottles with minimal headspace, sealed with Teflon®-lined lids at –20° C, 5° C, and room temperature (approximately 25° C), and for 3 hours under simulated animal room conditions.

Periodic analyses of the dose formulations of PCB 153 were conducted by the study laboratory using GC similar to system D. During the 2-year study, the dose formulations were analyzed at least every 3 months (Table C3). Of the dose formulations analyzed and used, 59 of 60 were within 10% of the target concentrations; all dose formulations were within 14% of target. Twenty-two of 23 animal room samples were within 10% of the target concentrations; all were within 12% of target.

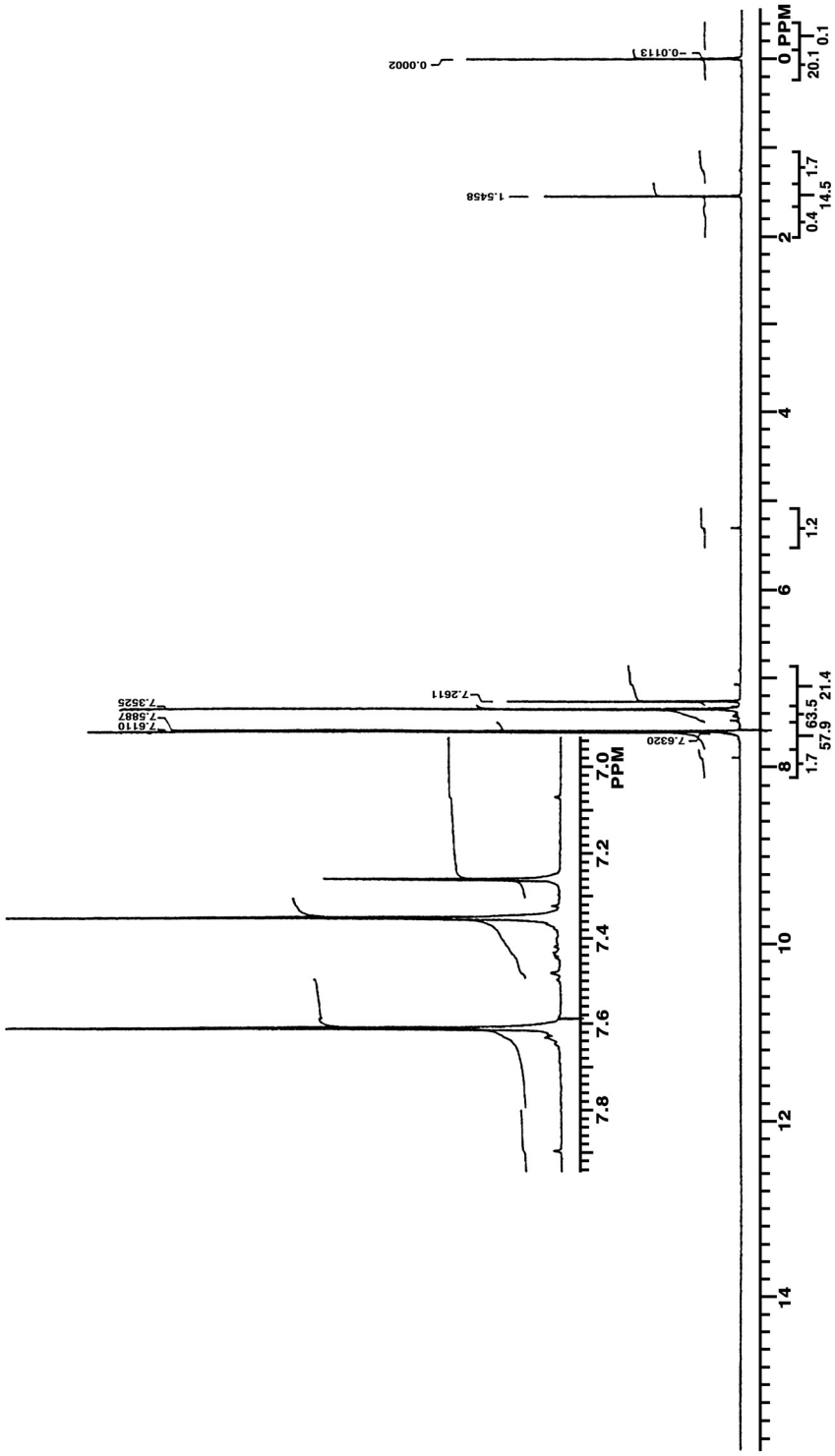

FIGURE C1
Proton Nuclear Magnetic Resonance Spectrum of PCB 153

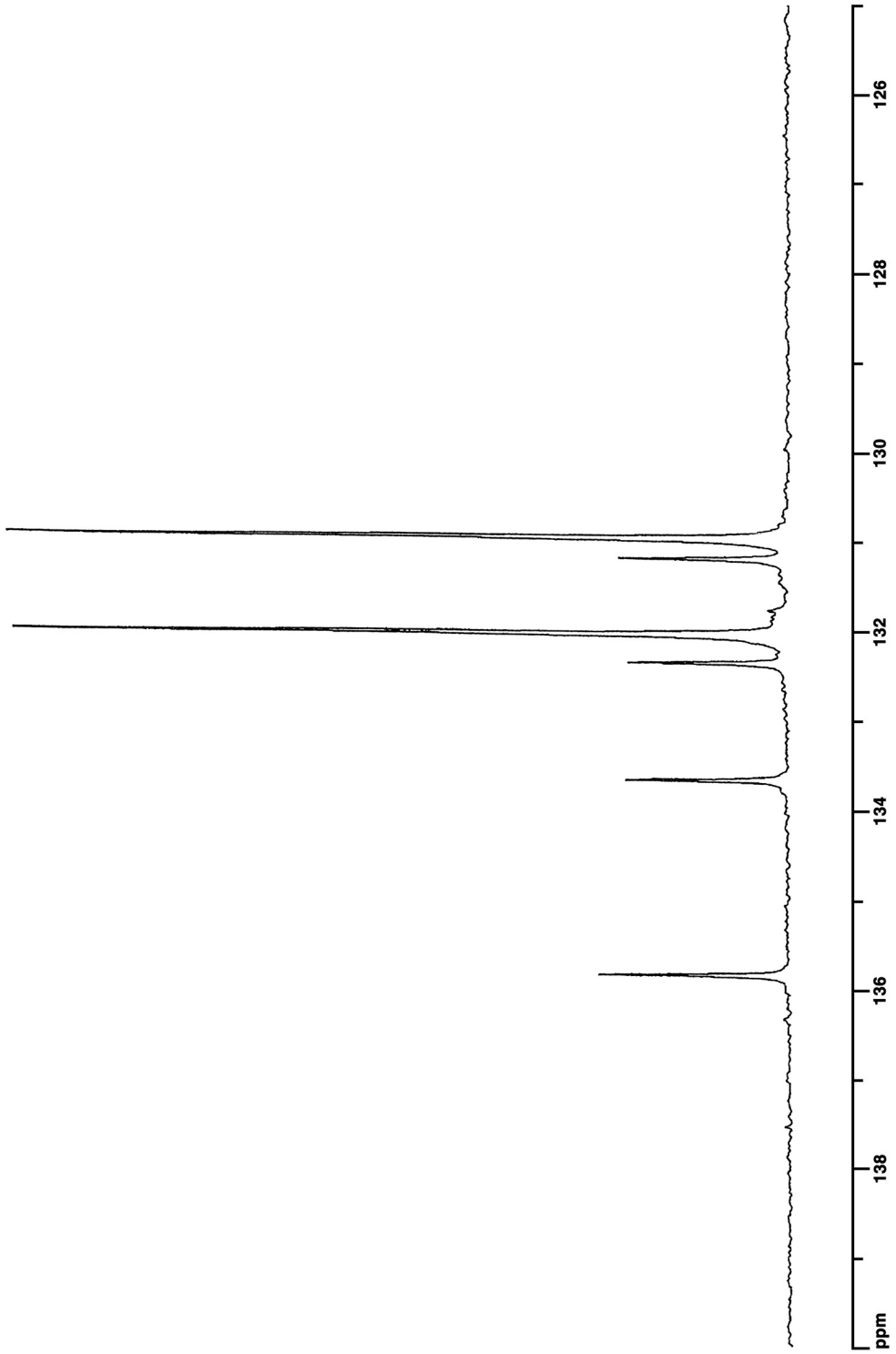

FIGURE C2
Expanded Carbon-13 Nuclear Magnetic Resonance Spectrum of PCB 153

TABLE C1
Gas Chromatography Systems Used in the 2-Year Gavage Study of PCB 153[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A High resolution mass spectrometry	J&W DB-5 MS, 15 m × 0.25 mm, 0.25-µm film thickness, (J&W Scientific, Folsom, CA)	Helium at 4 psi	50° C for 1 minute, then 8° C/minute to 300° C, held for 10 minutes
System B Flame ionization	Supelco PTE-5 (QTM), 15 m × 0.53 mm, 0.5-µm film thickness (Supelco, Inc., Bellefonte, PA)	Helium at 5 mL/minute	45° C for 5 minutes; then 15° C/minute to 300° C
System C Flame ionization	20% SP-2401/0.1% Carbowax 1500 on 100/120 Supelcoport, 2.4 m × 2 mm (Supelco, Inc.)	Helium at 30 mL/minute	40° C for 4 minutes, then 10° C/minute to 170° C
System D Electron capture	Supelco PTE-5, 15 m × 0.53 mm, 0.5-µm film thickness (Supelco, Inc.)	Helium, ultra high purity at 5 psi	150° C for 4 minutes, then 8° C/minute to 255° C, then 70° C/minute to 320° C, held for 1 minute

[a] The gas chromatographs were manufactured by VG (Cheshire, UK) (system A) and Hewlett-Packard (Palo Alto, CA) (systems B, C, and D). The mass spectrometer used in system A was manufactured by VG.

TABLE C2
Preparation and Storage of Dose Formulations in the 2-Year Gavage Study of PCB 153

Preparation
A working stock (8 mg/mL) was prepared by dissolving PCB 153 in acetone in a half-filled volumetric flask that was capped and shaken well. The flask was then filled to the desired level with acetone, capped, shaken, vortexed for 2 minutes, sonicated for 30 minutes in an ice-cooled water bath, and inverted at least 20 times.

The dose formulations were prepared by adding the appropriate volume of the 8 mg/mL working stock (for the 4 µg/mL dose formulation) or neat PCB 153 (for the 40, 120, 400, and 1,200 µg/mL dose formulations) to a volumetric flask half-filled with corn oil and an appropriate additional volume of acetone. The flask was capped, vigorously shaken, and filled to the desired final volume with corn oil. The contents of the flask were stirred on a stir plate for 3 or 24 hours with vigorous shaking done at least eight times over the stirring period. All dose formulations contained a final concentration of 1% acetone in corn oil.

Chemical Lot Number
31532-78

Maximum Storage Time
35 days

Storage Conditions
Dose formulations were stored in 120 or 250 mL amber glass screw-cap bottles with Teflon®-lined lids at room temperature (approximately 25° C).

Study Laboratory
Battelle Columbus Operations (Columbus, OH)

TABLE C3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of PCB 153

Date Prepared	Date Analyzed	Target Concentration (µg/mL)	Determined Concentration[a] (µg/mL)	Difference from Target (%)
August 10, 1998	August 19-20, 1998	4	4.065	+2
		40	29.76[b]	–26
		120	122.9	+2
		400	411.6[b]	+3
		1,200	1,189	–1
		1,200	1,189	–1
	September 16-17, 1998[c]	4	3.820	–5
		120	115.6	–4
		400	403.5	+1
		1,200	1,132	–6
		1,200	1,170	–3
August 17, 1998	August 19-20, 1998	40	41.05[d]	+3
		400	419.4[d]	+5
	September 16-17, 1998[c]	40	39.67	–1
October 5, 1998	October 8-9, 1998	4	3.642	–9
		40	36.44	–9
		120	113.1	–6
		400	371.0	–7
		1,200	1,152	–4
		1,200	1,143	–5
December 28, 1998	December 31, 1998, to January 6, 1999	4	3.741	–7
		40	41.93	+5
		120	124.5	+4
		400	408.2	+2
		1,200	1,261	+5
		1,200	1,174	–2
February 22, 1999	February 27, 1999	4	4.087	+2
		40	38.91	–3
		120	123.2	+3
		400	398.6	0
		1,200	1,198	0
		1,200	1,247	+4
	May 3-4, 1999[c]	4	3.898	–3
		40	37.59	–6
		120	105.7	–12
		400	401.7	0
		1,200	1,152	–4
		1,200	1,228	+2
May 17, 1999	May 21-22, 1999	4	3.778	–6
		40	38.65	–3
		120	118.0	–2
		400	393.4	–2
		1,200	1,091	–9

TABLE C3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of PCB 153

Date Prepared	Date Analyzed	Target Concentration (µg/mL)	Determined Concentration (µg/mL)	Difference from Target (%)
July 12, 1999	July 14, 1999	4	4.187	+5
		40	41.95	+5
		120	130.9	+9
		400	394.7	–1
		1,200	1,133	–6
October 4, 1999	October 20-21, 1999	4	3.445[e]	–14
		40	36.44	–9
		120	112.2	–7
		400	374.9	–6
		1,200	1,121	–7
	November 23-24, 1999[c]	4	3.816	–5
		40	39.10	–2
		120	116.2	–3
		400	395.5	–1
		1,200	1,222	+2
October 25, 1999	October 29-30, 1999	4	3.621[d]	–10
	November 23-24, 1999[c]	4	3.779	–6
November 29, 1999	December 2-3, 1999	4	3.829	–4
		40	38.25	–4
		120	124.2	+4
		400	406.7	+2
		1,200	1,212	+1
February 21, 2000	February 29 to March 1, 2000	4	3.765 ± 0.020	–6
		40	38.12 ± 0.16	–5
		120	120.0 ± 1.3	0
		400	377.1 ± 0.7	–6
		1,200	1,138 ± 6	–5
May 9, 2000	May 12-13, 2000	4	3.732 ± 0.023	–7
		40	39.01 ± 0.30	–3
		120	118.6 ± 0.8	–1
		400	387.5 ± 0.9	–3
		1,200	1,168 ± 8	–3
	July 11-19, 2000[c]	4	3.961 ± 0.057	–1
		40	40.17 ± 0.69	0
		120	121.0 ± 2.3	+1
		400	404.3 ± 5.4	+1
		1,200	1,205 ± 20	0

TABLE C3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of PCB 153

Date Prepared	Date Analyzed	Target Concentration (µg/mL)	Determined Concentration (µg/mL)	Difference from Target (%)
June 30, 2000	July 7-8, 2000	4	3.947 ± 0.116	–1
		40	43.08 ± 1.63	+8
		120	125.0 ± 3.6	+4
		400	404.1 ± 10.8	+1
		1,200	1,227 ± 44	+2

[a] Reported value is the average of duplicate analyses or the average ± standard deviation of quadruplicate analyses. Dosing volume=2.5 mL; 4 µg/mL=10 µg/kg, 40 µg/mL=100 µg/kg, 120 µg/mL=300 µg/kg, 400 µg/mL=1,000 µg/kg; 1,200 µg/mL=3,000 µg/kg
[b] Remixed, not used in study
[c] Animal room samples
[d] Results of remix
[e] Formulation was outside the acceptable range of ±10% of target concentration, but was used for 3 weeks at NTP's direction; after 3 weeks, the formulation was remixed.

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

TABLE D1 Ingredients of NTP-2000 Rat and Mouse Ration 146
TABLE D2 Vitamins and Minerals in NTP-2000 Rat and Mouse Ration 146
TABLE D3 Nutrient Composition of NTP-2000 Rat and Mouse Ration 147
TABLE D4 Contaminant Levels in NTP-2000 Rat and Mouse Ration 148
TABLE D5 Concentrations of PCBs and Dioxins in NTP-2000 Rat and Mouse Ration 149

TABLE D1
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 D2
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 D3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.5 ± 0.44	12.7 – 14.5	25
Crude fat (% by weight)	8.1 ± 0.25	7.6 – 8.6	25
Crude fiber (% by weight)	9.2 ± 0.66	7.9 – 10.5	25
Ash (% by weight)	5.0 ± 0.20	4.7 – 5.4	25
Amino Acids (% of total diet)			
Arginine	0.748 ± 0.053	0.670 – 0.850	12
Cystine	0.223 ± 0.027	0.150 – 0.250	12
Glycine	0.702 ± 0.043	0.620 – 0.750	12
Histidine	0.343 ± 0.023	0.310 – 0.390	12
Isoleucine	0.534 ± 0.041	0.430 – 0.590	12
Leucine	1.078 ± 0.059	0.960 – 1.140	12
Lysine	0.729 ± 0.065	0.620 – 0.830	12
Methionine	0.396 ± 0.053	0.260 – 0.460	12
Phenylalanine	0.611 ± 0.038	0.540 – 0.660	12
Threonine	0.492 ± 0.045	0.430 – 0.590	12
Tryptophan	0.129 ± 0.016	0.110 – 0.160	12
Tyrosine	0.378 ± 0.054	0.280 – 0.460	12
Valine	0.658 ± 0.049	0.550 – 0.710	12
Essential Fatty Acids (% of total diet)			
Linoleic	3.89 ± 0.278	3.49 – 4.54	12
Linolenic	0.30 ± 0.038	0.21 – 0.35	12
Vitamins			
Vitamin A (IU/kg)	5,768 ± 921	4,220 – 7,790	25
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	84.3 ± 17.06	52.0 – 110.0	12
Thiamine (ppm)[b]	8.0 ± 0.77	6.3 – 9.3	25
Riboflavin (ppm)	6.4 ± 2.11	4.20 – 11.20	12
Niacin (ppm)	78.6 ± 10.86	66.4 – 98.2	12
Pantothenic acid (ppm)	23.1 ± 3.61	17.4 – 29.1	12
Pyridoxine (ppm)[b]	8.88 ± 2.05	6.4 – 12.4	12
Folic acid (ppm)	1.84 ± 0.56	1.26 – 3.27	12
Biotin (ppm)	0.337 ± 0.13	0.225 – 0.704	12
Vitamin B_{12} (ppb)	64.8 ± 50.9	18.3 – 174.0	12
Choline (ppm)[b]	3,094 ± 292	2,700 – 3,790	12
Minerals			
Calcium (%)	0.997 ± 0.045	0.903 – 1.090	25
Phosphorus (%)	0.563 ± 0.028	0.505 – 0.618	25
Potassium (%)	0.668 ± 0.023	0.627 – 0.694	12
Chloride (%)	0.368 ± 0.033	0.300 – 0.423	12
Sodium (%)	0.189 ± 0.016	0.160 – 0.212	12
Magnesium (%)	0.200 ± 0.009	0.185 – 0.217	12
Sulfur (%)	0.176 ± 0.026	0.116 – 0.209	12
Iron (ppm)	177 ± 46.2	135 – 311	12
Manganese (ppm)	53.4 ± 6.42	42.1 – 63.1	12
Zinc (ppm)	52.5 ± 6.95	43.3 – 66.0	12
Copper (ppm)	6.64 ± 1.283	5.08 – 9.92	12
Iodine (ppm)	0.535 ± 0.242	0.233 – 0.972	12
Chromium (ppm)	0.545 ± 0.125	0.330 – 0.751	12
Cobalt (ppm)	0.23 ± 0.041	0.20 – 0.30	12

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

TABLE D4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.17 ± 0.081	0.10 – 0.37	25
Cadmium (ppm)	0.04 ± 0.006	0.04 – 0.07	25
Lead (ppm)	0.11 ± 0.104	0.05 – 0.54	25
Mercury (ppm)	<0.02		25
Selenium (ppm)	0.19 ± 0.034	0.14 – 0.28	25
Aflatoxins (ppb)	<5.00		25
Nitrate nitrogen (ppm)[c]	10.7 ± 3.00	9.04 – 21.1	25
Nitrite nitrogen (ppm)[c]	<0.61		25
BHA (ppm)[d]	<1.0		25
BHT (ppm)[d]	<1.0		25
Aerobic plate count (CFU/g)	10 ± 2	10 – 20	25
Coliform (MPN/g)	0.3 ± 1.0	0.0 – 3.6	25
Escherichia coli (MPN/g)	<10		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[e]	4.5 ± 1.53	2.1 – 8.8	25
N-Nitrosodimethylamine (ppb)[e]	1.8 ± 0.86	1.0 – 5.1	25
N-Nitrosopyrrolidine (ppb)[e]	2.7 ± 0.99	1.0 – 5.6	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl chlorpyrifos	0.149 ± 0.122	0.023 – 0.499	25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.211 ± 0.187	0.020 – 0.826	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] All samples were irradiated. 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] All values were corrected for percent recovery.

TABLE D5
Concentrations of PCBs and Dioxins in NTP-2000 Rat and Mouse Ration[a]

Analyte	Mean Concentration[b]	Standard Deviation	Mean LOQ	Standard Deviation
2,3,7,8-TCDD			0.0592	0.0106
1,2,3,7,8-PeCDD			0.119	0.0498
1,2,3,4,7,8-HxCDD			0.124	0.0366
1,2,3,6,7,8-HxCDD			0.120	0.0345
1,2,3,7,8,9-HxCDD			0.124	0.0387
1,2,3,4,6,7,8-HpCDD	0.573	0.417	0.573	0.417
OCDD	3.47	2.00	3.47	2.00
2,3,4,7,8-PeCDF	0.0413	0.0821	0.0934	0.0545
2,3,7,8-TCDF	0.0102		0.0692	0.0187
1,2,3,4,7,8-HxCDF	0.00753		0.0492	0.0213
1,2,3,6,7,8-HxCDF			0.0445	0.0155
1,2,3,7,8,9-HxCDF			0.0712	0.0259
2,3,4,6,7,8-HxCDF			0.0485	0.0176
1,2,3,7,8-PeCDF	0.00707		0.0871	0.0275
1,2,3,4,6,7,8-HpCDF	0.115	0.425	0.162	0.254
1,2,3,4,7,8,9-HpCDF			0.0870	0.0212
OCDF	0.207	0.272	0.330	0.211
2-Chlorobiphenyl	19.2	11.0	19.2	11.0
3-Chlorobiphenyl	1.73	0.465	4.99	0.893
4-Chlorobiphenyl	15.6	8.68	15.6	8.68
2,2′-Dichlorobiphenyl	62.0	54.3	62.0	54.3
2,3-Dichlorobiphenyl	267	244	267	244
2,3′-Dichlorobiphenyl	46.5	41.7	46.5	41.7
2,4-Dichlorobiphenyl/2,5-Dichlorobiphenyl	26.9	24.6	28.5	24.1
3,3′-Dichlorobiphenyl	101	108	101	108
3,4-Dichlorobiphenyl/3,4′-Dichlorobiphenyl	11.7	9.48	16.5	10.6
3,5-Dichlorobiphenyl			8.96	0.314
4,4′-Dichlorobiphenyl	63.5	64.8	78.5	67.8
2,2′,3-Trichlorobiphenyl/2,4′,6-Trichlorobiphenyl	112	102	112	103
2,2′,4-Trichlorobiphenyl	82.4	75.3	82.4	75.3
2,2′,5-Trichlorobiphenyl	202	183	202	183
2,2′,6-Trichlorobiphenyl	13.7	14.8	14.9	14.1
2,3,3′-Trichlorobiphenyl/2,3,4-Trichlorobiphenyl/2′,3,4-Trichlorobiphenyl	157	150	157	150
2,3,4′-Trichlorobiphenyl	80.5	76.3	80.5	76.3
2,3,5-Trichlorobiphenyl			4.48	0.158
2,3,6-Trichlorobiphenyl/2,3′,6-Trichlorobiphenyl	13.3	12.9	14.1	12.5
2,3′,4-Trichlorobiphenyl	21.4	20.2	21.8	20.0
2,3′,5-Trichlorobiphenyl	44.9	39.1	44.9	39.1
2,4,4′-Trichlorobiphenyl	222	215	222	215
2,4,5-Trichlorobiphenyl	1.11	2.14	4.78	0.945
2,4,6-Trichlorobiphenyl			4.48	0.158
2,4′,5-Trichlorobiphenyl	223	195	223	195
2′,3,5-Trichlorobiphenyl			4.48	0.158
3,3′,4-Trichlorobiphenyl	4.29	2.71	6.32	2.62
3,3′,5-Trichlorobiphenyl			4.48	0.158
3,4,4′-Trichlorobiphenyl	30.1	25.9	30.1	25.9
3,4,5-Trichlorobiphenyl			4.48	0.158
3,4′,5-Trichlorobiphenyl			4.48	0.158
2,2′,3,3′-TeCB	14.4	15.4	19.2	15.4
2,2′3,4-TeCB/2,3,4′,6-TeCB/2,3′,4′,6-TeCB/2,3′,5,5′-TeCB	108	106	108	106
2,2′,3,4′-TeCB/2,3,3′,6-TeCB	35.7	35.5	37.3	34.8
2,2′,3,5-TeCB/2,2′4,5′-TeCB	141	142	141	142
2,2′,3,5′-TeCB	173	192	173	192

Table D5
Concentrations of PCBs and Dioxins in NTP-2000 Rat and Mouse Ration

Analyte	Mean Concentration	Standard Deviation	Mean LOQ	Standard Deviation
2,2′,3,6-TeCB	17.7	18.1	21.7	17.8
2,2′,3,6′-TeCB	5.75	3.36	11.4	3.97
2,2′,4,4′-TeCB	45.1	39.3	45.1	39.3
2,2′,4,5-TeCB/2,4,4′,6-TeCB	26.1	27.2	29.4	26.6
2,2′,4,6-TeCB			8.96	0.314
2,2′,4,6′-TeCB	6.15	3.60	11.8	4.51
2,2′,5,5′-TeCB/2,3′,4,6-TeCB	371	441	371	441
2,2′,5,6′-TeCB	20.0	19.3	24.1	19.9
2,2′,6,6′-TeCB			8.96	0.314
2,3,3′,4-TeCB			8.96	0.314
2,3,3′,4,′-TeCB/2,3,4,4′-TeCB	70.4	80.9	70.4	80.9
2,3,3′,5-TeCB			8.96	0.314
2,3,3′,5′-TeCB			8.96	0.314
2,3,4,5-TeCB			8.96	0.314
2,3,4,6-TeCB			8.96	0.314
2,3,4′,5-TeCB	1.25		9.40	1.49
2,3,5,6-TeCB			8.96	0.314
2,3′,4,4′-TeCB	104	116	104	116
2,3′,4,5-TeCB			8.96	0.314
2,3′,4,5′-TeCB			8.96	0.314
2,3′,4′,5-TeCB	197	238	197	238
2,3′,5′,6-TeCB			8.96	0.314
2,4,4′,5-TeCB	67.2	80.3	68.0	78.7
2′,3,4,5-TeCB			8.96	0.314
3,3′,4,4′-TeCB	6.95	3.92	12.6	5.59
3,3′,4,5-TeCB			8.96	0.314
3,3′,4,5′-TeCB			8.96	0.314
3,3′,5,5′-TeCB			8.96	0.314
3,4,4′,5-TeCB			8.96	0.314
2,2′,3,3′,4-PeCB	16.7	24.2	20.8	20.5
2,2′,3,3′,5-PeCB			8.96	0.314
2,2′,3,3′,6-PeCB/2,2′,3,5,5′-PeCB	106	124	106	124
2,2′,3,4,4′-PeCB	27.6	38.1	30.9	34.3
2,2′,3,4,5-PeCB			8.96	0.314
2,2′,3,4,5′-PeCB/2,3,4′,5,6-PeCB/2′,3,4,5,6′-PeCB	66.5	79.2	66.5	79.2
2,2′,3,4,6-PeCB/2,2′,3,4′,6-PeCB	38.1	47.7	41.4	45.0
2,2′,3,4,6′-PeCB	0.882		9.03	0.385
2,2′,3,4′,5-PeCB/2,2′,4,5,5′-PeCB	233	252	233	252
2,2′,3,5,6-PeCB			8.96	0.314
2,2′,3,5,6′-PeCB			8.96	0.314
2,2′,3,5′,6-PeCB/2,2′,3′,4,6-PeCB/2,2′,4,5,6′-PeCB	237	287	237	287
2,2′,3,6,6′-PeCB			8.96	0.314
2,2′,3′,4,5-PeCB	61.3	77.5	62.9	74.3
2,2′,4,4′,5-PeCB	109	116	109	116
2,2′,4,4′,6-PeCB			8.96	0.314
2,2′,4,5′,6-PeCB			8.96	0.314
2,2′,4,6,6′-PeCB			8.96	0.314
2,3,3′,4,4′-PeCB	32.4	31.4	32.4	31.4
2,3,3′,4,5-PeCB	142	187	142	187
2,3,3′,4′,5-PeCB/2,3,3′,4,6-PeCB	7.59	6.23	13.2	6.96
2,3,3′,4,5′PeCB/2,3,3′,5,6-PeCB	6.10	7.90	12.5	7.23
2,3,3′,4′,6-PeCB	127	142	127	142
2,3,3′,5,5′-PeCB/2,3,4,4′,6-PeCB	3.88	6.58	10.3	3.86
2,3,3′,5′,6-PeCB			8.96	0.314

TABLE D5
Concentrations of PCBs and Dioxins in NTP-2000 Rat and Mouse Ration

Analyte	Mean Concentration	Standard Deviation	Mean LOQ	Standard Deviation
2,3,4,4′,5-PeCB	0.927		9.08	0.487
2,3′,4,4′,5-PeCB	130	198	131	192
2,3′,4,4′,6-PeCB	1.26		9.40	1.49
2,3′,4,5,5′-PeCB			8.96	0.314
2,3′,4,5′,6-PeCB			8.96	0.314
2′,3,3′,4,5-PeCB			8.96	0.314
2′,3,4,4′,5-PeCB			8.96	0.314
2′,3,4,5,5′-PeCB	1.49		9.64	2.26
3,3′,4,4′,5-PeCB			8.96	0.314
3,3′,4,4,5′-PeCB			8.96	0.314
2,2′,3,3′,4,4′-HxCB/2,3,3′,4′,5,5′-HxCB	7.48	7.04	13.1	7.06
2,2′,3,3′,4,5-HxCB			8.96	0.314
2,2′,3,3′,4,5′-HxCB	2.52	0.495	9.86	2.00
2,2′,3,3′,4,6-HxCB			8.96	0.314
2,2′,3,3′,4,6′-HxCB/2,3,3′,4,5′,6-HxCB	18.9	18.6	21.3	17.5
2,2′,3,3′,5,5′-HxCB/2,2′,3,4,5,6-HxCB	3.45	1.45	9.90	1.88
2,2′,3,3′,5,6-HxCB/2,2′,3,4,5,6′-HxCB	2.79	2.62	10.1	2.75
2,2′,3,3′,5,6′-HxCB	14.0	12.9	18.0	12.6
2,2′,3,3′,6,6′-HxCB	16.1	18.9	20.9	18.3
2,2′,3,4,4′,5-HxCB			8.96	0.314
2,2′,3,4,4′,5′-HxCB/2,3,3′,4′,5,6-HxCB/2,3,3′,4′,5′,6-HxCB	88.3	65.5	88.3	65.5
2,2′,3,4,4′,6-HxCB	89.2	68.4	89.2	68.4
2,2′,3,4,4′,6′-HxCB			8.96	0.314
2,2′,3,4,5,5′-HxCB	6.01	4.88	11.7	4.70
2,2′,3,4,5′,6-HxCB	1.31		9.46	1.67
2,2′,3,4, 6,6′-HxCB			8.96	0.314
2,2′,3,4′,5,5′-HxCB/2,3,3′,4′,5′6-HxCB	25.0	21.5	25.8	21.2
2,2′,3,4′,5,6-HxCB	1.03		9.18	0.768
2,2′,3,4′,5,6′-HxCB			8.96	0.314
2,2′,3,4′,6,6′-HxCB			8.96	0.314
2,2′,3,5,5′,6-HxCB	21.9	18.2	24.3	18.1
2,2′,3,5,6,6′-HxCB			8.96	0.314
2,2′,4,4′,5,5′-HxCB	587	1,513	587	1,514
2,2′,4,4′,5,6′-HxCB	1.59		9.75	2.59
2,2′,4,4′,6,6′-HxCB			8.96	0.314
2,3,3′,4,4′,5-HxCB	1.79	0.382	9.05	0.423
2,3,3′,4,4′,5′-HxCB			8.96	0.314
2,3,3′,4,4′,6-HxCB/2,3,3′,4,5,6-HxCB	3.79	2.82	10.2	2.67
2,3,3′,4,5,5′-HxCB			8.96	0.314
2,3,4,4′,5,6-HxCB			8.96	0.314
2,3′,4,4′,5,5′-HxCB	0.865		9.02	0.352
2,3′,4,4′,5′,6-HxCB			8.96	0.314
3,3′,4,4′,5,5′-HxCB			8.96	0.314
2,2′,3,3′,4,4′,5-HpCB	10.9	9.25	14.1	8.29
2,2′,3,3′,4,4′,6-HpCB	0.945		9.10	0.532
2,2′,3,3′,4,5,5′-HpCB			8.96	0.314
2,2′,3,3′,4,5,6-HpCB			8.96	0.314
2,2′,3,3′,4,5,6′-HpCB	9.18	8.79	13.2	7.48
2,2′,3,3′,4,5′,6-HpCB			8.96	0.314
2,2′,3,3′,4,6,6′-HpCB			8.96	0.314
2,2′,3,3′,4′,5,6-HpCB	8.07	9.24	12.9	7.46
2,2′,3,3′,5,5′,6-HpCB	4.98	7.90	11.4	5.64
2,2′,3,3′,5,6,6′-HpCB	4.77	8.51	11.3	5.51
2,2′,3,4,4′,5,5′-HpCB	33.4	21.9	33.4	21.9
2,2′,3,4,4′,5,6-HpCB			8.96	0.314

TABLE D5
Concentrations of PCBs and Dioxins in NTP-2000 Rat and Mouse Ration

Analyte	Mean Concentration	Standard Deviation	Mean LOQ	Standard Deviation
2,2′,3,4,4′,5,6′-HpCB/2,2′,3,4′,5,5′,6-HpCB	38.1	34.0	38.1	34.0
2,2′,3,4,4′,5′,6-HpCB	7.49	9.53	12.3	7.22
2,2′,3,4,4′,6,6′-HpCB			8.96	0.314
2,2′,3,4,5,5′,6-HpCB			8.96	0.314
2,2′,3,4,5,6,6′-HpCB			8.96	0.314
2,2′,3,4′,5,6,6′-HpCB			8.96	0.314
2,3,3′,4,4′,5,5′-HpCB			8.96	0.314
2,3,3′,4,4′,5,6-HpCB			8.96	0.314
2,3,3′,4,4′,5′,6-HpCB			8.96	0.314
2,3,3′,4,5,5′,6-HpCB			8.96	0.314
2,3,3′,4′,5,5′,6-HpCB			8.96	0.314
2,2′,3,3′,4,4′,5,5′-OCB	2.41		14.2	4.22
2,2′,3,3′,4,4′,5,6-OCB			13.0	1.07
2,2′,3,3′,4,4′,5,6′-OCB/2,2′,3,4,4′,5,5′,6-OCB	6.94	15.4	16.6	8.94
2,2′,3,3′,4,4′,6,6′-OCB			13.0	1.07
2,2′,3,3′,4,5,5′,6-OCB			13.0	1.07
2,2′,3,3′,4,5,6,6′-OCB	7.65	17.5	17.3	10.4
2,2′,3,3′,4,5′,6,6′-OCB			13.0	1.07
2,2′,3,3′,4,5,5′,6′-OCB	1.64		13.4	1.85
2,2′,3,3′,5,5′,6,6′-OCB	3.18		15.0	6.73
2,2′,3,4,4′,5,6,6′-OCB			13.0	1.07
2,3,3′,4,4′,5,5′,6-OCB			13.0	1.07
2,2′,3,3′,4,4′,5,5′,6-NCB	6.15		18.0	16.5
2,2′,3,3′,4,4′,5,6,6′-NCB	1.65		13.4	1.90
2,2′,3,3′,4,5,5′,6,6′-NCB	4.36		16.1	10.6
DeCB	6.17		18.0	16.6

[a] Data presented as pg analyte/g feed; LOQ=Limit of quantitation. Dioxin and dibenzofuran congeners were analyzed by EPA Method 1613, using GC with high resolution mass spectrometry and isotope dilution. PCB congeners were analyzed by EPA Method 1668, using GC with high resolution mass spectrometry.

[b] Mean concentration of samples with measurable concentrations; blanks indicate concentrations below the limit of detection in all samples.

APPENDIX E
SENTINEL ANIMAL PROGRAM

Methods 154
Results 154

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 male and female sentinel rats at 1 month, male sentinel rats at 6, 12, and 18 months, and from randomly selected 3,000 µg/kg female rats at the end of the study. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to MA Bioservices/BioReliance (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.

Method and Test	Time of Analysis
ELISA	
Mycoplasma arthritidis	Study termination
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	
Parvovirus	1, 6, 12, and 18 months, study termination

RESULTS

All test results were negative.

APPENDIX F
PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

INTRODUCTION 156
MODEL DEVELOPMENT 157
RESULTS AND DISCUSSION 158
TABLE F1 Parameter Estimates and Partition Coefficients for PCB 153 and TCDD 159
FIGURE F1 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the Vehicle Control Group in the 2-Year Study 160
FIGURE F2 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the 10 µg/kg Group in the 2-Year Study 161
FIGURE F3 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the 100 µg/kg Group in the 2-Year Study 162
FIGURE F4 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the 300 µg/kg Group in the 2-Year Study 163
FIGURE F5 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the 1,000 µg/kg Group in the 2-Year Study 164
FIGURE F6 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the 3,000 µg/kg Group in the 2-Year Study 165
FIGURE F7 Model Predictions and Individual Tissue Data for Tissue Concentrations of PCB 153 and Enzyme Activities for the 3,000 µg/kg Stop-Exposure Group in the 2-Year Study 166

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

INTRODUCTION

A physiologically based pharmacokinetic (PBPK) model for PCB 153 was developed in support of the dioxin toxic equivalency factor (TEF) evaluation studies. The model is based on a PBPK model for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (NTP, 2006b). A goal for the PBPK modeling of the disposition data from the TEF evaluation studies is a general model for the tissue distribution of dioxin-like chemicals and mixtures of compounds that interact with the aryl hydrocarbon receptor (AhR) in the Sprague-Dawley rat.

One key aspect to understanding the toxicity of an agent is how dose is related to the toxicity of concern. The utility of a PBPK model is in its ability to predict alternate measures of "dose" other than those that are readily measured (such as administered dose or tissue concentrations). In addition, the kinetics of tissue distribution of a compound can be compared between different routes and patterns of exposure. Also, an understanding of the factors that govern the tissue distribution of a compound and its metabolites and subsequent molecular/biochemical responses may provide insights into the factors governing the dose response of toxicity, site specificity, and mode of action of the compound under study.

In general, PBPK models have been validated in the observable response range for numerous compounds in both animals and humans, making them useful for risk assessment, especially for cross-species extrapolation. They also aid in extrapolation from one chemical to other structurally related chemicals because many of the components of the model are the same or can be deduced for related compounds.

The time course of behavior in each compartment of a PBPK model is defined by equations and model parameters for input and loss of chemical. The specific structure of a PBPK model and the assumptions used to develop the model are encoded in the equations. The model's physiological parameters are, in many cases, compound independent, well established, and available in the literature (e.g., rates of blood flow, blood volume, tissue volumes, etc.). Physicochemical parameters are used that are often specific to a given compound but can be measured experimentally and may be available in the literature. Some of these parameters may not be available *a priori* and so have to be determined within the framework of the model by an iterative process of changing the parameter, fitting the model to a given dataset, and evaluating the goodness of the fit of the model to the data. Careful evaluation of any PBPK model must involve the adequacy of its fit to the data, the relationship of its structure to the underlying biology, and the mathematical details linking these two. In addition, the biological plausibility of optimized parameters needs to be considered. Validation of the model using datasets that were not used in its construction lends more credence to the predictive power of a model.

The disposition of a chemical within the body is governed by the absorption of an administered chemical and its distribution among tissues, metabolism, and elimination from the body (ADME). These processes for TCDD and related dioxin-like compounds in part depend upon their physicochemical properties (e.g., tissue permeation constants, partition coefficients, kinetic constants, and biochemical parameters) and physiological parameters (e.g., organ volumes and blood flow rates). A PBPK model for TCDD describes the pharmacokinetics of TCDD by a series of mass-balance differential equations in which the state variables represent the concentration of TCDD in anatomically distinct regions or "compartments" of the body. These tissue compartments are linked by a physiologically realistic pattern of blood perfusion and flow through the different tissue compartments.

A model for PCB 153 was built from a model for TCDD. Data for tissue concentrations, 7-ethoxyresorufin-*O*-deethylase (EROD) and acetanilide-4-hydroxylase (A4H) in female Sprague-Dawley rats chronically dosed with PCB 153 were available to aid the model development. These data were used to estimate model parameters that should be different between TCDD and PCB 153. With the estimated parameters, the model fits the data across

the dose range. The key result is that the model fits the fat and liver data when there is almost no binding of PCB 153 to AhR or CYP1A2.

Model Development

The same basic model structure was used for all compounds studied in the dioxin TEF evaluation, with some of the model parameters unique to each compound such as those parameters involved in metabolism or binding to AhR. The common model for individual compounds was based upon the model of Kohn *et al.* (2001). The Kohn model is an extension of earlier PBPK models for TCDD in rats (Kohn *et al.*, 1993, 1996) that with each iteration has gone through further rounds of refinement and inclusion of increased biological complexity. A thorough summary of PBPK modeling for TCDD including the basic model used in this study can be found elsewhere (USEPA, 2000a).

Kohn's model for TCDD includes compartments for fat, liver, kidney, gastrointestinal tract, muscle, and viscera. Blood is distributed among arterial, venous, and tissue capillary spaces. The model includes equations for the liver amounts of AhR, CYP1A1, CYP1A2, and CYP1B1, as well as equations describing the basal expression, induction by TCDD, and degradation of the mRNA for each of these. The amount of each enzyme depends on the time-lagged concentration of the corresponding mRNA. TCDD in the liver may bind to CYP1A2 and AhR. A key to the model is that the induction rates of all four represented mRNAs depend on the time-lagged concentration of AhR bound to TCDD. Induction increases from zero to a maximum rate as the concentration of AhR-TCDD increases. The model also includes a blood protein that can bind TCDD. Since transthyretin (also known as prealbumin) can bind hydroxylated polychlorinated dibenzodioxins (PCDDs), and single doses of TCDD can cause a prolonged decrease in this protein, a dose-dependent decrease of blood protein was included in the model. This protein bound TCDD cannot enter the tissues in the model but may become free in the blood by dissociation or proteolysis. To fit data at both low and high doses, this model includes loss of TCDD from the liver by lysis of dead cells (as a result of hepatotoxicity), where the rate of cell death was assumed to increase as a hyperbolic function of the cumulative amount of unbound hepatic TCDD.

There were several steps to building a PBPK model for the dioxin TEF evaluation studies; addition of a lung compartment because the data for the NTP TEF studies includes lung tissue concentrations, converting the body weight function, functional links between model protein levels and activity data, linking the mixtures together. The lung compartment is diffusion-limited and includes the same equations as those used in the liver for AhR, CYP1A1, and CYP1B1. The lung and liver compartments use the same gene expression parameters on a per liter basis. Values of the lung partition coefficient and the lung permeability factor parameters were estimated by optimization, fitting the model predictions to TCDD tissue data (liver, lung, fat, blood).

Kohn's model (Kohn *et al.*, 2001) has a specific time-dependent function for the body weight. This function does not apply to the female Sprague-Dawley rats. Body weights were available weekly for the first 12 weeks of the studies and then monthly for the remainder of the studies, so these weights were used in the model. For each dose group, the interpolated mean body weights were used as the time-dependent body weight function.

Functional relationships linking CYP1A1 to EROD activity and CYP1A2 to A4H activity were added to the model. Kohn's TCDD model (Kohn *et al.*, 2001) was used to set up these relationships. The model was run for the TEF TCDD doses (0, 3, 10, 22, 46, or 100 ng/kg per day) to get model-predicted CYP1A1 (nmole) and CYP1A2 (nmole) at 13, 30, and 52 weeks for each dose. EROD data was fit as a Hill function of model-predicted CYP1A1 while A4H activity was fit as a linear function of CYP1A2.

Partition coefficients for PCB 153 were based on the partition coefficients in Kohn's TCDD model. Kohn fit the TCDD partition coefficients along with the tissue permeability. Assuming that the permeability is the same for TCDD and PCB 153, the permeability values from Kohn's model can be used and only the partition coefficients

are needed for PCB 153. The ratio of n-octanol to water partition coefficients (logP) was used to scale the TCDD partition coefficients to the partition coefficients of PCB 153. Tissue partition coefficients (PC) of TCDD were multiplied by the ratio of logP values, i.e.:

$$PC_{PCB\ 153}=PC_{TCDD} * \log P_{PCB\ 153}/\log P_{TCDD}$$

While many model parameters might be different for each dioxin-like chemical, the procedure was to start with a small set of the most likely parameters. The parameters for binding to AhR, CYP1A2, and blood protein were the first group. In turn, parameters for metabolism, absorption, and hepatotoxicity were added to the list of chemical-specific parameters. The binding, metabolic, hepatotoxic, and absorption parameters were estimated by fitting the model predictions to logarithmic values of liver EROD and A4H activities and tissue data (liver, fat, blood, lung). Two parameters describing hepatotoxicity, k_{lysis} and $k_{recovery}$, are included in the optimizations because they are multipliers of the chemical concentration in the cytotoxicity equations (Kohn *et al.*, 2001). Thus, the model can represent the differences in the amount of chemical causing liver tissue damage among the dioxin-like chemicals. The background PCB 153 concentration used in the model was 29.5 ng/kg per day. The background concentration in the NTP diet had a range of 1.7 to 257 ng/kg per day so additional optimizations were also run with the background an adjustable parameter. All of the other model parameters are kept as constants from Kohn's model. The model was written in Simulink® and all optimizations were run in Matlab®.

One potentially important difference between modeling PCBs and TCDD not included in the present model is a rat liver cytosolic protein different from AhR and CYP1A2 that binds PCBs but not dioxin (Buff and Brundl, 1992, Brundl and Buff, 1993). While little is known about this PCB binding protein, its effects may need to be added in applications of the model involving multiple PCBs in a mixture.

Results and Discussion

Nine parameters were estimated by fitting the model predictions to data (Table F1). All other model parameters were the same as the TCDD model. The model fits the lung, fat, and liver tissue data but predictions of blood concentration are consistently too high. The parameter estimates suggest there is very little binding of PCB 153 to blood protein, AhR, or CYP1A2. Also, there is very little metabolism of PCB 153. The EROD and A4H data and model predictions stay within control ranges across doses, further indicating no binding of PCB 153 to AhR. The binding parameter for PCB 153 (1.7×10^{-5}) is much smaller than the constant for TCDD (1,000/nmole per day) and the data can be fit with binding set to zero. However, the best fit includes a small amount of binding. The predictions for fat in the control data were too low with a background level of 29.5 ng/kg per day. The optimized background dose (150 ng/kg per day) is higher than 29.5 ng/kg per day, but it is in the range of possible levels. Both values are small compared to the administered doses. The background level only impacts the control dose predictions. For the 10 µg/kg per day PCB 153 dose, 150 ng/kg per day is only 1.5% of the administered dose and the background is less the 1% of the dose for all the other doses. The optimizations with background fixed at 29.5 ng/kg per day were equal to the 150 ng/kg per day except that the 29.5 ng/kg values had a lower prediction for fat concentration in the control dose. The plots are shown for 150 ng/kg per day.

The fits of the A4H and EROD data would probably be improved by refining the functional forms relating these endpoints to model predictions of CYP1A2 and CYP1A1, respectively. The control levels of A4H and EROD in the model are very dependent on these functional forms and on the control activity levels in the TCDD experiment. The model for PCB 153 consistently predicts EROD below the data (Figures F1 to F7) but the control EROD data in the TCDD study were always higher than the EROD data in the PCB 153 data. In the TCDD study, the difference between control EROD and EROD for the other dosed levels (3, 10, 22, 46, 100 ng/kg per day) is two orders of magnitude. The difference between the TCDD and PCB 153 control EROD data is not significant compared to changes in EROD when CYP1A2 binds with a dioxin-like chemical. However, because the PCB 153

EROD levels stay low across doses and the TCDD data has lower control EROD than PCB 153, the PCB model has low predictions for PCB 153 EROD. The correction involves combining data across studies to change the function relating EROD to CYP1A2 and will be considered in the next revision of the model. Control levels of A4H are nearly identical for the TCDD and PCB 153 studies so the PCB 153 model makes accurate predictions of the A4H levels.

TABLE F1
Parameter Estimates and Partition Coefficients for PCB 153 and TCDD

	PCB 153	TCDD	Unit
Parameter Estimates			
Background	150.0	0.082	ng/kg per day
$Kd_{protein}$ (blood binding protein)	0.015	10	nM
K_{AhR}	4.28	0.27	nM
K_{CYP1A2}	15.91	30	nM
$V_{metabolism}$	1.0×10^{-4}	9.12	nmole/L per day
$K_{metabolism}$	2.51	0.968	nM
$n_{metabolism}$	—	1.12	—
$k_{absorption}$	0.71	4.8	$kg^{0.75}$/day
$k_{binding}$	1.7×10^{-5}	1,000	/nmole per day
k_{lysis}	0.47	200	/day
Partition Coefficients			
Fat	206.0	187.0	
Muscle	4.93	4.48	
Viscera	3.69	3.35	
Liver	5.06	4.60	
Kidney	3.69	3.35	
Gastrointestinal tract	3.69	3.35	
Lung	5.06	4.57[a]	

[a] This coefficient is estimated.

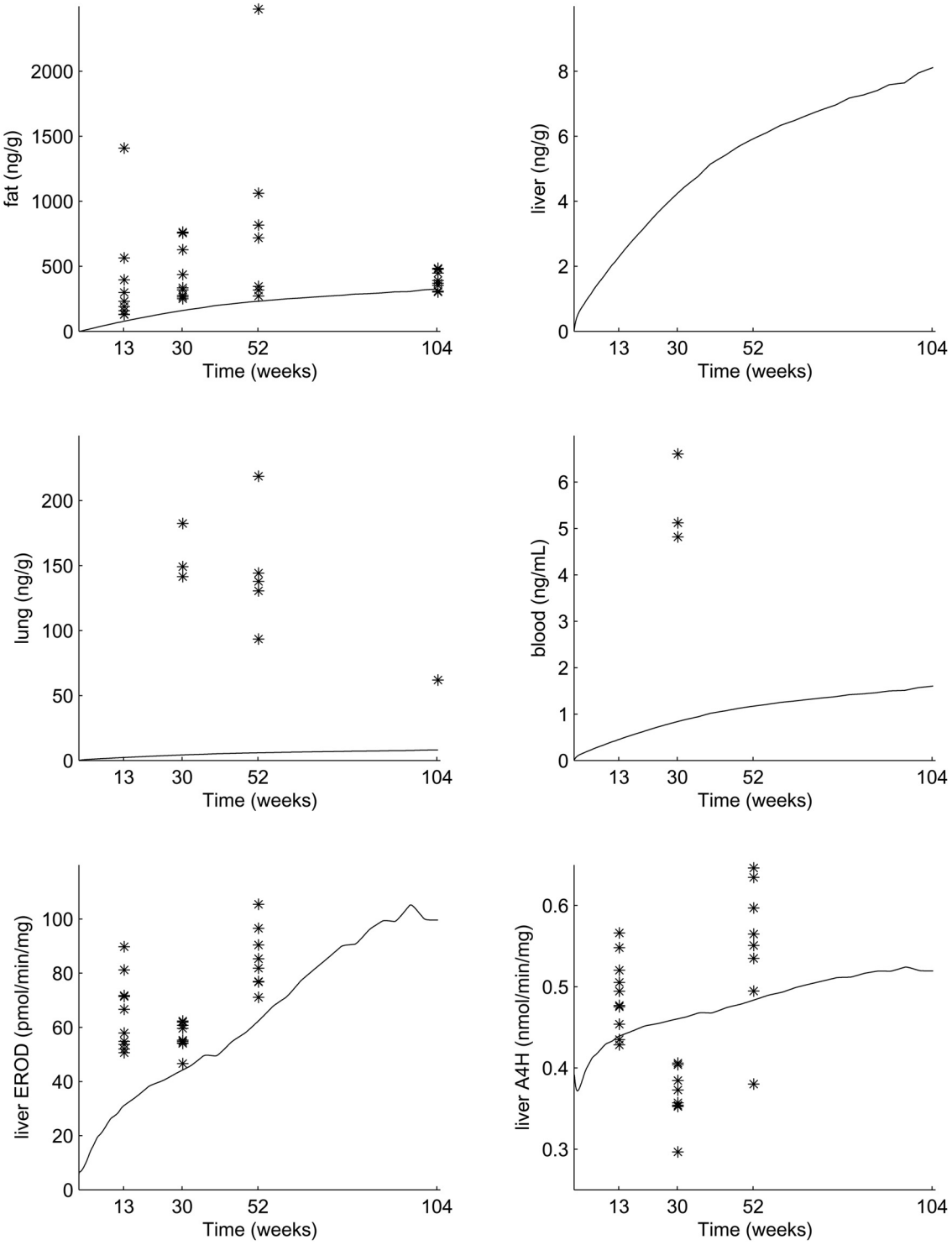

FIGURE F1
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the Vehicle Control Group in the 2-Year Study

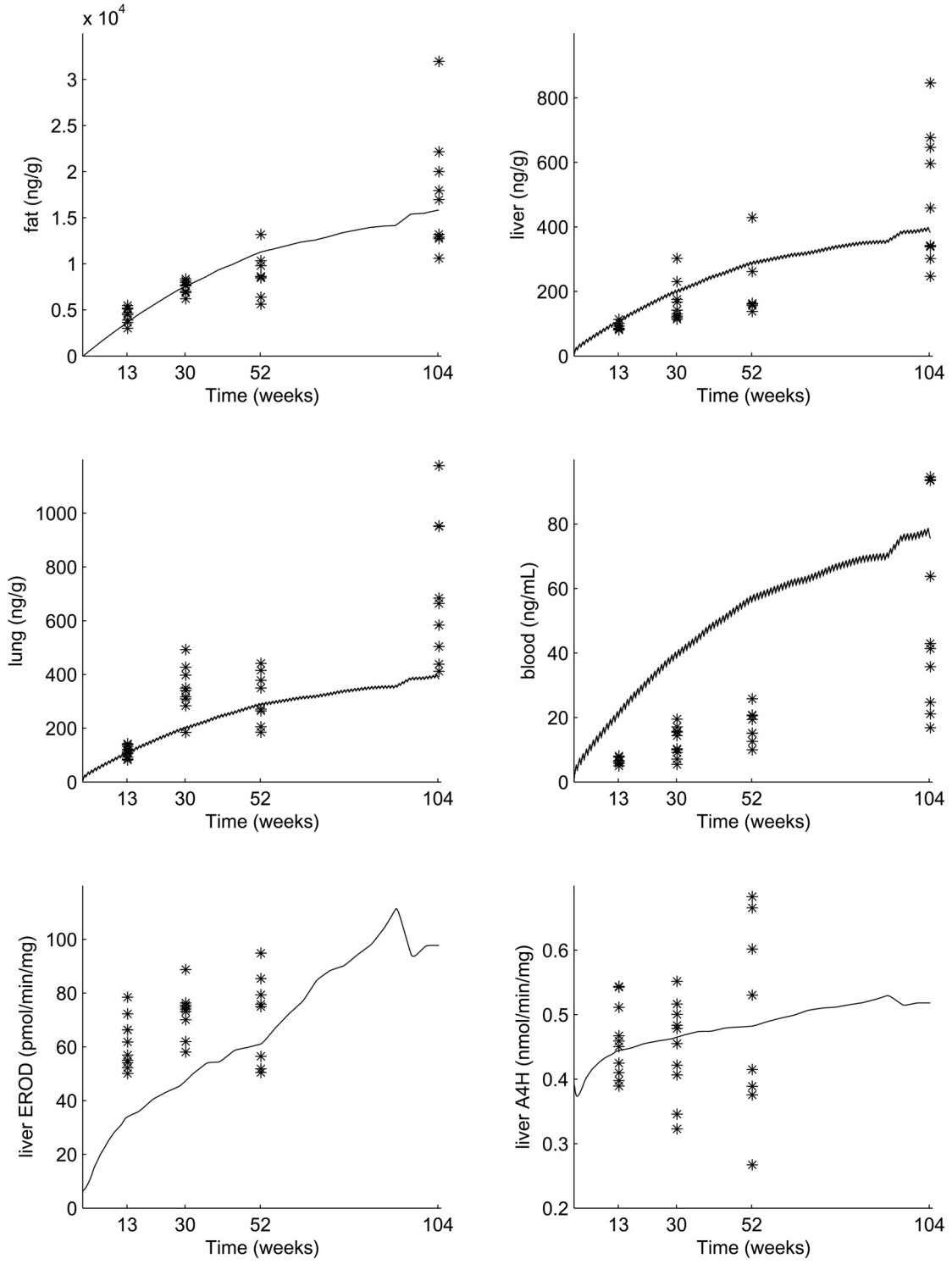

FIGURE F2
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the 10 µg/kg Group in the 2-Year Study

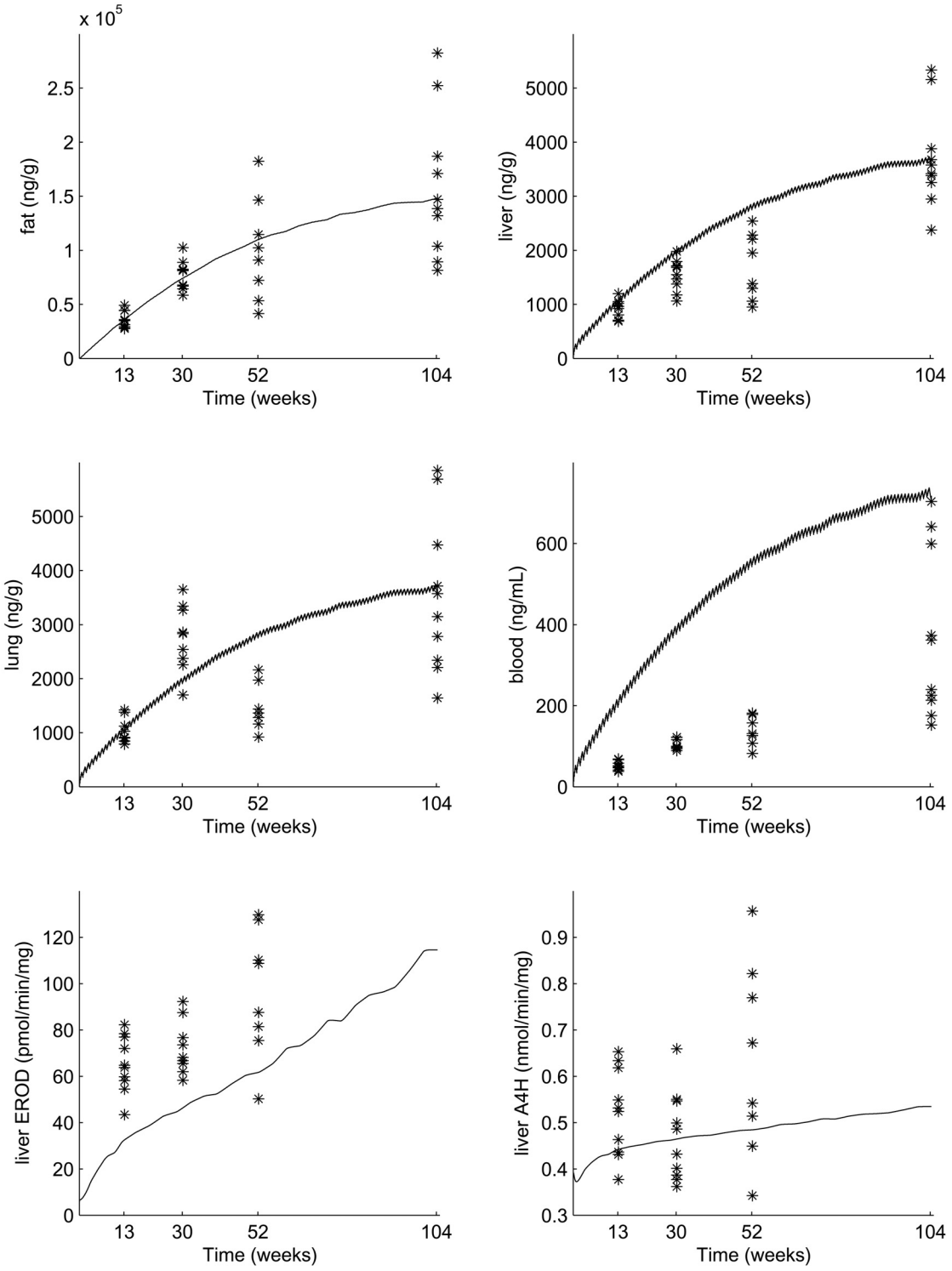

FIGURE F3
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the 100 µg/kg Group in the 2-Year Study

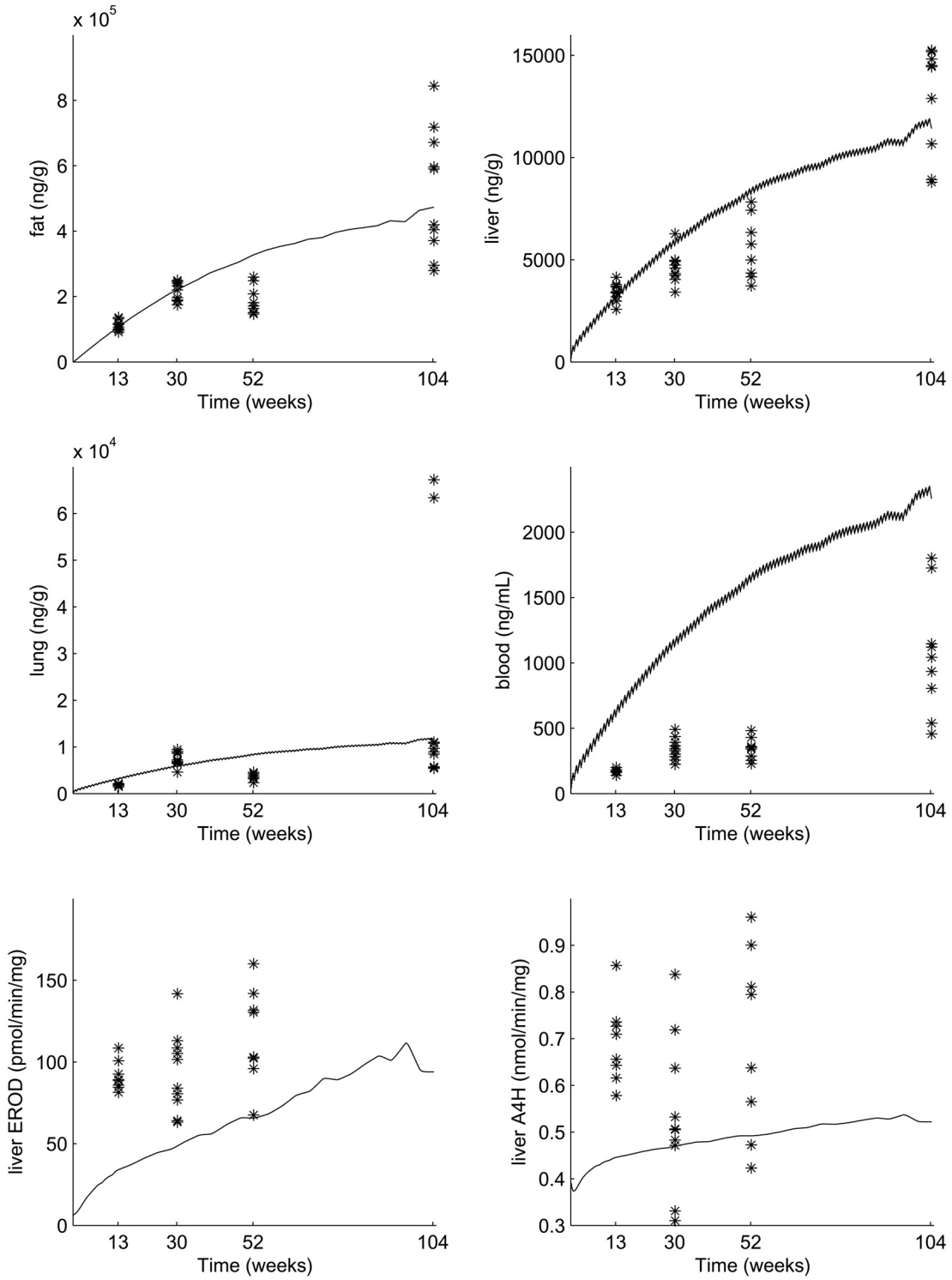

FIGURE F4
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the 300 µg/kg Group in the 2-Year Study

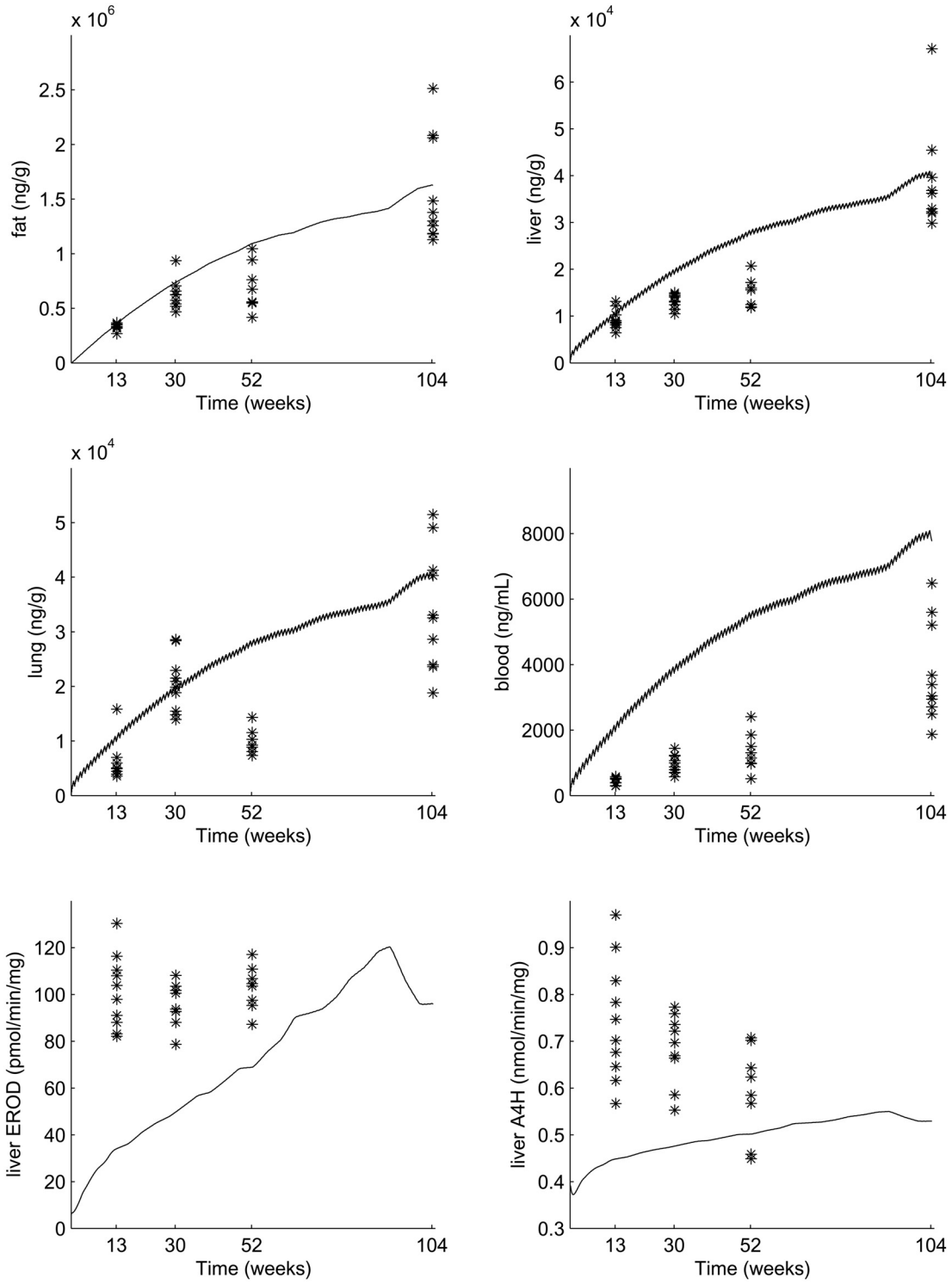

FIGURE F5
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the 1,000 µg/kg Group in the 2-Year Study

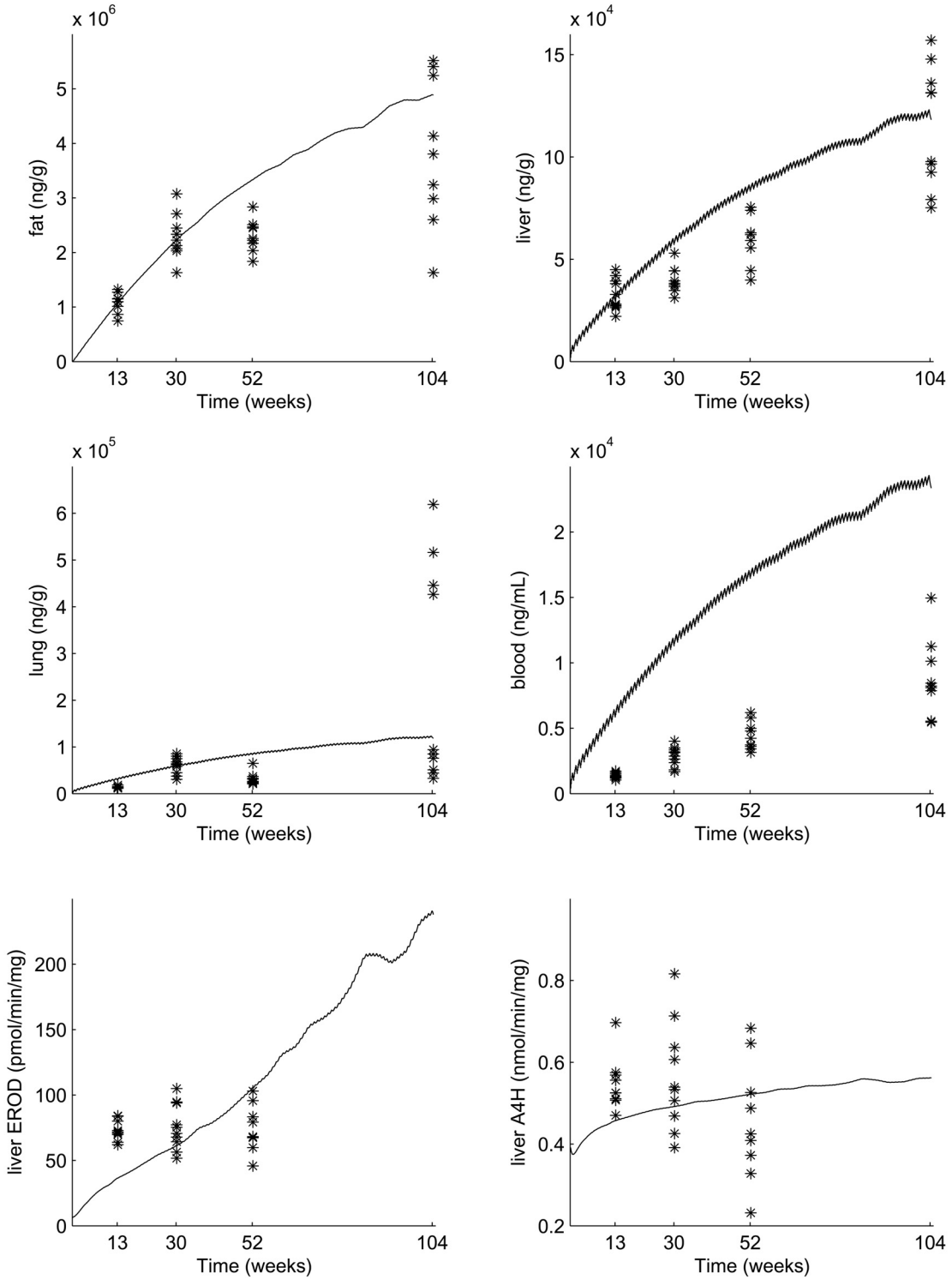

FIGURE F6
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the 3,000 µg/kg Group in the 2-Year Study

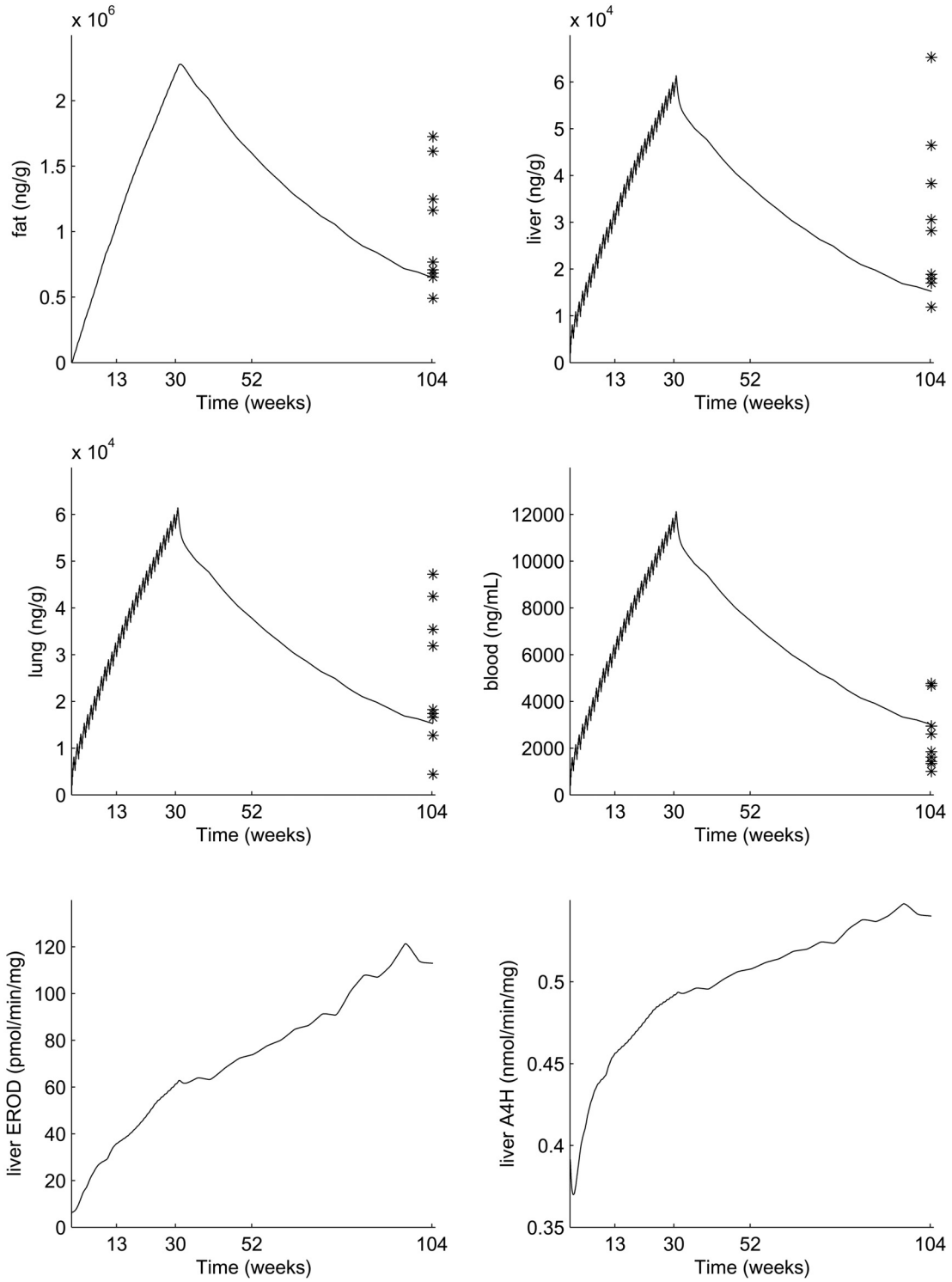

FIGURE F7
Model Predictions (—) and Individual Tissue Data (*) for Tissue Concentrations of PCB 153 and Enzyme Activities for the 3,000 µg/kg Stop-Exposure Group in the 2-Year Study

APPENDIX G
ASSOCIATED PUBLICATIONS

The following peer reviewed journal publications have been published using data or special study samples obtained from this study and other studies carried out as part of the dioxin TEF evaluation.

Brix, A.E., Jokinen, M.P., Walker, N.J., Sells, D.M., and Nyska, A. (2004). Characterization of bronchiolar metaplasia of the alveolar epithelium in female Sprague-Dawley rats exposed to 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126). *Toxicol. Pathol.* **32**, 333-337.

Brix, A.E., Nyska, A., Haseman, J.K., Sells, D.M., Jokinen, M.P., and Walker, N.J. (2005). Incidences of selected lesions in control and female Harlan Sprague-Dawley rats from two year studies performed by the National Toxicology Program. *Toxicol. Pathol.* **33**, 477-483.

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