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

NTP Technical Report on the Toxicology and Carcinogenesis Studies of 3,3′,4,4′,5-Pentachlorobiphenyl (PCB 126) (CAS No. 57465-28-8) in Female Harlan Sprague-Dawley Rats (Gavage Studies)

NTP TR 520

JANUARY 2006

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

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

(CAS NO. 57465-28-8)

IN FEMALE HARLAN SPRAGUE-DAWLEY RATS

(GAVAGE STUDIES)

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

January 2006

NTP TR 520

NIH Publication No. 06-4454

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.

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

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CONTENTS

SUMMARY

Background
3,3′4,4′5-Pentachlorobiphenyl (PCB 126) is one of a large family of hydrocarbons containing chlorine (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. This study evaluated the effects of PCB 126 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 dissolved in corn oil through a tube directly into their stomachs five days a week for two years. Daily doses of PCB 126 were 30, 100, 175, 300, 550, or 1,000 nanograms (ng) per kilogram of body weight. Tissues from more than forty sites were examined for every animal.

Results
Exposure to PCB 126 caused a variety of diseases in several organs. Cancers of the liver, lung, and mouth were seen in female rats exposed to PCB 126. A variety of other toxic lesions observed in exposed animals included hypertrophy, hyperplasia, and fibrosis of the liver, metaplasia of the lung, atrophy of the adrenal gland, inflammation and atrophy of the pancreas, kidney nephropathy, cardiomyopathy of the heart, hypertrophy of the adrenal gland, atrophy of the thymus and spleen, and inflammation of the mesentery.

Conclusions
We conclude that PCB 126 caused cancer and other toxic effects at several sites in female rats.

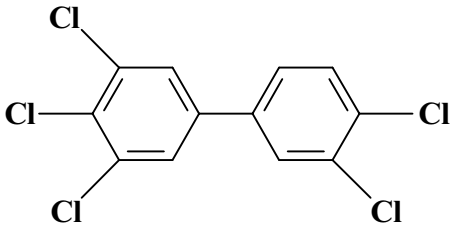
ABSTRACT

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 that bind to the AhR and exhibit biological actions similar to TCDD are commonly referred to as "dioxin-like compounds" (DLCs). 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 tissue, mainly adipose, resulting in chronic lifetime human exposure.

Since human exposure to DLCs always involves 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, which is the most potent congener. This allows for the estimation of the potential 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.



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

CAS No. 57465-28-8

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

Synonyms: 1,1′-Biphenyl, 3,3′,4,4′,5-pentachloro-(9CI)

3,3′,4,4′,5-Pentachlorobiphenyl (PCB 126) was produced commercially before 1977 for the electric industry as a dielectric insulating fluid for transformers and capacitors. Manufacture and use of the chemical was stopped because of 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 by-products during the manufacture of certain organic chemicals, and during combustion of some waste materials. Bioaccumulation of PCB 126 results in persistent levels in animal and human tissues and the biological responses to PCB 126 are similar to those of TCDD, a known human carcinogen. PCB 126 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 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 126 was included since this is the most potent coplanar PCB that has dioxin-like activities. While one of the aims of the dioxin TEF evaluation was a comparative analysis across studies, in this Technical Report only the results of the PCB 126 study are presented and discussed. Female Harlan Sprague-Dawley rats were administered PCB 126 (99% pure) in corn oil with acetone by gavage for 14, 31, or 53 weeks or 2 years.

2-Year Study

Groups of 81 female rats were administered 30, 100, 175, 300, 550, or 1,000 ng PCB 126/kg body weight in corn oil:acetone (99:1) by gavage, 5 days per week, for up to 104 weeks; a group of 81 vehicle control female rats received the corn oil/acetone vehicle alone. A group of 28 rats received 10 ng/kg for up to 53 weeks only. Up to 10 rats per group were evaluated at 14, 31, or 53 weeks. A stop-exposure group of 50 female rats was administered 1,000 ng/kg PCB 126 in corn oil:acetone (99:1) by gavage for 30 weeks then the vehicle for the remainder of the study.

Mean body weights of 30 and 100 ng/kg rats were similar to those of the vehicle controls during most of the study, mean body weights of 175 and 300 ng/kg rats were less than those of the vehicle controls during year 2 of the study, and mean body weights of 550 ng/kg, 1,000 ng/kg core study, and 1,000 ng/kg stop-exposure rats were less than those of the vehicle controls after week 17.

Thyroid Hormone Concentrations

Alterations in serum thyroid hormone levels were evaluated at the 14-, 31- and 53-week interim evaluations. In the 550 and 1,000 ng/kg rats, total thyroxine (T_4) and free T_4 levels were significantly lower than those of vehicle controls and serum triiodothyronine (T_3) and thyroid stimulating hormone (TSH) levels were significantly higher than vehicle controls at the 14-week interim evaluation. Serum T_3 was also significantly higher in the 300 ng/kg rats compared to vehicle controls at 14 weeks. At 31 weeks, T_3 was significantly higher at doses of 100 ng/kg or greater compared to vehicle controls. TSH levels were higher in 550 and 1,000 ng/kg rats than in vehicle controls. At 53 weeks, significantly lower serum concentrations of total T_4 and free T_4 were observed compared to vehicle controls in groups administered 175 ng/kg or greater and 30 ng/kg or greater, respectively. Serum T_3 levels were significantly higher at doses of 175 ng/kg or greater compared to vehicle controls. No changes in TSH levels were observed between vehicle controls and dosed rats at 53 weeks.

Hepatic Cell Proliferation Data

To evaluate hepatocyte replication, analysis of labeling of replicating hepatocytes with 5-bromo-2′-deoxyuridine was conducted at the 14-, 31-, and 53-week interim evaluations. The hepatocellular labeling index was significantly higher at doses of 300 ng/kg or greater at 14 weeks and 175 ng/kg or greater at 31 weeks compared to vehicle controls. No statistically significant differences were observed between vehicle controls and PCB 126 dosed rats at 53 weeks. However, at 53 weeks, a 5.8-fold increase above the vehicle controls was observed in the 1,000 ng/kg group.

Cytochrome P450 Enzyme Activities

To evaluate the expression of known dioxin-responsive genes, CYP1A1-associated 7-ethoxyresorufin-*O*-deethylase (EROD) activity and CYP1A2-associated acetanilide 4-hydroxylase (A4H) activity were evaluated at the 14-, 31-, and 53-week interim evaluations. In addition, CYP2B associated pentoxyresorufin-*O*-deethylase (PROD) activity was analyzed. Hepatic PROD (CYP2B1) and hepatic and pulmonary EROD (CYP1A1) activities were significantly greater in all dosed groups than in vehicle controls at weeks 14, 31, and 53. Hepatic A4H (CYP1A2) activity was significantly greater in the 30 ng/kg and greater groups compared to vehicle controls at weeks 14, 31, and 53.

Determinations of PCB 126 Concentrations in Tissues

The tissue disposition of PCB 126 was analyzed in the liver, lung, fat, and blood of all rats in vehicle controls and all dosed groups at the 14-, 31-, and 53-week interim evaluations and in 10 rats per group including vehicle controls at the end of the 2-year study (104 weeks). Detectable concentrations of PCB 126 were observed in the liver, fat, lung, and blood. Measurable concentrations of PCB 126 were present in the liver and fat at weeks 31, 53, and 104. Hepatic and fat concentrations increased with increasing doses of PCB 126. Measurable concentrations of PCB 126 were present in vehicle control lung tissue at 53 and 104 weeks. No PCB 126 was observed in the blood from the vehicle control rats. Lung and blood concentrations tended to increase with increasing doses of PCB 126, with a few exceptions. In the stop-exposure group, PCB 126 concentrations in liver and fat were lower than the levels observed in the 30 ng/kg group. In the stop-exposure group, lung tissue PCB 126 concentrations were equivalent to the levels observed in the 30 ng/kg group. In blood from the stop-exposure group, PCB 126 concentrations were equivalent to the levels observed in the 100 ng/kg group.

Pathology and Statistical Analyses

Absolute and relative liver weights were significantly increased at all time points and correlated with increased incidences of hepatocellular hypertrophy. At 2 years, there were significant treatment-related increases in the incidences of cholangiocarcinoma and hepatocellular adenoma. Three hepatocholangiomas were seen in the 1,000 ng/kg core study group and a single incidence of cholangioma each occurred in the 550 and 1,000 ng/kg core study groups.

At 2 years, a significant dose-related increase in hepatic toxicity was observed and was characterized by increased incidences of numerous lesions including hepatocyte hypertrophy, multinucleated hepatocytes, diffuse fatty change, bile duct hyperplasia, bile duct cyst, oval cell hyperplasia, necrosis, pigmentation, inflammation, nodular hyperplasia, portal fibrosis, cholangiofibrosis, and toxic hepatopathy. The incidences of these lesions were generally decreased in the 1,000 ng/kg stop-exposure group compared to the 1,000 ng/kg core study group.

The lung weights of 1,000 ng/kg rats were generally significantly increased at weeks 14, 31, and 53. At 2 years, treatment related increases in the incidences of cystic keratinizing epithelioma and squamous cell carcinomas were observed. In addition, dose-related increases in the incidences of bronchiolar metaplasia of the alveolar epithelium and squamous metaplasia were also observed.

The incidence of gingival squamous cell carcinoma of the oral mucosa was significantly increased in the 1,000 ng/kg core study group at 2 years. Gingival squamous cell carcinoma, although reduced in incidence as compared to the 1,000 ng/kg core study group, was still present in the 1,000 ng/kg stop-exposure group.

At 2 years, adenomas and/or carcinomas were present in the adrenal cortex of most core study groups and in the 1,000 ng/kg stop-exposure group. Dose-related effects on the incidences of adrenal cortex atrophy and cytoplasmic vacuolization were also seen.

There were dose-related increases in the incidences of numerous nonneoplastic responses including: chronic active inflammation, acinar atrophy, and acinar cytoplasmic vacuolation of the pancreas and chronic active inflammation of the pancreatic arteries; nephropathy; cardiomyopathy; follicular cell hypertrophy of the thyroid gland; thymic atrophy; clitoral gland cystic ducts; chronic active inflammation of the mesenteric artery; and, lymphoid follicular atrophy of the spleen.

CONCLUSIONS

Under the conditions of this 2-year gavage study there was *clear evidence of carcinogenic activity** of PCB 126 in female Harlan Sprague-Dawley rats based on increased incidences of cholangiocarcinoma of the liver, squamous neoplasms of the lung (cystic keratinizing epithelioma and squamous cell carcinoma), and gingival squamous cell carcinoma of the oral mucosa. Hepatocellular adenoma and hepatocholangioma of the liver were also considered to be related to the administration of PCB 126. Neoplasms of the adrenal cortex and cholangioma of the liver may have been related to administration of PCB 126.

PCB 126 administration caused increased incidences of nonneoplastic lesions of the liver, lung, adrenal cortex, pancreas, kidney, heart, thyroid gland, thymus, spleen, clitoral gland, and mesenteric artery in female rats.

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

Summary of the 2-Year Carcinogenesis Study of PCB 126 in Female Sprague-Dawley Rats

Doses in corn oil/acetone by gavage
0, 30, 100, 175, 300, 550, or 1,000 ng/kg, and 1,000 ng/kg (stop-exposure)

Body weights
175, 300, 550, and 1,000 ng/kg core study and 1,000 ng/kg stop-exposure groups less than the vehicle control group

Survival rates
15/53, 25/55, 26/53, 22/53, 16/53, 23/53, 7/53, 28/50

Nonneoplastic effects
Liver:
hepatocyte hypertrophy (0/53, 23/55, 32/53, 36/53, 42/53, 50/51, 49/53, 21/50);
multinucleated hepatocyte (0/53, 2/55, 10/53, 14/53, 19/53, 46/51, 49/53, 20/50);
diffuse fatty change (5/53, 7/55, 14/53, 22/53, 30/53, 45/51, 47/53, 12/50);
bile duct hyperplasia (3/53, 7/55, 7/53, 13/53, 14/53, 45/51, 45/53, 16/50);
bile duct cyst (3/53, 6/55, 0/53, 2/53, 3/53, 8/51, 12/53, 5/50);
oval cell hyperplasia (0/53, 1/55, 6/53, 7/53, 10/53, 38/51, 40/53, 1/50);
necrosis (4/53, 2/55, 5/53, 8/53, 11/53, 15/51, 17/53, 4/50);
pigmentation (1/53, 11/55, 41/53, 39/53, 48/53, 51/51, 48/53, 48/50);
inflammation (36/53, 40/55, 49/53, 50/53, 51/53, 51/51, 51/53, 46/50);
nodular hyperplasia (0/53, 0/55, 0/53, 1/53, 3/53, 26/51, 39/53, 0/50);
portal fibrosis (0/53, 0/55, 0/53, 0/53, 2/53, 1/51, 10/53, 0/50);
cholangiofibrosis (0/53, 1/55, 1/53, 1/53, 3/53, 13/51, 22/53, 1/50);
toxic hepatopathy (0/53, 6/55, 22/53, 27/53, 39/53, 51/51, 49/53, 15/50)
Lung:
alveolar epithelium, metaplasia, bronchiolar (0/53, 29/55, 34/53, 41/53, 39/53, 47/51, 40/51, 32/50);
squamous metaplasia (1/53, 0/55, 1/53, 2/53, 3/53, 9/51, 4/51, 0/50)
Adrenal Cortex:
atrophy (1/52, 3/55, 5/53, 3/53, 5/53, 19/52, 30/53, 9/50);
cytoplasmic vacuolization (5/52, 3/55, 5/53, 2/53, 9/53, 4/52, 17/53, 6/50)
Pancreas:
chronic active inflammation (5/51, 1/55, 3/53, 4/53, 4/53, 6/52, 13/51, 4/48);
acinar atrophy (5/51, 3/55, 2/53, 7/53, 2/53, 11/52, 18/51, 7/48);
acinar cytoplasmic vacuolization (0/51, 0/55, 1/53, 4/53, 9/53, 20/52, 23/51, 1/48);
arterial chronic active inflammation (0/51, 4/55, 2/53, 4/53, 8/53, 15/52, 11/51, 1/48)
Kidney:
nephropathy (32/53, 29/55, 38/53, 35/53, 38/53, 42/52, 47/53, 38/50);
severity of nephropathy: (1.3, 1.3, 1.5, 1.3, 1.5, 2.1, 2.1, 1.4)
Heart:
cardiomyopathy (9/52, 16/54, 17/53, 16/53, 24/53, 28/51, 32/51, 15/50)
Thyroid Gland:
follicular cell hypertrophy (9/52, 13/55, 13/52, 17/51, 28/52, 26/50, 16/48, 22/47)
Thymus:
atrophy (37/50, 34/52, 41/46, 45/48, 36/41, 47/49, 41/44, 39/43);
severity of atrophy: (2.5, 2.6, 2.8, 2.8, 3.3, 3.5, 3.5, 3.0)
Spleen:
lymphoid follicular atrophy (0/52, 5/55, 3/52, 2/53, 5/53, 3/52, 6/52, 4/50)
Clitoral Gland:
cystic duct (29/50, 32/55, 34/52, 37/50, 39/53, 42/52, 45/51, 39/48)
Mesentery:
arterial chronic active inflammation (0/53, 0/55, 2/53, 2/53, 6/53, 10/53, 7/53, 0/50)

Summary of the 2-Year Carcinogenesis Study of PCB 126 in Female Sprague-Dawley Rats

Neoplastic effects
Liver:
cholangiocarcinoma (0/53, 0/55, 1/53, 0/53, 5/53, 6/51, 22/53, 2/50);
hepatocellular adenoma (1/53, 2/55, 1/53, 0/53, 2/53, 4/51, 7/53, 0/50);
hepatocholangioma (0/53, 0/55, 0/53, 0/53, 0/53, 0/51, 3/53, 0/50)
Lung:
cystic keratinizing epithelioma (0/53, 0/55, 0/53, 0/53, 1/53, 11/51, 35/51, 0/50);
squamous cell carcinoma (0/53, 0/55, 0/53, 0/53, 0/53, 1/51, 2/51, 0/50)
Oral Mucosa:
gingival squamous cell carcinoma (0/53, 1/55, 1/53, 1/53, 2/53, 2/53, 7/53, 2/50)

Equivocal findings
Adrenal Cortex:
adenoma or carcinoma (0/52, 2/55, 1/53, 0/53, 1/53, 1/52, 4/53, 3/50)
Liver:
cholangioma (0/53, 0/55, 0/53, 0/53, 0/53, 1/51, 1/53, 0/50)

Level of evidence of carcinogenic activity
Clear 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 126 on February 17, 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 February 17, 2004, the draft Technical Report on the toxicology and carcinogenesis studies of 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) 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). Dr. J.R. Hailey, NIEHS, described the pathology review process for the TEF studies and presented examples of the characteristic spectra of neoplasms and nonneoplastic lesions of the liver and lung for these compounds.

Dr. Walker introduced the toxicology and carcinogenesis studies of PCB 126 by noting that of the dioxin-like PCBs, PCB 126 is the most potent. Dr. Walker described the study design and the spectrum of lesions in the liver, lung, and oral mucosa, and a variety of nonneoplastic lesions. The proposed conclusions were *clear evidence of carcinogenic activity* of PCB 126 in female Harlan Sprague-Dawley rats.

Dr. Klaunig, the first principal reviewer, thought that the study was well designed and agreed with the proposed conclusions. He inquired about the cause of apparent iron accumulation in the Kupffer cells. Dr. Walker responded that this was likely caused by alteration in porphyrin metabolism.

Dr. Piegorsch, the second principal reviewer, also agreed with the proposed conclusions.

Dr. Storer, the third principal reviewer, thought that the study was well designed, and he agreed with the proposed conclusions. Dr. Storer suggested adding a listing of the outside grantees who obtained materials from these studies to facilitate referencing their additional research.

Dr. Klaunig moved that the conclusions be accepted as written, *clear evidence of carcinogenic activity* of PCB 126 in female Harlan Sprague-Dawley rats. Dr. Piegorsch seconded the motion. The motion was passed unanimously with 12 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 adipose tissue, resulting in chronic lifetime human exposure (Schecter *et al*., 1994).

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, ten PCDFs, and thirteen 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 characteristic 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 very 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 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, 1994a), 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., ratio 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.

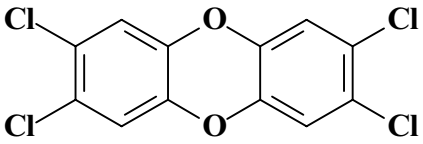
One of the implicit assumptions in the use of TEFs is that the TEQ for different compounds is dose additive. While dose additivity is supported for certain mixtures, for some biological endpoints in some models, this may not be true. As outlined by Van den Berg *et al.* (1998), the TEF methodology is 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

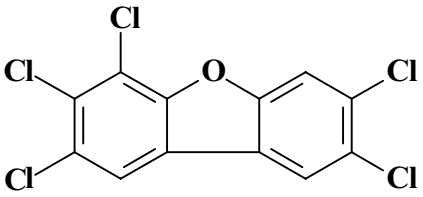


2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
(TCDD)

CAS No. 1746-01-6

Chemical Formula: $C_{12}H_4Cl_4O_2$
Molecular weight: 321.97

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 1.0. TCDD is classified as a known human carcinogen by the NTP and the International Agency for Research on Cancer.

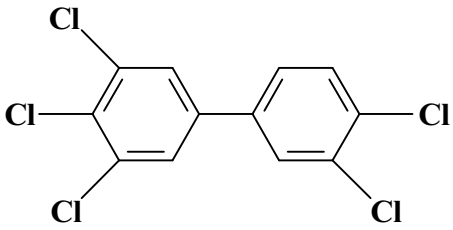


2,3,4,7,8-Pentachlorodibenzofuran
(PeCDF)

CAS No. 57117-31-4

Chemical Formula: $C_{12}H_3Cl_5O$
Molecular weight: 340.42

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.

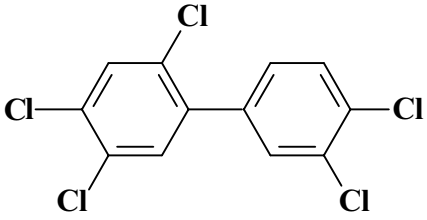


3,3′,4,4′,5-Pentachlorobiphenyl
(PCB 126)

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.

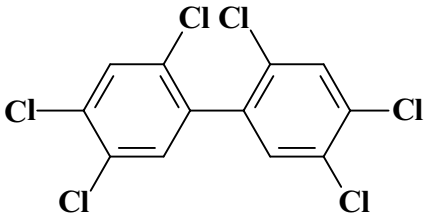


2,3′,4,4′,5-Pentachlorobiphenyl
(PCB 118)

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, PCB 126, and PeCDF

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, PCB 126, and PeCDF. 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 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 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 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.

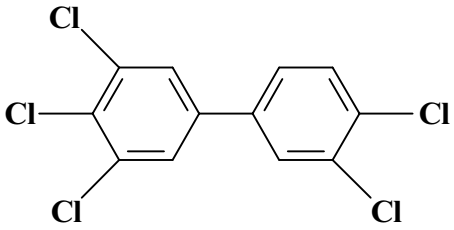
Additional "special study" animals were included at each interim necropsy. Tissues from these animals were provided to specific extramural grantees to facilitate the conduct of additional mechanistic studies. These animals were not evaluated as part of the core study.

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, and 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



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

CAS No. 57465-28-8

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

Synonyms: 1,1′-Biphenyl, 3,3′,4,4′,5-pentachloro-(9CI)

Chemical and Physical Properties

PCB 126 was produced commercially before 1977 as a component of technical grade polychlorinated biphenyl (PCB) mixtures, which include Aroclors 1016, 1242, 1248, and 1254 (Mayes *et al.*, 1998). Lower chlorinated Aroclors (1221, 1232, 1016, 1242, and 1248) are colorless mobile oils. Increasing the chlorine content results in the mixture taking on the consistency of a viscous liquid (Aroclor 1254) or sticky resin (Aroclors 1260 and 1262) (ATSDR, 2000). PCB 126 has a melting point of 160° to 161° C, a water solubility of 1.03×10^{-3} at 25° C, a vapor pressure of 2.96×10^{-7} at 25° C, and a log octanol:water partition coefficient of 6.89.

Production, Use, and Human Exposure

PCB mixtures, including PCB 126, 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, 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 bioconcentrate and bioaccumulate in the environment. The biota-sediment accumulation factor for PCB 126 in lake trout is 3.21. PCBs are widespread in their distribution and are found in virtually all media, including air, soil, water, sediment, and biota (USEPA, 2000b).

The majority (90%) of ambient human exposure to DLCs occurs through the ingestion of food containing PCB residues. Levels of PCB 126 in food range from 0.05 to 0.83 pg/g. Human exposure to all DLCs is usually calculated in terms of toxic equivalents (TEQs).

On a TEQ basis, it is estimated that humans are exposed via food to 22 pg TEQ/day (for a 70 kg person) from dioxin-like PCBs of which PCB 126 (13 pg/day) accounts for 60% of the TEQ intake. By comparison, intake from PCDDs and PCDFs is approximately 40 pg TEQ/day from food (beef, pork, chicken, dairy, and fish) (USEPA, 2000b). Bioaccumulation of PCB 126 results in persistent levels of PCB 126 in human tissues. PCB 126 concentration in an average tissue is 23 pg TEQ/g lipid. PCB 126 (12 pg TEQ/g lipid) accounts for 52% of the PCB TEQ in human tissues (USEPA, 2000b).

TOXICOKINETICS

There is an extensive body of literature examining the toxicokinetics of DLCs such as PCB 126 (USEPA, 2000c). However, only pertinent information regarding rodent pharmacokinetics is provided here. Several studies have examined absorption of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) from the gastrointestinal tract (Piper *et al.*, 1973; Rose *et al.*, 1976). The absorption of TCDD from the gastrointestinal tract in Sprague-Dawley rats given a single dose of 1 µg TCDD/kg body weight in acetone:corn oil (1:25) is 84% (range 66% to 93%). Similar results have been observed after repeated exposure (0.1 to 1 µg/kg per day) and higher doses. Once absorbed, DLCs are transported primarily through the lymphatic systems by chylomicrons and are readily distributed throughout the body. The main sites of distribution of DLCs in rats within the first few days of exposure are the liver, adipose tissue, and to a lesser amount, the skin and thyroid gland (Pohjanvirta *et al.*, 1990). In blood, DLC distributions are associated mainly with lipoproteins, serum lipids, and a smaller fraction of albumin and cellular components. The pattern of distribution in rats is governed by the lipophilicity of the compound and binding to cytochrome P450 1A2 (Gillner *et al.*, 1987; Diliberto *et al.*, 1997). Cytochrome P450 1A2 is a known binding protein for DLCs and is also inducible by exposure to aryl hydrocarbon receptor (AhR) ligands. Since CYP1A2 is inducible only in the liver and nasal passages, DLCs tend to sequester in the liver at levels that would not be predicted based on their lipophilicity alone. The hepatic sequestration by TCDD is not seen in CYP1A2 knockout mice, demonstrating the critical involvement of CYP1A2 in this process (Diliberto *et al.*, 1999).

PCB 126 Toxic Equivalency Factor

The World Health Organization WHO_{98} toxicity equivalence factor (TEF) for PCB 126 is 0.1 (Van den Berg *et al.*, 1998).

TOXICITY

Due to the lack of chlorine substitutions in either ortho position on the phenyl rings, PCB 126 has a planar structure (Safe, 1990). As such, PCB 126 is the most potent PCB in terms of its ability to bind and activate the AhR. *In vitro* receptor binding assays show that PCB 126 has an affinity for the AhR of 1.2×10^{-7} M, approximately tenfold lower than that of TCDD (1×10^{-8} M), the most potent AhR ligand.

Given this high AhR binding capability, most of the biological responses to PCB 126 are very similar to those of TCDD including altered transcription of TCDD-responsive genes such as CYP1 family cytochromes P450 and induction of UDP-glucuronosyl transferases (ATSDR 2000). The toxicity profile for PCB 126 is similar to that of TCDD and includes induction of a wasting syndrome, mortality, suppression of body weight gain in subchronic studies, increased liver weight, thymic atrophy, induction of preneoplastic lesions in tumor promotion studies, alteration in porphyrin metabolism, altered retinoid metabolism, and induction of cleft palate (Safe, 1994; Van Birgelen *et al.*, 1994, 1995a; ATSDR, 2000; USEPA, 2000c).

Different animal species vary widely in the sensitivity to the lethal toxicity of TCDD. The oral LD_{50} of TCDD varies over 5,000-fold. Consequently the range of acute lethality for PCB 126 is likely to be similar. The oral LD_{50} for 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) in guinea pigs (the most sensitive species for TCDD-induced lethality) is 10 µg/kg; by comparison the LD_{50} for TCDD is 1 µg/kg. In all species tested, the acute lethal doses of TCDD and related potent DLCs have a latency period of 1 to 2 weeks, during which animals exhibited a wasting syndrome.

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, but mainly within the liver (hepatocellular neoplasms). In addition, in studies where both sexes have been studied, female rodents appeared to be more sensitive than males. While 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 individual studies on the carcinogenicity of PCB 126 alone. No epidemiology studies of PCB 126 were found in a review of the literature. Furthermore, there have been no published studies examining the carcinogenicity of an individual PCB congener. The most recent 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. The incidence of hepatocellular neoplasms was significantly increased by PCB exposure with the rank order of Aroclor 1254 > Aroclor 1260 > Aroclor 1242 > Aroclor 1016. Increased incidences of neoplasms were seen for hepatocellular adenoma, hepatocellular carcinoma, hepatocholangioma, hepatocholangiocarcinoma, and follicular cell adenoma of the thyroid gland. The incidence of liver tumors was more extensive in female rats than in male rats. Within this context, Aroclor 1254 has the highest dioxin-like activity, measured on a TEQ basis, compared to the other PCB mixtures due to the presence of specific coplanar PCBs, PCDDs and PCDFs in the mixture. In female rats at the highest dose of Aroclor 1254 used (100 ppm, equivalent to 6.1 mg/kg per day), the incidences of liver adenomas and carcinomas were 54% and 12%, respectively.

Based on the relative potency of 0.1 for PCB 126 and the similarity in mechanism of action compared to TCDD, it is expected that the carcinogenicity of PCB 126 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). TCDD administered by gavage induced tumors in male and female Osborne-Mendel rats and B6C3F_1 mice (NTP, 1982a). In the previous NTP (1982a) study, significantly increased incidences of thyroid gland follicular cell adenoma were observed in high dose male and female rats and high dose female mice. TCDD gavage administration also produced an increased incidence of neoplastic liver nodules in high dose female mice and increased incidences of hepatocellular carcinoma in high dose male and female mice. TCDD administered by dermal application (NTP, 1982b) caused tumors in female Swiss-Webster mice (but equivocal evidence in male mice). TCDD administered by dermal application caused an increased incidence of fibrosarcoma of the integumentary system in high dose female mice. Based on the NTP (1982b) studies, there is substantial evidence of carcinogenicity of TCDD in male and female rats and mice.

One of the most cited carcinogenicity studies for TCDD is a 2-year feed study conducted by Dow Chemical (Kociba *et al.*, 1978). TCDD administered by feed to Sprague-Dawley rats at up to 100 ng/kg per day for 2 years resulted in an elevated incidence of tumors at multiple sites. Increased incidences of liver hyperplastic nodules (females), hepatocellular carcinoma (females), keratinizing squamous cell carcinoma of the lung (females), adenoma of the adrenal cortex (males), squamous cell carcinoma of nasal turbinates/hard palate (males and females), and stratified squamous cell carcinoma of the tongue (males) were observed. In addition, significantly lower tumor incidences were observed for pheochromocytoma of the adrenal gland (male), subcutaneous fibroma/fibroadenoma/lipoma (male), benign uterine neoplasms, benign tumors of the mammary gland, mammary carcinoma, pituitary gland adenoma (female), and acinar adenoma of the pancreas (male). Two reevaluations of the pathology of the female liver tumor data confirmed significant increases in hepatocellular adenoma and carcinoma (Squire, 1980; Goodman and Sauer, 1992).

Humans

Humans have not been exposed to significant amounts of PCB 126 alone. PCB 126 occurs in mixtures containing other structurally related compounds such as PCDDs, PCDFs, and PCBs.

Two accidental poisoning incidents in Japan and Taiwan resulted from exposures to cooking oil that was highly contaminated with PCDFs and PCBs. In addition to extensive reproductive and developmental effects in these populations, early follow-up studies indicated an increased mortality from liver disease and cancer, particularly liver cancer (IARC, 1997). Although recent follow-up studies do not show an increased mortality from cancer, mortality from liver disease was still elevated (Yu *et al.*, 1997).

Cancer mortality was also investigated in a Swedish population that consumed fatty fish from the Baltic Sea.

The predominant exposure was to PeCDF and other PCDFs contained in the fish. In this population there was an increase in mortality from stomach cancer, squamous cell cancer of the skin, and multiple myeloma (IARC, 1997). There have been several studies examining the 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).

Other studies have examined occupational cohorts of phenoxy herbicide workers who were exposed to mixtures of PCDDs or PCDFs. Studies on the phenoxy herbicide workers indicated an increase in mortality from all cancers combined, soft tissue sarcoma, non-Hodgkins lymphoma, and lung cancer (Kogevinas *et al.*, 1997; Steenland *et al.*, 1999). Also, a study was performed on a population in Seveso, Italy, which was accidentally exposed to TCDD after a chemical plant explosion in 1976 (USEPA, 2000c). The most recent follow-up of the Seveso cohort also showed similar effects, an increase in all cancers combined with several specific cancers including rectal cancer, lung cancer, Hodgkins disease, non-Hodgkins lymphoma, and myeloid leukemia (Bertazzi *et al.*, 2001).

Tumor Promotion Studies

The majority of studies examining the *in vivo* and *in vitro* genotoxicity of PCBs demonstrate that PCBs are negative (Silberhorn *et al.*, 1990). These indicate that the likely carcinogenic mechanism for PCB is as a tumor promoter. In the liver, clonal expansion of genetically altered cells leads to the formation of putative preneoplastic altered hepatocellular focal (AHF) lesions identified by alterations in histomorphology or gene expression. These lesions are believed to be precursors in the development of liver tumors (Pitot *et al.*, 1991). There have been numerous studies demonstrating the ability of PCBs to enhance the development of preneoplastic liver lesions (Silberhorn *et al.*, 1990). Studies in Sprague-Dawley rats indicate that DLCs, including PCB 126, can enhance the development of AHF lesions (Waern *et al.*, 1991), which is indicative of a tumor promotion effect. Haag-Gronlund *et al.* (1998) demonstrated that PCB 126 alone and in combination with other PCBs enhances the development of AHF lesions. In a comparison study of PCB 126 and TCDD, the relative ability of PCB 126 to enhance altered hepatic foci development was about 1/10th that of TCDD (Hemming *et al.*, 1995). Moreover, the activity of PCB 126 and TCDD, when tested in combination, was additive.

Numerous studies have examined the promotion of putative preneoplastic liver lesions by TCDD within the framework of a two-stage initiation-promotion protocol (Dragan and Schrenk, 2000). These studies demonstrate that TCDD is a potent liver tumor promoter and that these effects are dose dependent (Pitot *et al.*, 1980; Maronpot *et al.*, 1993; Teeguarden *et al.*, 1999), duration of exposure dependent, and reversible (Dragan *et al.*, 1992; Walker *et al.*, 1998, 2000). Also, studies show that TCDD promotes more neoplasms in female rat liver than in male rat liver and that this is due to the enhancing effect of estrogens on the promotion of preneoplastic lesions (Lucier *et al.*, 1991; Wyde *et al.*, 2001a, 2002). Also, studies in Sprague-Dawley rats show that PeCDF can enhance the development of AHF lesions (Waern *et al.*, 1991), which is indicative of a tumor promotion effect. Van der Plas *et al.* (1999) indicate that a mixture of PCDDs, PCDFs, and PCBs lead to the increased development of putative preneoplastic AHF lesions.

Tests of the tumor initiating and promoting capacity of DLCs have been conducted in two-stage (initiation-TCDD promotion) models of mouse skin tumorigenesis (IARC, 1997; Dragan and Schrenk, 2000; USEPA, 2000c). Dermal painting studies of PeCDF in HRS/J mice indicate that it is a skin tumor promoter (Hebert *et al.*, 1990). Similar studies demonstrate that TCDD is at least two orders of magnitude more potent than the prototypical promoter tetradecanoyl phorbol acetate in those skin tumor promotion models (Poland *et al.*, 1982).

Tumor promotion by PCB 126 has not been evaluated in transgenic models. However, transgenic models have been used to examine the carcinogenicity of TCDD in mice (Eastin *et al.*, 1998). These include the Tg.AC transgenic mouse that harbors an activated mouse v-Ha-*ras* oncogene (an intermediate in growth factor signaling). Dermal application of TCDD results in a significant increase in the incidence of squamous cell papillomas in male and female Tg.AC mice, which supports the conclusion that TCDD is a tumor promoter. Subsequent studies by NTP showed that the induction of papillomas and squamous cell carcinomas by dermal application of TCDD to hemizygous Tg.AC mice was dose dependent (van Birgelen *et al.*, 1999; Dunson *et al.*, 2000). In addition, the induction of skin papillomas in this model occurs when TCDD is given by oral administration. Based on the similarity of action of PCB 126 and TCDD, it is expected that PCB 126 would act similarly in the Tg.AC model.

In addition to the liver and skin, TCDD and PCDFs are tumor promoters in the lung (Anderson *et al.*, 1991; Beebe *et al.*, 1995). Anderson *et al.* (1986) also previously demonstrated that PCB mixtures can act as tumor promoters in the lung. However, no studies of PCB 126 have examined effects on tumor promotion in the lung. In Sprague-Dawley rats, which have a much lower spontaneous incidence rate of lung tumors, TCDD promotes the development of bronchiolar hyperplasia and alveolar bronchiolar metaplasia (Tritscher *et al.*, 2000). It was demonstrated that the induction of these lesions was reversible; incidences of these lesions returned to control levels following withdrawal of TCDD for 16 or 30 weeks.

Overall these data demonstrate that the mode of action of PCB 126 and other DLCs for carcinogenesis identifies them as likely potent tumor promoters.

Mechanism and Biochemical Effects

DLCs such as PCB 126 are generally classified as nongenotoxic and nonmutagenic. The common mechanism of action of DLCs involves an initial binding to the AhR (Poland and Knutson, 1982; Safe, 1990; Whitlock, 1990; Schmidt and Bradfield, 1996). The broad spectrum of effects of TCDD and DLCs on hormone and growth factor systems, cytokines, and other signal transducer pathways indicates that they are powerful growth dysregulators (Birnbaum, 1994a). Since they are not directly genotoxic (Wassom *et al.*, 1977), it is believed that the pathological responses associated with exposure are fundamentally due to binding to and activation of the AhR, subsequent altered expression of AhR-regulated genes, and altered signaling of biological pathways that interact with the AhR signal transduction mechanism.

Alterations in the expression of AhR-regulated genes occurs via a mechanism that involves a high affinity interaction of the ligand with an intracellular protein, the AhR, which functions as a ligand-activated transcription factor (Okey *et al.*, 1994; Schmidt and Bradfield, 1996). Ligand binding initiates a signaling pathway in which the cytosolic AhR dissociates from heat shock proteins and translocates to the nucleus (Whitlock, 1993). At some point subsequent to ligand binding, the AhR associates with another protein, aromatic hydrocarbon nuclear translocator protein (ARNT), to form the nuclear DNA-binding and transcriptionally active AhR complex. Both the AhR and ARNT are members of the basic helix-loop-helix family of transcription factors (Hoffman *et al.*, 1991; Burbach *et al.*, 1992; Ema *et al.*, 1992). The AhR-ARNT heterodimer binds with high affinity to a specific DNA sequence termed the dioxin response element (DRE). DREs have been identified in the enhancer regions of genes encoding several drug-metabolizing enzymes (Lai *et al.*, 1996). The characteristic response to TCDD and DLCs is the transcriptional induction of the cytochrome P450 1A1 gene (CYP1A1), which is mediated by binding of the AhR complex to DREs present in the 5′ flanking region of the gene. The AhR is expressed in all tissues examined (Dolwick *et al.*, 1993) with a definite tissue specificity in terms of level of expression and diversity of response, indicating that DLCs are likely to have some effect in every tissue. However, even with the same receptor and the same ligand, there are both qualitative and quantitative differences in response and these differences in response are likely to be involved in the tissue and species-specificity of the response. It is still not known how alterations in gene expression ultimately lead to the development of pathologies and adverse health effects associated with dioxin-like compound exposure. However, it is generally accepted that most, if not all, responses require an initial step of binding to the AhR.

The most well-studied response to DLCs is induction of the CYP1A cytochromes P450 (Whitlock, 1999). CYP1A1 is induced in most tissues including liver, lung, kidney, nasal passages, and small intestine with the highest induction in rats occurring in the liver. Induction of CYP1A1 is a sensitive response and serves as a useful marker for exposure to DLCs. DLCs induce CYP1A1 *in vivo* and *in vitro* in human and animal models. CYP1A2 is constitutively expressed in the liver at low levels and inducible by DLCs in liver and possibly the nasal turbinates of rats (Goldstein and Linko, 1984). Induction of 7-ethoxyresorufin-*O*-deethylase activity is a marker of CYP1A1 activity. CYP1A2 is induced by DLCs and expressed primarily in the liver. Induction of acetanilide-4-hydroxylase activity is a marker of CYP1A2 activity. In addition to the well characterized induction of CYP1A1 and CYP1A2, DLCs also induces another cytochrome P450, CYP1B1, in human cells (Sutter *et al.*, 1994) and rodent tissues (Walker *et al.*, 1995). CYP1B1 is active in the metabolism of numerous polycyclic aromatic hydrocarbons and arylamines and can catalyze the 4-hydroxylation of 17β-estradiol (Hayes *et al.*, 1996; Murray *et al.*, 2001).

DLCs are believed to disrupt thyroid hormone homeostasis via the induction of the phase II enzymes UDP-glucuronosyl transferases. Thyroxine (T_4) production and secretion are controlled by thyroid stimulating hormone (TSH), which is under negative and positive regulation from the hypothalamus, pituitary gland, and thyroid gland by thyrotrophin releasing hormone (TRH), TSH itself, T_4, and triiodothyronine (T_3). TCDD induces the synthesis of UDP-glucuronosyl transferase-1 mRNA by an AhR-dependent transcriptional mechanism. Consequently, a reduction in serum T_4 levels via an induction of UGT may lead to a decrease in the negative feedback inhibition on the pituitary gland. This would then lead to a rise in secreted TSH resulting in chronic hyperstimulation of the thyroid gland follicular cells.

DLCs have been shown to modulate numerous growth factor, cytokine, hormone, and metabolic pathways in animals and experimental systems (Birnbaum, 1994b; Sutter and Greenlee, 1992). Many, if not all of these, are parts of pathways involved in cellular proliferation and differentiation. These include the glucocorticoid receptor tyrosine kinases, interleukin-1, plasminogen activator inhibitor-2, urokinase type plasminogen activator, tumor necrosis factor-alpha, gonadotrophin releasing hormone, testosterone, and prostaglandin endoperoxide H synthase-2. More recently, the application of toxicogenomics analyses have increased our understanding of which genes/proteins are altered by TCDD both *in vitro* (Puga *et al.*, 2000; Martinez *et al.*, 2002) and *in vivo* (Bruno *et al.*, 2002; Kurachi *et al.*, 2002; Zeytun *et al.*, 2002). Most of the molecular details for induction of gene expression via the AhR have been characterized for the transcriptional activation of the CYP1A1 gene (Whitlock, 1999). While the expression of many genes has been shown to be affected by DLCs, there is a detailed characterization of transcriptional activation through the AhR for only a few of these.

Study Design Overview

The design of these studies on PCB 126 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 sexes, two species carcinogenicity testing paradigm. Consequently, many of the design rationales are based on the prior observations of the carcinogenicity of TCDD.

Study Design, Species, and Dose Selection Rationale

According to the World Health Organization TEF scheme, PCB 126 has a relative potency of 0.1. Since the known carcinogenicity of TCDD is within the dose range of 1 to 100 ng/kg per day, the dosages of PCB 126 for the current study were designed to match the range of TCDD after adjustment for the TEF of 0.1. 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 126

PCB 126 was obtained from AccuStandard, Inc. (New Haven, CT), in one lot (130494) and was used in the 2-year study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Battelle Memorial Institute (Columbus, OH), and the study laboratory, Battelle Columbus Operations (Columbus, OH) (Appendix C). Reports on analyses performed in support of the PCB 126 study are on file at the National Institute of Environmental Health Sciences.

Lot 130494 of the chemical, a white powder, was identified as PCB 126 by proton and carbon-13 nuclear magnetic resonance spectroscopy and melting point determination. All spectra were consistent with the structure of a pentachlorobiphenyl, and determination of the melting point (156.9° C) by differential scanning calorimetry agreed with the literature (Bolgar, *et al*., 1995).

The purity of lot 130494 was determined by the analytical chemistry laboratory and by the study laboratory using gas chromatography by high resolution mass spectrometry or flame ionization. The purity profile obtained by high resolution mass spectrometry detected four impurities with a combined relative area of 0.49%. Gas chromatography by flame ionization indicated a purity of 100.3% ± 0.7% relative to the reference sample. Two impurities were tetrachlorinated biphenyls and one was a pentachlorinated biphenyl. One impurity was not identified, but was determined not to be a PCDD, PCDF, or PCB. The overall purity of lot 130494 was determined to be greater than 99%.

PREPARATION OF STOCK SAMPLES

Lot 130494 was dissolved in acetone and prealiquotted for use as analytical stock or formulation stock in the study because of the very small amount of chemical that was required to prepare the dose formulations at the intended concentrations. Details concerning the preparation and use of these stock solutions are provided in Appendix C. The test article was stored at room temperature (approximately 25° C) and protected from light in amber glass bottles sealed with Teflon®-lined lids. Purity was monitored by periodic reanalysis. No degradation was observed during the course of the study.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by dissolving PCB 126 working stocks in acetone and diluting in corn oil (Spectrum Quality Products; Gardena, CA) such that the final formulation contained 1% acetone to give the required concentrations (Table C2). The dose formulations were stored at room temperature in amber glass bottles with minimal headspace and sealed with Teflon®-lined lids for up to 35 days.

Homogeneity studies of a 1,200 ng/mL dose formulation and stability studies of a 1.2 ng/mL formulation were performed by the analytical chemistry laboratory using gas chromatography by high resolution mass spectrometry with selected ion recording. The study laboratory (in prestart) performed homogeneity studies on the 4 and 400 ng/mL dose formulations using a similar system. The formulations were determined to be gavageable, homogeneity was confirmed, and stability was confirmed for at least 35 days for dose formulations stored in amber glass bottles with minimal headspace and sealed with Teflon®-lined lids at –20° C, 5° C, and room temperature and for 3 hours under simulated animal room conditions.

Periodic analyses of the dose formulations of PCB 126 were conducted by the study laboratory using gas chromatography with selected ion recording. During the 2-year study, the dose formulations were analyzed at least every 3 months (Table C3). Of the dose formulations analyzed, 64 of 76 were within 10% of the target concentrations. One dose formulation that was 78% of the target concentration was not used and the remix was within 10%; dose formulations that were within 14% of

the target concentrations were used. Of the animal room samples, 23 of 27 were within 10% of the target concentrations. Periodic analyses of the corn oil vehicle by the study laboratory demonstrated peroxide concentrations below the acceptable limit of 3 mEq/kg.

2-YEAR STUDY

Study Design

Groups of 81 female rats received PCB 126 in corn oil:acetone (99:1) by gavage at doses of 30, 100, 175, 300, 550, or 1,000 ng/kg body weight 5 days per week for up to 104 weeks; a group of 81 female rats received the corn oil:acetone (99:1) vehicle alone. A group of 28 rats received 10 ng/kg for up to 53 weeks only. 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 given 1,000 ng/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 15 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 1,000 ng/kg females at the end of the study.

Animal Maintenance

Male rats were housed three per cage and female rats were housed three to 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, monthly thereafter, and at the end of the study. Body weights were recorded on the first day of the study, weekly for 13 weeks, monthly 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, 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 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 1,000 ng/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 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 126, 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, extraction of the saponificate with hexanes, and two-stage sample extract clean up on columns using silica gel with hexanes elution and activated carbon with toluene elution by automated solid phase extraction. Concentrations of PCB 126 in the tissue extracts were measured by capillary gas chromatography with high resolution mass spectrometry 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, clitoral gland, harderian gland, heart, kidney, liver, lung, mesentery, oral mucosa, ovary, pancreas, spleen, stomach, thymus, and tooth.

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 126, along with three other studies (PeCDF, TCDD, and the TEF mixture) 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 four 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 provide additional guidance on the most appropriate classification of the hepatocellular proliferative lesions from these studies of DLCs (Hailey *et al.*, 2005). 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 126

Study Laboratory
Battelle Columbus Operations (Columbus, OH)

Strain and Species
Harlan Sprague-Dawley rats

Animal Source
Harlan Sprague-Dawley, Inc. (Indianapolis, IN)

Time Held Before Study
15 days

Average Age When Study Began
8 weeks

Date of First Dose (female rats only)
February 26, 1998

Duration of Dosing
5 days/week for 14, 31, or 53 (interim evaluation), 30 (stop-exposure), or 104 weeks

Date of Last Dose
February 21-23, 2000 (core study)
September 23, 1998 (stop-exposure)

Necropsy Dates
February 22-24, 2000

Average Age at Necropsy
112 weeks

Size of Study Groups
81 (vehicle control, 30, 100, 175, 300, 550, and 1,000 ng/kg), 28 (10 ng/kg), or 50 (1,000 ng/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 126

Animals per Cage
Male rats: 3
Female rats: 3 to 5

Method of Animal Identification
Tail tattoo

Diet
Irradiated NTP-2000 pelleted 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., Maywood, NJ), 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., Maywood, NJ), 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 (interim studies), 30, 100, 175, 300, 550, and 1,000 ng/kg

Type and Frequency of Observation
Observed twice daily; animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the study. Clinical findings were recorded on day 29, monthly 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, 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 10 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 10 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 126

Tissue Concentration Analysis
At 14, 31, 53 weeks, and 2 years, samples of blood, fat, liver, and lung were taken from up to 10 rats per group for analysis of PCB 126 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 1,000 ng/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; the thymus at 14 (550 ng/kg), 31, and 53 weeks; the lung at 31 (550 ng/kg) and 53 weeks; and the pancreas at 53 weeks (550 ng/kg).

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, A1c, A5a, A5b, and A5c 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, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed

that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each 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 currently limited to the seven gavage studies conducted as part of the dioxin TEF evaluation (the current PCB 126 study, TCDD, the TEF mixture, PeCDF, PCB 153, the PCB 126/PCB 153 mixture, and the PCB 126/PCB 118 mixture; 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 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 the female rats are shown in Table 3 and in the Kaplan-Meier survival curves (Figure 1). There was a significant change in the survival of 550 ng/kg and 1,000 ng/kg stop-exposure females with an increase observed relative to the vehicle control group.

Body Weights and Clinical Findings

Mean body weights of 30 and 100 ng/kg rats were similar to those of the vehicle controls during most of the study, mean body weights of 175 and 300 ng/kg rats were less than those of the vehicle controls during year 2 of the study, and mean body weights of 550 ng/kg, 1,000 ng/kg core study, and 1,000 ng/kg stop-exposure rats were less than those of the vehicle controls after week 17 (Table 4 and Figure 2). The mean body weights of 10 ng/kg rats were similar to those of the vehicle controls until they were sacrificed at week 14, 31, or 53 (data not shown in Table 4).

TABLE 3
Survival of Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Animals initially in study	81	28	81	81	81	81	81	81	50
14-Week interim evaluation[a]	10	10	9	10	10	10	10	10	
31-Week interim evaluation[a]	10	10	9	10	10	10	10	10	
53-Week interim evaluation[a]	8	8	8	8	8	8	8	8	
Accidental deaths[a]	3		3	0	1	1	0	0	1
Moribund	25		18	21	19	27	18	34	15
Natural deaths	10		9	6	11	9	12	12	6
Animals surviving to study termination	15		25[b]	26[b]	22	16	23	7	28
Percent probability of survival at end of study[c]	31		48	49	42	31	43	13	57
Mean survival (days)[d]	567		608	635	626	610	656	583	640
Survival analysis[e]	P=0.004		P=0.070N	P=0.057N	P=0.223N	P=0.589N	P=0.048N	P=0.219	P=0.013N

[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 10 ng/kg group or the 1,000 ng/kg stop-exposure group.

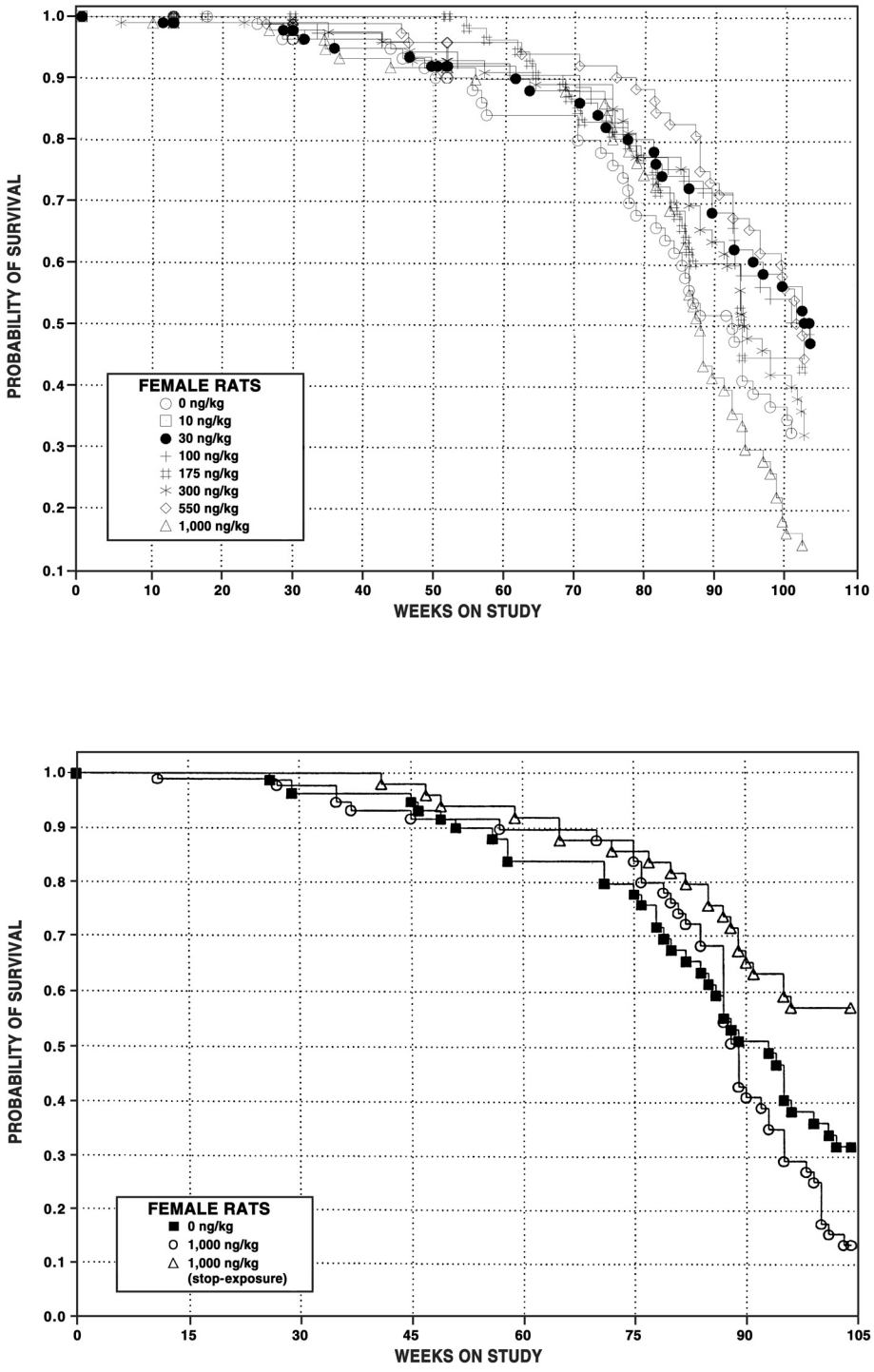


FIGURE 1
Kaplan-Meier Survival Curves for Female Rats Administered PCB 126 by Gavage for 2 Years

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of PCB 126[a]

Weeks on Study	Vehicle Control		30 ng/kg			100 ng/kg			175 ng/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	183	98	184	100	98	185	101	98	185	101	98
2	206	98	207	100	98	206	100	98	205	99	98
3	220	98	217	99	98	220	100	98	220	100	98
4	234	98	235	100	98	236	101	98	236	101	98
5	244	98	242	99	98	241	99	98	240	98	98
6	251	98	252	100	98	250	99	98	249	99	98
7	257	98	257	100	98	254	99	98	254	99	98
8	262	98	261	99	98	259	99	98	258	98	98
9	268	98	266	99	98	261	98	98	265	99	98
10	270	98	271	100	98	267	99	98	266	99	98
11	274	98	273	100	98	272	99	98	271	99	98
12	277	98	277	100	98	275	99	98	274	99	98
13	281	98	279	100	97	278	99	98	276	98	98
15	284	82	282	100	82	283	100	82	277	98	82
17	287	82	284	99	82	284	99	82	279	97	82
21	293	81	290	99	82	284	97	82	287	98	81
25	299	81	293	98	82	295	99	82	293	98	81
29	304	80	303	100	82	300	99	81	299	98	81
33	311	61	303	98	65	307	99	65	301	97	65
37	316	61	308	97	64	312	99	64	305	96	65
41	321	61	310	97	64	313	98	64	309	96	65
45	329	61	314	95	64	319	97	63	314	95	65
49	329	59	319	97	63	322	98	62	318	97	65
52	327	57	320	98	59	325	99	62	321	98	65
57	335	43	328	98	46	330	98	48	324	97	51
61	348	41	337	97	46	338	97	48	334	96	50
65	354	41	340	96	44	344	97	47	334	94	48
69	364	41	349	96	44	352	97	47	338	93	47
73	371	39	357	96	43	359	97	46	342	92	43
77	383	37	356	93	41	369	96	43	352	92	42
81	383	33	362	95	40	369	97	40	350	92	40
85	394	31	366	93	37	375	95	39	360	91	37
89	397	26	373	94	36	383	97	38	364	92	31
93	397	24	371	94	34	379	96	37	368	93	31
97	382	18	362	95	30	381	100	30	356	93	23
101	390	17	359	92	28	388	100	28	357	92	23
Mean for weeks											
1-13	248		248	100		246	99		247	100	
14-52	309		302	98		304	98		300	98	
53-101	375		355	95		364	97		348	93	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of PCB 126

300 ng/kg			550 ng/kg			1,000 ng/kg			1,000 ng/kg (Stop-Exposure)		
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	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
185	101	98	185	101	98	184	100	98	183	100	50
206	100	98	206	100	98	203	99	98	203	98	50
220	100	98	220	100	98	218	99	98	218	99	50
237	101	98	234	100	98	232	99	98	229	98	50
243	99	98	240	98	98	239	98	98	235	96	50
248	99	98	248	99	98	246	98	98	242	97	50
253	99	97	253	98	98	249	97	98	248	97	50
257	98	97	256	98	98	253	96	98	251	96	50
263	98	97	262	98	98	257	96	98	254	95	50
268	99	97	264	98	98	260	97	98	257	95	50
271	99	97	268	98	98	263	96	98	257	94	50
274	99	97	270	97	98	266	96	97	264	95	50
276	98	97	272	97	98	266	95	97	264	94	50
278	98	81	276	97	82	269	95	81	267	94	50
281	98	81	277	97	82	270	94	81	270	94	50
278	95	81	281	96	82	276	94	81	270	92	50
289	97	80	286	96	82	279	93	81	269	90	50
299	98	80	288	95	81	282	93	80	279	92	50
303	98	64	292	94	65	284	91	64	282	91	50
306	97	63	296	94	65	285	90	62	285	90	50
308	96	63	298	93	65	286	89	61	289	90	50
313	95	62	298	91	65	285	87	61	293	89	49
317	96	60	302	92	63	288	88	60	294	89	47
318	97	60	302	92	63	285	87	60	297	91	46
322	96	47	308	92	50	286	85	47	304	91	46
333	96	46	315	90	50	287	82	46	313	90	45
337	95	46	312	88	49	289	82	46	318	90	45
341	94	45	317	87	49	290	80	46	323	89	43
348	94	45	322	87	48	292	79	45	330	89	42
354	92	43	326	85	48	290	76	41	337	88	42
350	91	39	323	85	46	287	75	39	336	88	40
354	90	39	323	82	43	282	72	35	342	87	39
348	88	35	320	81	42	279	70	26	340	86	35
354	89	30	318	80	37	278	70	20	344	87	31
344	90	24	306	80	34	275	72	15	348	91	28
346	89	21	313	80	30	279	72	9	356	91	28
246	99		244	98		241	97		239	96	
300	98		291	94		281	91		281	91	
344	92		317	85		285	76		333	89	

[a] Interim evaluations occurred during weeks 14, 31, and 53; number of survivors includes 17 special study animals (except stop-exposure group).

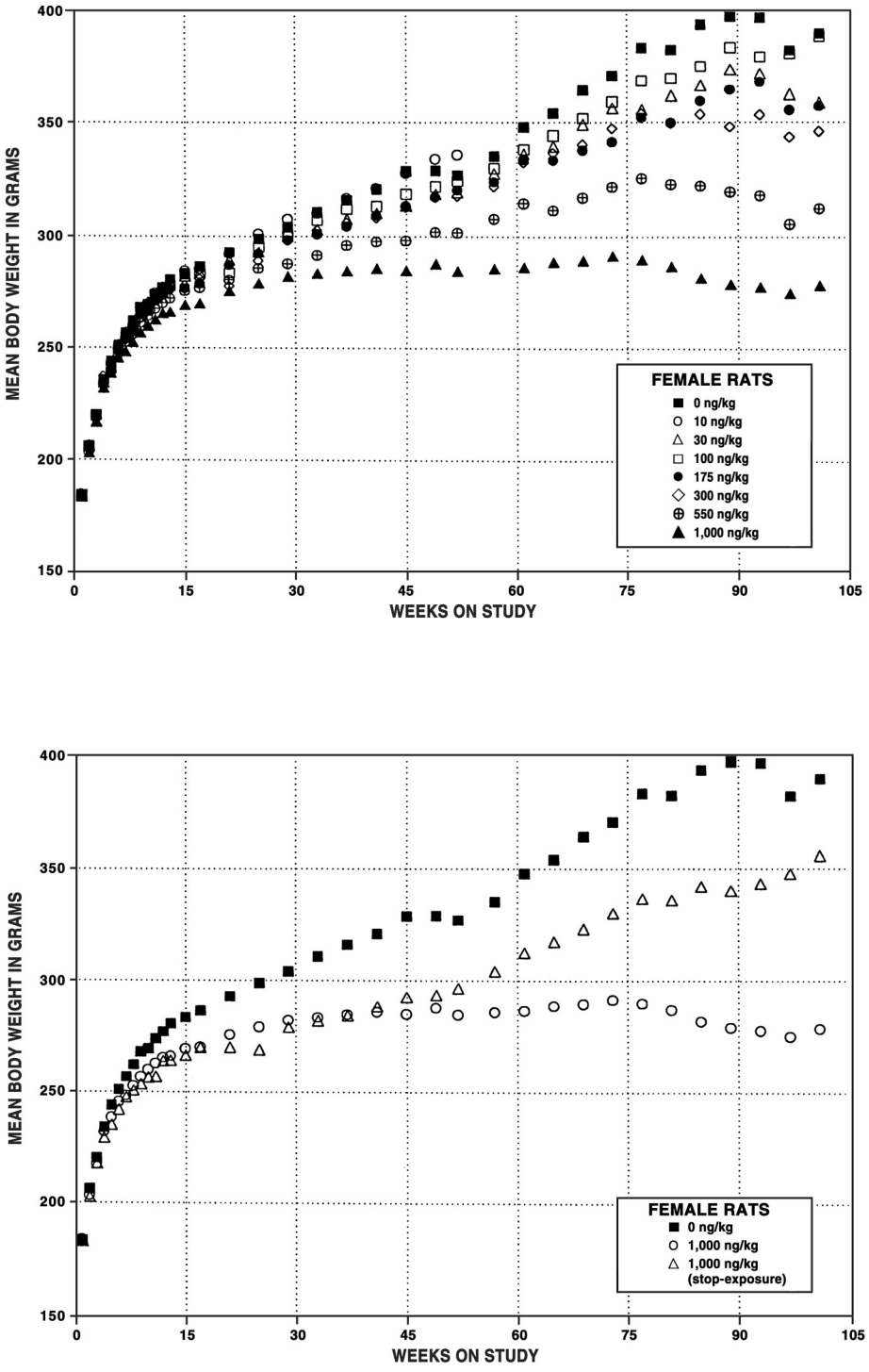


FIGURE 2
Growth Curves for Female Rats Administered PCB 126 by Gavage for 2 Years

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). A downward trend in serum total T_4 concentrations with higher PCB 126 concentrations (100 ng/kg and above) was evident at 14 weeks. The 550 and 1,000 ng/kg groups showed values that were significantly lower than vehicle controls by 30.9% and 38.7%, respectively. A downward trend was also observed in serum free T_4 concentrations at doses equal to or greater than 175 ng/kg. The serum free T_4 concentrations in the 550 and 1,000 ng/kg groups were significantly lower relative to vehicle controls. There was an increasing trend for serum concentrations of T_3 at 14 weeks for doses of 100 ng/kg or greater. This change was statistically higher than for vehicle controls at doses equal to or greater than 300 ng/kg, which exhibited values that exceeded the vehicle control value by 28.4%, 42.6%, and 58.7%, respectively. There was a trend toward increased serum TSH levels with increasing dose at the 14-week interim evaluation. Serum TSH levels were significantly higher in the 550 and 1,000 ng/kg groups compared to vehicle controls. Serum TSH levels in 1,000 ng/kg rats were 66.4% higher than vehicle controls.

At 31 weeks with doses greater than or equal to 175 ng/kg, serum total T_4 concentrations were lower, but not significantly different, than for vehicle controls. Vehicle control values for total T_4 were 74% of levels seen at 14 weeks and free T_4 was 68% of levels seen at 14 weeks. The 10 and 30 ng/kg dose groups showed total T_4 values that exceeded the vehicle control value by approximately 30%, but were not statistically significant. Serum free T_4 was elevated in the 10 and 30 ng/kg groups and depressed in the 550 and 1,000 ng/kg groups compared to vehicle controls, but these changes were not statistically significant most likely due to the low vehicle control values at 31 weeks. Actual levels were similar to those seen at 14 weeks in the 1,000 ng/kg group. All dose groups showed total T_3 concentrations that were increased, but these changes were only significantly different from the vehicle control values at the 100 ng/kg dose level or greater. There was a subtle trend toward increased serum TSH levels with increasing dose at the 31-week interim evaluation. Serum TSH levels were significantly higher in the 550 and 1,000 ng/kg groups compared to vehicle controls. Serum TSH levels in high dose rats were 63.2% higher at 31 weeks.

At 53 weeks, serum total T_4 concentrations were lower than the vehicle controls for the 30 ng/kg group or greater. The 175, 300, 550, and 1,000 ng/kg groups showed statistically significant decreases relative to vehicle controls of 30.7%, 24.3%, 31.7%, and 31.9%, respectively. There was also a trend of decreasing serum free T_4 levels with doses of 30 ng/kg or greater. The serum free T_4 concentrations for the 30, 100, 175, 300, 550, and 1,000 ng/kg groups were significantly reduced by 13.6%, 17.0%, 32.0%, 25.7%, 32.0%, and 34.0%, respectively, relative to vehicle controls. Serum T_3 levels were statistically higher at doses equal to or greater than 175 ng/kg compared to vehicle controls. TSH values for all dose groups were similar to vehicle control values at 53 weeks.

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 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Week 14								
n	10	10	9	10	10	10	10	10
Total T_4 (µg/dL)	5.30 ± 0.24	5.61 ± 0.26	5.68 ± 0.19	4.88 ± 0.35	4.38 ± 0.32	4.33 ± 0.30	3.66 ± 0.28**	3.25 ± 0.35**
Free T_4 (ng/dL)	2.24 ± 0.09	2.39 ± 0.12	2.21 ± 0.12	2.28 ± 0.15	2.00 ± 0.11	1.99 ± 0.11	1.82 ± 0.11**	1.60 ± 0.15**
Total T_3 (ng/dL)	102.75 ± 8.95	114.31 ± 11.55	98.11 ± 9.02	127.59 ± 7.98	132.38 ± 9.68	131.92 ± 5.16*	146.50 ± 10.06**	163.07 ± 10.58**
TSH (ng/mL)	16.09 ± 1.95	15.63 ± 1.70	22.41 ± 2.22	18.97 ± 1.91	20.43 ± 1.32	20.83 ± 2.46	22.61 ± 2.44*	26.78 ± 3.81**
Week 31								
n	10	10	9	10	10	10	10	10
Total T_4 (µg/dL)	3.90 ± 0.30	5.11 ± 0.31	5.08 ± 0.34	4.19 ± 0.10	3.77 ± 0.28	3.49 ± 0.22	2.81 ± 0.25	3.23 ± 0.28
Free T_4 (ng/dL)	1.53 ± 0.23	2.18 ± 0.15	2.24 ± 0.18	2.09 ± 0.09	1.92 ± 0.12	1.82 ± 0.14	1.40 ± 0.18	1.40 ± 0.12
Total T_3 (ng/dL)	130.27 ± 8.96	152.17 ± 6.20	148.46 ± 9.37	170.33 ± 5.69**	167.34 ± 6.66**	178.20 ± 6.07**	167.15 ± 9.81**	165.58 ± 7.89**
TSH (ng/mL)	11.46 ± 1.13	14.76 ± 1.47	15.77 ± 0.85	15.14 ± 1.74	14.64 ± 1.27	15.63 ± 1.60	16.64 ± 1.35**	18.70 ± 1.72**
Week 53								
n	8	8	8	8	8	8	8	8
Total T_4 (µg/dL)	4.04 ± 0.24	4.18 ± 0.28	3.68 ± 0.15	3.63 ± 0.26	2.80 ± 0.27**	3.06 ± 0.25**	2.76 ± 0.21**	2.75 ± 0.30**
Free T_4 (ng/dL)	2.06 ± 0.09	2.07 ± 0.09	1.78 ± 0.11*	1.71 ± 0.09*	1.40 ± 0.07**	1.53 ± 0.12**	1.40 ± 0.08**	1.36 ± 0.14**
Total T_3 (ng/dL)	144.44 ± 5.13	160.33 ± 4.49	142.04 ± 9.27	163.78 ± 6.93	165.42 ± 4.51*	172.62 ± 6.74**	166.36 ± 7.18*	172.68 ± 12.53*
TSH (ng/mL)	19.92 ± 3.19	20.51 ± 1.98	17.08 ± 2.07	22.17 ± 2.25	16.98 ± 1.25	16.89 ± 2.03	21.80 ± 1.83	19.35 ± 2.99

* Significantly different ($P \leq 0.05$) from the vehicle control group by 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. The consumption of the BrdU drinking water solutions prior to each interim evaluation was similar across groups (data not shown). The hepatocellular labeling index was significantly higher at doses of 300 ng/kg or greater at 14 weeks and 175 ng/kg or greater at 31 weeks. At 14 weeks, the labeling index was 1.6-, 1.8-, and 1.3-fold greater than vehicle controls for doses of 300, 550, and 1,000 ng/kg, respectively. At 31 weeks, the labeling index was 2.9-, 1.5-, 1.9-, and 1.8-fold greater than vehicle controls for doses of 175, 300, 550, and 1,000 ng/kg, respectively. The labeling index at week 53 was increased but not significantly different from that of vehicle controls at doses of 10, 175, 550, and 1,000 ng/kg. The mean labeling index was 5.8-fold increased above the vehicle controls at 1,000 ng/kg, but this was not statistically significant due to the large degree of variability in the individual animals' data at this dose.

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 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	8	10	10	10	10	10
Week 31	10	10	9	10	9	10	9	10
Week 53	8	8	8	8	8	8	8	8
Labeling index (%)								
Week 14	0.759 ± 0.109	0.818 ± 0.128	1.280 ± 0.372	0.753 ± 0.121	1.018 ± 0.093	1.226 ± 0.084**	1.391 ± 0.133**	0.964 ± 0.081*
Week 31	0.759 ± 0.121	0.747 ± 0.147	1.328 ± 0.230	1.045 ± 0.098	2.206 ± 0.299**	1.136 ± 0.162**	1.412 ± 0.136**	1.348 ± 0.179**
Week 53	1.131 ± 0.074	1.238 ± 0.121	0.820 ± 0.108	1.037 ± 0.204	2.324 ± 0.775	0.787 ± 0.097	1.329 ± 0.253	6.525 ± 2.243

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

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 was significantly higher in all dosed groups relative to vehicle controls at the 14-, 31-, and 53-week interim evaluations (Table 7). Significant induction of hepatic EROD occurred at the lowest dose (10 ng/kg) for all three sampling times (14, 31, and 53 weeks). Hepatic EROD activities were maximally induced 94-, 95-, and 59-fold over vehicle controls in the 1,000 ng/kg (14 weeks), 175 ng/kg (31 weeks), and 300 ng/kg (53 weeks) groups, respectively. Similarly, hepatic PROD activity was significantly higher in all dosed groups at all three interim evaluations (14, 31, and 53 weeks). Maximum induction of hepatic PROD activity was observed in the 550 ng/kg (14 weeks), 550 ng/kg (31 weeks), and 300 ng/kg (53 weeks) groups, with induction relative to vehicle controls of approximately 11-, 12-, and 10-fold, respectively. Hepatic A4H activity was significantly higher in groups administered 30 ng/kg or greater at the 14-, 31-, and 53-week interim evaluations. Hepatic A4H activity tended to increase with increasing dose and maximal activity occurred consistently in the high-dose groups across each interim evaluation. The maximum degree of induction relative to the vehicle control group was approximately 5.1-, 4.6-, and 5.1-fold at the 14-, 31-, and 53-week interim evaluations, respectively.

EROD activity in the lung was significantly greater in all dosed groups at the 14-, 31-, and 53-week interim evaluations. The maximum pulmonary EROD activity was observed in the 1,000 ng/kg (14 weeks), 300 ng/kg (31 weeks), and 500 ng/kg (53 weeks) groups. The maximum degree of induction relative to the vehicle control group was approximately 32- (14 weeks), 56- (31 weeks), and 49-fold (53 weeks), respectively.

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 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	9	10	10	10	10	10
Week 31	10	10	9	10	10	10	10	10
Week 53	8	8	8	8	8	8	8	8
Liver Microsomes								
Acetanilide-4-hydroxylase (A4H) (nmol/minute per mg microsomal protein)								
Week 14	0.455 ± 0.034	0.571 ± 0.075	1.086 ± 0.095**	1.842 ± 0.104**	2.007 ± 0.071**	1.779 ± 0.056**	2.059 ± 0.108**	2.330 ± 0.114**
Week 31	0.652 ± 0.048	0.734 ± 0.044	1.172 ± 0.110**	1.885 ± 0.139**	2.341 ± 0.188**	2.019 ± 0.145**	2.408 ± 0.145**	2.994 ± 0.233**
Week 53	0.393 ± 0.030	0.467 ± 0.027	0.840 ± 0.063**	1.197 ± 0.067**	1.375 ± 0.102**	1.978 ± 0.081**	1.871 ± 0.119**	2.019 ± 0.151**
7-Ethoxyresorufin-*O*-deethylase (EROD) (pmol/minute per mg microsomal protein)								
Week 14	13.29 ± 0.80	82.23 ± 6.58**	291.00 ± 30.97**	855.10 ± 60.78**	1,039.70 ± 46.79**	915.40 ± 63.32**	1,192.30 ± 72.99**	1,252.10 ± 95.30**
Week 31	22.86 ± 1.91	260.80 ± 20.17**	659.67 ± 85.25**	1,618.80 ± 170.34**	2,166.00 ± 116.47**	1,884.00 ± 130.14**	2,055.00 ± 110.28**	1,950.00 ± 138.94**
Week 53	40.39 ± 2.42	329.88 ± 30.69**	1,042.25 ± 51.02**	1,537.25 ± 121.53**	1,665.00 ± 121.66**	2,383.75 ± 149.98**	1,982.50 ± 68.32**	2,122.50 ± 132.65**
7-Pentoxyresorufin-*O*-deethylase (PROD) (pmol/minute per mg microsomal protein)								
Week 14	1.715 ± 0.135	3.954 ± 0.259**	7.056 ± 0.493**	14.080 ± 0.643**	17.880 ± 0.562**	17.260 ± 0.868**	19.650 ± 1.072**	16.820 ± 0.861**
Week 31	1.898 ± 0.152	5.841 ± 0.229**	8.354 ± 0.360**	15.360 ± 0.779**	20.140 ± 0.959**	18.700 ± 0.721**	22.600 ± 1.071**	22.050 ± 1.327**
Week 53	2.340 ± 0.142	3.269 ± 0.157**	8.475 ± 0.208**	14.475 ± 0.702**	16.450 ± 0.829**	23.300 ± 1.176**	19.175 ± 0.801**	20.150 ± 1.136**
Lung Microsomes								
7-Ethoxyresorufin-*O*-deethylase (EROD) (pmol/minute per mg microsomal protein)								
Week 14	2.109 ± 0.111	5.122 ± 0.448**	19.600 ± 2.628**	33.680 ± 1.239**	43.060 ± 1.895**	56.220 ± 2.607**	65.800 ± 1.543**	67.250 ± 3.229**
Week 31	1.023 ± 0.186[b]	5.878 ± 0.397**	15.350 ± 2.408**	26.161 ± 2.704**	40.590 ± 3.081**	56.690 ± 3.232**	56.410 ± 6.300**	56.150 ± 5.189**
Week 53	1.590 ± 0.403[c]	6.065 ± 0.544**	20.700 ± 2.228**	41.488 ± 1.837**	58.025 ± 2.674**	72.275 ± 5.282**	77.250 ± 4.602**	63.837 ± 8.049**

** Significantly different ($P \leq 0.01$) from the vehicle control group by Shirley's test
[a] Data are presented as mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=7

Determinations of PCB 126 Concentrations in Tissues

Concentrations of PCB 126 were determined in liver, lung, fat, and blood at the 14-, 31-, and 53-week interim evaluations and at the end of the 2-year study (104 weeks) (Table 8). The highest concentrations of PCB 126 were observed in the liver, followed by fat. The lowest determined tissue concentrations of PCB 126 were observed in blood. In vehicle control liver, PCB 126 concentrations were 360, 693, and 513 pg/g at 31, 53, and 104 weeks, respectively. At the 14-week interim evaluation, liver concentrations of PCB 126 in vehicle controls were below the experimental limit of quantitation. Hepatic concentrations were higher in groups with increasing doses of PCB 126. The highest hepatic concentrations were observed in the 1,000 ng/kg group with 413,000; 532,000; 780,000; and 536,000 pg/g at 14, 31, 53, and 104 weeks, respectively. In the liver tissue from the stop-exposure group, the PCB 126 concentration was 12,000 pg/g, which was lower than levels observed in the 30 ng/kg group (29,000 pg/g).

In fat of vehicle controls, PCB 126 concentrations were below the experimental limit of quantitation at 14 weeks and 298, 454, and 391 pg/g at 31, 53, and 104 weeks, respectively. Fat concentrations were higher in groups with increasing doses of PCB 126. The highest concentrations were observed in the 1,000 ng/kg group with 97,000; 113,000; 136,000; and 131,000 pg/g at 14, 31, 53, and 104 weeks, respectively. In the fat of the stop-exposure group, the PCB 126 concentration was 7,640 pg/g, which was nearly twofold lower than that observed in the 30 ng/kg group (14,400 pg/g).

PCB 126 concentrations in vehicle control lungs were 468 and 110 pg/g at 53 and 104 weeks, respectively. Lung concentrations tended to increase with increasing doses of PCB 126. The highest concentrations were observed in the 30 ng/kg group (1,630 pg/g) at 14 weeks, and the 1,000 ng/kg group with 2,070; 9,540; and 1,840 pg/g at 31, 53, and 104 weeks, respectively. In the lung tissue from the stop-study group, the PCB 126 concentration was 223 pg/g, which was equivalent to the level observed in the 30 ng/kg group (242 pg/g). PCB 126 concentrations were appreciably lower in blood than in the other tissue analyzed. Concentrations of PCB 126 in blood from the vehicle control group were all below the experimental limit of quantitation. With few exceptions, blood concentrations tended to increase with increasing doses of PCB 126. The highest concentrations were observed in the 1,000 ng/kg group with 558, 381, 552, and 999 pg/g at 14, 31, 53, and 104 weeks, respectively. In blood from the stop-study group, the PCB 126 concentration was 102 pg/g, which was equivalent to the level observed in the 100 ng/kg group (97 pg/g).

TABLE 8
Tissue Concentrations of PCB 126 in Female Rats in the 2-Year Gavage Study of PCB 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	9	10	10	10	10	10
Week 31	10	10	9	10	10	10	10	10
Week 53	8	8	8	8	8	8	8	8
Fat								
Week 14	BLOQ	6,921 ± 6,950	11,257 ± 6,819	18,955 ± 3,067	25,900 ± 2,268	35,191 ± 6,179	60,738 ± 11,498	97,440 ± 13,252
Week 31	298.0 ± 88.1[b]	3,289 ± 483	6,652 ± 1,190	15,964 ± 3,737	25,405 ± 8,328	36,623 ± 7,284	50,058 ± 19,032	112,502 ± 18,836
Week 53	454.2 ± 208.0	4,142 ± 1,024	8,926 ± 1,079	20,699 ± 1,810	27,314 ± 2,219	44,916 ± 5,827	72,349 ± 4,815	136,079 ± 14,016
Liver								
Week 14	BLOQ	2,569 ± 462	8,570 ± 2,129	33,028 ± 4,982	70,956 ± 11,438	123,372 ± 18,719	220,515 ± 20,505	412,581 ± 73,487
Week 31	359.6[c]	3,666 ± 718	13,394 ± 2,921	55,862 ± 6,489	99,049 ± 23,279	144,235 ± 9,469	265,674 ± 38,372	531,900 ± 65,922
Week 53	693.2 ± 984.3[d]	5,218 ± 1,424	23,798 ± 3,167	77,800 ± 10,949	113,041 ± 22,055	242,626 ± 26,947	387,337 ± 55,231	780,006 ± 218,423
Lung								
Week 14	BLOQ	BLOQ	1,629 ± 2,550[e]	512.1 ± 557.2[f]	896.0 ± 1,733.6	910.0 ± 518.8	1,626 ± 1,996	1,458 ± 434
Week 31	BLOQ	BLOQ	123.2 ± 28.8	263.4 ± 45.4	391.7 ± 129.1	574.8 ± 279.8	1,077 ± 530	2,066 ± 1,294
Week 53	467.8 ± 433.7[b]	596.5 ± 420.8[g]	313.9 ± 84.1	649.2 ± 221.4	2,956 ± 6,209	5,057 ± 10,083	2,235 ± 1,046	9,543 ± 18,013[d]
Blood								
Week 14	BLOQ	BLOQ	40.80 ± 14.20[h]	90.49 ± 32.45	93.16 ± 43.24	124.9 ± 29.2	445.6 ± 100.7	588.0 ± 50.6
Week 31	BLOQ	17.74 ± 4.78[b]	BLOQ	48.59 ± 14.97	65.35 ± 13.09	119.2 ± 19.8	198.8 ± 43.5	380.5 ± 82.8
Week 53	BLOQ	63.91 ± 81.69[h]	51.27 ± 57.84	70.67 ± 10.13	86.88 ± 18.54	163.5 ± 15.0	258.1 ± 49.4	551.7 ± 86.6

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
n								
2 Years	10	10	10	10	10	10	7	10
Fat	391.2 ± 193.0	14,440 ± 2,209	34,807 ± 3,800	39,830 ± 8,311	74,873 ± 19,215	96,759 ± 26,394	130,507 ± 45,098	7,642 ± 2,272
Liver	512.8 ± 744.2[f]	29,042 ± 8,949	91,442 ± 19,445	127,567 ± 38,607	213,778 ± 40,070	363,146 ± 71,031	536,417 ± 63,579	11,564 ± 10,652
Lung	109.7 ± 33.6[b]	241.8 ± 99.0	473.9 ± 188.9	676.0 ± 237.8	553.6 ± 248.1[f]	1,162 ± 731	1,842 ± 736	223.0 ± 102.6[f]
Blood	BLOQ	44.22 ± 13.14	97.38 ± 13.13	164.4 ± 44.4	270.1 ± 71.7	518.0 ± 171.6	999.1 ± 300.5	102.4 ± 105.4

[a] Data are given in pg/g tissue (fat, liver, lung) or pg/mL (blood) as the mean ± standard deviation. Mean values do not include values that were below the experimental limit of quantitation. BLOQ=below the limit of quantitation; LOQ_{fat}=100 to 250 pg/g, LOQ_{liver}=50 to 100 pg/g, LOQ_{lung}=60 pg/g, LOQ_{blood}=15 pg/mL

[b] n=5 [c] n=2 [d] n=7 [e] n=8 [f] n=9 [g] n=6 [h] n=4

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, lung, oral mucosa, adrenal gland, pancreas, kidney, heart, thyroid gland, thymus, spleen, clitoral gland, mesentery, mammary gland, and pituitary gland. 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: Absolute and relative liver weights were significantly increased in all dosed groups at 14 and 31 weeks and in all groups administered 175 ng/kg or greater at 53 weeks (Table B1). At the 14-week interim evaluation, changes in the liver consisted of increased incidences and severities of hepatocyte hypertrophy (Tables 9 and A5a). Hypertrophy occurred in all dosed groups except the 10 ng/kg group at 14 weeks, and tended to correlate with increased liver weight. The severity was minimal in the 100, 175, and 300 ng/kg groups and tended to increase to mild in the 550 and 1,000 ng/kg groups.

At 31 weeks, hepatocyte hypertrophy occurred in all dosed groups and tended to correlate with increased liver weight (Tables 9 and A5a). Minimal to mild hypertrophy was seen in the 30 ng/kg or greater groups, while moderate hypertrophy was seen only in the 1,000 ng/kg group. Minimal multinucleated hepatocytes were seen in the 550 and 1,000 ng/kg groups. Altered hepatocellular foci (clear, basophilic, and mixed) were seen sporadically in dosed animals. The incidence of mixed cell foci was significantly increased in the 1,000 ng/kg group. Pigment-containing macrophages were minimal, and the incidences were significantly increased in the 175 ng/kg or greater groups. Increased severity from minimal to mild, as compared to vehicle controls, of acute to subchronic inflammation, was noted in the 550 and 1,000 ng/kg groups. Cholangiofibrosis occurred in one 300 ng/kg and one 550 ng/kg rat. Minimal to mild toxic hepatopathy was seen in the 1,000 ng/kg group.

At the 53-week interim evaluation, hepatocyte hypertrophy occurred in all dosed groups and tended to correlate with increased liver weight (Tables 9 and A5a). Minimal hypertrophy was seen in all dosed groups, mild hypertrophy was seen in the 100 ng/kg and greater groups, moderate hypertrophy was seen in the 550 ng/kg and greater groups, and marked hypertrophy occurred in the 1,000 ng/kg group. Dose-related minimal to mild incidences of multinucleated hepatocytes were seen in the 300 ng/kg and greater groups. Sporadic cases of eosinophilic foci were seen in the 175, 550, and 1,000 ng/kg groups. Incidences of mixed cell foci were seen in all groups and were increased in the 500 and 1,000 ng/kg groups. Increased incidences and severities of pigment-containing macrophages occurred in the 100 ng/kg and greater groups. Sporadic cases of cholangiofibrosis were seen in the 100, 175, and 550 ng/kg groups. Dose-related increased incidences and severities of toxic hepatopathy occurred in the 550 and 1,000 ng/kg groups. Increased severities of acute to subchronic inflammation were noted in the 550 and 1,000 ng/kg groups. The inflammation was associated with a minimal to mild grade of hepatocellular necrosis. Dose-related increased incidences of bile duct hyperplasia were seen in the 300 ng/kg and greater groups. Diffuse fatty change was seen sporadically in the 175 and 550 ng/kg groups, and the incidence was significantly increased in the 1,000 ng/kg group.

At 2 years, at least one cholangiocarcinoma was seen in all dosed groups except the 30 and 175 ng/kg groups; no cholangiocarcinomas have been seen in historical controls (Tables 10, A1b, and A4a). The highest incidence of cholangiocarcinoma was seen in the 1,000 ng/kg core study group and included a significant number of multiple cholangiocarcinomas. The incidence of hepatocellular adenoma was significantly increased in the 1,000 ng/kg core study group, and the incidences in the 550 and 1,000 ng/kg core study groups exceeded the range in the historical vehicle controls (Tables 10, A1b, and A4a). At 2 years, cholangiomas were seen in the 550 ng/kg and 1,000 ng/kg core study groups and three hepatocholangiomas occurred in the 1,000 ng/kg core study group; no cholangiomas or hepatocholangiomas have been seen in historical controls (Tables 10, A1b, and A4a). Two cholangiocarcinomas were seen in the 1,000 ng/kg stop-exposure group, and no hepatocellular adenomas occurred at this dose.

Cholangiocarcinoma consisted of an irregular, relatively large, non-circumscribed lesion that replaced normal liver parenchyma. The lesion consisted of fibrous connective tissue stroma containing numerous atypical bile ducts, which frequently contained mucinous material and cellular debris. The epithelium forming the atypical bile ducts was often discontinuous, consisted usually of

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
14-Week Interim Evaluation								
Number Examined Microscopically	10	10	9	10	10	10	10	10
Hepatocyte, Hypertrophy[a]	0	0	3 (1.0)[b]	3 (1.0)	3 (1.0)	6**(1.0)	10**(1.4)	10**(1.7)
31-Week Interim Evaluation								
Number Examined Microscopically	10	10	9	10	10	10	10	10
Hepatocyte, Hypertrophy	0	3 (1.0)	4* (1.3)	6**(1.0)	6**(1.3)	8**(1.0)	10**(1.4)	10**(2.2)
Hepatocyte, Multinucleated	0	0	0	0	0	0	2 (1.0)	8**(1.0)
Clear Cell Focus	0	1	0	0	0	1	0	0
Basophilic Focus	0	0	0	1	0	0	0	0
Mixed Cell Focus (includes multiple)	0	2	2	3	3	2	3	6**
Pigmentation	0	0	0	3 (1.0)	5* (1.0)	8**(1.0)	8**(1.0)	10**(1.0)
Inflammation	7 (1.1)	10 (1.2)	9 (1.3)	10 (1.3)	10 (1.6)	10 (1.7)	10 (1.8)	10 (1.8)
Cholangiofibrosis	0	0	0	0	0	1 (2.0)	1 (1.0)	0
Toxic Hepatopathy	0	0	0	0	0	0	0	10**(1.2)
53-Week Interim Evaluation								
Number Examined Microscopically	8	8	8	8	8	8	8	8
Hepatocyte, Hypertrophy	0	3 (1.0)	2 (1.0)	5* (1.2)	6**(1.0)	7**(1.0)	8**(1.5)	8**(2.8)
Hepatocyte, Multinucleated	0	0	0	0	0	1 (1.0)	3 (1.0)	8**(2.0)
Eosinophilic Focus	0	0	0	0	2	0	1	3
Mixed Cell Focus (includes multiple)	4	5	3	6	6	6	8*	8*
Pigmentation	0	0	3 (1.0)	8**(1.0)	7**(1.1)	8**(1.3)	8**(1.8)	8**(2.4)
Cholangiofibrosis	0	0	0	1 (1.0)	0	0	1 (2.0)	0
Toxic Hepatopathy	0	0	0	0	1 (1.0)	0	4* (1.3)	8**(2.5)
Inflammation	8 (1.1)	8 (1.0)	8 (1.1)	8 (1.0)	8 (1.1)	8 (1.3)	8 (1.6)	8 (1.6)
Bile Duct, Hyperplasia	0	0	0	0	0	1 (1.0)	4* (1.0)	6**(1.3)
Fatty Change, Diffuse	0	0	0	0	2 (1.0)	0	1 (1.0)	8**(1.0)

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

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Number Examined Microscopically	53	55	53	53	53	51	53	50
Hepatocyte, Hypertrophy[a]	0	23**(1.1)[b]	32**(1.2)	36**(1.3)	42**(1.4)	50**(2.3)	49**(3.4)	21**▲▲(1.4)
Hepatocyte, Multinucleated	0	2 (1.0)	10**(1.1)	14**(1.0)	19**(1.3)	46**(1.5)	49**(1.7)	20**▲▲(1.0)
Fatty Change, Diffuse	5 (1.2)	7 (1.0)	14* (1.4)	22**(1.1)	30**(1.1)	45**(1.4)	47**(1.8)	12▲▲ (1.3)
Fatty Change, Focal	2 (1.5)	6 (1.3)	8 (1.5)	6 (1.5)	3 (1.7)	2 (1.0)	0	11*▲▲ (1.5)
Bile Duct, Hyperplasia	3 (1.3)	7 (1.6)	7 (1.6)	13* (1.4)	14**(1.2)	45**(1.8)	45**(2.5)	16**▲▲(1.4)
Bile Duct, Cyst	3 (1.7)	6 (2.3)	0	2 (2.0)	3 (2.7)	8 (2.0)	12* (2.0)	5▲ (2.2)
Bile Duct, Fibrosis	4 (1.0)	4 (1.5)	3 (1.3)	2 (1.0)	1 (1.0)	4 (1.0)	5 (1.2)	4 (1.0)
Oval Cell, Hyperplasia	0	1 (1.0)	6* (1.2)	7* (1.1)	10**(1.2)	38**(1.8)	40**(2.2)	1▲▲ (1.0)
Necrosis	4 (2.3)	2 (2.0)	5 (1.6)	8 (2.1)	11 (1.9)	15* (2.0)	17**(2.2)	4▲▲ (2.8)
Pigmentation	1 (1.0)	11**(1.3)	41**(1.2)	39**(1.6)	48**(1.9)	51**(2.3)	48**(2.5)	48** (1.8)
Basophilic Focus (includes multiple)	7	10	10	13	4	5	5	16▲
Eosinophilic Focus (includes multiple)	11	10	13	21	17	24	17	12
Mixed Cell Focus (includes multiple)	21	24	32	32	30	29	9**	36**▲▲
Inflammation	36 (1.1)	40 (1.1)	49**(1.2)	50**(1.2)	51**(1.2)	51**(1.4)	51**(1.2)	46* (1.2)
Hyperplasia, Nodular	0	0	0	1	3	26**	39**	0▲▲
Portal Fibrosis	0	0	0	0	2 (2.0)	1 (1.0)	10**(2.1)	0▲▲
Cholangiofibrosis	0	1 (2.0)	1 (2.0)	1 (2.0)	3 (1.7)	13**(1.8)	22**(2.3)	1▲▲ (1.0)
Toxic Hepatopathy	0	6* (1.2)	22**(1.0)	27**(1.0)	39**(1.3)	51**(2.4)	49**(3.4)	15**▲▲(1.2)
Cholangioma[c]	0	0	0	0	0	1	1	0
Hepatocholangioma, Multiple	0	0	0	0	0	0	1	0
Hepatocholangioma (includes multiple)[c]								
Overall rate[d]	0/53 (0%)	0/55 (0%)	0/53 (0%)	0/53 (0%)	0/53 (0%)	0/51 (0%)	3/53 (6%)	0/50 (0%)
Adjusted rate[e]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	9.3%	0.0%
Terminal rate[f]	0/15 (0%)	0/25 (0%)	0/26 (0%)	0/22 (0%)	0/16 (0%)	0/23 (0%)	1/7 (14%)	0/28 (0%)
First incidence (days)	—[i]	—[j]	—	—	—	—	660	—
Poly-3 test[g]	P<0.001	—	—	—	—	—	P=0.122	—
Poly-3 test[h]								P=0.087N

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Number Examined Microscopically	53	55	53	53	53	51	53	50
Hepatocellular Adenoma, Multiple	0	0	0	0	0	0	1	0
Hepatocellular Adenoma (includes multiple)[k]								
Overall rate	1/53 (2%)	2/55 (4%)	1/53 (2%)	0/53 (0%)	2/53 (4%)	4/51 (8%)	7/53 (13%)	0/50 (0%)
Adjusted rate	3.2%	5.2%	2.5%	0.0%	5.5%	9.7%	20.9%	0.0%
Terminal rate	1/15 (7%)	1/25 (4%)	0/26 (0%)	0/22 (0%)	1/16 (6%)	4/23 (17%)	2/7 (29%)	0/28 (0%)
First incidence (days)	727 (T)	652	602	—	709	727 (T)	562	—
Poly-3 test	P<0.001	P=0.574	P=0.704N	P=0.465N	P=0.554	P=0.274	P=0.033	P=0.463N
Poly-3 test								P=0.004N
Cholangiocarcinoma, Multiple	0	0	0	0	0	4	15**	0▲▲
Cholangiocarcinoma (includes multiple)[c]								
Overall rate	0/53 (0%)	0/55 (0%)	1/53 (2%)	0/53 (0%)	5/53 (9%)	6/51 (12%)	22/53 (42%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	2.5%	0.0%	13.6%	14.0%	60.3%	5.3%
Terminal rate	0/15 (0%)	0/25 (0%)	1/26 (4%)	0/22 (0%)	3/16 (19%)	1/23 (4%)	6/7 (86%)	2/28 (7%)
First incidence (days)	—	—	727 (T)	—	659	618	562	727 (T)
Poly-3 test	P<0.001	—	P=0.546	—	P=0.045	P=0.040	P<0.001	P=0.263
Poly-3 test								P<0.001N

* 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 1,000 ng/kg core study group by the Poly-3 test
▲▲ P≤0.01
(T) Terminal sacrifice
[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] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] 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 lower incidence in the stop-exposure group is indicated by **N**.
[h] Pairwise comparison between the 1,000 ng/kg core and stop-exposure groups. A lower incidence in the stop-exposure group is indicated by **N**.
[i] Not applicable; no neoplasms in animal group
[j] Value of statistic cannot be computed.
[k] Historical incidence (mean ± standard deviation): 4/371 (1.1% ± 1.5%), range 0%-4%

large atypical cells, and displayed degenerative changes. Mitotic figures and localized invasion of adjacent liver parenchyma were also observed (Plates 1 to 3).

Cholangioma was a well demarcated mass consisting of multiple, often dilated bile ducts with little associated fibrous connective tissue stroma. The bile ducts were composed of a single layer of epithelium that sometimes formed acinar or papillary structures.

Hepatocholangioma was composed of a mixture of proliferating hepatocellular and bile duct elements. Hepatocholangioma was a rather large, nodular mass with a distinct border that produced compression of surrounding normal parenchyma. The hepatocellular element appeared similar to that seen in hepatocellular adenomas and consisted of a rather uniform population of pleomorphic hepatocytes that were generally normal sized or slightly larger than normal and were arranged in abnormal hepatic cords. Intermixed with the proliferating hepatocytes were numerous, variably-sized biliary structures surrounded by small amounts of dense fibrous tissue stroma, which appeared similar to the biliary structures seen within a cholangioma. The smaller biliary structures resembled proliferating small bile ducts while the large structures were generally irregular and sometimes moderately to markedly dilated. Some of the large structures became confluent producing highly irregular cystic biliary structures that were incompletely separated by short septae projecting into the lumen. Some of the ductular lumens contained homogeneous, lightly eosinophilic material but most were empty. The biliary structures were composed of a single layer of flattened to cuboidal to low columnar, somewhat pleomorphic, but otherwise relatively normal-appearing, bile duct epithelial cells.

Hepatocellular adenoma was a nodular mass that usually was larger than a focus, had a distinct border, and produced more compression of surrounding hepatic parenchyma (Plate 4). Adenoma was composed of rather uniform population of mildly to moderately pleomorphic hepatocytes that generally were normal size or slightly larger than normal and were arranged in abnormal lobular patterns. The hepatic cords within an adenoma usually intersected the surrounding normal hepatic cords at an oblique angle or sometimes even at a right angle. A few small proliferating bile ducts or oval cells were sometimes seen, but were not as numerous as in nodular hyperplasia. The uniform population of relatively normal sized, somewhat pleomorphic hepatocytes that were arranged in abnormal lobular patterns, and the lack of proliferating bile ducts were important features differentiating adenoma from nodular hyperplasia.

Hepatocellular carcinoma occurred in only one animal from the 175 ng/kg group. Microscopically, the hepatocellular carcinoma was a large, poorly demarcated, locally invasive mass composed of atypical hepatocytes that were arranged in trabeculae three or more cells thick and in glandular and solid growth patterns.

At 2 years, hepatocyte hypertrophy, multinucleated hepatocytes, diffuse fatty change, toxic hepatopathy, bile duct hyperplasia, and oval cell hyperplasia occurred in all core study dosed groups and tended to have dose-related increased incidences and severities (Tables 10 and A5b). Dose-related increased incidences of hepatocellular necrosis were seen in core study rats administered to 175 ng/kg or greater. In the 1,000 ng/kg stop-exposure group compared to the 1,000 ng/kg core study group, decreased incidences and severities of hepatocyte hypertrophy, multinucleated hepatocytes, diffuse fatty change, hepatocellular necrosis, toxic hepatopathy, bile duct hyperplasia, and oval cell hyperplasia were observed (Tables 10 and A5c).

Hepatocyte hypertrophy was characterized by hepatocytes, primarily in the portal areas, that were enlarged with increased amounts of brightly eosinophilic cytoplasm. Minimal hypertrophy affected periportal hepatocytes and as severity increased hepatocytes in other areas of the hepatic lobule were also affected. Multinucleated hepatocytes were characterized by scattered hepatocytes that were enlarged and contained multiple (more than two and often four to six) nuclei (Plate 5). The presence of binucleated hepatocytes was not sufficient to make this diagnosis.

Cholangiofibrosis occurred in all dosed groups, but tended to have a dose-related increased incidence and severity in the 300 ng/kg or greater groups. Cholangiofibrosis appeared relatively small in size and well demarcated, and did not show invasion (Plates 6 to 8). The incidence and severity of cholangiofibrosis were decreased in the 1,000 ng/kg stop-exposure group compared to the 1,000 ng/kg core study group.

Focal or diffuse fatty change was generally a minor change consisting of discrete clear vacuoles (consistent with lipid) in the cytoplasm of hepatocytes and involving either foci of hepatocytes (focal fatty change) or

scattered diffusely throughout the liver (diffuse fatty change). Oval cell hyperplasia consisted of small ovoid cells, with basophilic cytoplasm and a round to ovoid nucleus, that were arranged in single or double rows and located predominantly in the portal areas.

Necrosis consisted of scattered necrotic areas of hepatic parenchyma that were often randomly distributed, but occasionally, in more severe cases, were distributed more diffusely. Cytoplasmic alteration was a diffuse hepatocyte change in which the hepatocytes were enlarged with clear cytoplasm, consistent with glycogen storage. Cystic degeneration consisted of areas of cystic spaces or very large cells filled with lightly eosinophilic, often vacuolated material.

Pigmentation was observed in the macrophages, and in some of the more severe cases also in the hepatocytes, occurred in all dosed groups, and tended to have a dose-related increased incidence and severity (Tables 10 and A5b). Although the incidence of pigmentation was significantly increased in the 1,000 ng/kg stop-exposure group compared to the vehicle control group, the severity was less than that of rats administered 300 ng/kg or greater. 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.

The highest incidence of eosinophilic foci was seen in the 550 ng/kg dosed group. Eosinophilic foci (single or multiple) occurred in the vehicle control and all dosed groups, and the incidences were increased in the 100 ng/kg or greater groups. Mixed cell foci (single or multiple) occurred in the vehicle controls and all dosed groups, and the incidence was significantly decreased in the 1,000 ng/kg core study group. In the stop-exposure group, increased incidences of single or multiple basophilic and multiple mixed cell foci were observed when compared to the 1,000 ng/kg group of rats treated for 2 years.

Eosinophilic, mixed, basophilic, and clear cell foci were characterized by a focus of hepatocytes with altered tinctorial properties. Eosinophilic focus was composed of cells with eosinophilic cytoplasm. Mixed cell focus was composed of a mixture of cells with different staining properties, generally a mixture of eosinophilic cells and cells with clear cytoplasm (clear cells). To be classified as an eosinophilic focus at least 80% of the cells within the focus had to be eosinophilic cells. Otherwise the focus was classified as a mixed cell focus. Basophilic focus consisted of hepatocytes with basophilic cytoplasm, occasionally with basophilic linear (tigroid) intracytopasmic aggregates. Clear cell focus was composed of cells having clear cytoplasm. If two or more foci of a given type were present in a liver, it was diagnosed as multiple.

The treatment related foci were of the eosinophilic and mixed cell type, and often differed somewhat from those in vehicle control animals. Foci in vehicle controls consisted of hepatocytes that were generally somewhat larger than normal but appeared otherwise normal and were arranged in a relatively normal lobular pattern. The hepatic cords at the periphery of these foci generally merged imperceptibly with the surrounding normal liver resulting in an indistinct border and little or no compression of the adjacent liver parenchyma. In contrast, foci in treated animals generally had a more definite border, the cords within the focus often were not smoothly continuous with those in the surrounding parenchyma, and the foci consisted of cells that were often prominently enlarged with abundant eosinophilic or clear vacuolated cytoplasm. If more than 20% of the cells were vacuolated, the focus was classified as the mixed cell type, otherwise it was classified as an eosinophilic focus. In addition, some larger foci caused variable degrees of compression of the surrounding hepatic parenchyma. The cells were arranged in a relatively normal lobular pattern and foci sometimes contained large blood vessels and/or portal areas. The presence of proliferating bile ducts or oval cells was not considered characteristic of a focus. If proliferating bile ducts were present, this was considered indicative of nodular hyperplasia, described later.

An increased incidence of inflammation was noted in all dosed groups, but was not dose related. Portal fibrosis was seen in core study groups administered 300 ng/kg or greater. The incidence and severity of this change were increased in the 1,000 ng/kg core study group. In the 1,000 ng/kg stop-exposure group, decreased incidence and severity of portal fibrosis were observed relative to the 1,000 ng/kg core study group. Inflammation was generally a minor change consisting of accumulation of mononuclear cells (predominantly lymphocytes and plasma cells with occasional macrophages) most often within portal areas but also sometimes scattered randomly throughout the liver. Portal fibrosis consisted of

fibrous connective tissue accumulation that extended between adjacent portal areas.

Increased incidences of nodular hyperplasia occurred in the 550 and 1,000 ng/kg core study groups. Nodular hyperplasia was characterized by areas of focal hypertrophy and hyperplasia of hepatocytes that also contained proliferating bile ducts, and was considered to be the result of the presence of a proliferative stimulus. Areas of nodular hyperplasia varied in size with some areas being quite large while other were smaller and were the size of larger foci. In the dioxin toxic equivalency factor (TEF) evaluation studies, nodular hyperplasia was seen most commonly in the higher dose groups in which toxic changes were more prominent. However, a lesser degree of nodular hyperplasia was sometimes seen in lower dose animals in which toxic changes were minimal to inapparent. This suggested that nodular hyperplasia resulted from the presence of a hepatocellular proliferative stimulus that may have been independent of the toxic changes, but that the severity of the nodular hyperplasia was increased by toxicity. Nodular hyperplasia was not present in the 1,000 ng/kg stop-exposure group.

Nodular hyperplasia was characterized by few to numerous, small to large, nodular foci generally composed of hepatocytes that were considerably larger than normal hepatocytes (hepatocyte hypertrophy) sometimes mixed with areas of increased numbers of small hepatocytes (hepatocyte hyperplasia) (Plate 9). Areas of nodular hyperplasia sometimes blended with the surrounding parenchyma, although often they had a distinct border. Large, focal to multifocal areas of nodular hyperplasia were sometimes seen that caused compression of surrounding tissue, and/or bulging of the capsular surface. The cells within nodular hyperplasia generally were very large, larger than cells seen within adenomas and usually larger than cells seen within foci, with abundant eosinophilic cytoplasm and often with variable degrees of cytoplasmic vacuolation. In a few areas of nodular hyperplasia, however, the cells were of more normal size or sometimes slightly smaller than normal. The cells appeared to be arranged in normal cords, but the cells often were so large as to obscure the sinusoids between the cords giving the appearance of solid sheets of hepatocytes. Bile duct hyperplasia and portal areas were usually present within nodular hyperplasia. Blood vessels and/or central veins were also sometimes seen within areas of nodular hyperplasia, usually when hepatocytes were not so hypertrophic as to obscure completely the normal architecture. The presence of hypertrophic, vacuolated hepatocytes together with proliferating biliary epithelium were considered to be useful in the diagnosis of nodular hyperplasia.

An increased incidence of bile duct cyst was observed in the 1,000 ng/kg core study group. Bile duct cyst was characterized by either single or multiple dilated bile ducts that were lined by attenuated epithelium. Bile duct hyperplasia consisted of increased numbers of portal bile ducts.

The severity of the toxic hepatopathy was graded in order to give an overall severity grade for the degree of toxicity in a liver. This was to allow for easier comparison of the degree of toxic change among different dose groups than would be possible if the severities of all the individual nonneoplastic changes were compared among the different groups. This diagnosis was used in addition to, not instead of, any of the nonneoplastic diagnoses already made. The changes included under the diagnosis included focal cellular alteration, multinucleated hepatocytes, cystic degeneration, fatty change, inflammation, necrosis, pigmentation, nodular hyperplasia, bile duct cysts, bile duct hyperplasia, hepatocyte degeneration, hepatocyte hypertrophy, oval cell hyperplasia, and portal fibrosis (Plate 10). Some dosed animals occasionally had just a few of these changes present but this was not considered to be sufficient liver involvement to warrant a diagnosis of toxic hepatopathy.

Lung: The lung weights of 1,000 ng/kg rats were generally significantly increased at weeks 14, 31, and 53; lung weights of 10, 30, and 175 ng/kg rats were significantly increased at week 31 (Table B1). There were no biologically significant changes in the lung of dosed rats at 14 weeks (Tables A1a and A5a). At the 31-week interim evaluation, two cases of minimal bronchiolar metaplasia of the alveolar epithelium were seen in the 1,000 ng/kg group and a single case was seen in the 300 ng/kg dosed group (Tables 11 and A5a). At 53 weeks, dose-related increased incidences of minimal bronchiolar metaplasia of the alveolar epithelium were seen in the 175 ng/kg or greater groups.

At 2 years, dose-related increased incidences of cystic keratinizing epitheliomas occurred in the 300, 550, and 1,000 ng/kg core study groups and squamous cell carcinomas were seen in the 550 and 1,000 ng/kg core study groups (Tables 11, A1b, and A3a). No cystic keratinizing epitheliomas or squamous cell carcinomas have been seen in the historical controls (Tables 11 and A4b).

TABLE 11
Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Lung in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
31-Week Interim Evaluation								
Number Examined Microscopically	10	10	9	10	10	10	10	10
Alveolar Epithelium, Metaplasia, Bronchiolar[a]	0	0	0	0	0	1 (1.0)[b]	0	2 (1.0)
53-Week Interim Evaluation								
Number Examined Microscopically	8	8	8	8	8	8	8	8
Alveolar Epithelium, Metaplasia, Bronchiolar	0	0	0	0	1 (1.0)	1 (1.0)	2 (1.0)	6**(1.0)

TABLE 11
Incidences of Selected Neoplasms and Nonneoplastic Lesions of the Lung in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
2-Year Evaluation								
Number Examined Microscopically	53	55	53	53	53	51	51	50
Infiltration Cellular, Histiocyte	41 (1.7)	49 (1.7)	45 (1.7)	48 (1.6)	45 (1.6)	49**(1.7)	42 (1.5)	42 (1.5)
Alveolar Epithelium, Metaplasia, Bronchiolar	0	29**(1.3)	34**(1.6)	41**(1.8)	39**(1.7)	47**(2.1)	40**(1.9)	32**▲(1.5)
Alveolar Epithelium, Hyperplasia	12 (1.1)	1**(1.0)	0**	1**(3.0)	2**(1.0)	0**	0**	0**
Squamous, Metaplasia	1 (2.0)	0	1 (2.0)	2 (1.5)	3 (2.3)	9* (1.7)	4 (1.8)	0▲
Squamous Cell Carcinoma[c]	0	0	0	0	0	1	2	0
Cystic Keratinizing Epithelioma, Multiple	0	0	0	0	0	8**	30**	0▲▲
Cystic Keratinizing Epithelioma (includes multiple)[c]								
Overall rate[d]	0/53 (0%)	0/55 (0%)	0/53 (0%)	0/53 (0%)	1/53 (2%)	11/51 (22%)	35/51 (69%)	0/50 (0%)
Adjusted rate[e]	0.0%	0.0%	0.0%	0.0%	2.7%	26.0%	83.5%	0.0%
Terminal rate[f]	0/15 (0%)	0/25 (0%)	0/26 (0%)	0/22 (0%)	1/16 (6%)	5/23 (22%)	6/7 (86%)	0/28 (0%)
First incidence (days)	—[i]	—[j]	—	—	727 (T)	588	484	—
Poly-3 test[g]	P<0.001	—	—	—	P=0.531	P=0.002	P<0.001	—
Poly-3 test[h]								P<0.001N

* Significantly different (P≤0.05) from the vehicle control group by the Fisher exact test (interim evaluations) or by the Poly-3 test (2-year evaluation)
** P≤0.01
▲ Significantly different (P≤0.05) from the 1,000 ng/kg core study group by the Poly-3 test
▲▲ P≤0.01
(T) Terminal sacrifice
[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: 0/370.
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] 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.
[h] Pairwise comparison between the 1,000 ng/kg core and stop-exposure groups. A lower incidence in the stop-exposure group is indicated by **N**.
[i] Not applicable; no neoplasms in animal group
[j] Value of statistic cannot be computed.

Cystic keratinizing epitheliomas sometimes occurred singly but more commonly occurred as multiple lesions within the same lung. They ranged from relatively small to very large lesions that replaced much of the normal lung parenchyma. They were cystic structures consisting of a highly irregular wall of highly keratinized stratified squamous epithelium and a center filled with keratin. The outer portion of the lesion grew by expansion into the adjacent lung but evidence of invasion was not observed (Plate 11).

Squamous cell carcinomas occurred in two rats in the 1,000 ng/kg core study group. They were composed of numerous irregular clusters and cords of keratinizing stratified squamous epithelium with a scant to modest amount of dense fibrous tissue stroma. Localized invasive growth into the adjacent lung was present. Squamous cell carcinoma was distinguished from cystic keratinizing epithelioma by the presence of areas of solid growth and evidence of invasion into the surrounding lung parenchyma.

Increased incidences of bronchiolar metaplasia of alveolar epithelium occurred in all dosed groups (Tables 11, A5b, and A5c). The apparent decreased incidence of this change in the 1,000 ng/kg core study group may be due to the increased squamous cell neoplasms in this group. The incidence of squamous metaplasia was significantly increased in the 550 ng/kg group.

No squamous cell nonneoplastic lesions or neoplasms were seen in the 1,000 ng/kg stop-exposure group, but decreased incidences and severities of bronchiolar metaplasia of alveolar epithelium and squamous metaplasia occurred in the stop-exposure group compared to the 1,000 ng/kg core study group (Tables 11 and A5c).

Bronchiolar metaplasia of the alveolar epithelium consisted of replacement of the normal alveolar epithelium by cuboidal to columnar, sometimes ciliated cells, and was often accompanied by abundant mucus production in the affected area (Plate 12). The lesion generally diffusely affected the epithelium located at the bronchiolar-alveolar junction and adjacent alveoli. Aggregates of large alveolar macrophages were sometimes present in areas of bronchiolar metaplasia. This change was differentiated from alveolar epithelial hyperplasia, which was seen in the vehicle controls (Table A5b). In alveolar hyperplasia, the alveoli were lined by cuboidal epithelium. Unlike bronchiolar metaplasia in dosed animals, prominent mucus production was not observed, and very prominent inflammatory cell infiltrate, consisting of large aggregates of alveolar macrophages commonly mixed with focal aggregates of neutrophils, was usually associated with the affected areas. A decrease in the incidence of hyperplasia of alveolar epithelium was seen in all treated groups.

Squamous metaplasia of the alveolar 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 13). The incidence of histiocytic cellular infiltration was significantly increased in the 550 ng/kg group; this was considered to be a secondary lesion in the lung.

Oral Mucosa: At 2 years, occurrences of gingival squamous cell carcinoma were noted in all dosed groups. The incidence was significantly increased in the 1,000 ng/kg core study group and exceeded the historical control range (Tables 12, A3a, and A4c). Sporadic cases of gingival squamous cell hyperplasia were noted in all dosed groups except those administered 30 and 300 ng/kg (Tables 12 and A5b). Gingival squamous cell carcinoma, although reduced in incidence as compared to the 1,000 ng/kg core study group, was still present in the 1,000 ng/kg stop-exposure group (Tables 12 and A3b).

Squamous cell carcinoma occurred within the gingival epithelium and was located adjacent to the molars in nasal section III. It was characterized by irregular cords and clusters of stratified squamous epithelial cells that invaded deep into the underlying connective tissue and often invaded the bone of the maxilla (Plate 14).

Squamous hyperplasia was a focal lesion that occurred in the stratified squamous epithelium of the gingival oral mucosa adjacent to the molars in nasal section III. It consisted of varying degrees of thickening of the epithelium, often with the formation of epithelial rete pegs that extended a short distance into the underlying connective tissue (Plates 15 and 16). Ends of hair shafts and/or some degree of inflammation were often present in the areas of squamous hyperplasia suggesting, at least in these cases, the hyperplasia was secondary to the presence of the hair shafts and associated inflammation. It was unclear whether there was an association between squamous hyperplasia and squamous cell carcinoma.

Adrenal Gland: At 2 years, adrenal cortical adenomas were present in the 30, 100, 550, and 1,000 ng/kg core study groups and in the 1,000 ng/kg stop-exposure group

TABLE 12
Incidences of Neoplasms and Nonneoplastic Lesions of the Oral Mucosa in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Number Examined Microscopically	53	55	53	53	53	53	53	50
Gingival, Hyperplasia, Squamous[a]	1 (2.0)[b]	0	2 (1.0)	2 (2.0)	0	4 (1.5)	3 (2.7)	3 (2.3)
Squamous Cell Carcinoma[c]								
Overall rate[d]	0/53 (0%)	1/55 (2%)	1/53 (2%)	1/53 (2%)	2/53 (4%)	2/53 (4%)	7/53 (13%)	2/50 (4%)
Adjusted rate[e]	0.0%	2.6%	2.5%	2.7%	5.4%	4.7%	20.2%	5.2%
Terminal rate[f]	0/15 (0%)	0/25 (0%)	0/26 (0%)	1/22 (5%)	1/16 (6%)	0/23 (0%)	0/7 (0%)	0/28 (0%)
First incidence (days)	—[i]	681	651	727 (T)	618	498	523	618
Poly-3 test[g]	P<0.001	P=0.542	P=0.547	P=0.534	P=0.275	P=0.312	P=0.010	P=0.266
Poly-3 test[h]								P=0.052N

(T) Terminal sacrifice
[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 (mean ± standard deviation): 4/371 (1.1% ± 1.0%), range 0%-2%
[d] Number of animals with neoplasm per number of animals examined at necropsy
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] 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.
[h] Pairwise comparison between the 1,000 ng/kg core and stop-exposure groups. A lower incidence in the stop-exposure group is indicated by **N**.
[i] Not applicable; no neoplasms in animal group

and the incidences in the 1,000 ng/kg groups exceeded the historical control range (Tables 13, A1b, A3a, and A4d). Carcinomas were present in the 30, 300, and 1,000 ng/kg core study groups and in the 1,000 ng/kg stop-exposure group, and the incidence in the 1,000 ng/kg core study group exceeded the historical control range. The incidences of adenoma or carcinoma (combined) in the 1,000 ng/kg core study and stop-exposure groups exceeded the historical control range.

Cortical adenoma was a large, discrete lesion that replaced glandular parenchyma and caused compression of the remaining normal tissue. Adenoma was distinguished from hypertrophy or hyperplasia by the fact that adenoma consisted of somewhat atypical cortical cells that were arranged in abnormal patterns, rather than consisting of normal appearing cells arranged in the normal cord pattern as was the case with hypertrophy and hyperplasia. Large adenomas replaced much of the gland and caused enlargement of the gland. In contrast, cortical carcinoma was larger than adenoma and consisted of highly atypical cells arranged in highly abnormal patterns. Invasion through the capsule into adjacent tissue was also present. Carcinomas replaced much of the gland and caused enlargement of the gland.

The incidences and severities of adrenal cortical atrophy were increased in the 550 and 1,000 ng/kg core study groups and in the 1,000 ng/kg stop-exposure group (Tables 13, A5b, and A5c). There were slightly increased incidences of adrenal cortical hypertrophy in all treated groups without dose relation. This change appears unrelated to treatment. The incidence of adrenal cortical cytoplasmic vacuolation was increased in the 1,000 ng/kg core study group. The incidences of adrenal cortical atrophy and cytoplasmic vacuolation were lower in the 1,000 ng/kg stop-exposure group compared to the group administered 1,000 ng/kg for 2 years (Tables 13 and A5c).

Cortical hyperplasia was a focal to multifocal change, generally located in the zona fasciculata, consisting of a discrete area containing increased numbers of cortical cells. The hyperplastic cells were the same size or somewhat smaller than surrounding normal cortical cells, and had slightly basophilic cytoplasm. In some cases, especially with large lesions, there was compression of the surrounding tissue. However, these were distinguishable as hyperplasia by the fact that the cells still formed normal cords, particularly in the upper zona fasciculata. Cortical hypertrophy was also a focal to multifocal lesion consisting of discrete foci of enlarged cortical epithelial cells within the zona fasciculata and, in more severe cases, extending into the zona reticularis. Large lesions sometimes compressed adjacent parenchyma. Cortical hypertrophy and hyperplasia frequently occurred in the same gland.

Cortical atrophy was a locally extensive to diffuse change characterized by loss of cortical epithelial cells within the zona fasciculata and zona reticularis with a subsequent reduction in cortical thickness. The zona glomerulosa was spared. The remaining cells were sometimes vacuolated, especially in the more severe lesions. In severe cases the entire cortex was considerably reduced in thickness resulting in a smaller gland that often was surrounded by thickened capsule (Plates 17 and 18).

Cortical cytoplasmic vacuolation was a focal to multifocal to diffuse change consisting of small, discrete, clear intracytoplasmic vacuoles. Sometimes the cytoplasm contained a large single vacuole that displaced the nucleus. The changes were morphologically consistent with the accumulation of lipid.

The pathogenesis of the adrenal cortical proliferative lesions is unknown. However, focal regenerative hyperplasia was reported in rats, in the case of chemically induced damage or atrophy of the adrenal cortex (Yarrington and Reindel, 1996). It may be suggested that in the case of PCB 126, the cortical proliferative lesions are secondary to the primary cortical atrophy.

Significantly decreased incidences of adrenal medulla benign pheochromocytoma were observed in the 175 ng/kg, 300 ng/kg, and 1,000 ng/kg core study groups (vehicle control, 8/52; 30 ng/kg 3/55; 100 ng/kg, 4/53; 175 ng/kg, 2/53; 300 ng/kg, 2/53; 550 ng/kg, 4/52; 1,000 ng/kg, 0/53; Table A3a).

Pancreas: At the 31-week interim evaluation, single incidences of chronic active inflammation and acinar atrophy were observed in the 1,000 ng/kg group (Tables 14 and A5a). At 53 weeks, single incidences of chronic active inflammation and acinar atrophy were seen in the 300 and 1,000 ng/kg groups. A significantly increased incidence of pancreatic acinar cytoplasmic vacuolation was seen in the 1,000 ng/kg group.

At 2 years, acinar adenomas and carcinomas were seen sporadically in the treated groups. Two adenomas were

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Cortex in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Number Examined Microscopically	52	55	53	53	53	52	53	50
Hyperplasia[a]	23 (1.9)[b]	21 (2.4)	27 (2.1)	25 (2.0)	25 (2.4)	31 (2.7)	24 (2.5)	26 (2.0)
Atrophy	1 (1.0)	3 (2.3)	5 (1.2)	3 (1.0)	5 (1.6)	19** (1.8)	30** (2.2)	9*▲▲ (1.7)
Hypertrophy	34 (1.9)	41 (2.0)	40 (1.9)	41 (2.1)	40 (1.9)	41 (2.0)	41 (1.8)	42 (2.4)
Vacuolization Cytoplasmic	5 (1.2)	3 (1.7)	5 (2.0)	2 (2.0)	9 (1.9)	4 (1.0)	17** (1.9)	6▲▲ (1.5)
Adenoma[c]	0	1	1	0	0	1	2	2
Carcinoma[c]	0	1	0	0	1	0	2	1
Adenoma or Carcinoma[d]								
Overall rate[e]	0/52 (0%)	2/55 (4%)	1/53 (2%)	0/53 (0%)	1/53 (2%)	1/52 (2%)	4/53 (8%)	3/50 (6%)
Adjusted rate[f]	0.0%	5.2%	2.5%	0.0%	2.7%	2.4%	12.0%	8.0%
Terminal rate[g]	0/15 (0%)	2/25 (8%)	1/26 (4%)	0/22 (0%)	0/16 (0%)	0/23 (0%)	0/7 (0%)	3/28 (11%)
First incidence (days)	—[j]	727 (T)	727 (T)	—[k]	607	722	588	727 (T)
Poly-3 test[h]	P=0.022	P=0.285	P=0.546	—	P=0.533	P=0.555	P=0.065	P=0.144
Poly-3 test[i]								P=0.424N

* Significantly different (P≤0.05) from the vehicle control group by the Poly-3 test
** P≤0.01
▲▲ Significantly different (P≤0.01) from the 1,000 ng/kg core study group by the Poly-3 test
(T) Terminal sacrifice
[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 (mean ± standard deviation): 2/369 (0.5% ± 0.9%), range 0%-2%
[d] Historical incidence: 4/369 (1.1% ± 1.5%), range 0%-4%
[e] Number of animals with neoplasm per number of animals with adrenal cortex examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] 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.
[i] Pairwise comparison between the 1,000 ng/kg core and stop-exposure groups. A lower incidence in the stop-exposure group is indicated by **N**.
[j] Not applicable; no neoplasms in animal group
[k] Value of statistic cannot be computed.

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
14-Week Interim Evaluation								
Thyroid Gland[a]	10	2	4	3	3	4	5	10
Follicular Cell, Hypertrophy[b]	0	2 (1.5)[c]	4* (1.0)	3 (1.3)	3 (1.3)	4* (1.3)	5* (1.4)	3 (2.0)
Thymus	10	10	9	10	10	10	10	10
Atrophy	0	0	0	0	0	0	0	5** (1.4)
31-Week Interim Evaluation								
Pancreas	10	10	9	10	10	10	10	10
Inflammation, Chronic Active	0	0	0	0	0	0	0	1 (1.0)
Acinus, Atrophy	0	0	0	0	0	0	0	1 (1.0)
Thyroid Gland	10	3	3	5	6	5	5	10
Follicular Cell, Hypertrophy	0	3 (1.0)	3 (1.3)	5* (1.8)	6** (2.3)	5* (1.2)	5* (1.2)	7** (1.9)
Thymus	10	10	9	10	10	10	10	10
Atrophy	2 (1.0)	3 (1.0)	1 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)	8** (1.3)	10** (2.2)
53-Week Interim Evaluation								
Pancreas	8	8	7	8	8	8	8	8
Inflammation, Chronic Active	0	0	0	0	0	1 (1.0)	0	1 (1.0)
Acinus, Atrophy	0	0	0	0	0	1 (1.0)	0	1 (1.0)
Acinus, Vacuolization Cytoplasmic	0	0	0	0	0	0	1 (1.0)	6** (1.0)
Thyroid Gland	8	3	1	3	3	3	2	8
Follicular Cell, Hypertrophy	1 (1.0)	3* (1.3)	1 (1.0)	3* (1.0)	3* (1.0)	3* (1.0)	2 (1.5)	5 (1.2)
Thymus	8	8	8	8	7	8	8	7
Atrophy	7 (2.0)	5 (2.2)	6 (2.0)	5 (2.2)	5 (2.2)	7 (2.4)	8 (3.3)	7 (3.7)

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
2-Year Evaluation								
Pancreas	51	55	53	53	53	52	51	48
Inflammation, Chronic Active	5 (1.6)	1 (1.0)	3 (2.0)	4 (1.3)	4 (1.8)	6 (2.3)	13* (2.2)	4▲▲ (1.5)
Acinus, Atrophy	5 (2.0)	3 (1.3)	2 (2.5)	7 (1.6)	2 (2.5)	11 (2.2)	18** (2.1)	7▲▲ (1.4)
Acinus, Vacuolization Cytoplasmic	0	0	1 (1.0)	4 (1.5)	9** (1.0)	20** (1.1)	23** (1.4)	1▲▲ (1.0)
Artery, Inflammation, Chronic Active	0	4 (2.0)	2 (3.0)	4 (2.5)	8** (2.5)	15** (2.5)	11** (2.9)	1▲▲ (2.0)
Kidney	53	55	53	53	53	52	53	50
Nephropathy	32 (1.3)	29 (1.3)	38 (1.5)	35 (1.3)	38 (1.5)	42* (2.1)	47** (2.1)	38* (1.4)
Mineralization	32 (1.0)	39 (1.0)	44 (1.0)	44* (1.0)	44 (1.0)	39 (1.1)	37 (1.0)	45**▲ (1.0)
Transitional Epithelium, Hyperplasia	4 (2.0)	2 (2.5)	8 (1.9)	4 (2.5)	8 (1.6)	8 (2.3)	11 (2.0)	2▲▲ (2.0)
Heart	52	54	53	53	53	51	51	50
Cardiomyopathy	9 (1.0)	16 (1.1)	17 (1.1)	16 (1.2)	24** (1.1)	28** (1.1)	32** (1.2)	15▲▲ (1.2)
Thyroid Gland	52	55	52	51	52	50	48	47
Follicular Cell, Hypertrophy	9 (1.3)	13 (1.2)	13 (1.5)	17 (1.1)	28** (1.5)	26** (1.3)	16 (1.3)	22** (1.4)
Thymus	50	52	46	48	41	49	44	43
Atrophy	37 (2.5)	34 (2.6)	41 (2.8)	45** (2.8)	36* (3.3)	47** (3.5)	41** (3.5)	39 (3.0)
Spleen	52	55	52	53	53	52	52	50
Lymphoid Follicle, Atrophy	0	5 (2.6)	3 (2.0)	2 (1.5)	5 (2.0)	3 (2.3)	6* (2.3)	4 (2.5)
Clitoral Gland	50	55	52	50	53	52	51	48
Ducts, Cyst	29 (1.9)	32 (2.0)	34 (2.0)	37 (1.9)	39 (2.0)	42* (2.2)	45** (2.3)	39▲ (1.9)
Mesentery	53	55	53	53	53	53	53	50
Artery, Inflammation, Chronic Active	0	0	2 (3.0)	2 (3.5)	6 (3.2)	10** (2.6)	7* (2.7)	0▲

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test (interim evaluations) or by the Poly-3 test (2-year evaluation)
** $P \leq 0.01$
▲ Significantly different ($P \leq 0.05$) from the 1,000 ng/kg core study group by the Poly-3 test
▲▲ $P \leq 0.01$
[a] Number of animals with tissue examined microscopically except mesentery is number necropsied
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

seen in the 300 ng/kg group (vehicle control, 1/51; 30 ng/kg, 0/55; 100 ng/kg, 0/53; 175 ng/kg, 0/53; 300 ng/kg, 2/53; 550 ng/kg, 0/52; 1,000 ng/kg, 0/51; 1,000 ng/kg stop-exposure, 0/48; Tables A1b and A1c) and one carcinoma each was seen in the 175 and 1,000 ng/kg core study groups (vehicle control, 0/51; 30 ng/kg, 0/55; 100 ng/kg, 0/53; 175 ng/kg, 1/53; 300 ng/kg, 0/53; 550 ng/kg, 0/52; 1,000 ng/kg, 1/51; 1,000 ng/kg stop-exposure, 0/48; Tables A1b and A1c). The incidence of acinar adenoma in the 300 ng/kg group exceeded that in the historical controls (1/366, 0.3%); acinar carcinomas have not been seen in historical controls. Dose-related increased incidences and/or severities of chronic active inflammation, acinar atrophy, and acinar cytoplasmic vacuolation occurred in the 550 and/or 1,000 ng/kg core study groups (Tables 14 and A5b). The incidences of all treatment-related lesions in 1,000 ng/kg stop-exposure rats were decreased compared to those in the 1,000 ng/kg core study group (Tables 14, A5b, and A5c). A trend for dose-related increased incidence and severity of arterial chronic active inflammation was seen in the core study dosed groups (Tables 14 and A5b). The apparent decreased incidence of this lesion in the 1,000 ng/kg core study group, compared to the 550 ng/kg group, is suggested to be related to the reduced survival seen in this group.

Adenoma of the acinar cells was characterized microscopically by a discrete mass consisting of tubular and acinar structures composed of small acinar cells with brightly eosinophilic cytoplasm and lacking zymogen granules. In contrast, carcinoma was a large, multinodular lesion, with moderate amounts of dense fibrous stroma. Carcinomas were composed of densely packed clusters of poorly formed acinar structures consisting of small acinar cells with prominent vesicular nuclei and small amounts of eosinophilic cytoplasm with indistinct borders. Scattered solid areas composed of densely packed, highly pleomorphic, round to ovoid acinar cells with large vesicular nuclei and scant cytoplasm were also seen.

Atrophy was a focal to multifocal to diffuse change consisting of a reduction in the amount of acinar tissue with an associated increase in stromal fibrous connective tissue and fat. Chronic active inflammation was generally associated with atrophy and consisted of an infiltrate of mononuclear cells with occasional neutrophils within the stroma (Plate 19). Cytoplasmic vacuolation consisted of small, clear, discrete intracytoplasmic vacuoles within pancreatic acinar cells. Sometimes these vacuoles coalesced to form larger single vacuoles. The severity of the change was determined by the degree of vacuolization per cell and the amount of tissue involved. Arterial chronic active inflammation was a focal to multifocal change characterized by a thick mantle of macrophages, lymphocytes, and plasma cells around the arteries, with infiltration into the muscular layers of the artery. There was often fibrinoid necrosis of the vessel, and the tunica intima was frequently thickened. Endothelial cells were swollen or decreased in number (Plate 20). This inflammatory reaction often extended into the surrounding parenchyma.

Kidney: At 2 years, dose-related increased incidences and severities of nephropathy were noted in the 550 and 1,000 ng/kg core study groups (Table 14 and A5b). The incidences of mineralization in the 175 ng/kg core study and in the 1,000 ng/kg stop-exposure groups were significantly increased over controls, but the lack of a dose-relationship in the incidences of mineralization suggests that this change was not treatment related. An increased incidence of transitional cell hyperplasia was observed in the 1,000 ng/kg core study group. The lack of a dose-relationship for this change in the other dosed groups suggests that the incidences in these groups were not treatment related. The incidences of nephropathy and mineralization were increased in the 1,000 ng/kg stop-exposure group, but the severity of nephropathy was comparable to the vehicle control group (Tables 14 and A5c).

Nephropathy was generally a minimal to mild change, although sometimes moderate to marked nephropathy was seen. The appearance of this lesion was typical of that seen in aging rats, and was similar to that observed in F344/N rats (Barthold, 1998). Nephropathy was characterized by scattered foci of regenerative tubules lined by basophilic epithelium and sometimes surrounded by increased basement membrane, dilated tubules filled with proteinaceous casts and surrounded by fibrous connective tissue, and scattered foci of mixed inflammatory cells. Severity was graded based upon the number and extent of changes described above. Minimal nephropathy was characterized by small numbers of scattered affected tubules, usually involving less than 10% of the renal tubules. On the other extreme, marked nephropathy involved approximately 50% to 60% or more of the tubules. Transitional epithelium hyperplasia was a sometimes focal to multifocal, but generally diffuse, usually minimal to mild change consisting of varying degrees of thickening of the renal pelvic or papillary epithelium up to approximately 1.5 to 2 times normal thickness. Mineralization was generally a minimal

change consisting of small, basophilic mineralized concretions within tubular lumens, usually within the medulla, but occasionally at the corticomedullary junction or in the outer cortex.

Heart: At 2 years, a trend for increased incidences of cardiomyopathy occurred in the core study dosed groups (Tables 14 and A5b). The incidence of cardiomyopathy was decreased in the 1,000 ng/kg stop-exposure group compared to the 1,000 ng/kg core study group but was greater than that in the vehicle controls (Tables 14 and A5c).

Cardiomyopathy had the typical microscopic appearance of this lesion as seen in aging rats, and appeared similar to cardiomyopathy seen in aging F344/N rats (MacKenzie and Alison, 1990). It was a multifocal, generally minimal to mild lesion consisting of hypereosinophilic myofibers that lacked cross striations, infiltrates of mononuclear cells, separation of myofibers by myxomatous material (bluish material on H&E stain), and eventually replacement of myofibers by fibrous connective tissue. The severity was graded based upon the number and extent of foci of myocardial degeneration. Minimal cardiomyopathy consisted of a few scattered foci while mild cardiomyopathy consisted of a greater number of lesions more diffusely scattered within the myocardium.

Thyroid Gland: At 14, 31, and 53 weeks, the incidences of follicular cell hypertrophy were generally increased in all dosed groups (Tables 14 and A5a).

At 2 years, increased incidences of thyroid follicular cell hypertrophy were seen in all dosed groups and were significantly increased in the 300 and 550 ng/kg core study groups and in the 1,000 ng/kg stop-exposure group relative to vehicle controls (Tables 14, A5b, and A5c).

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, flocculent appearing material were often present. 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 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.

Thymus: Increased incidences and severities of atrophy occurred in the 1,000 ng/kg group at 14 weeks and in the 550 and 1,000 ng/kg groups at 31 weeks (Tables 14 and A5a). The severity was increased in the 1,000 ng/kg group at 53 weeks.

At 2 years, atrophy occurred in all groups including the vehicle controls (Tables 14 and A5b). The incidences of this lesion were significantly increased in the 175 ng/kg or greater core study groups, and the severities generally increased with increasing dose. The slightly lower incidence and severity of this lesion in the 1,000 ng/kg as compared to the 550 ng/kg group is because of the reduced survival in the 1,000 ng/kg core study group. The incidence and severity of atrophy in the 1,000 ng/kg stop-exposure group were greater than in the vehicle control group, which suggested a treatment-related effect (Tables 14 and A5c). Atrophy consisted of varying degrees of loss of lymphoid cells from the cortex resulting in reduction of cortical thickness.

Spleen: At 2 years, increased incidences of lymphoid follicular atrophy occurred in all dosed groups with the highest incidence in the 1,000 ng/kg core study group (Tables 14 and A5b). The incidences of lymphoid follicular atrophy was also elevated in the 1,000 ng/kg stop-exposure group (Tables 14 and A5c). Atrophy of lymphoid follicles was characterized by loss of lymphocytes with a subsequent decrease in the size of the lymphoid follicles.

Clitoral Gland: At 2 years, dose-related increased incidences of cystic ducts were noted in all dosed groups (Tables 14 and A5b). The incidence of cystic ducts was decreased in the 1,000 ng/kg stop-exposure group compared to the group treated with 1,000 ng/kg for 2 years, but was still higher than the vehicle controls (Tables 14 and A5c).

Cystic clitoral gland ducts consisted of dilated ducts that were filled with keratin and lined by attenuated epithelium. The severity varied from minimal to marked and was graded depending upon the size of the dilated ducts. Minimal lesions consisted of ducts dilated to approximately 2 to 3 mm and marked lesions consisted of ducts dilated to approximately 1 cm or more in diameter.

Mesentery: At 2 years, significantly increased incidences of arterial chronic active inflammation were noted in the 550 and 1,000 ng/kg core study groups (Tables 14 and A5b). The slightly lower incidence and severity of this lesion in the 1,000 ng/kg core study group as compared to the 550 ng/kg core study group is explained by the reduced survival observed in the 1,000 ng/kg core study group. The arterial chronic active inflammation that occurred appeared similar to that seen in the pancreas. In the 1,000 ng/kg stop-exposure group, no arterial chronic active inflammation was observed (Tables 14 and A5c).

Mammary Gland: Significantly decreased incidences of fibroadenoma, single or multiple, were noted in the 550 and 1,000 ng/kg core study groups and the 1,000 ng/kg stop-exposure group (vehicle control, 39/53; 30 ng/kg, 31/55; 100 ng/kg, 35/53; 175 ng/kg, 38/53; 300 ng/kg, 39/53; 550 ng/kg, 29/53; 1,000 ng/kg, 11/53; 1,000 ng/kg stop-exposure, 28/50; Tables A3a and A3b). The incidences of fibroadenoma in these groups were less than the historical range in vehicle controls [263/371 (71% ± 7%, range 62%-79%]. Significantly decreased incidences of carcinoma were noted in the 300, 550, and 1,000 ng/kg core study groups (6/53, 7/55, 9/53, 5/53, 0/53, 1/53, 1/53, 4/50; Tables A3a and A3b). The incidences of carcinoma in these groups were also lower than the historical range in vehicle controls [42/371 (11.3% ± 2.9%), range 8%-15%].

Pituitary Gland (Pars Distalis): A decrease in the incidence of adenoma was noted in the 1,000 ng/kg core study group (15/51, 18/54, 20/53, 16/53, 22/53, 14/53, 6/53, 17/48; Tables A3a and A3b), and the incidence was less than the historical range in vehicle controls [153/369 (41% ± 11%), range 28%-57%]. The incidence of this neoplasm in the stop-exposure group was relatively comparable to that in the vehicle control group.

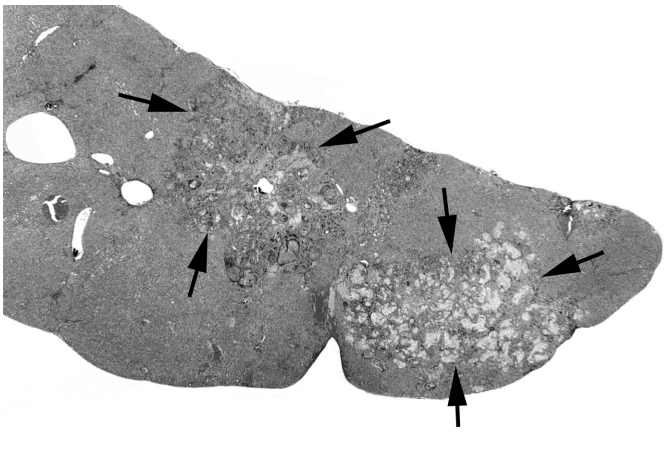


PLATE 1
Cholangiocarcinoma in the liver of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. The lesion margins are indicated by arrows. H&E; 10x

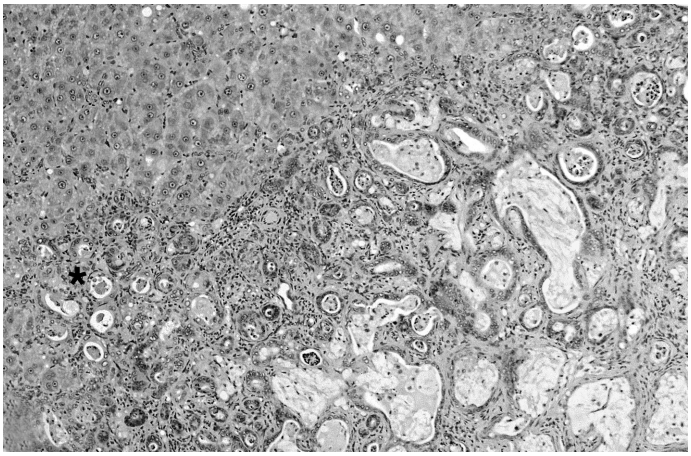


PLATE 2
Higher magnification of Plate 1. Note the prominent microinvasion (asterisk) at the periphery. H&E; 25x

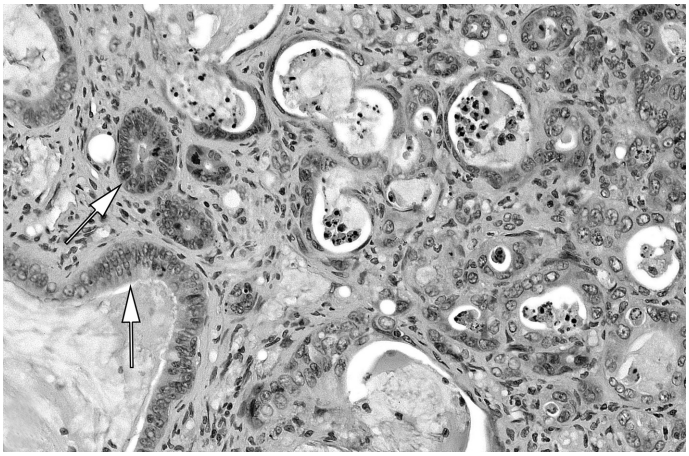


PLATE 3
Higher magnification of Plate 1. In contrast to cholangiofibrosis, the cholangiocarcinoma is larger in size, and the epithelium is more atypical (open arrows). H&E; 66x

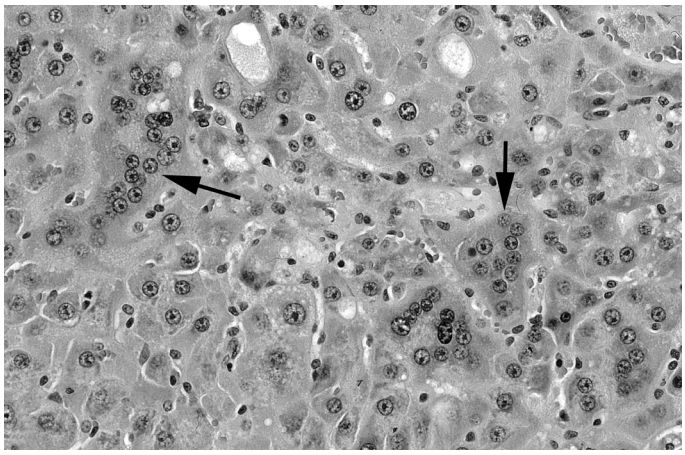


PLATE 4
Hepatocellular adenoma in the liver of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note distinct borders and compression of surrounding normal parenchyma (arrows). The hepatocytes are smaller than normal hepatocyes and have hyperbasophilic (darker) cytoplasm. H&E; 2.5x

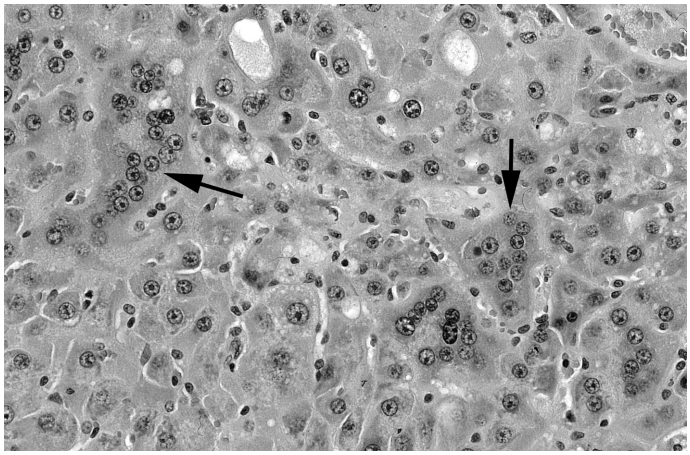


PLATE 5
Multinucleated hepatocytes (arrows) in the liver of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note that the hepatocytes have multiple nuclei. H&E; 80x

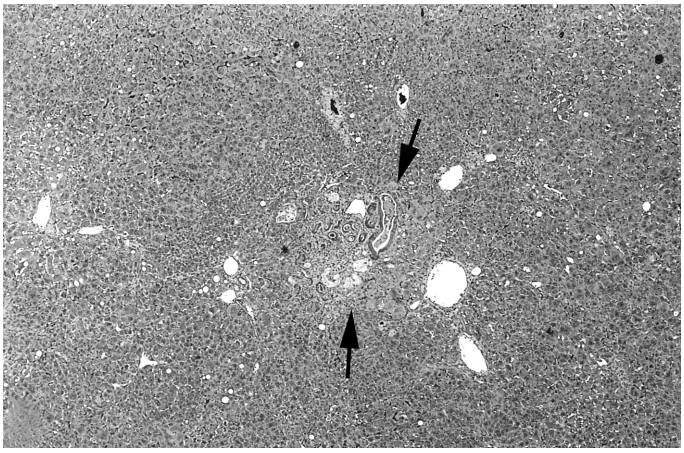


PLATE 6
Cholangiofibrosis (grade 2) (the lesion margins are indicated by arrows) in the liver of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. The glands are lined by a single layer of cells. H&E; 10x

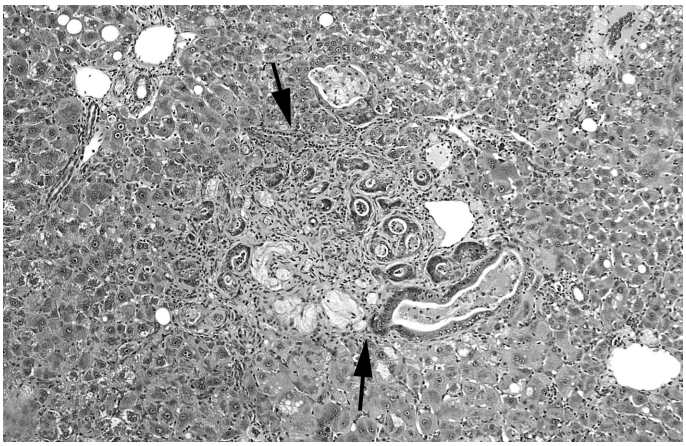


PLATE 7
Higher magnification of Plate 6. H&E; 25x

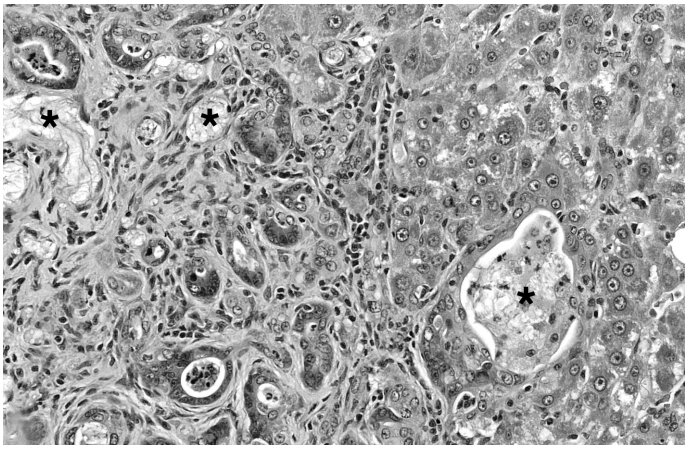


PLATE 8
Higher magnification of Plate 6. Note the well circumscribed proliferating biliary epithelium forming mucus-producing, crescent-shaped, glandular structures (asterisks) surrounded by concentric layers of connective tissue. H&E; 66x

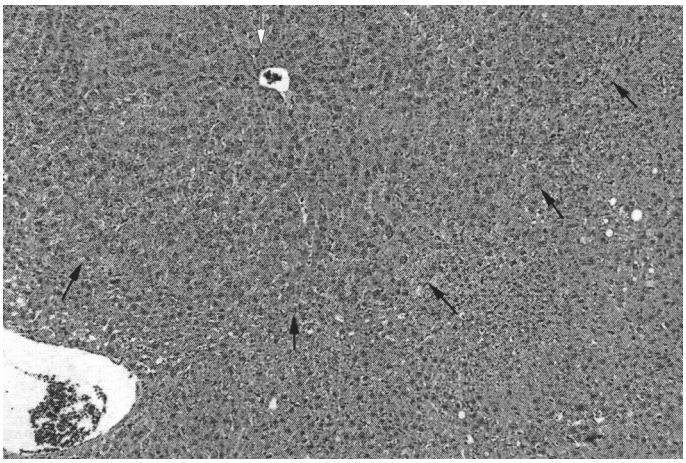


PLATE 9
Nodular hyperplasia in the liver of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note the nodule slightly compresses the surrounding tissue (dark arrows). The hepatocytes are slightly larger than normal hepatocytes, but otherwise look normal. There is a portal tract in the middle of the nodule (open arrow). H&E; 10x

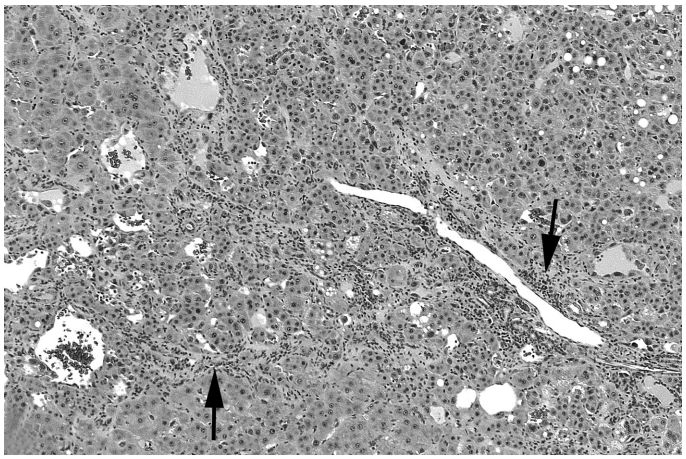


PLATE 10
Toxic hepatopathy in the liver of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Components of the diagnosis included focal cellular alteration, multinucleated hepatocytes, cystic degeneration, diffuse fatty change, inflammation (arrows), necrosis, pigmentation, regeneration, bile duct cysts, bile duct hyperplasia, hepatocyte degeneration, hepatocyte hypertrophy, oval cell hyperplasia, and portal fibrosis. H&E; 20x

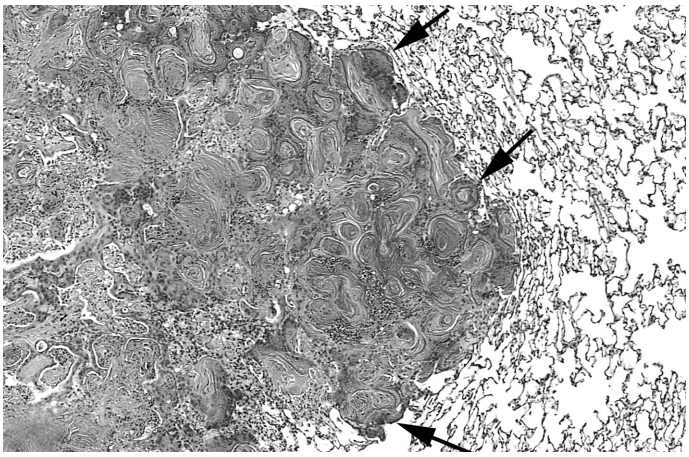


PLATE 11
Cystic keratinizing epithelioma in the lung of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note the contiguous alveoli are filled by squamous epithelium with a complex, thick wall and rough appearance (arrows) of the outer portion of the lesion. H&E; 16x

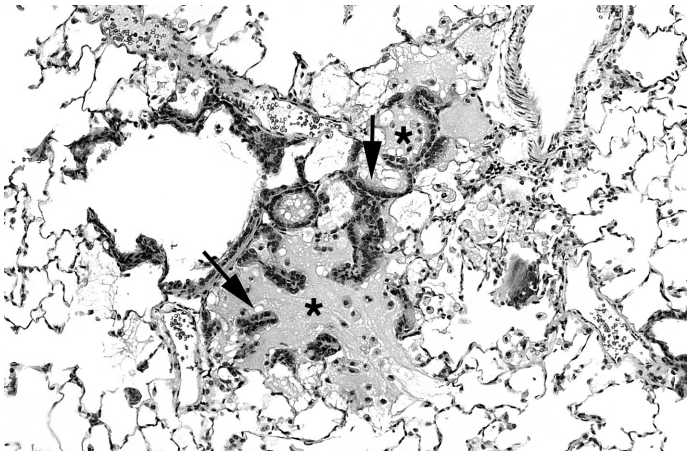


PLATE 12
Bronchiolar metaplasia of the alveolar epithelium in a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. The alveolar epithelium consists of columnar cells (arrows) with moderate amounts of mucus production (asterisks). The lesion is located at the bronchiolar-alveolar junction and extends into adjacent alveoli. H&E; 33x

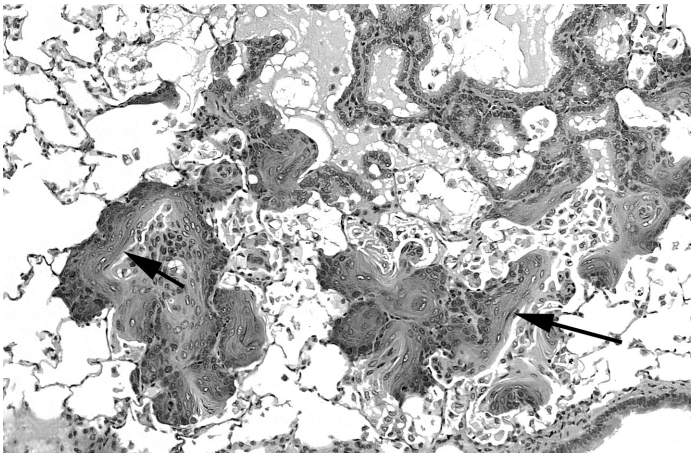


PLATE 13
Squamous metaplasia (arrows) of the alveolar epithelium in a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note the contiguous alveoli filled with mature squamous cells producing keratin. H&E; 33x

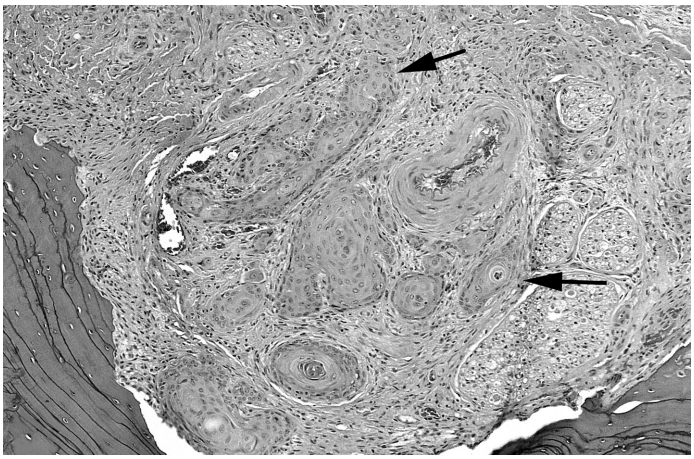


PLATE 14
Squamous cell carcinoma of the gingival epithelium in a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note the invasion of squamous cells (arrows) into the adjacent stroma. H&E; 33x

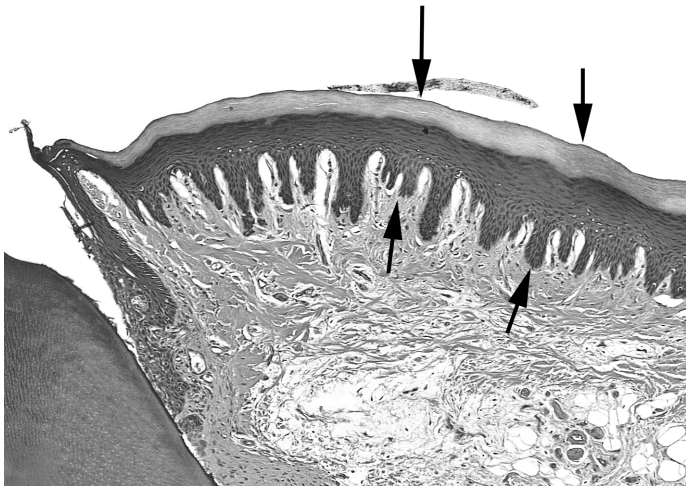


PLATE 15
Gingival mucosa (normal thickness is indicated by arrows) of a female vehicle control rat from the 2-year PCB 126 gavage study. H&E; 33x

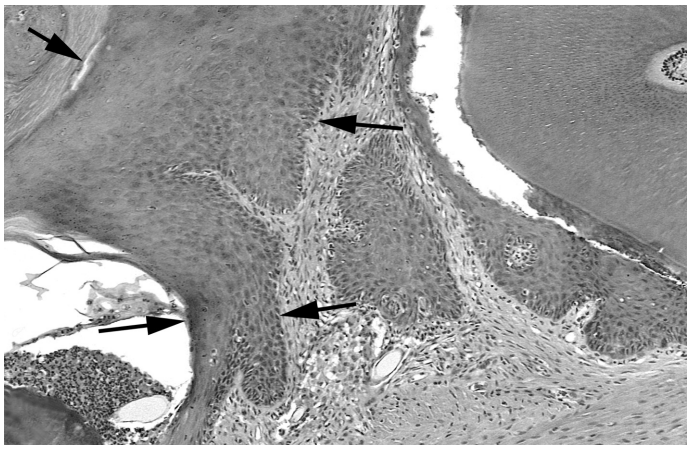


PLATE 16
Squamous hyperplasia of the gingival epithelium in a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note thickening (thickened mucosa is indicated by arrows) of the mucosa by mature squamous cells producing keratin. H&E; 33x

PLATE 17
Adrenal gland of a vehicle control female rat from the 2-year PCB 126 gavage study. H&E; 6.6x

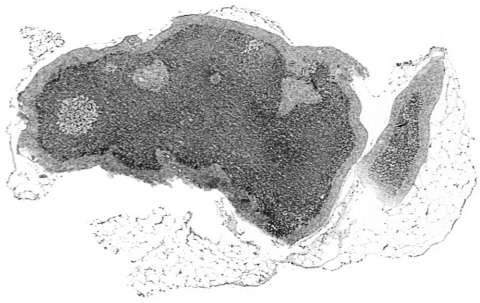


PLATE 18
Adrenal cortical atrophy (grade 4) in a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note the gland is smaller compared to that in Plate 17 and has a thickened capsule. The zona glomerulosa was unaffected. H&E; 8x

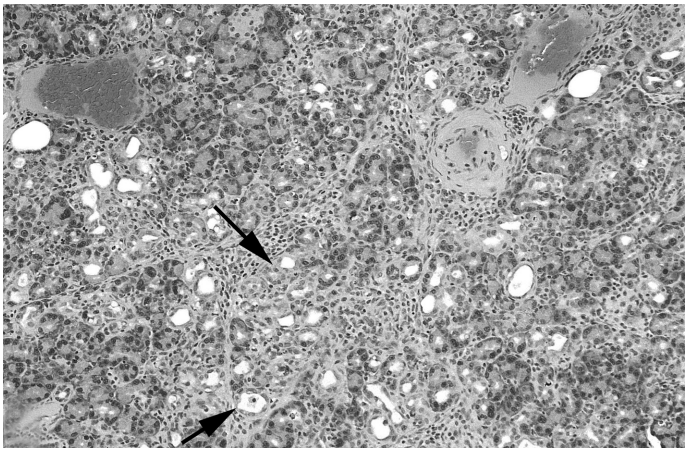


PLATE 19
Chronic active inflammation in the pancreas of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Mixed inflammatory cells are present throughout the parenchyma, associated with atrophy of the acini (arrows) and dilatation of the ducts. H&E; 33x

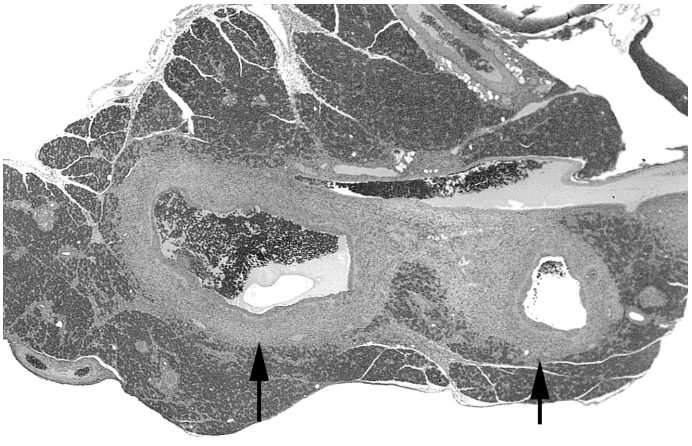


PLATE 20
Chronic active inflammation (arrows) of the artery in the pancreas of a female rat administered 1,000 ng/kg PCB 126 per day by gavage for 2 years. Note the mixed inflammatory cell infiltration around and within the muscular layers of the artery associated with fibrinoid necrosis of the wall. H&E; 5x

DISCUSSION AND CONCLUSIONS

This 2-year study of the chronic toxicity and carcinogenicity of PCB 126 in female Harlan Sprague-Dawley rats is one in a series of studies carried out as part of a multistudy NTP initiative examining the relative chronic toxicity and carcinogenicity of dioxin-like compounds (DLCs) and structurally related polychlorinated biphenyls (PCBs) (see Overview section). While one of the primary aims of this dioxin toxic equivalency factor (TEF) evaluation was an analysis of the comparative carcinogenicity of TCDD, PeCDF, and PCB 126, in this Technical Report only the results of the PCB 126 toxicology and carcinogenicity study are described and, where appropriate, a qualitative comparison to neoplastic responses seen in the gavage study of TCDD (NTP, 2006a) conducted as part of the dioxin TEF evaluation. A quantitative analysis of the effects observed in this study to responses observed with other compounds studied as part of the dioxin TEF evaluation are presented elsewhere (Toyoshiba *et al.*, 2004; Walker *et al.*, 2005).

PCB 126 is the most potent coplanar PCB for the induction of TCDD-like activities. Dose selection for this study of PCB 126 was based on prior observations made in a 2-year carcinogenicity study of TCDD by Dow Chemical Company (Kociba *et al.*, 1978). In that study, Spartan Sprague-Dawley rats were exposed to doses of 1, 10, or 100 ng TCDD/kg body weight per day. Increases in liver adenomas were observed at doses of 10 and 100 ng/kg. Given the World Health Organization's (WHO) TEF for PCB 126 of 0.1, the dose range for the present study was selected as 10 to 1,000 ng PCB 126/kg body weight per day. For the carcinogenicity study, doses of 30, 100, 175, 300, 550, and 1,000 ng/kg per day were used to provide more information on the shape of the dose response curve.

In the current study, survival in the 550 ng/kg group and the stop-exposure group was significantly greater than in the vehicle controls. Survival in the 1,000 ng/kg group was not significantly different from the vehicle control group. Survival in the vehicle control group was somewhat lower than vehicle controls in other studies of Sprague-Dawley rats conducted as part of the dioxin TEF evaluation (NTP, 2006a,b,c). Daily administration of PCB 126 at doses greater than 175 ng/kg led to a dose-related reduction in body weight gain over the course of the 2-year study. Reduction in body weight gain is a characteristic toxic response to dioxin-like compounds. The mean body weight in survivors administered the highest dose of 1,000 ng/kg was 72% of that observed in vehicle controls.

The reduction in body weight gain was treatment related and required daily continuous administration. In the stop-exposure group, daily administration of compound ceased after 30 weeks and was followed by daily gavage with corn oil:acetone (99:1) alone. Thereafter, the rate of body weight gain in these animals returned to normal and was similar to vehicle control animals. At the end of the study, the mean body weight in the stop-exposure group was 92% that of vehicle controls.

The principal findings of this study were increased incidences of benign and malignant neoplasms in several organs, specifically in the liver (cholangiocarcinoma and hepatocellular adenoma), lung (cystic keratinizing epithelioma and squamous cell carcinoma), and oral mucosa (gingival squamous cell carcinoma). The highest neoplastic response was in the lung (cystic keratinizing epithelioma) with an adjusted incidence rate of 84%.

The principal nonneoplastic finding in this study was a significant increase in the incidence and severity of hepatotoxicity in the liver. In addition, numerous organs exhibited increased incidences of nonneoplastic lesions; notably the lung, adrenal cortex, pancreas, kidney, heart, thyroid gland, thymus, spleen, clitoral gland, and mesentery.

Chronic exposure led to significant accumulation of PCB 126 in liver, fat, lung, and detectable levels in blood. The significant accumulation in fat is consistent with the lipophilic nature of this compound. Previous studies of dioxin-like compounds (DLCs) indicate that the liver and fat are the main depots for DLCs in rodents and together contribute approximately 70% to 80% of the total body burden in rodents (DeVito *et al.*, 1995). As expected, the levels in liver were higher than those in

fat on a wet weight basis. This is likely due to the sequestration of DLCs in the liver as a result of binding to CYP1A2 that is inducible by DLCs in the liver (Diliberto *et al.*, 1997).

Analysis of liver tissue levels of PCB 126 in this study indicated that administration at dose levels of 100, 175, 300, 550, and 1,000 ng PCB 126/kg per day for up to 2 years resulted in mean liver levels of 91, 128, 214, 363, and 536 ng PCB 126/g tissue, respectively. The relationship between intake and liver levels was linear. In the TCDD feed study by Kociba *et al.* (1978), terminal liver TCDD levels were 24 ng/g at the 100 ng/kg dose and 5.1 ng/g at the 10 ng/kg dose. By comparison, terminal liver levels of TCDD in the study conducted as part of the dioxin TEF evaluation were 2.2 and 9.3 ng/g at the 10 and 100 ng/kg doses, respectively (NTP, 2006a). On a toxic equivalents (TEQs) basis (using the WHO TEF of 0.1 for PCB 126), the liver burden of PCB 126 at the 100 ng/kg and 1,000 ng/kg doses (9.1 ng TEQ/g and 55 ng TEQ/g) were approximately four to sixfold higher than those seen in the dioxin TEF evaluation TCDD study (NTP, 2006a) and approximately 2-fold higher than that observed for TCDD in the Kociba *et al.* (1978) study.

Cessation of daily treatment with PCB 126 in the stop-exposure study group led to a decline in levels of PCB 126 in all tissues examined. At the end of the study, mean levels of PCB 126 in the liver of the stop-exposure group animals was 11.6 ng/g compared to 536 ng/g in animals exposed for the full 2 years at the same dose. This level of 11.6 ng/g was almost threefold lower than that observed at the end of the study in animals exposed for 2 years to 30 ng/kg per day (mean liver level of 29 ng/g). Similarly, the mean adipose level of PCB 126 in the stop-exposure animals (7.6 ng/g) was significantly lower than that seen in the 1,000 ng/kg group (131 ng/g) and approximately twofold lower than that observed in animals exposed to an equivalent total dose, 30 ng/kg per day (14.4 ng/g). Therefore, interpretation of the pathology results in the stop-exposure animals has to be made in light of the fact that exposure *per se* does not end on cessation of daily administration of compounds. While PCB 126 levels in the 1,000 ng/kg stop-exposure group declined significantly over the remainder of the study, due to the lipophilic nature of the compound, animals were still continually exposed throughout the course of the study. In addition, exposure to DLCs also can occur as a result of exposure to low levels of these compounds that are present in rodent feed.

There was measurable PCB 126 in vehicle control animals at the longer durations of exposure. These concentrations can be attributed to the ingestion of very low levels of PCB 126 that are normally present in rodent chow (Feeley and Jordan, 1998; Jordan and Feeley, 1999). Accumulation of PCDDs and PCDFs has also been observed in vehicle control animals in other studies (Vanden Heuvel *et al.*, 1994). The levels of PCBs were analyzed in NTP-2000 feed; the level of PCB 126 was below the limit of quantitation (i.e., <9 pg/g feed) (Table D5). PCB 126 levels of 0.4 ppt (pg/g feed) have been reported in rat feed (Jordan and Feeley, 1999). This level of PCB 126 would result in a daily intake of approximately 200 pg/kg per day (for a 200 g rat ingesting 10 g feed per day). Based on the observation that the relationship between daily PCB 126 dose and tissue levels is linear, the level of PCB 126 in vehicle controls corresponds to an approximate median daily intake of 54 pg PCB 126/kg per day (range 31 to 1,385 pg/kg), which is consistent with that predicted from levels measured in rodent feed.

Therefore, with respect to all the TEF studies, it is important to note that in essence all experimental treatments are made on top of a background of prior exposure to DLCs normally present in feed and, therefore, the vehicle control group exposure is not zero. However, as one can see from the estimated intake, the background intake is 2 to 3 orders of magnitude lower than the doses where neoplastic responses were observed. Consequently, the additional contribution of this background exposure rate to the observed tumor responses to administered PCB 126 is negligible.

Increased expression of CYP1A1 and CYP1A2 are characteristic responses to DLCs in the liver and are directly linked to binding and activation of the aryl hydrocarbon receptor (AhR) by DLCs (Whitlock, 1993). In many cases, the relative potency for induction of CYP1A1 *in vivo* is an appropriate surrogate for the dioxin-like activity of a given compound and provides the basis for many TEFs (Van den Berg *et al.*, 1998). In this study, increased CYP1A1 and CYP1A2 activity as a result of PCB 126 exposure were observed at all time points and at all doses used. PCB 126 is a coplanar PCB that has the highest affinity of this class of PCBs for the AhR. Consequently, the finding that the liver was a target following exposure to PCB 126 was expected. It was also expected that exposure to this compound would lead to increases in these specific dioxin-like responses. While not discussed in this Technical Report, data on altered

expression of CYP1A1 and CYP1A2 together with data from the other studies of DLCs conducted as part of the dioxin TEF evaluation have been used for an evaluation of the additivity of relative potency of DLCs for these endpoints (Toyoshiba *et al.*, 2004).

Numerous studies have examined the toxicity of DLCs and PCBs and have demonstrated that the liver is a principal target organ for the action of these compounds. In the present study of PCB 126, the principal hepatic neoplasm observed was cholangiocarcinoma. The liver effects seen in this study with PCB 126 are consistent with those seen in the dioxin TEF evaluation study of TCDD (NTP, 2006a). In that study, there was a significant increase in the incidence of cholangiocarcinoma in the 100 ng/kg group.

The incidence and pattern of hepatic toxicity exhibited a clear dose and duration dependence and preceded neoplastic effects in the liver. In this study, there was a significant increase in hepatic toxicity with increases in severity occurring at higher doses and longer durations of treatment. Hepatic toxicity was characterized by foci of cellular alteration, multinucleated hepatocytes, cystic degeneration, diffuse fatty change, inflammation, necrosis, pigmentation, nodular hyperplasia, bile duct cysts, bile duct hyperplasia, hepatocyte degeneration, hepatocyte hypertrophy, oval cell hyperplasia, and portal fibrosis. A comprehensive term of toxic hepatopathy was also used, reflecting the overall severity of the nonneoplastic effects. The purpose of the use of this term was to allow for easier comparison of the toxic changes among different dose groups than would be possible if the severities of all the individual nonneoplastic changes had to be compared among the different groups. This diagnosis was used in addition to, not instead of, any of the nonneoplastic diagnoses already made. Some treated animals occasionally had just a few of these changes present, but this was not considered to be sufficient liver involvement to warrant a diagnosis of toxic hepatopathy.

The increased incidences and severities of hepatotoxicity and increased incidences of hepatocellular adenoma are consistent with previously observed effects of TCDD and hexachlorodioxins of the liver (Kociba *et al.*, 1978; NCI, 1980; NTP, 1982a). However, in this study the most significant effect was on the incidences of cholangiocarcinoma. The increased incidences of cholangiocarcinoma and hepatocellular adenoma are consistent with the effects of TCDD seen in the study conducted as part of the dioxin TEF evaluation (NTP, 2006a). Previous studies of DLCs and PCBs have only rarely seen cholangiocarcinomas despite data showing that bile ducts are targets for DLCs. In a 60-week initiation-promotion study, cholangiocarcinoma was seen in 1/14 DEN-initiated female rats exposed to 100 ng TCDD/kg body weight per day for 60 weeks (Walker *et al.*, 2000). In the 2-year bioassay of Aroclor 1254, no cholangiocarcinomas were observed (Mayes *et al.*, 1998). In addition, there was no increased incidence of cholangiocarcinoma in the TCDD feed study by Kociba *et al.* (1978).

One aspect to consider with the liver neoplasms is that pathology nomenclature practices have changed since the Kociba *et al.* (1978) study indicated a 47% incidence of "hepatocellular hyperplastic nodules" in the 100 ng TCDD/kg body weight group compared to a 9% incidence in control animals. Subsequent to the Kociba *et al.* (1978) study there was an evolution of nomenclature for hepatocellular proliferative lesions, and a reevaluation of the slides from the study. In that evaluation, neoplastic lesions were classified as adenoma or carcinoma. Using the newer nomenclature, the incidence of hepatocellular adenoma was 31% at the highest dose of 100 ng TCDD/kg body weight (Goodman and Sauer, 1992). A summary of the pathology reevaluation is provided in the NTP toxicology and carcinogenesis studies of TCDD (NTP 2006a). It is clear from the pathology reevaluations that some of the hyperplastic nodules originally seen in the Kociba *et al.* (1978) study were indeed nonneoplastic. Significant hepatotoxicity was noted in the Kociba *et al*. (1978) TCDD study (Goodman and Sauer, 1992), in the NCI (1980) TCDD study, and in the NTP (1982a) TCDD studies.

In the reevaluation of the Kociba *et al.* (1978) TCDD dosed feed study, the incidences of hepatocellular adenomas were 2/86, 9/50, and 14/45 in the 0, 10, and 100 ng/kg groups, respectively. By comparison, in the present PCB 126 study, the incidences of hepatocellular adenoma were 1/53, 1/53, and 7/53 in the vehicle control, 100, and 1,000 ng/kg groups, respectively. In the NTP (1982a) gavage study of Osborne-Mendel rats, the incidence of liver "neoplastic nodules" in female rats was 12/49 (24%) at a weekly dose of 500 ng TCDD/kg body weight per day, similar to the current study. The incidence of neoplastic nodules or hepatocellular carcinoma was 14/49 (29%). There was no significant effect in male rats. In the NCI (1980) study of a mixture of 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin in Osborne-Mendel rats,

the incidences of neoplastic nodules or hepatocellular carcinoma (combined) were 5/75 (7%), 10/50 (20%), 12/50 (24%), 30/50 (60%) at weekly doses of 0, 1,250, 2,500, or 5,000 ng/kg, respectively. Given the TEF of 0.1 for hexachlorodioxins (Van den Berg *et al.*, 1998), these weekly doses are over a similar range of TEQs as used in the present gavage study.

The spectrum of hepatocellular proliferative lesions observed in the present study is not common in NTP studies, and there is a lack of biological information relative to the progression and behavior of these lesions. These lesions generally occurred on a background of toxic hepatopathy, the components of which are listed above and described in the Results section. It is generally accepted that in the rat, hepatocellular adenoma and hepatocellular carcinoma represent a morphological and biological continuum (Narama *et al.*, 2003; Hailey *et al.*, 2005). Foci of cellular alteration are often part of that continuum, but not always. In the high dose group (1,000 ng/kg), proper categorization of the lesions was further complicated by the presence of the toxic hepatopathy. While the biological behavior of hepatocellular lesions within this study and other studies conducted as part of the dioxin TEF evaluation is uncertain, the morphology suggests that in this study, eosinophilic foci and mixed cell foci, nodular hyperplasia, and potentially adenoma were a continuum.

The foci of cellular alterations seen in dosed animals generally differed from the typical foci seen in vehicle controls. Foci seen in vehicle controls were usually smaller, lacked discrete borders and blended with the surrounding parenchyma, produced little or no compression, and consisted of cells that were normal-sized or slightly smaller or larger than normal. In contrast, foci in the livers of dosed animals generally had discrete borders, produced some compression of the adjacent parenchyma, and consisted of large, hypertrophic, often vacuolated cells. The significantly increased incidences of hypertrophy resulted in a greater degree of compression of adjacent hepatic parenchyma than is often seen with foci of hepatocellular alteration. At 2 years, focal lesions were observed that resembled foci of hepatocellular alteration, but were larger and often nodular, with greater compression of surrounding hepatic parenchyma, and more disorganization of hepatic cords. As with foci, these lesions generally contained a somewhat normal hepatic structure including portal triads with biliary tracts. Additionally, these focal lesions contained variable numbers of randomly scattered biliary epithelium that often formed profiles of small glands/ductules. The large size of the lesions and presence of scattered biliary epithelium suggested a proliferative response of both hepatocellular and biliary cells, and therefore, these lesions were considered to have progressed beyond a simple focus of cellular alteration. However, because of the somewhat normal hepatic structure and the dual cellular composition, the lesions were considered to be hyperplastic rather than neoplastic and were diagnosed as nodular hyperplasia.

In the higher dose (550 and 1,000 ng/kg) animals with severe toxic hepatopathy, there was evidence of hepatocyte degeneration and loss and a regenerative response by the damaged liver. The term "hyperplasia, nodular" was selected as the inclusive term and was characterized by areas of focal hypertrophy and hyperplasia of hepatocytes that also contained proliferating biliary epithelium. This lesion was considered to be the result of the presence of a proliferative stimulus. Nodular hyperplasia varied in size, but generally appeared morphologically similar whether in a high dose (1,000 ng/kg) animal with severe toxic hepatopathy or in a lower dose (175 ng/kg) animal where the toxic hepatopathy was minimal to nonexistent. In the dioxin TEF evaluation studies, nodular hyperplasia was seen most commonly in the higher dose groups in which prominent toxic changes were present. However, a lesser degree of nodular hyperplasia was sometimes seen in lower dose animals in which the only evidence of liver pathology may have been hepatocyte hypertrophy.

Morphologically, a hyperplastic nodule associated with regeneration cannot be distinguished from a hyperplastic nodule of another pathogenesis. The morphological alterations suggest that regeneration is a significant contributor to the proliferative response in animals with toxic hepatopathy. However, this does not explain these responses in animals that lack toxic hepatopathy. This indicates that some type of other stimulus, rather than regeneration secondary to degeneration and necrosis of the hepatic parenchyma, may have contributed to the proliferative lesions observed in this study.

Dealing with the potential pathogenesis for the foci and nodular hyperplasia, the earliest treatment-related hepatocellular change seen in these studies, noted at the 14-, 31-, and 53-week interim evaluations, was a diffuse hepatocyte hypertrophy. With continued dosing, poorly demarcated foci of prominent hypertrophic, often vacuolated hepatocytes, resembling those seen in foci and

nodular hyperplasia, were seen superimposed on the background of diffuse hypertrophy. It appeared that with continued dosing the poorly demarcated foci of hypertrophic cells grew giving rise to lesions diagnosed as foci, and that with continued dosing, in some instances aided by toxic changes, may have progressed to nodular hyperplasia.

In contrast to nodular hyperplasia, hepatocellular adenoma was a nodular mass that usually was larger than a focus, had a distinct border, and produced more compression of surrounding normal hepatic parenchyma. Adenomas were composed of mildly to moderately pleomorphic hepatocytes with a subjectively increased nucleus to cytoplasmic ratio. Cells lacked the normal architectural arrangements of hepatic lobules and while a few bile ducts may have been present within an adenoma, they were usually found at the periphery of the lesion and were considered entrapped. Proliferating biliary epithelium or oval cells were generally absent. The lack of proliferating bile duct epithelium or oval cells was an important feature differentiating adenoma from nodular hyperplasia.

The increased incidence of cholangiocarcinoma following exposure was an unexpected finding but consistent with observations made in other studies conducted as part of the dioxin TEF evaluation (NTP, 2006a,b,c,d,e,f). Spontaneous cholangioma and cholangiocarcinoma are apparently rare in Harlan Sprague-Dawley rats and were not observed in 371 vehicle control animals from these seven studies. These neoplasms are characterized by glandular structures lined by a single layer of well-differentiated epithelium (benign lesions), or single or multiple layers of epithelial cells that have malignant characteristics (e.g., high nuclear to cytoplasmic ratio, pleomorphism and anisokaryosis, and an increased mitotic rate).

In the present study, cholangiocarcinoma was diagnosed, and while it differed morphologically from spontaneous cholangiocarcinoma, it was similar to chemically induced cholangiocarcinoma in another study (Maronpot *et al.*, 1991). In this study, cholangiocarcinomas were variably sized, often multiple lesions composed of irregular and atypical bile ducts in a matrix of fibrous connective tissue. The bile ducts themselves were often incomplete, or crescent-shaped, and lined by very basophilic, cuboidal to columnar cells with large, euchromatic nuclei. Stratification of these epithelial cells was present in some areas. Atypical biliary epithelium was often identified within the adjacent hepatic parenchyma, suggesting invasion. The fibrous connective tissue component was frequently profound; much more than that seen in the scirrhous reaction that may be observed with spontaneous cholangiocarcinoma. The lesions seen in this study were sometimes large, effacing an entire liver lobe.

Cholangiofibrosis was the term used to describe small lesions that were less aggressive in appearance. Cholangiofibrosis often originated in the portal area, and tended to have a more mature fibrous connective tissue component, and less atypia associated with the epithelial cells. Most often, cholangiofibrosis and cholangiocarcinomas seen in this study did not compress the surrounding hepatic parenchyma or expand beyond the existing hepatic profile. However, cholangiocarcinomas often did expand within the liver lobe.

While cholangiofibrosis and cholangiocarcinoma appear to be a morphological continuum, there is limited biological information relative to the pathogenesis or progression of these lesions. As a result, the most appropriate classification scheme for these lesions is somewhat uncertain and controversial. While the characteristic of malignancy, distant metastasis, was not observed in any animals in the present study, other characteristics of malignancy were present, such as atypical appearance of the epithelial cells and apparent localized invasion. It was clear that some of these cholangiolar lesions were small and very benign appearing and warranted a nonneoplastic diagnosis, and there were lesions at the other end of the spectrum that appeared aggressive. While there were specific diagnostic criteria for cholangiofibrosis versus cholangiocarcinoma, some of the lesions did not readily fit the criteria and posed a diagnostic challenge.

Other chemicals, including furan, have increased the incidence of lesions similar to those observed in the present study (Maronpot *et al.*, 1991). In the Maronpot *et al.* (1991) furan study, the lesions appeared more aggressive, yet even in that study, where there was nearly a 100% incidence in treated animals, there were few metastases. In this study, it appears that the cholangiocarcinomas were slow growing neoplasms of relatively low-grade malignancy. Transplantation studies done in the furan study were positive for growth and metastases. Transplantation studies were not done with lesions from the present study.

There were single occurrences of cholangioma in each of the 550 and 1,000 ng/kg core study groups and three

hepatocholangiomas in the 1,000 ng/kg group. Both neoplasm types appear to be rare spontaneously, and did not occur in 371 vehicle control animals from this study or the six other dioxin TEF evaluation studies (NTP, 2006a,b,c,d,e,f). Hepatocholangiomas were mixed neoplasms with areas of hepatocytes that appeared identical to hepatocellular adenoma and areas of ductular structures lined by biliary epithelium that appeared identical to cholangioma. The pluripotent nature of these neoplasms was demonstrated by occasional ductular structures lined by cells resembling both hepatocytes and biliary epithelium. In contrast to the cholangiofibrosis and cholangiocarcinomas, a schirrhous response was not present within these neoplasms. While the histogenesis of hepatocholangioma is not clear, there was evidence of proliferation of hepatocytes, biliary epithelium, and oval cells within these studies. Therefore, the occurrence of three rare hepatocholangiomas in the 1,000 ng/kg group was considered related to the administration of PCB 126. Single incidences of cholangioma in the 550 and 1,000 ng/kg core study groups may have been related to the administration of PCB 126.

The mechanism underlying the increase in incidences of cholangiocarcinoma is likely to be multifactorial. There was clearly an effect on bile duct proliferation in this study. This may be an indirect response to the toxicity observed as a result of the action of the DLC on the hepatocytes or due to a direct effect on the biliary cells themselves. Tritscher *et al.* (1995) showed a high degree of staining for TGF alpha in bile duct cells after TCDD administration in female rats. The observed bile duct proliferation may represent a process of excessive and long term repair following specific damage to hepatocytes, leading to the death of hepatocytes and perhaps also of the bile duct epithelium. The proliferative response may be a reparative response of proliferating hepatocytes, bile duct cells, and scarring tissue (cholangiofibrosis). The inflammation also observed can produce oxidative stress that may also result in promotion of DNA damage. Consequently, the oxidative stress may be only a secondary phenomenon due to the ongoing response to the toxic hepatopathy. In addition, there may be a direct stimulatory effect on the oval cells themselves. This is supported by the observed increased incidence of oval cell hyperplasia in the present study. Since oval cells may differentiate into both hepatocytes and/or biliary epithelium this may explain why both hepatocellular proliferative and biliary lesions were associated with exposure.

There has been a considerable amount of research examining the potential mode of action of DLCs in the liver. There is a general scientific consensus that almost all responses of TCDD and related compounds require initial binding to the AhR. Recent data indicate that the acute toxic responses (including hepatotoxicity) to TCDD require AhR binding and nuclear localization (Bunger *et al.*, 2003). In addition, transgenic mouse studies indicate that constitutive activation of the AhR alone can lead to an induction of stomach tumors (Andersson *et al.*, 2002).

The dioxin-like effects of PCB 126 are likely AhR-mediated. Due to the lack of direct genotoxicity the action of PCB 126 is likely as a potent tumor promoter. There are essentially three potential modes of action via the AhR: increased numbers of initiated cells capable of undergoing promotion; increased net growth rate of initiated cells due to selective growth advantage, or decreased rate of cell death via suppression of apoptosis.

Numerous studies have shown in initiation-promotion models of hepatocarcinogenesis that PCDDs, PCDFs and PCBs such as PCB 126 can promote the development of altered hepatic foci. Given that TCDD and related compounds are not direct-acting genotoxic agents and are potent growth dysregulators it is believed that their predominant mode of action is as tumor promoters. Within a conceptual multistage model of carcinogenesis, promotion mediated by these compounds via the AhR may be due to an increase in net growth rate of initiated cells due to selective growth advantage or decreased rate of cell death via suppression of apoptosis. In studies with TCDD, there are significant increases in hepatocyte replication as judged by BrdU labeling studies (Maronpot *et al.*, 1993; Walker *et al.*, 1998; Wyde *et al.*, 2001a). Studies by Stinchcombe *et al.* (1995), Worner and Schrenk (1996), and Bohnenberger *et al.* (2001) have also shown a suppression of apoptosis by TCDD and PCBs. In addition, altered growth regulation may be due to alterations in intercellular communication, which have also been observed in the livers of rats exposed to DLCs (Baker *et al.*, 1995; Warngard *et al.*, 1996; Bager *et al.*, 1997). While DLCs are not direct acting genotoxic agents there are data indicating that persistent AhR active compounds may be indirectly genotoxic. This may contribute to an increase in the number of cells within the liver capable of undergoing promotion (Moolgavkar *et al.*, 1996; Portier *et al.*, 1996). It is hypothesized that the indirect genotoxicity

may be via an AhR dependent induction of CYP1 family cytochromes P450 that leads to an induction of oxidative stress due to either inefficient electron transfer during P450 metabolism (Park *et al.*, 1996) or the production of redox active estradiol metabolites as a result of CYP1 mediated estrogen metabolism (Lucier *et al.*, 1991; Kohn *et al.*, 1993). Studies have shown an induction of oxidative stress and DNA damage by high dose acute exposure to TCDD (Stohs *et al.*, 1990). The induction of lipid peroxidation and single stranded DNA breaks was also observed in tissues from the present study (Hassoun *et al.*, 2000). Other studies on the female specific tumor promotion response in rats have shown an induction of oxidative DNA damage and hepatocyte replication by TCDD that is female specific and estrogen dependent (Lucier *et al.*, 1991; Tritscher *et al.*, 1996; Wyde *et al.*, 2001a,b).

In the present study of PCB 126, the highest increase in the incidence for any neoplasm was for cystic keratinizing epithelioma (CKE) of the lung. Histopathologically these lesions varied in size and number and appeared as cystic structures consisting of a highly irregular wall of highly keratinized stratified squamous epithelium, with a center filled with keratin. These lesions were absent in vehicle control animals but observed in 69% of animals treated at the highest dose (1,000 ng/kg). A significant increase in incidence of CKE was also seen at the 550 ng/kg dose.

Like PCB 126, a significant increase in the incidence of lung CKE was also observed in TCDD-treated animals in the dioxin TEF evaluation study (NTP, 2006a). In the 2-year feed study of TCDD, conducted by Kociba *et al.* (1978) an increased incidence of keratinizing squamous cell carcinoma of the lung was observed following exposure to a 100 ng TCDD/kg body weight per day. In the present PCB 126 study, squamous cell carcinomas were identified and were distinguished from CKE by the presence of areas of solid growth and evidence of invasion. While no direct comparison has been made between CKE and the keratinizing squamous cell carcinoma observed in the Kociba *et al.* (1978) study, given the keratinizing nature of the lesion it is possible that these may be similar lesions. It should be noted that CKE was not a diagnostic term consistently used at the time of the Kociba *et al.* (1978) evaluation. Diagnostic criteria for classification of CKE as a lesion distinct from squamous cell carcinoma were later developed at a workshop held in the mid 1990s (Boorman *et al.*, 1996).

In contrast to the present study, a recent study of the carcinogenicity of the high TEQ PCB mixture Aroclor 1254 demonstrated no increases in the incidences of any type of lung tumor (Mayes *et al.*, 1998). While Aroclor 1254 contains a significant TEQ contribution by PCB 126, this mixture also contains mono-*ortho* and di-*ortho* PCBs.

In addition to an increase in the incidences of CKE, there was a significant increase in the incidences of bronchiolar metaplasia of the alveolar epithelium at both 53 weeks and 2 years. The incidences of this lesion were significantly increased in all dosed groups at 2 years. In addition, there were increases in the incidences of alveolar squamous metaplasia, seen in groups administered 175 ng/kg or greater. These findings are consistent with prior observations of an increase in the incidences of alveolar-bronchiolar metaplasia following exposure to TCDD within the framework of a two stage initiation-promotion model in Sprague-Dawley rat lung (Tritscher *et al.*, 2000).

Alveolar ducts and alveoli are normally composed of type I alveolar epithelial cells and type II alveolar epithelial cells, which are cuboidal. Type I cells are very susceptible to damage, and the typical response in the lung, subsequent to the damage to the type I cells, is a proliferation of the type II cells. This is often diagnosed as alveolar epithelial hyperplasia. Interestingly, there were significantly decreased incidences of alveolar epithelial hyperplasia in all dosed groups in the present study. PCB 126 induced a multifocal lesion that was found throughout the lung at the junction of the terminal bronchioles and alveolar ducts. The epithelium was cuboidal to columnar, and ciliated in contrast to type II alveolar epithelial cells. Also, scattered throughout the ciliated cells were dome-shaped nonciliated cells, consistent with Clara cells. Clara cells are normally found in the lining of the bronchioles, but not alveoli or alveolar ducts. Histochemical analyses of mucin and GSTPi in lung tissue from the dioxin TEF evaluation studies indicates that this does appear to be similar to bronchiolar epithelium and is distinct from alveolar epithelial hyperplasia (Brix *et al.*, 2004). It is not clear though if this lesion represents a destruction of type I alveolar epithelial cells with replacement by bronchiolar type epithelium (bronchiolar metaplasia) or rather an extension of bronchiolar epithelium from the terminal bronchiole (bronchiolar hyperplasia).

There are at least two potential mechanisms involved in the increased incidences of these neoplasms and non-neoplastic lesions in the lung. CYP1A1 is known to be inducible in the lung by TCDD in several species (Beebe *et al.*, 1990; Walker *et al.*, 1995). This was confirmed in

the present study by the observed increase in lung CYP1A1 associated EROD activity. The inducibility of CYP1A1 by TCDD is observable in Clara cells and bronchiolar cells, and to a lesser degree in type II cells (Tritscher *et al.*, 2000). This indicates that the bronchiolar epithelium is clearly responsive to AhR ligands and suggests the potential for a direct effect on the lung. *In vitro* studies of normal human lung epithelial cells (mixed type II, Clara cell type) also demonstrate the alteration of numerous cell signaling pathways by TCDD including the Ah battery, altered retinoid signaling and altered cytokine signaling pathways (Martinez *et al.*, 2002).

Another possible mechanism for the action of DLCs on the lung may be an indirect effect due to the disruption of retinoid homeostasis in the liver. It is known that in rodents, mobilization of retinoid stores by TCDD and DLCs leads to a disruption in retinoid homeostasis and vitamin A deficiency (Van Birgelen *et al.*, 1994, 1995b; Fiorella *et al.*, 1995; Fattore *et al.*, 2000; Schmidt *et al.*, 2003). A characteristic of retinoid deficiency is abnormal epithelial differentiation to a keratinized squamous phenotype (Lancillotti *et al.*, 1992; Lotan, 1994). The action of DLCs may therefore be a disruption of retinoid action leading to altered growth and differentiation of the lung epithelium resulting in squamous metaplasia and ultimately neoplasia.

Gingival squamous cell carcinoma of the oral mucosa was observed in all dosed groups, and the incidence was significantly increased in the 1,000 ng/kg core study group only. Similarly, in the TCDD gavage study conducted as part of the dioxin TEF evaluation (NTP, 2006a) there was a significant increase in the incidence of gingival squamous cell carcinoma of the oral mucosa. In the TCDD feed study by Kociba *et al.* (1978), there were increases in the incidences of stratified squamous cell carcinoma of the hard palate/nasal turbinates in both male and female rats. The location of the squamous cell carcinomas in the present study was adjacent to the molars and invaded into the hard palate/nasal turbinate areas. This suggests that the lesions seen in the NTP (2006a) and Kociba *et al.* (1978) studies are similar.

In recent years there has been an increasing awareness of the sensitivity of the oral cavity to the effects of DLCs. In two PCB/PCDF human poisoning episodes one of the toxic responses observed in humans was early tooth eruption (Grassman *et al.*, 1998). More recent studies have shown that TCDD can accelerate incisor tooth eruption and delay molar eruption. Proliferation of the periodontal squamous epithelium has been seen in juvenile mink exposed to PCB 126 (Render *et al.*, 2001) but not in juvenile Otsuka Long-Evans Tokushima Fatty (OLETF) rats exposed to 100 ppb PCB 126 or 10 ppb TCDD for 101 days (Aulerich *et al.*, 2001). Studies suggest that the effect of TCDD on tooth development is due to a disruption in EGFR-mediated signaling (Partanen *et al.*, 1998) as has been shown for other developmental effects of TCDD such as cleft palate (Abbott *et al.*, 2003). In addition, as noted above for the effects of PCB 126 on the lung, the squamous lesions in the oral cavity may also be related to the alteration in retinoid homeostasis that is known to be induced by PCB 126.

In the present PCB 126 study, there were increases in the incidences of adrenal cortical atrophy and cytoplasmic vacuolization in the 1,000 ng/kg group. Elevated incidences of atrophy were seen in the 500 ng/kg group and the 1,000 ng/kg stop-exposure group, albeit at a lower incidence level than in the 1,000 ng/kg core study group. In addition, there was equivocal evidence of an increased incidence of adrenal cortical adenoma and carcinoma in the 1,000 ng/kg group. In the Kociba *et al.* (1978) feed study of TCDD, there was a significant increase in the incidence of adrenal cortical adenoma in male but not female rats at the 100 ng/kg dose. In the dioxin TEF evaluation TCDD study (NTP, 2006a), there were sporadic cases of adenoma of the adrenal cortex, in both vehicle control and TCDD-treated animals, but no significant TCDD-related increase in incidence. The cortical atrophy seen in the present PCB 126 study was a prominent effect and may reflect the continued stress in these animals, leading to depletion of corticosteroid hormones or some other unknown mechanisms (Sapolsky *et al.*, 1987).

The pathogenesis of the adrenal cortical proliferative lesions is unknown. However, focal regenerative hyperplasia was reported in rats, in the case of chemically induced damage or atrophy of the adrenal cortex (Yarrington and Reindel, 1996). It may be suggested that in the case of PCB 126 the cortical proliferative lesions are secondary to the primary cortical atrophy.

In the present PCB 126 study, there was also a significant reduction in the incidence of benign pheochromocytoma with the lowest observed effect occurring at 175 ng/kg. A lower incidence was also observed in the stop-exposure group, but this was not significant. Adrenal pheochromocytoma occurs spontaneously in the rat, and usually occurs at a higher incidence in males compared to females. In this study, there was a lower

incidence of benign pheochromocytoma in PCB 126-treated female rats than in vehicle controls, but this change was not statistically significant. A significant reduction in the incidence of benign pheochromocytoma was previously observed in male rats only in the 2 year TCDD feed study by Kociba *et al.* (1978) (33% and 14% in vehicle controls and 100 ng TCDD/kg body weight per day, respectively). There was no effect on benign pheochromocytoma in the dioxin TEF evaluation TCDD gavage study (NTP, 2006a).

In the present PCB 126 study, the incidences of pancreatic inflammation, acinar atrophy, acinar cytoplasmic vacuolization, and pancreatic arterial inflammation were all greater than those in the vehicle controls after 2 years of exposure to 1,000 ng/kg. Acinar cytoplasmic vacuolization and arterial inflammation were also elevated at doses as low as 300 ng/kg. No significant effect of PCB 126 on the incidence of any pancreatic lesion was seen in the 1,000 ng/kg stop-exposure animals.

Acinar atrophy of the pancreas may be related to the down regulation of cholecystokinin (CCK). As shown by Lee *et al.* (2000) in samples from the present PCB 126 study, intestinal CCK is reduced by PCB 126 exposure. Down-regulation of CCK is likely due to a general endocrine effect as a result of the reduction in body weight gain following exposure to PCB 126. CCK is an important regulator of pancreatic growth and function (Baldwin, 1995; Varga *et al.*, 1998). Previous studies have shown that increased apoptosis and pancreatic acinar atrophy is observed in OLETF rats that lack the CCK-A receptor gene (Jimi *et al.*, 1997). In addition, antagonism of CCK action can lead to reduced pancreatic growth (Ohlsson *et al.*, 1995).

In the present PCB 126 study, the incidence of kidney nephropathy was significantly higher in both the 1,000 ng/kg core study animals and the stop-exposure group compared to vehicle controls. In addition, the incidence of kidney mineralization was significantly increased in both the 175 ng/kg animals and the stop-exposure group. While it is known that the kidney is directly responsive to the AhR agonist TCDD, the kidney historically has not been a target for DLC-induced neoplasia.

Administration of PCB 126 to female Harlan Sprague-Dawley rats in this study significantly increased the incidences of cardiomyopathy in a dose-related manner (Jokinen *et al.*, 2003). However, the average severity of cardiomyopathy was unaffected. Cardiomyopathy is a common, spontaneously occurring degenerative change of myocardial fibers that is seen in rats as they age. Its cause in the rat is unknown, but age of onset and severity are affected by diet, environment, and stress. Significant increases in the incidence of cardiomyopathy were observed at doses of 300 ng/kg or greater. While the incidence of cardiomyopathy was higher in the stop-exposure group compared to vehicle controls, it was not statistically significant. The microscopic appearance of cardiomyopathy was the same in both the vehicle control and treated animals and was typical of that described for spontaneous lesions. This finding may suggest that exposure to the chemicals increased the occurrence of the spontaneous change.

The heart is a known target for TCDD and related DLCs in both rodents and humans (Peterson *et al.*, 1993; Flesch-Janys *et al.*, 1995; Walker and Catron, 2000; Heid *et al.*, 2001). In the 2-year study in which Sprague-Dawley rats were administered up to 0.1 µg/kg per day of TCDD in the feed, Kociba *et al.* (1978) also reported an increase of myocardial degenerative change above background levels in females only.

In this PCB 126 study, the incidence of thymic atrophy was significantly elevated after 31 weeks at all doses greater than 550 ng/kg and at all doses above 175 ng/kg at the end of the study. Thymic atrophy is one of the hallmark immunotoxic responses to DLCs (Poland and Knutson, 1982) and is due to an AhR-mediated alteration in lymphocyte growth and differentiation (Staples *et al.*, 1998; Gasiewicz *et al.*, 2000). Also atrophy of the lymphoid follicles in the spleen was seen at the highest dose (1,000 ng/kg) but only after 2 years. Thymic atrophy and other hematopoietic changes may in part be related to the reduction in body weight gain observed in these animals as seen in short term feed restriction studies (Levin *et al.*, 1993).

In the present PCB 126 study, there were increases in the incidences of thyroid gland follicular cell hypertrophy in the high dose group (1,000 ng/kg) at the 31- and 53-week interim evaluation time points. At the end of the study, however, there were no effects on follicular cell neoplasms. By comparison, in the NTP 2-year gavage study of TCDD in Osborne-Mendel rats, there was a significant increase in the incidence of follicular cell adenomas in male rats and a nonsignificant increase in females (NTP, 1982a).

Alteration in thyroid hormone homeostasis by PCB 126 and TCDD is well established (Van Birgelen *et al.*, 1994,

1995a; Schmidt *et al.*, 2003). Analyses of thyroid hormones in the present PCB 126 study confirmed the alterations in thyroid hormone homeostasis by PCB 126. The disruption of thyroid hormone homeostasis by DLCs is believed to be due to the increase in thyroxine (T_4) glucuronidation as a result of increased expression of UDP-GT. This leads to a decreased negative feedback inhibition of the thyroid gland leading to overexpression of thyroid stimulating hormone (TSH) (Curran and DeGroot, 1991). Kohn *et al.* (1996) developed a mathematical model of the effects of TCDD on UDP-GT expression and thyroid hormone homeostasis that is consistent with this mechanism. 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 126 study, it was observed that despite alteration in T_4 and TSH at the early time points, the effects on TSH were not seen at 53 weeks despite a significant effect on T_4. It is possible, therefore, that the lack of follicular cell neoplasia in this study reflects a lack of a sustained long-term increase on TSH sufficient to promote neoplasia.

In this PCB 126 study, there was a significantly lower adjusted incidence of mammary gland neoplasms following PCB 126 administration. Fibroadenoma is a spontaneous lesion in female Sprague-Dawley rats and occurred at high incidence (86%) in the vehicle control group. Mammary gland carcinoma was also seen in vehicle control animals, at a lower incidence (19%). The incidences of fibroadenoma and carcinoma in the 1,000 ng/kg group were 31% and 3%, respectively. In addition, there was a significantly lower incidence of spontaneous pituitary gland (pars distalis) adenoma following PCB 126 exposure. In vehicle control animals, 46% exhibited pituitary neoplasms but the incidence was only 18% in the 1,000 ng/kg group.

It is believed that the lower incidences of mammary gland and pituitary gland neoplasms in dosed rodents are related to a general endocrine effect as a result of reductions in body weight gain associated with exposure. A significant association between reduced body weight gain and lower incidence of mammary gland and pituitary gland neoplasms has been observed in many NTP studies (Seilkop, 1995). Significantly lower incidences of mammary gland and pituitary gland neoplasms were also observed in animals exposed to 100 ng TCDD/kg body weight in the 2 year feed study of Kociba *et al.* (1978). Similarly, there were significantly lower incidences of spontaneous mammary gland and pituitary gland neoplasms in the dioxin TEF evaluation TCDD gavage study (NTP, 2006a)

Reductions in IGF-1 may underlie the inhibitory effect of reduced body weight gain on tumor development. It is known that caloric restriction leads to lower levels of IGF-1 and reduction in background tumor rates (Hursting *et al.*, 2003). One of the major intestinal hormones expressed in the proximal gastrointestinal tract is CCK. CCK regulates gallbladder contraction, pancreatic secretion, stomach emptying, and intestinal motility and can also inhibit food intake. In an analysis of intestinal tissue obtained from the present PCB 126 study, Lee *et al.* (2000) showed lower levels of intestinal CCK and an induction of IGFBP3 by PCB 126 in this NTP study. Alterations in CCK processing enzymes by TCDD were also observed in cultured intestinal cells suggesting direct effects of PCB 126 on intestinal cells. The authors hypothesized that alterations in CCK may be due to alterations in processing enzymes and lower IGF-1 levels as a result of alterations in IGFBP3.

CONCLUSIONS

Under the conditions of this 2-year gavage study there was *clear evidence of carcinogenic activity** of PCB 126 in female Harlan Sprague-Dawley rats based on increased incidences of cholangiocarcinoma of the liver, squamous neoplasms of the lung (cystic keratinizing epithelioma and squamous cell carcinoma), and gingival squamous cell carcinoma of the oral mucosa. Hepatocellular adenoma and hepatocholangioma of the liver were also considered to be related to the administration of PCB 126. Neoplasms of the adrenal cortex and cholangioma of the liver may have been related to administration of PCB 126.

PCB 126 administration caused increased incidences of nonneoplastic lesions of the liver, lung, adrenal cortex, pancreas, kidney, heart, thyroid gland, thymus, spleen, clitoral gland, and mesenteric artery in female rats.

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

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APPENDIX A
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF PCB 126

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 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
Disposition Summary				
Animals initially in study	28	28	26	28
14-Week interim evaluation	10	10	9	10
31-Week interim evaluation	10	10	9	10
53-Week interim evaluation	8	8	8	8
Animals examined microscopically	28	28	26	28
14-Week Interim Evaluation				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(9)	(10)
Lymphoma malignant			1 (11%)	
Systems Examined 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)			
Fibroadenoma				
Respiratory System				
Lung	(10)	(10)	(9)	(10)
Nephroblastoma, metastatic, kidney				
Urinary System				
Kidney				
Nephroblastoma				

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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Disposition Summary				
Animals initially in study	28	28	28	28
14-Week interim evaluation	10	10	10	10
31-Week interim evaluation	10	10	10	10
53-Week interim evaluation	8	8	8	8
Animals examined microscopically	28	28	28	28
14-Week Interim Evaluation				
Systemic Lesions				
Multiple organs	(10)	(10)	(10)	(10)
Lymphoma malignant				
Systems Examined 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	(1)	(1)		(10)
Fibroadenoma	1 (100%)	1 (100%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Nephroblastoma, metastatic, kidney			1 (10%)	
Urinary System				
Kidney			(1)	
Nephroblastoma			1 (100%)	

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
31-Week Interim Evaluation (continued)				
Systems Examined with No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
53-Week Interim Evaluation				
Integumentary System				
Mammary gland	(8)			(1)
Fibroadenoma				1 (100%)
Fibroadenoma, multiple				
Systems Examined 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				
Urinary 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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
31-Week Interim Evaluation (continued)				
Systems Examined No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
53-Week Interim Evaluation				
Integumentary System				
Mammary gland	(2)		(1)	(8)
Fibroadenoma	1 (50%)		1 (100%)	
Fibroadenoma, multiple	1 (50%)			
Systems Examined 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				
Urinary 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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]				
14-Week interim evaluation			1	
31-Week interim evaluation				
53-Week interim evaluation				1
Total primary neoplasms				
14-Week interim evaluation			1	
31-Week interim evaluation				
53-Week interim evaluation				1
Total animals with benign neoplasms				
31-Week interim evaluation				
53-Week interim evaluation				1
Total benign neoplasms				
31-Week interim evaluation				
53-Week interim evaluation				1
Total animals with malignant neoplasms				
14-Week interim evaluation			1	
31-Week interim evaluation				
Total malignant neoplasms				
14-Week interim evaluation			1	
31-Week interim evaluation				
Total animals with metastatic neoplasms				
31-Week interim evaluation				
Total metastatic neoplasms				
31-Week interim evaluation				

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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Neoplasm Summary				
Total animals with primary neoplasms				
14-Week interim evaluation				
31-Week interim evaluation	1	1	1	
53-Week interim evaluation	2		1	
Total primary neoplasms				
14-Week interim evaluation				
31-Week interim evaluation	1	1	1	
53-Week interim evaluation	2		1	
Total animals with benign neoplasms				
31-Week interim evaluation	1	1		
53-Week interim evaluation	2		1	
Total benign neoplasms				
31-Week interim evaluation	1	1		
53-Week interim evaluation	2		1	
Total animals with malignant neoplasms				
14-Week interim evaluation				
31-Week interim evaluation			1	
Total malignant neoplasms				
14-Week interim evaluation				
31-Week interim evaluation			1	
Total animals with metastatic neoplasms				
31-Week interim evaluation			1	
Total metastatic neoplasms				
31-Week interim evaluation			1	

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

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126[a]

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Disposition Summary							
Animals initially in study	53	55	53	53	53	53	53
Early deaths							
Accidental deaths	3	3		1	1		
Moribund	25	18	21	19	27	18	34
Natural deaths	10	9	6	11	9	12	12
Survivors							
Died last week of study		1	1				
Terminal sacrifice	15	24	25	22	16	23	7
Animals examined microscopically	53	55	53	53	53	53	53
Alimentary System							
Intestine large, colon	(52)	(55)	(53)	(53)	(53)	(51)	(53)
Serosa, carcinoma, metastatic, uterus		1 (2%)					
Intestine large, cecum	(52)	(54)	(53)	(51)	(53)	(52)	(53)
Intestine large, rectum	(52)	(55)	(53)	(52)	(53)	(52)	(53)
Intestine small, duodenum	(52)	(55)	(52)	(53)	(53)	(51)	(53)
Intestine small, jejunum	(52)	(54)	(53)	(53)	(53)	(51)	(53)
Leiomyosarcoma			2 (4%)				
Serosa, carcinoma, metastatic, uterus		1 (2%)					
Intestine small, ileum	(52)	(54)	(52)	(51)	(53)	(52)	(53)
Carcinoma, metastatic, islets, pancreatic			1 (2%)				
Serosa, carcinoma, metastatic, uterus		1 (2%)					
Liver	(53)	(55)	(53)	(53)	(53)	(51)	(53)
Carcinoma, metastatic, islets, pancreatic			1 (2%)				
Cholangiocarcinoma			1 (2%)		5 (9%)	2 (4%)	7 (13%)
Cholangiocarcinoma, multiple						4 (8%)	15 (28%)
Cholangioma						1 (2%)	1 (2%)
Hepatocellular carcinoma				1 (2%)			
Hepatocellular adenoma	1 (2%)	2 (4%)	1 (2%)		2 (4%)	4 (8%)	6 (11%)
Hepatocellular adenoma, multiple							1 (2%)
Hepatocholangioma							2 (4%)
Hepatocholangioma, multiple							1 (2%)
Schwannoma malignant, metastatic, heart			1 (2%)				
Mesentery	(1)		(4)	(2)	(7)	(13)	(11)
Carcinoma, metastatic, islets, pancreatic			1 (25%)				
Sarcoma, metastatic, kidney						1 (8%)	
Sarcoma stromal, metastatic, uterus						1 (8%)	
Oral mucosa	(1)	(1)	(3)	(4)	(2)	(6)	(11)
Gingival, squamous cell carcinoma		1 (100%)	1 (33%)	1 (25%)	2 (100%)	2 (33%)	7 (64%)
Pancreas	(51)	(55)	(53)	(53)	(53)	(52)	(51)
Sarcoma stromal, metastatic, uterus						1 (2%)	
Acinus, adenoma	1 (2%)				2 (4%)		
Acinus, carcinoma				1 (2%)			1 (2%)

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Alimentary System (continued)							
Salivary glands	(51)	(54)	(53)	(51)	(52)	(51)	(51)
Carcinoma					1 (2%)		
Stomach, forestomach	(52)	(55)	(53)	(53)	(53)	(51)	(53)
Serosa, carcinoma, metastatic, uterus		1 (2%)					
Stomach, glandular	(51)	(53)	(53)	(53)	(53)	(51)	(53)
Schwannoma malignant, metastatic, heart			1 (2%)				
Serosa, carcinoma, metastatic, uterus		1 (2%)					
Cardiovascular System							
Blood vessel	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Heart	(52)	(54)	(53)	(53)	(53)	(51)	(51)
Schwannoma benign					1 (2%)		
Schwannoma malignant		1 (2%)	2 (4%)		2 (4%)		
Endocrine System							
Adrenal cortex	(52)	(55)	(53)	(53)	(53)	(52)	(53)
Adenoma		1 (2%)	1 (2%)			1 (2%)	2 (4%)
Carcinoma		1 (2%)			1 (2%)		2 (4%)
Schwannoma malignant, metastatic, heart			1 (2%)				
Adrenal medulla	(52)	(55)	(53)	(53)	(53)	(52)	(53)
Pheochromocytoma malignant			1 (2%)	1 (2%)		1 (2%)	
Pheochromocytoma complex					1 (2%)		
Pheochromocytoma benign	8 (15%)	3 (5%)	4 (8%)	2 (4%)	2 (4%)	4 (8%)	
Schwannoma malignant, metastatic, heart			1 (2%)				
Islets, pancreatic	(52)	(54)	(53)	(53)	(53)	(52)	(51)
Adenoma		2 (4%)		1 (2%)			1 (2%)
Carcinoma			1 (2%)				
Parathyroid gland	(47)	(50)	(48)	(46)	(49)	(47)	(46)
Adenoma		1 (2%)				1 (2%)	
Pituitary gland	(51)	(54)	(53)	(53)	(53)	(53)	(53)
Sarcoma, metastatic, brain		1 (2%)					
Squamous cell carcinoma, metastatic, oral mucosa							1 (2%)
Pars distalis, adenoma	14 (27%)	18 (33%)	20 (38%)	16 (30%)	22 (42%)	13 (25%)	6 (11%)
Pars distalis, adenoma, multiple	1 (2%)					1 (2%)	
Pars distalis, carcinoma				1 (2%)		1 (2%)	
Pars intermedia, adenoma	1 (2%)	2 (4%)	1 (2%)				
Thyroid gland	(52)	(55)	(52)	(51)	(52)	(50)	(48)
Adenoma							1 (2%)
Bilateral, C-cell, adenoma	3 (6%)	4 (7%)	3 (6%)	2 (4%)	3 (6%)	2 (4%)	
C-cell, adenoma	12 (23%)	11 (20%)	12 (23%)	11 (22%)	9 (17%)	10 (20%)	9 (19%)
C-cell, carcinoma		1 (2%)	2 (4%)			2 (4%)	
General Body System							
Tissue NOS						(1)	
Carcinoma						1 (100%)	

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Genital System							
Ovary	(52)	(54)	(53)	(52)	(52)	(52)	(53)
Cystadenoma						1 (2%)	
Granulosa cell tumor benign				1 (2%)			
Granulosa-theca tumor malignant			1 (2%)				
Sarcoma stromal, metastatic, uterus					1 (2%)		
Uterus	(52)	(55)	(53)	(52)	(53)	(52)	(53)
Adenoma						1 (2%)	
Adenoma, multiple							1 (2%)
Carcinoma		3 (5%)	1 (2%)	1 (2%)		1 (2%)	
Hemangiosarcoma				1 (2%)			
Polyp stromal	4 (8%)	5 (9%)	7 (13%)	3 (6%)	8 (15%)	5 (10%)	4 (8%)
Sarcoma stromal				1 (2%)	1 (2%)	2 (4%)	
Sarcoma stromal, multiple				1 (2%)			
Schwannoma malignant						1 (2%)	
Squamous cell papilloma			1 (2%)			1 (2%)	
Cervix, sarcoma stromal					1 (2%)		
Cervix, schwannoma malignant					1 (2%)	1 (2%)	
Vagina	(1)		(1)		(1)		(1)
Sarcoma	1 (100%)						
Sarcoma stromal, metastatic, uterus					1 (100%)		
Squamous cell carcinoma			1 (100%)				
Hematopoietic System							
Bone marrow	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Lymph node	(2)	(6)	(6)	(6)	(4)	(7)	(12)
Lumbar, sarcoma stromal, metastatic, uterus						1 (14%)	
Mediastinal, carcinoma, metastatic, islets, pancreatic			1 (17%)				
Mediastinal, carcinoma, metastatic, thyroid gland						1 (14%)	
Renal, nephroblastoma, metastatic, kidney	1 (50%)						
Lymph node, mandibular	(52)	(53)	(51)	(51)	(52)	(51)	(51)
Osteosarcoma, metastatic, bone	1 (2%)						
Lymph node, mesenteric	(52)	(54)	(52)	(52)	(53)	(51)	(53)
Hemangiosarcoma	1 (2%)						
Spleen	(52)	(55)	(52)	(53)	(53)	(52)	(52)
Sarcoma stromal, metastatic, uterus						1 (2%)	
Schwannoma malignant, metastatic, heart			1 (2%)				
Capsule, carcinoma, metastatic, uterus		1 (2%)					
Thymus	(50)	(52)	(46)	(48)	(41)	(49)	(44)
Carcinoma, metastatic, mammary gland	1 (2%)						

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Integumentary System							
Mammary gland	(52)	(55)	(53)	(53)	(53)	(52)	(53)
Adenoma	2 (4%)		2 (4%)		1 (2%)		
Carcinoma	5 (10%)	6 (11%)	9 (17%)	4 (8%)		1 (2%)	1 (2%)
Carcinoma, multiple	1 (2%)	1 (2%)		1 (2%)			
Fibroadenoma	18 (35%)	17 (31%)	21 (40%)	21 (40%)	26 (49%)	24 (46%)	11 (21%)
Fibroadenoma, multiple	21 (40%)	14 (25%)	14 (26%)	17 (32%)	13 (25%)	5 (10%)	
Skin	(52)	(55)	(53)	(53)	(53)	(53)	(53)
Fibroma	1 (2%)	1 (2%)					
Fibrous histiocytoma					1 (2%)	1 (2%)	
Keratoacanthoma	1 (2%)		1 (2%)				1 (2%)
Squamous cell carcinoma						1 (2%)	
Subcutaneous tissue, fibroma, multiple			1 (2%)				
Musculoskeletal System							
Bone	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Osteosarcoma	1 (2%)						
Skeletal muscle	(1)	(1)	(1)				(1)
Carcinoma, metastatic, islets, pancreatic			1 (100%)				
Rhabdomyosarcoma		1 (100%)					
Nervous System							
Brain	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Astrocytoma malignant	2 (4%)				1 (2%)		
Carcinoma, metastatic, pituitary gland				1 (2%)		1 (2%)	
Medulloblastoma malignant			1 (2%)		1 (2%)		
Oligodendroglioma malignant	1 (2%)						
Meninges, sarcoma		1 (2%)					
Respiratory System							
Lung	(53)	(55)	(53)	(53)	(53)	(51)	(51)
Adenocarcinoma, mucinous						1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)			1 (2%)			
Alveolar/bronchiolar carcinoma		1 (2%)					
Carcinoma, metastatic, adrenal cortex							1 (2%)
Carcinoma, metastatic, islets, pancreatic			1 (2%)				
Carcinoma, metastatic, mammary gland	1 (2%)		1 (2%)	1 (2%)			
Cystic keratinizing epithelioma					1 (2%)	3 (6%)	5 (10%)
Cystic keratinizing epithelioma, multiple						8 (16%)	30 (59%)
Osteosarcoma, metastatic, bone	1 (2%)						
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)			
Sarcoma, metastatic, kidney						1 (2%)	
Sarcoma stromal, metastatic, uterus						1 (2%)	
Schwannoma malignant, metastatic, heart			1 (2%)				

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Respiratory System (continued)							
Lung (continued)	(53)	(55)	(53)	(53)	(53)	(51)	(51)
Squamous cell carcinoma						1 (2%)	2 (4%)
Squamous cell carcinoma, metastatic, oral mucosa		1 (2%)					
Mediastinum, carcinoma, metastatic, mammary gland				1 (2%)			
Nose	(53)	(54)	(52)	(53)	(52)	(53)	(53)
Osteosarcoma, metastatic, bone	1 (2%)						
Squamous cell carcinoma, metastatic, oral mucosa							1 (2%)
Trachea	(53)	(55)	(53)	(53)	(53)	(52)	(52)
Peritracheal tissue, schwannoma malignant, metastatic, heart					1 (2%)		
Special Senses System							
Eye	(51)	(55)	(53)	(53)	(53)	(52)	(52)
Optic nerve, squamous cell carcinoma, metastatic, oral mucosa							1 (2%)
Harderian gland	(53)	(53)	(53)	(53)	(53)	(52)	(52)
Squamous cell carcinoma, metastatic, oral mucosa							1 (2%)
Urinary System							
Kidney	(53)	(55)	(53)	(53)	(53)	(52)	(53)
Hemangiosarcoma	1 (2%)						
Nephroblastoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)			2 (4%)
Schwannoma malignant, metastatic, heart			1 (2%)				
Stromal nephroma		1 (2%)		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Transitional epithelium, carcinoma						1 (2%)	
Urinary bladder	(51)	(54)	(53)	(52)	(52)	(52)	(53)
Serosa, carcinoma, metastatic, uterus		1 (2%)					
Systemic Lesions							
Multiple organs[b]	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Leukemia granulocytic		1 (2%)					
Leukemia mononuclear							1 (2%)
Lymphoma malignant		2 (4%)		2 (4%)	1 (2%)	1 (2%)	2 (4%)

TABLE A1b
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Neoplasm Summary							
Total animals with primary neoplasms[c]	49	51	51	47	49	50	49
Total primary neoplasms	103	104	113	93	110	111	123
Total animals with benign neoplasms	45	45	48	45	46	45	42
Total benign neoplasms	89	81	89	75	90	85	82
Total animals with malignant neoplasms	13	19	18	15	16	23	33
Total malignant neoplasms	14	23	24	18	20	26	41
Total animals with metastatic neoplasms	3	3	3	3	2	4	2
Total metastatic neoplasms	6	9	14	4	3	9	5

[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 A1c
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)[a]

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Disposition Summary			
Animals initially in study	53	53	50
Early deaths			
Accidental deaths	3		1
Moribund	25	34	15
Natural deaths	10	12	6
Survivors			
Terminal sacrifice	15	7	28
Animals examined microscopically	53	53	50
Alimentary System			
Liver	(53)	(53)	(50)
Cholangiocarcinoma		7 (13%)	2 (4%)
Cholangiocarcinoma, multiple		15 (28%)	
Cholangioma		1 (2%)	
Hepatocellular adenoma	1 (2%)	6 (11%)	
Hepatocellular adenoma, multiple		1 (2%)	
Hepatocholangioma		2 (4%)	
Hepatocholangioma, multiple		1 (2%)	
Oral mucosa	(1)	(11)	(6)
Gingival, squamous cell carcinoma		7 (64%)	2 (33%)
Pancreas	(51)	(51)	(48)
Acinus, adenoma	1 (2%)		
Acinus, carcinoma		1 (2%)	
Cardiovascular System			
None			
Endocrine System			
Adrenal cortex	(52)	(53)	(50)
Adenoma		2 (4%)	2 (4%)
Carcinoma		2 (4%)	1 (2%)
Adrenal medulla	(52)	(53)	(50)
Pheochromocytoma benign	8 (15%)		2 (4%)
Bilateral, pheochromocytoma benign			1 (2%)
Islets, pancreatic	(52)	(51)	(50)
Adenoma		1 (2%)	1 (2%)
Parathyroid gland	(47)	(46)	(44)
Adenoma			1 (2%)
Pituitary gland	(51)	(53)	(48)
Squamous cell carcinoma, metastatic, oral mucosa		1 (2%)	
Pars distalis, adenoma	14 (27%)	6 (11%)	17 (35%)
Pars distalis, adenoma, multiple	1 (2%)		
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(52)	(48)	(47)
Adenoma		1 (2%)	
Bilateral, C-cell, adenoma	3 (6%)		5 (11%)
C-cell, adenoma	12 (23%)	9 (19%)	11 (23%)
C-cell, carcinoma			1 (2%)

TABLE A1c
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
General Body System			
None			
Genital System			
Ovary	(52)	(53)	(50)
Granulosa-theca tumor benign			1 (2%)
Uterus	(52)	(53)	(50)
Adenoma			1 (2%)
Adenoma, multiple		1 (2%)	
Polyp stromal	4 (8%)	4 (8%)	5 (10%)
Vagina	(1)	(1)	
Sarcoma	1 (100%)		
Hematopoietic System			
Bone marrow	(53)	(53)	(50)
Lymph node	(2)	(12)	(2)
Renal, nephroblastoma, metastatic, kidney	1 (50%)		
Lymph node, mandibular	(52)	(51)	(49)
Osteosarcoma, metastatic, bone	1 (2%)		
Lymph node, mesenteric	(52)	(53)	(50)
Hemangiosarcoma	1 (2%)		
Spleen	(52)	(52)	(50)
Thymus	(50)	(44)	(43)
Carcinoma, metastatic, mammary gland	1 (2%)		
Integumentary System			
Mammary gland	(52)	(53)	(50)
Adenoma	2 (4%)		
Carcinoma	5 (10%)	1 (2%)	4 (8%)
Carcinoma, multiple	1 (2%)		
Fibroadenoma	18 (35%)	11 (21%)	15 (30%)
Fibroadenoma, multiple	21 (40%)		13 (26%)
Skin	(52)	(53)	(50)
Fibroma	1 (2%)		
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System			
Bone	(53)	(53)	(50)
Osteosarcoma	1 (2%)		1 (2%)
Nervous System			
Brain	(53)	(53)	(50)
Astrocytoma malignant	2 (4%)		1 (2%)
Oligodendroglioma malignant	1 (2%)		

TABLE A1c
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Respiratory System			
Lung	(53)	(51)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Carcinoma, metastatic, adrenal cortex		1 (2%)	
Carcinoma, metastatic, mammary gland	1 (2%)		1 (2%)
Cystic keratinizing epithelioma		5 (10%)	
Cystic keratinizing epithelioma, multiple		30 (59%)	
Osteosarcoma, metastatic, bone	1 (2%)		
Squamous cell carcinoma		2 (4%)	
Nose	(53)	(53)	(50)
Osteosarcoma, metastatic, bone	1 (2%)		
Squamous cell carcinoma, metastatic, oral mucosa		1 (2%)	
Special Senses System			
Eye	(51)	(52)	(50)
Optic nerve, squamous cell carcinoma, metastatic, oral mucosa		1 (2%)	
Harderian gland	(53)	(52)	(50)
Squamous cell carcinoma, metastatic, oral mucosa		1 (2%)	
Urinary System			
Kidney	(53)	(53)	(50)
Hemangiosarcoma	1 (2%)		
Nephroblastoma	1 (2%)	2 (4%)	
Stromal nephroma		1 (2%)	
Systemic Lesions			
Multiple organs[b]	(53)	(53)	(50)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant		2 (4%)	1 (2%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	49	49	44
Total primary neoplasms	103	123	89
Total animals with benign neoplasms	45	42	41
Total benign neoplasms	89	82	76
Total animals with malignant neoplasms	13	33	12
Total malignant neoplasms	14	41	13
Total animals with metastatic neoplasms	3	2	1
Total metastatic neoplasms	6	5	1

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

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: Vehicle Control

Number of Days on Study	12	17	20	20	22	30	32	34	35	39	40	40	49	49	51	53	54	56	57	57	58	59	60	60
	06	66	01	11	22	29	13	13	34	10	10	05	66	66	19	11	11	67	54	44	33	22	00	03
Carcass ID Number	09	05	06	07	06	07	08	07	07	02	09	09	05	02	12	04	08	04	95	14	13	37	59	12	77
	98	87	63	44	62	75	77	11	12	22	66	11	15	11	22	84	88	44	55	44	33	77	59	22	77
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery										+															
Oral mucosa																									
Pancreas	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	M	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth												+					+								
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X					X		X		
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+		+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Pars distalis, adenoma																									X
Pars distalis, adenoma, multiple																									
Pars intermedia, adenoma																			X						
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																						X			
C-cell, adenoma															X										
General Body System																									
None																									

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

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: Vehicle Control

Number of Days on Study	6 0 7	6 1 1	6 1 8	6 4 4	6 5 0	6 5 2	6 6 0	6 6 0	6 6 0	6 7 1	6 8 8	7 0 5	7 0 9	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 7 8	0 8 9	0 8 6	0 5 2	0 6 6	0 6 9	0 2 5	0 5 1	0 8 4	0 4 0	0 9 0	0 9 4	0 0 3	0 1 1	0 2 3	0 3 8	0 3 9	0 5 3	0 5 8	0 6 7	0 7 0	0 9 2	0 9 3	0 1 5	0 6 5	0 7 3	0 8 3	0 8 5	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular adenoma																											X		1
Mesentery																													1
Oral mucosa																				+									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinus, adenoma																				X									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth		+			+							+			+	+			+	+	+	+					+		12
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign									X				X	X				X			X								8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Parathyroid gland		+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma	X			X					X	X			X		X	X	X		X			X	X	X				X	14
Pars distalis, adenoma, multiple														X															1
Pars intermedia, adenoma																													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, C-cell, adenoma																			X									X	3
C-cell, adenoma				X			X			X	X		X		X	X		X		X				X			X		12
General Body System																													
None																													

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: Vehicle Control

Number of Days on Study	1 2 6	1 7 6	2 0 1	2 0 1	2 2 2	3 0 2	3 2 1	3 4 3	3 5 4	3 9 1	4 0 0	4 0 5	4 9 6	4 9 6	5 1 9	5 3 1	5 4 1	5 4 6	5 4 7	5 5 4	5 7 4	5 8 3	5 9 2	6 0 0	6 0 3
Carcass ID Number	0 0 9 8	0 5 7	0 6 3	0 7 4	0 6 2	0 7 5	0 8 7	0 7 1	0 7 2	0 0 2	0 0 9 6	0 9 1	0 0 5	0 2 1	0 2 2	0 0 4	0 8 8	0 6 4	0 9 5	0 1 4	0 1 3	0 3 7	0 5 9	0 1 2	0 1 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct																									
Uterus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Vagina																								+	
Sarcoma																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+																							
Renal, nephroblastoma, metastatic, kidney		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland											X														
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma											X														
Carcinoma, multiple																									
Fibroadenoma						X	X					X	X	X						X	X				X
Fibroadenoma, multiple								X	X							X	X	X	X			X	X		
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Keratoacanthoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																								X	
Oligodendroglioma malignant			X																						
Peripheral nerve			+																						
Spinal cord			+																						

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: Vehicle Control

Number of Days on Study	6 0 7	6 1 1	6 1 8	6 4 4	6 5 0	6 5 2	6 6 0	6 6 0	6 6 0	6 7 1	6 8 8	7 0 5	7 0 9	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 0 7 8	0 0 8 9	0 0 8 6	0 0 5 2	0 0 6 6	0 0 6 9	0 0 2 5	0 0 5 1	0 0 8 4	0 0 4 0	0 0 9 0	0 0 9 4	0 0 3 3	0 1 1 1	0 2 3 3	0 3 3 8	0 3 3 9	0 5 5 3	0 5 5 8	0 6 7 7	0 7 7 0	0 9 9 2	0 9 9 3	0 1 1 5	0 6 5 5	0 7 7 3	0 8 8 3	0 8 8 5	Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Oviduct													+																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Polyp stromal							X				X							X							X				4
Vagina																													1
Sarcoma																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node			+																										2
Renal, nephroblastoma, metastatic, kidney																													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Osteosarcoma, metastatic, bone												X																	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																												X	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																													1
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																					X						X		2
Carcinoma											X		X		X												X		5
Carcinoma, multiple																								X					1
Fibroadenoma	X			X			X		X	X		X			X							X		X		X			18
Fibroadenoma, multiple		X	X		X	X		X					X			X		X	X				X		X		X	X	21
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibroma																											X		1
Keratoacanthoma															X														1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma												X																	1
Skeletal muscle																													1
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant																			X										2
Oligodendroglioma malignant																													1
Peripheral nerve				+																									2
Spinal cord				+																									2

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: Vehicle Control

Number of Days on Study	1 2 6	1 7 6	2 0 1	2 0 1	2 2 2	3 0 2	3 2 1	3 4 3	3 5 4	3 9 1	4 0 0	4 0 5	4 9 6	4 9 6	5 1 9	5 3 1	5 4 1	5 4 6	5 4 7	5 5 4	5 7 4	5 8 3	5 9 2	6 0 0	6 0 3
Carcass ID Number	0 9 8	0 5 7	0 6 3	0 7 4	0 6 2	0 7 5	0 8 7	0 7 1	0 7 2	0 2 2	0 9 6	0 9 1	0 0 5	0 2 1	0 2 2	0 0 4	0 8 8	0 6 4	0 9 5	0 1 4	0 1 3	0 3 7	0 5 9	0 1 2	0 7 7
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Carcinoma, metastatic, mammary gland											X														
Osteosarcoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Nephroblastoma		X																							
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: Vehicle Control

Number of Days on Study	6 0 7	6 1 1	6 1 8	6 4 4	6 5 0	6 5 2	6 6 0	6 6 0	6 6 0	6 7 1	6 8 8	7 0 5	7 0 9	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 7 8	0 8 9	0 8 6	0 5 2	0 6 6	0 6 9	0 2 5	0 5 1	0 8 4	0 4 0	0 9 0	0 9 4	0 0 3	0 1 1	0 2 3	0 3 8	0 3 9	0 5 3	0 5 8	0 6 7	0 7 0	0 9 2	0 9 3	0 1 5	0 6 5	0 7 3	0 8 3	0 8 5	Total Tissues/ Tumors
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma																													1
Carcinoma, metastatic, mammary gland																													1
Osteosarcoma, metastatic, bone												X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic, bone												X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangiosarcoma										X																			1
Nephroblastoma																													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 30 ng/kg

Number of Days on Study	0 8 2	2 0 2	2 2 3	2 5 3	3 2 8	3 5 0	3 5 6	3 5 6	3 5 6	4 3 4	4 4 8	4 9 8	5 1 6	5 2 4	5 4 6	5 7 2	5 7 4	5 8 0	6 0 7	6 3 0	6 3 0	6 5 2	6 5 2	6 5 2	6 7 1
Carcass ID Number	2 1 2	2 5 6	2 4 4	2 3 9	2 2 2	2 5 1	2 5 3	2 5 4	2 5 5	2 4 7	2 5 0	2 2 6	2 4 0	2 4 1	2 6 5	2 2 5	2 3 0	2 9 4	2 6 4	2 3 3	2 6 7	2 0 4	2 2 3	2 3 8	2 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, uterus																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, uterus																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, uterus																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, uterus																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, uterus																									
Tooth				+																	+				
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																							X		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Adenoma																									X
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, brain		X																							
Pars distalis, adenoma										X				X		X		X	X				X	X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																					X				
C-cell, adenoma														X	X		X	X							
C-cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 30 ng/kg

Number of Days on Study	6 8 1	7 0 0	7 2 0	7 2 0	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 6 2	2 4 9	2 4 3	2 6 9	2 9 3	2 0 7	2 1 0	2 2 4	2 3 5	2 3 7	2 4 5	2 6 1	2 8 8	2 9 1	2 9 7	3 0 6	2 2 8	2 3 1	2 3 6	2 4 2	2 8 6	2 9 0	2 9 8	3 0 5	3 0 8	2 2 1	2 6 8	2 8 9	2 9 2	2 9 5	Total Tissues/ Tumors
Alimentary System																															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Serosa, carcinoma, metastatic, uterus		X																													1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Serosa, carcinoma, metastatic, uterus		X																													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Serosa, carcinoma, metastatic, uterus		X																													1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Hepatocellular adenoma												X																			2
Oral mucosa	+																														1
Gingival, squamous cell carcinoma	X																														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Serosa, carcinoma, metastatic, uterus		X																													1
Stomach, glandular	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Serosa, carcinoma, metastatic, uterus		X																													1
Tooth	+					+	+	+		+		+	+	+			+	+													12
Cardiovascular System																															
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	54
Schwannoma malignant																															1
Endocrine System																															
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Adenoma																					X										1
Carcinoma																										X					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Pheochromocytoma benign													X					X													3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Adenoma																										X					2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	50
Adenoma																															1
Pituitary gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Sarcoma, metastatic, brain																															1
Pars distalis, adenoma		X	X	X		X	X				X						X			X		X	X							X	18
Pars intermedia, adenoma																X								X		+	+	+	+	+	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Bilateral, C-cell, adenoma							X								X														X		4
C-cell, adenoma		X	X					X		X	X							X	X												11
C-cell, carcinoma																											X				1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 30 ng/kg

Number of Days on Study	0 8 2	2 0 2	2 2 3	2 5 3	3 2 8	3 5 0	3 5 6	3 5 6	3 5 6	4 3 4	4 4 8	4 9 8	5 1 6	5 2 4	5 4 6	5 7 2	5 7 4	5 8 0	6 0 7	6 3 0	6 3 0	6 5 2	6 5 2	6 5 2	6 7 1
Carcass ID Number	2 1 2	2 5 6	2 4 4	2 3 9	2 2 2	2 5 1	2 5 3	2 5 4	2 5 5	2 4 7	2 5 0	2 2 6	2 4 0	2 4 1	2 6 5	2 2 5	2 3 0	2 9 4	2 6 4	2 3 3	2 6 7	2 0 4	2 2 3	2 3 8	2 0 1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct															+										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal																					X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+													+		+				+			+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma, metastatic, uterus																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X					X		
Carcinoma, multiple																									
Fibroadenoma									X		X	X		X	X	X			X		X				
Fibroadenoma, multiple													X				X			X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Rhabdomyosarcoma					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, sarcoma		X																							

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 30 ng/kg

Number of Days on Study	6 8 1	7 0 0	7 2 0	7 2 0	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 6 2	2 4 9	2 4 3	2 6 9	2 9 3	2 0 7	2 1 0	2 2 4	2 3 5	2 3 7	2 4 5	2 6 1	2 8 8	2 9 1	2 9 7	2 0 6	2 2 8	2 3 1	2 3 6	2 4 2	2 8 6	2 9 0	2 9 8	2 0 5	2 0 8	2 2 1	2 6 8	2 8 9	2 9 2	2 9 5	Total Tissues/ Tumors
General Body System																															
None																															
Genital System																															
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Oviduct																															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Carcinoma		X							X			X																			3
Polyp stromal		X	X																						X		X			5
Hematopoietic System																															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Lymph node																+															6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Capsule, carcinoma, metastatic, uterus		X																													1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	52
Integumentary System																															
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Carcinoma			X									X				X												X			6
Carcinoma, multiple					X																										1
Fibroadenoma							X	X					X						X		X	X		X	X			X			17
Fibroadenoma, multiple	X					X			X		X	X											X			X	X		X	X	14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Fibroma																															1
Musculoskeletal System																															
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Skeletal muscle																															1
Rhabdomyosarcoma																															1
Nervous System																															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Meninges, sarcoma																															1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 30 ng/kg

Number of Days on Study	0	2	2	2	3	3	3	3	3	4	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6
	8	0	2	5	2	5	5	5	5	3	4	9	1	2	4	7	7	8	0	3	3	5	5	5	7
	2	2	3	3	8	0	6	6	6	4	8	8	6	4	6	2	4	0	7	0	0	2	2	2	1
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	5	4	3	2	5	5	5	5	4	5	2	4	4	6	2	3	9	6	3	6	0	2	3	0
	2	6	4	9	2	1	3	4	5	7	0	6	0	1	5	5	0	4	4	3	7	4	3	8	1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Squamous cell carcinoma, metastatic, oral mucosa																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma			X	X																					
Stromal nephroma																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, uterus																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic																									
Lymphoma malignant	X															X									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 30 ng/kg

Number of Days on Study	6 8 1	7 0 0	7 2 0	7 2 0	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 6 2	2 4 9	2 4 3	2 6 9	2 9 3	2 0 7	2 1 0	2 2 4	2 3 5	2 3 7	2 4 5	2 6 1	2 8 8	2 9 1	2 9 7	2 0 6	2 2 8	2 3 1	2 3 6	2 4 2	2 8 6	2 9 0	2 9 8	2 0 5	2 0 8	2 2 1	2 6 8	2 8 9	2 9 2	2 9 5	Total Tissues/ Tumors
Respiratory System																																
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Alveolar/bronchiolar carcinoma								X																								1
Squamous cell carcinoma, metastatic, oral mucosa	X																															1
Nose	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Special Senses System																																
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary System																																
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Nephroblastoma																																2
Stromal nephroma																																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Serosa, carcinoma, metastatic, uterus		X																														1
Systemic Lesions																																
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Leukemia granulocytic			X																													1
Lymphoma malignant																																2

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 100 ng/kg

Number of Days on Study	1 8 8	2 3 6	3 0 0	3 2 8	3 7 6	4 2 8	4 9 8	5 0 9	5 3 1	5 3 3	5 4 1	5 5 4	5 5 5	5 8 6	6 0 2	6 2 1	6 5 1	6 5 1	6 5 1	6 5 2	6 5 3	6 5 3	6 5 9	6 7 8	6 8 8
Carcass ID Number	3 5 7	3 9 7	3 3 5	3 7 3	3 3 2	3 4 7	3 8 6	3 8 7	3 3 7	3 5 4	3 9 5	3 3 6	3 9 3	3 2 1	3 1 2	3 8 2	3 0 5	3 1 1	3 7 4	3 5 2	3 0 9	3 3 1	3 9 0	3 1 9	3 5 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic														X											
Cholangiocarcinoma																									
Hepatocellular adenoma															X										
Schwannoma malignant, metastatic, heart															X										
Mesentery														+											
Carcinoma, metastatic, islets, pancreatic														X											
Oral mucosa																	+								+
Gingival, squamous cell carcinoma																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart															X										
Tooth			+		+																	+			+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant															X								X		

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 100 ng/kg

Number of Days on Study	7 0 9	7 0 9	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	3 3 9	3 8 4	3 0 1	3 1 0	3 1 3	3 3 3	3 4 9	3 7 1	3 7 2	3 7 5	3 8 3	3 8 8	3 9 6	3 1 6	3 2 2	3 2 4	3 3 4	3 5 3	3 0 6	3 0 7	3 0 8	3 1 5	3 1 8	3 4 0	3 4 6	3 4 8	3 8 1	3 9 8	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leiomyosarcoma													X								X								2
Intestine small, ileum	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma, metastatic, islets, pancreatic																													1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, islets, pancreatic																													1
Cholangiocarcinoma													X																1
Hepatocellular adenoma																													1
Schwannoma malignant, metastatic, heart																													1
Mesentery						+																			+	+			4
Carcinoma, metastatic, islets, pancreatic																													1
Oral mucosa	+																												3
Gingival, squamous cell carcinoma																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Schwannoma malignant, metastatic, heart																													1
Tooth	+		+			+									+			+					+						10
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Schwannoma malignant																													2

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 100 ng/kg

Number of Days on Study	1 8 8	2 3 6	3 0 0	3 2 8	3 7 6	4 2 8	4 9 8	5 0 9	5 3 1	5 3 3	5 4 1	5 5 4	5 5 5	5 8 6	6 0 2	6 2 1	6 5 1	6 5 1	6 5 1	6 5 2	6 5 3	6 5 3	6 5 9	6 7 8	6 8 8
Carcass ID Number	3 5 7	3 9 7	3 3 5	3 7 3	3 3 2	3 4 7	3 8 6	3 8 7	3 3 7	3 5 4	3 9 5	3 3 6	3 9 3	3 2 1	3 1 2	3 8 2	3 0 5	3 1 1	3 7 4	3 5 2	3 0 9	3 3 1	3 9 0	3 1 9	3 5 1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Schwannoma malignant, metastatic, heart															X										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign														X										X	
Schwannoma malignant, metastatic, heart															X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma														X											
Parathyroid gland	+	+	+		+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X			X			X	X							X			X	X	X
Pars intermedia, adenoma				X																					
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma											X		X	X		X	X	X				X	X		
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X		
Polyp stromal																				X				X	
Squamous cell papilloma														X											
Vagina																									+
Squamous cell carcinoma																									X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+									+		+	+										
Mediastinal, carcinoma, metastatic, islets, pancreatic														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart															X										
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 100 ng/kg

Number of Days on Study	7 0 9	7 0 9	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	3 3 3 9	3 3 8 4	3 3 0 1	3 3 1 0	3 3 1 3	3 3 1 3	3 3 4 9	3 3 7 1	3 3 7 2	3 3 7 5	3 3 8 3	3 3 8 8	3 3 9 6	3 3 1 6	3 3 2 2	3 3 2 4	3 3 3 4	3 3 5 3	3 3 0 6	3 3 0 7	3 3 0 8	3 3 1 5	3 3 1 8	3 4 0	3 4 4 6	3 4 4 8	3 4 8 1	3 3 9 8	Total Tissues/ Tumors
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma			X																										1
Schwannoma malignant, metastatic, heart																													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant	X																												1
Pheochromocytoma benign														X	X														4
Schwannoma malignant, metastatic, heart																													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																													1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma		X	X		X							X		X	X	X		X			X		X		X				20
Pars intermedia, adenoma																													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, C-cell, adenoma								X				X				X													3
C-cell, adenoma			X						X						X										X				12
C-cell, carcinoma	X				X																								2
General Body System																													
None																													
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa-theca tumor malignant						X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																													1
Polyp stromal		X		X						X									X								X	7
Squamous cell papilloma																													1
Vagina																													1
Squamous cell carcinoma																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node																										+	+		6
Mediastinal, carcinoma, metastatic, islets, pancreatic																													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	52
Schwannoma malignant, metastatic, heart																													1
Thymus	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	46

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 100 ng/kg

Number of Days on Study	1 8 8	2 3 6	3 0 0	3 2 8	3 7 6	4 2 8	4 9 8	5 0 9	5 3 1	5 3 3	5 4 1	5 5 4	5 5 5	5 8 6	6 0 2	6 2 1	6 5 1	6 5 1	6 5 1	6 5 2	6 5 3	6 5 3	6 5 9	6 7 8	6 8 8
Carcass ID Number	3 5 7	3 9 7	3 3 5	3 7 3	3 3 2	3 4 7	3 8 6	3 8 7	3 3 7	3 5 4	3 9 5	3 3 6	3 9 3	3 2 1	3 1 2	3 8 2	3 0 5	3 1 1	3 7 4	3 5 2	3 0 9	3 3 1	3 9 0	3 1 9	3 5 1
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma										X							X				X				
Fibroadenoma	X		X	X			X	X			X	X				X			X		X		X		
Fibroadenoma, multiple									X									X		X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								X	
Subcutaneous tissue, fibroma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+											
Carcinoma, metastatic, islets, pancreatic														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulloblastoma malignant				X																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic														X											
Carcinoma, metastatic, mammary gland										X															
Schwannoma malignant, metastatic, heart															X										
Nose	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma		X																							
Schwannoma malignant, metastatic, heart															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 126: 100 ng/kg

Number of Days on Study	7 0 9	7 0 9	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	3 3 3 9	3 8 4	3 0 1	3 1 0	3 1 3	3 3 3	3 4 9	3 7 1	3 7 2	3 7 5	3 8 3	3 8 8	3 9 6	3 1 6	3 2 2	3 2 4	3 4 4	3 5 3	3 0 6	3 0 7	3 0 8	3 1 5	3 1 8	3 4 0	3 4 6	3 4 8	3 8 1	3 9 8	Total Tissues/ Tumors
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma									X																					2
Carcinoma													X		X						X	X	X			X				9
Fibroadenoma			X		X		X		X				X		X								X	X	X				X	21
Fibroadenoma, multiple	X	X								X	X			X			X		X	X	X					X				14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Keratoacanthoma																														1
Subcutaneous tissue, fibroma, multiple												X																		1
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Skeletal muscle																														1
Carcinoma, metastatic, islets, pancreatic																														1
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Medulloblastoma malignant																														1
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, islets, pancreatic																														1
Carcinoma, metastatic, mammary gland																														1
Schwannoma malignant, metastatic, heart																														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nephroblastoma																														1
Schwannoma malignant, metastatic, heart																														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 126: 175 ng/kg

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

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 175 ng/kg

Number of Days on Study	6 5 8	6 5 9	6 6 0	6 6 0	6 6 0	7 2 0	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	4 4 4	4 5 1	4 0 7	4 0 8	4 7 2	4 4 7	4 0 1	4 0 2	4 0 6	4 1 1	4 1 7	4 2 5	4 7 1	4 7 3	4 8 6	4 9 6	4 1 3	4 1 6	4 3 7	4 4 1	4 5 2	4 5 4	4 7 4	4 0 9	4 1 9	4 8 3	4 9 1	4 9 2	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular carcinoma														X															1
Mesentery												+												+					2
Oral mucosa								+												+		+							4
Gingival, squamous cell carcinoma																						X							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Acinus, carcinoma												X																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth								+			+	+								+									9
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
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	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma		X			X	X	X		X	X		X					X	X									X	X	16
Pars distalis, carcinoma																							X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, C-cell, adenoma						X																							2
C-cell, adenoma							X	X				X		X			X								X	X	X		11
General Body System																													
None																													

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 175 ng/kg

Number of Days on Study	1 2 4	3 8 5	4 0 5	4 3 6	4 4 8	4 5 4	4 8 1	4 8 7	4 9 6	5 0 0	5 3 0	5 4 6	5 5 9	5 7 3	5 7 4	5 7 6	5 9 2	6 0 5	6 0 0	6 0 4	6 0 7	6 1 1	6 5 8	6 6 8	6 5 8
Carcass ID Number	4 4 8 2	4 4 9 2 3	4 4 0 5	4 4 9 7	4 4 2 2	4 4 8 7	4 4 4 2	4 4 8 8	4 4 4 9	4 4 5 3	4 4 8 1	4 4 4 8	4 4 0 4	4 4 8 4	4 4 2 1	4 4 3 6	4 4 0 3	4 4 1 5	4 4 2 0	4 4 2 4	4 4 5 0	4 4 8 5	4 4 1 8	4 4 3 9	4 4 4 0
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hemangiosarcoma																									
Polyp stromal																								X	
Sarcoma stromal																							X		
Sarcoma stromal, multiple																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+						+				+											+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X								X								
Carcinoma, multiple																									
Fibroadenoma		X		X		X		X	X	X		X	X		X			X		X			X	X	
Fibroadenoma, multiple			X																X		X				X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, mammary gland																	X								
Pheochromocytoma malignant, metastatic, adrenal medulla										X															
Mediastinum, carcinoma, metastatic, mammary gland																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 175 ng/kg

Number of Days on Study	6 5 8	6 5 9	6 6 0	6 6 0	6 6 0	7 2 0	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	4 4 4	4 5 1	4 0 7	4 0 8	4 7 2	4 4 7	4 0 1	4 0 2	4 0 6	4 1 1	4 1 7	4 2 5	4 7 1	4 7 3	4 8 6	4 9 6	4 1 3	4 1 6	4 3 7	4 4 1	4 5 2	4 5 4	4 7 4	4 0 9	4 1 9	4 8 3	4 9 1	4 9 2	Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Granulosa cell tumor benign																			X										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma																						X							1
Hemangiosarcoma							X																						1
Polyp stromal											X							X											3
Sarcoma stromal																													1
Sarcoma stromal, multiple																						X							1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+										+																		6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	48
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma									X							X													4
Carcinoma, multiple										X																			1
Fibroadenoma					X				X					X	X					X	X			X		X			21
Fibroadenoma, multiple	X		X	X		X				X	X	X				X	X		X			X	X		X				17
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, pituitary gland																							X						1
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma																						X							1
Carcinoma, metastatic, mammary gland																													1
Pheochromocytoma malignant, metastatic, adrenal medulla																													1
Mediastinum, carcinoma, metastatic, mammary gland																													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 175 ng/kg

Number of Days on Study	1	3	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	
	2	8	0	3	4	5	8	8	9	0	3	4	5	7	7	7	9	9	0	0	0	1	5	5	
	4	5	5	6	8	4	1	7	6	0	0	6	9	3	4	6	2	5	0	4	7	1	8	8	
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
	8	9	0	9	2	8	4	8	4	5	8	4	0	8	2	3	0	1	2	2	5	8	1	3	
	2	3	5	7	2	7	2	8	9	3	1	8	4	4	1	6	3	5	0	4	0	5	8	9	
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nephroblastoma					X																				
Stromal nephroma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant																							X		

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 175 ng/kg

Number of Days on Study	6 5 8	6 5 9	6 6 0	6 6 0	6 6 0	7 2 0	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	4 4 4	4 5 1	4 0 7	4 0 8	4 7 2	4 4 7	4 0 1	4 0 2	4 0 6	4 1 1	4 1 7	4 2 5	4 7 1	4 7 3	4 8 6	4 9 6	4 1 3	4 1 6	4 3 7	4 4 1	4 5 2	4 5 4	4 7 4	4 0 9	4 1 9	4 8 3	4 9 1	4 9 2	Total Tissues/ Tumors	
Special Senses System																														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Nephroblastoma																													1	
Stromal nephroma																													1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52	
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53	
Lymphoma malignant	X																												2	

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 300 ng/kg

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

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 300 ng/kg

Number of Days on Study	6 5 9	6 5 9	6 6 2	6 6 5	6 8 0	6 8 8	6 8 8	7 0 9	7 1 5	7 1 9	7 2 2	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	5 5 4	5 6 5	5 0 6	5 3 8	5 3 1	5 1 7	5 8 3	5 2 6	5 7 8	5 0 9	5 8 8	5 9 0	5 2 3	5 2 5	5 3 0	5 3 2	5 3 6	5 4 1	5 4 5	5 5 3	5 7 4	5 9 8	5 3 3	5 4 0	5 4 2	5 4 3	5 7 1	5 7 5	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
Cholangiocarcinoma	X									X						X							X			X			5
Hepatocellular adenoma								X												X									2
Mesentery			+				+												+			+	+	+					7
Oral mucosa																								+					2
Gingival, squamous cell carcinoma																								X					2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Acinus, adenoma											X				X														2
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma																													1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth		+				+				+								+		+		+					+		10
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Schwannoma benign										X																			1
Schwannoma malignant					X			X																					2
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma complex																		X											1
Pheochromocytoma benign								X																				X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma		X					X	X	X	X		X	X	X	X	X			X	X		X	X				X	X	22
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, C-cell, adenoma				X																									3
C-cell, adenoma							X					X				X				X	X								9
General Body System																													
None																													

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 300 ng/kg

Number of Days on Study	0 4 0	1 6 3	2 4 7	3 0 1	3 2 8	3 3 1	4 0 3	4 5 4	5 3 1	5 3 1	5 4 1	5 4 6	5 5 4	5 5 5	5 5 4	5 9 9	6 0 7	6 0 7	6 0 7	6 1 8	6 1 8	6 3 0	6 4 2	6 4 5	6 5 8	6 5 8
Carcass ID Number	5 5 8 5	5 6 2	5 8 4	5 2 4	5 8 7	5 5 9	5 3 9	5 3 7	5 6 3	5 7 7	5 1 9	5 7 3	5 5 1	5 9 7	5 8 1	5 2 1	5 2 2	5 2 7	5 7 9	5 8 0	5 1 6	5 8 9	5 7 6	5 3 4	5 6 1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																										
Oviduct																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal											X														X	
Sarcoma stromal																										
Cervix, sarcoma stromal																										
Cervix, Schwannoma malignant																								X		
Vagina																										
Sarcoma stromal, metastatic, uterus																										
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+															+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	M	+	M	M	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Fibroadenoma			X	X	X				X	X		X		X	X	X	X	X	X	X	X	X		X		
Fibroadenoma, multiple								X					X											X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																	X									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant											X															
Medulloblastoma malignant																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystic keratinizing epithelioma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peritracheal tissue, schwannoma malignant, metastatic, heart																										

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 300 ng/kg

Number of Days on Study	6 5 9	6 5 9	6 6 2	6 6 5	6 8 0	6 8 8	6 8 8	7 0 9	7 1 5	7 1 9	7 2 2	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	5 5 4	5 6 5	5 0 6	5 3 8	5 3 1	5 1 7	5 8 3	5 2 6	5 7 8	5 0 9	5 8 8	5 9 0	5 2 3	5 2 5	5 3 0	5 3 2	5 3 6	5 4 1	5 4 5	5 5 3	5 7 4	5 9 8	5 3 3	5 4 0	5 4 2	5 4 3	5 7 1	5 7 5	Total Tissues/ Tumors
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma stromal, metastatic, uterus								X																					1
Oviduct											+																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Polyp stromal			X										X	X		X								X		X			8
Sarcoma stromal								X																					1
Cervix, sarcoma stromal																											X		1
Cervix, Schwannoma malignant																													1
Vagina								+																					1
Sarcoma stromal, metastatic, uterus								X																					1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node				+									+																4
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	41
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma													X																1
Fibroadenoma		X	X				X	X					X		X				X			X	X	X					26
Fibroadenoma, multiple	X					X				X	X	X		X			X									X	X		13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibrous histiocytoma																													1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant																													1
Medulloblastoma malignant										X																			1
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cystic keratinizing epithelioma																			X										1
Nose	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Peritracheal tissue, schwannoma malignant, metastatic, heart					X																								1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 300 ng/kg

Number of Days on Study	0	1	2	3	3	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	4	6	4	0	2	3	0	5	3	3	4	4	5	5	9	0	0	0	1	1	3	4	4	5	5
	0	3	7	1	8	1	3	4	1	1	1	6	4	4	9	7	7	7	8	8	0	2	5	8	8
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	8	6	8	2	8	5	3	3	6	7	1	7	5	9	8	2	2	2	7	8	1	8	7	3	6
	5	2	4	4	7	9	9	7	3	7	9	3	1	7	1	1	2	7	9	0	6	9	6	4	1
Special Senses System																									
Ear				+																					
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stromal nephroma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X																

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 300 ng/kg

Number of Days on Study	6 5 9	6 5 9	6 6 2	6 6 5	6 8 0	6 8 8	6 8 8	7 0 9	7 1 5	7 1 9	7 2 2	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	5 5 4	5 6 5	5 0 6	5 3 8	5 3 1	5 1 7	5 8 3	5 2 6	5 7 8	5 0 9	5 8 8	5 9 0	5 2 3	5 2 5	5 3 0	5 3 2	5 3 6	5 4 1	5 4 5	5 5 3	5 7 4	5 9 8	5 3 3	5 4 0	5 4 2	5 4 3	5 7 1	5 7 5	Total Tissues/ Tumors
Special Senses System																													
Ear																													1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lacrimal gland						+																							1
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stromal nephroma																													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymphoma malignant																													1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 550 ng/kg

Number of Days on Study	1 8 5	3 2 0	3 2 7	4 4 0	4 9 8	5 3 5	5 5 4	5 7 3	5 7 4	5 8 8	6 1 4	6 1 8	6 1 8	6 1 8	6 2 8	6 3 7	6 5 1	6 5 1	6 6 7	6 7 8	6 7 8	6 9 9	7 0 0	7 0 2	7 1 2
Carcass ID Number	6 1 9	6 0 7	6 7 1	6 8 4	6 5 0	6 0 5	6 6 1	6 0 4	6 5 3	6 9 7	6 3 4	6 0 3	6 1 1	6 6 9	6 3 5	6 4 6	6 3 7	6 4 0	6 3 1	6 5 2	6 6 5	6 6 6	6 7 4	6 8 1	6 8 6
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma												X	X												
Cholangiocarcinoma, multiple																X				X					
Cholangioma																									
Hepatocellular adenoma																									
Mesentery	+							+		+						+			+	+			+	+	
Sarcoma, metastatic, kidney	X																								
Sarcoma stromal, metastatic, uterus																									
Oral mucosa					+												+								
Gingival, squamous cell carcinoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																									
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+									+								
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign													X							X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X		X	X								X		
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	A	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																			X						
C-cell, adenoma										X					X	X									X
C-cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 550 ng/kg

Number of Days on Study	7 1 4	7 1 4	7 2 0	7 2 2	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	
Carcass ID Number	6 7 0	6 8 3	6 4 9	6 3 2	6 4 7	6 0 2	6 0 6	6 2 4	6 2 5	6 5 1	6 6 8	6 7 3	6 8 5	6 8 7	6 8 9	6 0 1	6 0 9	6 2 1	6 2 2	6 3 8	6 3 9	6 5 5	6 6 3	6 6 7	6 7 2	6 8 8	6 6 4	6 6 9	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cholangiocarcinoma																													2
Cholangiocarcinoma, multiple			X																X										4
Cholangioma																									X				1
Hepatocellular adenoma												X			X					X	X								4
Mesentery		+	+				+						+			+													13
Sarcoma, metastatic, kidney																													1
Sarcoma stromal, metastatic, uterus		X																											1
Oral mucosa			+			+													+	+									6
Gingival, squamous cell carcinoma			X																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma stromal, metastatic, uterus		X																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth				+		+		+							+				+	+								+	9
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma					X																								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma malignant																						X							1
Pheochromocytoma benign									X															X					4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	47
Adenoma																				X									1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma			X		X								X	X					X			X			X	X			13
Pars distalis, adenoma, multiple																X													1
Pars distalis, carcinoma																												X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																						X							2
C-cell, adenoma							X							X				X						X	X	X			10
C-cell, carcinoma									X			X																	2

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 550 ng/kg

Number of Days on Study	1 8 5	3 2 0	3 2 7	4 4 0	4 9 8	5 3 5	5 5 4	5 7 3	5 7 4	5 8 8	6 1 4	6 1 8	6 1 8	6 1 8	6 2 8	6 3 7	6 5 1	6 5 1	6 6 7	6 7 8	6 7 8	6 9 9	7 0 0	7 0 2	7 1 2
Carcass ID Number	6 1 9	6 0 7	6 7 1	6 8 4	6 5 0	6 0 5	6 6 1	6 0 4	6 5 3	6 9 7	6 3 4	6 0 3	6 1 1	6 6 1 9	6 3 5	6 4 6	6 3 7	6 4 0	6 3 1	6 5 2	6 5 6	6 6 6	6 7 4	6 8 1	6 8 6
General Body System																									
Tissue NOS																									
Carcinoma																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Oviduct																		+							
Uterus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Carcinoma																									
Polyp stromal																						X			
Sarcoma stromal																									
Schwannoma malignant																									
Squamous cell papilloma																									
Cervix, schwannoma malignant																						X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+					+					+					+		
Lumbar, sarcoma stromal, metastatic, uterus																									
Mediastinal, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																									
Thymus	+	M	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma				X			X			X		X	X	X		X	X	X						X	X
Fibroadenoma, multiple									X													X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma		X																							
Squamous cell carcinoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 550 ng/kg

Number of Days on Study	7 1 4	7 1 4	7 2 0	7 2 2	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	
Carcass ID Number	6 7 0	6 8 3	6 4 9	6 3 2	6 4 7	6 0 2	6 0 6	6 2 4	6 2 5	6 5 1	6 6 8	6 7 3	6 8 5	6 8 7	6 8 9	6 0 1	6 0 9	6 2 1	6 2 2	6 3 8	6 3 9	6 5 5	6 6 3	6 6 7	6 7 2	6 8 8	6 6 4	6 9 6	Total Tissues/ Tumors
General Body System																													
Tissue NOS									+																				1
Carcinoma									X																				1
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cystadenoma			X																										1
Oviduct								+														+							3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																													1
Carcinoma								X																					1
Polyp stromal												X					X				X						X	5
Sarcoma stromal		X													X														2
Schwannoma malignant														X															1
Squamous cell papilloma																									X				1
Cervix, schwannoma malignant																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node		+							+							+													7
Lumbar, sarcoma stromal, metastatic, uterus		X																											1
Mediastinal, carcinoma, metastatic, thyroid gland									X																				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma stromal, metastatic, uterus		X																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma																X													1
Fibroadenoma	X					X		X	X	X	X	X				X					X	X		X	X		X		24
Fibroadenoma, multiple				X																X						X			5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibrous histiocytoma																													1
Squamous cell carcinoma																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 550 ng/kg

Number of Days on Study	1 8 5	3 2 0	3 2 7	4 4 0	4 9 8	5 3 5	5 5 4	5 7 3	5 7 4	5 8 8	6 1 4	6 1 8	6 1 8	6 1 8	6 2 8	6 3 7	6 5 1	6 5 1	6 6 7	6 7 8	6 7 8	6 9 9	7 0 0	7 0 2	7 1 2
Carcass ID Number	6 1 9	6 0 7	6 7 1	6 8 4	6 5 0	6 0 5	6 6 1	6 0 4	6 5 3	6 9 7	6 3 4	6 0 3	6 1 1	6 6 1 9	6 3 5	6 4 6	6 3 7	6 4 0	6 3 1	6 5 2	6 5 6	6 6 6	6 7 4	6 8 1	6 8 6
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, mucinous																									
Cystic keratinizing epithelioma																	X					X			
Cystic keratinizing epithelioma, multiple										X											X			X	
Sarcoma, metastatic, kidney	X																								
Sarcoma stromal, metastatic, uterus																									
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stromal nephroma	X																								
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant								X																	

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 550 ng/kg

Number of Days on Study	7 1 4	7 1 4	7 2 0	7 2 2	7 2 2	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	
Carcass ID Number	6 7 0	6 8 3	6 4 9	6 3 2	6 4 7	6 0 2	6 0 6	6 2 4	6 2 5	6 5 1	6 6 8	6 7 3	6 8 5	6 8 7	6 8 9	6 0 1	6 0 9	6 2 1	6 2 2	6 3 8	6 3 9	6 5 5	6 6 3	6 6 7	6 7 2	6 8 8	6 6 4	6 9 6	Total Tissues/ Tumors
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, pituitary gland																												X	1
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma, mucinous				X																									1
Cystic keratinizing epithelioma						X																							3
Cystic keratinizing epithelioma, multiple				X					X	X		X											X						8
Sarcoma, metastatic, kidney																													1
Sarcoma stromal, metastatic, uterus		X																											1
Squamous cell carcinoma											X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																													
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stromal nephroma																													1
Transitional epithelium, carcinoma															X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymphoma malignant																													1

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg

Number of Days on Study	0 7 2	1 8 8	2 4 3	2 4 4	2 5 8	3 0 9	3 9 4	4 8 4	5 2 3	5 2 5	5 3 0	5 3 1	5 4 7	5 5 5	5 6 2	5 7 4	5 8 8	5 8 8	6 0 3	6 0 3	6 0 3	6 0 7	6 0 7	6 0 7	6 0 7
Carcass ID Number	7 5 8	7 3 7	8 0 2	8 4 6	8 2 4	7 5 2	8 3 6	8 4 0	7 7 4	8 3 7	7 3 6	8 2 6	7 7 2	8 0 5	7 6 6	8 4 7	7 6 9	7 7 0	8 2 1	8 2 5	8 4 4	7 3 8	7 5 7	7 6 5	8 0 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma															X				X					X	
Cholangiocarcinoma, multiple																X					X				
Cholangioma																									
Hepatocellular adenoma															X		X								
Hepatocellular adenoma, multiple																									
Hepatocholangioma																									
Hepatocholangioma, multiple																									
Mesentery															+							+		+	
Oral mucosa									+			+		+											
Gingival, squamous cell carcinoma									X					X											
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Acinus, carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth		+		+			+					+		+	+			+	+			+			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X					X	
Carcinoma																	X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa																									
Pars distalis, adenoma																							X		
Thyroid gland	+	+	A	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	M	A	+
Adenoma																									
C-cell, adenoma							X			X						X			X						

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg

Number of Days on Study	6 1 1	6 1 4	6 1 8	6 2 1	6 2 1	6 2 1	6 3 0	6 4 2	6 5 0	6 5 0	6 6 0	6 6 3	6 6 3	6 8 1	6 8 8	6 9 4	6 9 4	7 0 0	7 0 0	7 0 4	7 2 0	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	7 6 7	8 2 9	8 4 3	7 5 5	7 6 4	7 7 5	7 6 0	8 3 8	7 5 4	8 3 0	7 5 9	7 3 3	7 3 4	7 3 2	8 0 4	8 0 1	8 0 9	7 6 1	7 7 3	7 5 1	8 4 1	7 3 1	7 5 3	7 5 6	7 6 3	7 7 1	8 0 6	8 0 7	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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
Cholangiocarcinoma								X			X															X	X	7
Cholangiocarcinoma, multiple			X				X						X	X	X		X		X	X	X	X	X		X	X			15
Cholangioma																									X			1
Hepatocellular adenoma				X													X			X					X			6
Hepatocellular adenoma, multiple																								X				1
Hepatocholangioma											X		X															2
Hepatocholangioma, multiple																								X				1
Mesentery			+		+		+			+			+							+		+	+				11
Oral mucosa		+	+					+	+	+		+							+						+			11
Gingival, squamous cell carcinoma		X	X					X	X			X																7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinus, carcinoma													X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tooth						+				+				+					+	+	+		+	+		+	+	19
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																												2
Carcinoma																	X											2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Islets, pancreatic	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											X	1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell carcinoma, metastatic, oral mucosa												X																1
Pars distalis, adenoma	X																	X		X	X				X			6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																								X				1
C-cell, adenoma						X							X					X			X						X	9

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg

Number of Days on Study	0	1	2	2	2	3	3	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6
	7	8	4	4	5	0	9	8	2	2	3	3	4	5	6	7	8	0	0	0	0	0	0	0
	2	8	3	4	8	9	4	4	3	5	0	1	7	5	2	4	8	3	3	3	7	7	7	7
Carcass ID Number	7	7	8	8	8	7	8	8	7	8	7	8	7	8	7	8	7	7	8	8	8	7	7	7	8
	5	3	0	4	2	5	3	4	7	3	3	2	7	0	6	4	6	7	2	2	4	3	5	6	0
	8	7	2	6	4	2	6	0	4	7	6	6	2	5	6	7	9	0	1	5	4	8	7	5	8
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple																									
Polyp stromal																									
Vagina																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+		+	+	+											
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	M	+	M	M	+	+	+	+	M	+	+	+	M	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Fibroadenoma					X		X			X									X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg

Number of Days on Study	6 1 1	6 1 4	6 1 8	6 2 1	6 2 1	6 2 1	6 3 0	6 4 2	6 5 0	6 5 0	6 6 0	6 6 3	6 6 3	6 8 1	6 8 8	6 9 4	6 9 4	7 0 0	7 0 0	7 0 4	7 2 0	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	7 6 7	8 2 9	8 4 3	7 5 5	7 6 4	7 7 5	7 6 0	8 3 8	7 5 4	8 3 0	7 5 9	7 3 3	7 3 4	7 3 2	8 0 4	8 0 1	8 0 9	7 6 1	7 7 3	7 5 1	8 4 1	7 3 1	7 5 3	7 5 6	7 6 3	7 7 1	8 0 6	8 0 7	Total Tissues/ Tumors
General Body System																												
None																												
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Oviduct																										+		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma, multiple																		X										1
Polyp stromal				X	X				X																		X	4
Vagina															+													1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+		+						+	+								+			+	+						12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	44
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																												1
Fibroadenoma			X			X				X						X						X	X		X			11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Keratoacanthoma					X																							1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Skeletal muscle																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg

Number of Days on Study	0 7 2	1 8 8	2 4 3	2 4 4	2 5 8	3 0 9	3 9 4	4 8 4	5 2 3	5 2 5	5 3 0	5 3 1	5 4 7	5 5 5	5 6 2	5 7 4	5 8 8	5 8 8	6 0 3	6 0 3	6 0 3	6 0 7	6 0 7	6 0 7	6 0 7
Carcass ID Number	7 5 8	7 3 7	8 0 2	8 4 6	8 2 4	7 5 2	8 3 6	8 4 0	7 4 7	8 3 7	7 3 6	8 2 6	7 7 2	8 0 5	7 6 6	8 4 7	7 6 9	7 7 0	8 2 1	8 2 5	8 4 4	7 3 8	7 5 7	7 6 5	8 0 8
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Carcinoma, metastatic, adrenal cortex																	X								
Cystic keratinizing epithelioma														X										X	
Cystic keratinizing epithelioma, multiple								X		X		X	X		X	X	X	X	X	X		X			X
Squamous cell carcinoma														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Special Senses System																									
Ear																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Optic nerve, squamous cell carcinoma, metastatic, oral mucosa																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Squamous cell carcinoma, metastatic, oral mucosa																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma		X	X																						
Stromal nephroma										X															
Ureter						+											+								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymphoma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg

Number of Days on Study	6 1 1	6 1 4	6 1 8	6 2 1	6 2 1	6 2 1	6 3 0	6 4 2	6 5 0	6 5 0	6 6 0	6 6 3	6 6 3	6 8 1	6 8 8	6 9 4	6 9 4	7 0 0	7 0 0	7 0 4	7 2 0	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	7 6 7	8 2 9	8 4 3	7 5 5	7 6 4	7 7 5	7 6 0	8 3 8	7 5 4	8 3 0	7 5 9	7 3 3	7 3 4	7 3 2	8 0 4	8 0 1	8 0 9	7 6 1	7 7 3	7 5 1	8 4 1	7 3 1	7 5 3	7 5 6	7 6 3	7 7 1	8 0 6	8 0 7	Total Tissues/ Tumors
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, adrenal cortex																												1
Cystic keratinizing epithelioma							X																	X	X			5
Cystic keratinizing epithelioma, multiple	X	X	X	X		X			X		X	X		X		X	X	X	X	X		X	X	X			X		30
Squamous cell carcinoma	X																											2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell carcinoma, metastatic, oral mucosa												X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																												
Ear																			+									1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Optic nerve, squamous cell carcinoma, metastatic, oral mucosa												X																1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma, metastatic, oral mucosa												X																1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nephroblastoma																												2
Stromal nephroma																												1
Ureter											+																	3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear																										X		1
Lymphoma malignant	X						X																					2

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg (Stop-Exposure)

Number of Days on Study	2 8 4	3 2 0	3 2 8	3 3 7	4 1 1	4 5 4	4 5 4	5 0 2	5 3 7	5 5 4	5 7 4	5 9 2	5 9 3	6 0 7	6 1 1	6 1 8	6 1 8	6 2 5	6 3 7	6 5 9	6 6 0	6 7 1	7 2 7	7 2 7	7 2 7
Carcass ID Number	7 0 2	7 7 8	7 9 2	7 7 9	7 2 5	7 1 0	7 7 7	7 0 3	7 9 4	7 8 4	7 8 9	7 2 2	7 9 5	7 1 7	7 9 8	7 8 2	7 9 3	7 8 5	7 2 4	7 2 1	7 8 7	7 0 8	7 0 1	7 0 4	7 0 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Oral mucosa																+				+		+			
Gingival, squamous cell carcinoma																X						X			
Pancreas	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+		+	+		+		+										+	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X												X				
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma																									
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X			X	X	X		X	X			X		
Thyroid gland	A	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																								X	
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 126: 1,000 ng/kg (Stop-Exposure)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	7 0 0 7	7 0 9	7 1 1	7 7 6	7 8 3	7 9 1	7 9 7	7 0 6	7 1 2	7 1 3	7 1 4	7 1 5	7 1 8	7 2 3	7 8 0	7 8 6	7 9 0	7 9 9	7 1 6	7 1 9	7 2 0	7 8 1	7 8 8	7 9 6	8 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma												X			X											2
Oral mucosa									+				+										+			6
Gingival, squamous cell carcinoma																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+				+				+									+					+	+		12
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X	X					2
Carcinoma													X													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Bilateral, pheochromocytoma benign											X															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									X	1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma																X										1
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma			X	X	X					X		X		X						X		X	X	X		17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bilateral, C-cell, adenoma		X							X		X											X				5
C-cell, adenoma				X		X						X		X	X											11
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 126: 1,000 ng/kg (Stop-Exposure)

Number of Days on Study	2 8 4	3 2 0	3 2 8	3 3 7	4 1 1	4 5 4	4 5 4	5 0 2	5 3 7	5 5 4	5 7 4	5 9 2	5 9 3	6 0 7	6 1 1	6 1 8	6 1 8	6 2 5	6 3 7	6 5 9	6 6 0	6 7 1	7 2 7	7 2 7	7 2 7
Carcass ID Number	7 0 2	7 7 8	7 9 2	7 7 9	7 2 5	7 1 0	7 7 7	7 0 3	7 9 4	7 8 4	7 8 9	7 2 2	7 9 5	7 1 7	7 9 8	7 8 2	7 9 3	7 8 5	7 2 4	7 2 1	7 8 7	7 0 8	7 0 1	7 0 4	7 0 5
Genital System																									
Clitoral gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																									
Oviduct							+																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+																
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	M	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Fibroadenoma			X			X		X	X	X						X			X	X	X		X		
Fibroadenoma, multiple											X	X	X												X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg (Stop-Exposure)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	7 0 0 7	7 0 9	7 1 1	7 7 6	7 8 3	7 9 1	7 9 7	7 0 6	7 1 2	7 1 3	7 1 4	7 1 5	7 1 8	7 2 3	7 8 0	7 8 6	7 9 0	7 9 9	7 1 6	7 1 9	7 2 0	7 8 1	7 8 8	7 9 6	8 0 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign											X															1
Oviduct																				+						2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Polyp stromal							X						X				X				X				X	5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node															+											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X				X	X																				4
Fibroadenoma						X				X	X		X								X					15
Fibroadenoma, multiple	X	X						X				X		X	X		X			X			X			13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma											X															1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant														X												1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg (Stop-Exposure)

Number of Days on Study	2 8 4	3 2 0	3 2 8	3 3 7	4 1 1	4 5 4	4 5 4	5 0 2	5 3 7	5 5 4	5 7 4	5 9 2	5 9 3	6 0 7	6 1 1	6 1 8	6 1 8	6 2 5	6 3 7	6 5 9	6 6 0	6 7 1	7 2 7	7 2 7	7 2 7
Carcass ID Number	7 0 2	7 7 8	7 9 2	7 7 9	7 2 5	7 1 0	7 7 7	7 0 3	7 9 4	7 8 4	7 8 9	7 2 2	7 9 5	7 1 7	7 9 8	7 8 2	7 9 3	7 8 5	7 2 4	7 2 1	7 8 7	7 0 8	7 0 1	7 0 4	7 0 5
Special Senses System																									
Ear																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of PCB 126: 1,000 ng/kg (Stop-Exposure)

Number of Days on Study	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	7 0 7	7 0 9	7 1 1	7 7 6	7 8 3	7 9 1	7 9 7	7 0 6	7 1 2	7 1 3	7 1 4	7 1 5	7 1 8	7 2 3	7 8 0	7 8 6	7 9 0	7 9 9	7 1 6	7 1 9	7 2 0	7 8 1	7 8 8	7 9 6	8 0 0	Total Tissues/ Tumors
Special Senses System																										
Ear										+																1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant															X											1

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg
Adrenal Cortex: Adenoma or Carcinoma				
Overall rate[a]	0/52 (0%)	2/55 (4%)	1/53 (2%)	0/53 (0%)
Adjusted rate[b]	0.0%	5.2%	2.5%	0.0%
Terminal rate[c]	0/15 (0%)	2/25 (8%)	1/26 (4%)	0/22 (0%)
First incidence (days)	—[e]	727 (T)	727 (T)	—[f]
Poly-3 test[d]	P=0.022	P=0.285	P=0.546	—
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	8/52 (15%)	3/55 (5%)	4/53 (8%)	2/53 (4%)
Adjusted rate	24.1%	7.7%	9.9%	5.3%
Terminal rate	3/15 (20%)	2/25 (8%)	2/26 (8%)	1/22 (5%)
First incidence (days)	531	607	586	660
Poly-3 test	P=0.027N	P=0.052N	P=0.093N	P=0.025N
Adrenal Medulla: Benign, Complex, Malignant, or Pheochromocytoma				
Overall rate	8/52 (15%)	3/55 (5%)	5/53 (9%)	3/53 (6%)
Adjusted rate	24.1%	7.7%	12.4%	7.8%
Terminal rate	3/15 (20%)	2/25 (8%)	2/26 (8%)	1/22 (5%)
First incidence (days)	531	607	586	500
Poly-3 test	P=0.037N	P=0.052N	P=0.158N	P=0.055N
Brain: Astrocytoma or Oligodendroglioma				
Overall rate	3/53 (6%)	0/55 (0%)	0/53 (0%)	0/53 (0%)
Adjusted rate	9.2%	0.0%	0.0%	0.0%
Terminal rate	1/15 (7%)	0/25 (0%)	0/26 (0%)	0/22 (0%)
First incidence (days)	201	—	—	—
Poly-3 test	P=0.149N	P=0.091N	P=0.088N	P=0.096N
Liver: Cholangiocarcinoma				
Overall rate	0/53 (0%)	0/55 (0%)	1/53 (2%)	0/53 (0%)
Adjusted rate	0.0%	0.0%	2.5%	0.0%
Terminal rate	0/15 (0%)	0/25 (0%)	1/26 (4%)	0/22 (0%)
First incidence (days)	—	—	727 (T)	—
Poly-3 test	P<0.001	—	P=0.546	—
Liver: Hepatocholangioma				
Overall rate	0/53 (0%)	0/55 (0%)	0/53 (0%)	0/53 (0%)
Adjusted rate	0.0%	0.0%	0.0%	0.0%
Terminal rate	0/15 (0%)	0/25 (0%)	0/26 (0%)	0/22 (0%)
First incidence (days)	—	—	—	—
Poly-3 test	P<0.001	—	—	—
Liver: Hepatocellular Adenoma				
Overall rate	1/53 (2%)	2/55 (4%)	1/53 (2%)	0/53 (0%)
Adjusted rate	3.2%	5.2%	2.5%	0.0%
Terminal rate	1/15 (7%)	1/25 (4%)	0/26 (0%)	0/22 (0%)
First incidence (days)	727 (T)	652	602	—
Poly-3 test	P<0.001	P=0.574	P=0.704N	P=0.465N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/53 (2%)	2/55 (4%)	1/53 (2%)	1/53 (2%)
Adjusted rate	3.2%	5.2%	2.5%	2.7%
Terminal rate	1/15 (7%)	1/25 (4%)	0/26 (0%)	1/22 (5%)
First incidence (days)	727 (T)	652	602	727 (T)
Poly-3 test	P<0.001	P=0.574	P=0.704N	P=0.722N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	300 ng/kg	550 ng/kg	1,000 ng/kg
Adrenal Cortex: Adenoma or Carcinoma			
Overall rate	1/53 (2%)	1/52 (2%)	4/53 (8%)
Adjusted rate	2.7%	2.4%	12.0%
Terminal rate	0/16 (0%)	0/23 (0%)	0/7 (0%)
First incidence (days)	607	722	588
Poly-3 test	P=0.533	P=0.555	P=0.065
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate	2/53 (4%)	4/52 (8%)	0/53 (0%)
Adjusted rate	5.5%	9.5%	0.0%
Terminal rate	1/16 (6%)	2/23 (9%)	0/7 (0%)
First incidence (days)	709	618	—
Poly-3 test	P=0.027N	P=0.081N	P=0.003N
Adrenal Medulla: Benign, Complex, Malignant, or Pheochromocytoma			
Overall rate	3/53 (6%)	5/52 (10%)	0/53 (0%)
Adjusted rate	8.2%	11.9%	0.0%
Terminal rate	2/16 (13%)	3/23 (13%)	0/7 (0%)
First incidence (days)	709	618	—
Poly-3 test	P=0.064N	P=0.140N	P=0.003N
Brain: Astrocytoma or Oligodendroglioma			
Overall rate	1/53 (2%)	0/53 (0%)	0/53 (0%)
Adjusted rate	2.7%	0.0%	0.0%
Terminal rate	0/16 (0%)	0/23 (0%)	0/7 (0%)
First incidence (days)	541	—	—
Poly-3 test	P=0.260N	P=0.080N	P=0.121N
Liver: Cholangiocarcinoma			
Overall rate	5/53 (9%)	6/51 (12%)	22/53 (42%)
Adjusted rate	13.6%	14.0%	60.3%
Terminal rate	3/16 (19%)	1/23 (4%)	6/7 (86%)
First incidence (days)	659	618	562
Poly-3 test	P=0.045	P=0.040	P<0.001
Liver: Hepatocholangioma			
Overall rate	0/53 (0%)	0/51 (0%)	3/53 (6%)
Adjusted rate	0.0%	0.0%	9.3%
Terminal rate	0/16 (0%)	0/23 (0%)	1/7 (14%)
First incidence (days)	—	—	660
Poly-3 test	—	—	P=0.122
Liver: Hepatocellular Adenoma			
Overall rate	2/53 (4%)	4/51 (8%)	7/53 (13%)
Adjusted rate	5.5%	9.7%	20.9%
Terminal rate	1/16 (6%)	4/23 (17%)	2/7 (29%)
First incidence (days)	709	727 (T)	562
Poly-3 test	P=0.554	P=0.274	P=0.033
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	2/53 (4%)	4/51 (8%)	7/53 (13%)
Adjusted rate	5.5%	9.7%	20.9%
Terminal rate	1/16 (6%)	4/23 (17%)	2/7 (29%)
First incidence (days)	709	727 (T)	562
Poly-3 test	P=0.554	P=0.274	P=0.033

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg
Lung: Cystic Keratinizing Epithelioma				
Overall rate	0/53 (0%)	0/55 (0%)	0/53 (0%)	0/53 (0%)
Adjusted rate	0.0%	0.0%	0.0%	0.0%
Terminal rate	0/15 (0%)	0/25 (0%)	0/26 (0%)	0/22 (0%)
First incidence (days)	—	—	—	—
Poly-3 test	P<0.001	—	—	—
Mammary Gland: Fibroadenoma				
Overall rate	39/53 (74%)	31/55 (56%)	35/53 (66%)	38/53 (72%)
Adjusted rate	86.3%	68.4%	73.4%	79.5%
Terminal rate	11/15 (73%)	18/25 (72%)	18/26 (69%)	16/22 (73%)
First incidence (days)	309	356	188	385
Poly-3 test	P<0.001N	P=0.029N	P=0.085N	P=0.263N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	40/53 (75%)	31/55 (56%)	36/53 (68%)	38/53 (72%)
Adjusted rate	88.5%	68.4%	74.6%	79.5%
Terminal rate	12/15 (80%)	18/25 (72%)	18/26 (69%)	16/22 (73%)
First incidence (days)	309	356	188	385
Poly-3 test	P<0.001N	P=0.013N	P=0.058N	P=0.165N
Mammary Gland: Carcinoma				
Overall rate	6/53 (11%)	7/55 (13%)	9/53 (17%)	5/53 (9%)
Adjusted rate	18.5%	17.8%	22.1%	13.0%
Terminal rate	3/15 (20%)	3/25 (12%)	6/26 (23%)	3/22 (14%)
First incidence (days)	400	580	533	496
Poly-3 test	P<0.001N	P=0.591N	P=0.466	P=0.379N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	7/53 (13%)	7/55 (13%)	10/53 (19%)	5/53 (9%)
Adjusted rate	21.6%	17.8%	24.5%	13.0%
Terminal rate	4/15 (27%)	3/25 (12%)	7/26 (27%)	3/22 (14%)
First incidence (days)	400	580	533	496
Poly-3 test	P<0.001N	P=0.459N	P=0.493	P=0.259N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	42/53 (79%)	36/55 (65%)	38/53 (72%)	39/53 (74%)
Adjusted rate	91.0%	78.1%	78.2%	80.8%
Terminal rate	12/15 (80%)	19/25 (76%)	19/26 (73%)	16/22 (73%)
First incidence (days)	309	356	188	385
Poly-3 test	P<0.001N	P=0.064N	P=0.064N	P=0.114N
Oral Cavity (Oral Mucosa): Squamous Cell Carcinoma				
Overall rate	0/53 (0%)	1/55 (2%)	1/53 (2%)	1/53 (2%)
Adjusted rate	0.0%	2.6%	2.5%	2.7%
Terminal rate	0/15 (0%)	0/25 (0%)	0/26 (0%)	1/22 (5%)
First incidence (days)	—	681	651	727 (T)
Poly-3 test	P<0.001	P=0.542	P=0.547	P=0.534
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	15/51 (29%)	18/54 (33%)	20/53 (38%)	16/53 (30%)
Adjusted rate	46.1%	43.6%	45.5%	39.7%
Terminal rate	9/15 (60%)	8/25 (32%)	10/26 (39%)	8/22 (36%)
First incidence (days)	603	434	328	487
Poly-3 test	P=0.003N	P=0.511N	P=0.574N	P=0.377N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	300 ng/kg	550 ng/kg	1,000 ng/kg
Lung: Cystic Keratinizing Epithelioma			
Overall rate	1/53 (2%)	11/51 (22%)	35/51 (69%)
Adjusted rate	2.7%	26.0%	83.5%
Terminal rate	1/16 (6%)	5/23 (22%)	6/7 (86%)
First incidence (days)	727 (T)	588	484
Poly-3 test	P=0.531	P=0.002	P<0.001
Mammary Gland: Fibroadenoma			
Overall rate	39/53 (74%)	29/53 (55%)	11/53 (21%)
Adjusted rate	80.9%	61.9%	30.6%
Terminal rate	10/16 (63%)	14/23 (61%)	3/7 (43%)
First incidence (days)	247	440	258
Poly-3 test	P=0.327N	P=0.004N	P<0.001N
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	39/53 (74%)	29/53 (55%)	11/53 (21%)
Adjusted rate	80.9%	61.9%	30.6%
Terminal rate	10/16 (63%)	14/23 (61%)	3/7 (43%)
First incidence (days)	247	440	258
Poly-3 test	P=0.219N	P=0.002N	P<0.001N
Mammary Gland: Carcinoma			
Overall rate	0/53 (0%)	1/53 (2%)	1/53 (2%)
Adjusted rate	0.0%	2.4%	3.0%
Terminal rate	0/16 (0%)	1/23 (4%)	0/7 (0%)
First incidence (days)	—	727 (T)	72
Poly-3 test	P=0.009N	P=0.024N	P=0.049N
Mammary Gland: Adenoma or Carcinoma			
Overall rate	1/53 (2%)	1/53 (2%)	1/53 (2%)
Adjusted rate	2.7%	2.4%	3.0%
Terminal rate	1/16 (6%)	1/23 (4%)	0/7 (0%)
First incidence (days)	727 (T)	727 (T)	72
Poly-3 test	P=0.017N	P=0.010N	P=0.024N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	39/53 (74%)	29/53 (55%)	12/53 (23%)
Adjusted rate	80.9%	61.9%	32.5%
Terminal rate	10/16 (63%)	14/23 (61%)	3/7 (43%)
First incidence (days)	247	440	72
Poly-3 test	P=0.121N	P<0.001N	P<0.001N
Oral Cavity (Oral Mucosa): Squamous Cell Carcinoma			
Overall rate	2/53 (4%)	2/53 (4%)	7/53 (13%)
Adjusted rate	5.4%	4.7%	20.2%
Terminal rate	1/16 (6%)	0/23 (0%)	0/7 (0%)
First incidence (days)	618	498	523
Poly-3 test	P=0.275	P=0.312	P=0.010
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	22/53 (42%)	14/53 (26%)	6/53 (11%)
Adjusted rate	55.1%	31.9%	18.2%
Terminal rate	10/16 (63%)	7/23 (30%)	1/7 (14%)
First incidence (days)	531	588	607
Poly-3 test	P=0.289	P=0.150N	P=0.011N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	15/51 (29%)	18/54 (33%)	20/53 (38%)	17/53 (32%)
Adjusted rate	46.1%	43.6%	45.5%	42.2%
Terminal rate	9/15 (60%)	8/25 (32%)	10/26 (39%)	9/22 (41%)
First incidence (days)	603	434	328	487
Poly-3 test	P=0.004N	P=0.511N	P=0.574N	P=0.463N
Thyroid Gland (C-Cell): Adenoma				
Overall rate	15/52 (29%)	15/55 (27%)	15/52 (29%)	13/51 (25%)
Adjusted rate	44.8%	36.4%	35.2%	33.2%
Terminal rate	8/15 (53%)	8/25 (32%)	7/26 (27%)	8/22 (36%)
First incidence (days)	519	524	541	385
Poly-3 test	P=0.085N	P=0.304N	P=0.265N	P=0.211N
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	15/52 (29%)	16/55 (29%)	17/52 (33%)	13/51 (25%)
Adjusted rate	44.8%	38.8%	39.8%	33.2%
Terminal rate	8/15 (53%)	9/25 (36%)	8/26 (31%)	8/22 (36%)
First incidence (days)	519	524	541	385
Poly-3 test	P=0.080N	P=0.385N	P=0.417N	P=0.211N
Uterus: Stromal Polyp				
Overall rate	4/53 (8%)	5/55 (9%)	7/53 (13%)	3/53 (6%)
Adjusted rate	12.6%	12.8%	17.4%	8.0%
Terminal rate	2/15 (13%)	2/25 (8%)	4/26 (15%)	2/22 (9%)
First incidence (days)	660	630	652	658
Poly-3 test	P=0.444N	P=0.628	P=0.407	P=0.408N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/53 (8%)	5/55 (9%)	7/53 (13%)	5/53 (9%)
Adjusted rate	12.6%	12.8%	17.4%	13.2%
Terminal rate	2/15 (13%)	2/25 (8%)	4/26 (15%)	3/22 (14%)
First incidence (days)	660	630	652	658
Poly-3 test	P=0.516N	P=0.628	P=0.407	P=0.610
Uterus: Carcinoma				
Overall rate	0/53 (0%)	3/55 (5%)	1/53 (2%)	1/53 (2%)
Adjusted rate	0.0%	7.8%	2.5%	2.7%
Terminal rate	0/15 (0%)	2/25 (8%)	0/26 (0%)	1/22 (5%)
First incidence (days)	—	700	659	727 (T)
Poly-3 test	P=0.170N	P=0.159	P=0.547	P=0.534
All Organs: Benign Neoplasms				
Overall rate	45/53 (85%)	45/55 (82%)	48/53 (91%)	45/53 (85%)
Adjusted rate	97.9%	94.7%	93.8%	92.7%
Terminal rate	15/15 (100%)	24/25 (96%)	23/26 (89%)	21/22 (96%)
First incidence (days)	309	356	188	385
Poly-3 test	P=0.207N	P=0.377N	P=0.296N	P=0.180N
All Organs: Malignant Neoplasms				
Overall rate	13/53 (25%)	19/55 (35%)	18/53 (34%)	15/53 (28%)
Adjusted rate	37.0%	41.9%	40.9%	36.6%
Terminal rate	5/15 (33%)	6/25 (24%)	8/26 (31%)	8/22 (36%)
First incidence (days)	176	82	236	448
Poly-3 test	P<0.001	P=0.414	P=0.451	P=0.583N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	300 ng/kg	550 ng/kg	1,000 ng/kg
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	22/53 (42%)	15/53 (28%)	6/53 (11%)
Adjusted rate	55.1%	34.2%	18.2%
Terminal rate	10/16 (63%)	8/23 (35%)	1/7 (14%)
First incidence (days)	531	588	607
Poly-3 test	P=0.289	P=0.205N	P=0.011N
Thyroid Gland (C-Cell): Adenoma			
Overall rate	12/52 (23%)	12/50 (24%)	9/48 (19%)
Adjusted rate	30.8%	28.3%	27.2%
Terminal rate	3/16 (19%)	7/23 (30%)	1/7 (14%)
First incidence (days)	454	588	394
Poly-3 test	P=0.155N	P=0.101N	P=0.096N
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rate	12/52 (23%)	14/50 (28%)	9/48 (19%)
Adjusted rate	30.8%	33.0%	27.2%
Terminal rate	3/16 (19%)	9/23 (39%)	1/7 (14%)
First incidence (days)	454	588	394
Poly-3 test	P=0.155N	P=0.204N	P=0.096N
Uterus: Stromal Polyp			
Overall rate	8/53 (15%)	5/53 (9%)	4/53 (8%)
Adjusted rate	21.2%	11.8%	12.1%
Terminal rate	5/16 (31%)	4/23 (17%)	1/7 (14%)
First incidence (days)	541	700	621
Poly-3 test	P=0.263	P=0.601N	P=0.628N
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rate	10/53 (19%)	7/53 (13%)	4/53 (8%)
Adjusted rate	26.5%	16.6%	12.1%
Terminal rate	6/16 (38%)	5/23 (22%)	1/7 (14%)
First incidence (days)	541	700	621
Poly-3 test	P=0.124	P=0.443	P=0.628N
Uterus: Carcinoma			
Overall rate	0/53 (0%)	1/53 (2%)	0/53 (0%)
Adjusted rate	0.0%	2.4%	0.0%
Terminal rate	0/16 (0%)	1/23 (4%)	0/7 (0%)
First incidence (days)	—	727 (T)	—
Poly-3 test	—	P=0.558	—
All Organs: Benign Neoplasms			
Overall rate	46/53 (87%)	45/53 (85%)	42/53 (79%)
Adjusted rate	93.7%	93.8%	91.8%
Terminal rate	14/16 (88%)	23/23 (100%)	7/7 (100%)
First incidence (days)	247	440	258
Poly-3 test	P=0.285N	P=0.270N	P=0.135N
All Organs: Malignant Neoplasms			
Overall rate	16/53 (30%)	23/53 (43%)	33/53 (62%)
Adjusted rate	39.6%	48.9%	76.7%
Terminal rate	6/16 (38%)	10/23 (44%)	6/7 (86%)
First incidence (days)	40	185	72
Poly-3 test	P=0.502	P=0.192	P<0.001

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/53 (92%)	51/55 (93%)	51/53 (96%)	47/53 (89%)
Adjusted rate	99.6%	97.4%	97.8%	94.4%
Terminal rate	15/15 (100%)	24/25 (96%)	25/26 (96%)	21/22 (96%)
First incidence (days)	176	82	188	385
Poly-3 test	P=0.579N	P=0.466N	P=0.543N	P=0.125N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of PCB 126

	300 ng/kg	550 ng/kg	1,000 ng/kg
All Organs: Benign or Malignant Neoplasms			
Overall rate	49/53 (92%)	50/53 (94%)	49/53 (92%)
Adjusted rate	97.5%	97.9%	97.6%
Terminal rate	15/16 (94%)	23/23 (100%)	7/7 (100%)
First incidence (days)	40	185	72
Poly-3 test	P=0.481N	P=0.576N	P=0.504N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, brain, liver, lung, 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 dose 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 126

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Adrenal Cortex: Adenoma or Carcinoma			
Overall rate[a]	0/52 (0%)	4/53 (8%)	3/50 (6%)
Adjusted rate[b]	0.0%	12.0%	8.0%
Terminal rate[c]	0/15 (0%)	0/7 (0%)	3/28 (11%)
First incidence (days)	—[f]	588	727 (T)
Poly-3 test[d]		P=0.065	P=0.144
Poly-3 test[e]			P=0.424N
Adrenal Medulla: Benign Pheochromocytoma			
Overall rate	8/52 (15%)	0/53 (0%)	3/50 (6%)
Adjusted rate	24.1%	0.0%	7.8%
Terminal rate	3/15 (20%)	0/7 (0%)	1/28 (4%)
First incidence (days)	531	—	537
Poly-3 test		P=0.003N	P=0.052N
Poly-3 test			P=0.146
Adrenal Medulla: Benign, Complex, Malignant, or Pheochromocytoma			
Overall rate	8/52 (15%)	0/53 (0%)	3/50 (6%)
Adjusted rate	24.1%	0.0%	7.8%
Terminal rate	3/15 (20%)	0/7 (0%)	1/28 (4%)
First incidence (days)	531	—	537
Poly-3 test		P=0.003N	P=0.054N
Poly-3 test			P=0.146
Brain: Astrocytoma or Oligodendroglioma			
Overall rate	3/53 (6%)	0/53 (0%)	1/50 (2%)
Adjusted rate	9.2%	0.0%	2.7%
Terminal rate	1/15 (7%)	0/7 (0%)	1/28 (4%)
First incidence (days)	201	—	727 (T)
Poly-3 test		P=0.121N	P=0.246N
Poly-3 test			P=0.533
Liver: Cholangiocarcinoma			
Overall rate	0/53 (0%)	22/53 (42%)	2/50 (4%)
Adjusted rate	0.0%	60.3%	5.3%
Terminal rate	0/15 (0%)	6/7 (86%)	2/28 (7%)
First incidence (days)	—	562	727 (T)
Poly-3 test		P<0.001	P=0.263
Poly-3 test			P<0.001N
Liver: Hepatocholangioma			
Overall rate	0/53 (0%)	3/53 (6%)	0/50 (0%)
Adjusted rate	0.0%	9.3%	0.0%
Terminal rate	0/15 (0%)	1/7 (14%)	0/28 (0%)
First incidence (days)	—	660	—
Poly-3 test		P=0.122	—
Poly-3 test			P=0.087N
Liver: Hepatocellular Adenoma			
Overall rate	1/53 (2%)	7/53 (13%)	0/50 (0%)
Adjusted rate	3.2%	20.9%	0.0%
Terminal rate	1/15 (7%)	2/7 (29%)	0/28 (0%)
First incidence (days)	727 (T)	562	—
Poly-3 test		P=0.033	P=0.463N
Poly-3 test			P=0.004N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 126

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rate	1/53 (2%)	7/53 (13%)	0/50 (0%)
Adjusted rate	3.2%	20.9%	0.0%
Terminal rate	1/15 (7%)	2/7 (29%)	0/28 (0%)
First incidence (days)	727 (T)	562	—
Poly-3 test		P=0.033	P=0.463N
Poly-3 test			P=0.004N
Lung: Cystic Keratinizing Epithelioma			
Overall rate	0/53 (0%)	35/51 (69%)	0/50 (0%)
Adjusted rate	0.0%	83.5%	0.0%
Terminal rate	0/15 (0%)	6/7 (86%)	0/28 (0%)
First incidence (days)	—	484	—
Poly-3 test		P<0.001	—[g]
Poly-3 test			P<0.001N
Mammary Gland: Fibroadenoma			
Overall rate	39/53 (74%)	11/53 (21%)	28/50 (56%)
Adjusted rate	86.4%	30.6%	63.8%
Terminal rate	11/15 (73%)	3/7 (43%)	16/28 (57%)
First incidence (days)	309	258	328
Poly-3 test		P<0.001N	P=0.009N
Poly-3 test			P<0.001
Mammary Gland: Carcinoma			
Overall rate	6/53 (11%)	1/53 (2%)	4/50 (8%)
Adjusted rate	18.5%	3.0%	10.4%
Terminal rate	3/15 (20%)	0/7 (0%)	3/28 (11%)
First incidence (days)	400	72	337
Poly-3 test		P=0.049N	P=0.254N
Poly-3 test			P=0.221
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma			
Overall rate	42/53 (79%)	12/53 (23%)	30/50 (60%)
Adjusted rate	91.0%	32.5%	67.0%
Terminal rate	12/15 (80%)	3/7 (43%)	17/28 (61%)
First incidence (days)	309	72	328
Poly-3 test		P<0.001N	P=0.003N
Poly-3 test			P<0.001
Oral Cavity (Oral Mucosa): Squamous Cell Carcinoma			
Overall rate	0/53 (0%)	7/53 (13%)	2/50 (4%)
Adjusted rate	0.0%	20.2%	5.2%
Terminal rate	0/15 (0%)	0/7 (0%)	0/28 (0%)
First incidence (days)	—	523	618
Poly-3 test		P=0.010	P=0.266
Poly-3 test			P=0.052N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	15/51 (29%)	6/53 (11%)	17/48 (35%)
Adjusted rate	46.1%	18.2%	43.7%
Terminal rate	9/15 (60%)	1/7 (14%)	11/27 (41%)
First incidence (days)	603	607	592
Poly-3 test		P=0.011N	P=0.511N
Poly-3 test			P=0.015

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 126

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rate	15/51 (29%)	6/53 (11%)	17/48 (35%)
Adjusted rate	46.1%	18.2%	43.7%
Terminal rate	9/15 (60%)	1/7 (14%)	11/27 (41%)
First incidence (days)	603	607	592
Poly-3 test		P=0.011N	P=0.517N
Poly-3 test			P=0.015
Thyroid Gland (C-Cell): Adenoma			
Overall rate	15/52 (29%)	9/48 (19%)	16/47 (34%)
Adjusted rate	44.8%	27.2%	40.7%
Terminal rate	8/15 (53%)	1/7 (14%)	12/28 (43%)
First incidence (days)	519	394	502
Poly-3 test		P=0.096N	P=0.446N
Poly-3 test			P=0.160
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rate	15/52 (29%)	9/48 (19%)	17/47 (36%)
Adjusted rate	44.8%	27.2%	43.2%
Terminal rate	8/15 (53%)	1/7 (14%)	13/28 (46%)
First incidence (days)	519	394	502
Poly-3 test		P=0.096N	P=0.535N
Poly-3 test			P=0.111
Uterus: Stromal Polyp			
Overall rate	4/53 (8%)	4/53 (8%)	5/50 (10%)
Adjusted rate	12.6%	12.1%	13.3%
Terminal rate	2/15 (13%)	1/7 (14%)	5/28 (18%)
First incidence (days)	660	621	727 (T)
Poly-3 test		P=0.628N	P=0.599
Poly-3 test			P=0.578
All Organs: Benign Neoplasms			
Overall rate	45/53 (85%)	42/53 (79%)	41/50 (82%)
Adjusted rate	97.9%	91.8%	90.9%
Terminal rate	15/15 (100%)	7/7 (100%)	26/28 (93%)
First incidence (days)	309	258	328
Poly-3 test		P=0.135N	P=0.120N
Poly-3 test			P=0.605N
All Organs: Malignant Neoplasms			
Overall rate	13/53 (25%)	33/53 (62%)	12/50 (24%)
Adjusted rate	37.0%	76.7%	30.0%
Terminal rate	5/15 (33%)	6/7 (86%)	8/28 (29%)
First incidence (days)	176	72	337
Poly-3 test		P<0.001	P=0.338N
Poly-3 test			P<0.001N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Evaluation of PCB 126

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
All Organs: Benign or Malignant Neoplasms			
Overall rate	49/53 (92%)	49/53 (92%)	44/50 (88%)
Adjusted rate	99.6%	97.6%	93.7%
Terminal rate	15/15 (100%)	7/7 (100%)	26/28 (93%)
First incidence (days)	176	72	328
Poly-3 test		P=0.504N	P=0.121N
Poly-3 test			P=0.313N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, brain, liver, lung, 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. 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 dose group is indicated by **N**.
[e] Pairwise comparison between the 1,000 ng/kg core and stop-exposure groups. A lower incidence in the stop-exposure group is indicated by **N**.
[f] Not applicable; no neoplasms in animal group
[g] 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	Hepatocholangioma	Hepatocellular Adenoma	Cholangiocarcinoma
Historical Incidence				
PCB 126	0/53	0/53	1/53	0/53
PCB 126/PCB 118 Mixture	0/53	0/53	2/53	0/53
PCB 126/PCB 153 Binary Mixture	0/53	0/53	0/53	0/53
PCB 153	0/53	0/53	0/53	0/53
PeCDF	0/53	0/53	1/53	0/53
TCDD	0/53	0/53	0/53	0/53
TEF Mixture	0/53	0/53	0/53	0/53
Overall Historical Incidence				
Total (%)	0/371	0/371	4/371 (1.1%)	0/371
Mean ± standard deviation			1.1% ± 1.5%	
Range			(0%-4%)	

[a] Data as of February 24, 2005

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

Study	Incidence in Controls	
	Cystic Keratinizing Epithelioma	Squamous Cell Carcinoma
Historical Incidence		
PCB 126	0/53	0/53
PCB 126/PCB 118 Mixture	0/53	0/53
PCB 126/PCB 153 Binary Mixture	0/53	0/53
PCB 153	0/52	0/52
PeCDF	0/53	0/53
TCDD	0/53	0/53
TEF Mixture	0/53	0/53
Overall Historical Incidence		
Total	0/370	0/370

[a] Data as of February 24, 2005

TABLE A4c
Historical Incidence of Gingival Squamous Cell Carcinoma of the Oral Mucosa in Vehicle Control Female Sprague-Dawley Rats[a]

Study	Incidence in Controls
Historical Incidence	
PCB 126	0/53
PCB 126/PCB 118 Mixture	1/53
PCB 126/PCB 153 Binary Mixture	0/53
PCB 153	0/53
PeCDF	1/53
TCDD	1/53
TEF Mixture	1/53
Overall Historical Incidence	
Total (%)	4/371 (1.1%)
Mean ± standard deviation	1.1% ± 1.0%
Range	0%-2%

[a] Data as of February 24, 2005

TABLE A4d
Historical Incidence of Adrenal Cortex Neoplasms in Vehicle Control Female Sprague-Dawley Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence			
PCB 126	0/52	0/52	0/52
PCB 126/PCB 118 Mixture	0/53	1/53	1/53
PCB 126/PCB 153 Binary Mixture	0/53	0/53	0/53
PCB 153	0/53	0/53	0/53
PeCDF	1/53	1/53	2/53
TCDD	1/53	0/53	1/53
TEF Mixture	0/52	0/52	0/52
Overall Historical Incidence			
Total (%)	2/369 (0.5%)	2/369 (0.5%)	4/369 (1.1%)
Mean ± standard deviation	0.5% ± 0.9%	0.5% ± 0.9%	1.1% ± 1.5%
Range	0%-2%	0%-2%	0%-4%

[a] Data as of February 24, 2005

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 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
Disposition Summary				
Animals initially in study	28	28	26	28
14-Week interim evaluation	10	10	9	10
31-Week interim evaluation	10	10	9	10
53-Week interim evaluation	8	8	8	8
Animals examined microscopically	28	28	26	28
14-Week Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Clear cell focus				
Inflammation	10 (100%)	9 (90%)	7 (78%)	10 (100%)
Mixed cell focus				
Mixed cell focus, multiple				
Hepatocyte, hypertrophy			3 (33%)	3 (30%)
Pancreas	(10)	(10)	(9)	(10)
Acinus, atrophy				
Endocrine System				
Adrenal cortex	(10)	(10)	(9)	(10)
Hypertrophy	3 (30%)			
Vacuolization cytoplasmic				1 (10%)
Pituitary gland	(10)			
Cyst	1 (10%)			
Thyroid gland	(10)	(2)	(4)	(3)
Follicular cell, hypertrophy		2 (100%)	4 (100%)	3 (100%)
Genital System				
Ovary	(10)	(10)	(9)	(10)
Atrophy	1 (10%)			
Uterus	(10)			
Metaplasia, squamous				
Endometrium, hyperplasia, cystic				
Hematopoietic System				
Spleen	(10)			
Pigmentation	9 (90%)			
Thymus	(10)	(10)	(9)	(10)
Atrophy				
Cyst				

[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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Disposition Summary				
Animals initially in study	28	28	28	28
14-Week interim evaluation	10	10	10	10
31-Week interim evaluation	10	10	10	10
53-Week interim evaluation	8	8	8	8
Animals examined microscopically	28	28	28	28
14-Week Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Clear cell focus		1 (10%)		
Inflammation	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Mixed cell focus	1 (10%)			
Mixed cell focus, multiple			1 (10%)	
Hepatocyte, hypertrophy	3 (30%)	6 (60%)	10 (100%)	10 (100%)
Pancreas	(10)	(10)		
Acinus, atrophy		1 (10%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hypertrophy				1 (10%)
Vacuolization cytoplasmic				
Pituitary gland				(10)
Cyst				
Thyroid gland	(3)	(4)	(5)	(10)
Follicular cell, hypertrophy	3 (100%)	4 (100%)	5 (100%)	3 (30%)
Genital System				
Ovary	(10)	(10)	(10)	(10)
Atrophy	1 (10%)	2 (20%)	3 (30%)	6 (60%)
Uterus				(10)
Metaplasia, squamous				2 (20%)
Endometrium, hyperplasia, cystic				1 (10%)
Hematopoietic System				
Spleen				(10)
Pigmentation				10 (100%)
Thymus	(10)	(10)	(10)	(10)
Atrophy				5 (50%)
Cyst	1 (10%)			

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
14-Week Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(9)	(10)
Hemorrhage	1 (10%)			3 (30%)
Inflammation, chronic active				
Systems Examined with No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
31-Week Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Basophilic focus				1 (10%)
Cholangiofibrosis				
Clear cell focus		1 (10%)		
Degeneration, cystic		1 (10%)		
Fatty change, diffuse				
Hepatocyte, multinucleated				
Inflammation	7 (70%)	10 (100%)	9 (100%)	10 (100%)
Mixed cell focus		2 (20%)	2 (22%)	3 (30%)
Mixed cell focus, multiple				
Necrosis				1 (10%)
Pigmentation				3 (30%)
Toxic hepatopathy				
Hepatocyte, hypertrophy		3 (30%)	4 (44%)	6 (60%)
Pancreas	(10)	(10)	(9)	(10)
Basophilic focus				
Inflammation, chronic active				
Acinus, atrophy				
Endocrine System				
Adrenal cortex	(10)	(10)	(9)	(10)
Angiectasis		1 (10%)		
Degeneration, cystic				
Hyperplasia			1 (11%)	1 (10%)
Hypertrophy	2 (20%)	3 (30%)	2 (22%)	3 (30%)
Adrenal medulla	(10)			
Hyperplasia	1 (10%)			
Thyroid gland	(10)	(3)	(3)	(5)
Follicular cell, hypertrophy		3 (100%)	3 (100%)	5 (100%)

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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
14-Week Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)		
Inflammation, chronic active	1 (10%)			
Systems Examined with No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
31-Week Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus				
Cholangiofibrosis		1 (10%)	1 (10%)	
Clear cell focus		1 (10%)		
Degeneration, cystic				
Fatty change, diffuse				1 (10%)
Hepatocyte, multinucleated			2 (20%)	8 (80%)
Inflammation	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Mixed cell focus	1 (10%)	1 (10%)	2 (20%)	2 (20%)
Mixed cell focus, multiple	2 (20%)	1 (10%)	1 (10%)	4 (40%)
Necrosis			1 (10%)	2 (20%)
Pigmentation	5 (50%)	8 (80%)	8 (80%)	10 (100%)
Toxic hepatopathy				10 (100%)
Hepatocyte, hypertrophy	6 (60%)	8 (80%)	10 (100%)	10 (100%)
Pancreas	(10)	(10)	(10)	(10)
Basophilic focus		1 (10%)		
Inflammation, chronic active				1 (10%)
Acinus, atrophy				1 (10%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Angiectasis				
Degeneration, cystic	1 (10%)			
Hyperplasia				1 (10%)
Hypertrophy	2 (20%)	4 (40%)		4 (40%)
Adrenal medulla			(1)	(10)
Hyperplasia				
Thyroid gland	(6)	(5)	(5)	(10)
Follicular cell, hypertrophy	6 (100%)	5 (100%)	5 (100%)	7 (70%)

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
31-Week Interim Evaluation (continued)				
Genital System				
Ovary	(10)	(10)	(9)	(10)
Atrophy	8 (80%)	8 (80%)	4 (44%)	10 (100%)
Uterus	(10)			(1)
Inflammation, suppurative	1 (10%)			
Metaplasia, squamous	5 (50%)			
Endometrium, hyperplasia, cystic	1 (10%)			1 (100%)
Hematopoietic System				
Spleen	(10)			
Hematopoietic cell proliferation				
Pigmentation	10 (100%)			
Thymus	(10)	(10)	(9)	(10)
Atrophy	2 (20%)	3 (30%)	1 (11%)	3 (30%)
Respiratory System				
Lung	(10)	(10)	(9)	(10)
Infiltration cellular, histiocyte	2 (20%)	3 (30%)	2 (22%)	3 (30%)
Alveolar epithelium, metaplasia, bronchiolar				
Systems Examined with No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
53-Week Interim Evaluation				
Alimentary System				
Liver	(8)	(8)	(8)	(8)
Basophilic focus	2 (25%)	2 (25%)		1 (13%)
Cholangiofibrosis				1 (13%)
Clear cell focus				
Clear cell focus, multiple				
Eosinophilic focus				
Eosinophilic focus, multiple				
Fatty change, diffuse				
Fatty change, focal				
Hepatocyte, multinucleated				
Inflammation	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Mixed cell focus	3 (38%)	3 (38%)	1 (13%)	
Mixed cell focus, multiple	1 (13%)	2 (25%)	2 (25%)	6 (75%)
Necrosis	1 (13%)			
Pigmentation			3 (38%)	8 (100%)
Toxic hepatopathy				

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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
31-Week Interim Evaluation (continued)				
Genital System				
Ovary	(10)	(10)	(10)	(10)
Atrophy	9 (90%)	10 (100%)	7 (70%)	4 (40%)
Uterus	(1)			(10)
Inflammation, suppurative	1 (100%)			1 (10%)
Metaplasia, squamous	1 (100%)			4 (40%)
Endometrium, hyperplasia, cystic	1 (100%)			
Hematopoietic System				
Spleen			(1)	(10)
Hematopoietic cell proliferation			1 (100%)	
Pigmentation				10 (100%)
Thymus	(10)	(10)	(10)	(10)
Atrophy	3 (30%)	3 (30%)	8 (80%)	10 (100%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Infiltration cellular, histiocyte	1 (10%)	1 (10%)	1 (10%)	4 (40%)
Alveolar epithelium, metaplasia, bronchiolar		1 (10%)		2 (20%)
Systems Examined with No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
53-Week Interim Evaluation				
Alimentary System				
Liver	(8)	(8)	(8)	(8)
Basophilic focus	2 (25%)		1 (13%)	2 (25%)
Cholangiofibrosis			1 (13%)	
Clear cell focus		1 (13%)	1 (13%)	
Clear cell focus, multiple		1 (13%)		
Eosinophilic focus	1 (13%)			
Eosinophilic focus, multiple	1 (13%)		1 (13%)	3 (38%)
Fatty change, diffuse	2 (25%)		1 (13%)	8 (100%)
Fatty change, focal			1 (13%)	
Hepatocyte, multinucleated		1 (13%)	3 (38%)	8 (100%)
Inflammation	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Mixed cell focus	3 (38%)	2 (25%)	1 (13%)	
Mixed cell focus, multiple	3 (38%)	4 (50%)	7 (88%)	8 (100%)
Necrosis			1 (13%)	
Pigmentation	7 (88%)	8 (100%)	8 (100%)	8 (100%)
Toxic hepatopathy	1 (13%)		4 (50%)	8 (100%)

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
53-Week Interim Evaluation (continued)				
Alimentary System (continued)				
Liver (continued)	(8)	(8)	(8)	(8)
Vacuolization cytoplasmic				
Bile duct, cyst				
Bile duct, hyperplasia				
Hepatocyte, hypertrophy		3 (38%)	2 (25%)	5 (63%)
Pancreas	(8)	(8)	(7)	(8)
Inflammation, chronic active				
Acinus, atrophy				
Acinus, vacuolization cytoplasmic				
Endocrine System				
Adrenal cortex	(8)	(8)	(8)	(8)
Atrophy				
Degeneration, cystic				
Hyperplasia		1 (13%)	1 (13%)	3 (38%)
Hypertrophy	5 (63%)	6 (75%)	3 (38%)	3 (38%)
Vacuolization cytoplasmic				1 (13%)
Pituitary gland	(8)			
Pars distalis, hyperplasia	2 (25%)			
Thyroid gland	(8)	(3)	(1)	(3)
C-cell, hyperplasia	2 (25%)			
Follicular cell, hypertrophy	1 (13%)	3 (100%)	1 (100%)	3 (100%)
Genital System				
Ovary	(8)	(8)	(8)	(8)
Atrophy	8 (100%)	7 (88%)	7 (88%)	8 (100%)
Cyst		1 (13%)		
Uterus	(8)		(2)	
Inflammation, suppurative	3 (38%)		2 (100%)	
Metaplasia, squamous	8 (100%)		1 (50%)	
Cervix, cyst				
Endometrium, hyperplasia, cystic			2 (100%)	
Hematopoietic System				
Spleen	(8)			
Infarct				
Pigmentation	8 (100%)			
Thymus	(8)	(8)	(8)	(8)
Atrophy	7 (88%)	5 (63%)	6 (75%)	5 (63%)
Integumentary System				
Mammary gland	(8)			(1)
Galactocele	1 (13%)			
Hyperplasia				

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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
53-Week Interim Evaluation (continued)				
Alimentary System (continued)				
Liver (continued)	(8)	(8)	(8)	(8)
Vacuolization cytoplasmic				1 (13%)
Bile duct, cyst		1 (13%)		
Bile duct, hyperplasia		1 (13%)	4 (50%)	6 (75%)
Hepatocyte, hypertrophy	6 (75%)	7 (88%)	8 (100%)	8 (100%)
Pancreas	(8)	(8)	(8)	(8)
Inflammation, chronic active		1 (13%)		1 (13%)
Acinus, atrophy		1 (13%)		1 (13%)
Acinus, vacuolization cytoplasmic			1 (13%)	6 (75%)
Endocrine System				
Adrenal cortex	(8)	(8)	(8)	(8)
Atrophy				1 (13%)
Degeneration, cystic		1 (13%)		2 (25%)
Hyperplasia	1 (13%)	1 (13%)	2 (25%)	3 (38%)
Hypertrophy	1 (13%)	4 (50%)	5 (63%)	5 (63%)
Vacuolization cytoplasmic	1 (13%)			
Pituitary gland				(8)
Pars distalis, hyperplasia				
Thyroid gland	(3)	(3)	(2)	(8)
C-cell, hyperplasia				
Follicular cell, hypertrophy	3 (100%)	3 (100%)	2 (100%)	5 (63%)
Genital System				
Ovary	(8)	(8)	(8)	(8)
Atrophy	6 (75%)	8 (100%)	7 (88%)	7 (88%)
Cyst			1 (13%)	1 (13%)
Uterus		(2)		(8)
Inflammation, suppurative		2 (100%)		1 (13%)
Metaplasia, squamous		2 (100%)		7 (88%)
Cervix, cyst				1 (13%)
Endometrium, hyperplasia, cystic		1 (50%)		1 (13%)
Hematopoietic System				
Spleen			(1)	(8)
Infarct			1 (100%)	
Pigmentation			1 (100%)	8 (100%)
Thymus	(7)	(8)	(8)	(7)
Atrophy	5 (71%)	7 (88%)	8 (100%)	7 (100%)
Integumentary System				
Mammary gland	(2)		(1)	(8)
Galactocele				
Hyperplasia				1 (13%)

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg
53-Week Interim Evaluation				
Respiratory System				
Lung	(8)	(8)	(8)	(8)
Infiltration cellular, histiocyte	3 (38%)	4 (50%)	6 (75%)	5 (63%)
Inflammation, chronic active	1 (13%)			1 (13%)
Alveolar epithelium, metaplasia, bronchiolar				
Interstitium, inflammation				
Systems Examined with No Lesions Observed				
Cardiovascular System				
General Body 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 126

	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
53-Week Interim Evaluation				
Respiratory System				
Lung	(8)	(8)	(8)	(8)
Infiltration cellular, histiocyte	4 (50%)	2 (25%)	3 (38%)	6 (75%)
Inflammation, chronic active				
Alveolar epithelium, metaplasia, bronchiolar	1 (13%)	1 (13%)	2 (25%)	6 (75%)
Interstitium, inflammation	1 (13%)			
Systems Examined with No Lesions Observed				
Cardiovascular System				
General Body 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 126[a]

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Disposition Summary							
Animals initially in study	53	55	53	53	53	53	53
Early deaths							
Accidental deaths	3	3		1	1		
Moribund	25	18	21	19	27	18	34
Natural deaths	10	9	6	11	9	12	12
Survivors							
Died last week of study		1	1				
Terminal sacrifice	15	24	25	22	16	23	7
Animals examined microscopically	53	55	53	53	53	53	53
Alimentary System							
Esophagus	(52)	(55)	(53)	(53)	(53)	(52)	(52)
Cyst							1 (2%)
Hemorrhage						1 (2%)	
Hyperplasia, focal, squamous			1 (2%)				
Muscularis, degeneration					1 (2%)		
Muscularis, inflammation	2 (4%)	1 (2%)		1 (2%)	1 (2%)	2 (4%)	1 (2%)
Periesophageal tissue, inflammation, suppurative					1 (2%)		
Intestine large, colon	(52)	(55)	(53)	(53)	(53)	(51)	(53)
Hyperplasia, adenomatous			1 (2%)				
Inflammation			1 (2%)				
Parasite metazoan		1 (2%)	2 (4%)	1 (2%)			1 (2%)
Intestine large, rectum	(52)	(55)	(53)	(52)	(53)	(52)	(53)
Infiltration cellular, lymphocyte			1 (2%)				
Inflammation, chronic active				1 (2%)			
Mineralization		1 (2%)					
Parasite metazoan	2 (4%)	2 (4%)	3 (6%)		1 (2%)		1 (2%)
Artery, inflammation, chronic active				1 (2%)			
Intestine large, cecum	(52)	(54)	(53)	(51)	(53)	(52)	(53)
Edema		1 (2%)					
Hyperplasia, lymphoid					1 (2%)		
Inflammation		1 (2%)					
Intestine small, duodenum	(52)	(55)	(52)	(53)	(53)	(51)	(53)
Erosion	1 (2%)						2 (4%)
Ulcer							1 (2%)
Epithelium, hyperplasia							1 (2%)
Intestine small, ileum	(52)	(54)	(52)	(51)	(53)	(52)	(50)
Hyperplasia, lymphoid					1 (2%)		
Mineralization		1 (2%)					
Epithelium, hyperplasia				1 (2%)			
Serosa, inflammation, chronic active	1 (2%)						
Intestine small, jejunum	(52)	(54)	(53)	(53)	(53)	(51)	(53)
Hyperplasia, lymphoid							1 (2%)
Liver	(53)	(55)	(53)	(53)	(53)	(51)	(53)
Angiectasis	3 (6%)	8 (15%)	4 (8%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Basophilic focus	2 (4%)	4 (7%)	6 (11%)	7 (13%)	2 (4%)	3 (6%)	2 (4%)
Basophilic focus, multiple	5 (9%)	6 (11%)	4 (8%)	6 (11%)	2 (4%)	2 (4%)	3 (6%)
Cholangiofibrosis		1 (2%)	1 (2%)	1 (2%)	3 (6%)	13 (25%)	22 (42%)

[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 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Alimentary System (continued)							
Liver (continued)	(53)	(55)	(53)	(53)	(53)	(51)	(53)
Clear cell focus	1 (2%)	1 (2%)					
Clear cell focus, multiple	1 (2%)						
Cytoplasmic alteration			1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Degeneration, cystic					1 (2%)	1 (2%)	2 (4%)
Eosinophilic focus	6 (11%)	4 (7%)	7 (13%)	4 (8%)	2 (4%)	3 (6%)	6 (11%)
Eosinophilic focus, multiple	5 (9%)	6 (11%)	6 (11%)	17 (32%)	15 (28%)	21 (41%)	11 (21%)
Fatty change, diffuse	5 (9%)	7 (13%)	14 (26%)	22 (42%)	30 (57%)	45 (88%)	47 (89%)
Fatty change, focal	2 (4%)	6 (11%)	8 (15%)	6 (11%)	3 (6%)	2 (4%)	
Hematopoietic cell proliferation						1 (2%)	
Hepatocyte, multinucleated		2 (4%)	10 (19%)	14 (26%)	19 (36%)	46 (90%)	49 (92%)
Hepatodiaphragmatic nodule	1 (2%)	1 (2%)		1 (2%)			1 (2%)
Hyperplasia, nodular				1 (2%)	3 (6%)	26 (51%)	39 (74%)
Inflammation	36 (68%)	40 (73%)	49 (92%)	50 (94%)	51 (96%)	51 (100%)	51 (96%)
Mixed cell focus	4 (8%)	6 (11%)	7 (13%)	3 (6%)		3 (6%)	4 (8%)
Mixed cell focus, multiple	17 (32%)	18 (33%)	25 (47%)	29 (55)%)	30 (57%)	26 (51)%)	5 (9%)
Necrosis	4 (8%)	2 (4%)	5 (9%)	8 (15%)	11 (21%)	15 (29%)	17 (32%)
Pigmentation	1 (2%)	11 (20%)	41 (77%)	39 (74%)	48 (91%)	51 (100%)	48 (91%)
Toxic hepatopathy		6 (11%)	22 (42%)	27 (51%)	39 (74%)	51 (100%)	49 (92%)
Vacuolization cytoplasmic		1 (2%)					
Artery, inflammation, chronic active				1 (2%)	1 (2%)	1 (2%)	
Bile duct, cyst	3 (6%)	6 (11%)		2 (4%)	3 (6%)	8 (16%)	12 (23%)
Bile duct, fibrosis	4 (8%)	4 (7%)	3 (6%)	2 (4%)	1 (2%)	4 (8%)	5 (9%)
Bile duct, hyperplasia	3 (6%)	7 (13%)	7 (13%)	13 (25%)	14 (26%)	45 (88%)	45 (85%)
Bile duct, inflammation							1 (2%)
Hepatocyte, degeneration	3 (6%)	1 (2%)	1 (2%)		1 (2%)	1 (2%)	7 (13%)
Hepatocyte, hypertrophy		23 (42%)	32 (60%)	36 (68%)	42 (79%)	50 (98%)	49 (92%)
Oval cell, hyperplasia		1 (2%)	6 (11%)	7 (13%)	10 (19%)	38 (75%)	40 (75%)
Portal, fibrosis					2 (4%)	1 (2%)	10 (19%)
Serosa, inflammation		1 (2%)					1 (2%)
Mesentery	(1)		(4)	(2)	(7)	(13)	(11)
Inflammation, chronic active	1 (100%)						3 (27%)
Artery, inflammation, chronic active			2 (50%)	2 (100%)	6 (86%)	10 (77%)	7 (64%)
Fat, necrosis			1 (25%)		1 (14%)	1 (8%)	1 (9%)
Oral mucosa	(1)	(1)	(3)	(4)	(2)	(6)	(11)
Gingival, cyst, squamous							1 (9%)
Gingival, hyperplasia, squamous	1 (100%)		2 (67%)	2 (50%)		4 (67%)	3 (27%)
Pancreas	(51)	(55)	(53)	(53)	(53)	(52)	(51)
Basophilic focus		1 (2%)		1 (2%)			
Cyst						1 (2%)	1 (2%)
Inflammation, chronic active	5 (10%)	1 (2%)	3 (6%)	4 (8%)	4 (8%)	6 (12%)	13 (25%)
Necrosis							1 (2%)
Acinus, atrophy	5 (10%)	3 (5%)	2 (4%)	7 (13%)	2 (4%)	11 (21%)	18 (35%)
Acinus, hyperplasia		1 (2%)	1 (2%)	1 (2%)	1 (2%)		
Acinus, vacuolization cytoplasmic			1 (2%)	4 (8%)	9 (17%)	20 (38%)	23 (45%)
Artery, inflammation, chronic active		4 (7%)	2 (4%)	4 (8%)	8 (15%)	15 (29%)	11 (22%)
Artery, mineralization		1 (2%)				1 (2%)	
Duct, dilatation							2 (4%)
Duct, hyperplasia						1 (2%)	1 (2%)
Duct, inflammation, chronic active						2 (4%)	

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Alimentary System (continued)							
Salivary glands	(51)	(54)	(53)	(51)	(52)	(51)	(51)
Atrophy				1 (2%)	1 (2%)		
Cyst		1 (2%)			1 (2%)		
Inflammation, acute					1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)				1 (2%)		
Stomach, forestomach	(52)	(55)	(53)	(53)	(53)	(51)	(53)
Edema	1 (2%)		1 (2%)		1 (2%)		
Erosion		1 (2%)					
Hyperkeratosis		3 (5%)	1 (2%)	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, squamous	3 (6%)	4 (7%)	6 (11%)	2 (4%)	5 (9%)	6 (12%)	8 (15%)
Inflammation, acute	1 (2%)						
Inflammation, chronic active		1 (2%)	2 (4%)	1 (2%)	1 (2%)		
Mineralization	1 (2%)		1 (2%)	1 (2%)		1 (2%)	2 (4%)
Necrosis, focal			1 (2%)				
Ulcer	3 (6%)	1 (2%)		1 (2%)	3 (6%)	2 (4%)	2 (4%)
Stomach, glandular	(51)	(53)	(53)	(53)	(53)	(51)	(53)
Erosion	1 (2%)	1 (2%)		1 (2%)			
Inflammation, chronic active							1 (2%)
Metaplasia, focal			1 (2%)				
Mineralization	1 (2%)	1 (2%)		1 (2%)			1 (2%)
Artery, inflammation, chronic active							1 (2%)
Glands, ectasia							1 (2%)
Glands, hyperplasia							1 (2%)
Tooth	(12)	(12)	(10)	(9)	(10)	(9)	(19)
Peridontal tissue, fibrosis							1 (5%)
Peridontal tissue, inflammation, chronic active	2 (17%)					1 (11%)	
Peridontal tissue, inflammation, suppurative	10 (83%)	12 (100%)	10 (100%)	9 (100%)	10 (100%)	8 (89%)	18 (95%)
Cardiovascular System							
Blood vessel	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Aorta, mineralization	3 (6%)	1 (2%)	1 (2%)			2 (4%)	
Heart	(52)	(54)	(53)	(53)	(53)	(51)	(51)
Cardiomyopathy	9 (17%)	16 (30%)	17 (32%)	16 (30%)	24 (45%)	28 (55)%	32 (63%)
Degeneration	1 (2%)	1 (2%)				1 (2%)	
Inflammation		1 (2%)					
Mineralization	1 (2%)	1 (2%)				1 (2%)	
Thrombosis	1 (2%)					1 (2%)	1 (2%)
Artery, inflammation, chronic active				1 (2%)			
Endocardium, myocardium, inflammation, acute							1 (2%)
Epicardium, inflammation, chronic active					1 (2%)		1 (2%)
Epicardium, inflammation, suppurative	2 (4%)			1 (2%)			
Myocardium, inflammation					1 (2%)	1 (2%)	

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Endocrine System							
Adrenal cortex	(52)	(55)	(53)	(53)	(53)	(52)	(53)
Angiectasis	11 (21%)	13 (24%)	25 (47%)	19 (36%)	20 (38%)	8 (15%)	1 (2%)
Atrophy	1 (2%)	3 (5%)	5 (9%)	3 (6%)	5 (9%)	19 (37%)	30 (57%)
Degeneration, cystic	11 (21%)	14 (25%)	10 (19%)	14 (26%)	14 (26%)	16 (31%)	10 (19%)
Hyperplasia	23 (44%)	21 (38%)	27 (51%)	25 (47%)	25 (47%)	31 (60%)	24 (45%)
Hypertrophy	34 (65%)	41 (75%)	40 (75%)	41 (77%)	40 (75%)	41 (79%)	41 (77%)
Inflammation, suppurative			1 (2%)				
Mineralization	1 (2%)					1 (2%)	1 (2%)
Necrosis	1 (2%)	1 (2%)		1 (2%)	1 (2%)	1 (2%)	2 (4%)
Thrombosis						1 (2%)	
Vacuolization cytoplasmic	5 (10%)	3 (5%)	5 (9%)	2 (4%)	9 (17%)	4 (8%)	17 (32%)
Adrenal medulla	(52)	(55)	(53)	(53)	(53)	(52)	(53)
Angiectasis			2 (4%)	1 (2%)	2 (4%)	2 (4%)	
Hyperplasia	8 (15%)	18 (33%)	11 (21%)	11 (21%)	12 (23%)	6 (12%)	1 (2%)
Necrosis				1 (2%)			
Islets, pancreatic	(52)	(54)	(53)	(53)	(53)	(52)	(51)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	1 (2%)		1 (2%)	
Parathyroid gland	(47)	(50)	(48)	(46)	(49)	(47)	(46)
Hyperplasia		1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)	
Pituitary gland	(51)	(54)	(53)	(53)	(53)	(53)	(53)
Angiectasis	14 (27%)	15 (28%)	22 (42%)	12 (23%)	16 (30%)	19 (36%)	9 (17%)
Cyst		3 (6%)	1 (2%)	1 (2%)		2 (4%)	1 (2%)
Cytoplasmic alteration		1 (2%)	1 (2%)	1 (2%)	3 (6%)	1 (2%)	
Inflammation, focal, granulomatous						1 (2%)	
Necrosis					1 (2%)		
Pigmentation					1 (2%)		
Vacuolization cytoplasmic		1 (2%)	1 (2%)				
Pars distalis, hyperplasia	18 (35%)	20 (37%)	23 (43%)	17 (32%)	21 (40%)	26 (49%)	17 (32%)
Thyroid gland	(52)	(55)	(52)	(51)	(52)	(50)	(48)
Angiectasis		1 (2%)	4 (8%)				
Atrophy							1 (2%)
Infiltration cellular, lymphocyte							1 (2%)
Cyst				1 (2%)		1 (2%)	
C-cell, hyperplasia	12 (23%)	21 (38%)	17 (33%)	19 (37%)	18 (35%)	16 (32%)	19 (40%)
Follicle, cyst			1 (2%)				
Follicular cell, hyperplasia			1 (2%)	1 (2%)			1 (2%)
Follicular cell, hypertrophy	9 (17%)	13 (24%)	13 (25%)	17 (33%)	28 (54)%)	26 (52)%)	16 (33%)
General Body System							
None							
Genital System							
Clitoral gland	(50)	(55)	(52)	(50)	(53)	(52)	(51)
Hyperplasia		1 (2%)					
Hyperplasia, squamous			1 (2%)				
Inflammation	28 (56%)	36 (65%)	39 (75%)	28 (56%)	30 (57%)	27 (52)%)	22 (43%)
Duct, cyst	29 (58%)	32 (58%)	34 (65%)	37 (74%)	39 (74%)	42 (81%)	45 (88%)

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Genital System (continued)							
Ovary	(52)	(54)	(53)	(52)	(52)	(52)	(53)
Atrophy	45 (87%)	49 (91%)	46 (87%)	45 (87%)	47 (90%)	46 (88%)	33 (62%)
Cyst	12 (23%)	17 (31%)	17 (32%)	15 (29%)	16 (31%)	18 (35%)	11 (21%)
Inflammation, chronic active				1 (2%)	1 (2%)		
Inflammation, suppurative		1 (2%)				2 (4%)	
Necrosis					1 (2%)		
Artery, inflammation, chronic active			1 (2%)	1 (2%)			
Oviduct	(1)	(1)			(1)	(3)	(1)
Cyst						1 (33%)	
Inflammation, chronic active					1 (100%)		
Inflammation, suppurative	1 (100%)	1 (100%)				2 (67%)	1 (100%)
Uterus	(52)	(55)	(53)	(52)	(53)	(52)	(53)
Adenomyosis		1 (2%)		1 (2%)		2 (4%)	
Cyst		1 (2%)					
Erosion			1 (2%)				
Hemorrhage				1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active				2 (4%)	1 (2%)	1 (2%)	
Inflammation, granulomatous	1 (2%)						
Inflammation, suppurative	12 (23%)	12 (22%)	11 (21%)	16 (31%)	10 (19%)	6 (12%)	4 (8%)
Metaplasia, squamous	26 (50%)	33 (60%)	25 (47%)	28 (54%)	29 (55%)	27 (52%)	11 (21%)
Thrombosis				1 (2%)		1 (2%)	
Ulcer		1 (2%)					
Vacuolization cytoplasmic			2 (4%)				
Artery, inflammation, chronic active			1 (2%)			1 (2%)	
Cervix, cyst					1 (2%)		
Cervix, hyperplasia, stromal						1 (2%)	
Endometrium, hyperplasia, cystic	23 (44%)	33 (60%)	28 (53)%)	24 (46%)	26 (49%)	32 (62%)	9 (17%)
Epithelium, hyperplasia	1 (2%)			1 (2%)			
Epithelium, necrosis			1 (2%)	1 (2%)			
Vagina	(1)		(1)		(1)		(1)
Cyst							1 (100%)
Hematopoietic System							
Bone marrow	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Angiectasis						1 (2%)	
Atrophy							1 (2%)
Fibrosis			1 (2%)				
Hyperplasia	47 (89%)	37 (67%)	35 (66%)	44 (83%)	45 (85%)	46 (87%)	46 (87%)
Lymph node	(2)	(6)	(6)	(6)	(4)	(7)	(12)
Ectasia				1 (17%)			
Deep cervical, ectasia			1 (17%)				
Inguinal, hyperplasia, plasma cell			1 (17%)				
Inguinal, pigmentation			1 (17%)				
Lumbar, ectasia						2 (29%)	
Lumbar, hyperplasia						1 (14%)	
Lumbar, hyperplasia, lymphoid		1 (17%)					
Lumbar, hyperplasia, plasma cell				2 (33%)	1 (25%)		
Mediastinal, angiectasis							1 (8%)
Mediastinal, ectasia		2 (33%)	3 (50%)				5 (42%)
Mediastinal, hemorrhage			2 (33%)	1 (17%)	1 (25%)		6 (50%)
Mediastinal, hyperplasia, lymphoid					1 (25%)		1 (8%)

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Hematopoietic System (continued)							
Lymph node (continued)	(2)	(6)	(6)	(6)	(4)	(7)	(12)
Mediastinal, hyperplasia, plasma cell					1 (25%)	1 (14%)	
Mediastinal, inflammation, suppurative					1 (25%)		
Mediastinal, pigmentation							2 (17%)
Pancreatic, hemorrhage							1 (8%)
Pancreatic, hyperplasia, plasma cell						1 (14%)	
Lymph node, mandibular	(52)	(53)	(51)	(51)	(52)	(51)	(51)
Atrophy							1 (2%)
Ectasia	1 (2%)	1 (2%)	4 (8%)	4 (8%)	4 (8%)	4 (8%)	3 (6%)
Hemorrhage					1 (2%)		1 (2%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)	2 (4%)		1 (2%)
Hyperplasia, plasma cell	18 (35%)	24 (45%)	31 (61%)	21 (41%)	29 (56%)	11 (22%)	15 (29%)
Lymph node, mesenteric	(52)	(54)	(52)	(52)	(53)	(51)	(53)
Atrophy			1 (2%)				1 (2%)
Ectasia	1 (2%)					1 (2%)	1 (2%)
Hemorrhage	2 (4%)	3 (6%)		1 (2%)	1 (2%)		2 (4%)
Hyperplasia, histiocytic	3 (6%)					1 (2%)	1 (2%)
Hyperplasia, lymphoid							2 (4%)
Hyperplasia, plasma cell					1 (2%)		
Pigmentation						1 (2%)	
Spleen	(52)	(55)	(52)	(53)	(53)	(52)	(52)
Hematopoietic cell proliferation	39 (75%)	43 (78%)	46 (88%)	45 (85%)	41 (77%)	42 (81%)	37 (71%)
Hyperplasia, lymphoid			1 (2%)		1 (2%)	1 (2%)	3 (6%)
Necrosis		1 (2%)					
Pigmentation	49 (94%)	50 (91%)	51 (98%)	51 (96%)	52 (98%)	52 (100%)	50 (96%)
Lymphoid follicle, atrophy		5 (9%)	3 (6%)	2 (4%)	5 (9%)	3 (6%)	6 (12%)
Red pulp, atrophy			4 (8%)	1 (2%)	1 (2%)		2 (4%)
Thymus	(50)	(52)	(46)	(48)	(41)	(49)	(44)
Atrophy	37 (74%)	34 (65%)	41 (89%)	45 (94%)	36 (88%)	47 (96%)	41 (93%)
Fibrosis			1 (2%)				
Hemorrhage	1 (2%)	1 (2%)					
Inflammation	1 (2%)			1 (2%)			
Integumentary System							
Mammary gland	(52)	(55)	(53)	(53)	(53)	(52)	(53)
Cyst	8 (15%)	3 (5%)	1 (2%)	4 (8%)	5 (9%)	1 (2%)	1 (2%)
Fibrosis, focal					1 (2%)		
Hyperplasia	32 (62%)	33 (60%)	30 (57%)	29 (55)%)	21 (40%)	23 (44%)	9 (17%)
Inflammation, chronic active	1 (2%)			2 (4%)	2 (4%)		
Inflammation, granulomatous	2 (4%)	2 (4%)		1 (2%)			
Skin	(52)	(55)	(53)	(53)	(53)	(53)	(53)
Cyst, squamous	1 (2%)	1 (2%)					1 (2%)
Ulcer			1 (2%)				
Dermis, inflammation, focal	1 (2%)						
Subcutaneous tissue, inflammation, suppurative				1 (2%)			

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Musculoskeletal System							
Bone	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Inflammation, chronic active	1 (2%)						
Osteopetrosis			1 (2%)		2 (4%)		
Cartilage, hypertrophy, focal						1 (2%)	
Skeletal muscle	(1)	(1)	(1)				(1)
Inflammation, chronic active	1 (100%)						1 (100%)
Nervous System							
Brain	(53)	(55)	(53)	(53)	(53)	(53)	(53)
Hemorrhage						1 (2%)	1 (2%)
Hydrocephalus	1 (2%)		2 (4%)			1 (2%)	
Inflammation, focal, suppurative							1 (2%)
Necrosis, focal							1 (2%)
Respiratory System							
Lung	(53)	(55)	(53)	(53)	(53)	(51)	(51)
Congestion	1 (2%)	1 (2%)			1 (2%)		
Hemorrhage							1 (2%)
Infiltration cellular, histiocyte	41 (77%)	49 (89%)	45 (85%)	48 (91%)	45 (85%)	49 (96%)	42 (82%)
Inflammation, chronic active	5 (9%)	3 (5%)		1 (2%)	1 (2%)		2 (4%)
Inflammation, granulomatous	3 (6%)		2 (4%)				
Inflammation, suppurative						1 (2%)	
Metaplasia, squamous	1 (2%)		1 (2%)	2 (4%)	3 (6%)	9 (18%)	4 (8%)
Mineralization		1 (2%)	1 (2%)			1 (2%)	1 (2%)
Thrombosis		2 (4%)				1 (2%)	
Alveolar epithelium, hyperplasia	12 (23%)	1 (2%)		1 (2%)	2 (4%)		
Alveolar epithelium, metaplasia, bronchiolar		29 (53)%)	34 (64%)	41 (77%)	39 (74%)	47 (92%)	40 (78%)
Serosa, fibrosis			2 (4%)				
Serosa, inflammation, chronic active		1 (2%)					
Serosa, inflammation, suppurative	2 (4%)			1 (2%)	1 (2%)		
Squamous, metaplasia	1 (2%)		1 (2%)	2 (4%)	3 (6%)	9 (18%)	4 (8%)
Vein, thrombosis				1 (2%)			
Nose	(53)	(54)	(52)	(53)	(52)	(53)	(53)
Goblet cell, respiratory epithelium, hyperplasia							1 (2%)
Nasolacrimal duct, inflammation		1 (2%)		1 (2%)	1 (2%)		1 (2%)
Nasolacrimal duct, glands, hyperplasia						1 (2%)	
Nasolacrimal duct, respiratory epithelium, hyperplasia					1 (2%)		1 (2%)
Nasopharyngeal duct, inflammation, suppurative	1 (2%)		1 (2%)				
Nasopharyngeal duct, respiratory epithelium, hyperplasia							1 (2%)
Olfactory epithelium, inflammation, suppurative	1 (2%)		1 (2%)				
Respiratory epithelium, hyperplasia	2 (4%)		1 (2%)	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Respiratory epithelium, inflammation, suppurative			1 (2%)		1 (2%)	1 (2%)	
Respiratory epithelium, metaplasia	1 (2%)				1 (2%)		

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Respiratory System (continued)							
Nose (continued)	(53)	(54)	(52)	(53)	(52)	(53)	(53)
Turbinate, cyst						1 (2%)	1 (2%)
Turbinate, inflammation, suppurative	2 (4%)		1 (2%)	1 (2%)	2 (4%)		4 (8%)
Vomeronasal organ, vacuolization cytoplasmic							1 (2%)
Trachea	(53)	(55)	(53)	(53)	(53)	(52)	(52)
Inflammation	1 (2%)						
Peritracheal tissue, inflammation	1 (2%)						
Special Senses System							
Ear					(1)		
Inflammation					1 (100%)		
Eye	(51)	(55)	(53)	(53)	(53)	(52)	(52)
Atrophy			1 (2%)	1 (2%)			
Cataract					1 (2%)	1 (2%)	
Edema					1 (2%)		
Anterior chamber, inflammation, suppurative						1 (2%)	1 (2%)
Anterior chamber, ciliary body, cornea, inflammation, suppurative			1 (2%)				
Cornea, inflammation, suppurative						1 (2%)	2 (4%)
Optic nerve, degeneration							1 (2%)
Retina, atrophy			3 (6%)	1 (2%)		1 (2%)	4 (8%)
Retina, degeneration						1 (2%)	
Harderian gland	(53)	(53)	(53)	(53)	(53)	(52)	(52)
Inflammation	2 (4%)	3 (6%)	6 (11%)	6 (11%)	3 (6%)	3 (6%)	6 (12%)
Urinary System							
Kidney	(53)	(55)	(53)	(53)	(53)	(52)	(53)
Calculus microscopic observation only			1 (2%)	1 (2%)		1 (2%)	
Casts protein	4 (8%)	3 (5%)	1 (2%)	6 (11%)			2 (4%)
Cyst				2 (4%)			
Inflammation, chronic active	2 (4%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Inflammation, suppurative			3 (6%)			1 (2%)	2 (4%)
Mineralization	32 (60%)	39 (71%)	44 (83%)	44 (83%)	44 (83%)	39 (75%)	37 (70%)
Necrosis			1 (2%)		1 (2%)	1 (2%)	1 (2%)
Nephropathy	32 (60%)	29 (53%)	38 (72%)	35 (66%)	38 (72%)	42 (81%)	47 (89%)
Papilla, angiectasis					1 (2%)		
Papilla, necrosis							1 (2%)
Pelvis, dilatation	2 (4%)	1 (2%)				1 (2%)	2 (4%)
Pelvis, hemorrhage							1 (2%)
Pelvis, inflammation, chronic active		2 (4%)	2 (4%)	2 (4%)			1 (2%)
Pelvis, inflammation, suppurative	2 (4%)				3 (6%)		
Pelvis, metaplasia, squamous							1 (2%)
Renal tubule, accumulation, hyaline droplet		1 (2%)					
Renal tubule, dilatation				1 (2%)			
Transitional epithelium, hyperplasia	4 (8%)	2 (4%)	8 (15%)	4 (8%)	8 (15%)	8 (15%)	11 (21%)

TABLE A5b
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126

	Vehicle Control	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
Urinary System (continued)							
Ureter			(1)				(3)
Inflammation							1 (33%)
Metaplasia, squamous							2 (67%)
Mineralization			1 (100%)				2 (67%)
Transitional epithelium, hyperplasia			1 (100%)				3 (100%)
Urinary bladder	(51)	(54)	(53)	(52)	(52)	(52)	(53)
Edema				1 (2%)			
Hemorrhage				1 (2%)			
Inflammation	4 (8%)	6 (11%)	10 (19%)	6 (12%)	7 (13%)	4 (8%)	6 (11%)
Metaplasia, squamous							1 (2%)
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)	2 (4%)	2 (4%)

TABLE A5c
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)[a]

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Disposition Summary			
Animals initially in study	53	53	50
Early deaths			
Accidental deaths	3		1
Moribund	25	34	15
Natural deaths	10	12	6
Survivors			
Terminal sacrifice	15	7	28
Animals examined microscopically	53	53	50
Alimentary System			
Esophagus	(52)	(52)	(50)
Cyst		1 (2%)	
Muscularis, inflammation	2 (4%)		1 (2%)
Intestine large, colon	(52)	(53)	(50)
Parasite metazoan		1 (2%)	
Intestine large, rectum	(52)	(53)	(50)
Parasite metazoan	2 (4%)	1 (2%)	1 (2%)
Intestine small, duodenum	(52)	(53)	(50)
Erosion	1 (2%)	2 (4%)	
Ulcer		1 (2%)	
Epithelium, hyperplasia		1 (2%)	
Intestine small, ileum	(52)	(53)	(50)
Serosa, inflammation, chronic active	1 (2%)		
Intestine small, jejunum	(52)	(53)	(50)
Hyperplasia, lymphoid		1 (2%)	
Liver	(53)	(53)	(50)
Angiectasis	3 (6%)	2 (4%)	8 (16%)
Basophilic focus	2 (4%)	2 (4%)	7 (14%)
Basophilic focus, multiple	5 (9%)	3 (6%)	9 (18%)
Cholangiofibrosis		22 (42%)	1 (2%)
Clear cell focus	1 (2%)		1 (2%)
Clear cell focus, multiple	1 (2%)		4 (8%)
Cytoplasmic alteration		1 (2%)	
Degeneration, cystic		2 (4%)	3 (6%)
Eosinophilic focus	6 (11%)	6 (11%)	3 (6%)
Eosinophilic focus, multiple	5 (9%)	11 (21%)	9 (18%)
Fatty change, diffuse	5 (9%)	47 (89%)	12 (24%)
Fatty change, focal	2 (4%)		11 (22%)
Hepatocyte, multinucleated		49 (92%)	20 (40%)
Hepatodiaphragmatic nodule	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, nodular		39 (74%)	
Inflammation	36 (68%)	51 (96%)	46 (92%)
Mixed cell focus	4 (8%)	4 (8%)	1 (2%)
Mixed cell focus, multiple	17 (32%)	5 (9%)	35 (70%)
Multinucleated			1 (2%)
Necrosis	4 (8%)	17 (32%)	4 (8%)
Pigmentation	1 (2%)	48 (91%)	48 (96%)
Toxic hepatopathy		49 (92%)	15 (30%)

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

TABLE A5c
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Alimentary System (continued)			
Liver (continued)	(53)	(53)	(50)
Bile duct, cyst	3 (6%)	12 (23%)	5 (10%)
Bile duct, fibrosis	4 (8%)	5 (9%)	4 (8%)
Bile duct, hyperplasia	3 (6%)	45 (85%)	16 (32%)
Bile duct, inflammation		1 (2%)	
Hepatocyte, degeneration	3 (6%)	7 (13%)	
Hepatocyte, hypertrophy		49 (92%)	21 (42%)
Oval cell, hyperplasia		40 (75%)	1 (2%)
Portal, fibrosis		10 (19%)	
Serosa, inflammation		1 (2%)	
Mesentery	(1)	(11)	
Inflammation, chronic active	1 (100%)	3 (27%)	
Artery, inflammation, chronic active		7 (64%)	
Fat, necrosis		1 (9%)	
Oral mucosa	(1)	(11)	(6)
Gingival, cyst, squamous		1 (9%)	
Gingival, hyperplasia, squamous	1 (100%)	3 (27%)	3 (50%)
Pharyngeal, hyperplasia, squamous			1 (17%)
Pancreas	(51)	(51)	(48)
Basophilic focus			1 (2%)
Cyst		1 (2%)	
Inflammation, chronic active	5 (10%)	13 (25%)	4 (8%)
Necrosis		1 (2%)	
Acinus, atrophy	5 (10%)	18 (35%)	7 (15%)
Acinus, vacuolization cytoplasmic		23 (45%)	1 (2%)
Artery, inflammation, chronic active		11 (22%)	1 (2%)
Duct, dilatation		2 (4%)	
Duct, hyperplasia		1 (2%)	
Salivary glands	(51)	(51)	(49)
Atrophy			1 (2%)
Cyst			2 (4%)
Inflammation, acute		1 (2%)	
Inflammation, chronic active	1 (2%)		
Stomach, forestomach	(52)	(53)	(50)
Edema	1 (2%)		2 (4%)
Hyperkeratosis		2 (4%)	
Hyperplasia, squamous	3 (6%)	8 (15%)	2 (4%)
Inflammation, acute	1 (2%)		
Mineralization	1 (2%)	2 (4%)	
Ulcer	3 (6%)	2 (4%)	
Stomach, glandular	(51)	(53)	(50)
Erosion	1 (2%)		1 (2%)
Inflammation, chronic active		1 (2%)	
Mineralization	1 (2%)	1 (2%)	
Artery, inflammation, chronic active		1 (2%)	
Glands, ectasia		1 (2%)	
Glands, hyperplasia		1 (2%)	
Tooth	(12)	(19)	(12)
Peridontal tissue, fibrosis		1 (5%)	1 (8%)
Peridontal tissue, inflammation, chronic active	2 (17%)		
Peridontal tissue, inflammation, suppurative	10 (83%)	18 (95%)	11 (92%)

TABLE A5c
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Cardiovascular System			
Blood vessel	(53)	(53)	(50)
Aorta, mineralization	3 (6%)		1 (2%)
Heart	(52)	(51)	(50)
Cardiomyopathy	9 (17%)	32 (63%)	15 (30%)
Degeneration	1 (2%)		
Mineralization	1 (2%)		1 (2%)
Thrombosis	1 (2%)	1 (2%)	1 (2%)
Artery, inflammation, chronic active			1 (2%)
Endocardium, myocardium, inflammation, acute		1 (2%)	
Epicardium, inflammation, chronic active		1 (2%)	
Epicardium, inflammation, suppurative	2 (4%)		1 (2%)
Endocrine System			
Adrenal cortex	(52)	(53)	(50)
Angiectasis	11 (21%)	1 (2%)	14 (28%)
Atrophy	1 (2%)	30 (57%)	9 (18%)
Degeneration, cystic	11 (21%)	10 (19%)	20 (40%)
Hyperplasia	23 (44%)	24 (45%)	26 (52%)
Hypertrophy	34 (65%)	41 (77%)	42 (84%)
Inflammation, suppurative			1 (2%)
Mineralization	1 (2%)	1 (2%)	
Necrosis	1 (2%)	2 (4%)	2 (4%)
Vacuolization cytoplasmic	5 (10%)	17 (32%)	6 (12%)
Adrenal medulla	(52)	(53)	(50)
Hyperplasia	8 (15%)	1 (2%)	9 (18%)
Islets, pancreatic	(52)	(51)	(50)
Hyperplasia	1 (2%)		
Parathyroid gland	(47)	(46)	(44)
Cyst			1 (2%)
Hyperplasia			2 (5%)
Pituitary gland	(51)	(53)	(48)
Angiectasis	14 (27%)	9 (17%)	14 (29%)
Cyst		1 (2%)	1 (2%)
Cytoplasmic alteration			1 (2%)
Pars distalis, hyperplasia	18 (35%)	17 (32%)	17 (35%)
Thyroid gland	(52)	(48)	(47)
Angiectasis			1 (2%)
Atrophy		1 (2%)	
Infiltration cellular, lymphocyte		1 (2%)	
C-cell, hyperplasia	12 (23%)	19 (40%)	18 (38%)
Follicular cell, hyperplasia		1 (2%)	
Follicular cell, hypertrophy	9 (17%)	16 (33%)	22 (47%)
General Body System			
None			

TABLE A5c
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Genital System			
Clitoral gland	(50)	(51)	(48)
Inflammation	28 (56%)	22 (43%)	32 (67%)
Duct, cyst	29 (58%)	45 (88%)	39 (81%)
Ovary	(52)	(53)	(50)
Atrophy	45 (87%)	33 (62%)	47 (94%)
Cyst	12 (23%)	11 (21%)	17 (34%)
Oviduct	(1)	(1)	(2)
Inflammation, suppurative	1 (100%)	1 (100%)	2 (100%)
Uterus	(52)	(53)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic active			1 (2%)
Inflammation, granulomatous	1 (2%)		
Inflammation, suppurative	12 (23%)	4 (8%)	11 (22%)
Metaplasia, squamous	26 (50%)	11 (21%)	28 (56%)
Endometrium, hyperplasia, cystic	23 (44%)	9 (17%)	31 (62%)
Epithelium, hyperplasia	1 (2%)		1 (2%)
Vagina	(1)	(1)	
Cyst		1 (100%)	
Hematopoietic System			
Bone marrow	(53)	(53)	(50)
Atrophy		1 (2%)	
Hyperplasia	47 (89%)	46 (87%)	34 (68%)
Lymph node	(2)	(12)	(2)
Iliac, ectasia			1 (50%)
Mediastinal, angiectasis		1 (8%)	
Mediastinal, ectasia		5 (42%)	
Mediastinal, hemorrhage		6 (50%)	
Mediastinal, hyperplasia, lymphoid		1 (8%)	
Mediastinal, pigmentation		2 (17%)	
Pancreatic, hemorrhage		1 (8%)	
Lymph node, mandibular	(52)	(51)	(49)
Atrophy		1 (2%)	
Ectasia	1 (2%)	3 (6%)	3 (6%)
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Hyperplasia, plasma cell	18 (35%)	15 (29%)	21 (43%)
Lymph node, mesenteric	(52)	(53)	(50)
Atrophy		1 (2%)	2 (4%)
Ectasia	1 (2%)	1 (2%)	
Hemorrhage	2 (4%)	2 (4%)	
Hyperplasia, histiocytic	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		2 (4%)	
Hyperplasia, plasma cell			1 (2%)
Spleen	(52)	(52)	(50)
Hematopoietic cell proliferation	39 (75%)	37 (71%)	37 (74%)
Hyperplasia, lymphoid		3 (6%)	
Pigmentation	49 (94%)	50 (96%)	50 (100%)
Lymphoid follicle, atrophy		6 (12%)	4 (8%)
Red pulp, atrophy		2 (4%)	
Thymus	(50)	(44)	(43)
Atrophy	37 (74%)	41 (93%)	39 (91%)
Hemorrhage	1 (2%)		

TABLE A5c
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Integumentary System			
Mammary gland	(52)	(53)	(50)
Cyst	8 (15%)	1 (2%)	13 (26%)
Hyperplasia	32 (62%)	9 (17%)	22 (44%)
Skin	(52)	(53)	(50)
Cyst, squamous	1 (2%)	1 (2%)	2 (4%)
Dermis, inflammation, focal	1 (2%)		
Musculoskeletal System			
Skeletal muscle	(1)	(1)	
Inflammation, chronic active	1 (100%)	1 (100%)	
Nervous System			
Brain	(53)	(53)	(50)
Hemorrhage		1 (2%)	
Hydrocephalus	1 (2%)		
Inflammation, focal, suppurative		1 (2%)	
Necrosis, focal		1 (2%)	
Respiratory System			
Lung	(53)	(51)	(50)
Congestion	1 (2%)		
Hemorrhage		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	41 (77%)	42 (82%)	42 (84%)
Inflammation, chronic active	5 (9%)	2 (4%)	
Inflammation, granulomatous	3 (6%)		
Metaplasia, squamous	1 (2%)	4 (8%)	
Mineralization		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	12 (23%)		
Alveolar epithelium, metaplasia, bronchiolar		40 (78%)	32 (64%)
Serosa, inflammation, suppurative	2 (4%)		1 (2%)
Nose	(53)	(53)	(50)
Goblet cell, respiratory epithelium, hyperplasia		1 (2%)	
Nasolacrimal duct, inflammation		1 (2%)	1 (2%)
Nasolacrimal duct, respiratory epithelium, hyperplasia		1 (2%)	
Nasopharyngeal duct, respiratory epithelium, hyperplasia		1 (2%)	
Nasopharyngeal duct, inflammation, suppurative	1 (2%)		
Olfactory epithelium, inflammation, suppurative	1 (2%)		
Respiratory epithelium, hyperplasia	2 (4%)	1 (2%)	1 (2%)
Respiratory epithelium, metaplasia	1 (2%)		
Turbinate, cyst		1 (2%)	
Turbinate, inflammation, suppurative	2 (4%)	4 (8%)	1 (2%)
Vomeronasal organ, vacuolization cytoplasmic		1 (2%)	
Trachea	(53)	(52)	(50)
Inflammation	1 (2%)		
Peritracheal tissue, inflammation	1 (2%)		

TABLE A5c
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of PCB 126 (Stop-Exposure)

	Vehicle Control	1,000 ng/kg	1,000 ng/kg (Stop-Exposure)
Special Senses System			
Eye	(51)	(52)	(50)
Anterior chamber, inflammation, suppurative		1 (2%)	1 (2%)
Cornea, inflammation, suppurative		2 (4%)	1 (2%)
Optic nerve, degeneration		1 (2%)	
Retina, atrophy		4 (8%)	
Harderian gland	(53)	(52)	(50)
Inflammation	2 (4%)	6 (12%)	9 (18%)
Urinary System			
Kidney	(53)	(53)	(50)
Casts protein	4 (8%)	2 (4%)	3 (6%)
Inflammation, chronic active	2 (4%)		
Inflammation, suppurative		2 (4%)	
Mineralization	32 (60%)	37 (70%)	45 (90%)
Necrosis		1 (2%)	
Nephropathy	32 (60%)	47 (89%)	38 (76%)
Papilla, necrosis		1 (2%)	
Pelvis, dilatation	2 (4%)	2 (4%)	1 (2%)
Pelvis, hemorrhage		1 (2%)	
Pelvis, inflammation, chronic active		1 (2%)	1 (2%)
Pelvis, inflammation, suppurative	2 (4%)		
Pelvis, metaplasia, squamous		1 (2%)	
Transitional epithelium, hyperplasia	4 (8%)	11 (21%)	2 (4%)
Ureter		(3)	
Inflammation		1 (33%)	
Metaplasia, squamous		2 (67%)	
Mineralization		2 (67%)	
Transitional epithelium, hyperplasia		3 (100%)	
Urinary bladder	(51)	(53)	(50)
Inflammation	4 (8%)	6 (11%)	3 (6%)
Metaplasia, squamous		1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)	2 (4%)	

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 126[a]

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	9	10	10	10	10	10
Week 31	10	10	9	10	10	10	10	10
Week 53	8	8	8	8	8	8	8	8
Necropsy body wt								
Week 14	281 ± 4	280 ± 5	282 ± 6	274 ± 5	278 ± 3	280 ± 6	278 ± 4	262 ± 5*
Week 31	284 ± 8	303 ± 9	307 ± 10	293 ± 8	300 ± 9	289 ± 5	293 ± 11	285 ± 6
Week 53	313 ± 3	332 ± 7	307 ± 12	328 ± 11	334 ± 12	302 ± 7	306 ± 7	279 ± 7*
L. Kidney								
Week 14								
Absolute	0.801 ± 0.015	0.863 ± 0.019	0.865 ± 0.025	0.800 ± 0.016	0.899 ± 0.016**	0.826 ± 0.022	0.848 ± 0.024	0.799 ± 0.021
Relative	2.858 ± 0.069	3.082 ± 0.056	3.072 ± 0.084	2.922 ± 0.057	3.238 ± 0.058**	2.957 ± 0.049	3.050 ± 0.067	3.053 ± 0.070
Week 31								
Absolute	0.751 ± 0.024	0.843 ± 0.031	0.856 ± 0.027*	0.841 ± 0.019	0.853 ± 0.025*	0.803 ± 0.020	0.853 ± 0.042*	0.807 ± 0.019
Relative	2.646 ± 0.039	2.790 ± 0.085	2.796 ± 0.083	2.878 ± 0.045	2.855 ± 0.066	2.785 ± 0.058	2.917 ± 0.082*	2.831 ± 0.046
Week 53								
Absolute	0.994 ± 0.018	1.077 ± 0.023	0.983 ± 0.022	1.013 ± 0.033	0.996 ± 0.027	0.938 ± 0.021	0.968 ± 0.027	0.933 ± 0.031
Relative	3.175 ± 0.058	3.264 ± 0.108	3.214 ± 0.062	3.090 ± 0.059	3.004 ± 0.109	3.115 ± 0.075	3.168 ± 0.053	3.340 ± 0.082
Liver								
Week 14								
Absolute	8.424 ± 0.190	9.515 ± 0.244*	10.097 ± 0.672*	8.958 ± 0.264*	10.319 ± 0.317**	10.082 ± 0.329**	10.813 ± 0.353**	10.433 ± 0.288**
Relative	29.989 ± 0.438	34.021 ± 0.965**	35.756 ± 2.111**	32.604 ± 0.401**	37.079 ± 0.839**	36.007 ± 0.626**	38.882 ±1.049**	39.786 ± 0.540**
Week 31								
Absolute	7.018 ± 0.482	9.582 ± 0.373**	9.550 ± 0.439**	9.292 ± 0.302**	10.931 ± 0.635**	10.004 ± 0.276**	10.752 ± 0.737**	10.347 ± 0.337**
Relative	24.580 ± 1.265	31.619 ± 0.729**	31.019 ± 0.667**	31.723 ± 0.477**	36.342 ± 1.407**	34.713 ± 0.967**	36.507 ± 1.443**	36.245 ± 0.676**
Week 53								
Absolute	10.405 ± 0.399	11.394 ± 0.524	10.253 ± 0.306	11.162 ± 0.502	14.419 ± 1.694*	11.560 ± 0.486*	12.859 ± 0.473*	12.814 ± 0.839*
Relative	33.192 ± 1.090	34.399 ± 1.479	33.532 ± 0.960	33.996 ± 0.852	42.514 ± 3.530**	38.276 ± 1.306**	41.996 ± 0.755**	45.734 ± 2.374**

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	9	10	10	10	10	10
Week 31	10	10	9	10	10	10	10	10
Week 53	8	8	8	8	8	8	8	8
Necropsy body wt								
Week 14	281 ± 4	280 ± 5	282 ± 6	274 ± 5	278 ± 3	280 ± 6	278 ± 4	262 ± 5*
Week 31	284 ± 8	303 ± 9	307 ± 10	293 ± 8	300 ± 9	289 ± 5	293 ± 11	285 ± 6
Week 53	313 ± 3	332 ± 7	307 ± 12	328 ± 11	334 ± 12	302 ± 7	306 ± 7	279 ± 7*
Lung								
Week 14								
Absolute	1.784 ± 0.055	1.918 ± 0.066	1.931 ± 0.051	1.686 ± 0.046	1.924 ± 0.085	1.810 ± 0.067	1.810 ± 0.041	1.898 ± 0.086
Relative	6.354 ± 0.190	6.867 ± 0.280	6.879 ± 0.237	6.156 ± 0.160	6.919 ± 0.292	6.462 ± 0.153	6.508 ± 0.081	7.244 ± 0.297*
Week 31								
Absolute	1.716 ± 0.066	2.139 ± 0.064**	2.125 ± 0.084**	1.840 ± 0.078	2.096 ± 0.066**	1.907 ± 0.068	1.879 ± 0.067	2.074 ± 0.056**
Relative	6.057 ± 0.197	7.093 ± 0.194**	6.953 ± 0.300*	6.305 ± 0.265	7.014 ± 0.183*	6.608 ± 0.209	6.448 ± 0.175	7.278 ± 0.148**
Week 53								
Absolute	2.198 ± 0.080	2.081 ± 0.078	2.105 ± 0.129	2.274 ± 0.091	1.954 ± 0.114	2.010 ± 0.063	2.359 ± 0.180	2.865 ± 0.132**
Relative	7.030 ± 0.287	6.288 ± 0.229	6.841 ± 0.303	6.969 ± 0.319	5.935 ± 0.470	6.671 ± 0.206	7.726 ± 0.565	10.301 ± 0.542**
Ovary								
Week 14								
Absolute	0.072 ± 0.004	0.072 ± 0.005	0.078 ± 0.005	0.064 ± 0.004	0.068 ± 0.003	0.071 ± 0.005	0.062 ± 0.003	0.057 ± 0.004*
Relative	0.256 ± 0.013	0.254 ± 0.015	0.277 ± 0.018	0.233 ± 0.012	0.246 ± 0.010	0.254 ± 0.012	0.224 ± 0.011	0.215 ± 0.015
Week 31								
Absolute	0.055 ± 0.002	0.054 ± 0.003	0.059 ± 0.004	0.046 ± 0.002	0.048 ± 0.002[b]	0.050 ± 0.003	0.057 ± 0.005	0.053 ± 0.003
Relative	0.195 ± 0.008	0.177 ± 0.007	0.193 ± 0.009	0.160 ± 0.009	0.163 ± 0.005[b]	0.173 ± 0.009	0.194 ± 0.014	0.185 ± 0.011
Week 53								
Absolute	0.055 ± 0.003	0.062 ± 0.001[c]	0.060 ± 0.007	0.063 ± 0.004	0.071 ± 0.009	0.060 ± 0.004	0.061 ± 0.007	0.054 ± 0.004
Relative	0.174 ± 0.009	0.191 ± 0.004[c]	0.194 ± 0.020	0.191 ± 0.012	0.209 ± 0.019	0.198 ± 0.014	0.197 ± 0.019	0.194 ± 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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	9	10	10	10	10	10
Week 31	10	10	9	10	10	10	10	10
Week 53	8	8	8	8	8	8	8	8
Necropsy body wt								
Week 14	281 ± 4	280 ± 5	282 ± 6	274 ± 5	278 ± 3	280 ± 6	278 ± 4	262 ± 5*
Week 31	284 ± 8	303 ± 9	307 ± 10	293 ± 8	300 ± 9	289 ± 5	293 ± 11	285 ± 6
Week 53	313 ± 3	332 ± 7	307 ± 12	328 ± 11	334 ± 12	302 ± 7	306 ± 7	279 ± 7*
Spleen								
Week 14								
Absolute	0.572 ± 0.012	0.602 ± 0.014	0.596 ± 0.015[d]	0.563 ± 0.023	0.567 ± 0.020	0.554 ± 0.022	0.559 ± 0.011	0.498 ± 0.015**
Relative	2.041 ± 0.044	2.149 ± 0.044	2.126 ± 0.073[d]	2.055 ± 0.082	2.042 ± 0.070	1.978 ± 0.056	2.013 ± 0.035	1.901 ± 0.053
Week 31								
Absolute	0.516 ± 0.029	0.561 ± 0.030	0.563 ± 0.031	0.525 ± 0.019	0.511 ± 0.022	0.482 ± 0.016	0.448 ± 0.021[b]	0.458 ± 0.011
Relative	1.810 ± 0.073	1.852 ± 0.077	1.824 ± 0.047	1.797 ± 0.052	1.700 ± 0.038	1.673 ± 0.054	1.550 ± 0.036**[b]	1.609 ± 0.033**
Week 53								
Absolute	0.507 ± 0.019	0.553 ± 0.019	0.525 ± 0.016	0.527 ± 0.018	0.499 ± 0.016	0.456 ± 0.022	0.504 ± 0.018	0.467 ± 0.023
Relative	1.620 ± 0.059	1.668 ± 0.039	1.727 ± 0.085	1.611 ± 0.053	1.501 ± 0.048	1.514 ± 0.075	1.646 ± 0.038	1.665 ± 0.046
Thymus								
Week 14								
Absolute	0.277 ± 0.013	0.297 ± 0.024	0.274 ± 0.015	0.255 ± 0.017	0.301 ± 0.026	0.275 ± 0.014	0.276 ± 0.013	0.209 ± 0.018
Relative	0.989 ± 0.053	1.057 ± 0.079	0.975 ± 0.053	0.931 ± 0.063	1.079 ± 0.091	0.986 ± 0.048	0.999 ± 0.056	0.797 ± 0.069

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 126

	Vehicle Control	10 ng/kg	30 ng/kg	100 ng/kg	175 ng/kg	300 ng/kg	550 ng/kg	1,000 ng/kg
n								
Week 14	10	10	9	10	10	10	10	10
Week 31	10	10	9	10	10	10	10	10
Week 53	8	8	8	8	8	8	8	8
Necropsy body wt								
Week 14	281 ± 4	280 ± 5	282 ± 6	274 ± 5	278 ± 3	280 ± 6	278 ± 4	262 ± 5*
Week 31	284 ± 8	303 ± 9	307 ± 10	293 ± 8	300 ± 9	289 ± 5	293 ± 11	285 ± 6
Week 53	313 ± 3	332 ± 7	307 ± 12	328 ± 11	334 ± 12	302 ± 7	306 ± 7	279 ± 7*
Thyroid gland								
Week 14								
Absolute	0.021 ± 0.001	0.021 ± 0.001	0.024 ± 0.002	0.021 ± 0.001	0.021 ± 0.001	0.021 ± 0.001	0.020 ± 0.002	0.024 ± 0.002
Relative	0.077 ± 0.004	0.076 ± 0.004	0.085 ± 0.005	0.078 ± 0.004	0.076 ± 0.005	0.076 ± 0.004	0.071 ± 0.006	0.090 ± 0.007
Week 31								
Absolute	0.026 ± 0.002	0.028 ± 0.001	0.028 ± 0.002	0.030 ± 0.002	0.028 ± 0.002	0.027 ± 0.002	0.028 ± 0.003	0.026 ± 0.001
Relative	0.092 ± 0.005	0.094 ± 0.006	0.092 ± 0.005	0.101 ± 0.006	0.092 ± 0.005	0.095 ± 0.005	0.096 ± 0.009	0.092 ± 0.004
Week 53								
Absolute	0.029 ± 0.002	0.031 ± 0.002	0.031 ± 0.003	0.027 ± 0.002	0.027 ± 0.001	0.028 ± 0.002	0.030 ± 0.002	0.028 ± 0.002
Relative	0.092 ± 0.007	0.095 ± 0.007	0.101 ± 0.009	0.083 ± 0.004	0.080 ± 0.004	0.094 ± 0.007	0.097 ± 0.006	0.099 ± 0.006

* 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=9
[c] n=7
[d] n=8

APPENDIX C
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

PCB 126

PCB 126 was obtained from AccuStandard, Inc. (New Haven, CT), in one lot (130494) and was used in the 2-year study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Battelle Memorial Institute (Columbus, OH), and the study laboratory, Battelle Columbus Operations (Columbus, OH). Reports on analyses performed in support of the PCB 126 study are on file at the National Institute of Environmental Health Sciences.

Lot 130494 of the chemical, a white powder, was identified as PCB 126 by proton and carbon-13 nuclear magnetic resonance spectroscopy and melting point determination. All spectra were consistent with the structure of a pentachlorobiphenyl, and determination of the melting point (156.9° C) by differential scanning calorimetry agreed with the literature (Bolgar, *et al*., 1995). Proton and carbon-13 nuclear magnetic resonance spectra are presented in Figures C1 and C2.

The purity of lot 130494 was determined by the analytical chemistry laboratory using gas chromatography coupled to a high resolution mass spectrometer by system A (Table C1) and by the study laboratory using gas chromatography by system B (Table C1). The purity profile obtained by system A detected four impurities with a combined relative area of 0.49%. Two impurities were tetrachlorinated biphenyls and one was a pentachlorinated biphenyl. One impurity was not identified, but it was determined not to be a dioxin, dibenzofuran, or PCB. Gas chromatography by system B indicated a purity of 100.3% ± 0.7% for lot 130494 relative to the reference sample. The overall purity of lot 130494 was determined to be greater than 99%.

Formulation Materials

Acetone was obtained from Spectrum Quality Products (Gardena, CA) in six lots and was used with corn oil as the vehicle in the 2-year gavage study. The identity of each lot was confirmed by the study laboratory by infrared spectroscopy. The purity of each lot was determined by the study laboratory using gas chromatography by system C (Table C1). Purity analyses indicated no impurities with the exception of two occasions when a single impurity was found with a relative concentration greater than 0.1%. Periodic analyses of the corn oil vehicle by the study laboratory demonstrated peroxide concentrations below the acceptable limit of 3 mEq/kg.

PREPARATION OF STOCK SAMPLES

Lot 130494 was dissolved in acetone and prealiquotted for use as analytical stock or formulation stock in the study because of the very small amount of chemical that was required to prepare the dose formulations at the intended concentrations. An analytical stock solution was prepared at a target concentration of 100 µL by dissolving 10 mg of accurately weighed PCB 126 in 100 mL of acetone. A formulation stock solution was prepared at a target concentration of 125 µg/mL by dissolving 250 mg of accurately weighed PCB 126 in 2,000 mL of acetone. Following analysis to confirm proper concentration, these solutions were used to prepare analytical standard stocks of 50 and 100 µg, frozen reference stocks and chemical reference stocks of 100 µg for periodic purity determinations, and dose formulation working stocks. They were prepared by transferring the required volumes of respective solutions into appropriately sized glass containers and evaporating the solvent. The test article was stored at room temperature (approximately 25° C) and protected from light in amber glass bottles sealed with Teflon®-lined lids. Purity was monitored by periodic reanalysis. No degradation was observed during the course of the study.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by dissolving PCB 126 working stocks in acetone and diluting in corn oil (Spectrum Quality Products, Gardena, CA) such that the final formulation contained 1% acetone to give the required concentrations (Table C2). The dose formulations were stored at room temperature in amber glass bottles with minimal headspace and sealed with Teflon®-lined lids for up to 35 days.

Homogeneity studies of a 1,200 ng/mL dose formulation and stability studies of a 1.2 ng/mL formulation were performed by the analytical chemistry laboratory using gas chromatography similar to system A with selected ion recording. The study laboratory (in prestart) performed homogeneity studies on the 4 and 400 ng/mL dose formulations by a similar system. The formulations were determined to be gavageable, homogeneity was confirmed, and stability was confirmed for at least 35 days for dose formulations stored in amber glass bottles with minimal headspace and sealed with Teflon®-lined lids at –20° C, 5° C, and room temperature and for 3 hours under simulated animal room conditions.

Periodic analyses of the dose formulations of PCB 126 were conducted by the study laboratory using gas chromatography similar to system A with selected ion recording. During the 2-year study, the dose formulations were analyzed at least every 3 months (Table C3). Of the dose formulations analyzed, 64 of 76 were within 10% of the target concentrations. One dose formulation that was 78% of the target concentration was not used and the remix was within 10%; dose formulations that were within 14% of the target concentrations were used. Of the animal room samples, 23 of 27 were within 10% of the target concentrations.

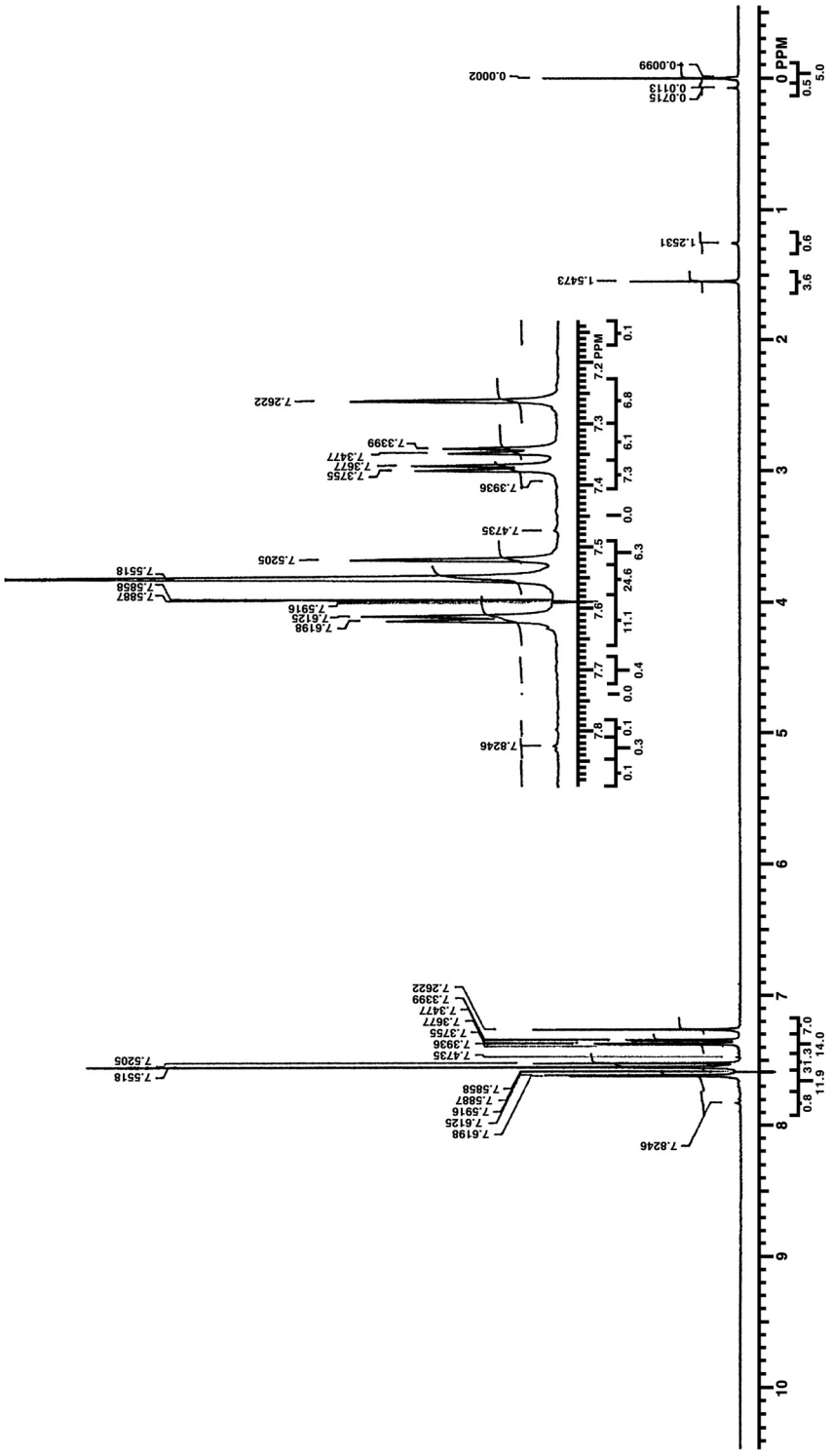

FIGURE C1
Proton Nuclear Magnetic Resonance Spectrum of PCB 126

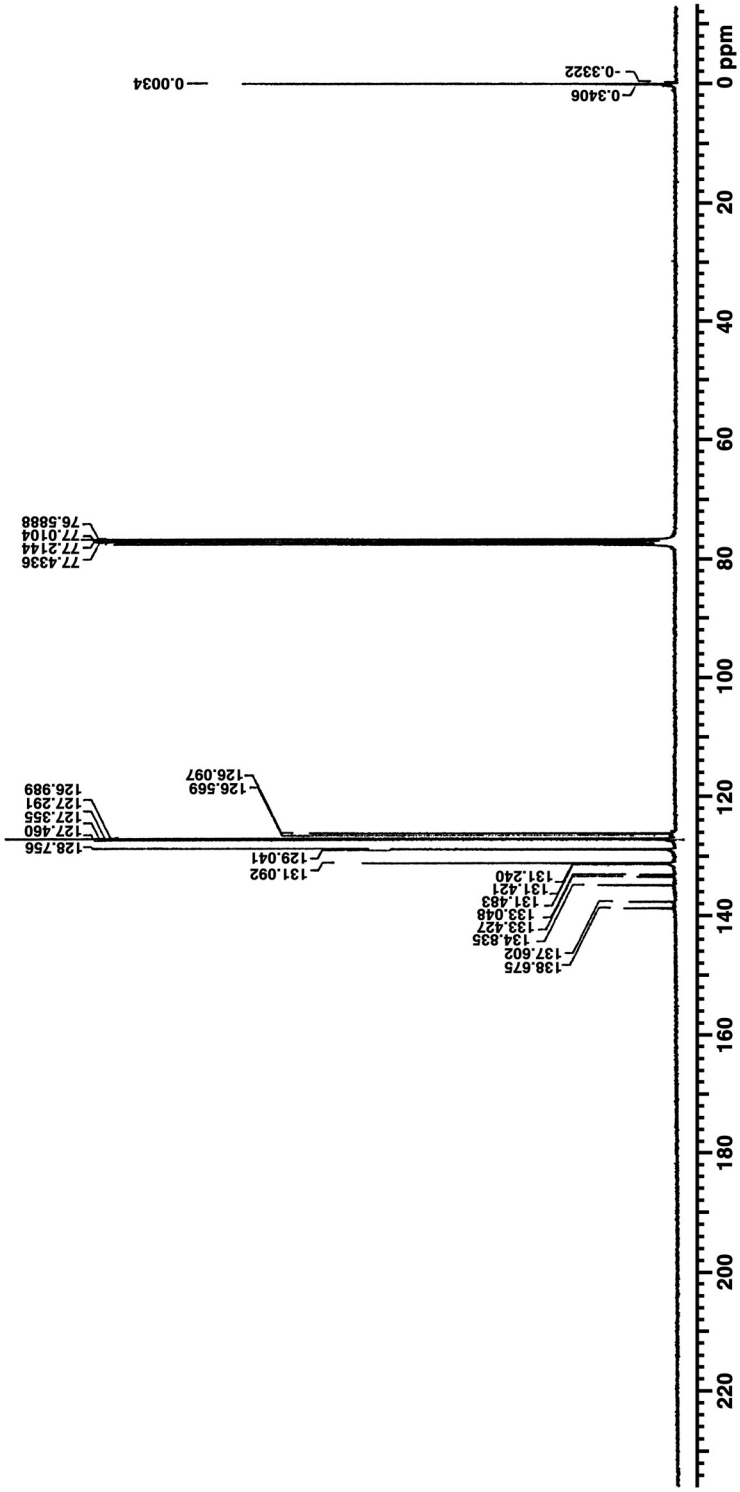

FIGURE C2
Carbon-13 Nuclear Magnetic Resonance Spectrum of PCB 126

TABLE C1
Gas Chromatography Systems Used in the 2-Year Gavage Study of PCB 126[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
High resolution mass spectrometry	DB-5MS 15 m × 0.25 mm diameter, 0.25-µm film thickness, capillary	Helium at 6 mL/minute	50° C for 1 minute, increased at 10° C/minute to 300° C, held for 10 minutes
System B			
Flame ionization	Supelco PTE-5 15 m × 0.53 mm (ID), 0.5-µm film thickness, capillary	Helium at 15 mL/minute	45° C for 5 minutes; increased 15° C/minute to 300° C
System C			
Flame ionization	Supelco 20% SP-2401/0.1% Carbowax 1500 on 100/120 Supelcoport, 2.4 m × 2 mm (ID), capillary	Nitrogen at 30 mL/minute	40° C for 4 minutes, increased at 10° C/minute to 170° C

[a] The gas chromatographs were manufactured by Carlo Erba/Fisons, Ltd. (Valencia, CA) or Hewlett Packard (Palo Alto, CA)

TABLE C2
Preparation and Storage of Dose Formulations in the 2-Year Gavage Study of PCB 126

Preparation
Using two PCB 126 stock standards, six intermediate stock solutions in acetone were prepared and stored in individual 2-mL amber glass vials, the acetone evaporated, and the vials sealed and stored.

Dose formulations were prepared by adding 1 liter of corn oil to a 2-liter volumetric flask. Twenty mL of acetone was measured in a graduated cylinder, and added in four 5 mL aliquots to the appropriate stock standard vial; capped, shaken, and sonicated for 30 seconds, and transferred by pipet to the volumetric flask after each rinse. Volumetric flask contents were diluted to volume with corn oil, capped, and stirred on a stirplate for 3 hours, with periodic inverting and shaking.

Chemical Lot Number
130494

Maximum Storage Time
35 days

Storage Conditions
Stocks of PCB 126 were stored in 2-mL amber glass vials, sealed with Teflon®-lined lids at –70° C.
Formulations were stored in 120-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 126[a]

Date Prepared	Date Analyzed	Target Concentration (ng/mL)	Determined Concentration (ng/mL)	Difference from Target (%)
February 16, 1998	February 19-20, 1998	4	3.769	–6
		12	11.03	–8
		40	36.79	–8
		70	63.71	–9
		120	115.9	–3
		220	225.0	+2
		400	373.7	–7
	April 2-3, 1998[b]	4	3.693	–8
		12	11.15	–7
		40	36.67	–8
		70	63.21	–10
		120	110.6	–8
		220	200.4	–9
		400	366.9	–8
April 13, 1998	April 15-16, 1998	4	3.658	–9
		12	11.13	–7
		40	36.80	–8
		70	64.78	–7
		120	112.8	–6
		220	203.5	–8
		400	368.4	–8
		400	313.2[c]	–22
April 27, 1998	April 30, 1998	400	362.2[d]	–9
July 7, 1998	July 9-10, 1998	4	3.490[e]	–13
		12	10.50[e]	–13
		40	37.34	–7
		70	66.11	–6
		120	112.9	–6
		220	192.7[e]	–12
		400	364.6	–9
		400	345.9[e]	–14
August 31, 1998	September 2-3, 1998	4	3.460[e]	–14
		12	10.77	–10
		40	34.94[e]	–13
		70	61.17[e]	–13
		120	104.4[e]	–13
		220	195.4[e]	–11
		400	371.0	–7
		400	345.5[e]	–14
	October 8-9, 1998[b]	4	3.433	–14
		12	11.22	–7
		40	35.89	–10
		70	59.34	–15
		120	113.3	–6
		220	202.1	–8
		400	394.8	–1
		400	398.5	0

TABLE C3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of PCB 126

Date Prepared	Date Analyzed	Target Concentration (ng/mL)	Determined Concentration (ng/mL)	Difference from Target (%)
November 18, 1998	November 24-25, 1998	4	3.794	–5
		12	10.94	–9
		40	38.74	–3
		70	64.35	–8
		120	112.9	–6
		220	206.7	–6
		400	374.4	–6
January 18, 1999	January 20-21, 1999	4	3.690	–8
		12	11.04	–8
		40	37.71	–6
		70	63.36	–9
		120	117.4	–2
		220	216.5	–2
		400	366.7	–8
April 12, 1999	April 14-15, 1999	12	12.53	+4
		40	38.01	–5
		70	65.47	–6
		120	118.1	–2
		220	211.9	–4
		400	409.3	+2
	May 22-23, 1999[b]	12	11.87	–1
		40	34.89	–13
		70	65.61	–6
		120	115.6	–4
		220	202.7	–8
		400	385.4	–4
June 7, 1999	June 9-10, 1999	12	11.47	–4
		40	39.47	–1
		70	65.49	–6
		120	112.8	–6
		220	210.4	–4
		400	388.4	–3
August 30, 1999	September 2-3, 1999	12	11.02	–8
		40	38.39	–4
		70	65.98	–6
		120	117.0	–3
		220	212.7	–3
		400	377.9	–6

TABLE C3
Results of Analyses of Dose Formulations Administered to Rats in the 2-Year Gavage Study of PCB 126

Date Prepared	Date Analyzed	Target Concentration (ng/mL)	Determined Concentration (ng/mL)	Difference from Target (%)
October 25, 1999	October 28-29, 1999	12	11.07	–8
		40	39.31	–2
		120	107.8	–10
		220	206.8	–6
		400	378.5	–5
	November 1, 1999	70	66.16	–5
	December 10-11, 1999[b]	12	10.99	–8
		40	36.41	–9
		70	63.72	–9
		120	104.6	–13
		220	212.1	–4
		400	369.1	–8
January 11, 2000	January 17-20, 2000	12	10.88	–9
		40	38.90	–3
		70	65.40	–7
		120	111.6	–7
		220	195.5[e]	–11
		400	379.4	–5

[a] Results of duplicate analyses. Dosing volume=2.5 mL/kg; 4 ng/mL=10 ng/kg, 12 ng/mL=30 ng/kg, 40 ng/mL=100 ng/kg, 70 ng/mL=175 ng/kg, 120 ng/mL=300 ng/kg, 220 ng/mL=550 ng/kg; 400 ng/mL=1,000 ng/kg
[b] Animal room samples
[c] Remixed; not used in study
[d] Results of remix
[e] Formulation was outside the acceptable range of ±10% of target concentration but was used at NTP's direction.

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

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)	13.3 ± 0.45	12.7 – 14.5	25
Crude fat (% by weight)	8.1 ± 0.23	7.6 – 8.6	25
Crude fiber (% by weight)	9.1 ± 0.62	7.9 – 10.0	25
Ash (% by weight)	4.9 ± 0.19	4.7 – 5.4	25
Amino Acids (% of total diet)			
Arginine	0.731 ± 0.050	0.670 – 0.800	8
Cystine	0.224 ± 0.012	0.210 – 0.240	8
Glycine	0.684 ± 0.041	0.620 – 0.740	8
Histidine	0.333 ± 0.018	0.310 – 0.350	8
Isoleucine	0.524 ± 0.046	0.430 – 0.590	8
Leucine	1.061 ± 0.061	0.960 – 1.130	8
Lysine	0.708 ± 0.056	0.620 – 0.790	8
Methionine	0.401 ± 0.035	0.350 – 0.460	8
Phenylalanine	0.598 ± 0.036	0.540 – 0.640	8
Threonine	0.501 ± 0.051	0.430 – 0.590	8
Tryptophan	0.126 ± 0.014	0.110 – 0.150	8
Tyrosine	0.390 ± 0.056	0.280 – 0.460	8
Valine	0.640 ± 0.049	0.550 – 0.690	8
Essential Fatty Acids (% of total diet)			
Linoleic	3.97 ± 0.284	3.59 – 4.54	8
Linolenic	0.30 ± 0.042	0.21 – 0.35	8
Vitamins			
Vitamin A (IU/kg)	5,716 ± 968	3,940 – 7,790	25
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)[b]	7.8 ± 0.86	6.1 – 9.3	25
Riboflavin (ppm)	5.6 ± 1.12	4.20 – 7.70	8
Niacin (ppm)	74.3 ± 5.94	66.4 – 85.8	8
Pantothenic acid (ppm)	22.5 ± 3.96	17.4 – 29.1	8
Pyridoxine (ppm)[b]	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (ppm)[b]	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	0.983 ± 0.043	0.903 – 1.060	25
Phosphorus (%)	0.548 ± 0.029	0.496 – 0.592	25
Potassium (%)	0.659 ± 0.022	0.627 – 0.691	8
Chloride (%)	0.357 ± 0.027	0.300 – 0.392	8
Sodium (%)	0.189 ± 0.019	0.160 – 0.212	8
Magnesium (%)	0.199 ± 0.009	0.185 – 0.213	8
Sulfur (%)	0.178 ± 0.021	0.153 – 0.209	8
Iron (ppm)	160 ± 14.7	135 – 177	8
Manganese (ppm)	50.3 ± 4.82	42.1 – 56.0	8
Zinc (ppm)	50.7 ± 6.59	43.3 – 61.1	8
Copper (ppm)	6.29 ± 0.828	5.08 – 7.59	8
Iodine (ppm)	0.461 ± 0.187	0.233 – 0.843	8
Chromium (ppm)	0.542 ± 0.128	0.330 – 0.707	7
Cobalt (ppm)	0.23 ± 0.049	0.20 – 0.30	7

[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 ± 0.096	0.10 – 0.50	25
Cadmium (ppm)	0.04 ± 0.006	0.04 – 0.07	25
Lead (ppm)	0.09 ± 0.052	0.05 – 0.25	25
Mercury (ppm)	<0.02		25
Selenium (ppm)	0.18 ± 0.033	0.13 – 0.28	25
Aflatoxins (ppb)	<5.00		25
Nitrate nitrogen (ppm)[c]	12.7 ± 6.88	9.04 – 39.6	25
Nitrite nitrogen (ppm)[c]	<0.61		25
BHA (ppm)[d]	1.1 ± 0.29	1.0 – 2.5	25
BHT (ppm)[d]	<1.0		25
Aerobic plate count (CFU/g)	<10		25
Coliform (MPN/g)	0.12 ± 0.6	0.0 – 3.0	25
Escherichia coli (MPN/g)	<10		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[e]	4.8 ± 1.75	2.1 – 8.8	25
N-Nitrosodimethylamine (ppb)[e]	1.9 ± 0.93	1.0 – 5.1	25
N-Nitrosopyrrolidine (ppb)[e]	2.8 ± 1.14	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	0.119 ± 0.114	0.020 – 0.499	25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.324 ± 0.561	0.020 – 2.81	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

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 1,000 ng/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
M. arthritidis	Study termination

RESULTS

All test results were negative.

APPENDIX F
SINGLE-DOSE TOXICOKINETIC STUDY IN FEMALE SPRAGUE-DAWLEY RATS

SINGLE-DOSE TOXICOKINETIC STUDY IN FEMALE SPRAGUE-DAWLEY RATS

Introduction

A single dose of PCB 126 was administered by gavage to female Harlan Sprague-Dawley rats at 10 or 1,000 ng/kg. PCB 126 levels were determined in postdose blood, lung, liver, and fat tissue samples at multiple time points for up to one year postdosing and the results were analyzed to establish basic toxicokinetic parameters. Bioavailability was not determined from this study since no intravenous administration was conducted.

Materials and Methods

PCB 126 was procured in one lot (130494) from AccuStandard, Inc. (New Haven, CT), and was subaliquoted and stored at room temperature. The material was analyzed for purity and identity and the results and analytical systems are presented in Appendix C. Formulations for the study were prepared in corn oil with 1% acetone as described in Appendix C.

Female rats (20 to 22 weeks of age at the start of the study) were used for the study. They were administered 10 or 1,000 ng/kg of formulation in a volume of 2.5 mL/kg. Groups of five rats per time point were bled and then tissues were harvested at 0.5, 1, 1.5, 2, 3, 8, 16, or 24 hours and then 5, 12, 32, 61, 92, 120, 166, 212, 250, 281, 309, 341, and 365 days postdosing. The animals were anesthetized with a CO_2/O_2 mixture and as much blood as possible was collected from each rat by cardiac puncture. Blood samples were collected in EDTA tubes and stored at 5° C for analysis. Following blood collection, the rats were euthanized with CO_2 and their lungs, livers, and mesenteric fat were collected. Tissue weights were recorded and the samples were stored frozen at –20° C for analysis.

For analysis, 100 µL of 1,000 pg/mL ^{13}C-PCB 126 was added to each 1.0 mL or gram of blood or tissue sample as an internal standard and the sample was saponified with 40% potassium hydroxide in ethanol. The samples were extracted with hexane and the extract was further cleaned on silica gel and activated carbon solid phase extraction columns. The eluate from the activated carbon column was evaporated to dryness and reconstituted in nonane. The nonane solutions were analyzed using gas chromatography with high resolution mass spectrometry on a RTX-5 MS column (15 m × 0.25 mm), 0.25 µm film thickness (Restek, Bellefonte, PA) using an oven program of 100° C for 1 minute, to 240° C at 15° C/minute, to 285° C at 40° C/minute, then held for 2 minutes. Spectra were collected at 50 eV at 323.8834/0.3 ms for PCB 126 and 335.9236/0.3 ms for the internal standard. Responses for PCB 126 were quantitated using least-squares linear regression of a calibration curve generated from matched tissues from untreated Sprague-Dawley rats spiked with PCB 126. Table F1 provides figures of merit from the validation of the methods used.

Noncompartmental modeling with PROC NLIN in SAS version 8.2 (SAS Institute, Inc., Cary, NC) was used to derive toxicokinetic parameters from lung concentration versus time data from the 1,000 ng/kg group and liver and fat tissue concentration versus time data above the limit of quantitation (LOQ).

Results and Discussion

Toxicokinetic parameters were not established for blood versus time or the 10 ng/kg lung versus time data because the results were lower than the LOQ for the method (Table F2). Measured blood PCB 126 concentrations for the 10 and 1,000 ng/kg groups were generally indistinguishable from background levels, suggesting rapid absorption and systemic distribution. Lung tissue from the 10 ng/kg group exhibited concentrations of PCB 126 less than the LOQ for the method.

The data from tissues having PCB 126 levels above the LOQ are presented in Figures F1 to F5. Extrahepatic distribution occurred, as evidenced by the presence of PCB 126 in lung (1,000 ng/kg group) and fat (10 and 1,000 ng/kg groups). PCB 126 liver/fat concentration ratios in the 1,000 ng/kg group exceeded unity for up to approximately 166 days. Estimation of toxicokinetic parameters for PCB 126 in this study was complicated by several factors. Given the significant influence of hepatic sequestration on disposition, simple linear compartmental analysis could not be applied to estimate toxicokinetic parameters. Also, since PCB 126 concentrations in blood were generally indistinguishable from background levels, absorption and elimination kinetics from blood were not obtained. Therefore, volume of distribution and clearance were not calculated.

Toxicokinetic modeling using the data generated in this study was limited to simple noncompartmental analyses that included calculations of areas under the concentration versus time curve and estimates of terminal elimination rate constants where appropriate. However, several observations are possible from the data. T_{max} occurred within the first day for all tissues except fat, where T_{max} was not reached until 5 (10 ng/kg) or 12 (1,000 ng/kg) days postdosing (Table F2). The difference in values for C_{max} was not distinguishable for liver and fat samples from the 10 ng/kg dose group, but for the 1,000 ng/kg group C_{max} increased in the following order:
blood <<< lung << fat < liver.

A comparison of elimination half-lives revealed that PCB 126 is more persistent in fat than in liver. Greater concentrations of PCB 126 were measured in fat than in liver in the 10 ng/kg group (Table F2), whereas in the 1,000 ng/kg group, fat and liver AUC values were approximately equivalent, consistent with hepatic sequestration of PCB 126 via binding to CYP1A2 protein. The elimination rate constant in liver for the 1,000 ng/kg group was markedly lower than the rate constant for the 10 ng/kg group, whereas elimination rate constants from fat did not change appreciably with dose. At 1,000 ng/kg, the elimination half-life of PCB 126 in liver was only approximately 1.3 times faster than in fat; at 10 ng/kg, there was a 440-fold difference between the elimination half-lives in the two tissues. The half-life of PCB 126 in liver was very dose-dependent, being 170-fold longer in the 1,000 ng/kg group than in the 10 ng/kg group; the half-life in fat was dose-independent, or nearly so. This observation suggests that the low concentration of PCB 126 entering the liver in the 10 ng/kg group was efficiently metabolized, while in the 1,000 ng/kg group metabolism was saturated and an increased amount of PCB 126 accumulated due to binding to the increased amount of CYP1A2 protein that resulted from enzyme induction.

TABLE F1
Figures of Merit for Assays of PCB 126 in the Single Gavage Dose Toxicokinetic Study in Female Sprague-Dawley Rats

Tissue	Linearity[a]	Limit of Quantitation	Precision[b]	Accuracy[c]
Blood	>0.99	15 pg/mL	Within 15%	15% or less
Lung	>0.99	60 pg/g	Within 15%	15% or less
Liver	>0.99	50 pg/g	Within 15%	15% or less
Fat	>0.99	50 pg/g	Within 15%	15% or less

[a] Correlation coefficient
[b] Standard deviation of quality control samples
[c] Relative error in determined versus prepared concentration of calibration standards

TABLE F2
Toxicokinetic Parameter Estimates in Female Sprague-Dawley Rats after a Single Gavage Dose of PCB 126

Parameter	Dose (ng/kg)	Tissue Parameter Estimate[a]		
		Lung	Liver	Fat
$C_{(max)}$ (observed) (pg/g)	10	—	459 ± 291	444 ± 295
	1,000	409 ± 165	17,700 ± 2,500	5,230 ± 360
$T_{(max)}$ (observed) (days)	10	—	0.125	5
	1,000	0.125	1	12
k_{elim} (day^{-1})	10	—	1.15 ± 0.87	0.00263 ± 0.00104
	1,000	1.75 ± 0.99	0.00661 ± 0.00091	0.00494 ± 0.00055
$t_{½\ elim}$ (days)	10	—	0.603 ± 0.455	264 ± 105
	1,000	0.397 ± 0.224	105 ± 14	140 ± 16
AUC_T[b] (days • pg/g)	10	—	303 ± 86	90,000 ± 17,000
	1,000	160 ± 23	903,000 ± 71,000	829,000 ± 49,000
AUC_∞[c] (days • pg/g)	10	—	431 ± 128	126,000 ± 22,000
	1,000	255 ± 57	996,000 ± 72,000	1,020,000 ± 54,000
AUC_T[b]/Dose (days • pg/g)/(ng/kg)	10	—	30.3 ± 8.6	9,000 ± 1,700
	1,000	0.16 ± 0.023	903 ± 71	829 ± 49
AUC_∞[c]/Dose (days • pg/g)/(ng/kg)	10	—	43.1 ± 12.8	12,600 ± 2,200
	1,000	0.25 ± 0.057	996 ± 72	1,020 ± 54

[a] Values are reported as the absolute value or mean ± standard deviation.
[b] AUC_T values were calculated by the trapezoidal method, assuming that the PCB 126 concentration at t=0 was 0 pg/g tissue, and using the observed tissue PCB 126 concentration-time data from time 0 to the last time point (T) where T is greater than LOQ.
[c] AUC_∞ values were calculated by the trapezoidal method assuming that the PCB 126 concentration at t=0 was 0 pg/g tissue, using the observed tissue PCB 126 concentration-time data, and extrapolating to infinity using k_{elim}.

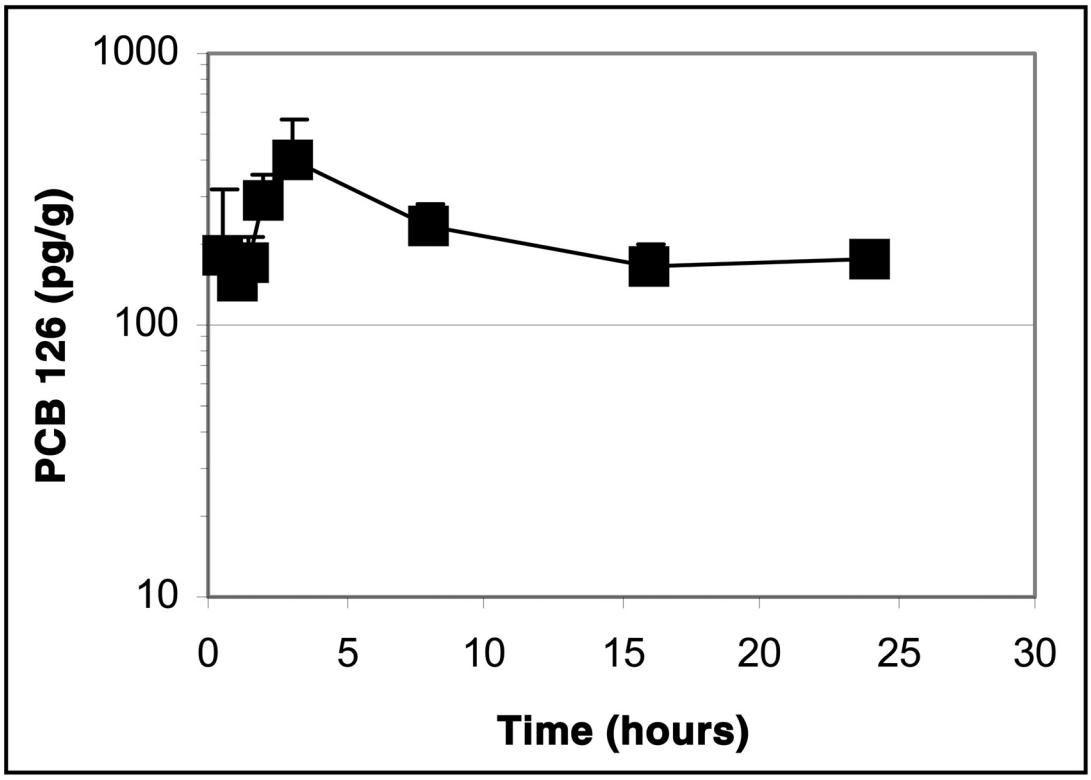

FIGURE F1
Lung Concentrations of PCB 126 in Female Sprague-Dawley Rats after a Single Gavage Dose of 1,000 ng/kg PCB 126

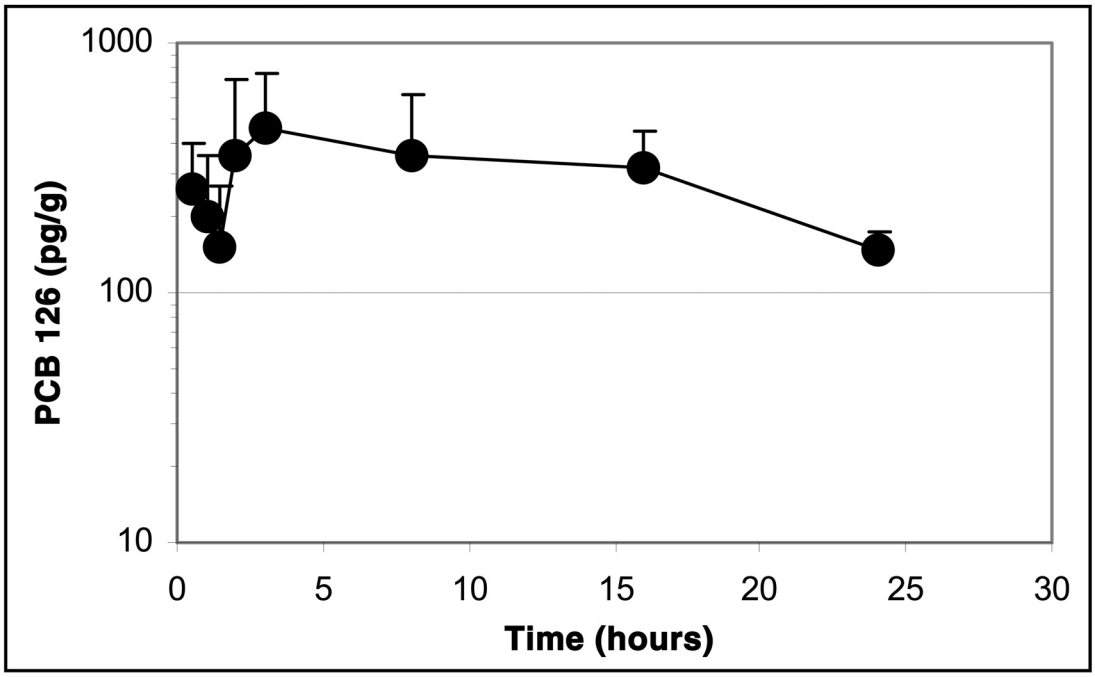

FIGURE F2
Liver Concentrations of PCB 126 in Female Sprague-Dawley Rats after a Single Gavage Dose of 10 ng/kg PCB 126

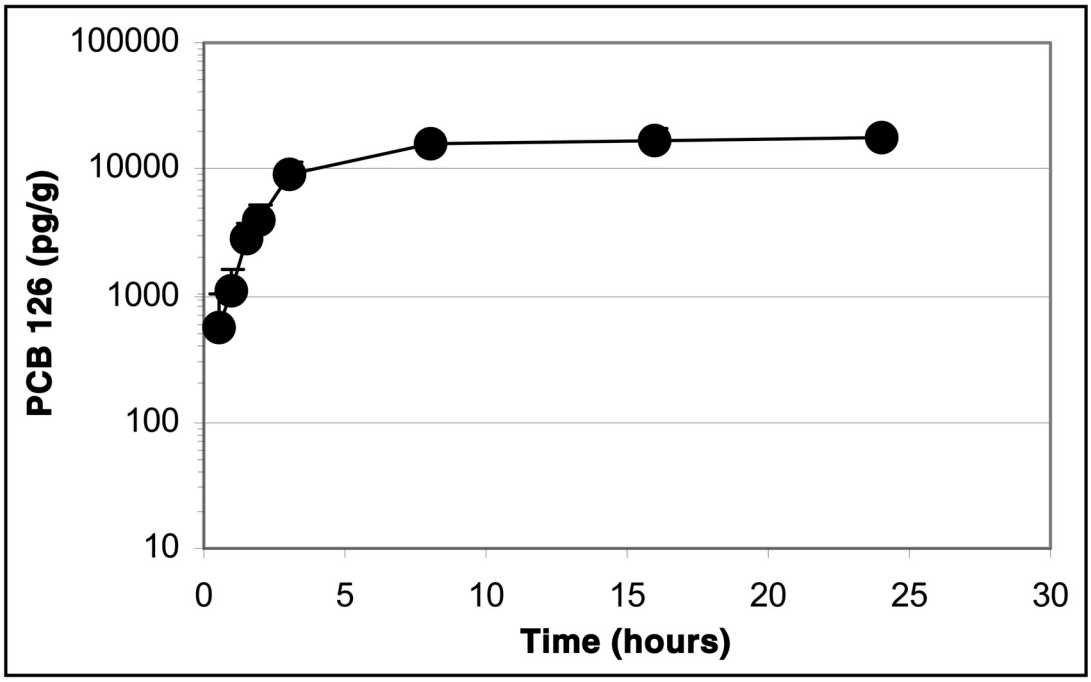

FIGURE F3
Liver Concentrations of PCB 126 in Female Sprague-Dawley Rats after a Single Gavage Dose of 1,000 ng/kg PCB 126

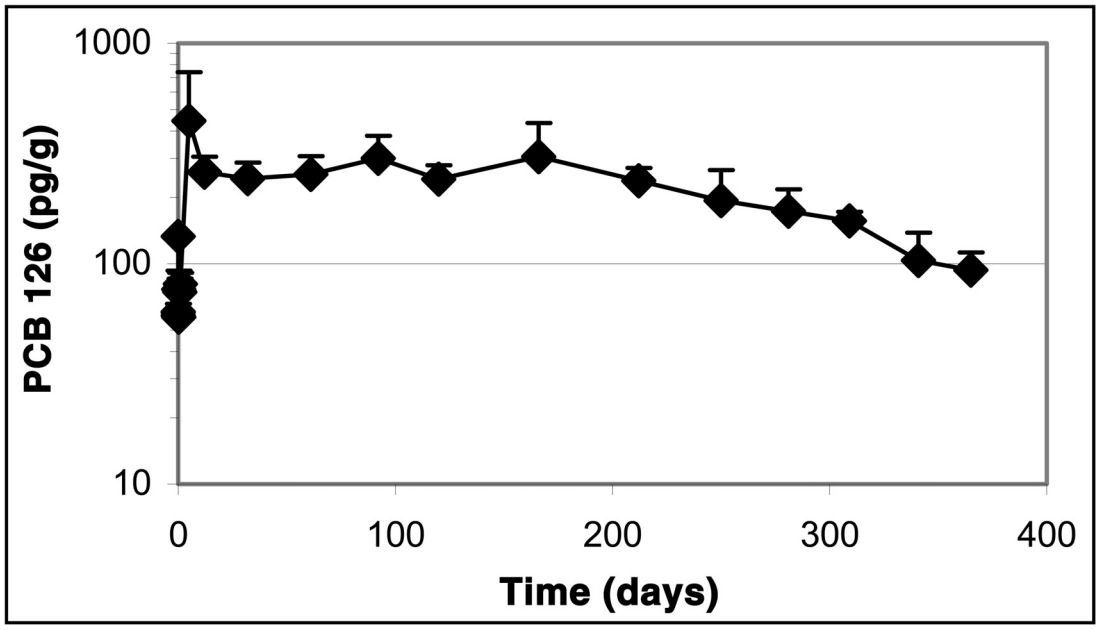

FIGURE F4
Fat Concentrations of PCB 126 in Female Sprague-Dawley Rats after a Single Gavage Dose of 10 ng/kg PCB 126

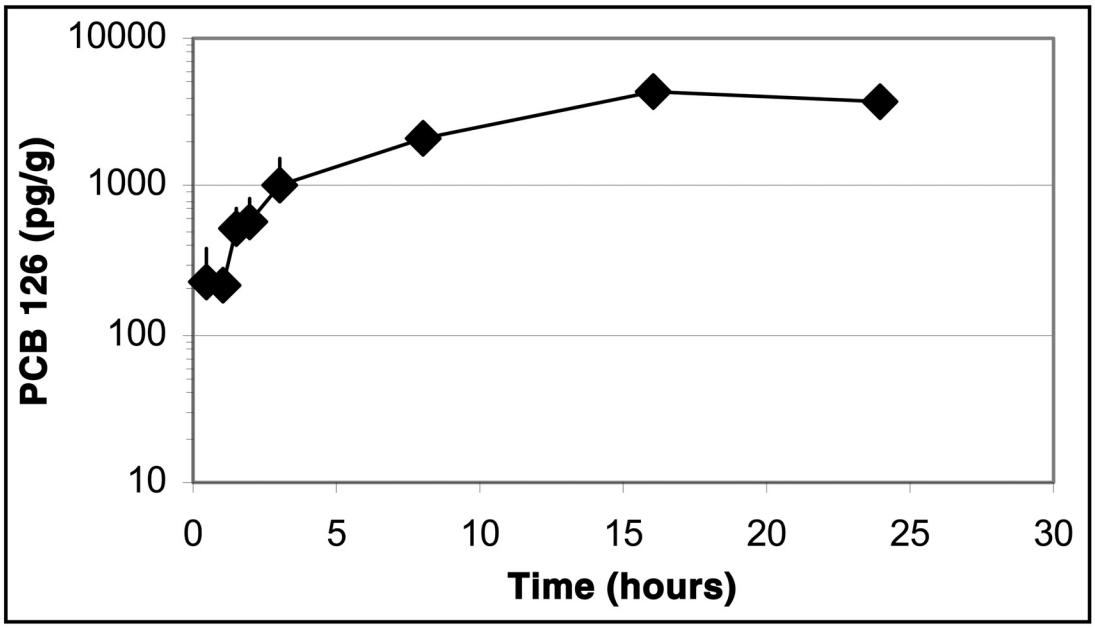

FIGURE F5
Fat Concentrations of PCB 126 in Female Sprague-Dawley Rats after a Single Gavage Dose of 1,000 ng/kg PCB 126

APPENDIX G
PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

INTRODUCTION

A goal for the physiologically based pharmacokinetic (PBPK) modeling of the disposition data from the dioxin toxic equivalency factor (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, 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 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 and partition coefficients, kinetic constants, and biochemical parameters) and physiological parameters (e.g., organ volumes and blood flow rates).

A PBPK model is a mathematical structure that describes the relationship between these factors and ADME and describes the pharmacokinetics of the compound by a series of mass-balance differential equations in which the state variables represent the concentration of the compound in anatomically distinct regions, "compartments" of the body. These tissue compartments are linked by a physiologically realistic pattern of blood perfusion and flow through the different tissue compartments.

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.

MODEL DEVELOPMENT

For the current dioxin TEF evaluation studies the same basic model structure was used for all compounds studied, with some of the model parameters, such as metabolism or binding to the AhR, unique to each model. The model was based upon the model for TCDD 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 have gone through further rounds of refinement and inclusion of increased biological complexity. A thorough summary of PBPK modeling for TCDD and the evolution of these and other PBPK models of TCDD can be found elsewhere (USEPA, 2000c).

Kohn's TCDD model included compartments for fat, liver, kidney, gastrointestinal tract, muscle, and viscera. Blood is distributed among arterial, venous, and tissue capillary spaces. The model also includes equations for the liver amounts of AhR, CYP1A1, CYP1A2, and CYP1B1, as well as equations describing 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 for 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. Since transthyretin (also known as prealbumin) can bind hydroxylated polychlorinated dibenzodioxins and single doses of TCDD can cause prolonged decrease in this protein, a dose-dependent decrease was included in the model. This bound TCDD cannot enter the tissues in the model and may become free in the blood by dissociation or proteolysis. To allow the model to fit data at both low and high doses, the 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 three main steps to building a PBPK model for the dioxin TEF evaluation studies; conversion of Kohn's model, addition of a lung compartment, and addition of the study-specific body weights to the model. A copy of Kohn's model coded in the ScoP simulation was converted to both a Matlab model and a Simulink model. Simulations from the three models were compared to each other to confirm that the conversion to Matlab/Simulink was accurate. Next, a lung compartment was added to the Simulink model because the NTP data for the TEF studies includes lung tissue concentrations. The lung compartment is diffusion-limited and includes the same equations used in the lung for AhR, CYP1A1, and CYP1B1. The lung and liver compartments use the same gene expression parameters on a per liter basis. The final step was to include the rat body weights from each study rather than the body weight function from Kohn's model. Body weights were available weekly for the first 12 weeks of the studies and then monthly for the remainder of the studies. Interpolation of the mean body weights was used to estimate the body weight as a function of time.

Several additions to Kohn's model were needed to model PCB 126. Many of the parameters in Kohn's model are specifically for TCDD and need to be changed for PCB 126. The parameters to change relate to tissue partition coefficients, diffusion, binding, metabolism, and enzyme induction. The partition coefficient estimates from the literature (Parham, 1997) for the muscle, GI tract, liver, viscera, and kidney were used in the model while the fat and adipose partition coefficients were estimated. Similarly, the diffusion values for fat and adipose were estimated while the diffusion for the other tissues used Kohn's TCDD values. Two metabolism parameters in the Hill equation ($V_{metabolism}$ and $K_{metabolism}$) were estimated. The model has a single parameter, $k_{binding}$, for binding of PCB 126 to the AhR, CYP1A2, and blood protein. There are different parameters for the dissociation from AhR, CYP1A2, and protein in the blood, K_{AhR}, $K_{CYP1A2\ PCB\ 126}$, and $Kd_{Protein}$, respectively. All four of these binding parameters were estimated from the PCB 126 data. The last group of parameters that was estimated for PCB 126 relates to the induction of the AhR and CYP1A2. The values of all 14 parameters were estimated simultaneously by optimization, fitting the model predictions to the liver, lung, fat, and blood data.

RESULTS AND DISCUSSION

Many attempts were made to fit the model to the tissue data. The first option used literature methods to estimate the partition coefficients (Parham *et al.,* 1997) and metabolism (Parham and Portier, 1998). The diffusion values remained the same as those used in Kohn's TCDD model. Then a set of parameters ($k_{binding}$, $Kd_{Protein}$, K_{AhR}, $K_{CYP1A2\ PCB\ 126}$, $V_{CYP1A2\ induction}$, $V_{AhR\ induction}$, $K_{AhR\ induction}$, background) was estimated by fitting the model predictions to the tissue data. The results of this approach were parameters that fit the adipose data but not the liver or vice versa.

The next attempts to fit the model to the data added six more parameters to be estimated. The parameters were for metabolism, diffusion, and partitioning ($V_{metabolism}$, $K_{metabolism}$, Fat Diffusion, Lung Diffusion, Fat Partition, Lung Partition) for a total of 14 parameters. The values of these parameters were allowed to vary widely. For example, the partition coefficient for fat should be near 190, but it was allowed to take values greater than 1,000 in the optimization. A parameter that ends up with an unrealistic value may be an indication that the model lacks some necessary physiology or biochemistry. Changing the lung and fat partition coefficients along with the diffusion to these tissues makes the model fit the liver and fat data at the same time (Figures G1 to G9). However, the model under-predicts the concentrations in the lung and blood. The partition coefficient estimate of 1,553 for fat is unrealistically high; most methods would predict fat partition coefficients between 180 and 350. The high partition coefficient needed to fit the fat tissue data results in low blood and lung levels because any PCB 126 reaching the fat stays in the fat.

Dozens of optimizations have been tried with all 14 parameters or subsets of the 14 parameters. None of the optimizations fit all the data across dose levels and tissues. The search has been thorough enough that simply missing the right combination of parameters is unlikely. One possible solution is to expand the number of parameters to change. A second possibility is that there is something related to PCB 126 that is missing from a model developed for TCDD. Without additional changes, the TCDD model does not work as a model for PCB 126.

TABLE G1
Parameter Estimates for PCB 126

Parameter	Estimated Value for PCB 126	Value from the TCDD Model	Unit
$k_{binding}$	78.6	1,000.0	/nmole per day
$Kd_{Protein}$	120.8	10.0	nM
K_{AhR}	0.03	0.27	nM
$K_{CYP1A2\ PCB\ 126}$	1.7	30.0	nM
$V_{CYP1A2\ induction}$	55.0	28.4	nmole/L per day
$V_{AhR\ induction}$	0.08	0.14	nmole/L per day
$K_{AhR\ induction}$	8.3	4.0	nM
Background	0.6	0.08	ng/kg per day
$V_{metabolism}$	66.0	9.12	nmole/L per day
$K_{metabolism}$	1.8	0.96	nM
Fat Partition	1,553.0	187.0	–
Fat Diffusion	3.0	0.02	–
Lung Partition	1.3	4.57	–
Lung Diffusion	1.4	0.8	–

TABLE G2
Fixed Parameters from the TCDD Model

Parameter	Model Value	Unit
lt (lag time for induced expression)	0.2	day
Cardiac Output	14.7	L/hour per $kg^{0.7}$
$V_{Protein}$ (blood binding protein)	300	nmole/L per day
$Ki_{Protein}$ (inhibition of blood protein production)	0.0006	nM
$n_{metabolism}$	1.12	–
$k_{subchronic\ absorption}$	0.65	$kg^{0.75}$/day
$k_{absorption}$	4.8	$kg^{0.75}$/day
$k_{binding}$	1,000	/nmole per day
$k_{Ah\ degradation}$	2.16	/day
$k_{AhPCB\ 126\ degradation}$	5.15	/day
$k_{proteolysis}$	0.2727	/day
$k_{deadenylation}$	576	nt/day
$k_{mRNA\ degradation}$	13.4	/day
k_{urine}	5.36	/day
k_{bile}	3.81	/day
k_{feces}	1.152	/day
k_{lysis}	200	/day
$critical_{accumulation}$	0.6	nmole
$k_{recovery}$	0.01	/day
$critical_{concentration}$	2	nM

TABLE G3
Partition Coefficients and Permeability Coefficients

	Partition	Permeability
Fat	1,553.0[a]	3.0[a]
Muscle	7.2	0.171
Viscera	6.0	0.334
Liver	8.9	1.49
Kidney	6.0	0.559
Gastrointestinal tract	6.0	0.248
Lung	1.3[a]	1.4[a]

[a] From optimization

TABLE G4
Gene Expression Parameters Given in the Kohn *et al.* (2001) Model

	Aryl Hydrocarbon Receptor (AhR)	CYP1A1	CYP1A2	CYP1B1
Expression nmole/L per day	0.0177	0.023	0.42	0.00001
Induction *(V)* nmole/L per day	0.08[a]	13.5	55.0[a]	3.92
Induction *(K)* nM	8.3[a]	2.04	4.41	13
Induction *(N)* nt	128	156	196	74
Induction *(Ka)* nM	NA	1.16	NA	10.0
Synthesis *(V)* nmole/L per day	3,000	3,000	2,400	520
$K_{ribosome}$ nM	2.68	NA	NA	NA

[a] From optimization

TABLE G5
Physiological Parameters

	Fraction of Body Weight	Fraction Capillary	Fraction of Cardiac Output
Liver	0.0373	0.138	0.039
Fat	0.07	0.02	0.065
Muscle	0.542	0.02	0.334
Viscera	0.163	0.075	0.248
Kidney	0.0148	0.16	0.133
Gastrointestinal tract	0.075	0.0265	0.181
Lung	0.005	0.36	—
Arterial	0.0044	—	—
Venous	0.0132	—	—

TABLE G6
Initial Conditions for Protein in Blood[a]

Arterial	0.539
Venous	1.616
Gastrointestinal tract	0.0755
Fat	0.283
Muscle	0.741
Viscera	0.413
Liver	0.328
Kidney	0.0778

[a] Conditions are measured in nmoles.

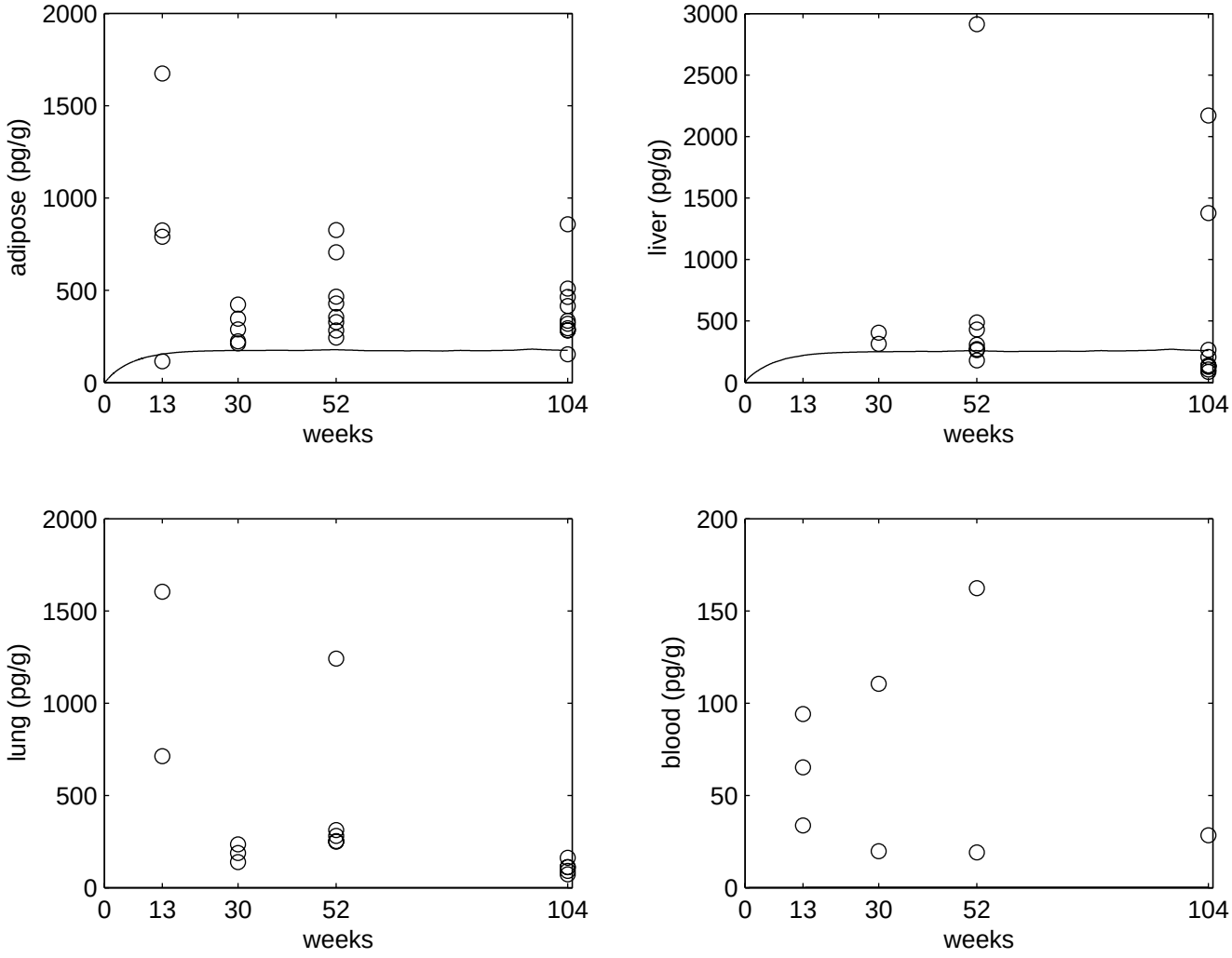

FIGURE G1
Model Predictions (–) and Individual Tissue Data (○) for the Vehicle Control Group in the 2-Year Study

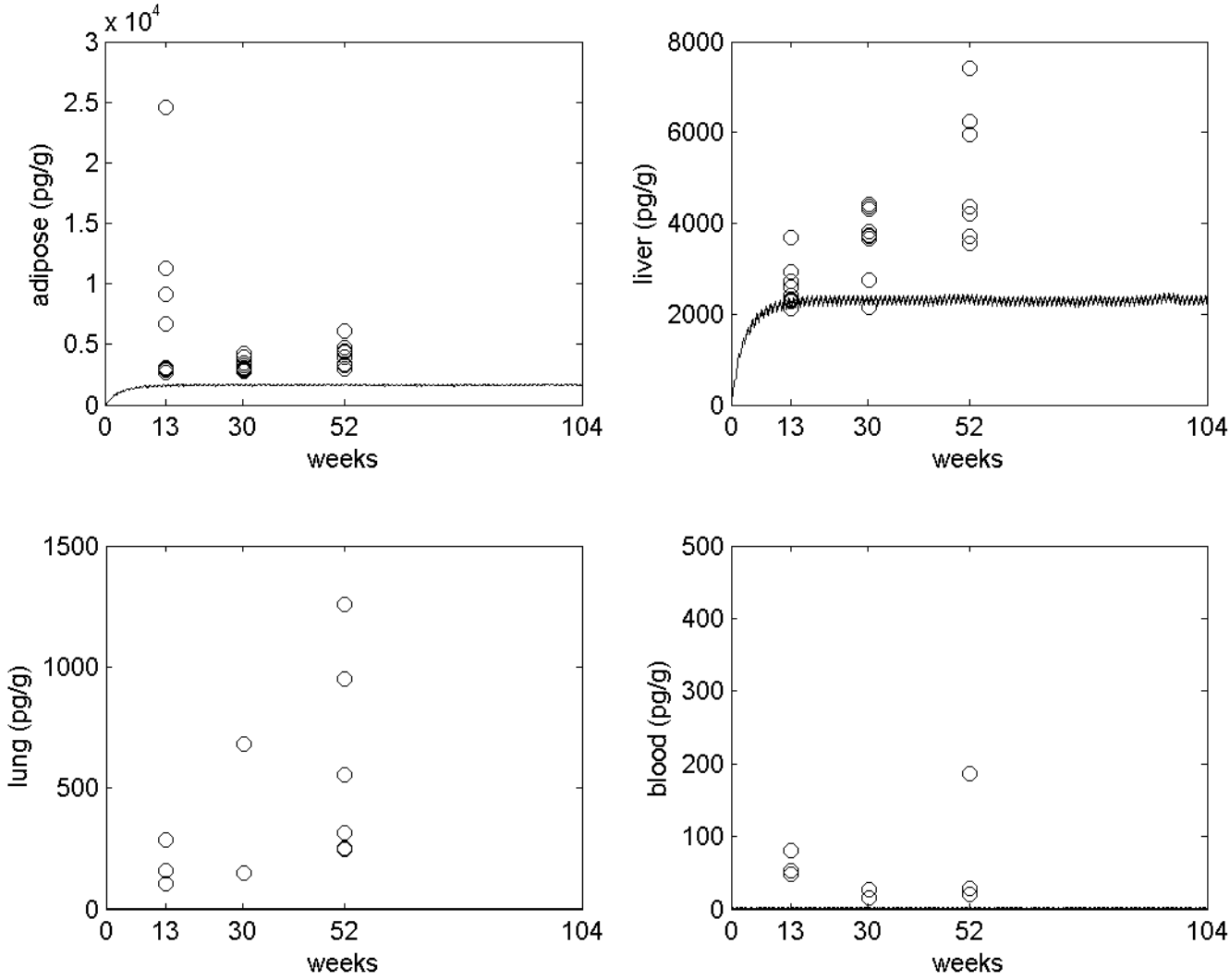

FIGURE G2
Model Predictions (–) and Individual Tissue Data (○) for the 10 ng/kg Group in the 2-Year Study

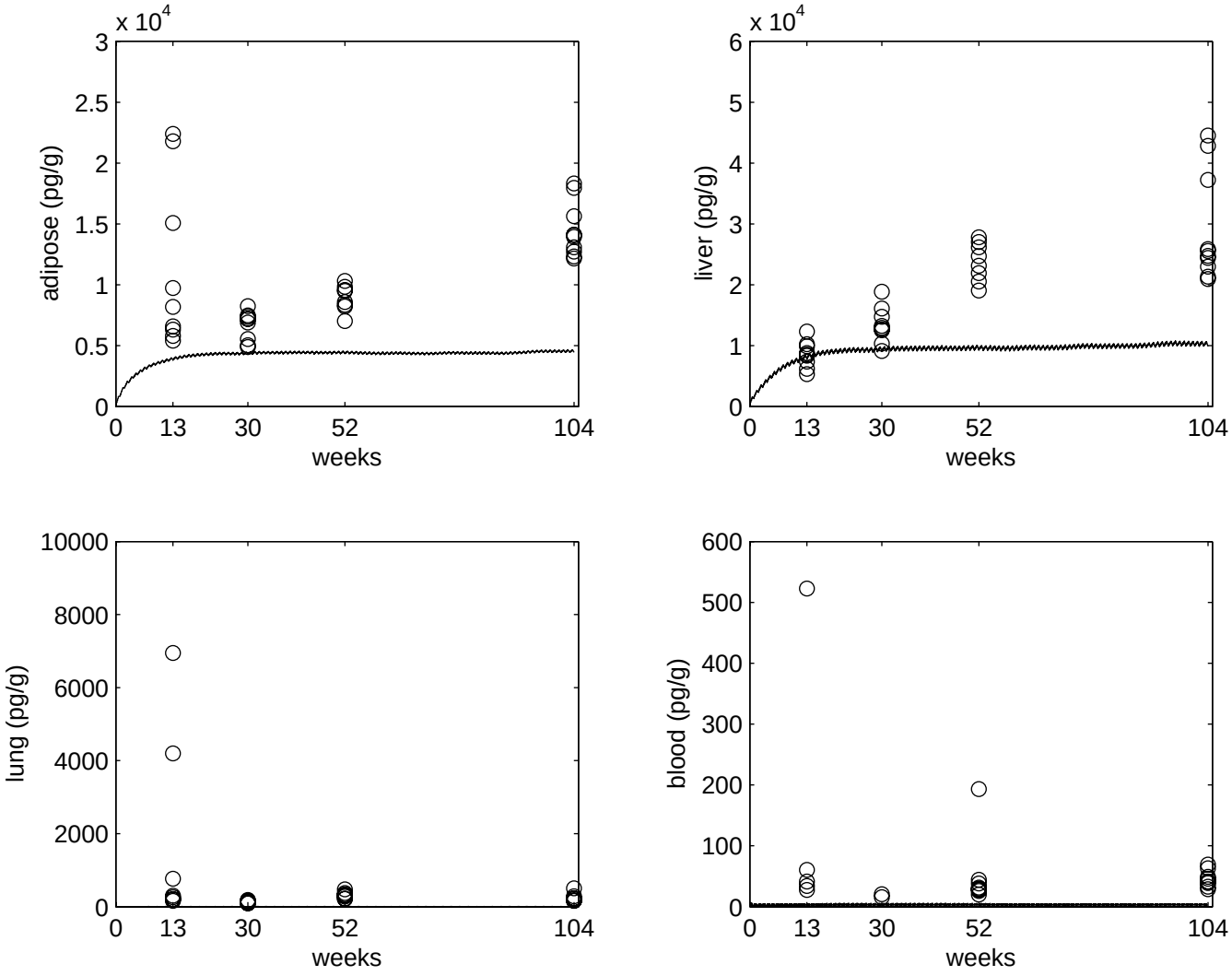

FIGURE G3
Model Predictions (–) and Individual Tissue Data (○) for the 30 ng/kg Group in the 2-Year Study

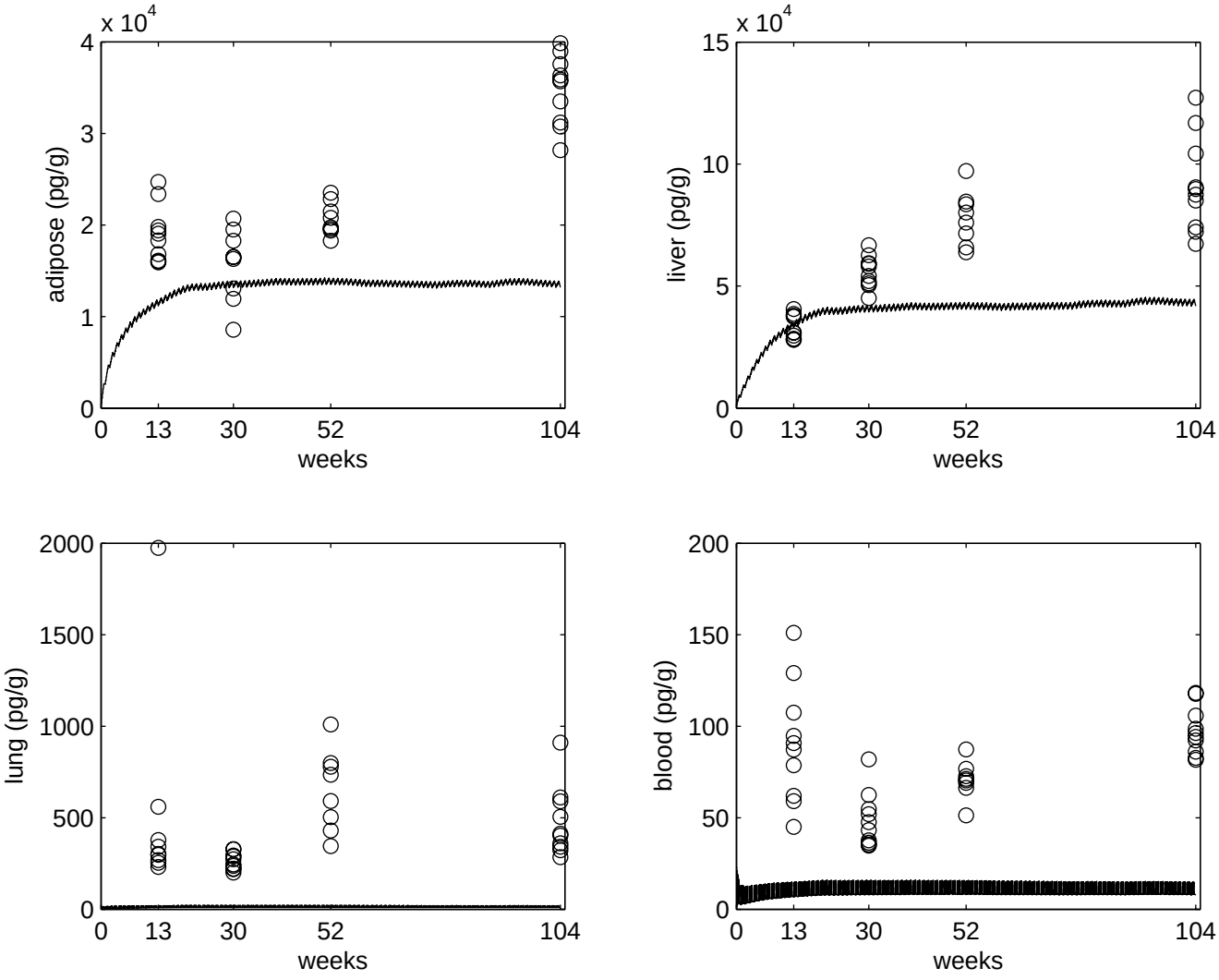

FIGURE G4
Model Predictions (–) and Individual Tissue Data (○) for the 100 ng/kg Group in the 2-Year Study

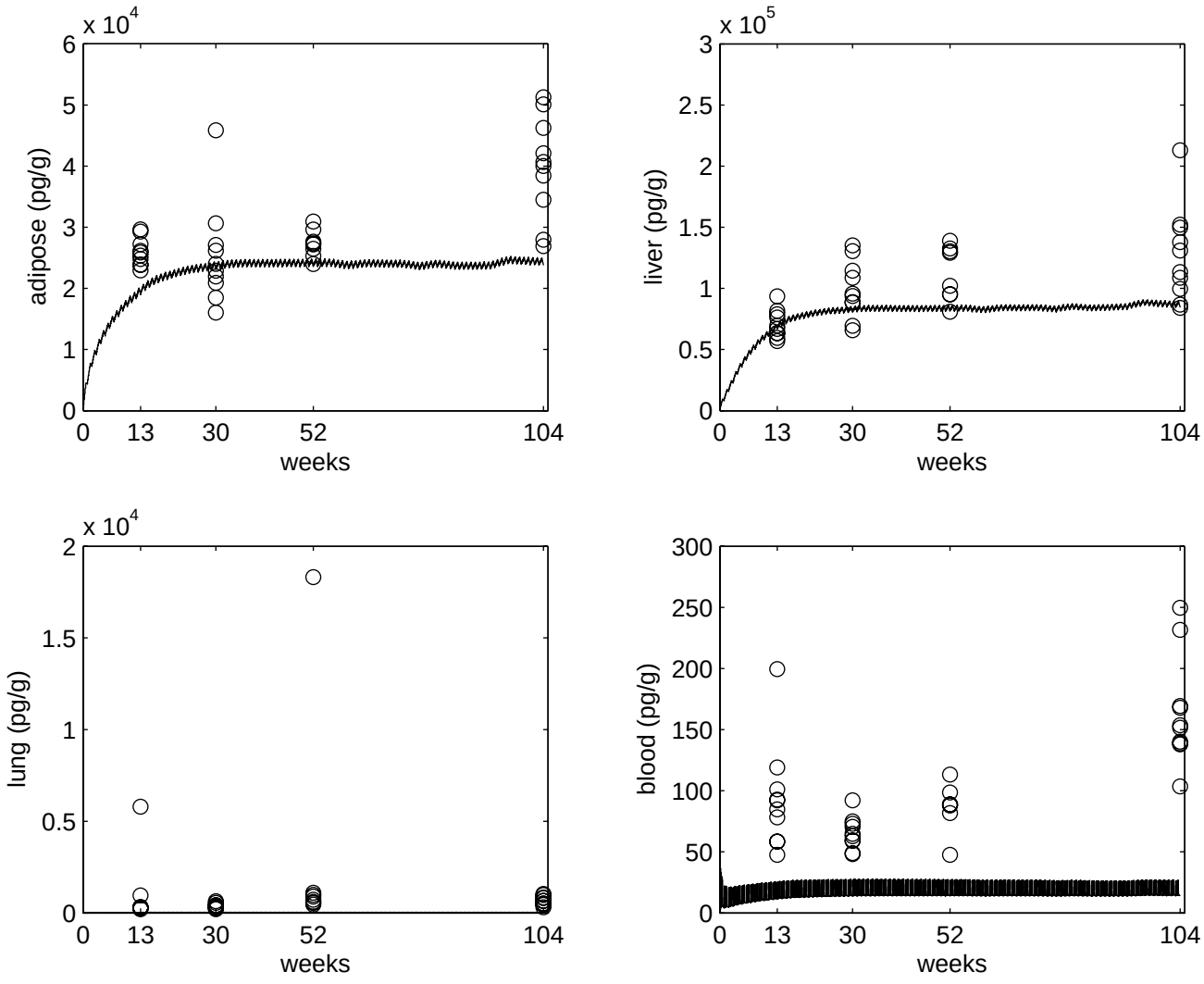

FIGURE G5
Model Predictions (–) and Individual Tissue Data (○) for the 175 ng/kg Group in the 2-Year Study

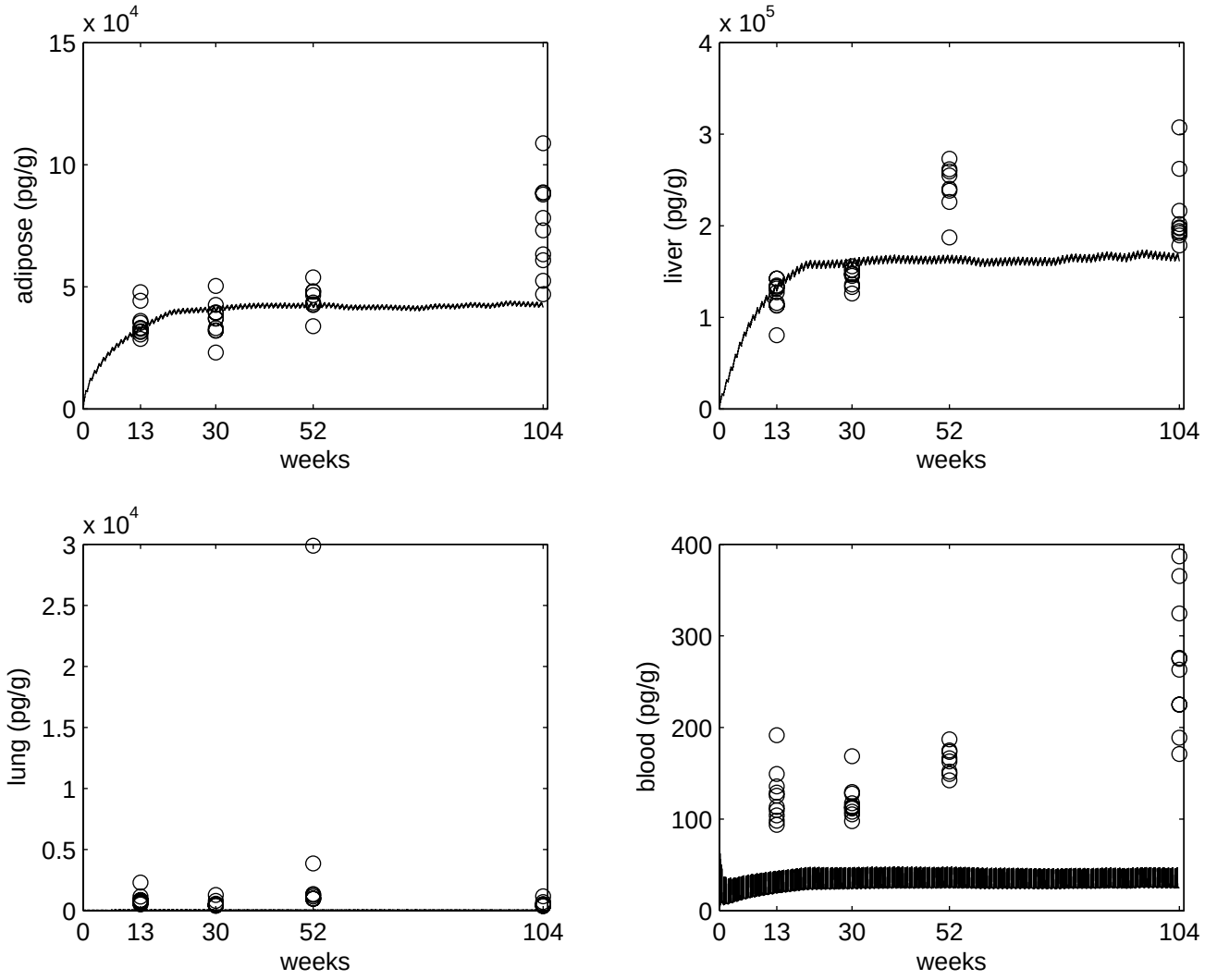

FIGURE G6
Model Predictions (–) and Individual Tissue Data (○) for the 300 ng/kg Group in the 2-Year Study

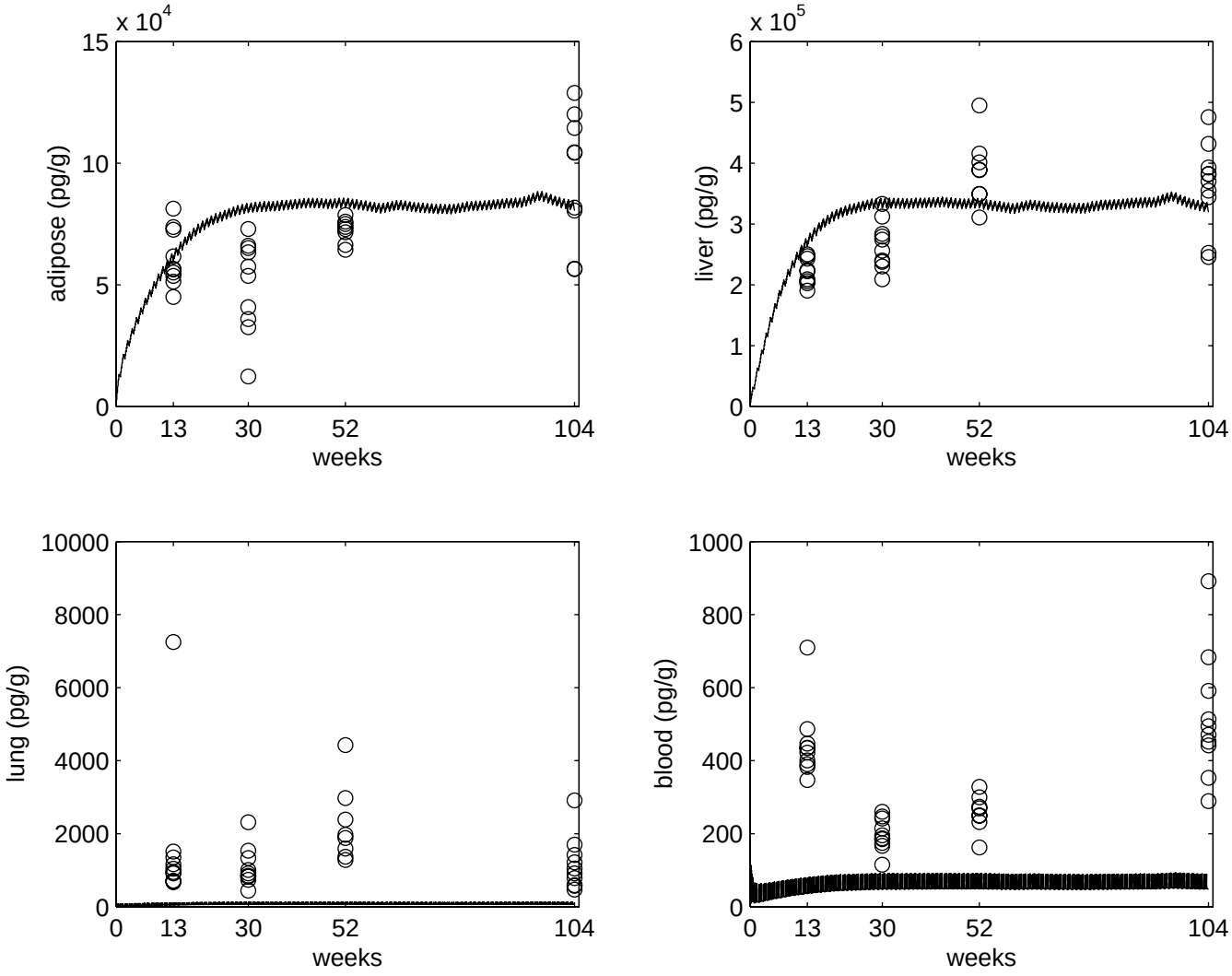

FIGURE G7
Model Predictions (–) and Individual Tissue Data (○) for the 550 ng/kg Group in the 2-Year Study

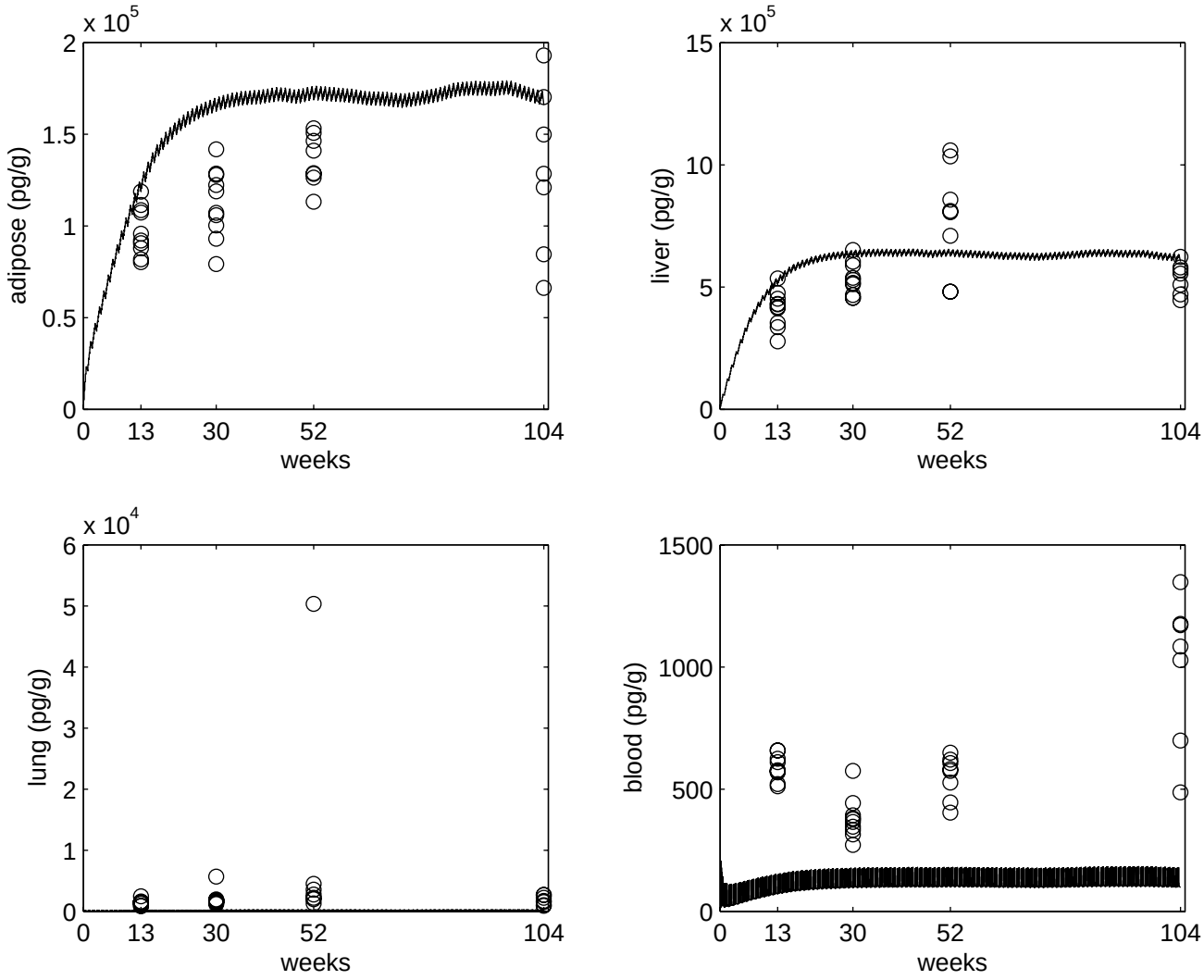

FIGURE G8
Model Predictions (–) and Individual Tissue Data (○) for the 1,000 ng/kg Group in the 2-Year Study

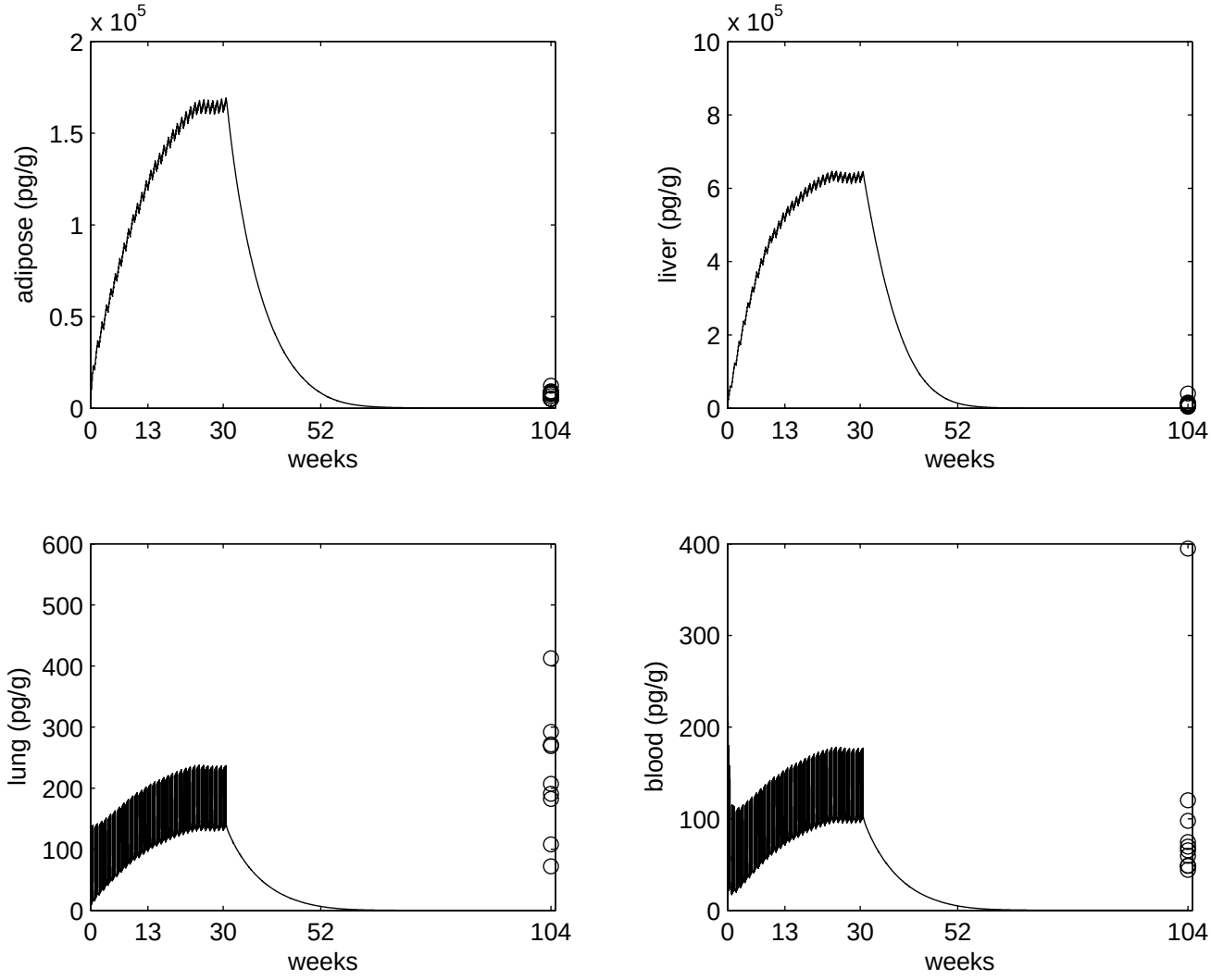

FIGURE G9
Model Predictions (–) and Individual Tissue Data (○) for the 1,000 ng/kg Stop-Exposure Group in the 2-Year Study

APPENDIX H
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 (PCB126). *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 female Harlan Sprague-Dawley rats from two-year studies performed by the National Toxicology Program. *Toxicol. Pathol.* **33**, 477-483.

Hailey, J.R., Walker, N.J., Sells, D.M., Brix, A.E., Jokinen, M.P., and Nyska, A. (2005). Classification of proliferative hepatocellular lesions in Harlan Sprague-Dawley rats chronically exposed to dioxin-like compounds. *Toxicol. Pathol.* **33**, 165-174.

Hassoun, E.A., Li, F., Abushaban, A., and Stohs, S.J. (2000). The relative abilities of TCDD and its congeners to induce oxidative stress in the hepatic and brain tissues of rats after subchronic exposure. *Toxicology* **145**, 103-113.

Hassoun, E.A., Li, F., Abushaban, A., and Stohs, S.J. (2001). Production of superoxide anion, lipid peroxidation and DNA damage in the hepatic and brain tissues of rats after subchronic exposure to mixtures of TCDD and its congeners. *J. Appl. Toxicol.* **21**, 211-219.

Hassoun, E.A., Wang, H., Abushaban, A., and Stohs, S.J. (2002). Induction of oxidative stress in the tissues of rats after chronic exposure to TCDD, 2,3,4,7,8-pentachlorodibenzofuran, and 3,3′,4,4′,5-pentachlorobiphenyl. *J. Toxicol. Environ. Health* A **65**, 825-842.

Jokinen, M.P., Walker, N.J., Brix, A.E., Sells, D.M., Haseman, J.K., and Nyska, A. (2003). Increase in cardiovascular pathology in female Sprague-Dawley rats following chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3,3′,4,4′,5-pentachlorobiphenyl. *Cardiovasc. Toxicol.* **3**, 299-310.

Lee, H.M., He, Q., Englander, E.W., and Greeley, G.H., Jr. (2000). Endocrine disruptive effects of polychlorinated aromatic hydrocarbons on intestinal cholecystokinin in rats. *Endocrinology* **141**, 2938-2944.

Nyska, A., Jokinen, M.P., Brix, A.E., Sells, D.M., Wyde, M.E., Orzech, D., Haseman, J.K., Flake, G., and Walker, N.J. (2004). Exocrine pancreatic pathology in female Harlan Sprague-Dawley rats after chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin and dioxin-like compounds. *Environ. Health Perspect.* **112**, 903-909.

Nyska, A., Yoshizawa, K., Jokinen, M.P., Brix, A.E., Sells, D.M., Wyde, M.E., Orzech, D.P., Kissling, G.E., and Walker, N.J. (2005). Olfactory epithelial metaplasia and hyperplasia in female Harlan Sprague-Dawley rats following chronic treatment with polychlorinated biphenyls. *Toxicol. Pathol.* **33**, 371-377.

Tani, Y., Maronpot, R.R., Foley, J.F., Haseman, J.K., Walker, N.J., and Nyska, A. (2004). Follicular epithelial cell hypertrophy induced by chronic oral administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin in female Harlan Sprague-Dawley rats. *Toxicol. Pathol.* **32**, 41-49.

Toyoshiba, H., Walker, N.J., Bailer, A.J., and Portier, C.J. (2004). Evaluation of toxic equivalency factors for induction of cytochromes P450 CYP1A1 and CYP1A2 enzyme activity by dioxin-like compounds. *Toxicol. Appl. Pharmacol.* **194**, 156-168.

Vezina, C.M., Walker, N.J., and Olson, J.R. (2004). Subchronic exposure to TCDD, PeCDF, PCB126, and PCB153: Effect on hepatic gene expression. *Environ. Health Perspect.* **112**, 1636-1644.

Walker, N.J., Crockett, P.W., Nyska, A., Brix, A.E., Jokinen, M.P., Sells, D.M., Hailey, J.R., Easterling, M., Haseman, J.K., Yin, M., Wyde, M.E., Bucher, J.R., and Portier, C.J. (2005). Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds." *Environ. Health Perspect.* **113**, 43-48.

Yoshizawa, K., Marsh, T., Foley, J.F., Cai, B., Peddada, S., Walker, N.J., and Nyska, A. (2005). Mechanisms of exocrine pancreatic toxicity induced by oral treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin in female Harlan Sprague-Dawley rats. *Toxicol. Sci.* **85**, 594-606.

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