NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 244

CARCINOGENESIS STUDIES OF POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)

(CAS NO. 67774-32-7)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

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

NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was designed and conducted at the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Studies should be directed to the National Toxicology Program, located at Research Triangle Park, NC 27709 (919-541-3991) or at Room 835B, Westwood Towers, 5401 Westbard Ave., Bethesda, MD 20205 (301-496-1152).

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NTP TECHNICAL REPORT
ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF A POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)

(CAS NO. 67774-32-7)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709

June 1983

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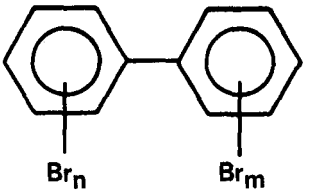

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POLYBROMINATED BIPHENYL MIXTURE

CAS NO. 67774-32-7

ABSTRACT

Firemaster FF-1, a flame retardant composed of polybrominated biphenyls (PBB), was responsible for widespread environmental contamination and animal losses in Michigan starting in 1973. This study was undertaken to characterize the long-term toxic and carcinogenic potential of this PBB mixture in rats and mice of each sex. Fischer 344/N rats and B6C3F$_1$ mice were given 125 oral doses of PBB over a 6-month period — 0, 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg body weight/day (5 days/week).

A dose-related decrease in body weight gain was observed in both male and female rats and male mice, although there was no significant difference in food consumption. At the end of the 6-month exposure, there was a dose-dependent decrease in thymus weights in rats. The liver appeared to be the primary target organ. Dose-related hepatotoxic effects were characterized by a marked increase in liver weight, with accentuation of hepatic lobular markings. Microscopically, there was moderate to marked hepatocellular swelling, disorganization and single cell necrosis of hepatocytes, fatty infiltration, and bile duct proliferation. At the 6-month observation, atypical hepatocellular foci were observed at a low incidence in dosed rats and mice. Hepatic porphyrin levels were markedly increased in both rats and mice, excessively in females. Levels of porphyrin tended to decrease gradually, primarily in mice, following cessation of exposure. The significant decreases in serum thyroxine (T_4) and triiodothyronine (T_3) in rats suggest that PBB may interfere with thyroid hormone secretion.

Total serum protein was decreased in dose-related fashion in female rats primarily due to dose-related decreases in albumin. There was a significant increase in the serum levels of gamma glutamyl transpeptidase (GGTP) in female rats given 10.0 mg/kg of PBB. There was a dose-related decrease in serum glucose in female rats, a dose-related decrease in the serum triglyceride level in dosed male rats, except at the lowest dose (0.1 mg/kg), and a dose-related increase in the serum levels of cholesterol in both male and female rats.

Serum levels of GGTP were increased only in female mice given 10.0 mg/kg of PBB. There was a 5- to 6-fold increase in the activity of serum glutamic pyruvic transaminase (SGPT) in male and female mice in 10.0 mg/kg groups. Serum enzyme activity of alkaline phosphatase (AP) was also increased in mice given the highest dose of PBB. There was a significant dose-related increase in the serum levels of cholesterol in female mice, and the highest dose group was significantly greater than the control female mice. Serum glucose was significantly decreased in female mice administered 10.0 mg/kg of PBB.

To determine the carcinogenic potential of PBB, rats and mice dosed for 6 months were observed without exposure to PBB for an additional 23 or 24 months, respectively (lifetime observation). The dosing (0.3 mg/kg or higher dose levels) shortened the survival time in male rats, whereas no such effect was observed in dosed females. There was also evidence of shortened survival time in the 10.0 mg/kg PBB-dosed mice. A significantly higher incidence of atypical hepatocellular foci, neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas was observed in dosed rats. The incidence of hepatocellular carcinoma was increased in both male and female mice (highest dose level) compared with control male and female mice. The incidence of hepatic neoplasms appeared to be dose dependent in rats and mice. Liver tumors were observed primarily in those groups of animals to which PBB was given in doses sufficient to induce readily observable hepatic toxicity.

Under the conditions of these studies, polybrominated biphenyl mixture (Firemaster FF-1) was carcinogenic for Fischer 344/N rats and B6C3F$_1$ mice of each sex, inducing neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice. Other toxicities included porphyrogenic effects and hepatotoxicity.

CONTRIBUTORS

National Toxicology Program
P.O. Box 12233
Research Triangle Park
North Carolina 27709

This toxicology and carcinogenesis bioassay was conducted at the National Institute of Environmental Health Sciences/National Toxicology Program. The chronic study using Fischer 344/N rats was begun in October 1977, exposure terminated in April 1978 (6 months), and completed in February 1980 (29 months); the study using B6C3F$_1$ mice began in February 1978, exposure stopped in August 1978 (6 months), and completed in August 1980 (30 months).

The polybrominated biphenyl mixture (Firemaster FF-1) used in this toxicology and carcinogenesis bioassay was supplied by Michigan Chemical Corporation, St. Louis, Michigan, and analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110.

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SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)

On 23 June 1981, this toxicology and carcinogenesis studies technical report on polybrominated biphenyl mixture (Firemaster FF-1) underwent peer review and was approved by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts at an open meeting held in Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Hitchcock, a principal reviewer, agreed that this polybrominated biphenyl mixture (PBB) was carcinogenic for Fischer 344/N rats and $B6C3F_1$ mice of both sexes, inducing neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice. Other toxicities observed included porphyrogenic effects and hepatotoxicity. The test compound also affected the body weight gain in male and female rats and male mice, although there was no significant difference in food consumption. Dr. Hitchcock noted that this study was the first to be completed under NTP with an experimental protocol which expands the traditional two-dose two-species design. For both rats and mice, there were 6 dose groups ranging from 0 (controls) to 0.1 to 10.0 mg/kg, 5 days/week for 6 months. To determine the carcinogenic potential of PBB, rats and mice dosed for 6 months were observed for an additional 23 or 24 months, respectively.

Of great importance, she said, was the demonstration that liver tumors were observed only in those animals which exhibited frank hepatotoxicity. For this protocol she commented on the unfortunate absence of historical control tumor incidence data for the 6-month time period. She said this made it difficult to determine the importance of the squamous cell carcinoma of the bladder in a female rat administered 10 mg/kg. Furthermore, the small number of animals available after two additional years may have introduced some bias in the final result. She concluded, however, that the evidence for carcinogenicity was clear. Since the test compound is a mixture, the results of this study can be applied only to the mixture used and not to other mixtures of different combinations of PBBs or those with different contaminants. Nonetheless, she indicated that this was indeed the specific chemical mixture involved in the accidental exposure in Michigan.

As a second principal reviewer, Dr. Shore said it was refreshing to see a study using multiple dose groups and looking at several toxicity end-points. However, there were weaknesses in the carcinogenesis part of the study relating to the rather small numbers of animals in the controls and some of the dose groups. He asked whether the animals used for immunology and subchronic pathology were selected randomly. Dr. Moore, NTP, replied that the selection was essentially random, but whether this was planned prior to sacrifice or by animal number at the outset is not clear. Dr. Shore suggested it would have been a better design to start with more animals. Dr. Williams asked that information be inserted which reports the lack of mutagenic effects of PBBs in several *Salmonella* tester strains.

Dr. Hitchcock recommended that the report on the bioassay of polybrominated biphenyl mixture (Firemaster FF-1) be accepted with the additions suggested. Dr. Shore seconded the motion, and the technical report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

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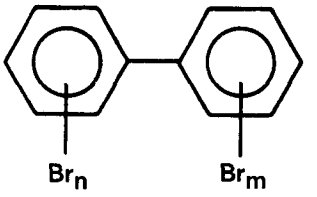

$n + m = 5 - 7$

POLYBROMINATED BIPHENYL MIXTURE

CAS NO. 67774-32-7

Fire safety legislation during the last decade greatly stimulated the production and application of flame retardant chemicals (Anderson, 1976). By 1975 production of these compounds reached approximately 350 million pounds. At present, more than 60% of the total production of flame retardant is used to fireproof carpets and rugs. The balance is impregnated into clothing, home furnishing, and a wide variety of construction, electrical, and electronic products.

Firemaster BP-6 is a mixture of several polybrominated biphenyls (PBB) and was used as a plastics flame retardant because it added a high level of flame resistance to polymer systems. Commercially, Firemaster BP-6 was blended with an anticaking agent (2% calcium trisilicate) and renamed Firemaster FF-1. This PBB mixture (Firemaster BP-6) was found to contain at least 13 different bromobiphenyls and was also contaminated with approximately 200 ppm of bromonaphthalenes (Hass et al., 1978). The major components of Firemaster BP-6 analyzed by gas chromatography/mass spectrometry are given in Table 1.

TABLE 1. POLYBROMINATED BIPHENYL ISOMERS FOUND BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY ANALYSIS OF FIREMASTER BP-6 *(a)*

Isomers	Percentage
Pentabromobiphenyl	2.8 *(d)*
Pentabromobiphenyl	1.2 *(d)*
Hexabromobiphenyl	1.4 *(d)*
Hexabromobiphenyl	56.0 *(b)*
Hexabromobiphenyl	5.2 *(d)*
Heptabromobiphenyl	4.0 *(d)*
Heptabromobiphenyl	27.3 *(c)*
Heptabromobiphenyl	2.1 *(d)*
Total	100.0 %

(a) Hass et al. (1978).
(b) 2,2',4,4',5,5'-Hexabromobiphenyl.
(c) 2,2',3,4,4',5,5'-Heptabromobiphenyl.
(d) Isomeric configuration unknown.

I. INTRODUCTION

PBBs were first used commercially in 1970, and their manufacture increased 100-fold by 1974 (Mumma and Wallace, 1975). Firemaster BP-6 was manufactured solely by the Michigan Chemical Corporation, St. Louis, Michigan. The single U.S. producer of hexabromobiphenyl (HBB) ceased production in November 1974, having produced an estimated 2.2 million kg in 1974 and about 5.1 million kg in the period 1970-1974 (IARC, 1978). During 1970-1973, 45,350 kg of octabromobiphenyl and decabromobiphenyl were produced by a New Jersey chemical firm (Mumma and Wallace, 1975).

Pure hexabromobiphenyl, the major component of Firemaster BP-6, begins to melt at 72°C and decomposes in the range of 300° to 400°C (IARC, 1978), and no residue remains at 500°C (Anon., 1971). Virtually insoluble in water, it is highly soluble in organic solvents and fat (lipophilic). Polybrominated biphenyls are not easily degraded in the environment (Jacobs et al., 1978), and therefore, potential exists for long-term cumulative environmental build-up similar to that with the closely-related polychlorinated biphenyls (Kay, 1977; Kasza et al., 1978). However, under laboratory conditions, ultraviolet radiation readily degraded the PBB (2,2',4,4',5,5'-hexabromobiphenyl and Firemaster BP-6) in methanol solution (Ruzo and Zabik, 1975).

Widespread animal toxicity due to Firemaster FF-1 occurred in Michigan in 1973 as a result of inadvertent substitution of this flame retardant for a mineral feed supplement, magnesium oxide (Mercer et al., 1976; Cook et al., 1978). The Michigan PBB incident has been termed the most costly and disastrous chemical contamination ever to occur in United States agriculture. The most commonly cited hypothesis as to how the Michigan PBB disaster came about has been recorded by Carter (1976). Sometime during the summer of 1973, ten to twenty 50-pound bags of "Firemaster" were somehow included in a truck load of "Nutrimaster" (magnesium oxide, a compound used to "sweeten" acidic feeds) and was shipped to a large feed mill. Under normal circumstances, the Firemaster, which resembled Nutrimaster in physical appearance, would have been packaged in bags lettered in red. Because of a shortage of bags with preprinted labeling, the Firemaster as well as the Nutrimaster were packaged in plain brown bags on which the trade names were stenciled in black. How the Firemaster and Nutrimaster bags became mixed at the manufacturing plant remains unknown.

There is no question that 500 to 1,000 pounds of PBB were mixed into animal feeds that were then widely sold and distributed to Michigan farmers. The circumstantial human error and the events that followed this tragedy have been well documented by Carter (1976). The contaminated feed was consumed by a large number of farm animals and poultry. A toxic syndrome associated with the feeding of PBB contaminated protein concentrate to dairy cattle was first reported by Jackson and Halbert (1974). The clinical signs in affected cattle included anorexia, decreased milk production, increased frequency of urination, lacrimation, lameness, hematoma, loss of hair, and abnormal growth of the hooves. The time of exposure was approximately 9 months, and during this period the contaminated dairy products and eggs were widely consumed by farmers and their families, and later, by the general population of Michigan (Humphrey and Hayner, 1975).

Due to this contamination, at least 29,800 cattle, 5,920 hogs, 1,470 sheep, and 1.5 million chickens were destroyed (Carter, 1976; Dunckel, 1975). Also removed from the commercial market were at least 865 tons of animal feed, 17,790 pounds of cheese, 2,630 pounds of butter, 34,000 pounds of dry milk products and nearly 5 million eggs (Carter, 1976). This mixing error has been alleged to have caused health problems in people who consumed the milk and food contaminated with PBB (Brown and Nixon, 1979). However, in other reports, positive correlation between exposure (as determined by serum or adipose tissue PBB levels) and reported health problems in some residents of Michigan was not observed (Meester and McCoy, 1977; Isbister, 1977; Humphrey et al., 1979; Barr, 1980). There has been a recent report of primary hypothyroidism in 4 men (11.4% of 35 men examined) employed in a plant which produced the PBBs, decabromobiphenyl, and decabromobiphenyl oxide (Bahn et al., 1980). Hepatic porphyria has not been found in people exposed to PBBs in Michigan; nonetheless, an alteration in the urinary porphyrin pattern, which may reflect preliminary changes, has been reported (Strik et al., 1979).

Polybrominated biphenyl was discovered in human hair samples, fish, plants, soil, and water near two New Jersey facilities which manufactured PBBs for export (Anon., 1977). PBBs were also found in human hair, fish, and soil near a chemical firm on Staten Island, New York. This

chemical firm did not manufacture PBB, but used it in the manufacture of wire coatings (Anon., 1977). Oil extracted samples of hair from men from Staten Island contained as much as 17 ppm, whereas hair samples taken near the New Jersey firms had PBB levels as high as 210 ppm.

The Michigan Department of Health evaluated 298 persons exposed to PBB-contaminated products (Humphrey and Hayner, 1975). Blood samples from adults showed that the exposed group had a median PBB value of 0.014 ppm and ranged from 0.002 ppm to 2.26 ppm. Human breast milk has been found to contain PBB from 0.21 to 92.66 ppm (median 10.80 ppm). Concentrations of PBB in adipose tissue ranged from 0.1 to 174.0 ppm. In another report, a comparison was made in the serum PBB levels of residents of Michigan exposed to PBB and in that of the residents of Wisconsin, not known to have been exposed to PBB (Wolff et al., 1979). Among the 993 dairy farm residents and 55 chemical workers in Michigan, 96% (902 persons) had higher than 0.3 ppb of PBB in the serum, whereas only 5% (8 persons) of those from Wisconsin had similar levels: 6 of the 8 people with detectable PBB in their sera were members of a family who recently moved from Michigan to Wisconsin (Wolff et al., 1979). Nine farm residents and 14 employees of the chemical company which manufactured PBB were reexamined after 18 months. In each case, serum values for PBB were similar to previous findings.

To determine the extent of human exposure, PBB concentrations were measured in human breast milk, collected in a random sample survey from nursing mothers throughout Michigan (Brilliant et al., 1978); 51 of 53 (96%) breast milk samples from the lower peninsula and 18 of 42 (43%) samples from the less densely-populated upper peninsula contained detectable amounts of PBB. Theoretically, 8 million of Michigan's 9.1 million residents had detectable amounts of PBB (Brilliant et al., 1978). A detailed continuing survey of the general population of Michigan for health effects of PBB exposure was also reported by Selikoff and Anderson (1979).

Matthews et al. (1977) observed that PBB concentration in adipose tissue from rodents would not be expected to show an appreciable decline during the lifetime of the animal. The intestinal absorption, distribution, and excretion of 2,2',4,4',5,5'-hexabromobiphenyl, the major component of Firemaster BP-6, was studied in the rat (Matthews et al., 1977). Radiolabeled 2,2',4,4',5,5'-[^{14}C] hexabromobiphenyl was administered orally as well as intravenously. Hexabromobiphenyl was readily absorbed from the intestine, initially distributed throughout the body, and finally stored primarily in the adipose tissue of the rat. There was no appreciable metabolism of PBB, which was excreted almost exclusively in the feces at a very slow rate. Approximately 90% of an oral dose was absorbed from the rat intestine. The extrapolation of the data from the rate of excretion to infinity indicated that less than 10% of the total dose would ever be excreted (Matthews et al., 1977).

Polybrominated biphenyl was reported to have a relatively low acute toxicity; the single oral LD_{50} in the laboratory rat was stated to be 21.5 g/kg body weight (Anon., 1971; 1976; Hill Top Research, 1970). However, PBB was found to be more toxic when given in small repeated doses (Gupta and Moore, 1979). In Fischer 344 rats, PBB was given orally at 30, 100, 300, and 1,000 mg/kg body weight/day (5 days/week, 22 total doses) for 4.5 weeks and observed for 90 days after the start of dosing. The LD_{50} for female rats was estimated to be 65 mg/kg/day (total 1.43 g/kg) and for male rats, 149 mg/kg/day (total 3.28 g/kg) when given in multiple doses and observed for 90 days.

A comparative toxicity study of Firemaster FF-1 and pure 2,2',4,4',5,5'-hexabromobiphenyl, the major component of Firemaster FF-1, was conducted in rats and mice (Gupta et al., 1981). The Firemaster FF-1 was found to be more toxic than the pure hexabromobiphenyl, as determined by measurement of porphyrins and severity of pathologic findings principally in the liver. Rats and mice treated with hexabromobiphenyl tended to recover during the postexposure period (Gupta et al., 1981). Several previous studies have shown that the hepatic toxicity of PBB was quite similar to that induced by PCB in rats (Kasza et al., 1978). In another study, rats fed a diet containing 10 ppm PBB for 30 days developed a slight hepatotoxic effect, and pups nursed by PBB-exposed dams also had microscopic and ultrastructural lesions in the liver (Sleight and Sanger, 1976). Hepatic changes such as necrosis, fibrosis, and neoplastic nodules were found in rats 10 months after a single large oral dose (1.0 g/kg) of PBB (Kimbrough et al., 1977; 1978). Atypical foci in the liver were also observed in rats as early as 6 months after exposure to 22 daily doses of PBB

at 30.0 or 100.0 mg/kg body weight over a one-month period (Gupta and Moore, 1979). In a recent report, liver tumors were induced by PBB in female Sherman rats given either a single dose of 1,000 mg PBB/kg or 12 doses of 100 mg PBB/kg body weight; the respective incidence of hepatocellular carcinoma was 41.4 and 67.8% during a 2-year period (Kimbrough et al., 1981).

Polybrominated biphenyl was shown to be embryotoxic and teratogenic to rat embryos (Beaudoin, 1977; Corbett et al., 1975; Harris et al., 1978). Other studies have shown that PBB transfers to the fetus transplacentally (Aftosmis et al., 1972; Detering et al., 1975; Rickert et al., 1978) and is readily excreted in the milk (Fries and Marrow, 1975; Fries, 1978; Gutenmann and Lisk, 1975; Moore et al., 1978). Toxicity and distribution of PBB were investigated by feeding rations containing different concentrations of PBB to sows during pregnancy and lactation (Werner and Sleight, 1981). Mortality was increased among pigs nursed by sows fed rations containing PBB. Although transplacental passage of PBB resulted in an appreciable amount of PBB in tissues of new-born pigs, far more PBBs were transferred to the pigs through the milk (Werner and Sleight, 1981).

In a long-term feeding study in mink, PBB derived from contaminated beef and poultry tissues was more toxic than the Firemaster FF-1 commercial mixture of PBB incorporated experimentally into beef (Aulerich and Ringer, 1979). Toxicity of polybrominated biphenyl in poultry and the compound's effects on avian reproduction have also been reported (Cecil and Bitman, 1978; Ringer and Polin, 1975 and 1977; Chang and Zindel, 1975; Lillie et al., 1975).

Norris et al. (1975) found evidence of thyroid hyperplasia in rats fed octabromobiphenyl for 30 days at 8.0 mg/kg/day. Morphologic changes in thyroid glands were also observed in male rats exposed to PBB (Kasza et al., 1978; Gupta and Moore, 1979). Increased thyroid gland weights, slight hyperplasia of follicular cells of the thyroid, thin and scant colloid, and decreased serum concentrations of thyroid hormones of pigs nursed by PBB-exposed sows have been reported (Werner and Sleight, 1981).

Since the PBB mishap in Michigan, several investigators have tried to lower the body burden of PBB after experimental exposures. McConnell et al. (1980) used activated charcoal and cholestyramine, along with restricted caloric intake, in an effort to mobilize PBBs stored in fat. Neither these compounds nor the restricted caloric intake was found effective in reducing tissue bromine levels. In another study, different diets and mineral oil were used to study the PBB concentration in tissues (Kimbrough et al., 1980). Chemical analyses for PBBs in blood, liver, and adipose tissue showed no significant differences among the differently treated groups.

PBB exposure severely depressed cell-mediated immunity in both mice and rats (Luster et al., 1978). It was concluded that PBB exposure may lead to suppression of both humoral and particularly cell-mediated immune responses.

Several studies have been carried out at the National Institute of Environmental Health Sciences/National Toxicology Program to achieve a greater understanding of the chemical disposition, toxicological, behavioral and immunological effects of PBB in rats, mice, and guinea pigs (Luster et al., 1980; Goldstein et al., 1979; Tilson et al., 1978; Tilson and Cabe, 1979; Matthews et al., 1977). Hexabromobiphenyl (36355-01-8) did not induce any mutagenic response in *Salmonella typhimurium* tester strains TA98, 100, 1535, and 1537 (with or without metabolic activation). Exogenous metabolic activation was provided by 9000 x g liver supernatant (S-9) fractions from Aroclor 1254®-induced male Sprague-Dawley rats and male Syrian hamsters. Likewise, this chemical did not cause chromosome aberrations or sister chromatid exchanges in Chinese hamster ovary cells (NTP, unpublished results). The toxicological, pathological, and carcinogenic studies of PBB in rats and mice are described in this technical report.

II. MATERIALS AND METHODS

Test Chemical

Animals and Husbandry

Experimental Design (Six-Month Administration)

Dose Selection

Necropsy Examination

Clinical Pathologic Examination

Electron Microscopic Examination

Excess Porphyrin Determination

Carcinogenic Potential of Polybrominated Biphenyl After Six-Month Exposure

Experimental Design

Statistical Analysis

Test Chemical

Firemaster FF-1 (Firemaster BP-6 and 2% calcium trisilicate, Lot No. 1312 FT Batch 03) was obtained from Michigan Chemical Corporation, St. Louis, Michigan. The chemical composition of the PBB mixture was analyzed (Table 1) and reported earlier by Hass et al. (1978).

Firemaster FF-1 (PBB) was mixed with corn oil. Stock solutions of PBB were diluted 1:5 and the concentrations were verified by measuring the 2,2',4,4',5,5'-hexabromobiphenyl (HBB) content of the corn oil using selected ion monitoring gas chromatography/mass spectrometry. The calculated amount of PBB in stock solutions was 20.0 mg/ml; the estimated amount was 20.2 ±20% mg/ml when analyzed and compared with a standard of 2,2',4,4',5,5'-hexabromobiphenyl in corn oil. Standard curves were generated using 2,2',4,4',5,5'-HBB.

Animals and Husbandry

Seven- to 8-week-old male and female Fischer 344/N rats (Charles River Laboratories, Wilmington, MA) and B6C3F$_1$ mice (Harlan Industries, Indianapolis, IN) were used. Details of animal maintenance are given in Table 2. Groups of 3 rats or 5 mice of each sex were housed in polycarbonate cages. Pelleted food and water were provided *ad libitum*. Ground corn cob was used as bedding for rats, and hard wood chips for mice. Cool white fluorescent light was provided 12 hours per day. The temperature was maintained at 70° ± 2°F, and relative humidity was 50% ± 5%.

Experimental Design (Six-Month Administration)

The rats and mice were ranked according to body weight and then randomly assigned to one of six groups (51 rats of each sex and 50 mice of each sex per group). PBB was administered by gavage at doses of 0, 0.1, 0.3, 1.0, 3.0 or 10.0 mg/kg body weight on 5 consecutive days per week for 25 consecutive weeks (125 total doses during a 6-month period). The concentrations of the solutions in corn oil were adjusted weekly based on the mean body weight of the dose group, so that each rat received a constant volume of 0.2 ml/day and each mouse 0.1 ml/day. Animals that received no PBB received equal volumes of corn oil.

All animals were observed daily for clinical appearance. Each animal was weighed once per week; food consumption by cage was determined once each week.

Dose Selection

The LD_{50} of PBB was mathematically determined to be 65 mg/kg/day (total 1.43 g/kg) for F344/N female rats and 149 mg/kg/day (total 3.28 g/kg) for the males (Gupta and Moore, 1979). These results were obtained from rats exposed to 22 multiple doses of PBB during a one-month period, and observed for 90 days. There was 100% and 38% mortality in female and male rats respectively given doses of PBB at 100 mg/kg, and no deaths in the 30 mg/kg dose groups.

On the basis of the above observations (mortality, body weight gain effect, thymic atrophy, and hepatotoxicity), 10.0 mg/kg of PBB was selected as the highest dose level for a 6-month study. The lower 4 doses were selected on a logarithmic basis, i.e., 10.0, 3.0, 1.0, 0.3, and 0.1 mg/kg/day.

At the termination of this 6-month dosing period, potential hepatocarcinogenic effects of PBB were suspected because of a high dose-related incidence of atypical foci in the liver. Therefore, it was decided to observe for their lifetime those rats that were not killed at 6 months.

Necropsy Examination

At the end of the 6-month exposure, randomly selected groups of 10 rats or mice/dose/sex were killed. The rats were anesthetized by exposure to high levels of CO_2 until respiration ceased; the mice were anesthetized with methoxyfluorane. Blood samples were then collected from the rat via orbital sinus and from the mouse by cardiac puncture. All animals were then killed by exsanguination. Weights of lung, heart, liver, spleen, thymus, right kidney, right adrenal gland, right gonad, both thyroid glands, uterus, and brain were recorded and organ to body weight ratios calculated. In addition to the organs weighed, tissue samples from pinna, ear and ear canal, eye, trachea, urinary bladder, sternum, quadriceps muscle, accessory male and female sex organs, six levels of gastro-intestinal tract, lumbar spinal cord, sciatic nerve, spinal ganglion,

salivary glands, mesenteric and thoracic lymph nodes, mammary glands, and nasal turbinates were fixed in buffered, pH 7.0, 10% formalin for histopathologic examination. These specimens were embedded in paraffin, sectioned 6 μm thick and stained with hematoxylin and eosin. Cryostat prepared sections (10 μm thick) of formalin-fixed liver were also stained with oil red O for examination of neutral lipids. Paraffin sections of liver and spleen from selected rats and mice of each sex were also stained with Mallory's method for iron (Luna, 1968). Tumor-bearing hepatic tissues were also stained with periodic acid Schiff (PAS).

Clinical Pathologic Examination

Blood examinations were conducted using routine hematologic and serum chemistry procedures. Hematologic examinations included total erythrocyte (RBC) counts, erythrocyte indices, hemoglobin (Hb) concentration, packed cell volume (PCV), platelet counts, leukocyte counts (WBC), and differential counts of leukocytes. Serum chemistry included serum glutamic pyruvic transaminase (SGPT), gamma glutamyl transpeptidase (GGTP), alkaline phosphatase (AP), blood (serum) urea nitrogen (BUN), glucose, triglycerides, cholesterol, total protein, albumin, and total globulin and globulin fractions.

Serum thyroxine (T_4) concentrations and triiodothyronine (T_3) uptake were determined using TETRA-TAB and TRI-TAB T_3 uptake kits (Nuclear Medical Labs, Dallas, TX). The test was performed as recommended by the manufacturer except that 20 μl of bovine serum was used for T_4 determination instead of 10 μl. T_3 was determined using the Serulate Total T-3 Kit (Ames Co., Division of Miles Laboratories, Elkhart, IN) with the following modifications: the T_3 antiserum was diluted to provide approximately 40% retention of ^{131}I-T_3 on the column in the absence of nonradioactive T_3 (zero standard), and the incubation period was changed from 2 hours to 1 hour.

Electron Microscopic Examination

Portions of liver from selected male and female rats (highest dose group and control) were fixed in 2.5% glutaraldehyde and 2.0% paraformaldehyde in cacodylate buffer (pH 7.4) for 6 hours, then washed with cacodylate buffer (pH 7.4) for 2 hours, dehydrated in alcohol and propylene oxide, and embedded in Epon 812. Thick sections (0.5 μm) for light microscopy were cut with an ultramicrotome and stained with toluidine blue. Thin sections (400-600 Å) were stained with uranyl acetate and Reynolds' lead citrate (Reynolds, 1963) for electron microscopic examination (Philips 200 electron microscope).

Excess Porphyrin Determination

At necropsy, liver, sternum, bones, and incisor teeth of all rats and mice were examined under long wavelength (366 nm) ultraviolet (UV) light (model B-100 Black-Ray Ultraviolet Lamp, Ultraviolet Products, Inc., San Gabriel, CA) for reddish pink fluorescence as an indication of excess porphyrin accumulation. A portion of liver from rats and mice was frozen for determination of total hepatic porphyrins (Abritti and De Matteis, 1971).

CARCINOGENIC POTENTIAL OF POLYBROMINATED BIPHENYL AFTER SIX-MONTH EXPOSURE

Experimental Design

Since the results of the 6-month evaluation showed tissue changes suggestive of preneoplasia, the surviving animals were kept for lifetime observation. No PBB was given during this period.

After termination of the 6-month dosing, 320 rats and 229 mice (treated and controls of each sex) were kept for 23 and 24 additional months, respectively, for further observation (Tables 2 and 3). At this time, ~ 10% of the surviving rats and mice were killed.

The number of animals remaining in each group for lifetime observation varied from 11 to 40 for rats (Table 3), and 8 to 27 for mice (Table 4). The main reason for this vast range in the number of animals among different groups and for the small sample size was the utilization of some animals by immunotoxicologists, biochemists, and behavioral toxicologists to study the other parameters of PBB toxicity (Luster et al., 1978; 1980; Goldstein et al., 1979; Tilson et al., 1978; Tilson and Cabe, 1979).

TABLE 2. SOURCES AND DESCRIPTIONS OF MATERIALS USED FOR ANIMAL MAINTENANCE IN THE PBB STUDIES.

Item	Manufacturer	Specifications	Frequency of Change or Cleaning
Cages	Lab Products, Inc. Rochelle Park, NJ	Polycarbonates cages Rats—45x20x20 cm Mice—30x17x12 cm	1 x week
Racks	Contracted by NIH	Stainless steel Rats—25 cages/rack Mice—30 cages/rack	1 x week
Bedding			
Rats—Bed-o'cobs	The Andersons Maumee, OH	Ground corn cob 50 lb/bag	1 x week
Mice—Betta Chip® Bedding	Granville Milling Co. Creedmoore, NC	Hardwood chips 50 lb/bag	1 x week
Water Bottles	Girton Manufacturing Co. Millville, PA	Polypropylene	1 x week
Watering Tubes	Ancare Products Manhassett, NY	TD100, 21" length	1 x week
Feed (pelleted)	Zeigler Brother Gardners, PA	NIH-31 25 lb/bag	1 x week
Water	City of Durham	Public Utility	
Cage & Bottle Washer	Girton Manufacturing Co. Millville, PA	Tunnel wash	Daily check; Quarterly maintenance
Rack Washer	Girton Manufacturing Co. Millville, PA	—	Daily check; Quarterly maintenance
Autoclave	Castle Rochester, NY	Sterox-o-matic	Monthly maintenance
Washing Compound	Economic Labs, Inc. St. Paul, MN	Spearhead	

TABLE 3. UTILIZATION OF RATS EXPOSED TO PBB FOR 6 MONTHS

	0.0 mg/kg		0.1 mg/kg		0.3 mg/kg		1.0 mg/kg		3.0 mg/kg		10.0 mg/kg	
	M	F	M	F	M	F	M	F	M	F	M	F
No. Available at end of 6 months	50 *(a)*	51	50 *(a)*	51	50 *(a)*	51	51	51	51	50 *(a)*	51	51
Subchronic pathology	10 *(b)*	10	10	10	10	10	10	10	10	10	10	10
Immunology *(c)*	—	21	—	20	—	20	—	21	—	21	—	21
Behavioral Toxicology *(d)*	7(8) *(e)*	-(12)	—	—	—	—	8	8	7(8)	-(8)	7(8)	-(8)
No. available for lifetime observation	33	20	40	21	40	21	33	12	34	19	34	20
No. examined for pathology	33	20	39 *(f)*	21	40	21	31 *(f)*	11 *(f)*	33 *(f)*	19	32 *(f)*	20

(a) Difference in numbers shown and 51 rats per group at start is number lost to study due to gavage error.

(b) Five males and females from all treatment groups used for clinical pathology and T_3, T_4 assays. All rats of each sex used for organ weights, hepatic porphyrin levels and histopathology.

(c) Luster, et al., (1980).

(d) Tilson and Cabe (1979).

(e) Numbers indicate rats removed for behavioral toxicology at end of six months. ( ) = additional rats tested for behavioral toxicology during 6 months exposure but included in lifetime observation group.

(f) Difference in number examined for pathology and number available is due to post mortem autolysis.

TABLE 4. UTILIZATION OF MICE EXPOSED TO PBB FOR 6 MONTHS

	0.0 mg/kg		0.1 mg/kg		0.3 mg/kg		1.0 mg/kg		3.0 mg/kg		10.0 mg/kg	
	M	F	M	F	M	F	M	F	M	F	M	F
No. Available at end of 6 months	46 *(a)*	50	49 *(a)*	50	47 *(a)*	47 *(a)*	48 *(a)*	43 *(a)*	45 *(a)*	49 *(a)*	44 *(a)*	38 *(a)*
Subchronic pathology	10 *(b)*	10	10	10	10	10	10	10	10	10	10	10
Immunology *(c)*	11	21	11	21	11	21	11	21	11	21	11	20
Behavioral Toxicology	(15) *(d)*	(15)	—	—	—	—	(10)	(10)	(10)	(10)	(8)	(8)
No. available for lifetime observation	25	19	28	19	26	16	27	12	24	18	23	8
No. examined for pathology	25	13 *(e)*	27 *(e)*	19	24 *(e)*	15 *(e)*	25 *(e)*	11 *(e)*	23 *(e)*	17	22 *(e)*	8

(a) Difference in numbers shown and 50 mice per group at start is number lost to study due to gavage error.

(b) Five males and females from all treatment groups used for clinical pathology. Ten mice of each sex used for organ weights, hepatic porphyrin levels, and histopathology.

(c) Luster et al. (1980).

(d) ( ) = Mice tested during exposure phase and included in lifetime observation group.

(e) Difference in number examined for pathology and number available is due to accidental deaths or post mortem autolysis.

Statistical Analysis

For weight gain, organ weight, hematology, and clinical chemistry data, the Kruskal-Wallis nonparametric analysis of variance (Hollander and Wolfe, 1973) was used to determine the significance of among-group differences. The significance of dose-response trends was assessed by Jonckheere's test (Jonckheere, 1954). If an overall effect were detected, then pairwise comparisons were made by Mann-Whitney U tests (Hollander and Wolfe, 1973).

Probabilities of survival were estimated by the product limit procedure of Kaplan and Meier (1958), and survival differences were analyzed by life table analysis (Cox, 1972).

For the statistical analysis of neoplastic and nonneoplastic lesions, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high- and low-dosed groups with controls and tests for overall dose-response trends.

For lesions judged to be "nonfatal" (i.e., those observed at necropsy in animals dying of an unrelated cause), the incidental tumor test proposed by Peto et al. (1980) was employed to compare incidence rates in PBB and control groups. By means of this approach, the observed proportions of necropsied animals with lesions were compared in each of five time intervals: 0-1.75 years, 1.75-2 years, 2-2.25 years, 2.25 years-terminal kill, and terminal kill. These results were then combined by the Mantel-Haenszel methods to obtain an overall P-value. For male rats, when markedly reduced survival made the incidental tumor test not feasible (since, e.g., there was little overlapping survival in the highest and control groups), Fisher's exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979) were employed to compare incidence rates. Lesions considered to be nonfatal were bile duct hyperplasia, hyperplastic gastropathy, hepatocellular adenoma, and atypical foci or neoplastic nodules of the liver.

For lesions judged to be "fatal" (i.e., that either directly or indirectly caused the death of the animal), life table methodology was employed to compare incidence rates in PBB and control groups (Cox, 1972). Examples of these lesions include hepatocellular carcinoma, cholangiocarcinoma, and malignant lymphoma.

III. RESULTS

RESULTS OF SIX-MONTH OBSERVATION

Clinical Observation
Food Consumption
Organ Weights
Hematologic Findings
Clinical Chemistry
Necropsy Findings
Histopathologic Findings

RESULTS OF LIFETIME OBSERVATION

Survival Time in Rats
Survival Time in Mice
Body Weights in Rats and Mice
Necropsy Findings in Rats and Mice
Histopathologic Findings in Rats
Necropsy Findings in Mice
Histopathologic Findings in Mice

RESULTS OF SIX-MONTH OBSERVATION

Clinical Observation

During the 6-month dosing period, animals were clinically normal in appearance. No deaths related to PBB administration were observed. There were depressed rates of body weight gain in rats as a function of time and dose (Fig. 1). The body weight gain in female mice (10.0 mg/kg/day) was elevated, whereas in the male mice, it was depressed (Fig. 2). There was no significant difference in body weight gain in other groups of dosed and control mice.

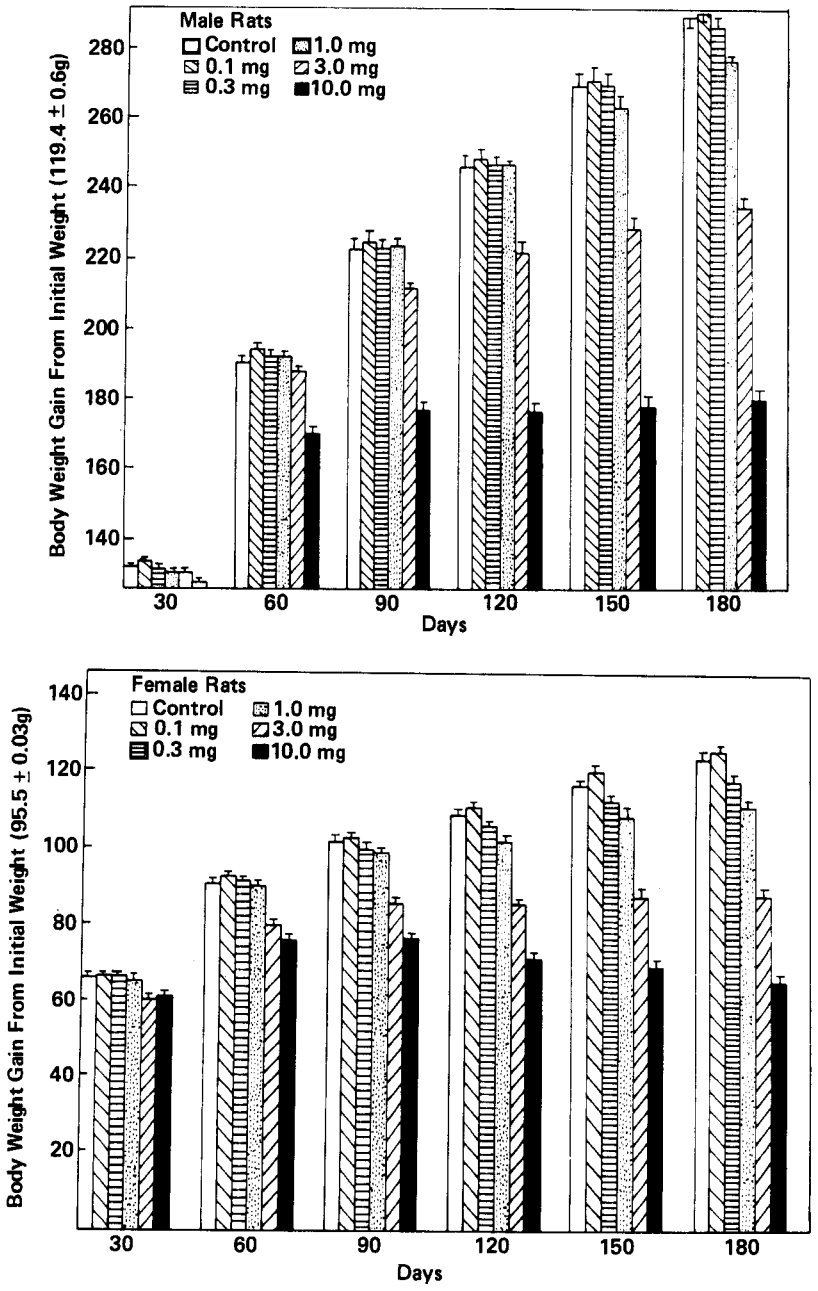

Figure 1. Histogram Showing Difference in Body Weight Gain in Rats Exposed to Polybrominated Biphenyl Mixture, a Total of 125 Doses During a 6-Month Period

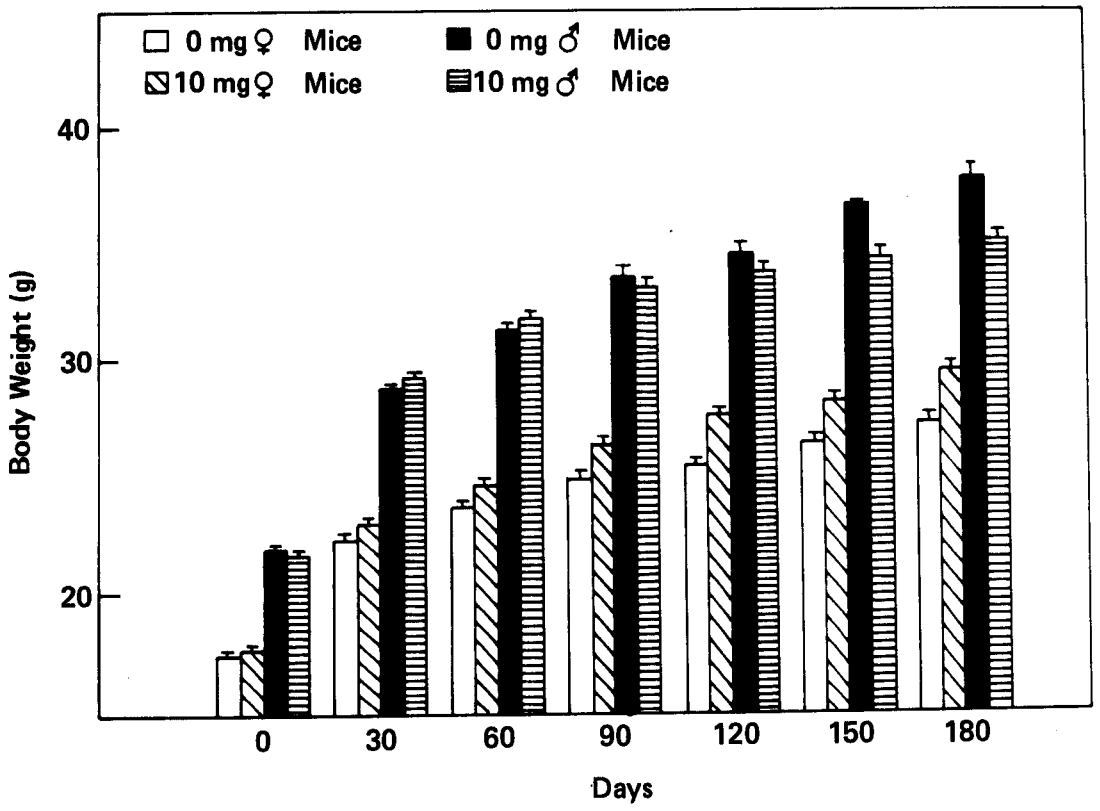

Figure 2. Histogram Showing Changes in the Body Weights of Male and Female Mice Exposed to Polybrominated Biphenyl Mixture at 10.0mg/kg Body Weight/Day, 125 Total Doses During a 6-Month Period

Food Consumption

During the 6-month dosing phase, there was no difference in food consumption in either rats or mice (Tables 5-8). However, there was a slight decrease in food intake in the female rats administered 10.0 mg/kg/day of PBB during the last 6 weeks of administration (Table 6).

TABLE 5. FOOD CONSUMPTION BY MALE RATS RECEIVING PBB

		0.1 mg/kg		0.3 mg/kg		1.0 mg/kg		3.0 mg/kg		10 mg/kg	
Week	Control *(a)*	Absolute *(a)*	Relative *(b)*	Absolute *(a)*	Relative *(b)*	Absolute *(a)*	Relative *(b)*	Absolute *(a)*	Relative *(b)*	Absolute *(a)*	Relative *(b)*
1	17.3	17.3	1.00	17.4	1.01	17.2	0.99	17.2	0.99	17.5	1.01
2	18.8	18.8	1.00	19.1	1.02	18.2	0.97	18.9	1.01	19.1	1.02
3	17.5	17.8	1.02	17.6	1.01	17.5	1.00	17.7	1.01	18.2	1.04
4	17.2	17.5	1.02	17.5	1.02	17.5	1.02	17.7	1.03	17.5	1.02
5	17.9	18.1	1.01	18.1	1.01	18.3	1.02	18.2	1.02	18.2	1.02
6	18.0	18.1	1.01	18.5	1.03	18.6	1.03	18.5	1.03	18.6	1.03
7	18.8	19.2	1.02	19.6	1.04	19.8	1.05	19.8	1.05	19.6	1.04
8	17.3	17.7	1.02	17.6	1.02	17.8	1.03	17.9	1.03	17.6	1.02
9	17.9	18.3	1.02	18.5	1.03	18.5	1.03	18.6	1.04	18.3	1.02
10	17.5	17.7	1.01	18.0	1.03	18.1	1.03	17.8	1.02	17.3	0.99
11	17.1	17.4	1.02	17.8	1.04	18.0	1.05	17.8	1.04	17.1	1.00
12	17.5	17.3	0.99	18.0	1.03	18.0	1.03	17.8	1.02	17.2	0.98
13	18.6	17.3	0.93	17.9	0.96	17.6	0.95	17.2	0.92	16.7	0.90
14	16.7	16.8	1.01	17.2	1.03	17.6	1.05	17.1	1.02	16.1	0.96
15	16.8	17.0	1.01	17.5	1.04	17.8	1.06	17.4	1.04	16.9	1.01
16	16.9	17.0	1.01	16.9	1.00	17.4	1.03	17.1	1.01	17.0	1.01
17	16.0	16.9	1.06	16.9	1.06	17.4	1.09	17.0	1.06	16.1	1.01
18	17.6	18.0	1.02	18.2	1.03	18.4	1.05	18.3	1.04	18.2	1.03
19	17.4	17.4	1.00	17.3	0.99	17.8	1.02	17.4	1.00	17.1	0.98
20	18.0	17.8	0.99	18.1	1.01	18.5	1.03	18.2	1.01	17.6	0.98
21	17.9	18.2	1.02	18.6	1.04	18.5	1.03	18.3	1.02	17.9	1.00
22	17.0	17.8	1.05	17.6	1.04	17.7	1.04	17.5	1.03	17.2	1.01
23	18.7	18.9	1.01	19.0	1.02	19.3	1.03	18.8	1.01	18.4	0.98
24	18.4	18.6	1.01	18.9	1.03	19.2	1.04	18.8	1.02	18.5	1.01
25	18.2	18.3	1.01	18.8	1.03	18.7	1.03	18.3	1.01	17.8	0.98
Mean	17.64	17.81	1.01	18.02	1.02	18.14	1.03	18.00	1.02	17.67	1.00
SD *(c)*	0.71	0.64	0.02	0.71	0.02	0.65	0.03	0.69	0.03	0.85	0.03
CV *(d)*	4.04	3.62	2.21	3.93	1.92	3.59	2.78	3.84	2.52	4.82	2.98

(a) Grams of food consumed per animal per day

(b) Ratio of food consumption per day for the dosed group to that for the controls

(c) Standard deviation

(d) Coefficient of variation = $\left(\frac{\text{Standard Deviation} \times 100}{\text{Mean}}\right)$

TABLE 6. FOOD CONSUMPTION BY FEMALE RATS RECEIVING PBB

Week	Control (a)	0.1 mg/kg Absolute (a)	0.1 mg/kg Relative (b)	0.3 mg/kg Absolute (a)	0.3 mg/kg Relative (b)	1.0 mg/kg Absolute (a)	1.0 mg/kg Relative (b)	3.0 mg/kg Absolute (a)	3.0 mg/kg Relative (b)	10 mg/kg Absolute (a)	10 mg/kg Relative (b)
1	12.5	12.6	1.01	12.5	1.00	12.4	0.99	12.2	0.98	12.7	1.02
2	12.8	12.8	1.00	12.7	0.99	12.8	1.00	12.4	0.97	12.9	1.01
3	12.3	12.1	0.98	12.4	1.01	12.1	0.98	12.0	0.98	12.4	1.01
4	11.1	11.3	1.02	11.0	0.99	11.1	1.00	10.9	0.98	11.4	1.03
5	12.1	13.0	1.07	12.0	0.99	12.2	1.01	11.7	0.97	12.6	1.04
6	12.7	11.9	0.94	12.1	0.95	12.5	0.98	11.8	0.93	12.9	1.02
7	12.6	12.7	1.01	12.4	0.98	12.5	0.99	12.0	0.95	13.0	1.03
8	11.5	11.9	1.03	11.6	1.01	11.6	1.01	11.0	0.96	12.0	1.04
9	11.7	11.9	1.02	11.7	1.00	11.7	1.00	11.3	0.97	12.3	1.05
10	12.0	12.0	1.00	11.8	0.98	11.8	0.98	11.4	0.95	12.7	1.06
11	11.5	11.3	0.98	11.2	0.97	11.4	0.99	11.0	0.96	11.8	1.03
12	11.4	11.3	0.99	11.2	0.98	11.4	1.00	10.9	0.96	11.3	0.99
13	11.6	11.6	1.00	11.3	0.97	11.7	1.01	11.0	0.95	11.0	0.95
14	11.5	12.0	1.04	11.5	1.00	11.4	0.99	11.2	0.97	10.8	0.94
15	11.0	11.1	1.01	10.7	1.06	11.0	1.00	10.9	0.99	10.6	0.96
16	11.8	12.0	1.02	11.7	0.99	11.7	0.99	11.5	0.97	11.0	0.93
17	11.0	10.5	0.95	10.3	0.94	10.6	0.96	10.2	0.93	9.6	0.87
18	11.3	12.9	1.14	11.6	1.03	12.2	1.08	11.3	1.00	11.2	0.99
19	11.6	11.8	1.02	11.3	0.97	11.6	1.00	11.2	0.97	10.4	0.90
20	12.5	12.2	0.98	12.0	0.96	12.6	1.01	11.9	0.95	10.7	0.86
21	11.1	11.5	1.04	11.1	1.00	11.8	1.06	11.0	0.99	9.2	0.83
22	12.0	11.6	0.97	11.5	0.96	12.0	1.00	11.2	0.93	9.9	0.83
23	12.4	12.2	0.98	12.0	0.97	12.7	1.02	11.4	0.92	9.7	0.78
24	12.1	12.2	1.01	11.8	0.98	12.5	1.03	11.7	0.97	9.6	0.79
25	12.0	12.2	1.02	11.9	0.99	12.5	1.04	11.4	0.95	9.5	0.79
Mean	11.84	11.94	1.01	11.69	0.99	11.91	1.01	11.38	0.96	11.25	0.95
SD (c)	0.55	0.60	0.04	0.53	0.03	0.58	0.03	0.50	0.02	1.23	0.09
CV (d)	4.66	5.00	3.96	4.57	2.57	4.87	2.53	4.36	2.12	10.97	9.67

(a) Grams of food consumed per animal per day

(b) Ratio of food consumption per day for the dosed group to that for the controls

(c) Standard deviation

(d) Coefficient of variation = $\left(\frac{\text{Standard Deviation x 100}}{\text{Mean}}\right)$

TABLE 7. FOOD CONSUMPTION BY MALE MICE RECEIVING PBB

Week	Control (a)	0.1 mg/kg Absolute (a)	0.1 mg/kg Relative (b)	0.3 mg/kg Absolute (a)	0.3 mg/kg Relative (b)	1.0 mg/kg Absolute (a)	1.0 mg/kg Relative (b)	3.0 mg/kg Absolute (a)	3.0 mg/kg Relative (b)	10 mg/kg Absolute (a)	10 mg/kg Relative (b)
1	3.2	3.5	1.09	3.1	0.97	3.1	0.97	3.1	0.97	2.9	0.91
2	3.6	3.7	1.03	4.0	1.11	3.4	0.94	3.8	1.06	3.6	1.00
3	4.4	4.4	1.00	4.4	1.00	4.5	1.02	4.3	0.98	4.6	1.05
4	4.3	4.4	1.02	4.3	1.00	4.3	1.00	4.5	1.05	4.3	1.00
5	4.7	4.8	1.02	4.7	1.00	4.8	1.02	4.9	1.04	4.9	1.04
6	5.0	4.8	0.96	4.8	0.96	4.8	0.69	5.1	1.02	4.9	0.98
7	4.8	5.0	1.04	4.8	1.00	4.8	1.00	5.3	1.10	5.2	1.08
8	4.8	5.0	1.04	4.7	0.98	4.8	1.00	5.4	1.13	4.9	1.02
9	4.7	4.9	1.04	5.0	1.06	4.7	1.00	4.9	1.04	4.9	1.04
10	4.8	5.0	1.04	5.0	1.04	4.7	0.98	4.8	1.00	4.8	1.00
11	4.7	4.9	1.04	4.2	1.11	5.2	1.11	4.9	1.04	4.9	1.04
12	4.7	4.9	1.04	4.9	1.04	4.9	1.04	5.0	1.06	4.9	1.04
13	4.4	4.7	1.07	4.7	1.07	4.7	1.07	4.6	1.05	4.8	1.09
14	4.6	4.7	1.02	4.9	1.07	4.9	1.07	4.9	1.07	4.3	0.93
15	4.7	4.6	0.98	5.1	1.09	4.9	1.04	4.7	1.00	4.6	0.98
16	4.8	4.7	0.98	4.9	1.02	4.7	0.98	4.9	1.02	4.8	1.00
17	4.7	4.9	1.04	5.2	1.11	4.8	1.02	4.9	1.04	4.9	1.04
18	4.6	4.8	1.04	4.8	1.04	4.6	1.00	4.9	1.07	5.1	1.11
19	4.6	4.7	1.02	4.7	1.02	4.6	1.00	4.6	1.00	4.9	1.07
20	5.0	5.1	1.02	5.2	1.04	4.7	0.94	5.7	1.14	5.7	1.14
21	5.0	5.2	1.04	5.3	1.06	4.9	0.98	5.3	1.06	5.7	1.14
22	4.9	5.3	1.08	5.2	1.06	5.0	1.02	5.2	1.06	5.9	1.20
23	4.8	5.1	1.06	5.0	1.04	4.8	1.00	5.0	1.04	5.6	1.17
24	4.7	4.7	1.00	4.7	1.00	4.7	1.00	5.3	1.13	5.4	1.15
25	4.6	4.8	1.04	4.7	1.02	4.7	1.02	4.8	1.04	5.0	1.09
26	4.7	4.8	1.02	4.8	1.02	4.7	1.00	4.7	1.00	5.1	1.09
Mean	4.61	4.75	1.03	4.77	1.04	4.64	1.01	4.83	1.06	4.87	1.05
SD (c)	0.40	0.40	0.03	0.45	0.04	0.44	0.04	0.52	0.04	0.63	0.07
CV (d)	8.66	8.41	2.05	9.47	4.00	9.58	3.74	10.67	4.15	12.86	6.77

(a) Grams of food consumed per animal per day

(b) Ratio of food consumption per day for the dosed group to that for the controls

(c) Standard deviation

(d) Coefficient of variation = $\left(\frac{\text{Standard Deviation} \times 100}{\text{Mean}}\right)$

TABLE 8. FOOD CONSUMPTION BY FEMALE MICE RECEIVING PBB

Week	Control (a)	0.1 mg/kg Absolute (a)	0.1 mg/kg Relative (b)	0.3 mg/kg Absolute (a)	0.3 mg/kg Relative (b)	1.0 mg/kg Absolute (a)	1.0 mg/kg Relative (b)	3.0 mg/kg Absolute (a)	3.0 mg/kg Relative (b)	10 mg/kg Absolute (a)	10 mg/kg Relative (b)
1	3.7	4.1	1.11	3.3	0.89	4.0	1.08	3.4	0.92	3.4	0.92
2	3.6	3.5	0.97	3.3	0.92	3.3	0.92	3.5	0.97	3.2	0.89
3	3.8	3.7	0.97	3.6	0.95	3.7	0.97	3.7	0.97	4.0	1.05
4	3.9	3.8	0.97	4.0	1.03	4.0	1.03	3.9	1.00	4.2	1.08
5	4.2	4.2	1.00	4.3	1.02	4.5	1.07	4.4	1.05	4.5	1.07
6	4.0	4.2	1.05	4.3	1.08	4.4	1.10	4.1	1.03	4.3	1.08
7	3.9	4.0	1.03	4.2	1.08	4.4	1.13	4.0	1.03	4.3	1.10
8	4.0	4.2	1.05	4.3	1.08	3.8	0.95	4.1	1.03	4.3	1.08
9	4.0	4.1	1.03	4.2	1.05	4.3	1.08	4.2	1.05	4.4	1.10
10	3.9	3.9	1.00	4.1	1.05	4.3	1.10	4.0	1.03	4.4	1.13
11	4.1	4.2	1.02	4.2	1.02	5.0	1.22	4.3	1.05	4.7	1.15
12	3.9	3.8	0.97	3.7	0.95	4.4	1.13	3.8	0.97	4.2	1.08
13	4.0	4.2	1.05	4.3	1.08	4.3	1.08	4.2	1.05	4.6	1.15
14	3.8	3.4	0.89	4.0	1.05	3.0	0.79	3.7	0.97	4.1	1.08
15	3.6	3.8	1.06	3.9	1.08	4.3	1.19	3.9	1.08	4.3	1.19
16	3.7	3.9	1.05	4.2	1.14	4.3	1.16	3.9	1.05	4.6	1.24
17	3.9	3.9	1.00	4.2	1.08	4.2	1.08	4.1	1.05	4.8	1.23
18	3.9	4.1	1.05	4.0	1.03	4.4	1.13	4.1	1.05	4.7	1.21
19	4.0	3.9	0.98	4.1	1.03	4.3	1.08	4.1	1.03	4.6	1.15
20	4.8	4.2	0.88	4.3	0.90	4.5	0.94	4.3	0.90	4.7	0.98
21	4.1	4.2	1.02	4.4	1.07	4.5	1.10	4.4	1.07	4.9	1.20
22	4.2	4.4	1.05	4.4	1.05	4.4	1.05	4.4	1.05	4.8	1.14
23	4.1	3.6	0.88	4.1	1.00	4.7	1.15	4.2	1.02	5.8	1.41
24	4.0	4.0	1.00	4.2	1.05	4.5	1.13	4.2	1.05	4.7	1.18
25	3.9	3.9	1.00	4.2	1.08	4.3	1.10	4.1	1.05	4.7	1.21
26	4.0	3.9	0.98	4.2	1.05	4.3	1.08	4.2	1.05	4.8	1.20
Mean	3.96	3.97	1.00	4.08	1.03	4.23	1.07	4.05	1.02	4.46	1.13
SD (c)	0.23	0.24	0.06	0.30	0.06	0.41	0.09	0.26	0.05	0.49	0.11
CV (d)	5.89	6.13	5.59	7.29	6.01	9.72	8.64	6.49	4.43	10.96	9.37

(a) Grams of food consumed per animal per day

(b) Ratio of food consumption per day for the dosed group to that for the controls

(c) Standard deviation

(d) Coefficient of variation = $\left(\frac{\text{Standard Deviation x 100}}{\text{Mean}}\right)$

Organ Weights

There was a dose-related increase in the absolute and relative liver weights in dosed female rats and in male rats receiving 0.3 mg/kg/day or more of PBB (Tables 9 and 10). Thymus weights were significantly ($P<0.05$) decreased in rats given 0.3 mg/kg or more of PBB. The weight of the spleen was increased in those rats given 1.0 mg/kg or more of PBB (Tables 9 and 10).

Dose-related increases in liver weights were observed in male and female mice (Table 11). No significant differences in the thymus weights were observed. Spleen weight was increased only in higher-dose female mice. Another notable effect was a decrease in uterine weights at the 10.0 mg dose.

TABLE 9. ABSOLUTE AND RELATIVE WEIGHTS (% OF BODY WEIGHT) OF LIVER, SPLEEN, AND THYMUS OF MALE RATS AFTER A 6-MONTH EXPOSURE TO PBB

Dose (mg/kg/day)	Liver Weight		Spleen Weight		Thymus Weight	
	Absolute (g)	Relative (%)	Absolute (g)	Relative (%)	Absolute (g)	Relative (%)
0	13.2 ±.14	3.2 ±.03	0.58 ±.03	0.14 ±.01	0.14 ±.01	0.034 ±.001
0.1	13.9 ±.43	3.4 ±.08 *(a)*	0.57 ±.02	0.14 ±.01	0.13 ±.01	0.033 ±.002
0.3	15.8 ±.27 *(b)*	4.0 ±.15 *(b)*	0.63 ±.02	0.16 ±.01	0.12 ±.01 *(a)*	0.030 ±.001
1.0	18.8 ±.32 *(b)*	4.8 ±.04 *(b)*	0.64 ±.02 *(a)*	0.16 ±.01 *(a)*	0.11 ±.00 *(b)*	0.029 ±.001 *(b)*
3.0	21.4 ±.51 *(b)*	5.9 ±.08 *(b)*	0.77 ±.03 *(b)*	0.21 ±.01 *(b)*	0.07 ±.01 *(b)*	0.020 ±.002 *(b)*
10.0	20.8 ±.34 *(b)*	6.7 ±.05 *(b)*	0.76 ±.04 *(b)*	0.25 ±.01 *(b)*	0.04 ±.00 *(b)*	0.012 ±.001 *(b)*
Dose Response	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

Data are expressed as mean ± SEM of 10 rats.

(a) Significantly ($P < 0.05$) different compared with control.

(b) Significantly ($P < 0.01$) different compared with control.

TABLE 10. ABSOLUTE AND RELATIVE WEIGHTS (% OF BODY WEIGHT) OF LIVER, SPLEEN, AND THYMUS OF FEMALE RATS AFTER A 6-MONTH EXPOSURE TO PBB

Dose (mg/kg/day)	Liver Weight		Spleen Weight		Thymus Weight	
	Absolute (g)	Relative (%)	Absolute (g)	Relative (%)	Absolute (g)	Relative (%)
0	6.2 ±.12	2.9 ±.06	0.38 ±.01	0.18 ±.01	0.14 ±.00	0.070 ±.002
0.1	6.8 ±.23 *(a)*	3.1 ±.07 *(a)*	0.38 ±.01	0.17 ±.01	0.13 ±.01	0.061 ±.002
0.3	6.6 ±.21 *(a)*	3.3 ±.11 *(b)*	0.39 ±.01	0.19 ±.01	0.12 ±.01 *(b)*	0.056 ±.002 *(b)*
1.0	7.1 ±.27 *(a)*	3.4 ±.09 *(b)*	0.41 ±.01	0.20 ±.01 *(a)*	0.11 ±.01 *(b)*	0.052 ±.002 *(b)*
3.0	7.8 ±.22 *(a)*	4.3 ±.10 *(b)*	0.49 ±.02 *(b)*	0.27 ±.01 *(b)*	0.07 ±.00 *(b)*	0.037 ±.002 *(b)*
10.0	8.6 ±.24 *(b)*	5.6 ±.09 *(b)*	0.43 ±.02 *(b)*	0.28 ±.01 *(b)*	0.04 ±.01 *(b)*	0.024 ±.004 *(b)*
Dose Response	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

Data are expressed as mean ± SEM of 10 rats.

(a) Significantly ($P < 0.05$) different compared with control.

(b) Significantly ($P < 0.01$) different compared with control.

TABLE 11. ABSOLUTE WEIGHT (g) AND RELATIVE (%) LIVER TO BODY WEIGHT OF MALE AND FEMALE MICE AFTER A 6-MONTH EXPOSURE TO PBB

Dose (mg/kg/day)	Liver Weight of Male Mice		Liver Weight of Female Mice	
	Absolute (g)	Relative (%)	Absolute (g)	Relative (%)
0	1.8 ±.06	5.0 ±.15	1.2 ±.04	4.5 ±.08
0.1	2.0 ±.03	4.9 ±.08	1.3 ±.03	4.5 ±.07
0.3	1.8 ±.05	4.9 ±.11	1.3 ±.03 *(a)*	4.9 ±.07 *(b)*
1.0	2.1 ±.08 *(a)*	5.6 ±.16 *(a)*	1.6 ±.06 *(b)*	5.7 ±.19 *(b)*
3.0	2.5 ±.07 *(b)*	6.4 ±.17 *(b)*	1.9 ±.03 *(b)*	6.7 ±.09 *(b)*
10.0	4.3 ±.10 *(b)*	12.4 ±.32 *(b)*	4.6 ±.10 *(b)*	15.0 ±.29 *(b)*
Dose Response	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

Data are expressed as mean ± SEM of 10 mice.

(a) Significantly ($P < 0.05$) different compared with control.

(b) Significantly ($P < 0.01$) different compared with control.

Hematologic Findings

The hemoglobin and packed cell volume values were decreased in both male and female rats at the two highest dose levels (Table 12). Similarly, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were also decreased. The WBC count was significantly ($P<0.05$) increased in dosed female rats at dose levels of 1.0, 3.0 and 10.0 mg/kg due to an increase in both neutrophils and lymphocytes (Table 13). However, this trend was not observed in treated male rats.

TABLE 12. ERYTHROCYTE VALUES AND PLATELET COUNTS OF RATS AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Hemoglobin (g/100 ml)	Packed Cell Volume (%)	Red Blood Cells (10^6/cmm)	Mean Corpuscular Volume (μ^3)	Mean Corpuscular Hemoglobin ($\mu\mu$g)	Platelets (10^6/cmm)
MALE	0	16.9 ±0.3	50.6 ±0.9	5.8 ±0.1	85.9 ±1.3	29.2 ±0.5	138.6 ± 7.3
	0.1	17.0 ±0.4	49.4 ±0.9	5.6 ±0.3	89.3 ±5.1	30.8 ±2.1	165.8 ± 7.4 *(a)*
	0.3	16.6 ±0.2	48.1 ±0.3 *(a)*	6.1 ±0.1	79.4 ±1.5 *(a)*	27.4 ±0.7	150.3 ± 8.6
	1.0	15.5 ±0.2 *(a)*	45.7 ±0.8 *(b)*	5.5 ±0.1	83.0 ±2.5	28.2 ±1.0	161.1 ± 5.1 *(a)*
	3.0	15.0 ±0.3 *(a)*	43.8 ±0.5 *(b)*	6.3 ±0.2 *(a)*	69.4 ±2.2 *(a)*	23.9 ±1.0 *(a)*	180.0 ±10.9 *(a)*
	10.0	13.6 ±0.2 *(a)*	39.5 ±1.1 *(b)*	5.6 ±0.1	71.2 ±1.8 *(a)*	24.5 ±0.2 *(a)*	117.2 ±12.7
	Dose Response	$P<0.01$	$P<0.01$	NS	$P<0.01$	$P<0.01$	NS
FEMALE	0	17.8 ±0.3	50.0 ±1.4	5.4 ±0.2	91.9 ±1.9	32.8 ±0.7	134.7 ± 2.8
	0.1	17.2 ±0.5	48.1 ±0.7	5.3 ±0.1	90.8 ±1.0	32.6 ±0.7	125.5 ± 4.1
	0.3	16.7 ±0.3 *(a)*	49.2 ±1.2	6.3 ±0.2 *(a)*	77.6 ±0.9 *(a)*	26.4 ±0.7 *(a)*	240.9 ±63.2
	1.0	17.0 ±0.5	48.1 ±0.7	6.0 ±0.1 *(a)*	80.3 ±1.3 *(b)*	28.4 ±0.6 *(b)*	218.3 ±39.7
	3.0	16.1 ±0.4 *(a)*	43.9 ±0.8 *(a)*	5.7 ±0.03	77.6 ±1.5 *(b)*	28.5 ±0.6 *(b)*	124.5 ± 6.7
	10.0	16.3 ±0.6 *(a)*	46.2 ±1.5	6.1 ±0.3	76.1 ±1.8 *(b)*	26.9 ±0.9 *(b)*	113.8 ±10.3
	Dose Response	$P<0.01$	$P<0.01$	NS	$P<0.01$	$P<0.01$	NS

Values are the Mean ± SEM

(a) $P<0.05$, significantly different compared with control of same sex.

(b) $P<0.01$, significantly different compared with control of same sex.

TABLE 13. BLOOD LEUKOCYTE AND DIFFERENTIAL COUNTS OF RATS AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Total Leukocytes (10^3/cmm)	Lymphocytes (10^3/cmm)	Neutrophils (10^3/cmm)	Eosinophils (10^3/cmm)	Monocytes (10^3/cmm)
MALE	0	9.9 ±0.9	7.4 ±0.7	2.2 ±0.3	0.1 ±0.02	0.3 ±0.1
	0.1	12.3 ±3.0	6.9 ±0.3	4.7 ±2.8	0.1 ±0.05	0.6 ±0.1
	0.3	9.0 ±0.5	6.6 ±0.5	2.1 ±0.1	0.1 ±0.03	0.3 ±0.1
	1.0	12.0 ±2.2	6.8 ±0.6	2.3 ±0.2	0.1 ±0.02	0.5 ±0.1
	3.0	16.1 ±2.2 *(a)*	9.3 ±0.6 *(a)*	6.0 ±2.1	0.2 ±0.00	0.8 ±0.2
	10.0	7.8 ±0.7	5.8 ±0.4	1.8 ±0.3	0.0 ±0.00	0.3 ±0.1
	Dose Response	NS	NS	NS	NS	NS
FEMALE	0	5.3 ±0.4	4.0 ±0.3	0.9 ±0.2	0.1 ±0.01	0.3 ±0.1
	0.1	6.3 ±0.2 *(a)*	4.5 ±0.1	1.5 ±0.2 *(a)*	0.1 ±0.04	0.2 ±0.03
	0.3	5.5 ±0.5	4.3 ±0.6	1.3 ±0.4	0.1 ±0.04	0.2 ±0.03
	1.0	7.7 ±0.2 *(b)*	5.7 ±0.5 *(a)*	1.7 ±0.3	0.1 ±0.03	0.3 ±0.04
	3.0	7.8 ±1.0 *(a)*	6.0 ±0.8	1.5 ±0.2	0.1 ±0.00	0.3 ±0.1
	10.0	10.7 ±1.6 *(b)*	8.3 ±1.6 *(b)*	2.1 ±0.4 *(b)*	0.0 ±0.00	0.3 ±0.02
	Dose Response	$P<0.01$	$P<0.01$	$P<0.01$	NS	NS

Values are the Mean ± SEM

(a) $P<0.05$, significantly different compared with control of same sex.

(b) $P<0.01$, significantly different compared with control of same sex.

There was a significant ($P<0.01$) dose-related increase in the RBC count in male and in female mice (Table 14). The MCV was decreased in both male and female mice in a dose-related fashion. Platelet counts were significantly ($P<0.01$) decreased in the female mice given 3.0 and 10.0 mg/kg of PBB, but these was no difference between dosed and control male mice (Table 14). Leukocytosis was due primarily to an increase in lymphocytes in female mice at the highest dose level(Table 15). No consistent dose-related effect on these parameters was observed in mice.

TABLE 14. ERYTHROCYTE VALUES AND PLATELET COUNTS OF MICE AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Hemoglobin (g/100 ml)	Packed Cell Volume (%)	Red Blood Cells (10^6/cmm)	Mean Corpuscular Volume (μ^3)	Mean Corpuscular Hemoglobin ($\mu\mu$g)	Platelets (10^3/cmm)
MALE	0	16.4 ±0.7	43.3 ±1.4	5.36 ±0.3	81.6 ±4.7	30.8 ±1.7	269.5 ±26.0
	0.1	15.0 ±0.5	42.3 ±1.1	5.33 ±0.4	81.4 ±6.7	28.9 ±2.1	305.6 ±21.4
	0.3	17.4 ±0.3	45.5 ±0.8	6.28 ±0.1 *(b)*	72.5 ±0.2	27.7 ±0.5	308.1 ±24.9
	1.0	16.5 ±0.4	44.2 ±0.6	6.07 ±0.1 *(a)*	72.5 ±0.7	27.2 ±0.5	279.3 ±18.1
	3.0	17.3 ±0.2	44.9 ±0.8	6.17 ±0.3 *(a)*	73.5 ±3.3	28.3 ±1.5	297.8 ±20.9
	10.0	17.1 ±0.2	43.9 ±0.4	6.19 ±0.1 *(b)*	71.0 ±1.3 *(b)*	27.7 ±0.5	268.0 ±13.5
	Dose Response	NS	NS	$P < 0.01$	$P < 0.01$	NS	NS
FEMALE	0	16.0 ±0.6	45.8 ±0.4	6.40 ±0.1	71.6 ±0.9	25.0 ±0.9	291.2 ± 2.7
	0.1	16.1 ±0.6	46.5 ±0.7	6.25 ±0.1	74.5 ±2.0	25.8 ±1.0	254.1 ±13.6
	0.3	15.1 ±0.8	44.7 ±0.9	6.49 ±0.1	68.9 ±0.4 *(b)*	23.3 ±0.9	277.7 ±17.9
	1.0	16.6 ±0.1	46.4 ±0.5	6.63 ±0.1 *(a)*	70.0 ±0.6	25.1 ±0.3	221.3 ±30.2 *(b)*
	3.0	16.6 ±0.2	46.0 ±0.4	7.32 ±0.1 *(c)*	62.8 ±0.2 *(c)*	22.7 ±0.1	210.7 ± 7.2 *(c)*
	10.0	16.7 ±0.3	45.5 ±0.7	7.08 ±0.1 *(c)*	64.3 ±0.8 *(c)*	23.6 ±0.4	191.1 ± 8.1 *(c)*
	Dose Response	NS	NS	$P < 0.01$	$P < 0.01$	$P = 0.026$	$P < 0.01$

Values are the Mean ± SEM

(a) P ▫ 0.056, significantly different compared with control of same sex.

(b) $P < 0.05$, significantly different compared with control of same sex.

(c) $P < 0.01$, significantly different compared with control of same sex.

TABLE 15. BLOOD LEUKOCYTE AND DIFFERENTIAL COUNTS OF MICE AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Total Leukocytes (10^3/cmm)	Lymphocytes (10^3/cmm)	Neutrophils (10^3/cmm)	Eosinophils (10^3/cmm)	Monocytes (10^3/cmm)
MALE	0	6.9±0.8	4.5±0.6	2.2±0.7	0.03±0.03	0.2±0.04
	0.1	8.9±3.2	5.7±2.1	2.9±1.3	0.0 ±0.00	0.2±0.07
	0.3	11.4±1.2	7.7±0.7 *(b)*	3.4±0.9	0.0 ±0.00	0.3±0.07
	1.0	9.0±1.2	5.9±0.4	2.9±1.1	0.0 ±0.00	0.2±0.06
	3.0	6.6±0.3	4.9±0.4	1.6±0.4	0.03±0.03	0.1±0.02
	10.0	7.1±0.8	4.6±0.6	2.3±0.3	0.0 ±0.00	0.2±0.06
	Dose Response	NS	NS	NS	NS	NS
FEMALE	0	4.0±0.7	3.0±0.5	0.9±0.2	0.0 ±0.00	0.1±0.03
	0.1	4.0±0.4	3.2±0.3	0.7±0.2	0.02±0.02	0.1±0.02
	0.3	3.4±0.4	2.7±0.3	0.6±0.1	0.0 ±0.00	0.1±0.02
	1.0	4.8±1.3	3.6±0.8	1.1±0.5	0.0 ±0.00	0.1±0.04
	3.0	4.1±0.8	3.2±0.6	0.8±0.1	0.0 ±0.00	0.1±0.02
	10.0	6.3±0.6	4.9±0.4 *(a)*	1.3±0.2	0.0 ±0.00	0.1±0.04
	Dose Response	NS	$P = 0.06$	NS	NS	NS

Values are the Mean± SEM

(a) $P = 0.06$, significantly different compared with control of same sex.

(b) $P < 0.05$, significantly different compared with control of same sex.

Clinical Chemistry

Total serum protein was decreased in a dose-related fashion in female rats, primarily due to a dose-related decrease in albumin (Table 16). There was a significant ($P < 0.05$) increase in the serum levels of gamma glutamyl transpeptidase (GGTP) only in female rats given 10.0 mg/kg dose (Table 17). There was a dose-related decrease in serum glucose in female rats, a dose-related decrease in the serum triglyceride level in treated male rats, except at the lowest dose (0.1 mg/kg), and a dose-related increase in the serum levels of cholesterol in both male and female rats (Table 17). No significant differences were observed in SGPT, AP, and BUN values in male and female dosed and control rats.

Serum levels of GGTP were increased only in female mice given 10.0 mg/kg of PBB (Table 18). There was a 5- to 6-fold increase in the activity of SGPT in male and female mice in the 10.0 mg/kg groups (Table 18). Serum enzyme activity of AP was also increased in mice given the highest dose of PBB. There was a significant increase in the serum levels of cholesterol in female mice at the highest dose (Table 18). Serum glucose was significantly ($P < 0.05$) decreased in female mice administered 10.0 mg/kg of PBB.

TABLE 16. SERUM PROTEIN VALUES OF RATS AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Total Protein (g/100 ml)	Albumin (g/100 ml)	Total Globulin (g/100 ml)	A/G Ratio
MALE	0	6.89 ±.55	3.33 ±.22	3.57 ±.34	0.94 ±.03
	0.1	7.34 ±.68	3.51 ±.19	3.83 ±.51	0.95 ±.06
	0.3	6.66 ±.26	3.30 ±.12	3.35 ±.15	0.99 ±.03
	1.0	6.63 ±.22	3.28 ±.09	3.34 ±.15	0.99 ±.03
	3.0	6.19 ±.56	2.94 ±.28	3.25 ±.29	0.91 ±.03
	10.0	6.66 ±.19	3.16 ±.09	3.50 ±.10	0.90 ±.01
	Dose Response	NS	NS	NS	NS
FEMALE	0	6.62 ±.10	3.52 ±.09	3.10 ±.05	1.14 ±.03
	0.1	6.61 ±.22	3.51 ±.10	3.10 ±.14	1.14 ±.04
	0.3	6.43 ±.13	3.44 ±.09	3.00 ±.06	1.15 ±.03
	1.0	5.73 ±.09 *(a)*	2.71 ±.07 *(a)*	3.02 ±.04	0.90 ±.02 *(a)*
	3.0	5.95 ±.19 *(a)*	2.75 ±.10 *(a)*	3.20 ±.11	0.86 ±.03 *(a)*
	10.0	5.75 ±.26 *(a)*	2.67 ±.15 *(a)*	3.08 ±.12	0.86 ±.02 *(a)*
	Dose Response	$P < 0.01$	$P < 0.01$	NS	$P < 0.01$

Values are the Mean ± SEM

(a) $P < 0.05$, significantly different compared with control of same sex.

TABLE 17. SERUM CLINICAL CHEMISTRY VALUES OF RATS AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Gamma glutamyl transpepti-dase (IU/Liter)	Serum glucose (mg/100 ml)	Serum triglyceride (mg/100 ml)	Serum cholesterol (mg/100 ml)
MALE	0	3.1 ±0.7	135 ±12	335 ±146	89 ±12
	0.1	3.3 ±0.8	133 ±13	324 ±139	110 ±21
	0.3	2.6 ±0.6	138 ±12	155 ± 15	94 ± 6
	1.0	3.0 ±0.5	143 ±10	119 ± 8 *(b)*	116 ± 5
	3.0	3.5 ±0.3	120 ± 4	152 ± 12 *(a)*	160 ±18 *(a)*
	10.0	3.9 ±0.6	122 ± 6	155 ± 18	243 ±15 *(a)*
	Dose Response	NS	NS	$P < 0.05$	$P < 0.01$
FEMALE	0	3.3 ±0.7	131 ±13	109 ± 7	123 ± 5
	0.1	3.2 ±0.5	118 ± 3	110 ± 13	136 ±10
	0.3	2.6 ±0.4	120 ± 8	122 ± 32	141 ± 6
	1.0	2.2 ±0.4	113 ± 6	91 ± 19	146 ± 6 *(a)*
	3.0	4.5 ±0.6	116 ± 4	115 ± 10	181 ±11 *(a)*
	10.0	7.9 ±1.2 *(a)*	101 ±10	107 ± 5	147 ±12
	Dose Response	$P < 0.05$	$P < 0.05$	NS	$P < 0.01$

Values are the Mean ± SEM

(a) $P < 0.05$, significantly different compared with control of same sex.

(b) $P < 0.01$, significantly different compared with control of same sex.

TABLE 18. SERUM CLINICAL CHEMISTRY VALUES OF MICE AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Gamma Glutamyl Trans-peptidase (IU/Liter)	Serum Glutamic Pyruvic Transaminase (IU/Liter)	Serum Cholesterol (mg/100 ml)	Serum Glucose (mg/100 ml)	Serum Alkaline Phosphatase (IU/Liter)
MALE	0	1 ±0.0	36 ±14	108 ± 6	143 ±16	30 ± 4
	0.1	2 ±0.4	34 ± 7	116 ± 5	128 ±23	27 ± 4
	0.3	2 ±0.3	77 ±29	107 ± 4	148 ±18	30 ± 3
	1.0	1 ±0.4	43 ±10	103 ± 5	149 ± 6	34 ± 2
	3.0	1 ±0.3	61 ± 8	98 ± 2	150 ±19	31 ± 2
	10.0	2 ±1.0	214 ±34 *(a)*	131 ± 9	146 ± 8	127 ±10 *(a)*
	Dose Response	NS	$P < 0.01$	NS	NS	$P < 0.01$
FEMALE	0	1 ±0.2	58 ±12	79 ± 4	151 ±17	64 ± 7
	0.1	1 ±0.3	29 ± 5	83 ± 4	148 ±12	70 ± 3
	0.3	1 ±0.2	22 ± 3 *(a)*	81 ± 2	159 ±10	64 ± 6
	1.0	1 ±0.2	24 ± 2 *(a)*	81 ±11	147 ±11	72 ±19
	3.0	1 ±0.2	79 ±45	96 ± 9	137 ±12	68 ± 2
	10.0	15 ±4.7 *(a)*	312 ±30 *(a)*	213 ± 8 *(a)*	108 ± 2 *(a)*	103 ±11 *(a)*
	Dose Response	NS	NS	$P < 0.01$	$P < 0.05$	$P < 0.05$

Values are the Mean ± SEM

(a) $P < 0.05$, significantly different compared with control of same sex.

There was a dose-related decrease in serum thyroxine (T_4) values in male and female rats (Table 19). Serum triiodothyronine (T_3) levels were decreased in dose-related fashion in female rats.

PBB produced dose-related hepatic porphyria in male and female rats and mice (Table 20). At the highest doses, hepatic prophyrin levels were increased several hundred-fold in females of each species. Male rats and mice were affected much less than females.

TABLE 19. SERUM THYROID HORMONE VALUES IN RATS AFTER A 6-MONTH EXPOSURE TO PBB

Dose (mg/kg)	T_4 (μg/100 ml)		T_3 (ng/100 ml)		T_3 Uptake	
	Male	Female	Male	Female	Male	Female
Control	5.3 ±.2	3.7 ±.2	126 ± 7	123 ±14	61.9 ±0.9	58.1 ±1.0
0.1	4.5 ±.8	3.6 ±.3	99 ±15	106 ± 9	62.6 ±1.4	58.4 ±0.7
0.3	4.4 ±.3 *(a)*	3.3 ±.4	111 ±13	112 ± 8	59.9 ±0.6	58.7 ±0.5
1.0	4.0 ±.3 *(a)*	2.1 ±.2 *(b)*	133 ±11	86 ±10	58.9 ±0.7	61.7 ±0.6 *(a)*
3.0	3.0 ±.3 *(b)*	1.7 ±.2 *(b)*	107 ±10	80 ± 8 *(a)*	59.7 ±1.4	59.2 ±0.6
10.0	2.1 ±.1 *(b)*	1.5 ±.2 *(b)*	104 ± 3	77 ± 9 *(a)*	56.1 ±0.5 *(b)*	60.3 ±0.6
Dose Response	P < 0.01	P < 0.01	NS	P < 0.01	P < 0.01	P = 0.02

Values represent the mean ± SEM of 10 rats.

(a) Significantly (P < 0.05) different compared with control.

(b) Significantly (P < 0.01) different compared with control.

TABLE 20. HEPATIC PORPHYRIN LEVELS (μg/g) IN RATS AND MICE AFTER A 6-MONTH EXPOSURE TO PBB

Dose (mg/kg)	Rats		Mice	
	Male	Female	Male	Female
Control	1.0 ± 0.2	0.7 ± 0.1	1.0 ± 0.1	1.1 ± 0.2
0.1	0.8 ± 0.1	0.5 ± 0.1	1.0 ± 0.1	0.7 ± 0.1
0.3	2.0 ± 0.3 *(b)*	15.8 ± 8.2 *(b)*	1.2 ± 0.1 *(a)*	0.9 ± 0.1
1.0	15.3 ± 4.2 *(b)*	1002.0 ±65.0 *(b)*	1.7 ± 0.1 *(b)*	3.5 ± 2.0
3.0	36.1 ± 8.3 *(b)*	1369.0 ±65.0 *(b)*	18.7 ± 4.3 *(b)*	97.0 ±23.0 *(b)*
10.0	45.3 ±11.0 *(b)*	517.0 ±80.0 *(b)*	58.0 ±10.0 *(b)*	435.0 ±20.0 *(b)*
Dose Response	P < 0.01	P < 0.01	P < 0.01	P < 0.01

Values represent the mean ± SEM of 10 animals.

(a) Significantly (P < 0.05) increased compared with controls.

(b) Significantly (P < 0.01) increased compared with controls.

III. RESULTS: SIX-MONTH OBSERVATION

Necropsy Findings

Liver, bones, and teeth of female rats given 1.0 to 10.0 mg/kg of PBB had slight to marked reddish pink fluorescence under UV light, denoting excess porphyrin accumulation. The number of positive samples and intensity of red fluorescence was less in dosed male rats compared with the dosed females. These tissues from all female mice administered 10.0 mg/kg of PBB showed slight to marked fluorescence, whereas only 8 out of 10 male mice were positive in the same dose level.

The livers of dosed rats and mice of each sex were moderately to markedly enlarged, especially at the higher dose levels. Two male rats (one given 0.3 mg/kg and the other 10.0 mg/kg) had several grayish white nodules (about 5 mm in diameter) in the liver. One female rat out of 10 given 10.0 mg/kg of PBB had a grayish white space-occupying mass involving the interior of the urinary bladder. The thymus of dosed rats (10.0 mg/kg) appeared smaller compared with the control. No lesions were observed in other organs.

Eight of 10 male mice and 1 of 10 females in the 10.0 mg/kg groups had several small grayish white foci in the liver. One male mouse out of 10 controls also showed a similar lesion.

Histopathologic Findings

Microscopic alterations in the liver of rats and mice related to PBB administration are given in Table 21. Dose-related changes were observed in the liver in all groups of dosed male rats and in the 1.0, 3.0, and 10.0 mg/kg female groups. The microscopic appearance of these livers was characterized by disorganization of trabecular cords, moderate to marked enlargement of hepatocytes, some of which were multinucleated, moderate fatty infiltration (oil red O stain) and hyalinization of cytoplasm of other hepatocytes. Some of the hepatocytes had a foamy appearance. Numerous granulomatous foci with occasional multinucleated giant cells were observed, primarily near the central vein. These foci invariably contained golden brown granular pigment which was positive for iron (Mallory's method for iron; Luna, 1968). Occasionally, the reacting cells in the center of these granulomas formed rosette-like structures around the hemosiderin granules. Small fatty acid clefts were occasionally observed in these foci. Single cell hepatocellular necrosis with infiltration of neutrophils was also observed. There was slight to moderate focal or diffuse bile duct proliferation in the liver. Lipid accumulation was more prominent in male than female rats (Table 22) and was primarily located around the central veins.

TABLE 21. HEPATIC LESIONS IN RATS *(a)* AND MICE *(a)* AFTER A 6-MONTH EXPOSURE TO PBB

		Microscopic Alterations in the Liver			
				No. of Livers Positive for Atypical Foci	
Sex	Dose (mg/kg/day)	Rat Liver	Mouse Liver	Rat	Mouse
MALE	0	Normal	Normal	0	1
	0.1	A few foamy cells	Normal	0	0
	0.3	Slight swelling, foamy cells	Normal	0	1
	1.0	Slight swelling, foamy cells	Slight swelling	1	0
	3.0	Marked swelling	Moderate swelling	0	0
	10.0	Marked swelling, fatty	Marked swelling	0	8
FEMALE	0	Normal	Normal	0	0
	0.1	Normal	Normal	0	0
	0.3	Normal	Normal	0	0
	1.0	Slight swelling, foamy cells	Slight swelling	1	0
	3.0	Moderate swelling	Moderate swelling	1	0
	10.0	Marked swelling, fatty	Marked swelling	0 *(b)*	2

(a) There were 10 rats or mice/group/sex at each dose level examined after 6-month exposure.

(b) One female rat of this group developed squamous cell carcinoma involving urinary bladder.

Atypical foci were observed in the livers of 3 of 100 (3.0%) dosed rats, although no definite dose or sex relationship was observed (Table 21). None were observed in control rats. These foci were well delineated groups of hypertrophic hepatocytes with enlarged nuclei containing prominent nucleoli and foamy or eosinophilic ground glass cytoplasm.

Observed on ultrastructural examination of the liver were increased amounts of rough endoplasmic reticulum (RER) and lipid globules of different sizes in the hepatocytes of male rats given the highest dose of PBB. In the dosed female rats (highest dose), the changes in the liver were much more severe, as denoted by marked proliferation and disorganization of RER, dilated cristae, and dense mitochondrial matrices. Occasionally, intramitochondrial flocculent deposits were also observed.

The space-occupying mass in the urinary bladder of a female rat in the 10.0 mg/kg group was diagnosed as a squamous cell carcinoma. This neoplastic mass protruded into the lumen and was covered with one to several layers of atypical flattened epithelium. Composed of islands of squamous epithelium, some contained concentric laminations of keratin. The connective tissue stroma was heavily infiltrated with inflammatory cells. Although the neoplastic cells infiltrated into the deeper muscular wall of the urinary bladder, no metastases were observed.

Although there was no significant difference in thyroid gland weights, slight to moderate morphologic changes were observed, primarily in the male rats administered 10.0 mg/kg of PBB. Microscopic changes in the thyroid gland were characterized by thin, sparse, or bluish colloid with basophilic stippling. Some follicles were lined with columnar epithelium and also contained a few epithelial papillary projections. Changes in the thyroid gland of dosed female rats (highest dose) were not very remarkable compared with the female controls.

The kidneys of male rats at the 10.0 mg/kg dose level of PBB consistently showed atrophy of a few glomerular tufts with marked dilation of Bowman's capsule, which contained amorphous eosinophilic staining material. A few glomerular tufts also appeared edematous. Some renal tubules in both cortical and medullary regions were dilated and contained either serous fluid or proteinaceous casts. Significant lesions were not observed in the other organs.

Microscopic alterations in the livers of male and female mice (10.0 mg/kg dose levels) were marked swelling of hepatocytes, primarily around the central veins, foamy or vacuolated cytoplasm with hyaline bodies, and focal coagulative necrosis or scattered single cell necrosis of hepatocytes. Only slight to moderate swelling of hepatocytes was observed in mice administered 1.0 and 3.0 mg/kg of PBB, and no lesions were observed at lower doses (Table 21). Atypical hepatocellular foci were present in 9 male and 2 female dosed mice of 100 examined (11.0%), and in 1 of 20 (5.0%) control mice (Table 21). These foci were similar to those described in the rat.

Iron positive granules, probably hemosiderin, were observed primarily in the red pulp of the spleen of all dosed and control animals. However, these granules were more prominent in the spleen of the dosed female rats than in that of the dosed male rats, and they were more prominent in dosed rats of either sex than in the controls. There was no difference in the spleens of dosed and control male mice. However, the spleen of control female mice tended to have more iron positive granules compared with the PBB-dosed female mice.

TABLE 22. MICROSCOPIC OBSERVATION OF EXCESS LIPID ACCUMULATION (OIL RED O STAIN) IN THE LIVER OF RATS AFTER A 6-MONTH EXPOSURE TO PBB

Sex	Dose (mg/kg/day)	Staining Intensity *(a)*	Size of Lipid Globules	Location of Positive Hepatocytes
MALE	0	±	Fine to medium	Scattered or midzonal
	0.1	±	Fine	Scattered
	0.3	+	Fine to medium	Centrilobular
	1.0	++	Medium to large	Centrilobular
	3.0	++	Fine to large	Midzonal and centrilobular
	10.0	+++	Fine to large	All over
FEMALE	0	±	Fine to medium	Scattered
	0.1	±	Fine	Centrilobular
	0.3	±	Fine	Scattered
	1.0	±	Fine	Scattered
	3.0	+	Fine to large	Scattered
	10.0	++	Fine to large	Midzonal and centrilobular

(a) Increasing order of intensity = ±, +, ++, and +++

RESULTS OF LIFETIME OBSERVATION

Survival Time in Rats

A dose-dependent decline in survival time was observed in dosed male rats (Fig. 3, Table 23). Male rats given 1.0, 3.0, or 10.0 mg/kg of PBB lived an average life of 677, 680, or 615 days, respectively, as compared to control survival of 762 days. The mean survival time in control female rats was 702 days, and the dosed (0.1, 0.3, 1.0, and 3.0 mg/kg) groups lived longer than the controls (Fig. 4, Table 23). Although the survival time in 10.0 mg/kg dosed female rats was slightly lower (662 vs. 702 days) than that in the controls, this difference was not statistically significant.

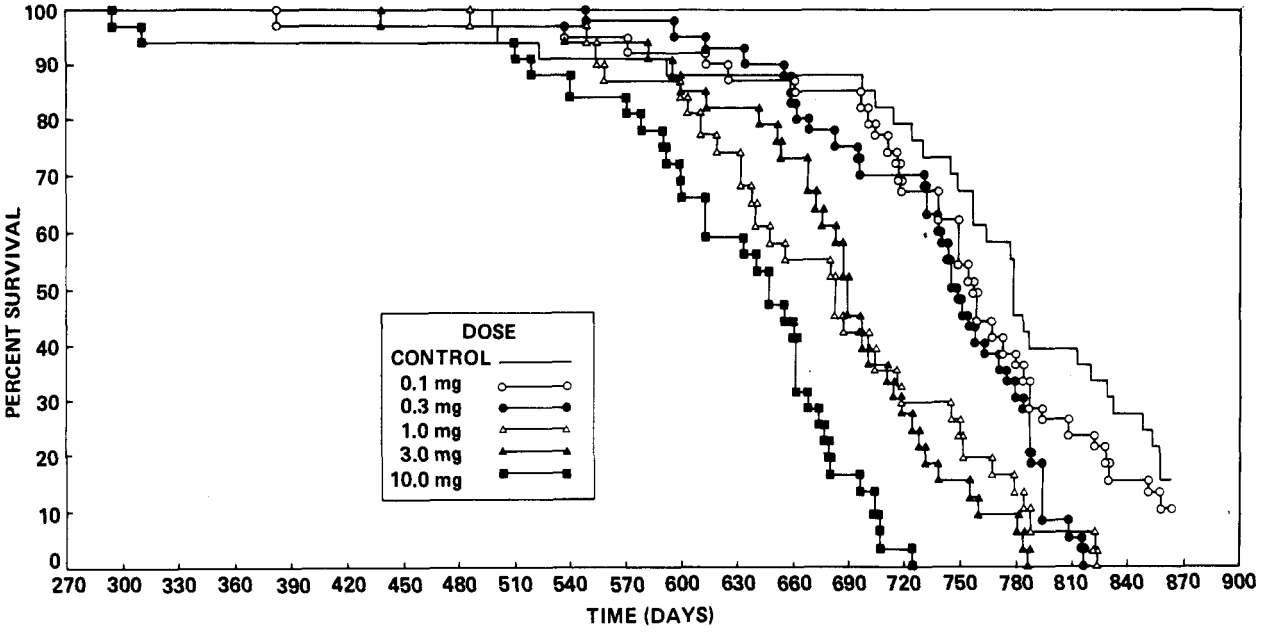

Figure 3. Survival Curves for Male Rats Administered Polybrominated Biphenyl Mixture in Corn Oil by Gavage

TABLE 23. EFFECT OF POLYBROMINATED BIPHENYL ADMINISTRATION ON SURVIVAL IN RATS AND MICE

Sex	Dose (mg/kg/day)	Survival Time (Days) *(a)*	
		Rats	Mice
MALE	0	762 ±18(33)	784 ±23(25)
	0.1	744 ±16(39)	785 ±25(27)
	0.3	733 ±10(40) *(c)*	766 ±28(24)
	1.0	677 ±15(31) *(c)*	765 ±30(25)
	3.0	680 ±13(33) *(c)*	790 ±29(23)
	10.0	615 ±18(32) *(c)*	682 ±28(22) *(b)*
	Dose Response	$P < 0.01$	$P = 0.01$
FEMALE	0	702 ±33(20)	813 ±28(13)
	0.1	756 ±22(21)	840 ±24(19)
	0.3	800 ±16(21) *(b)*	843 ±27(15)
	1.0	830 ±18(11) *(c)*	871 ±21(11)
	3.0	761 ±25(19)	842 ±18(17)
	10.0	662 ±42(20)	741 ±37(8)
	Dose Response	NS	NS

(a) Data reported as mean ±SE (number of animals examined).

(b) Survival significantly ($P < 0.05$) different than controls.

(c) Survival significantly ($P < 0.01$) different than controls.

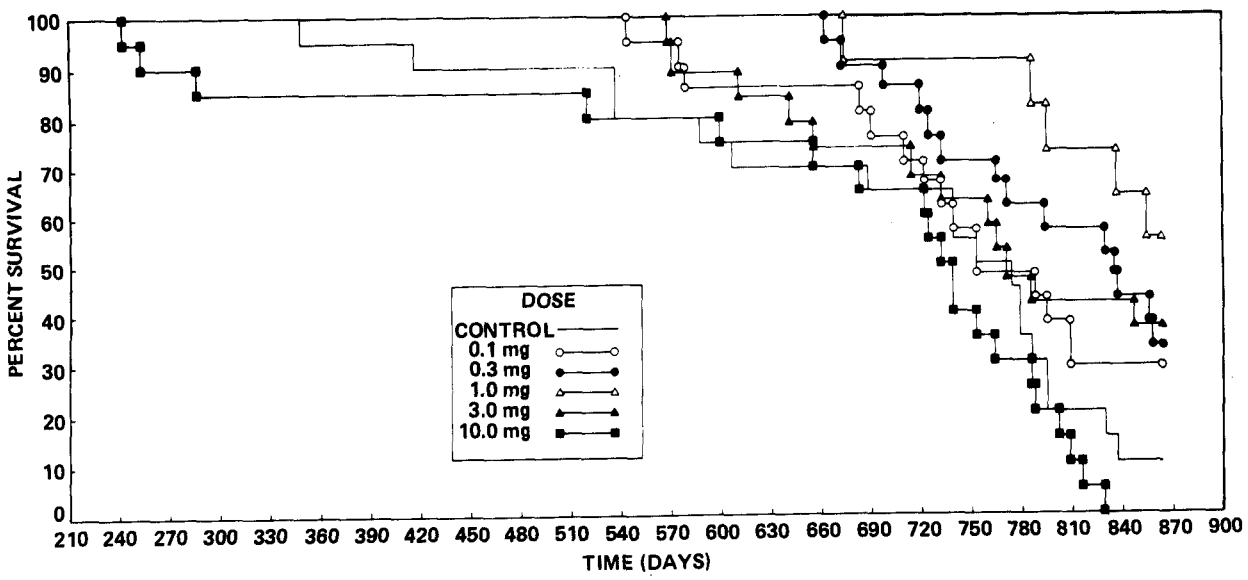

Figure 4. Survival Curves for Female Rats Administered Polybrominated Biphenyl Mixture in Corn Oil by Gavage

Survival Time in Mice

There was significant ($P<0.05$) reduction in the survival time in male mice at the highest dose (10.0 mg/kg group) when compared with the controls (Fig. 5, Table 23). There was no statistically significant difference in the survival time between the dosed females (all dosage groups) and the control females (Fig. 6, Table 23).

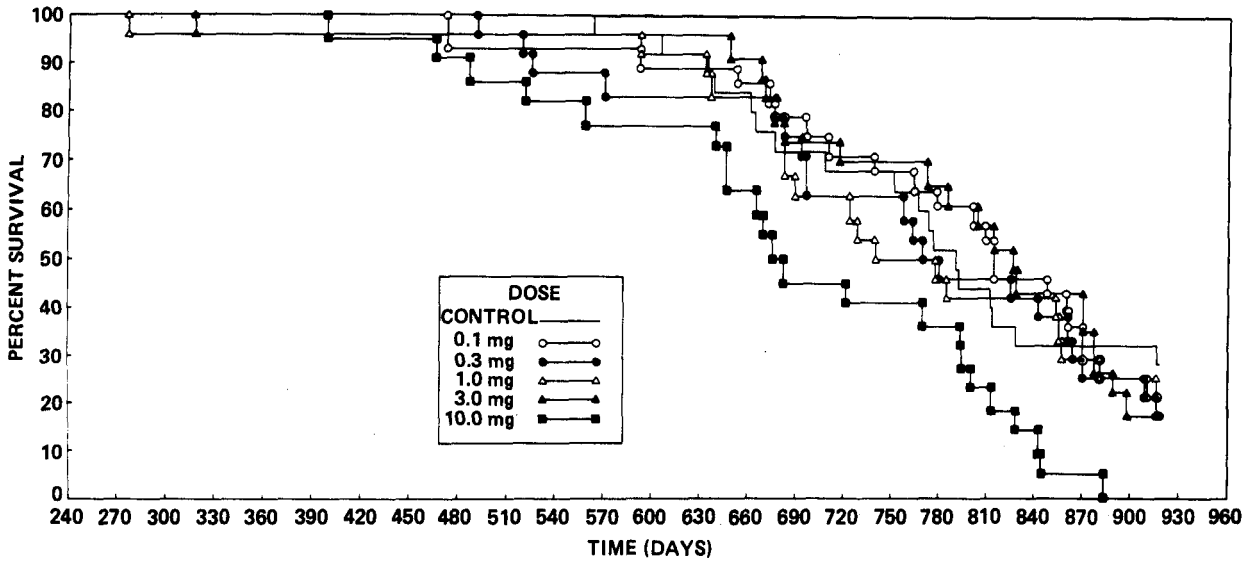

Figure 5. Survival Curves for Male Mice Administered Polybrominated Biphenyl Mixture in Corn Oil by Gavage

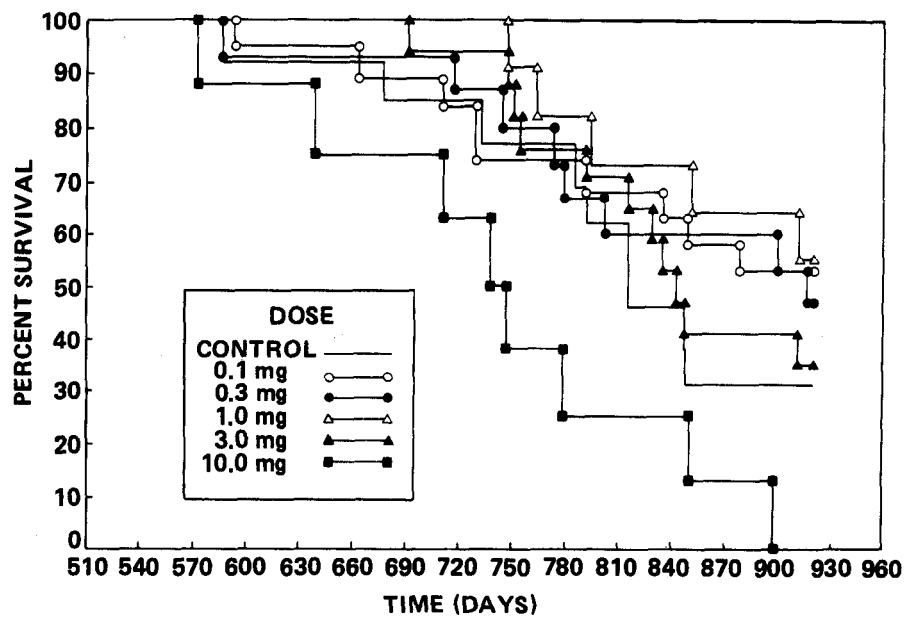

Figure 6. Survival Curves for Female Mice Administered Polybrominated Biphenyl Mixture in Corn Oil by Gavage

Body Weights in Rats and Mice

The dose-related body weight differences in rats that existed at the end of the 6-month dosing persisted throughout the lifetime of the animals (Tables 24 and 25). The body weights of male mice were slightly reduced only at the 10.0 mg dose level (Table 26). However, there appeared to be no dose-related effect on body weight in the female mice (Table 27).

TABLE 24. BODY WEIGHTS (g) OF MALE RATS DURING LIFETIME OBSERVATION PHASE OF PBB STUDY

Weeks Post Exposure	Control	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg
0	407 ±3(51) *(a)*	408 ±3(50)	405 ±3(50)	395 ±3(51)	353 ±3(51)	298 ±3(51)
12	453 ±6(20)	454 ±5(26)	444 ±4(26)	437 ±5(18)	388 ±5(20)	327 ±5(20)
24	482 ±6(20)	477 ±5(26)	474 ±5(26)	463 ±5(18)	417 ±6(20)	354 ±4(19)
36	498 ±6(20)	497 ±5(25)	493 ±5(26)	481 ±5(18)	432 ±6(20)	378 ±5(19)
48	491 ±6(18)	493 ±5(25)	488 ±4(26)	483 ±7(17)	429 ±5(19)	376 ±6(18)
60	490 ±6(17)	490 ±4(24)	483 ±4(25)	463 ±6(16)	414 ±11(16)	379 ±4(15)
72	469 ±5(17)	474 ±5(23)	463 ±8(20)	433 ±14(11)	409 ±11(11)	350 ±12(5)
84	412 ±11(12)	421 ±12(12)	407 ±15(11)	414 ±25(4)	370 ±34(2)	— (0)
96	380 ±13(5)	368 ±9(4)	— (0)	— (0)	(0)	(0)

Data presented are Mean ±SEM

(a) Data in parentheses indicate the number of rats examined at that time point.

TABLE 25. BODY WEIGHTS (g) OF FEMALE RATS DURING LIFETIME OBSERVATION PHASE OF PBB STUDY

Weeks Post Exposure	Control	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg
0	218 ±2(51) *(a)*	221 ±1(51)	213 ±2(51)	205 ±2(51)	183 ±1(50)	161 ±1(51)
12	242 ±3(20)	243 ±3(20)	236 ±3(20)	229 ±5(11)	197 ±2(19)	184 ±2(18)
24	264 ±4(19)	264 ±4(20)	257 ±4(20)	258 ±7(11)	215 ±3(19)	195 ±2(17)
36	294 ±5(18)	297 ±6(20)	287 ±4(20)	291 ±8(11)	236 ±5(19)	204 ±2(17)
48	307 ±5(18)	310 ±6(20)	304 ±3(20)	306 ±7(11)	260 ±6(19)	214 ±4(17)
60	322 ±5(15)	334 ±7(17)	320 ±4(20)	325 ±6(11)	279 ±7(17)	225 ±5(16)
72	318 ±5(14)	332 ±10(17)	325 ±7(18)	333 ±6(10)	294 ±7(14)	232 ±5(14)
84	286 ±9(9)	318 ±13(9)	317 ±6(13)	317 ±6(10)	283 ±9(10)	226 ±6(6)
96	293 ±12(2)	344 ±10(6)	312 ±8(7)	305 ±5(6)	266 ±9(7)	— (0)

Data presented are Mean ±SEM

(a) Data in parentheses indicate the number of rats examined at that time point.

TABLE 26. BODY WEIGHTS (g) OF MALE MICE DURING LIFETIME OBSERVATION PHASE OF PBB STUDY

Weeks Post Exposure	Control	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg
0	38 ±1(46) *(a)*	38 ±1(49)	39 ±1(47)	38 ±1(48)	37 ±0(45)	35 ±0(44)
12	40 ±1(25)	39 ±1(28)	41 ±1(26)	39 ±1(27)	39 ±1(24)	37 ±0(23)
24	43 ±1(25)	40 ±1(28)	42 ±1(26)	41 ±1(26)	41 ±1(23)	38 ±1(23)
36	41 ±1(25)	41 ±1(28)	42 ±1(26)	41 ±1(26)	41 ±1(23)	38 ±1(22)
48	42 ±1(25)	41 ±1(26)	43 ±1(25)	42 ±1(26)	42 ±1(23)	38 ±1(20)
60	43 ±1(24)	42 ±1(25)	44 ±1(21)	43 ±1(25)	43 ±1(23)	39 ±1(18)
100	35 ±1(7)	33 ±2(6)	35 ±1(4)	37 ±3(5)	36 ±2(4)	— (0)

Data presented are Mean ±SEM

(a) Data in parentheses indicate the number of mice examined at that time point.

TABLE 27. BODY WEIGHTS (g) OF FEMALE MICE DURING LIFETIME OBSERVATION PHASE OF PBB STUDY

Weeks Post Exposure	Control	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg
0	27 ±0(50) *(a)*	27 ±0(50)	28 ±0(47)	28 ±0(43)	28 ±0(10)	30 ±0(39)
12	31 ±1(19)	30 ±1(19)	30 ±0(16)	31 ±1(12)	31 ±1(18)	31 ±1(8)
24	32 ±1(19)	31 ±1(19)	31 ±1(16)	33 ±1(12)	33 ±1(18)	32 ±1(8)
36	34 ±1(19)	33 ±1(19)	33 ±1(16)	34 ±1(12)	36 ±2(18)	34 ±1(8)
48	36 ±1(19)	34 ±1(19)	35 ±1(16)	36 ±2(12)	36 ±1(18)	36 ±1(8)
60	41 ±1(19)	37 ±1(18)	36 ±1(15)	39 ±2(12)	40 ±1(18)	38 ±2(7)
100	39 ±2(4)	33 ±1(10)	35 ±2(7)	40 ±3(6)	35 ±3(6)	— (0)

Data presented are Mean ±SEM

(a) Data in parentheses indicate the number of mice examined at that time point.

Necropsy Findings in Rats and Mice

Under UV light, slight to marked reddish pink fluorescence of teeth, bones and liver was observed in male and female rats held for lifetime observation. The incidence (%) of rats showing reddish pink fluorescence and its intensity was dose dependent. In male rats, 7/33 (21%) showed reddish pink fluorescence; in female rats, 5/19 (26%) showed this. In the 10.0 mg/kg dose groups, the incidence of positive results in rats was 91% (29/32) in males and 80% (16/20) in females. Only 1 male rat of 31 (3%) in the 1.0 mg dose group showed slight fluorescence. Reddish pink fluorescence of the teeth, bones, or liver was not observed in control rats or in rats in the 0.1 and 0.3 mg/kg dose groups.

Slight to moderate fluorescence was observed in 3/23 (13%) male mice in the 3.0 mg/kg dose group. Male mice in other dosed groups including the 10.0 mg/kg dose level and all female mice (dosed and control) were negative for reddish pink fluorescence during the lifetime observation.

Most of the livers of dosed rats (higher dose groups) were either enlarged, pale, or mottled and contained pinpoint to 2 mm white foci distributed throughout the hepatic parenchyma. Some livers, primarily in rats in the 3.0 and 10.0 mg dose groups, developed 3 to 10 mm grayish-white nodules which appeared raised from the hepatic surface. Occasionally, a small cauliflower-like glistening white mass, about 5 to 6 mm in diameter, raised in the periphery and depressed in the center, was observed in the livers of dosed rats. A few rats had 2 to 10 ml of serosanguineous fluid in the abdominal cavity. The kidneys in most dosed rats were either pale with a pitted capsule or were darker in color. Altogether, 7/320 rats (6 dosed and 1 control) developed 1 to 3 mm papillomatous growths on the dorsum of the tongue. Changes in other organs were not remarkably different from those in the organs of the controls.

Histopathologic Findings in Rats

Histopathologic findings on lesions occurring in rats are summarized in Appendix A, Tables A1-A12, and Appendix C, Tables C1 and C2. The pinpoint to 2 mm white foci were either foci of coagulative necrosis or atypical foci. The incidence of atypical foci in the liver was significantly ($P<0.01$) increased in male rats receiving 0.3, 1.0, 3.0 and 10.0 mg/kg PBB, and in female rats receiving 10.0 mg/kg PBB (Tables 28 and 29). Larger white foci or nodules were either atypical foci, neoplastic nodules, or hepatocellular carcinoma. Hepatocellular carcinomas were observed with significantly ($P<0.01$) increased incidence in the 3.0 and 10.0 mg/kg PBB-dosed male rats and the 10.0 mg/kg-dosed female rats. However, no metastasis of this malignant hepatic neoplasm was observed in any rat. The white glistening cauliflower-like growths observed in the liver at necropsy were intrahepatic cholangiocarcinomas (listed as bile duct carcinoma in Appendix C, Tables C1 and C2), observed only in rats receiving 10.0 mg/kg.

TABLE 28. INCIDENCE (%) OF MICROSCOPIC LESIONS IN THE LIVER OF MALE RATS EXPOSED TO PBB FOR 6 MONTHS AND EXAMINED DURING LIFETIME OBSERVATION PHASE

Dose (mg/kg)	Atypical Foci	Neoplastic Nodules	Hepatocellular Carcinoma	Bile Duct Hyperplasia	Cholangiocarcinoma
0	3(1/33)*(a)*	0(0/33)	0(0/33)	24(8/33)	0(0/33)
0.1	8(3/39)	0(0/39)	5(2/39)	23(9/39)	0(0/39)
0.3	30(12/40)*(c)*	2(1/40)	0(0/40)	25(10/40)	0(0/40)
1.0	35(11/31)*(c)*	13(4/31)*(b)*	3(1/33)	42(13/31)	0(0/31)
3.0	39(13/33)*(c)*	12(4/33)	21(7/33)*(c)*	42(14/33)	0(0/33)
10.0	39(12/31)*(c)*	3(1/31)	23(7/31)*(c)*	29(9/31)	6(2/31) *(d)*
Dose Response	$P<0.01$	NS	$P<0.01$	NS	$P<0.01$

(a) Data in parentheses indicate number positive number examined.

(b) Significantly ($P<0.05$) increased compared with control.

(c) Significantly ($P<0.01$) increased compared with control.

(d) Increased ($P=0.06$) compared with control.

TABLE 29. INCIDENCE (%) OF MICROSCOPIC LESIONS IN THE LIVER OF FEMALE RATS EXPOSED TO PBB FOR 6 MONTHS AND EXAMINED DURING LIFETIME OBSERVATION PHASE

Dose (mg/kg)	Atypical Foci	Neoplastic Nodules	Hepatocellular Carcinoma	Bile Duct Hyperplasia	Cholangio-carcinoma
0	0(0/20) *(a)*	0(0/20)	0(0/20)	10(2/20)	0(0/20)
0.1	0(0/21)	10(2/21)	0(0/21)	0(0/21)	0(0/21)
0.3	5(1/21)	0(0/21)	0(0/21)	0(0/21)	0(0/21)
1.0	18(2/11)	18(2/11)	0(0/11)	9(1/11)	0(0/11)
3.0	21(4/19)	26(5/19) *(b)*	16(3/19)	21(4/19)	0(0/19)
10.0	40(8/20) *(b)*	40(8/20) *(b)*	35(7/20) *(b)*	35(7/20)	35(7/20) *(b)*
Dose Response	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

(a) Data in parentheses indicate number positive/number examined.

(b) Significantly ($P < 0.01$) increased compared with control.

These tumors were characterized by small to large acinar formation, with some distended acini containing mucus. In some instances, the neoplasms contained large mucous (PAS positive) filled spaces and only a few epithelial cells, probably the remnant of preexisting acini which were ruptured due to distension by excess mucous secretion. Occasionally, tissue composed of bile duct epithelium protruded into the central veins of the liver. However, metastases of these cholangiocarcinomas were not observed in any rat. The term "cholangiocarcinoma" was used as a diagnosis for this tumor because of its morphologic appearance. However, the histogenesis of this neoplasm may actually be of hepatocellular rather than bile duct origin. The incidence of myelomonocytic (mononuclear cell) leukemia was found to be significantly ($P<0.05$) increased only in male rats at the 0.3 mg/kg dose level (Table 30).

TABLE 30. INCIDENCE (%) OF MODERATE OR MARKED CHRONIC PROGRESSIVE NEPHROPATHY (CPN) AND MYELOMONOCYTIC LEUKEMIA (ML) IN RATS EXPOSED TO PBB FOR 6 MONTHS AND EXAMINED DURING LIFETIME OBSERVATION PHASE

Dose (mg/kg)	Male Rat		Female Rat	
	CPN	ML	CPN	ML
0	39(13/33) *(a)*	9(3/33)	0(0/20)	25(5/20)
0.1	28(11/39)	13(5/39)	5(1/21)	19(4/21)
0.3	45(18/40) *(b)*	20(8/40) *(b)*	0(0/21)	19(4/21)
1.0	77(23/30) *(c)*	13(4/31)	0(0/11)	9(1/11)
3.0	82(27/33) *(c)*	6(2/33)	0(0/19)	11(2/19)
10.0	84(27/32) *(c)*	6(2/32)	5(1/20)	20(4/20)
Dose Response	$P < 0.01$	NS	NS	NS

(a) Data in parentheses indicate number positive/number examined.

(b) Significantly ($P < 0.05$) increased compared with controls.

(c) Significantly ($P < 0.01$) increased compared with controls.

Four (2 males and 2 females) out of 51 rats (8%) given the highest dose (10.0 mg/kg) of PBB developed foci of pancreas-like tissue in the liver. These were present primarily near or around the central veins of the liver. The epithelium forming the acini of pancreas-like tissue was tall columnar and the nuclei were located near the basal area of the cell. The apical portion of these cells contained red granules similar to the zymogen granules of pancreatic exocrine glands.

A significantly ($P<0.01$) higher incidence of chronic progressive nephropathy (Barthold, 1979) was observed in male rats at the 1.0, 3.0, and 10.0 mg/kg dose levels (Table 30). Both kidneys were moderately to markedly affected and were characterized by the presence of hyaline proteinaceous casts of varying staining intensity, sclerosis and thickening of glomerular tufts and Bowman's capsule, and interstitial fibrosis, along with mononuclear leukocyte infiltration.

Gastric ulcers and hyperplastic gastropathy of the glandular portion were observed with significantly ($P<0.05$) increased incidence in male rats receiving 3.0 and 10.0 mg/kg PBB (Table 31). The hyperplastic lesions were focal and diagnosed only on microscopic examination. These changes were characterized by hyperplasia of mucosal epithelium, metaplasia from parietal to mucous cells, hyperchromasia, and increased mitosis. These lesions were usually delineated from the rest of the gastric mucosa. There was microcystic dilatation of crypts and downward growth on extension. Frequently, the gastric pits were considerably elongated and occasionally formed small cysts. Usually, there was infiltration of lymphocytes in the vicinity of the lesion.

The papillomatous growths on the dorsum of the tongue of 7 rats (6 dosed and 1 control) were squamous cell papillomas.

TABLE 31. INCIDENCE (%) OF FOCAL HYPERPLASTIC GASTROPATHY AND GASTRIC ULCERS IN RATS EXPOSED TO PBB FOR 6 MONTHS AND EXAMINED DURING LIFETIME OBSERVATION PHASE

Dose (mg/kg)	Male Rat		Female Rat	
	Hyperplastic Gastropathy	Gastric Ulcers	Hyperplastic Gastropathy	Gastric Ulcers
0	0(0/33) *(a)*	24(8/33)	5(1/20)	10(2/20)
0.1	3(1/38)	13(5/38)	5(1/21)	14(3/21)
0.3	5(2/40)	20(8/40)	5(1/21)	29(6/21)
1.0	10(3/30)	30(9/30) *(b)*	0(0/11)	9(1/11)
3.0	18(6/33) *(b)*	55(18/33) *(c)*	5(1/19)	16(3/19)
10.0	14(4/29) *(b)*	41(12/29) *(c)*	15(3/20)	15(3/20)
Dose Response	P=0.03	$P < 0.01$	NS	NS

(a) Data in parentheses indicate number positive/number examined.

(b) Significantly ($P < 0.05$) increased compared with controls.

(c) Significantly ($P < 0.01$) increased compared with controls.

Necropsy Findings in Mice

The abdomen of most of the affected mice was markedly distended due to marked enlargement of the liver and the presence of serosanguineous fluid in the peritoneal cavity. Multifocal white foci and nodules 5 to 15 mm in diameter were observed in the liver. Some of the nodular livers were multicystic and contained serosanguineous fluid. The incidence of grossly observed hepatic nodules was higher in the highest-dose (10.0 mg/kg) mice of each sex compared with controls.

Histopathologic Findings in Mice

Histopathologic findings on lesions occurring in mice are summarized in Appendix B, Tables B1-B12, and Appendix C, Tables C3 and C4. Most of the hepatic nodules observed grossly were hepatocellular carcinomas and occasionally hepatoblastoma. The incidence of hepatocellular carcinoma was significantly ($P<0.01$) increased in both male and female mice at the 10.0 mg/kg dose compared with the control (Table 32). Hepatocellular carcinomas were trabecular or solid or both types in a single lesion. There was a significantly ($P<0.05$) increased incidence of metastases of hepatocellular carcinoma into the lungs of female mice receiving 10.0 mg/kg PBB (Table 32). The incidence of hepatocellular adenoma was not significantly increased in mice administered PBB compared with controls. The incidence of hepatoblastoma in control male mice was 12% (3/25), and 9% (2/22) in the dosed male mice (highest dose). Hepatoblastoma was not observed either in control or dosed female mice.

TABLE 32. INCIDENCE (%) OF MICROSCOPIC LESIONS IN THE LIVER OF MALE AND FEMALE MICE EXPOSED TO PBB FOR 6 MONTHS AND EXAMINED DURING LIFETIME OBSERVATION PHASE

Sex	Dose (mg/kg)	Hepatocellular Adenoma	Hepatocellular Carcinoma	Metastasis to Lung
MALE	0	8(2/25)*(a)*	48(12/25)	16(4/25)
	0.1	4(1/27)	30(8/27)	0(0/27)
	0.3	17(4/24)	33(8/24)	8(2/24)
	1.0	8(2/25)	48(12/25)	8(2/25)
	3.0	9(2/23)	65(15/23)	13(3/23)
	10.0	5(1/22)	95(21/22)*(b)*	19(4/21)
	Dose Response	NS	$P < 0.01$	NS
FEMALE	0	0(0/13)	0(0/13)	0(0/13)
	0.1	11(2/19)	0(0/19)	0(0/19)
	0.3	0(0/15)	13(2/15)	0(0/15)
	1.0	9(1/11)	18(2/11)	9(1/11)
	3.0	6(1/17)	18(3/17)	6(1/17)
	10.0	12(1/8)	88(7/8)*(b)*	38(3/8)*(c)*
	Dose Response	NS	$P < 0.01$	$P < 0.01$

(a) Data in parentheses indicate number positive/number examined.

(b) Significantly ($P < 0.01$) increased compared with controls.

(c) Significantly ($P < 0.05$) increased compared with controls.

The incidence of malignant lymphoma was significantly ($P < 0.05$) decreased in female mice receiving 0.1, 0.3, 1.0, or 3.0 mg/kg PBB (Table 33). Hyperplasia and adenoma of follicular cells of the thyroid tended to be increased in dosed mice. These findings, (1) decreased incidence of malignant lymphoma and (2) increased incidence of hyperplasia or adenoma of the follicular cells of the thyroid, may not be considered major findings because of the smaller sample size and low incidence.

TABLE 33. INCIDENCE OF MALIGNANT LYMPHOMA IN MICE EXPOSED TO PBB FOR 6 MONTHS AND EXAMINED DURING LIFETIME OBSERVATION PHASE

Dose (mg/kg)	Male Mice	Female Mice
0	16(4/25)*(a)*	77(10/13)
0.1	22(6/27)	32(6/19)*(b)*
0.3	29(7/24)	40(6/15)*(b)*
1.0	24(6/25)	45(5/11)*(b)*
3.0	13(3/23)	35(6/17)*(b)*
10.0	9(2/22)	25(2/8)
Dose Response	NS	NS

(a) Data in parentheses indicate number positive/number examined.

(b) Significantly ($P < 0.05$) decreased compared with control.

IV. DISCUSSION AND CONCLUSIONS

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Conflicting reports have been published regarding the relative toxicity of the flame retardant Firemaster FF-1. This PBB was considered to be relatively nontoxic because the LD_{50} of the single oral dose for rats was quoted to be 21.5 g/kg (Anon., 1971; 1976; Hill Top Research, 1970). However, Gupta and Moore (1979) demonstrated that the PBB was more toxic if given in small repeated doses, and the LD_{50} in female rats was lower than that in males. The LD_{50} for female rats was estimated to be 65 mg/kg/day (total 1.43 g/kg) and for male rats, 149 mg/kg/day (total 3.28 g/kg) when given in multiple doses and observed for 90 days. The lower 90-day LD_{50} in this experiment likely resulted from multiple dosing and increased duration of observation. The LD_{50} of halogenated aromatic hydrocarbons or those chemicals which may have a relatively long biological half-life with delayed toxicity is more accurately determined after multiple dosing and an extended period of observation (Gupta and Moore, 1979).

Firemaster FF-1, a flame retardant composed of polybrominated biphenyls, was responsible for widespread environmental contamination and animal losses in Michigan starting in 1973. This study was undertaken to characterize the long-term toxic and carcinogenic potential of this PBB mixture in rats and mice of each sex. Fischer 344/N rats and $B6C3F_1$ mice were given 125 oral doses of PBB over a 6-month period — 0, 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg body weight/day (5 days/week).

The effects of PBB were studied in rats and mice of each sex. There was no significant difference in feed consumption between PBB-dosed rats and mice compared with controls, yet there was a persistent decrease in body weight gain in dosed male and female rats and dosed male mice. This suggests that PBB may cause poor feed utilization. Similar weight-gain effects unrelated to feed intake have been observed in monkeys exposed to PBB (Allen et al., 1978), and in other species of animals with structurally similar halogenated aromatic hydrocarbons such as the PCB (Allen and Abrahamson, 1973), the dibenzodioxins (McConnell et al., 1978), and dioxin-contaminated technical grade pentachlorophenol (McConnell et al., 1980).

Interestingly, there was an increase in body weight of female mice administered PBB at 10.0 mg/kg/day, 125 total doses during a 6-month period. The explanation for this disparity is not clear. A more plausible explanation is that the body weight gain may be related to fluid accumulation in different tissues of the body. Extracellular fluid (subcutaneous edema, ascites, and hydropericardium) is often found in mice dying from acute intoxication from these classes of compounds (McConnell and Moore, 1979), and in fact mice showing this lesion do actually gain weight just prior to death.

The size and weight of the thymus were decreased in PBB-dosed (0.3 mg/kg or higher) rats but not in dosed mice at the end of the 6-month dosing. Administration of PBB to rats and mice was reported to cause suppression of both humoral and particularly cell-mediated immunity (Luster et al., 1978). In a 6-month administration of PBB to rats and mice, this chemical was not considered to be a potent immunosuppressant in rodents, since high doses were required to elicit immune effects (Luster et al., 1980).

The results of the comparative study clearly demonstrate that the pathologic changes in rats administered PBB are quantitatively much more pronounced than the pathologic changes in animals exposed to HBB (Gupta et al., 1981). Since the dose levels of HBB reflected a proportional amount of this pure isomer in the equivalent dose of PBB, i.e., 16.8 mg of 2,2',4,4',5,5'-hexabromobiphenyl represented the proportion of this isomer in 30.0 mg of PBB, the pathobiologic changes of PBB are not primarily due to this isomer. However, Firemaster BP-6 is a mixture of 13 different bromobiphenyls and also contains 200 ppm of brominated naphthalenes (Hass et al., 1978). While these naphthalenes (mainly hexa- and penta-isomers) are not potent inducers of mixed function oxidases (Goldstein et al., 1979), as are the more toxic chlorinated naphthalenes, they are highly toxic *in vivo* (McConnell, 1980). No evidence was found for the presence of bromodibenzo-*p*-dioxins or bromodibenzofurans in Firemaster BP-6 (Hass et al., 1978). The most logical explanation for the toxicity of PBB is that it probably represents an additive effect of the more toxic biphenyl isomers supplemented to some extent by the bromonaphthalenes.

Chronic administration of hexachlorobenzene, PCBs, or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) to rats produces hepatic porphyria characterized by delayed onset and massive accumulation of uroporphyrins in the liver (Ockner and Schmid, 1961; Goldstein et al., 1973; 1974; 1976). In the present study, PBBs also produced hepatic porphyria at doses as low as 0.3 mg/kg/day, with the rat being more sensitive than the mouse. In each species, the female

was much more susceptible than the male. This sex difference has been reported previously for the porphyrogenic action of hexachlorobenzene in rats (San Martin de Viale et al., 1970). However, this is the first report of a similar sex difference in mice. The porphyrogenic effects of PBBs in the rat may be of particular importance since an equivalent disease has been produced in humans through accidental consumption of hexachlorobenzene in Turkey in 1956 (Ockner and Schmid, 1961). Hepatic porphyria has not been found in people exposed to PBBs in Michigan; however, an alteration in the urinary porphyrin pattern which may reflect preliminary changes has been reported (Strik et al., 1979).

Under UV light, the incidence (%) of rats showing reddish pink fluorescence, an indication of excess porphyrin accumulation, and its intensity declined slightly in 1.0 and 3.0 mg/kg dose groups, but remained the same in 10.0 mg/kg dose groups (male and female rats) during the lifetime observation when compared with the 6-month results. However, results in all dosed female mice were negative, and only a few (3/23; 13% in the 3.0 mg/kg dose group) male mice showed slight to moderate reddish pink fluorescence during the lifetime observation. This further indicates that the rats are more sensitive than mice to the porphyrogenic effect of PBB and remain positive throughout the lifetime, even after discontinuation of the dosing.

The pigment (hemosiderin) accumulation in the liver and spleen probably represents by-products of a breakdown of erythrocytes, which in turn are phagocytized by the reticuloendothelial cells in these organs. Breakdown of RBCs would also explain the mild anemia. A slight decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) demonstrated that the anemia was microcytic and hypochromic. There was no indication of an increase in the number of circulating nucleated red blood cells. These findings suggest a direct depression of red blood cell precursors. Anemia and bone marrow depression have been observed in all species of animals exposed to toxic levels of dioxin and furans, especially in long-term studies (Huff et al., 1980).

PBB decreased the serum thyroxine (T_4) concentrations. The absence of any influence on uptake indicates that this effect was not due to alterations in binding to plasma protein. The binding of thyroid hormone to serum proteins was not affected by PBB, as indicated by the T_3 uptakes. Mild microscopic changes in thyroid glands were observed, but only at higher doses. Morphologic changes in thyroid glands were also observed in male rats exposed to PBB (Kasza et al., 1978), but serum levels of thyroid hormones were not measured. Norris et al. (1975) found evidence of thyroid hyperplasia in rats fed octabromobiphenyl for 30 days at 8.0 mg/kg/day.

TCDD and PCB have also been found to decrease serum thyroxine levels and produce goiters in rats (Bastomsky, 1974, 1977a, 1977b). The goiters were more evident in animals on a low iodine diet. The effect of TCDD and PCB on serum thyroxine concentrations appears to be secondary to an increase in the hepatic glucuronidation and bilary excretion of thyroxine. Interestingly, there has been a recent report of primary hypothyroidism in 4 men (11.4% of those examined) employed in a plant which produced the PBBs, decabromobiphenyl and decabromobiphenyl oxide (Bahn et al., 1980). From these data, it would seem advisable to examine serum thyroxine levels in people exposed to high levels of PBB.

Ulceration and focal hyperplastic gastropathy characterized by microcystic dilatation of crypts, downward growth of mucosa, and metaplasia of parietal cells to mucous cells were observed in PBB-dosed rats. Similar but more extensive hyperplastic gastrointestinal lesions were reported in monkeys exposed to PBB (Lambrecht et al., 1978; Allen et al., 1978), PCB (McConnell et al., 1979; Allen and Norback, 1973) or exposed to diesel motor lubricating oil (Lushbaugh, 1947; 1949); and in rats exposed to motor lubricating oil (Lushbaugh and Hackett, 1948). Although the pathogenesis of these gastrointestinal tract lesions is not known, the lesions may be due to the long latent period after the initial insult.

Several studies have shown that the liver is the target organ for PBB in most species and that these lesions persist even after withdrawal of the treatment. However, some PBB isomers have an extremely long biological half-life and significant levels of PBB are present in the liver and fat long after exposure ceases (Lee et al., 1975; Matthews et al., 1977; Tuey and Matthews, 1980). Neoplastic nodules were reported in the livers of rats 10 months after a single oral dose of PBB (Kimbrough et al., 1977; 1978). Similar atypical nodules in the liver were also observed in rats as early as 6 months after the rats were given multiple doses of PBB (Gupta and Moore, 1979).

IV. DISCUSSION AND CONCLUSIONS

Increases in the absolute and relative liver weights of rats and mice and microscopic alterations were the characteristics of hepatotoxicity. The primary target organ was the liver. The toxic changes were characterized by hepatomegaly due to cytomegaly, increase in endoplasmic reticulum, and excess lipid accumulation. The increase in GGTP and SGTP in mice was also probably related to hepatotoxicity.

At the end of the 6-month continuous administration 3.0% of dosed rats, no control rats, 11.0% of dosed mice, and 5.0% of control mice developed atypical hepatocellular foci. Since the incidence of atypical foci in the liver was so low at the 6-month observation, a definite conclusion for the potential hepatocarcinogenicity of PBB could not be drawn at that time.

However, rats exposed for 6 months and held for their lifetime showed a significantly ($P<0.05$) increased incidence of hepatocellular carcinoma and cholangiocarcinoma. A similar increased incidence of hepatocellular carcinoma has recently been reported in female Sherman rats exposed to PBB (Kimbrough et al., 1981). Hepatocellular carcinoma in exposed mice was also observed when the animals were held for lifetime observation. Hepatic neoplasms were observed only in those groups of animals in which PBB was given in sufficient dose to induce marked liver toxicity. Those dosed animals having less or minimal hepatotoxicity did not develop a significantly increased incidence of hepatic neoplasia when compared with controls.

Conclusions: Under the conditions of these studies, polybrominated biphenyl mixture (Firemaster FF-1) was carcinogenic for Fischer 344/N rats and B6C3F$_1$ mice of each sex, inducing neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats, and hepatocellular carcinomas in mice. Other toxicities included porphyrogenic effects and hepatotoxicity.

V. REFERENCES

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Abritti, G., and De Matteis, F. (1971). Decreased levels of cytochrome P-450 and catalase in hepatic porphyria caused by substituted acetamides and barbiturates. Chem.-Biol. Interact., 4:281-286.

Aftosmis, J.G., Culik, R., Lee, K.P., Sherman, H., and Waritz, R.S. (1972). Toxicology of brominated biphenyls. I. Oral toxicity and embryotoxicity. Toxicol. Appl. Pharmacol., 22:316 (Abstr.).

Allen, J.R., and Abrahamson, L.J. (1973). Morphological and biochemical changes in the liver of rats fed polychlorinated biphenyls. Arch. Environ. Cont. Toxicol., 1:265-280.

Allen, J.R., Lambrecht, L.K., and Barsotti, D.A. (1978). Effects of polybrominated biphenyls in nonhuman primates. J. Amer. Vet. Med. Assoc., 173:1485-1489.

Allen, J.R., and Norback, D.H. (1973). Polychlorinated biphenyl- and triphenyl-induced gastric mucosal hyperplasia in primates. Science, 179:498-499.

Anderson, E.V. (March 22, 1976). Government rules: problems, opportunity. Chem. Eng. News, 54:12.

Anonymous (1971). Firemaster BP-6. A new flame retardant additive from Michigan Chemical Corp. 2nd revision.

Anonymous (1976). Michigan State University Agricultural Experiment Station, MSU Research on PBBs. Mich. Sci. Action.

Anonymous (June 22, 1977). Pesticide and Toxic Chemical News, pp. 9-11.

Armitage, P. (1971). Statistical Methods in Medical Research. New York, John Wiley & Sons, Inc. pp. 362-365.

Aulerich, R.J., and Ringer, R.K. (1979). Toxic effects of dietary polybrominated biphenyls on mink. Arch. Environ. Contam. Toxicol., 8:487-498.

Bahn, A.K., Mills, J.L., Snyder, P.J., Gann, P.H., Houten, L., Bialik, O., Hollmann, L., and Utiger, R.D. (1980). Hypothyroidism in workers exposed to polybrominated biphenyls. New England J. Med., 302:31-33.

Barr, M. (1980). Pediatric aspects of the Michigan polybrominated biphenyl contamination. Environ. Res., 21:255-274.

Barthold, S.W. (1979). Chronic progressive nephropathy in aging rats. Toxicol. Pathol., 7:1-6.

Bastomsky, C.H. (1974). Effect of a polychlorinated biphenyl mixture (Aroclor 1254) and DDT on biliary thyroxine excretion in rats. Endocrinology, 95:1150-1155.

Bastomsky, C.H. (1977a). Enhanced thyroxine metabolism and high uptake goiters in rats after a single dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Endocrinology, 101:292-296.

Bastomsky, C.H. (1977b). Goiters in rats fed polychlorinated biphenyls. Can. J. Phys. Pharmacol., 55:288-292.

Beaudoin, A.R. (1977). Teratogenicity of polybrominated biphenyls in rats. Environ. Res., 14:81-86.

Brilliant, L.B., Wilcox, K., Amburg, G.V., Eyster, J., Isbister, J., Bloomer, A.W., Humphrey, H., and Price, H. (1978). Breast-milk monitoring to measure Michigan's contamination with polybrominated biphenyls. Lancet, No. 8091, Vol. II: 643-646.

Brown, G.G., and Nixon, R. (1979). Exposure to polybrominated biphenyls. Some effects on personality and cognitive functioning. J. Amer. Med. Assoc., 242:523-527.

Carter, L.J. (1976). Michigan's PBB incident: Chemical mix-up leads to disaster. Science, 192:240-243.

Cecil, H.C., and Bitman, J. (1978). Toxicity of polybrominated biphenyl and its effects on reproduction of White Leghorn hens. Poultry Sci., 57:1027-1036.

Chang, T.S., and Zindel, H.C. (1975). Toxic effects of polybrominated biphenyl on young poultry. Poultry Sci., 54:1743-1744.

Cook, H., Helland, D.R., Vanderweele, B.H., and Dejong, R.T. (1978). Histotoxic effects of polybrominated biphenyls in Michigan dairy cattle. Environ. Res., 15:82-89.

Corbett, T.H., Beaudoin, A.R., Cornell, R.G., Anver, M.R., Schumacher, R., Endres, J., and Szwabowska, M. (1975). Toxicity of polybrominated biphenyls (Firemaster BP-6) in rodents. Environ. Res., 10:390-396.

Cox, D.R. (1972). Regression models and life tables. J. R. Stat. Soc., B34:187-220.

Detering, C.N., Prewitt, L.R., Cook, R.M., and Fries, G.F. (1975). Placental transfer of polybrominated biphenyl by Holstein cows. J. Dairy Sci., 58:764 (Abstr.).

Dunckel, A.E. (1975). An updating on the polybrominated biphenyl disaster in Michigan. J. Amer. Vet. Med. Assoc., 167:838-841.

V. REFERENCES

Fries, G.F. (1978). Distribution and kinetics of polybrominated biphenyls and selected chlorinated hydrocarbons in farm animals. J. Amer. Vet. Med. Assoc., 173:1479-1484.

Fries, G.F., and Marrow, G.S. (1975). Excretion of polybrominated biphenyls into the milk of cows. J. Dairy. Sci., 58:947-951.

Gart, J., Chu, K., and Tarone, R. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst., 62:957-974.

Goldstein, J.A., Hickman, P., Bergman, H., and Vos, J.G. (1973). Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the mouse. Res. Commun. Chem. Pathol. Pharmacol., 6:919-928.

Goldstein, J.A., Hickman, P., and Jue, D.L. (1974). Experimental hepatic porphyria induced by polychlorinated biphenyls. Toxicol. Appl. Pharmacol., 27:437-448.

Goldstein, J.A., Hickman, P., and Bergman, H. (1976). Induction of hepatic porphyria and drug-metabolizing enzymes by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Fed. Proc., 35:708 (Abstr.).

Goldstein, J.A., Linko, P.C., Levy, L.A., McKinney, J.A., Gupta, B.N., and Moore, J.A. (1979). A comparison of a commercial polybrominated biphenyl mixture, 2,4,5,2',4',5'-hexabromobiphenyl and 2,3,6,7-tetrabromonaphthalene as inducers of liver microsomal drug-metabolizing enzymes. Biochem. Pharmacol., 28:2947-2956.

Gupta, B.N., and Moore, J.A. (1979). Toxicologic assessments of a commercial polybrominated biphenyl mixture in the rat. Amer. J. Vet. Res., 40, 1458-1468.

Gupta, B.N., McConnell, E.E., Harris, M.W., and Moore, J.A. (1981). Polybrominated biphenyl toxicosis in the rat and mouse. Toxicol. Appl. Pharmacol., 57:99-118.

Gutenmann, W.H., and Lisk, D.J. (1975). Tissue storage and excretion in milk of polybrominated biphenyls in ruminants. J. Agric. Food Chem., 23:1005-1007.

Harris, S.J., Cecil, H.C., and Bitman, J. (1978). Embryotoxic effects of polybrominated biphenyls (PBB) in rats. Environ. Health Perspect., 23:295-300.

Hass, R.J., McConnell, E.E., and Harvan, D.J. (1978). Chemical and toxicologic evaluation of Firemaster BP-6. Agricul. Food Chem., 26:94-99.

Hill Top Research (1970). Acute toxicity and irritation studies on Firemaster BP-6 hexabromobiphenyl for Michigan Chemical Corporation. Hill Top Research Inc.

Hollander, M., and Wolfe, D.A. (1973). Nonparametric Statistical Methods. Wiley, New York.

Huff, J.E., Moore, J.A., Saracci, R., and Tomatis, L. (1980). Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Environ. Health Perspect., 36:221-240.

Humphrey, H.E.B., and Hayner, N.S. (1975). Polybrominated biphenyls: An agricultural incident and its consequences. II. An epidemiological investigation of human exposure, p. 57-63. In: D.D. Hemphill (Ed.), Trace Substances in Environmental Health, IX. Univ. of Missouri Press, Columbia.

IARC, International Agency for Research on Cancer (1978). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Polychlorinated Biphenyls and Polybrominated Biphenyls. Vol. 18, Lyon, France.

Humphrey, H.E.B., Wilcox, K.R., Isbister, J.L., and Bloomer, A.W. (1979). Health status of persons exposed to PBB. Toxicol. Appl. Pharmacol., 48:175 (Abstr.).

Isbister, J.L. (1977). PBBs in human health. Clin. Med., 84:22-24.

Jackson, T.F., and Halbert, F.L. (1974). A toxic syndrome associated with the feeding of polybrominated biphenyl contaminated protein concentrate to dairy cattle. J. Amer. Vet. Med. Assoc., 165:437-439.

Jacobs, L.W., Chow, S.F., and Tiedje, J.M. (1978). Field concentrations and persistence of polybrominated biphenyls in soils and solubility of PBB in natural waters. Environ. Health Perspect., 23:1-8.

Jonckheere, A.R. (1954). A distribution-free K-sample test against ordered alternatives. Biometrika, 41:133-145.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation of incomplete observations. J. Amer. Stat. Assoc., 53:457-481.

Kasza, L., Collins, W.T., Capen, C.C., Garthoff, L.H., and Friedman, L. (1978). Comparative toxicity of polychlorinated biphenyl and polybrominated biphenyl in the rat thyroid gland: Light and electron microscopic alterations after subacute dietary exposure. J. Environ. Path. Toxicol., 1:587-599.

V. REFERENCES

Kasza, L., Weinberger, M.A., Hinton, D.E., Trump, B.F., Patel, C., Friedman, L., and Garthoff, L.H. (1978). Comparative toxicity of polychlorinated biphenyl and polybrominated biphenyl in the rat liver: Light and electron microscopic alterations and subacute dietary exposure. J. Environ. Pathol. Toxicol., 1:241-257.

Kay, K. (1977). Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973-1976. Environ. Res., 13:74-93.

Kimbrough, R.D., Burse, V.W., Liddle, J.A., and Fries, G.F. (1977). Toxicity of polybrominated biphenyl. Lancet, No. 8038(2):602-603.

Kimbrough, R.D., Burse, V.W., and Liddle, J.A. (1978). Persistent liver lesions in rats after a single oral dose of polybrominated biphenyls (Firemaster FF-1) and concomitant PBB tissue levels. Environ. Health Perspect., 23:265-273.

Kimbrough, R.D., Groce, D.F., Korver, M.P., and Burse, V.W. (1981). Induction of liver tumors in female Sherman strain rats by polybrominated biphenyls. J. Natl. Cancer Inst., 66:535-542.

Kimbrough, R.D., Korver, M.P., Burse, V.W., and Groce, D.F. (1980). The effect of different diets or mineral oil on liver pathology and polybrominated biphenyl concentration in tissues. Toxicol. Appl. Pharmacol., 52:442-453.

Lambrecht, L.K., Barsetti, D.A., and Allen, J.R. (1978). Responses of nonhuman primates to a polybrominated biphenyl mixture. Environ. Health Perspect., 23:139-145.

Lee, K.P., Herbert, R.R., Sherman, H., Aftosmis, J.G., and Waritz, R.S. (1975). Bromine tissue residue and hepatotoxic effects of octabromobiphenyl in rats. Toxicol. Appl. Pharmacol., 34:115-127.

Lillie, R.J., Cecil, H.C., Bitman, J., Fries, G.F., and Verrett, J. (1975). Toxicity of certain polychlorinated and polybrominated biphenyls on reproductive efficiency of caged chickens. Poultry Sci., 54:1550-1555.

Luna, L.G. (1968). Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology. 3rd Edition, McGraw-Hill Co., New York, pp. 183-184.

Lushbaugh, C.C. (1947). Experimental hyperplastic gastritis and gastric polyposis in monkeys. J. Natl. Cancer Inst., 7:313-320.

Lushbaugh, C.C. (1949). Infiltrating adenomatous lesions of the stomach, cecum and rectum of monkeys similar to early human carcinoma and carcinoma in situ. Cancer Res., 9:385-394.

Lushbaugh, C.C., and Hackett, A. (1948). An infiltrating adenomatous lesion of the colon of rats ingesting motor lubricating oil (SGF No. 1 oil). J. Natl. Cancer Inst., 9:159-172.

Luster, M.I., Boorman, G.A., Harris, M.W., and Moore, J.A. (1980). Laboratory studies on polybrominated biphenyl-induced immune alterations following low-level chronic or pre/postnatal exposure. Int. J. Immunopharmac., 2:69-80.

Luster, M.I., Faith, R.E., and Moore, J.A. (1978). Effects of polybrominated biphenyls (PBB) on immune response in rodents. Environ. Health Perspect., 23:227-232.

Mantel, N., and Haenszel, W. (1959). Statistical aspect of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst., 22:719-748.

Matthews, H.B., Kato, S., Morales, N.M., and Tuey, D.B. (1977). Distribution and excretion of 2,4,5,2',4',5'-hexabromobiphenyl, the major component of Firemaster BP-6. J. Toxicol. Environ. Health, 3:599-605.

McConnell, E.E. (1980). Acute and chronic toxicity, carcinogenesis, reproduction, teratogenesis, and mutagenesis in animals. In: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins, and Related Products. R. D. Kimbrough, Ed., Elsevier/North Holland Biomedical Press, New York, 109-150.

McConnell, E.E., Harris, M.W., and Moore, J.A. (1980). Studies on the use of activated charcoal and cholestyramine for reducing the body burden of polybrominated biphenyls. Drug. Chem. Toxicol., 3:277-292.

McConnell, E.E., Hass, J.R., Altman, N., and Moore, J.A. (1979). A spontaneous outbreak of polychlorinated biphenyl (PCB) toxicity in Rhesus monkeys *(Macaca mulatta)*: Toxicopathology. Lab. Anim. Sci., 29:666-673.

McConnell, E.E., and Moore, J.A. (1979). Toxicopathology characteristics of the halogenated aromatics. Ann. NY Acad. Sci., 320:138-150.

McConnell, E.E., Moore, J.A., and Dalgard, D.W. (1978). Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rhesus monkeys *(Macaca mulatta)* following a single oral dose. Toxicol. Appl. Pharmacol., 43:175-187.

McConnell, E.E., Moore, J.A., Gupta, B.N., Rakes, A.H., Luster, M.I., Goldstein, J.A., Haseman, J.K., and Parker, C.E. (1980). The chronic toxicity of technical and analytical pentachlorophenol in cattle. Toxicol. Appl. Pharmacol., 52:468-490.

V. REFERENCES

Meester, W.D., and McCoy, D.J. (1977). Human toxicology of polybrominated biphenyls. Clin. Toxicol., 10:474.

Mercer, H.D., Teske, R.H., Condon, R.J., Furr, A., Meerdink, G., Buck, W., and Fries, G. (1976). Herd health status of animals exposed to polybrominated biphenyls (PBB). J. Toxicol. Environ. Health, 2:335-349.

Moore, R.W., Dannan, G.A., and Aust, S.D. (1978). Induction of drug metabolizing enzymes in polybrominated biphenyls-fed lactating rats and their pups. Environ. Health Perspect., 23:159-165.

Mumma, C.E., and Wallace, D.D. (June 1975). Survey of industrial processing data. Task II - Pollution potential of polybrominated biphenyls. EPA-560/3-75-004.

Norris, J.M., Kociba, R.J., Schwetz, B.A., Rose, J.Q., Humiston, C.G., Jewett, G.L., Gehring, P.J., and Mailhes, J.B. (1975). Toxicology of octabromobiphenyl and decabromodiphenyl oxide. Environ. Health Perspect., 11:153-161.

Ockner, R.K., and Schmid, R. (1961). Acquired porphyria in man and rat due to hexachlorobenzene intoxication. Nature, 189:499.

Peto, R., Pike, M., Day, N., Gray, R., Lee, P., Parish, S., Peto, J., Richard, S., and Wahrendorf, J. (1980). Guidelines for simple, sensitive, significant tests for carcinogenic effects in long-term animal experiments. International Agency for Research Against Cancer. Monographs on the long-term and short-term screening assays for carcinogens: A critical appraisal. Geneva: World Health Organization. Supplement 2:311.

Reynolds, E.S. (1963). The use of lead citrate at high pH as an electron-opaque stain in electron microscopy. J. Cell. Biol., 17:208-212.

Rickert, D.E., Dent, J.G., Cagen, S.Z., McCormack, K.M., Melrose, P., and Gibson, J.E. (1978). Distribution of polybrominated biphenyls after dietary exposure in pregnant and lactating rats and their offspring. Environ. Health Perspect., 23:63-66.

Ringer, R.K., and Polin, D. (1975). Effects of polybrominated biphenyl on laying hens. Poultry Sci., 54:1810.

Ringer, R.K., and Polin, D. (1977). The biological effects of polybrominated biphenyls in avian species. Fed. Proc., 36:1894-1898.

Ruzo, L.O., and Zabik, M.J. (1975). Polyhalogenated biphenyls: Photolysis of hexabromo- and hexachlorobiphenyls in methanol solution. Bull. Environ. Contam. Toxicol., 13:181-182.

San Martin de Viale, I.C., Nacht, S., and Grinstein, M. (1970). Experimental porphyria induced in rats by hexachlorobenzene: A study of the prophyrins excreted by urine. Clin. Chim. Acta., 28:13-23.

Selikoff, I.J., and Anderson, H.A. (1979). A Survey of the General Population of Michigan for Health Effects of Polybrominated Biphenyl Exposure. Report to the Michigan Department of Public Health, September 30, 1979. Environmental Sciences Laboratory, Mount Sinai School of Medicine, New York, N.Y.

Sleight, S.D., and Sanger, V.L. (1976). Pathologic features of polybrominated biphenyl toxicosis in the rat and guinea pig. J. Amer. Vet. Med. Assoc., 169:1231-1235.

Strik, J.J.T.W.A., Doss, M., Schraa, G., Robertson, L.W., Tiepermann, R., and Harmisen, E.G.M. (1979). Coproporphyrinuria and chronic hepatic porphyria type A found in farm families from Michigan (USA).

Tilson, H.A., and Cabe, P.A. (1979). Studies on the neurobehavioral effects of polybrominated biphenyls in rats. Ann. N.Y. Acad. Sci., 320:325-336.

Tilson, H.A., Cabe, P.A., and Mitchell, C.L. (1978). Behavioral and neurological toxicity of polybrominated biphenyls in rats and mice. Environ. Health Perspect., 23:257-263.

Tuey, D.B., and Matthews, H.B. (1980). Distribution and excretion of 2,2',4,4',5,5'-hexabromobiphenyl in rats and man: Pharmacokinetic model predictions. Toxicol. Appl. Pharmacol., 53:420-431.

Werner, P.R., and Sleight, S.D. (1981). Toxicosis in sows and their pigs caused by feeding rations containing polybrominated biphenyls to sows during pregnancy and lactation. Am. J. Vet. Res., 42:183-188.

Wolff, M.S., Anderson, H.A., Rosenman, K.D. and Selikoff, I.J. (1979). Equilibrium of polybrominated biphenyl (PBB) residues in serum and fat of Michigan residents. Bull. Environ. Contam. Toxicol., 21:775-781.

APPENDIX A

INDIVIDUAL ANIMAL PATHOLOGY IN RATS ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

TABLE A1.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE RATS ADMINISTERED 10.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	21 5	39 4	04 8	46 1	19 0	18 1	04 7	17 5	20 1	24 3	03 7	21 6	16 9	14 6	09 4	24 2	12 2	08 7	01 8	28 0
Weeks on Study	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	42	44	73	74	77	81	82	84	84	85	86	87	87	90	91	92	92	94	94	94
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Fibroma																				
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myelomonocytic Leukemia												x					x			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci					x			x					x	x			x		x	
Neoplastic Nodule																				
Hepatocellular Carcinoma						x	x					x				x		x		x
Pancreas-like Tissue					x															
Bile Duct Hyperplasia		x		x		x	x						x						x	
Bile Duct Adenoma																				
Bile Duct Carcinoma																		x		
Pancreas	+	+	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Exocrine Cell Adenoma																				
Exocrine Cell Carcinoma																				
Stomach	+	+	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Ulcer									x				x		x	x		x	x	
Hyperplastic Gastropathy													x	x			x			x
Tongue	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large Intestine	+	0	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Adenomatous Polyp																				x
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chronic Progressive Nephropathy*					3	3	2	2	2	2	2	1	3	3	3	2	3	3	2	3
Transitional Cell Carcinoma																				
Pituitary Gland	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				
Thyroid Gland	+	+	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma																				
Follicular Cell Carcinoma																				
C-Cell Hyperplasia																				
C-Cell Adenoma									x											
Parathyroid Gland	+	+	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Hyperplasia						x											x			x
Adenoma														x						
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Leydig Cell Tumor				x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammation, Tympanic Bullae																		x		
Brain	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A1. MALE RATS: ANIMAL PATHOLOGY (CONTINUED) 10.0 mg

Animal Number	21242	04247	36715	11169	24848	02876	07624	12411	11105	01550	06043	04303	Total Tissues or Lesions
Weeks on Study	0 9 4	0 9 4	0 9 5	0 9 6	0 9 7	0 9 7	0 9 7	0 9 9	1 0 1	1 0 1	1 0 1	1 0 3	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	0	+	+	+	+	+	30
Fibroma										x			1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	32
Myelomonocytic Leukemia													2
Lung	+	+	+	+	+	+	0	+	+	+	+	+	31
Liver	+	+	+	+	+	+	0	+	+	+	+	+	31
Atypical Foci	x	x				x		x		x	x		12
Neoplastic Nodule									x				1
Hepatocellular Carcinoma												x	7
Pancreas-like Tissue										x			2
Bile Duct Hyperplasia				x				x	x				9
Bile Duct Adenoma										x			1
Bile Duct Carcinoma						x							2
Pancreas	+	+	+	+	+	+	0	+	+	+	+	+	29
Exocrine Cell Adenoma	x											x	2
Exocrine Cell Carcinoma			x										1
Stomach	+	+	+	+	+	+	0	+	+	+	+	+	29
Ulcer		x		x		x			x	x	x		12
Hyperplastic Gastropathy													4
Tongue	+	+	+	+	+	+	0	+	+	+	+	+	30
Large Intestine	+	+	+	+	+	+	+	+	+	+	+	+	29
Adenomatous Polyp													1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	32
Chronic Progressive Nephropathy*	3	2	3	3	2	3	3	2	3	2	3	3	28
Transitional Cell Carcinoma											x		1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	31
Adenoma		x								x			2
Thyroid Gland	+	+	+	+	+	+	0	+	+	+	+	+	29
Follicular Cell Adenoma										x			1
Follicular Cell Carcinoma								x					1
C-Cell Hyperplasia											x		1
C-Cell Adenoma													1
Parathyroid Gland	+	+	+	+	+	+	0	+	+	+	+	+	29
Hyperplasia	x			x							x		6
Adenoma													1
Adrenal Gland	+	+	+	+	+	+	0	+	+	+	+	+	31
Testes	+	+	+	+	+	+	+	+	+	+	+	+	30
Leydig Cell Tumor	x	x	x	x	x	x	x	x	x	x	x	x	28
Ear	+	+	+	+	+	+	+	+	+	+	+	+	32
Inflammation, Tympanic Bullae													1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	31

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A2.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE RATS ADMINISTERED 3.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	37 70	29 93	26 65	18 66	27 44	05 99	33 77	01 99	22 11	09 33	06 33	25 88	06 11	09 66	12 88	26 11	10 77	25 22	28 99	00 55
Weeks on Study	06 22	07 77	08 33	08 55	08 55	08 77	09 22	09 33	09 33	09 55	09 55	09 66	09 66	09 88	09 88	09 88	09 88	09 88	09 99	10 00
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																				
Mammary Gland Fibroadenoma																				
Preputial Gland Adenoma															x				x	
Basal Cell Tumor				x																
Mesothelioma, Abdominal Cavity														x						
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myelomonocytic Leukemia																				
Hemangiosarcoma (Spleen)																				
Plasma Cell Tumor	x																			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveologenic Adenoma													x							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci					x			x		x		x	x	x			x	x		x
Neoplastic Nodule									x											
Hepatocellular Carcinoma	x			x									x	x	x					
Bile Duct Hyperplasia		x		x				x	x		x	x	x	x	x		x	x		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Exocrine Cell Adenoma											x									
Exocrine Cell Carcinoma								x												
Islet Cell Adenoma				x																
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ulcer			x			x	x	x		x		x	x	x	x	x				
Hyperplastic Gastropathy		x	x		x	x														
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chronic Progressive Nephropathy*		2	2	1	3	3	1	3	3	3	3	3	3	3	2	3	3	3	3	2
Adenoma																	x			
Liposarcoma																	x			
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			x									x					x			
Carcinoma																				x
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma		x							x			x								
Follicular Cell Carcinoma											x									
C-Cell Adenoma																				
C-Cell Carcinoma																				
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplasia						x			x								x	x		
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical Hyperplasia																			x	
Pheochromocytoma										x										
Testes	+	0	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+
Leydig Cell Tumor					x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammation, Tympanic Bullae																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
  1 = Slight CPN
  2 = Moderate CPN
  3 = Marked CPN

TABLE A2. MALE RATS: ANIMAL PATHOLOGY (CONTINUED) 3.0 mg

Animal Number	27600	15002	28802	18803	23403	25404	19404	39705	12905	04508	41112	08112	29612	Total Tissues or Lesions
Weeks on Study	100	102	102	103	103	104	104	105	108	108	112	112	112	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Fibroma										x				1
Mammary Gland Fibroadenoma												x		1
Preputial Gland Adenoma														2
Basal Cell Tumor														1
Mesothelioma, Abdominal Cavity														1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Myelomonocytic Leukemia							x						x	2
Hemangiosarcoma (Spleen)							x							1
Plasma Cell Tumor														1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Alveologenic Adenoma														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Atypical Foci							x	x	x		x			13
Neoplastic Nodule		x								x		x		4
Hepatocellular Carcinoma	x									x				7
Bile Duct Hyperplasia			x	x		x								14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Exocrine Cell Adenoma									x		x			3
Exocrine Cell Carcinoma														1
Islet Cell Adenoma														1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Ulcer		x		x	x	x	x	x	x	x				18
Hyperplastic Gastropathy				x				x						6
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Chronic Progressive Nephropathy*	2	3	3	3	3	1	3	3	2	1	2	3	1	32
Adenoma														1
Liposarcoma														1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Adenoma					x		x							5
Carcinoma														1
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Follicular Cell Adenoma													x	4
Follicular Cell Carcinoma									x					2
C-Cell Adenoma								x						1
C-Cell Carcinoma					x									1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Hyperplasia						x	x					x		7
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Cortical Hyperplasia									x		x		x	4
Pheochromocytoma											x	x		3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Leydig Cell Tumor	x	x	x	x	x	x	x	x	x	x	x	x	x	28
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Inflammation, Tympanic Bullae			x										x	2
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	33

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
  1 = Slight CPN
  2 = Moderate CPN
  3 = Marked CPN

TABLE A3.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE RATS ADMINISTERED 1.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	136	208	022	329	029	162	226	395	140	407	196	222	287	133	052	102	161	197	417	117
Weeks on Study	069	078	079	080	085	086	087	088	090	090	091	091	092	094	097	097	097	098	100	101
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma/Fibroadenoma				x				x												x
Preputial Gland Adenoma																				
Basal Cell Tumor																				
Hemangioendothelioma																				
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myelomonocytic Leukemia	x					x	x						x							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveologenic Adenoma																			x	x
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci				x							x		x	x	x				x	
Neoplastic Nodule									x							x				
Hepatocellular Carcinoma																		x		
Bile Duct Hyperplasia		x				x	x	x				x	x				x	x		x
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+
Exocrine Cell Adenoma																				
Islet Cell Adenoma											x				x					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+
Ulcer			x		x	x					x	x						x		x
Hyperplastic Gastropathy										x										
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+
Chronic Progressive Nephropathy *		1	1	1	3	1	2	2	3	3	3	2	2	3	3	3		2	3	1
Adenoma																				
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										x								x		
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma																				x
Follicular Cell Carcinoma																				
C-Cell Hyperplasia																				
C-Cell Adenoma								x												
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplasia									x		x			x	x	x	x		x	
Adenoma																				
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+
Cortical Hyperplasia																			x	
Cortical Adenoma																				
Pheochromocytoma										x										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+
Leydig Cell Tumor		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammation, Tympanic Bullae																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

\+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A3. MALE RATS: ANIMAL PATHOLOGY (CONTINUED) 1.0 mg

Animal Number	11103	07302	08206	17607	10007	46505	42508	03807	09707	18307	17208	Total Tissue or Lesions
Weeks on Study	10002	10003	10006	10007	10007	11010	11011	11012	11012	11017	11018	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	31
Fibroma/Fibroadenoma		x		x					x			6
Preputial Gland Adenoma			x									1
Basal Cell Tumor										x		1
Hemangioendothelioma											x	1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	31
Myelomonocytic Leukemia												4
Lung	+	+	+	+	+	+	+	+	+	+	+	31
Alveologenic Adenoma												2
Liver	+	+	+	+	+	+	+	+	+	+	+	31
Atypical Foci	x	x		x		x					x	11
Neoplastic Nodule									x	x		4
Hepatocellular Carcinoma												1
Bile Duct Hyperplasia	x		x				x		x			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	30
Exocrine Cell Adenoma				x						x		2
Islet Cell Adenoma												2
Stomach	+	+	+	+	+	+	+	+	+	+	+	30
Ulcer					x					x		9
Hyperplastic Gastropathy	x	x										3
Tongue	+	+	+	+	+	+	+	+	+	+	+	31
Kidney	+	+	+	+	+	+	+	+	+	+	+	30
Chronic Progressive Nephropathy *	3	2	2	2	3	3	2	2	1	2	2	29
Adenoma				x								1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	31
Adenoma	x		x		x					x		6
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	31
Follicular Cell Adenoma			x									2
Follicular Cell Carcinoma											x	1
C-Cell Hyperplasia	x					x						2
C-Cell Adenoma												1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	31
Hyperplasia	x			x		x	x	x		x		13
Adenoma		x										1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	30
Cortical Hyperplasia									x	x		3
Cortical Adenoma							x					1
Pheochromocytoma						x						2
Testes	+	+	+	+	+	+	+	+	+	+	+	30
Leydig Cell Tumor		x	x	x	x	x	x	x	x	x	x	28
Ear	+	+	+	+	+	+	+	+	+	+	+	31
Inflammation, Tympanic Bullae						x	x					2
Brain	+	+	+	+	+	+	+	+	+	+	+	31

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A4.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE RATS ADMINISTERED 0.3 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	25 1	03 1	13 8	20 0	21 1	11 6	21 0	00 7	12 1	31 4	00 8	16 6	11 8	17 3	05 8	24 7	07 7	10 1	47 5	16 5
Weeks on Study	0 7 8	0 8 5	0 8 7	0 9 0	0 9 3	0 9 4	0 9 4	0 9 4	0 9 5	0 9 7	0 9 9	0 9 9	1 0 4	1 0 5	1 0 5	1 0 5	1 0 6	1 0 6	1 0 6	1 0 6
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma/Fibroadenoma								x										x		
Fibrosarcoma				x												x				
Preputial Gland Adenoma															x					
Odontoma			x																	
Basal Cell Tumor													x							
Mesothelioma, Abdominal Cavity																				
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiopericytoma, Malignant											x									
Myelomonocytic Leukemia		x			x	x						x					x			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Metastatic Tumors											x					x				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci		x			x		x					x		x	x	x				
Neoplastic Nodule																				
Bile Duct Hyperplasia	x		x			x				x		x							x	x
Metastatic Tumors											x					x				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Exocrine Cell Adenoma																				
Islet Cell Adenoma							x													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ulcer													x	x			x			x
Hyperplastic Gastropathy				x									x							
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous Cell Papilloma																		x		
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	x																			
Large Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous Polyp																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chronic Progressive Nephropathy*	2	1	1	1	1	1	3	1	1	2	1	1	2	3	3	1	1	1	2	1
Adenoma																				
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								x											x	x
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma							x													x
C-Cell Hyperplasia																				
C-Cell Adenoma													x							
C-Cell Carcinoma																				
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplasia							x								x				x	
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical Hyperplasia																	x			
Pheochromocytoma																				x
Testes	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+
Leydig Cell Tumor	x	x	x	x	x	x	x		x			x	x	x	x	x	x	x	x	x
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammation, Tympanic Bullae																				x
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A4. MALE RATS: ANIMAL PATHOLOGY (CONTINUED) 0.3 mg

Animal Number	12 3	46 9	20 7	10 9	05 6	31 8	20 4	39 6	35 7	35 1	12 5	28 6	43 6	22 0	40 1	13 0	06 2	23 3	46 4	15 4	Total Tissue or Lesions
Weeks on Study	1 07	1 07	1 08	1 08	1 09	1 10	1 11	1 11	1 12	1 12	1 12	1 12	1 13	1 13	1 13	1 13	1 13	1 15	1 16	1 16	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Fibroma/Fibroadenoma	x					x							x		x	x					7
Fibrosarcoma																					2
Preputial Gland Adenoma																					1
Odontoma																					1
Basal Cell Tumor																					1
Mesothelioma, Abdominal Cavity							x														1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hemangiopericytoma, Malignant																					1
Myelomonocytic Leukemia	x				x	x															8
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Metastatic Tumors																					2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Atypical Foci		x						x								x		x	x		12
Neoplastic Nodule													x								1
Bile Duct Hyperplasia				x			x									x					10
Metastatic Tumors																					2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Exocrine Cell Adenoma																	x			x	2
Islet Cell Adenoma																					1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Ulcer	x						x					x						x			8
Hyperplastic Gastropathy																					2
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Squamous Cell Papilloma																					1
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenocarcinoma																					1
Large Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenomatous Polyp														x							1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Chronic Progressive Nephropathy*	1	3	3	1	1	2	1	2	2	1	1	2	3	1	2	2	2	1	1	2	40
Adenoma				x																	1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma	x										x						x	x			7
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Follicular Cell Adenoma																	x		x		4
C-Cell Hyperplasia														x	x						2
C-Cell Adenoma			x							x						x					4
C-Cell Carcinoma	x																				1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hyperplasia			x	x				x					x		x	x	x	x		x	12
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	39
Cortical Hyperplasia		x	x												x						4
Pheochromocytoma								x			x	x			x					x	6
Testes	+	+	+	+	+	+	+	+	+	+	x	+	+	+	+	+	+	+	+	+	39
Leydig Cell Tumor	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	37
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Inflammation, Tympanic Bullae				x		x		x			x				x						6
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A5.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE RATS ADMINISTERED 0.1 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	0 3 2	1 0 8	0 8 3	1 5 3	0 6 8	2 7 5	0 3 3	0 4 9	2 9 5	3 0 3	1 4 7	2 5 3	2 5 9	1 1 5	3 0 5	1 2 7	1 7 4	0 7 0	1 3 1	4 7 0
Weeks on Study	0 5 4	0 7 7	0 8 1	0 8 7	0 8 9	0 9 4	0 9 9	1 0 0	1 0 1	1 0 2	1 0 2	1 0 2	1 0 3	1 0 5	1 0 5	1 0 7	1 0 7	1 0 7	1 0 8	1 0 8
Skin & Subcutaneous Tissue	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma/Fibroadenoma							x							x		x	x	x		x
Fibrosarcoma						x														
Preputial Gland Adenoma																				
Preputial Gland Carcinoma																				
Myxoma																				
Mesothelioma, Abdominal Cavity			x																	
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myelomonocytic Leukemia				x					x			x								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Metastatic Tumors																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci		x								x		x								
Hepatocellular Carcinoma						x	x													
Bile Duct Hyperplasia		x	x			x	x	x				x								
Pancreas	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Exocrine Cell Adenoma																				
Islet Cell Adenoma																				
Stomach	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ulcer											x			x					x	
Hyperplastic Gastropathy																	x			
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chronic Progressive Nephropathy*						1	1	2	1	1	2	2	3	3	1	1	3	1	1	1
Adenoma																				
Pituitary Gland	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								x		x		x	x							
Carcinoma											x									
Thyroid Gland	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma																				
C-Cell Hyperplasia																				x
C-Cell Carcinoma																				
Parathyroid Gland	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplasia										x			x				x			
Adenoma																				
Adrenal Gland	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical Hyperplasia											x									
Pheochromocytoma										x				x						
Testes	0	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
Leydig Cell Tumor		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Ear	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammation, Tympanic Bullae																x	x			
Brain	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A5. MALE RATS: ANIMAL PATHOLOGY (CONTINUED) 0.1 mg

Animal Number	46 8	44 5	20 9	15 6	26 8	09 9	35 4	26 9	45 9	23 1	08 9	26 6	17 1	09 1	31 2	14 1	27 0	15 8	16 8	Total Tissue or Lesions
Weeks on Study	108	108	110	110	111	112	112	122	123	125	127	128	128	222	222	223	223	223	223	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Fibroma/Fibroadenoma				x	x		x	x			x	x		x					x	14
Fibrosarcoma									x											2
Preputial Gland Adenoma						x														1
Preputial Gland Carcinoma																x				1
Myxoma										x										1
Mesothelioma, Abdominal Cavity																				1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Myelomonocytic Leukemia													x						x	5
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Metastatic Tumors									x							x			x	3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Atypical Foci																				3
Hepatocellular Carcinoma																				2
Bile Duct Hyperplasia	x						x			x										9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Exocrine Cell Adenoma				x														x		2
Islet Cell Adenoma																x				1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Ulcer													x					x		5
Hyperplastic Gastropathy																				1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Chronic Progressive Nephropathy*	1	1	2	2	3	2	2	1	1	1	1	1	1	1	1	1	1	1		33
Adenoma							x													1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Adenoma					x	x		x	x		x						x	x	x	12
Carcinoma	x	x																		3
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Follicular Cell Adenoma							x													1
C-Cell Hyperplasia				x				x			x					x				5
C-Cell Carcinoma					x														x	2
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Hyperplasia			x			x					x	x		x	x	x				10
Adenoma				x																1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Cortical Hyperplasia																		x		2
Pheochromocytoma			x	x	x		x		x			x			x				x	10
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Leydig Cell Tumor	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	36
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Inflammation, Tympanic Bullae							x										x		x	5
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A6.

INDIVIDUAL ANIMAL PATHOLOGY IN CONTROL MALE RATS ADMINISTERED 0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	37 13	05 53	04 66	22 33	25 55	11 14	45 11	30 11	40 05	26 33	05 11	19 11	09 92	39 11	08 55	00 33	25 66	32 44	30 77	18 55
Weeks on Study	00 71	00 71	00 75	11 84	11 00	11 01	11 02	11 03	11 04	11 06	11 07	11 08	11 08	11 09	11 11	11 11	11 11	11 11	11 12	11 13
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma/Fibroadenoma									x								x			
Fibrosarcoma	x																			
Preputial Gland Adenoma																				
Squamous Cell Carcinoma		x														x				
Zymbal Gland Adenoma																	x			
Mesothelioma, Abdominal Cavity				x							x									
Mesothelioma, Thoracic Cavity											x									
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myelomonocytic Leukemia																x	x			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveologenic Adenoma																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci															x					
Bile Duct Hyperplasia	x	x		x				x												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Exocrine Cell Adenoma																				
Islet Cell Carcinoma																				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ulcer						x				x					x		x		x	
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chronic Progressive Nephropathy *			1		3	3	3	3	1	2	1	1	1	1	2	2	2	1	2	2
Adenoma																				x
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						x		x			x			x	x					x
Carcinoma							x			x										
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma									x											
C-Cell Hyperplasia																			x	
C-Cell Adenoma														x			x			x
C-Cell Carcinoma													x					x		
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplasia										x										
Adenoma																				x
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical Hyperplasia								x												
Cortical Adenoma																				
Pheochromocytoma											x									
Testes	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leydig Cell Tumor		x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammation, Tympanic Bullae																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																			x	

\+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A6. MALE RATS: ANIMAL PATHOLOGY (CONTINUED) 0 mg

Animal Number	28104	05402	00241	24170	17072	07220	12043	43722	14423	26223	18033	10324	02423	Total Tissue or Lesions
Weeks on Study	16	17	18	19	21	22	22	22	23	23	23	23	23	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Fibroma/Fibroadenoma				x	x				x		x	x		7
Fibrosarcoma														1
Preputial Gland Adenoma			x						x					2
Squamous Cell Carcinoma														2
Zymbal Gland Adenoma														1
Mesothelioma, Abdominal Cavity														2
Mesothelioma, Thoracic Cavity														1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Myelomonocytic Leukemia								x						3
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Alveologenic Adenoma												x		1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Atypical Foci														1
Bile Duct Hyperplasia			x					x			x		x	8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Exocrine Cell Adenoma					x			x	x	x				4
Islet Cell Carcinoma		x												1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Ulcer	x	x						x						8
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Chronic Progressive Nephropathy *	1	1	1	1	2	2	2	1	1	1	1	1	1	30
Adenoma														1
Pituitary Gland	+	+	+	+	+	+	+	+	0	+	+	+	+	32
Adenoma	x					x		x		x	x	x	x	13
Carcinoma														2
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Follicular Cell Adenoma														1
C-Cell Hyperplasia	x													2
C-Cell Adenoma														3
C-Cell Carcinoma														2
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Hyperplasia					x	x	x							4
Adenoma														1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Cortical Hyperplasia														1
Cortical Adenoma	x													1
Pheochromocytoma			x	x	x	x	x					x		7
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Leydig Cell Tumor	x	x	x	x	x	x	x	x	x	x	x	x	x	31
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Inflammation, Tympanic Bullae		x	x							x				3
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Astrocytoma														1

+ Tissue examined
0 Tissue not examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN
3 = Marked CPN

TABLE A7.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE RATS ADMINISTERED 10.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	51 15	70 44	60 44	71 10	54 00	82 33	75 54	52 99	55 66	73 32	61 55	65 00	85 59	66 88	67 66	63 66	51 33	88 99	84 11	79 44	Total Tissues or Lesions
Weeks on Study	0 3 4	0 3 6	0 4 1	0 7 4	0 8 6	0 9 4	0 9 8	1 0 3	1 0 3	1 0 5	1 0 6	1 0 6	1 0 8	1 0 9	1 1 2	1 1 3	1 1 5	1 1 6	1 1 7	1 1 8	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Mammary Gland Fibroadenoma																	x		x		2
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Myelomonocytic Leukemia							x		x		x							x			4
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Metastasis, Ovarian carcinoma																			x		1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Atypical Foci	x			x				x	x			x		x	x			x			8
Neoplastic Nodule					x	x				x			x			x	x		x	x	8
Hepatocellular Carcinoma		x					x	x	x		x			x	x						7
Pancreas-Like Tissue	x																x				2
Bile Duct Hyperplasia	x			x			x					x			x		x			x	7
Bile Duct Carcinoma					x	x					x		x	x				x	x		7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Ulcer										x									x	x	3
Hyperplastic Gastropathy					x				x		x										3
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Chronic Progressive Nephropathy*						1		1	1	1	1	1	2	1	1	1	1	1	1	1	14
Metastatic Ovarian Carcinoma																			x		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Polyp					x																1
Adenocarcinoma																			x		1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Polyp							x														1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adenoma				x			x	x		x											4
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
C-Cell Hyperplasia									x								x				2
C-Cell Adenoma														x							1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Hyperplasia																		x			1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Cortical Hyperplasia												x							x		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Cyst										x											1
Carcinoma																		x			1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Inflammation, Tympanic Bullae											x					x				x	3
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Astrocytoma										x											1

+ Tissue examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN

TABLE A8.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE RATS ADMINISTERED 3.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	6 3 0	5 7 5	7 5 7	8 5 4	5 0 2	8 7 1	6 6 9	4 8 2	5 5 3	4 9 5	8 5 6	7 5 0	8 9 5	6 0 9	8 5 7	5 6 6	7 3 7	5 2 6	7 1 5	Total Tissues or Lesions
Weeks on Study	0 8 1	0 8 1	0 8 7	0 9 2	0 9 4	1 0 2	1 0 5	1 0 9	1 0 9	1 1 0	1 1 2	1 2 1	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 4	1 2 4	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Mammary Gland,Fibroadenoma								x			x						x	x	x	5
Zymbal Gland Adenoma						x														1
Clitoral Gland Adenoma										x										1
Epidermal Cyst												x								1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Myelomonocytic Leukemia				x			x													2
Spleen, Metastatic Granulosa Cell Tumor									x											1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Atypical Foci		x		x					x					x						4
Neoplastic Nodule			x		x		x	x			x									5
Hepatocellular carcinoma	x						x					x								3
Bile Duct Hyperplasia	x	x				x	x													4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Ulcer				x					x							x				3
Hyperplastic Gastropathy	x																			1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Squamous Cell Papilloma					x			x					x		x					4
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Chronic Progressive Nephropathy	1					1	1				1		1		1	1	1	1	1	10
Tubular Cell Hyperplasia, Focal													x							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Endometrial Cyst																	x			1
Adenoma											x									1
Carcinoma														x						1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adenoma												x	x	x			x	x		5
Carcinoma		x																		1
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
C-Cell Hyperplasia												x								1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Hyperplasia								x												1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Cortical Hyperplasia																			x	1
Cortical Adenoma								x												1
Pheochromocytoma																x				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Cyst															x					1
Granulosa Cell Tumor									x											1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Inflammation, Tympanic Bullae										x										1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19

+ Tissue examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN

TABLE A9.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE RATS ADMINISTERED 1.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	46020	60093	79304	50407	50722	52242	84273	84232	82355	60224	47924	Total Tissue or Lesions
Weeks on Study	09 6	11 2	11 4	12 0	12 2	12 3	12 3	12 3	12 3	12 4	12 4	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	11
Mammary Gland Fibroadenoma			x			x	x	x				4
Fibroma										x		1
Epidermal Cyst	x											1
Rhabdomyosarcoma									x			1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	11
Myelomonocytic Leukemia		x										1
Lung	+	+	+	+	+	+	+	+	+	+	+	11
Liver	+	+	+	+	+	+	+	+	+	+	+	11
Atypical Foci						x			x			2
Neoplastic Nodule	x		x									2
Bile Duct Hyperplasia	x											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	11
Stomach	+	+	+	+	+	+	+	+	+	+	+	11
Ulcer				x								1
Tongue	+	+	+	+	+	+	+	+	+	+	+	11
Kidney	+	+	+	+	+	+	+	+	+	+	+	11
Chronic Progressive Nephropathy *	1	1						1		1	1	5
Uterus	+	+	+	+	+	+	+	+	+	+	+	11
Endometrial Cyst										x		1
Vagina	+	+	+	+	+	+	+	+	+	+	+	11
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	11
Adenoma	x		x	x	x					x	x	6
Carcinoma		x					x					2
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	11
C-Cell Hyperplasia		x					x					2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	11
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	11
Ovary	+	+	+	+	+	+	+	+	+	+	+	11
Cyst		x		x								2
Granulosa Cell Tumor										x		1
Ear	+	+	+	+	+	+	+	+	+	+	+	11
Brain	+	+	+	+	+	+	+	+	+	+	+	11

+ Tissue examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN

TABLE A10.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE RATS ADMINISTERED 0.3 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	51 19	61 07	80 05	57 70	70 01	53 38	68 82	68 87	67 78	74 81	49 11	62 16	77 44	65 22	70 29	72 21	73 39	62 22	64 27	70 18	71 11	Total Tissues or Lesions
Weeks on Study	0 99	0 96	1 00	1 03	1 03	1 04	1 09	1 10	1 13	1 19	1 19	2 00	2 02	2 03	2 03	2 03	2 03	2 03	2 04	2 44	2 44	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Mammary Gland, Fibroadenoma	x		x				x					x	x	x	x			x		x	x	10
Clitoral Gland Adenoma								x												x		2
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Myelomonocytic Leukemia							x			x	x		x									4
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Alveologenic Adenoma			x																			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Atypical Foci						x																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Ulcer		x				x			x		x	x	x									6
Hyperplastic Gastropathy																					x	1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Chronic Progressive Nephropathy*		1	1	1		1	1	1				1		1				1		1	1	11
Tubular Cell Hyperplasia, Focal																					x	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Endometrial Polyp											x						x					2
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Pituitary Gland	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adenoma				x							x				x			x				4
Carcinoma		x				x						x	x	x							x	6
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
C-Cell Hyperplasia	x					x		x														3
C-Cell Adenoma			x															x		x	x	4
C-Cell Carcinoma																			x			1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Adenoma																				x		1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Cyst						x																1
Granulosa Cell Tumor														x					x			2
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Inflammation, Tympanic Bullae														x								1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21

Tissue examined
Lesions present
Chronic progressive nephropathy (CPN)
1 = Slight CPN

TABLE A11.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE RATS ADMINISTERED 0.1 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	50 09	59 04	76 03	52 03	84 04	78 09	53 06	77 09	62 09	53 09	60 07	73 08	83 05	48 03	86 01	77 01	80 00	67 03	54 06	89 08	75 06	Total Tissues or Lesions
Weeks on Study	0 78	0 82	0 83	0 98	0 99	1 01	1 03	1 05	1 06	1 08	1 08	1 13	1 14	1 16	1 16	2 23	2 33	2 44	2 44	2 44	2 44	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Mammary Gland, Fibroadenoma				x	x		x		x			x	x	x		x	x			x		10
Mammary Gland, Carcinoma																	x					1
Rhabdomyosarcoma													x									1
Fibrosarcoma								x														1
Clitoral Gland Adenoma												x						x				2
Hemangioma						x																1
Basal Cell Tumor																					x	1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Myelomonocytic Leukemia					x	x				x					x							4
Spleen, Metastatic Fibrosarcoma								x														1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Alveologenic Adenoma							x															1
Metastatic Carcinoma									x													1
Metastatic Fibrosarcoma								x														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Neoplastic Nodule								x							x							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Ulcer							x	x		x												3
Hyperplastic Gastropathy			x																			1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Squamous Cell Papilloma												x										1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Chronic Progressive Nephropathy			2			1	1	1		1				1	1			1		1	1	10
Metastatic Fibrosarcoma								x														1
Uterus	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Myxoma		x																				1
Endometrial Polyp						x																1
Hemangioma													x									1
Deciduoma															x							1
Vagina	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Polyp								x									x					2
Pituitary Gland	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adenoma			x	x		x	x	x				x	x	x	x		x	x				11
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
C-Cell Hyperplasia																x	x				x	3
C-Cell Adenoma													x									1
C-Cell Carcinoma				x					x													2
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Hyperplasia																	x					1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Adrenal Cortical Hyperplasia				x																		1
Pheochromocytoma															x							1
Ovary	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Cyst																		x				1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21

+ Tissue examined
x Lesions present
0 Tissue not examined
* Chronic progressive nephropathy (CPN)
1 = Slight CPN
2 = Moderate CPN

TABLE A12.

INDIVIDUAL ANIMAL PATHOLOGY IN CONTROL FEMALE RATS ADMINISTERED 0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATIONS)

Animal Number	52401	81909	80707	76474	83444	54475	66658	66888	64486	60803	78771	59616	79991	82121	83113	52747	87292	57707	63773	77878	Total Tissues or Lesions
Weeks on Study	0 5 0	0 5 9	0 7 7	0 7 7	0 8 4	0 8 7	0 9 8	1 0 6	1 0 6	1 0 8	1 1 1	1 1 1	1 1 1	1 1 2	1 1 4	1 1 4	1 1 9	1 2 0	1 2 3	1 2 4	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Mammary Gland, Fibroadenoma						x			x			x					x	x			5
Epidermal Cyst							x														1
Zymbal Gland Carcinoma											x			x							2
Clitoral Gland Adenoma																	x		x	x	3
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Myelomonocyic Leukemia								x		x		x	x				x				5
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Metastatic Carcinoma, C-Cell			x																		1
Metastatic Carcinoma, Zymbal Gland											x										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Metastatic Myxosarcoma		x																			1
Bile Duct Hyperplasia							x			x											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Ulcer												x	x								2
Hyperplastic Gastropathy																		x			1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Squamous Cell Papilloma																			x		1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Chronic Progressive Nephropathy *								1	1						1			1	1	1	6
Tubular Cell Adenoma							x														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Endometrial Polyp			x											x							2
Endometrial Cystic Hyperplasia										x											1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Myxosarcoma		x																			1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adenoma							x				x	x	x	x	x	x		x	x		9
Carcinoma									x	x											2
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Follicular Cell Carcinoma												x									1
C-Cell Hyperplasia							x									x				x	3
C-Cell Carcinoma			x			x															2
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Adrenal Cortical Adenoma	x																				1
Pheochromocytoma																		x			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Inflammation, Tympanic Bullae											x										1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20

+ Tissue examined
x Lesions present
* Chronic progressive nephropathy (CPN)
1 = Slight CPN

APPENDIX B

INDIVIDUAL ANIMAL PATHOLOGY IN MICE ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

TABLE B1.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE MICE ADMINISTERED 10.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	0 4 0	1 7 5	1 9 4	1 5 4	0 5 4	2 7 5	1 6 0	2 0 8	2 4 6	0 1 3	0 5 3	0 8 2	2 2 6	0 3 0	2 4 1	2 8 0	1 1 3	2 9 1	2 0 6	2 9 4	0 4 7	1 5 3	
Weeks on Study	0 5 7	0 6 6	0 6 9	0 7 4	0 8 0	0 9 1	1 9 2	1 9 2	1 9 5	1 9 6	1 9 6	1 9 7	1 0 0	1 0 3	1 1 0	1 1 3	1 1 3	1 1 4	1 1 6	1 1 8	1 2 0	1 2 6	Total Tissue or Lesions
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Fibrosarcoma						x												x					2
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Malignant Lymphoma														x					x				2
Lung	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	21
Metastatic Hepatocellular Carcinoma			x				x				x										x		4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Hepatocellular Adenoma				x																			1
Hepatocellular Carcinoma	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	21
Hepatoblastoma		x								x													2
Bile Duct Carcinoma		x																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	21
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	21
Parathyroid Gland	+	+	+	0	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	20
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Eye	+	+	+	+	+	+	+	+	0	+	+	+	0	+	+	+	+	+	+	+	+	+	20
Brain	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	21

+ Tissue examined
0 Tissue not examined
x Lesions present

TABLE B2.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE MICE ADMINISTERED 3.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	28 1	34 0	09 4	25 4	06 6	03 5	15 9	32 7	18 8	18 0	33 7	31 6	34 4	22 5	16 5	05 5	34 3	02 9	04 6	21 6	10 0	19 3	09 1	Total Tissue or Lesions
Weeks on Study	0 4 5	0 9 3	0 9 5	0 9 6	0 9 7	0 9 7	1 0 2	1 1 0	1 1 2	1 1 5	1 1 6	1 1 8	1 1 8	1 2 4	2 2 4	2 2 5	2 2 5	2 2 7	2 2 8	3 1 1	3 3 1	3 3 1	3 3 1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Fibroma															x						x			2
Fibrosarcoma								x					x				x	x						4
Rhabdomyosarcoma				x																				1
Preputial Gland Carcinoma														x										1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Malignant Lymphoma											x											x	x	3
Hemangioma, Spleen							x																	1
Hemangiosarcoma, Spleen																x								1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Adenomatosis							x						x											2
Alveologenic Adenoma								x						x		x								3
Metastatic Hepatocellular Carcinoma													x	x								x		3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Hepatocellular Adenoma																				x			x	2
Hepatocellular Carcinoma		x			x	x	x	x	x	x		x	x	x			x	x	x		x	x		15
Hemangiosarcoma																x								1
Metastatic Carcinoma												x												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Hyperplastic Gastropathy	x																							1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Large Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Carcinoma												x												1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Adenoma																						x		1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Adenoma												x												1
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Follicular Cell Hyperplasia												x		x										2
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Cortical Adenoma																					x			1
Cortical Carcinoma												x												1
Pheochromocytoma																	x							1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	23
Epidermal Cyst									x															1

\+ Tissue examined
x Lesions present

TABLE B3.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE MICE ADMINISTERED 1.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	041	132	081	042	109	329	283	213	099	199	276	342	196	118	255	310	224	307	133	250
Weeks on Study	039	085	090	091	097	097	097	097	098	033	044	066	111	122	222	222	222	224	226	231
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														x						
Fibrosarcoma		x	x										x						x	
Preputial Gland Adenoma												x								
Schwanoma																				
Rhabdomyosarcoma																				x
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant Lymphoma	x						x			x					x				x	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveologenic Adenoma			x																	x
Alveologenic Carcinoma																				
Metastatic Hepatocellular Carcinoma				x					x											
Metastatic Fibrosarcoma													x							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci																		x		
Hepatocellular Adenoma																				
Hepatocellular Carcinoma				x	x	x		x	x		x		x	x	x	x	x			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet Cell Adenoma																				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplastic Gastropathy																				
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									x											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Hyperplasia																				
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														x						
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian Gland Adenoma											x									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined
x Lesions present

TABLE B3. MALE MICE: ANIMAL PATHOLOGY (CONTINUED) 1.0 mg

Animal Number	07101	12201	31901	16101	28601	
Weeks on Study	13131	13131	13131	13131	13131	Total Tissue or Lesions
Skin & Subcutaneous Tissue	+	+	+	+	+	25
Fibroma						1
Fibrosarcoma						4
Preputial Gland Adenoma						1
Schwanoma				x		1
Rhabdomyosarcoma						1
Hematopoietic System	+	+	+	+	+	25
Malignant Lymphoma			x			6
Lung	+	+	+	+	+	25
Alveologenic Adenoma			x			3
Alveologenic Carcinoma		x				1
Metastatic Hepatocellular Carcinoma						2
Metastatic Fibrosarcoma						1
Liver	+	+	+	+	+	25
Atypical Foci						1
Hepatocellular Adenoma		x	x			2
Hepatocellular Carcinoma	x					12
Pancreas	+	+	+	+	+	25
Islet Cell Adenoma			x			1
Stomach	+	+	+	+	+	25
Hyperplastic Gastropathy				x		1
Tongue	+	+	+	+	+	25
Small Intestine	+	+	+	+	+	25
Adenocarcinoma						1
Kidney	+	+	+	+	+	25
Adenoma			x			1
Pituitary Gland	+	+	+	+	+	25
Thyroid Gland	+	+	+	+	+	25
Follicular Cell Hyperplasia			x			1
Parathyroid Gland	+	+	+	+	+	25
Adrenal Gland	+	+	+	+	+	25
Pheochromocytoma						1
Testes	+	+	+	+	+	25
Eye	+	+	+	+	+	25
Harderian Gland Adenoma						1
Brain	+	+	+	+	+	25

+ Tissue examined
x Lesions present

TABLE B4.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE MICE ADMINISTERED 0.3 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	0 7 2	0 1 9	1 0 6	0 2 8	0 7 6	3 2 3	1 7 4	2 0 3	2 5 7	0 2 5	2 5 3	0 8 9	3 2 2	3 2 5	0 4 5	0 1 6	2 1 9	2 3 2	2 6 0	3 4 1	1 1 2	2 7 0	1 4 6	3 3 4	Total Tissue or Lesions
Weeks on Study	0 7 0	0 7 4	0 7 5	0 8 1	0 9 7	0 9 7	0 9 9	0 9 9	0 9 9	1 0 8	1 0 9	1 1 0	1 1 1	1 1 8	1 2 0	1 2 3	1 2 3	1 2 4	1 3 0	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Fibroma																								x	1
Fibrosarcoma	x	x	x	x																					4
Leiomyosarcoma											x														1
Preputial Gland Carcinoma																	x								1
Hemangioma																						x			1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Malignant Lymphoma						x		x		x			x	x								x		x	7
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Adenomatosis										x															1
Alveologenic Adenoma																x		x		x					3
Metastatic Fibrosarcoma			x																						1
Metastatic Hepatocellular Carcinoma									x						x										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Hepatocellular Adenoma												x						x			x			x	4
Hepatocellular Carcinoma							x		x	x	x				x	x			x			x			8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Hyperplastic Gastropathy																						x			1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Hemangioma																		x							1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Adenoma																					x				1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Cortical Adenoma						x																			1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24
Harderian Gland Adenoma												x	x	x											3
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	24

+ Tissue examined
x Lesions present

TABLE B5.

INDIVIDUAL ANIMAL PATHOLOGY IN MALE MICE ADMINISTERED 0.1 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	01 7	29 7	08 4	01 2	15 5	20 9	28 8	05 8	04 8	05 9	29 6	30 2	21 2	07 3	33 1	32 1	20 0	31 1	08 5	01 5
Weeks on Study	0 6 7	0 6 7	0 8 5	0 9 3	0 9 6	0 9 7	0 9 9	1 0 1	1 0 6	1 0 9	1 1 1	1 1 4	1 1 6	1 1 6	1 1 6	1 2 1	1 2 3	1 2 3	1 2 4	1 2 6
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						x		x	x											
Fibrosarcoma		x	x	x	x		x				x							x		
Rhabdomyosarcoma																	x			
Basal Cell Tumor										x										
Xanthoma																x				
Hemangioma											x									
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant Lymphoma						x							x		x				x	x
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveologenic Carcinoma																x				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atypical Foci					x															
Hepatocellular Adenoma								x												
Hepatocellular Carcinoma							x		x			x		x	x	x	x			
Histiocytic Sarcoma										x										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet Cell Adenoma																				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hyperplastic Gastropathy														x						
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																				
Lipoma																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular Cell Adenoma																			x	
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined
x Lesions present

TABLE B5. MALE MICE: ANIMAL PATHOLOGY (CONTINUED) 0.1 mg

Animal Number	32 44	14 45	18 55	30 55	12 57	27 52	28 55	
Weeks on Study	1 3 0	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	Total Tissue or Lesions
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	27
Fibroma				x				4
Fibrosarcoma								7
Rhabdomyosarcoma								1
Basal Cell Tumor								1
Xanthoma								1
Hemangioma								1
Hematopoietic System	+	+	+	+	+	+	+	27
Malignant Lymphoma							x	6
Lung	+	+	+	+	+	+	+	27
Alveologenic Carcinoma								1
Liver	+	+	+	+	+	+	+	27
Atypical Foci								1
Hepatocellular Adenoma								1
Hepatocellular Carcinoma					x			8
Histiocytic Sarcoma								1
Pancreas	+	+	+	+	+	+	+	27
Islet Cell Adenoma					x			1
Stomach	+	+	+	+	+	+	+	27
Hyperplastic Gastropathy							x	2
Tongue	+	+	+	+	+	+	+	27
Small Intestine	+	+	+	+	+	+	+	27
Adenocarcinoma					x			1
Lipoma						x		1
Kidney	+	+	+	+	+	+	+	27
Pituitary Gland	+	+	+	+	+	+	+	27
Thyroid Gland	+	+	+	+	+	+	+	27
Follicular Cell Adenoma								1
Parathyroid Gland	+	+	+	+	+	+	+	27
Adrenal Gland	+	+	+	+	+	+	+	27
Testes	+	+	+	+	+	+	+	27
Eye	+	+	+	+	+	+	+	27
Brain	+	+	+	+	+	+	+	27

+ Tissue examined
x Lesions present

TABLE B6.

INDIVIDUAL ANIMAL PATHOLOGY IN CONTROL MALE MICE ADMINISTERED 0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	16 6	21 8	08 8	16 3	31 5	10 8	07 7	00 2	26 2	26 4	13 6	11 4	26 6	01 8	02 3	14 7	22 7	33 0	25 2	32 8	01 4	13 5	06 5	03 9	34 7	Total Tissues or Lesions
Weeks on Study	0 8 0	0 8 6	0 9 1	0 9 1	0 9 4	0 9 5	0 9 7	1 0 1	1 0 7	1 0 9	1 1 0	1 1 1	1 1 3	1 1 3	1 1 6	1 1 6	1 1 8	3 1	3 1	3 1	3 1	3 1	3 1	3 1	3 1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Fibroma																							x			1
Fibrosarcoma												x		x												2
Rhabdomyosarcoma	x																									1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Malignant Lymphoma									x		x					x									x	4
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Alveologenic Adenoma														x												1
Metastatic Hepatocellular Carcinoma						x	x															x			x	4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Hepatocellular Adenoma														x									x			2
Hepatocellular Carcinoma			x	x		x	x	x				x	x				x	x		x		x			x	12
Hepatoblastoma								x												x		x				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Adenoma										x																1
Large Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Adenocarcinoma					x																					1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Carcinoma																						x				1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Pheochromocytoma																	x									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25

+ Tissue examined
x Lesions present

TABLE B7.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE MICE ADMINISTERED 10.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	41323	42303	49202	66303	63807	56201	35101	36901	
Weeks on Study	08282	09101	01105	00107	00711	11121	12121	12128	Total Tissue or Lesions
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	8
Hematopoietic System	+	+	+	+	+	+	+	+	8
Malignant Lymphoma		x	x						2
Lung	+	+	+	+	+	+	+	+	8
Alveologenic Adenoma						x			1
Metastatic Hepatocellular Carcinoma	x	x			x				3
Liver	+	+	+	+	+	+	+	+	8
Hepatocellular Adenoma			x						1
Hepatocellular Carcinoma	x	x		x	x	x	x	x	7
Pancreas	+	+	+	+	+	+	+	+	8
Stomach	+	+	+	+	+	+	+	+	8
Tongue	+	+	+	+	+	+	+	+	8
Kidney	+	+	+	+	+	+	+	+	8
Pituitary Gland	+	+	+	+	+	+	+	+	8
Adenoma							x		1
Thyroid Gland	+	+	+	+	+	+	+	+	8
Follicular Cell Hyperplasia						x			1
Follicular Cell Adenoma							x		1
Parathyroid Gland	+	+	+	+	+	+	+	+	8
Adrenal Gland	+	+	+	+	+	+	+	+	8
Ovary	+	+	+	+	+	+	+	+	8
Cystic								x	1
Uterus	+	+	+	+	+	+	+	+	8
Leiomyosarcoma								x	1
Eye	+	+	+	+	+	+	+	+	8
Brain	+	+	+	+	+	+	+	+	8

+ Tissue examined
x Lesions present

TABLE B8.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE MICE ADMINISTERED 3.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	7 0 8	4 8 2	3 9 1	0 0 1	6 9 9	3 9 7	4 5 8	5 2 0	4 1 0	5 2 4	5 3 0	6 1 1	3 7 9	3 5 2	6 9 3	5 5 8	6 3 2	Total Tissue or Lesions
Weeks on Study	0 9 9	1 0 7	1 0 7	1 0 8	1 1 3	1 1 6	1 1 8	1 1 9	1 2 0	1 2 1	1 3 0	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Mammary Gland Adenoma					x													1
Clitoral Gland Adenoma							x											1
Clitoral Gland Carcinoma											x							1
Liposarcoma										x								1
Salivary Gland Cystadenoma															x			1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Malignant Lymphoma		x		x							x		x	x			x	6
Spleen, Mast Cell Tumor								x										1
Hemangioma																	x	1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Adenomatosis																	x	1
Alveologenic Adenoma									x							x		2
Alveologenic Carcinoma													x					1
Metastatic Hepatocellular Carcinoma																x		1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Atypical Foci									x		x				x			3
Hepatocellular Adenoma																	x	1
Hepatocellular Carcinoma	x													x		x		3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Exocrine Cell Adenoma		x																1
Islet Cell Adenoma															x			1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Hyperplastic Gastropathy																	x	1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Adenoma										x	x	x		x	x		x	6
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Follicular Cell Hyperplasia													x	x				2
Follicular Cell Adenoma					x			x									x	3
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Cystic		x														x	x	3
Granulosa Cell Tumor			x															1
Luteoma										x								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		17
Cystadenoma					x													1
Leiomyoma													x					1
Hemagiosarcoma																	x	1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17
Harderian Gland Adenoma															x			1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	17

+ Tissue examined
x Lesions present

TABLE B9.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE MICE ADMINISTERED 1.0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	40403	51303	63101	64303	53808	38707	41404	70606	61606	65404	48303	Total Tissue or Lesions
Weeks on Study	1 0 7	1 0 9	1 1 3	1 2 1	1 3 0	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	11
Fibroadenoma, Mammary Gland					x							1
Fibrosarcoma											x	1
Hemangioma										x		1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	11
Malignant Lymphoma		x		x		x				x	x	5
Lung	+	+	+	+	+	+	+	+	+	+	+	11
Alveologenic Carcinoma										x		1
Metastatic Hepatocellular Carcinoma	x											1
Liver	+	+	+	+	+	+	+	+	+	+	+	11
Hepatocellular Adenoma										x		1
Hepatocellular Carcinoma	x					x						2
Metastatic Leiomyosarcoma			x									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	11
Stomach	+	+	+	+	+	+	+	+	+	+	+	11
Ulcer			x									1
Tongue	+	+	+	+	+	+	+	+	+	+	+	11
Kidney	+	+	+	+	+	+	+	+	+	+	+	11
Pituitary Gland	+	0	+	+	+	+	+	+	+	+	+	10
Adenoma					x					x		2
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	11
Follicular Cell Hyperplasia							x					1
Follicular Cell Adenoma					x							1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	11
Hyperplasia									x			1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	11
Ovary	+	+	+	+	+	+	+	+	+	+	+	11
Granulosa Cell Tumor									x			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	11
Endometrial Cystic Hyperplasia								x	x			2
Leiomyosarcoma			x									1
Adenocarcinoma											x	1
Eye	+	0	+	+	+	+	+	+	+	+	+	10
Brain	+	0	+	+	+	+	+	+	+	+	+	10

+ Tissue examined
0 Tissue not examined
x Lesions present

TABLE B10.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE MICE ADMINISTERED 0.3 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	5 8 2	3 6 8	0 0 2	5 8 4	6 5 3	6 2 3	5 5 1	3 5 8	4 8 6	3 9 2	4 6 5	6 7 4	6 7 5	3 8 3	5 7 9	Total Tissue or Lesions
Weeks on Study	0 8 4	1 0 2	1 0 6	1 1 0	1 1 1	1 1 4	1 2 8	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	1 3 1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Fibrosarcoma														x		1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Malignant Lymphoma	x							x	x	x				x	x	6
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Adenomatosis			x													1
Alveologenic Carcinoma												x				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Hepatocellular Carcinoma			x												x	2
Metastatic Sarcoma				x		x										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Ulcer		x														1
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Adenoma					x				x			x	x			4
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Follicular Cell Hyperplasia									x				x		x	3
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Pheochromocytoma										x						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Cystic			x										x			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Endometrial Cystic Hyperplasia			x		x		x									3
Histiocytic Sarcoma				x												1
Leiomyosarcoma						x										1
Adenoma								x								1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15

+ Tissue examined
x Lesions present

TABLE B11.

INDIVIDUAL ANIMAL PATHOLOGY IN FEMALE MICE ADMINISTERED 0.1 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	44 40	46 46	47 70	57 78	67 71	64 72	39 75	49 71	61 70	70 72	59 75	51 76	50 73	67 77	42 77	51 70	39 79	44 71	68 72	Total Tissue or Lesions
Weeks on Study	0 85	0 95	1 01	1 04	1 04	1 13	1 19	2 01	2 25	3 01	3 01	3 01	3 01	3 01	3 01	3 01	3 01	3 01	3 01	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adenoma, Mammary Gland				x												x				2
Fibrosarcoma													x							1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Malignant Lymphoma		x	x				x	x					x						x	6
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Alveologenic Adenoma																			x	1
Metastatic Sarcoma									x											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Atypical Foci														x						1
Hepatocellular Adenoma										x					x					2
Angiosarcoma												x								1
Metastatic sarcoma									x											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Small Intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Hemangioma														x						1
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adenoma																			x	1
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Follicular Cell Hyperplasia											x									1
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Cystic						x				x										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Endometrial Cystic Hyperplasia	x				x			x						x						4
Myxoma											x									1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
Metastatic Sarcoma									x											1

\+ Tissue examined
x Lesions present

TABLE B12.

INDIVIDUAL ANIMAL PATHOLOGY IN CONTROL FEMALE MICE ADMINISTERED 0 mg POLYBROMINATED BIPHENYL MIXTURE/kg BODY WEIGHT IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Animal Number	43 9	69 1	36 0	62 0	36 7	58 7	38 6	68 8	38 2	42 8	67 2	56 7	46 4	Total Tissue or Lesions
Weeks on Study	0 8	0 9	1 0	1 1	1 1	1 1	1 1	1 2	1 2	1 3	1 3	1 3	1 3	
	4	7	4	2	3	6	6	1	1	1	1	1	1	
Skin & Subcutaneous Tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Mammary Gland Adenoma					x									1
Fibrosarcoma								x						1
Hematopoietic System	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Malignant Lymphoma		x		x	x	x	x		x	x	x	x	x	10
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Islet Cell Adenoma												x		1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Tongue	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Hemangioma										x				1
Pituitary Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Adenoma							x		x	x		x		4
Thyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Parathyroid Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Adenoma									x					1
Adrenal Gland	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Cyst			x								x			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Endometrial Cystic Hyperplasia			x						x					2
Hemangioma											x			1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Harderian Gland Adenoma		x							x					2
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Astrocytoma	x													1

\+ Tissue examined
x Lesions present

APPENDIX C

SUMMARY OF THE INCIDENCE OF LESIONS IN RATS AND MICE ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

TABLE C1. SUMMARY OF THE INCIDENCE OF LESIONS IN MALE RATS ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Skin and Subcutaneous Tissue	[33]	[38]	[40]	[31]	[33]	[30]
Fibroma/Fibroadenoma	7(21%)	14(37%)	7(18%)	6(19%)	2(6%)	1(3%)
Fibrosarcoma	1(3%)	2(5%)	2(5%)			
Preputial Gland Adenoma	2(6%)	1(3%)	1(2%)	1(3%)	2(6%)	
Preputial Gland Carcinoma		1(3%)				
Squamous Cell Carcinoma	2(6%)					
Zymbal Gland Adenoma	1(3%)					
Myxoma		1(3%)				
Odontoma			1(2%)			
Basal Cell Tumor			1(2%)	1(3%)	1(3%)	
Hemangioendothelioma				1(3%)		
Mesothelioma	3(9%)	1(3%)	1(2%)		1(3%)	
Hematopoietic System	[33]	[39]	[40]	[31]	[33]	[32]
Myelomonocytic Leukemia	3(9%)	5(13%)	8(20%)	4(13%)	2(6%)	2(6%)
Hemangiopericytoma, Malignant			1(2%)			
Hemangiosarcoma(Spleen)					1(3%)	
Plasma Cell Tumor					1(3%)	
Lung	[33]	[39]	[40]	[31]	[33]	[31]
Alveologenic Adenoma	1(3%)			2(6%)	1(3%)	
Metastatic Tumors		3(8%)	2(5%)			
Liver	[33]	[39]	[40]	[31]	[33]	[31]
Atypical Foci	1(3%)	3(8%)	12(30%)	11(35%)	13(39%)	12(39%)
Neoplastic Nodule			1(2%)	4(13%)	4(12%)	1(3%)
Hepatocellular Carcinoma		2(5%)		1(3%)	7(21%)	7(23%)
Pancreas-like Tissue						2(6%)
Bile Duct Hyperplasia	8(24%)	9(23%)	10(25%)	13(42%)	14(42%)	9(29%)
Bile Duct Adenoma						1(3%)
Bile Duct Carcinoma						2(6%)
Metastatic Tumor			2(5%)			
Pancreas	[33]	[38]	[40]	[30]	[33]	[29]
Exocrine Cell Adenoma	4(12%)	2(5%)	2(5%)	2(7%)	3(9%)	2(7%)
Exocrine Cell Carcinoma					1(3%)	1(3%)
Islet Cell Adenoma		1(3%)	1(2%)	2(7%)	1(3%)	
Islet Cell Carcinoma	1(3%)					

TABLE C1. SUMMARY OF THE INCIDENCE OF LESIONS IN MALE RATS ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION) (Continued)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Stomach	[33]	[38]	[40]	[30]	[33]	[29]
Ulcer	8 (24%)	5 (13%)	8 (20%)	9 (30%)	18 (55%)	12 (41%)
Hyperplastic Gastropathy		1 (3%)	2 (5%)	3 (10%)	6 (18%)	4 (14%)
Tongue	[33]	[39]	[40]	[31]	[33]	[30]
Squamous Cell Papilloma			1 (2%)			
Kidney	[33]	[39]	[40]	[30]	[33]	[32]
Chronic Progressive Nephropathy	30 (91%)	33 (85%)	40 (100%)	29 (97%)	32 (97%)	28 (88%)
Adenoma	1 (3%)	1 (3%)	1 (2%)	1 (3%)	1 (3%)	
Transitional Cell Carcinoma						1 (3%)
Liposarcoma					1 (3%)	
Pituitary Gland	[32]	[38]	[40]	[31]	[33]	[31]
Adenoma	13 (41%)	12 (32%)	7 (18%)	6 (19%)	5 (15%)	2 (6%)
Carcinoma	2 (6%)	3 (8%)			1 (3%)	
Thyroid Gland	[33]	[38]	[40]	[31]	[33]	[29]
Follicular Cell Adenoma	1 (3%)	1 (3%)	4 (10%)	2 (6%)	4 (12%)	1 (3%)
Follicular Cell Carcinoma				1 (3%)	2 (6%)	1 (3%)
C-Cell Hyperplasia	2 (6%)	5 (13%)	2 (5%)	2 (6%)		1 (3%)
C-Cell Adenoma	3 (9%)		4 (10%)	1 (3%)	1 (3%)	1 (3%)
C-Cell Carcinoma	2 (6%)	2 (5%)	1 (2%)		1 (3%)	
Parathyroid Gland	[33]	[38]	[40]	[31]	[33]	[29]
Hyperplasia	4 (12%)	10 (26%)	12 (30%)	13 (42%)	7 (21%)	6 (21%)
Adenoma	1 (3%)	1 (3%)		1 (3%)		1 (3%)
Adrenal Gland	[33]	[38]	[39]	[30]	[33]	[31]
Cortical Hyperplasia	1 (3%)	2 (5%)	4 (10%)	3 (10%)	4 (12%)	
Cortical Adenoma	1 (3%)			1 (3%)		
Pheochromocytoma	7 (21%)	10 (26%)	6 (15%)	2 (7%)	3 (9%)	
Testes	[32]	[37]	[39]	[30]	[31]	[30]
Leydig Cell Tumor	31 (97%)	36 (97%)	37 (95%)	28 (93%)	28 (90%)	28 (93%)
Ear	[33]	[38]	[40]	[31]	[33]	[32]
Inflammation, Tympanic Bullae	3 (9%)	5 (13%)	6 (15%)	2 (6%)	2 (6%)	1 (3%)
Brain	[33]	[38]	[40]	[31]	[33]	[31]
Astrocytoma	1 (3%)					

[ ]: Number of animals with tissue examined microscopically.

TABLE C2. SUMMARY OF THE INCIDENCE OF LESIONS IN FEMALE RATS ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Skin and Subcutaneous Tissue	[20]	[21]	[21]	[11]	[19]	[20]
Mammary Gland Fibroadenoma	5 (25%)	10 (48%)	10 (48%)	4 (36%)	5 (26%)	2 (10%)
Mammary Gland Carcinoma		1 (5%)				
Zymbal Gland Adenoma					1 (5%)	
Zymbal Gland Carcinoma	2 (10%)					
Clitoral Gland Adenoma	3 (15%)	2 (10%)	2 (10%)		1 (5%)	
Epidermal Cyst	1 (5%)			1 (9%)	1 (5%)	
Rhabdomyosarcoma		1 (5%)		1 (9%)		
Fibroma				1 (9%)		
Fibrosarcoma		1 (5%)				
Hemangioma		1 (5%)				
Basal Cell Tumor		1 (5%)				
Hematopoietic System	[20]	[21]	[21]	[11]	[19]	[20]
Myelomonocytic Leukemia	5 (25%)	4 (19%)	4 (19%)	1 (9%)	2 (11%)	4 (20%)
Spleen, Metastatic Granulosa Cell Tumor					1 (5%)	
Spleen, Metastatic Fibrosarcoma		1 (5%)				
Lung	[20]	[21]	[21]	[11]	[19]	[20]
Alveologenic Adenoma		1 (5%)	1 (5%)			
Metastatic Carcinoma	2 (10%)	1 (5%)				1 (5%)
Metastatic Fibrosarcoma		1 (5%)				
Liver	[20]	[21]	[21]	[11]	[19]	[20]
Atypical Foci			1 (5%)	2 (18%)	4 (21%)	8 (40%)
Neoplastic Nodule		2 (10%)		2 (18%)	5 (26%)	8 (40%)
Hepatocellular Carcinoma					3 (16%)	7 (35%)
Pancreas-like Tissue						2 (10%)
Bile Duct Hyperplasia	2 (10%)			1 (9%)	4 (21%)	7 (35%)
Bile Duct Carcinoma						7 (35%)
Metastatic Myxosarcoma	1 (5%)					
Pancreas	[20]	[21]	[21]	[11]	[19]	[20]
Stomach	[20]	[21]	[21]	[11]	[19]	[20]
Ulcer	2 (10%)	3 (14%)	6 (29%)	1 (9%)	3 (16%)	3 (15%)
Hyperplastic Gastropathy	1 (5%)	1 (5%)	1 (5%)		1 (5%)	3 (15%)

TABLE C2. SUMMARY OF THE INCIDENCE OF LESIONS IN FEMALE RATS ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION) (Continued)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Tongue	[20]	[21]	[21]	[11]	[19]	[20]
Squamous Cell Papilloma	1 (5%)	1 (5%)			4 (21%)	
Kidney	[20]	[21]	[21]	[11]	[19]	[20]
Chronic Progressive Nephropathy	6 (30%)	10 (48%)	11 (52%)	5 (45%)	10 (53%)	14 (70%)
Tubular Cell Adenoma	1 (5%)					
Tubular Cell Hyperplasia			1 (5%)		1 (5%)	
Metastatic Fibrosarcoma		1 (5%)				
Metastatic Ovarian Carcinoma						1 (5%)
Pituitary Gland	[20]	[20]	[20]	[11]	[19]	[20]
Adenoma	9 (45%)	11 (55%)	4 (20%)	6 (55%)	5 (26%)	4 (20%)
Carcinoma	2 (10%)		6 (30%)	2 (18%)	1 (5%)	
Thyroid Gland	[20]	[21]	[21]	[11]	[19]	[20]
C-Cell Hyperplasia	3 (15%)	3 (14%)	3 (14%)	2 (18%)	1 (5%)	2 (10%)
C-Cell Adenoma		1 (5%)	4 (19%)			1 (5%)
C-Cell Carcinoma	2 (10%)	2 (10%)	1 (5%)			
Follicular Cell Carcinoma	1 (5%)					
Parathyroid Gland	[20]	[21]	[21]	[11]	[19]	[20]
Hyperplasia		1 (5%)			1 (5%)	1 (5%)
Adenoma			1 (5%)			
Adrenal Gland	[20]	[21]	[21]	[11]	[19]	[20]
Cortical Hyperplasia		1 (5%)			1 (5%)	2 (10%)
Cortical Adenoma	1 (5%)				1 (5%)	
Pheochromocytoma	1 (5%)	1 (5%)			1 (5%)	
Ovary	[20]	[20]	[21]	[11]	[19]	[20]
Cyst		1 (5%)	1 (5%)	2 (18%)	1 (5%)	1 (5%)
Granulosa Cell Tumor			2 (10%)	1 (9%)	1 (5%)	
Carcinoma						1 (5%)
Uterus	[20]	[20]	[21]	[11]	[19]	[20]
Endometrial Cyst				1 (9%)	1 (5%)	
Adenoma					1 (5%)	
Carcinoma					1 (5%)	
Adenocarcinoma						1 (5%)
Polyp	2 (10%)	1 (5%)	2 (10%)			1 (5%)
Myxoma		1 (5%)				
Hemangioma		1 (5%)				
Deciduoma		1 (5%)				
Endometrial Cystic Hyperplasia	1 (5%)					

TABLE C2. SUMMARY OF THE INCIDENCE OF LESIONS IN FEMALE RATS ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION) (Continued)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Vagina	[20]	[20]	[21]	[11]	[19]	[20]
Myxosarcoma	1 (5%)					
Polyp		2 (10%)				1 (5%)
Ear	[20]	[21]	[21]	[11]	[19]	[20]
Inflammation, Tympanic Bullae	1 (5%)		1 (5%)		1 (5%)	3 (15%)
Brain	[20]	[21]	[21]	[11]	[19]	[20]
Astrocytoma						1 (5%)

[ ]: Number of animals with tissue examined microscopically.

TABLE C3. SUMMARY OF THE INCIDENCE OF LESIONS IN MALE MICE ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Skin and Subcutaneous Tissue	[25]	[27]	[24]	[25]	[23]	[22]
Fibrosarcoma	2(8%)	7(26%)	4(17%)	4(16%)	4(17%)	2(9%)
Fibroma	1(4%)	4(15%)	1(4%)	1(4%)	2(9%)	
Rhabdomyosarcoma	1(4%)	1(4%)		1(4%)	1(4%)	
Preputial Gland Carcinoma			1(4%)		1(4%)	
Preputial Gland Adenoma				1(4%)		
Schwanoma				1(4%)		
Leiomyosarcoma			1(4%)			
Hemangioma		1(4%)	1(4%)			
Basal Cell Tumor		1(4%)				
Xanthoma		1(4%)				
Hematopoietic System	[25]	[27]	[24]	[25]	[23]	[22]
Malignant Lymphoma	4(16%)	6(22%)	7(29%)	6(24%)	3(13%)	2(9%)
Hemangioma, Spleen					1(4%)	
Hemangiosarcoma, Spleen					1(4%)	
Lung	[25]	[27]	[24]	[25]	[23]	[21]
Alveologenic Carcinoma		1(4%)		1(4%)		
Alveologenic Adenoma	1(4%)		3(12%)	3(12%)	3(13%)	
Metastatic Hepatocellular Carcinoma	4(16%)		2(8%)	2(8%)	3(13%)	4(19%)
Adenomatosis			1(4%)		2(9%)	
Metastatic Fibrosarcoma			1(4%)	1(4%)		
Liver	[25]	[27]	[24]	[25]	[23]	[22]
Hepatocellular Adenoma	2(8%)	1(4%)	4(17%)	2(8%)	2(9%)	1(5%)
Hepatocellular Carcinoma	12(48%)	8(30%)	8(33%)	12(48%)	15(65%)	21(95%)
Hepatoblastoma	3(12%)					2(9%)
Bile Duct Carcinoma						1(5%)
Hemangiosarcoma					1(4%)	
Metastatic Carcinoma					1(4%)	
Atypical Foci		1(4%)		1(4%)		
Histiocytic Sarcoma		1(4%)				
Pancreas	[25]	[27]	[24]	[25]	[23]	[22]
Islet Cell Adenoma		1(4%)		1(4%)		
Stomach	[25]	[27]	[24]	[25]	[23]	[22]
Hyperplastic Gastropathy		2(7%)	1(4%)	1(4%)	1(4%)	

TABLE C3. SUMMARY OF THE INCIDENCE OF LESIONS IN MALE MICE ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION) (Continued)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Tongue	[25]	[27]	[24]	[25]	[23]	[22]
Kidney	[25]	[27]	[24]	[25]	[23]	[22]
Adenoma				1 (4%)	1 (4%)	
Carcinoma	1 (4%)					
Pituitary Gland	[25]	[27]	[24]	[25]	[23]	[21]
Adenoma					1 (4%)	
Thyroid Gland	[25]	[27]	[24]	[25]	[23]	[21]
Follicular Cell Hyperplasia				1 (4%)	2 (9%)	
Follicular Cell Adenoma		1 (4%)				
Parathyroid Gland	[25]	[27]	[24]	[25]	[23]	[20]
Adenoma			1 (4%)			
Adrenal Gland	[25]	[27]	[24]	[25]	[23]	[22]
Cortical Adenoma			1 (4%)		1 (4%)	
Cortical Carcinoma				1 (4%)	1 (4%)	
Pheochromocytoma	1 (4%)			1 (4%)	1 (4%)	
Small Intestine	[25]	[27]	[24]	[25]	[23]	[22]
Adenocarcinoma		1 (4%)		1 (4%)		
Lipoma		1 (4%)				
Adenoma	1 (4%)					
Hemangioma			1 (4%)			
Large Intestine	[25]	[27]	[24]	[25]	[23]	[22]
Carcinoma					1 (4%)	
Adenocarcinoma	1 (4%)					
Testes	[25]	[27]	[24]	[25]	[23]	[22]
Eye	[25]	[27]	[24]	[25]	[23]	[20]
Harderian Gland Adenoma			3 (12%)	1 (4%)		
Brain	[25]	[27]	[24]	[25]	[23]	[21]
Epidermal Cyst					1 (4%)	

[ ]: Number of animals with tissue examined microscopically.

TABLE C4. SUMMARY OF THE INCIDENCE OF LESIONS IN FEMALE MICE ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Skin and Subcutaneous Tissue	[13]	[19]	[15]	[11]	[17]	[8]
Mammary Gland Adenoma	1 (8%)	2 (11%)			1 (6%)	
Mammary Gland Fibroadenoma				1 (9%)		
Clitoral Gland Carcinoma					1 (6%)	
Clitoral Gland Adenoma					1 (6%)	
Salivary Gland Cystadenoma					1 (6%)	
Liposarcoma					1 (6%)	
Fibrosarcoma	1 (8%)	1 (5%)	1 (7%)	1 (9%)		
Hemangioma				1 (9%)		
Hematopoietic System	[13]	[19]	[15]	[11]	[17]	[8]
Malignant Lymphoma	10 (77%)	6 (32%)	6 (40%)	5 (45%)	6 (35%)	2 (25%)
Spleen, Mast Cell Tumor					1 (6%)	
Hemangioma					1 (6%)	
Lung	[13]	[19]	[15]	[11]	[17]	[8]
Alveologenic Adenoma		1 (5%)			2 (12%)	1 (12%)
Alveologenic Carcinoma			1 (7%)	1 (9%)	1 (6%)	
Adenomatosis			1 (7%)		1 (6%)	
Metastatic Hepatocellular Carcinoma				1 (9%)	1 (6%)	3 (38%)
Metastatic Sarcoma		1 (5%)				
Liver	[13]	[19]	[15]	[11]	[17]	[8]
Atypical Foci		1 (5%)			3 (18%)	
Hepatocellular Adenoma		2 (11%)		1 (9%)	1 (6%)	1 (12%)
Hepatocellular Carcinoma			2 (13%)	2 (18%)	3 (18%)	7 (88%)
Metastatic Sarcoma		1 (5%)	2 (13%)			
Metastatic Leiomyosarcoma				1 (9%)		
Angiosarcoma		1 (5%)				
Pancreas	[13]	[19]	[15]	[11]	[17]	[8]
Exocrine Cell Adenoma					1 (6%)	
Islet Cell Adenoma	1 (8%)				1 (6%)	
Stomach	[13]	[19]	[15]	[11]	[17]	[8]
Ulcer			1 (7%)	1 (9%)		
Hyperplastic Gastropathy					1 (6%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF LESIONS IN FEMALE MICE ADMINISTERED POLYBROMINATED BIPHENYL MIXTURE IN CORN OIL BY GAVAGE (LIFETIME OBSERVATION) (Continued)

Dose (mg PBB/kg)	0	0.1	0.3	1.0	3.0	10.0
Tongue	[13]	[19]	[15]	[11]	[17]	[8]
Kidney	[13]	[19]	[15]	[11]	[17]	[8]
Hemangioma	1 (8%)					
Pituitary Gland	[13]	[19]	[15]	[10]	[17]	[8]
Adenoma	4 (31%)	1 (5%)	4 (27%)	2 (20%)	6 (35%)	1 (12%)
Thyroid Gland	[13]	[19]	[15]	[11]	[17]	[8]
Follicular Cell Hyperplasia		1 (5%)	3 (20%)	1 (9%)	2 (12%)	1 (12%)
Follicular Cell Adenoma				1 (9%)	3 (18%)	1 (12%)
Parathyroid Gland	[13]	[19]	[15]	[11]	[17]	[8]
Hyperplasia				1 (9%)		
Adenoma	1 (8%)					
Adrenal Gland	[13]	[19]	[15]	[11]	[17]	[8]
Pheochromocytoma			1 (7%)			
Small Intestine	[13]	[19]	[15]	[11]	[17]	[8]
Hemangioma		1 (5%)				
Ovary	[13]	[19]	[15]	[11]	[17]	[8]
Cystic	2 (15%)	2 (11%)	2 (13%)		3 (18%)	1 (12%)
Granulosa Cell Tumor				1 (9%)	1 (6%)	
Luteoma					1 (6%)	
Uterus	[13]	[19]	[15]	[11]	[17]	[8]
Endometrial Cystic Hyperplasia	2 (15%)	4 (21%)	3 (20%)	2 (18%)		
Hemangioma	1 (8%)					
Myxoma		1 (5%)				
Histiocytic Sarcoma			1 (7%)			
Leiomyosarcoma			1 (7%)	1 (9%)		1 (12%)
Adenoma			1 (7%)			
Adenocarcinoma				1 (9%)		
Cystadenoma					1 (6%)	
Leiomyoma					1 (6%)	
Hemangiosarcoma					1 (6%)	
Eye	[13]	[19]	[15]	[10]	[17]	[8]
Harderian Gland Adenoma	2 (15%)				1 (6%)	
Brain	[13]	[19]	[15]	[10]	[17]	[8]
Astrocytoma	1 (8%)					
Metastatic Sarcoma		1 (5%)				

[ ]: Number of animals with tissue examined microscopically.

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