IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 152

Polybrominated Biphenyls

UNEP ILO

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Environmental Health Criteria 152

POLYBROMINATED BIPHENYLS

First draft prepared by Dr W. Gross, Dr J. Kielhorn and Dr C. Melber, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

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ENVIRONMENTAL HEALTH CRITERIA FOR POLYBROMINATED BIPHENYLS

A WHO Task Group on Environmental Health Criteria for Polybrominated biphenyls (PBBs) met at the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany, from 22 to 26 June 1992. Dr H. Galal-Gorchev, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director of the IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Group reviewed and revised the draft and made an evaluation of the risks for human health and the environment from exposure to PBBs.

The first draft was prepared by Dr W. Gross, Dr J. Kielhorn and Dr C. Melber of the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany, who also prepared the second draft, incorporating comments received following circulation of the first drafts to the IPCS Contact Points for Environmental Health Criteria monographs.

Dr H. Galal-Gorchev and Dr K.W. Jager of the IPCS Central Unit were responsible for the scientific content of the monograph, and Mrs M.O. Head of Oxford for the technical editing.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

1. SUMMARY AND EVALUATION, CONCLUSIONS AND RECOMMENDATIONS

1.1 Summary and evaluation

1.1.1 Identity, physical and chemical properties, analytical methods

The term polybrominated biphenyls or polybromobiphenyls (PBBs) refers to a group of halogenated hydrocarbons, formed by substituting hydrogen by bromine in biphenyl. PBBs are not known to occur as natural products. They have a molecular formula of $C_{12}\ H_{(10-x-y)}Br_{(x+y)}$ where both x and y = 1 to 5. Theoretically 209 congeners are possible. Only a few have been synthesized individually and characterized. PBBs, manufactured for commercial use, consist mainly of hexa-, octa-, nona-, and decabromobiphenyls, but also contain other homologues. They are additive type flame retardants, and when blended with the dry solid or liquid polymeric material, provide filter-type, flame retardant action with the chemical release of hydrogen bromide if ignited.

PBBs are manufactured using a Friedel-Crafts type reaction in which biphenyl is reacted with bromine with, or without, an organic solvent, using, e.g., aluminium chloride, aluminium bromide, or iron as catalyst.

Most research has been carried out on FireMaster BP-6 and FF-1, which were involved in the Michigan disaster when this compound was inadvertently added to animal feed instead of magnesium oxide. The ensuing contamination of farm animals resulted in the destruction of thousands of cattle, pigs, and sheep, and millions of chickens.

The composition of FireMaster® changes from batch to batch, but its main constituents are 2,2′,4,4′,5,5′-hexabromobiphenyl (60–80%), and 2,2′,3,4,4′,5,5′-heptabromobiphenyl (12–25%) together with lower brominated compounds because of incomplete bromination reaction. Mixed bromochlorobiphenyls and polybrominated naphthalenes have also been observed as minor components of FireMaster®. FireMaster FF-1 (white powder) is FireMaster BP-6 (brown flakes) to which 2% calcium silicate has been added as an anti-caking agent.

PBBs are solids with a low volatility that decreases with increasing bromine number. PBBs are virtually insoluble in water, soluble in fat, and slightly to highly soluble in various organic solvents; solubility also decreases with increasing bromine number. These compounds are relatively stable and chemically unreactive, though highly brominated PBB mixtures are photodegraded with reductive debromination upon exposure to ultraviolet radiation (UVR).

The products of the experimental thermal decomposition of PBBs depend on the temperature, the amount of oxygen present, and a number of other factors. Investigations into the pyrolysis of FireMaster BP-6 in the absence of oxygen (600-900 °C) have shown that bromobenzenes and lower brominated biphenyls are formed, but no polybrominated furans. In contrast, pyrolysis in the presence of oxygen (700-900 °C) yielded some di- to heptabromodibenzofurans. In the presence of polystyrene and polyethylene, higher levels were found. Pyrolysis of FireMaster BP-6 with PVC at 800 °C yielded mixed bromochlorobiphenyls. There is no information on the nature of the products of incineration of PBB-containing material. Little is known about the toxicities of brominated and brominated/chlorinated dioxins and furans, but they are estimated to be of about the same order as those of chlorinated dioxins and furans.

The primary analytical technique used for the biological monitoring of PBBs in environmental samples and biological tissues and fluids, after the Michigan disaster, was gas chromatography with electron capture detection. Individual congeners can be determined by capillary gas chromatography and more specific detection can be obtained with selected ion monitoring mass spectrometry. Because of the large numbers of congeners possible, investigations are hampered by lack of suitable synthetic standards. Methods for extracting PBBs from biological samples have been based on those for pesticides. PBBs are extracted with the fat, and then purified.

The recent finding of PBB congeners in background biological samples does not necessarily mean that concentrations are increasing in the environment. The development of more sensitive analytical techniques, such as negative ion chemical ionization mass spectrometry, may be the explanation. Thus, the need for retrospective studies is urgent. With improved clean-up methods, it is possible to carry out specific analyses of the toxic co-planar PBB congeners and such data are also needed.

1.1.2 Sources of human and environmental exposure

The commercial production of FireMaster® was started in the USA in 1970. After the Michigan disaster, production was discontinued (November 1974). The estimated production of PBBs in the USA between 1970 and 1976 was 6000 tonnes (commercial quantities). Octabromobiphenyl and decabromobiphenyl were produced in the USA until 1979. A mixture of highly brominated PBBs called Bromkal 80-9 D was produced in Germany until mid-1985. Technical grade decabromobiphenyl (Adine 0102) is currently produced in France. As far as is known, this is the only current production of PBBs.

PBBs were introduced as flame retardants in the early 1970s. Prior to November 1974, hexabromobiphenyl was the most commercially significant PBB in the USA and was incorporated into acrylonitrile-butadiene-styrene (ABS) plastics (PBB content 10%), used mainly in small appliance and automotive applications, coatings, lacquers, and polyurethane foam. The other PBB flame retardants have similar uses.

Losses of PBBs into the environment during normal production can occur through emission into the air, waste waters, losses into the soil, and to landfills, and have been found to be generally low.

These chemicals can also enter the environment during shipping and handling, and accidentally, as occurred in Michigan.

There is also the possibility of their entrance into the environment as a result of the incineration of materials containing PBBs as well as during accidental fires with the formation of other toxic chemicals, such as polybromodibenzofurans or mixed bromochloro derivatives.

The major part of the total volume of these compounds produced will ultimately enter into the environment, as such, or as breakdown products.

1.1.3 Environmental transport, distribution, and transformation

Long-range transport of PBBs in the atmosphere has not been proven, but the presence of these compounds in Arctic seal samples indicates a wide geographical distribution.

The principal known routes of PBBs into the aquatic environment are from industrial waste discharge and leachates

from industrial dumping sites into receiving waters and from erosion of polluted soils. PBBs are almost insoluble in water and are primarily found in sediments of polluted lakes and rivers.

Pollution of soils can originate from point sources, such as PBB plant areas and waste dumps. Once introduced into the soil, PBBs do not appear to be translocated readily. PBBs have been found to be 200 times more soluble in a landfill leachate than in distilled water; this may result in a wider distribution in the environment. The hydrophobic properties of PBBs make them easily adsorbed from aqueous solutions onto soils. Preferential adsorption of PBB congeners was noted, depending on the characteristics of the soil (e.g., organic content) and the degree and position of bromine substitution.

PBBs are stable and persistent, lipophilic, and only slightly soluble in water; some of the congeners are poorly metabolized and therefore accumulate in lipid compartments of biota. Once they have been released into the environment, they can reach the food chain, where they are concentrated.

PBBs have been detected in fish from several regions. Ingestion of fish is a source of PBB transfer to mammals and birds.

Degradation of PBBs by purely abiotic chemical reactions (excluding photochemical reactions) is considered unlikely. The persistence of PBBs under field conditions has been reported. Soil samples from a former PBB manufacturing site, analysed several years after the Michigan incident, still contained PBBs though the PBB congener composition was different, indicating a partial degradation of the PBB residues in the soil sample.

Under laboratory conditions, PBBs are easily degraded by UVR. Photodegradation of the commercial FireMaster® mixture led to diminished concentrations of the more highly substituted PBB congeners. The rates and extent of photolytic reactions of PBBs in the environment have not been determined in detail, though field observations indicate a high persistence of the original PBBs, or a partial degradation to the less brominated congeners.

In laboratory investigations, mixtures of PBBs appear to be fairly resistant to microbial degradation.

Neither uptake nor degradation of PBBs by plants has been recorded. In contrast, PBBs are easily absorbed by animals and

though they have been found to be very persistent in animals, small amounts of PBB metabolites have been detected. The main metabolic products were hydroxy-derivatives, and, in some cases, there was evidence of partially debrominated PBBs. No investigation of sulfur-containing metabolites analogous to those of PCBs have been reported.

The bioaccumulation of PBBs in fish has been investigated. Bioaccumulation of PBBs in terrestrial animals has been investigated in avian and mammalian species. Data were obtained through field observations, evaluation of the Michigan disaster and through controlled feeding studies. Generally, the accumulation of PBBs in body fat depended on the dosage and duration of exposure.

Bioaccumulation of individual PBB congeners has been found to increase with degree of bromination up to at least tetrabromobiphenyls. Higher brominated congeners can be expected to accumulate to an even greater extent. However, no information is available for decabromobiphenyl; it is possible that it is poorly absorbed.

Brominated dibenzofurans or partially debrominated PBBs have been reported as products of the thermal decomposition of PBBs. Their formation depends on several variables (e.g., temperature, oxygen).

1.1.4 Environmental levels and human exposure

Only one report is available on PBB levels in air. In this study, concentrations in the vicinity of three PBB-manufacturing or PBB-processing plants in the USA were measured.

Levels in surface waters in the same vicinity and in the Gratiot County landfill (Michigan, USA), which received over a hundred thousand kg of waste containing 60–70% PBBs between 1971 and 1973, were monitored.

Groundwater monitoring data from the Gratiot County landfill showed trace levels of PBBs even outside the landfill area, however, PBBs were not detected in drinking-water wells in the area.

Data on soil pollution by PBBs are available for areas of manufacture, use, or disposal of PBBs, and for soils from fields of the PBB-contaminated Michigan farms.

In the Michigan disaster, FireMaster® was inadvertently added to animal feed. It was almost a year later that the mixing error was discovered and the analyses indicated that PBBs were responsible. During this time (summer 1973 - May 1974), contaminated animals and their produce entered the human food supply and the environment of the state of Michigan. Hundreds of farms were affected, thousands of animals had to be slaughtered and buried, as well as thousands of tons of farm produce.

Most data available on the PBB-contamination of wildlife refer to fish and birds in the USA and Europe, primarily waterfowl, in the vicinity of industrial sites, and marine mammals.

Recent reports on the PBB-contamination of fish, terrestrial and marine mammals, and birds in the USA and Europe indicate a wide distribution of these compounds. The congener pattern found in fish samples is quite different from that found in commercial products. Many of the major peaks could well be the result of the photochemical debromination of decabromobiphenyl (BB 209), but this has not been confirmed.

Occupational exposure was found in employees in chemical plants in the USA, and in farm workers, as a result of the Michigan PBB incident. Median serum and adipose tissue PBB levels were higher among chemical workers. Information from other countries/companies on occupational exposure associated with manufacturing, formulation, and commercial uses is not available.

For most human populations, direct data on exposure to PBBs from various sources have not been documented. Widespread human exposure resulting from direct contact with contaminated feed and, primarily, from the consumption of PBBs in meat, eggs, and dairy products has been reported from Michigan, USA. At least 2000 families (primarily farmers and their neighbours) received heavy exposure. Recently, PBBs have been detected in cows' milk and human milk in Germany.

The congener patterns in these samples are different from that in fish. The relative concentration of BB 153 is higher in human milk than in fish.

The routes of exposure of the general population to PBBs are not well known. Present knowledge indicates that ambient air and water do not contain high levels. Lipid-rich food, especially from

contaminated waters, is probably of great importance. There is no information on levels of exposure in indoor air and dermal exposure levels from materials containing PBB flame retardants.

The PBB congener pattern found in human milk, collected in Germany, resembled that found in cows' milk from the same region, but levels in the human samples were substantially higher.

An estimate of the daily intake of PBB via food by the general population has to be based on very few data. If it is assumed that fish contains 20 μg PBB/kg lipid and 5% lipid and that a 60-kg person eats 100 g fish/day, the intake will be 0.002 μg/kg body weight per day. A PBB concentration of 0.05 μg/kg lipid in milk (4% lipid) and a milk consumption of 500 ml/day will give the same person a PBB intake of about 0.00002 μg/kg body weight per day.

An infant of 6 kg body weight consuming 800 ml human milk (3.5% lipid) per day will have an intake of 0.01 μg PBB/kg body weight per day, if the milk contains 2 μg PBB/kg lipid.

1.1.5 *Kinetics and metabolism*

Gastrointestinal absorption of PBBs varies according to the degree of bromination, the lower brominated compounds being more easily absorbed.

There is inadequate information on the absorption of DeBB and OcBB/NoBB.

PBBs are distributed throughout the animal species and human beings, the highest equilibrium concentrations being in adipose tissues. Relatively high levels have also been found in the liver, particularly of the more toxic congeners, which appear to be concentrated in the liver. The partitioning ratios of the various PBB congeners appear to differ between several tissues. Generally, there is a marked tendency for bioaccumulation. In mammals, transfer of PBBs to offspring occurs through transplacental and milk routes. Human milk was found to contain levels of 2,2',4,4',5,5'-hexabromobiphenyl that were more than 100 times the maternal serum levels. During a multigeneration study on rats, administration of PBBs to a single generation resulted in detectable residues in more than two subsequent generations. Eggs of avian species were also affected by maternal PBB body burden.

Many PBB congeners are persistent in biological systems. There was no evidence for significant metabolism or excretion of the more abundant components of the FireMaster® mixture or for octa- and decabromobiphenyl. *In vitro*-metabolism studies showed that structure-activity relationships exist for the metabolism of PBBs. PBBs could be metabolized by PB (phenobarbital)-induced microsomes only if they possessed adjacent non-brominated carbons, *meta* and *para* to the biphenyl bridge on at least one ring. Metabolism by MC (3-methylcholanthrene)-induced microsomes required adjacent non-brominated *ortho* and *meta* positions on at least one ring of lower substituted congeners and higher bromination appeared to prevent metabolism. Hydroxylated derivatives as major *in vitro*- and *in vivo*-metabolism products of lower brominated biphenyls have been identified in vertebrates. The metabolic yield was relatively low. The hydroxylation reaction probably proceeds via both arene oxide intermediates and by direct hydroxylation.

Humans, rats, rhesus monkeys, pigs, cows, and chickens eliminate PBBs mainly in the faeces. In most cases, excretion rates seem to be slow. Concentrations of 2,2′,4,4′,5,5′-hexabromobiphenyl observed in the bile and faeces of humans were about 1/2 to 7/10 of the serum levels and approximately 0.5% of the adipose levels. Treatment to enhance elimination of PBBs in animals or humans had no, or little, success. Another pathway of elimination is excretion through milk.

Complex and varied relationships were found in PBB tissue concentrations with time after PBB administration to rats and other animals. They are described by several compartmental models. A half-life of approximately 69 weeks was calculated for the elimination of 2,2′,4,4′,5,5′-hexabromobiphenyl from the body fat of rats. A half-life of more than 4 years was found in rhesus monkeys. Average half-lives in humans have been estimated to be between 8 and 12 years for 2,2′,4,4′,5,5′-hexabromobiphenyl. Ranges of 5-95 years have been suggested in the literature. There are some differences in retention and turnover between individual PBB congeners. Results of analyses of serum from farmers and chemical workers for 2,3′,4,4′,5-pentabromobiphenyl were inconsistent. This inconsistency was probably because of the different sources of exposure. The workers were exposed to all compounds of FireMaster®, while the Michigan population was exposed to contaminated meat and milk containing a different PBB mixture as a result of metabolic processes in farm animals. Bromine levels did not decrease in the adipose tissue of rats, when

technical octabromobiphenyl was given. No information is available on the retention of decabromobiphenyl.

Humans may have a greater tendency to retain certain PBB congeners than experimental animals. This factor should be taken into consideration in evaluating the human health hazards from these chemicals.

In conclusion, all available data indicate that PBBs have a marked tendency to bioaccumulate and persist. Metabolism is poor and half-lives in humans are of the order of 8-12 years or longer.

1.1.6 *Effects on organisms in the environment*

Only few data are available on the effects of PBBs on organisms in the environment. They refer to microorganisms, water fleas, waterbirds, and farm animals.

Waterbirds nesting on islands in northwestern Lake Michigan were studied to see if environmental contaminants were producing effects on reproduction. Seventeen contaminants, including PBBs, were measured, but none seemed to have a pronounced effect on reproduction.

Farm animals that ingested feed inadvertently containing Firemaster® FF-1 instead of magnesium oxide became sick. The estimated average exposure of cows on the first identified highly contaminated farm was 250 mg/kg body weight. The clinical signs of toxicity were a 50% reduction in feed consumption (anorexia) and a 40% decrease in milk production, a few weeks after ingestion of the contaminated feed. Although the supplemented feed was discontinued within 16 days, milk production was not restored. Some cows showed an increased frequency of urination, and lacrimation, and developed haematomas, abscesses, abnormal hoof growth, lameness, alopecia, hyperkeratosis, and cachexia; several died within 6 months of exposure. Altogether, the death rate on this farm was 24/400. The death rate of 6- to 18-month-old calves was much higher. About 50% died within 6 weeks, only 2 out of 12 surviving after 5 months. They developed hyperkeratosis over their entire bodies. There were also a variety of reproductive problems.

Necropsy findings have been reported for some of the mature cows that died in the 6 months following exposure.

Histopathological studies revealed variable liver and kidney changes.

Several clinical signs and pathological changes noted above were later confirmed in controlled feeding studies (anorexia, dehydration, excessive lacrimation, emaciation, hyperkeratosis, reproductive difficulties, some clinical chemistry changes, and renal damage).

A drop in production and sterility were reported in herds with low-level contamination. This contrasts with results of controlled studies, which did not show any significant differences between herds with low-level contamination and control herds.

Although it was cattle feed that was originally involved in the accidental substitution, other animal feeds became involved by cross contamination, e.g., in the mixing machinery of feed companies. It is likely that the exposure was not as high as that of cattle. Although other animals (poultry, swine, horses, rabbits, goats, and sheep) were reported as being contaminated and were killed, details of ill effects were not recorded.

No information is available on the effects of PBBs on the ecosystem.

1.1.7 *Effects on experimental animals and in vitro test systems*

The LD_{50} values of commercial mixtures show a relatively low order of acute toxicity (LD_{50} > 1 g/kg body weight) in rats, rabbits, and quails, following oral or dermal administration. Deaths and acute manifestations of toxicity were delayed after administration of PBB. The total dose administered determined the extent of toxicity, whether given as a single dose or as repeated doses over short periods (up to 50 days). The toxicity of PBBs was higher with multiple-dose rather than single-dose administration. Deaths after exposure to PBBs are delayed.

The few studies performed with commercial octa- and deca bromobiphenyl mixtures did not result in mortality in rats and fish. Of the individual PBB congeners, only three hexa isomers have been tested, 3,3′,4,4′,5,5′-HxBB; and 2,3′,4,4′,5,5′-HxBB being more toxic for rats than 2,2′,4,4′,5,5′-HxBB. On the basis of limited, available data, OcBB and DeBB appear to be less toxic than the PBB mixtures and less well absorbed.

In many acute and short-term studies, signs of PBB (mostly FireMaster) toxicity have included reductions in feed consumption. At lethal doses, the cause of death cannot be ascribed to pathology in a particular organ but rather to a "wasting syndrome" that the animals develop as a first indication of toxicity. At death, the loss in body weight can be as great as 30-40%. The few studies with technical OcBB and DeBB did not show any such effects.

Morphological and histopathological changes, caused by PBB exposure, are most prominent in the liver. Enlargement of the liver frequently occurred at doses lower than those required to produce body weight changes. The principal histopathological alterations in rodent species may consist of extensive swelling and vacuolation of hepatocytes, proliferation of smooth endoplasmatic reticulum, and single-cell necrosis. The severity of the lesions depends on the dose and the composition of the PBB material given.

Decreases in thymus weights were observed in rats, mice, and cattle after doses of FireMaster®, but not OcBB or DeBB.

There are some reports of increase in thyroid weight and histological changes in the thyroid of rats, which have been observed at low concentrations.

It is evident that individual PBB congeners differ in their pattern of toxicity. The more toxic isomers and congeners cause a decrease in thymus and/or body weight and produce pronounced histological changes in the liver and thymus. Categorization of halogenated biphenyls has been made on a structural basis. Category 1 comprises isomers and congeners lacking ortho-substituents (coplanar PBBs). Mono-ortho-substituted derivatives constitute the second category. Other PBBs (mainly those with two or more ortho-bromines) have been organized into the third category. Congeners of Category 1 tend to elicit the most severe effects, while the congeners of the second and third categories show decreasing toxicological changes. Within the category, the degree of bromination may also influence toxicity.

In all combinations tested, 3,3′,4,4′,5,5′-HxBB was found to be the most toxic PBB. This congener is present in low concentrations as a constituent of FireMaster®. Of the major FireMaster® constituents, 2,3,3′,4,4′,5-HxBB appeared to be the most toxic one followed by 2,3′,4,4′,5,5′-HxBB and 2,3′,4,4′,5-PeBB. The main component of the FireMaster® mixture, 2,2′,4,4′,5,5′-HxBB was

relatively non-toxic as was 2,2′,3,4,4′,5,5′-HpBB, the second most abundant constituent.

The toxicity of technical OcBB and DeBB mixtures in relation to their contents of various PBB congeners (and other possible contaminants) is not so well elucidated.

Common skin and eye irritation tests and sensitization tests resulted in no, or only mild, reactions to the technical PBB mixtures tested (OcBB and DeBB). However, hyperkeratosis and hair loss were seen in cattle, and lesions resembling chloracne were seen in Rhesus monkeys, following the ingestion of a FireMaster® mixture. Hyperkeratosis of the inner surface of the rabbit ear was produced by FireMaster, but not by its main components (2,2′,4,4′,5,5′-HxBB and 2,2′,3,4,4′5,5′-HpBB). Fractionation of FireMaster® revealed that most activity was associated with the more polar fractions containing minor components. Treatment with sunlight-irradiated HxBB caused severe hyperkeratosis in rabbit ears.

Low dose, long-term feeding of technical OcBB to rats did not affect food consumption and body weight, but an increase in the relative liver weights of exposed rats was found at 2.5 mg/kg body weight for 7 months. Long-term feeding of FireMaster® to rats at doses of 10 mg/kg body weight for 6 months did not affect food consumption. Doses of 1 mg/kg body weight over a 6-month period affected liver weight. The thymus weight was decreased in female rats administered 0.3 mg/kg body weight. Histopathological changes were also noted. Controlled, long-term feeding studies on cattle exposed to low doses of FireMaster® did not reveal any adverse effects as indicated by food intake, clinical signs, clinicopathological changes, or performance. Minks, guinea-pigs, and monkeys appeared to be more susceptible to PBB toxicity.

Long-term effects related to the retention of administered PBBs following pre- or perinatal exposure to high doses of FireMaster® have been recorded in rats.

The most common adverse effects on reproduction were fetal wastage and decrease in viability of offspring. Some effects were still noted in mink at concentrations of 1 mg/kg diet. Decreases in the viability of the offspring were observed in Rhesus monkeys following a 12.5 month exposure to FireMaster® (0.3 mg/diet). The monkeys received a daily dose of 0.01 mg/kg body weight and a total dose of 3.8 mg/kg body weight. Reproduction and

neurobehavioural studies on monkeys and rats with low-level exposure could not be evaluated since insufficient information was given in the published papers on the experimental design of the studies. A weak teratogenic potential was seen in rodents at high doses that may have caused some maternal toxicity.

PBBs interact with the endocrine system. Rats and pigs showed dose-related decreases in serum thyroxine and triiodothyronine. PBBs have also been reported to affect the levels of steroid hormones in most cases. The extent depends on the species as well as the dose and time administered.

PBBs produced porphyria in rats and male mice at doses as low as 0.3 mg/kg body weight per day. The no-effect level was 0.1 mg/kg body weight per day. There was a pronounced influence of PBBs on vitamin A storage as well as effects on the intermediary metabolism.

Atrophy of the thymus was a frequent observation following PBB exposure, and other lymphoid tissues have been shown to be affected. Further indicators of a suppressed immune function have also been demonstrated for FireMaster®. Data on OcBB, NoBB, DeBB, or individual PBB congeners are lacking.

One of the most intensively studied effects of PBBs is their induction of mixed function oxidase (MFO) enzymes. Consistently, FireMaster® was found to be a mixed-type inducer of hepatic microsomal enzymes in rats and all other animal species tested. Induction was also found to a lesser extent in other tissues. The ability to induce hepatic microsomal enzymes differed for individual PBB congeners. Correlations between structure and microsomal enzyme inducing activity have been demonstrated.

Several studies have revealed that PBBs are able to alter the biological activity of a variety of drugs and toxic substances. This may partly be because of the ability of PBBs to induce microsomal enzymes involved in the activation or deactivation of xenobiotics.

The FireMaster® mixture, and some of its major components, were found to be capable of inhibiting intercellular communication *in vitro*. This inhibition occurs at non-cytotoxic concentrations. Both the cytotoxicity and metabolic cooperation-inhibiting properties of PBB congeners seem to be related to their structure, i.e., presence or lack of ortho-substitution.

In vitro and *in vivo* assays (microbial and mammalian cell mutagenesis, mammalian cell chromosomal damage, mammalian cell transformation, and DNA damage and repair) have failed to indicate any mutagenicity or genotoxicity of individual PBB congeners or commercial mixtures.

Long-term toxicity studies have shown the liver to be the principal site of the carcinogenic effects of PBB. The incidences of hepatocellular carcinoma were significantly increased in both male and female mice and rats receiving oral doses of the FireMaster® mixture. Carcinogenic effects in the liver have been reported in mice receiving diets containing Bromkal 80-9D (technical nonabromobiphenyl) at 100 mg/kg (5 mg/kg body weight per day) or more for 18 months. The lowest dose of PBB that produced tumours (mostly adenomas) in rodents was 0.5 mg/kg body weight per day for 2 years. The rats receiving 0.15 mg/kg body weight per day in addition to pre- and perinatal exposure did not suffer any adverse effects. The carcinogenicity of technical octabromobiphenyl and decabromobiphenyl has not been studied.

Neither Firemaster BP-6 nor 2,2′,4,4′,5,5′-hexabromobiphenyl showed tumour-initiating (using TPA as promotor) or tumour-promoting (using DMBA as initiator) activity in a mouse skin bioassay. However, in other mouse skin models (using DMBA or MNNG as initiators), FM FF-1, 3,3′,4,4′,5,5′-hexabromobiphenyl, but not 2,2′,4,4′,5,5′-hexabromobiphenyl, showed tumour promoting activity. In a two-stage rat liver bioassay using phenobarbital as promotor, 3,3′,4,4′-tetrabromobiphenyl showed a weak initiating activity. In the two-stage rat liver model using diethylnitrosamine and partial hepatectomy, FM, 3,3′,4,4′-tetrabromobiphenyl, and 2,2′,4,4′,5,5′-hexabromobiphenyl, but not 3,3,′,4,4′,5,5′-hexabromobiphenyl, showed tumour promoting activity.

The results of the studies on cell communication, the negative results of studies on genotoxicity and mutagenicity, and the results of tumour promotion assays indicate that the mixtures and congeners studied cause cancer by epigenetic mechanisms. No information is available on technical octa-, nona-, or decabromobiphenyl.

The mechanisms of action underlying the many manifestations of the toxicity of PBBs and related compounds are not known. However, some of the effects, such as the wasting syndrome, thymus atrophy, hepatotoxicity, skin disorders, and reproductive

toxicity may be related to interaction with the so-called Ah- or TCDD-receptor causing alteration in the expression of a number of genes. Different PBB congeners vary in their interaction with the receptor, the coplanar congeners being more active.

Many of the effects of PBB are seen after long-term exposure. The reason for this may be the pronounced accumulation of some PBB congeners and the poor ability of the body to metabolize and eliminate them. This results in a build-up of the chemical in the body overcoming compensatory mechanisms leading to adverse effects.

Some polybrominated naphthalenes (PBNs), known contaminants of the FireMaster® mixture, are potent toxic substances and teratogens. Although PBNs are only present at low levels in the FireMaster® mixture, it is possible that they may contribute to its toxicity.

Studies on the FireMaster® mixture and its main component, 2,2′,4,4′,5,5′-HxBB showed that the photolysis products were more toxic than the original PBB. The pyrolysis products of FM caused MFO enzyme induction, body weight loss, and thymic atrophy. Liver enlargement was observed with pyrolysis products of technical OcBB.

1.1.8 Effects on humans

There was no example of acute PBB toxicosis in humans with which to compare the potential effects at lower exposures following the poisoning incident in Michigan, USA, 1973. The main epidemiological studies were conducted by the Michigan Department of Public Health (MDPH) and the Environmental Science Laboratory, Mount Sinai School of Medicine, New York (ESL).

It was estimated that the most highly exposed people consumed 5-15 g PBB over a 230-day period through milk. Some additional exposure may have occurred through meat. The exposure levels among some of the farmers and most of the general population in Michigan were much lower, i.e., the total exposure was 9-10 mg. However, some people in this group may have received a total exposure of about 800-900 mg. (A total dose of 9 mg corresponds to 0.15 mg/kg body weight, and 900 mg-15 mg/kg body weight for a 60-kg average adult; the dose/kg body weight would be higher for children).

In 1974, the first MDPH study compared the health status of people on quarantined farms with people on non-quarantined farms in the same area. Although a variety of symptoms were reported by both groups, there was no pattern of differences between the groups. No unusual abnormalities of the heart, liver, spleen, nervous system, urinanalysis, blood counts, or any other medical conditions examined could be found. In a later comprehensive MDPH study including groups with different levels of exposure, there was no positive association between serum concentrations of PBB and reported symptom or disease frequencies. The ESL studies involved about 990 farm residents, 55 chemical workers, and a group of Wisconsin dairy farmers who were used as a control. The incidence of symptoms in Michigan farmers was greater than the incidence in Wisconsin farmers. The greatest differences were in the broad classification of neurological and musculoskeletal symptoms. Elevated serum concentrations of some liver enzymes and carcinoembryonic antigen were more prevalent in Michigan farmers than in Wisconsin farmers. Chemical workers had a higher prevalence of chest and skin symptoms and a lower prevalence of musculoskeletal symptoms than farmers.

Although results of ESL studies were at times interpreted differently from results of comparable studies, there was one area of consistent agreement. Neither sets of studies demonstrated a positive dose-response relationship between PBB levels in serum or adipose tissue and the prevalence of symptoms or abnormal clinical measurements. Several clinical areas were investigated using more intensive special studies. Examination of neurological aspects by means of objective performance tests revealed in one study a negative correlation of serum PBB levels with performance test scores, particularly in males in older age groups. The other studies showed no association between serum or fat concentrations of PBBs and performance in a battery of tests measuring memory, motor strength, coordination, cortical-sensory perception, personality, higher cognitive functioning, and other functions.

Paediatric aspects of PBB exposure were examined in families of the ESL studies. Although many symptoms were reported, physical examination failed to reveal any objective alteration that could be attributed to PBB. There were different views about the more subtle neuropsychological effects in the offspring and the results of investigations of developmental abilities remain controversial, too. The same is true for the investigation of lymphocyte and immune function. One set of authors found no differences in lymphocyte count or functions between groups with

high and low serum PBB levels, the other found a significant decrease in T- and B-lymphocyte subpopulations in about 40% of an exposed Michigan group, compared with unexposed groups, and impaired lymphocyte function, i.e., decreased response to mitogens.

In the epidemiological studies reviewed, efforts have been made to evaluate the relationship between PBB exposure and a large number of adverse effects including behavioural effects and subjective complaints. However, most studies suffer from major failures in design introducing confounders that make it difficult, or impossible, to draw conclusions about the relationship between PBB exposure and possible health effects. The follow-up time has not been long enough to evaluate possible carcinogenic effects.

Two small groups of workers with occupational exposure to a mixture of PBBs or to DeBB and DBBO were identified. Lesions resembling chloracne were found in 13% of the workers exposed to the PBB mixture, such lesions were not seen in the DeBB-exposed workers. However, a significantly higher prevalence of hypothyroidism was seen in the latter group.

1.1.9 *Overall evaluation of toxicity and carcinogenicity*

The only lifetime study with a PBB mixture was conducted on rats and mice in a recent NTP bioassay. The lowest dose tested that still produced carcinogenic effects was 0.5 mg/kg body weight per day (liver tumours in rodents). In other carcinogenicity studies, 3 mg/kg body weight per day given for 6 months resulted in a carcinogenic response. The 6-month study demonstrates that less than lifetime exposure at similar doses will also result in similar adverse effects. Effects on reproduction in subhuman primates and mink may occur at lower doses.

In addition, in the 2-year NTP rat study, a daily dose of 0.15 mg/kg body weight per day and prenatal and perinatal exposure of the dam to 0.05 mg/kg body weight per day did not result in any adverse effects. Thus, the total daily intake from food, water, air, and soil should be less than 0.15 μg/kg body weight per day, extrapolating from a NOAEL (no-observed-adverse-effect level) of a positive carcinogenicity study, using an uncertainty (safety) factor of 1000, since these compounds probably produce cancer by an epigenetic mechanism.

The total dose received by the subpopulation in Michigan was estimated to have ranged from 0.15 to 15 mg/kg body weight over a 230-day period. For this population, dividing the doses over a

lifetime for the average human being would be equivalent to a daily dose ranging from 6 ng to 0.6 μg/kg body weight per day.

A total intake of 2 ng PBB/kg body weight per day, from known sources, has been estimated for adults in the general population and 10 ng/kg body weight per day for infants receiving human milk. It should be kept in mind that these estimates are based on a very limited and regional data base.

These calculations assume that a steady state for PBBs would not be reached over a lifetime and that short-term higher exposure can be substituted for long-term lower exposures, since these compounds are extremely poorly metabolized and excreted.

Insufficient information is available for OcBB, NoBB, and DeBB to calculate a total daily intake that would not result in adverse effects.

1.2 Conclusions

Most of the PBB congeners found in commercial flame retardants are lipophilic, persistent, and bioaccumulating. These compounds are biomagnified in environmental food webs and pose a threat, especially to organisms in the higher levels of these webs. Furthermore, some PBB products are precursors to toxic polybrominated dibenzofurans in combustion processes.

In addition to emissions during manufacture and use, PBB will enter the environment from the widespread use of flame retardant products. A considerable part of the PBB produced will ultimately reach the environment because of the high stability of these compounds.

PBBs are also found in environmental and human samples from places far from known point sources. The congener pattern in the environmental samples does not match those found in the technical products, which indicates an environmental alteration, possibly a photochemical debromination.

Very little information is available at present on the extent of the exposure of the general population to PBBs. However, in the few instances where measurements were made, trace amounts of PBBs were identified. At present, this exposure does not give rise to concern, but further build-up should be avoided. Human data from the Michigan episode suggest that exposures in Michigan

were several order of magnitude higher than the exposure of the general population. No definitive health effects that could be correlated with PBB exposure in the Michigan population have been identified, though the follow-up period has not been long enough for the development of cancer. Since PBB levels in adipose tissue and serum remain high in the Michigan population, their internal exposure continues. In contrast, toxicity was observed in cattle in Michigan. This discrepancy is explained by differences in the extent of the exposure of the cattle.

Occupational exposure has only been examined in two plants in the USA. It appears that chloracne-like lesions may develop in workers producing PBB, and hypothyroidism in workers exposed to DeBB. No studies have been conducted on workers incorporating deca- or octa-/nona-bromobiphenyl into commercial products.

PBBs are extremely persistent in living organisms and have been shown to produce chronic toxicity and cancer in animals. Although the acute toxicity was low, cancer was induced at a dose of 0.5 mg/kg body weight per day and the no-observed-effect level was 0.15 mg/kg body weight per day. A number of chronic toxic effects have been observed in experimental animals at doses of around 1 mg/kg body weight per day following long-term exposure.

1.3 Recommendations

1.3.1 General

The Task Group is of the opinion that human beings and the environment should not be exposed to PBBs in view of their high persistence and bioaccumulation and potential adverse effects at very low levels after long-term exposure. Therefore, PBBs should no longer be used commercially.

Because of the limited toxicity data on DeBB and OcBB, their extreme persistence and their potential break-down in the environment, and the more toxic persistent compounds formed through combustion, they should not be used commercially, unless their safety has been demonstrated.

It is known that observations on the Michigan cohort are still continuing. Publication of these data is required.

1.3.2 Future research

Future human and environmental PBB monitoring, including workplace monitoring in the manufacture and user industries, should be expanded, should be congener specific, and should include OcBB/NoBB and DeBB. These compounds should be included in monitoring programmes in progress for other halogenated compounds. The time trends and geographical distribution of PBB levels in the environment should continue to be monitored. Release of PBBs into the environment from waste disposal sites should be surveyed.

Thermolysis experiments simulating conditions of accidental fires and municipal incineration should be conducted. Additional research should be continued on the mechanisms of toxicity and carcinogenicity of PBBs and related compounds. PBBs may serve as model compounds for such mechanistic research. Purified congeners should be used in these studies.

The effects of PBBs on reproduction are not well elucidated. Therefore, well-designed, long-term, reproductive studies at low doses, using a sensitive species, should be performed.

There is also a need for more information on the bioavailability and toxicokinetics of OcBB/NoBB, DeBB, and selected congeners.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

2.1.1 Primary constituents

The term "polybrominated biphenyls" or "polybromobiphenyls" (PBBs) refers to a group of halogenated hydrocarbons, formed by substituting hydrogen by bromine in biphenyl (Fig. 1).

Molecular formula $C_{12}H_{(10-x-y)}Br_{x+y}$
(x and y = 1 to 5)

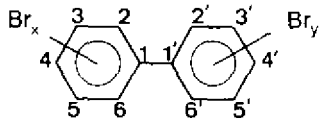


Fig. 1. General chemical structure of PBB congeners.

Molecular (empirical) formulae for PBB components of different degrees of substitution and their relative molecular masses are given in Table 1.

Theoretically, there can be 209 different forms (congeners) of a brominated biphenyl, depending on the number and position of the bromine (see Table 2).

At present, 101 individual PBB congeners are listed in the Chemical Abstracts Service (CAS) registry. Because bromobiphenyls are produced commercially by the bromination of biphenyl, the existence of any of the 209 congeners is possible in any commercial mixture (Aust et al., 1983). Some PBBs exist primarily as metabolites or accumulation or degradation products of the original mixture. With increasing advance in analysis techniques, the number of actually identified PBB compounds is growing.

Table 1. PBBs: molecular formula and relative molecular mass

PBB	Formula	Relative molecular mass
Monobromobiphenyl	$C_{12}H_9Br$	232.9
Dibromobiphenyl	$C_{12}H_8Br_2$	311.8
Tribromobiphenyl	$C_{12}H_7Br_3$	390.7
Tetrabromobiphenyl	$C_{12}H_6Br_4$	469.6
Pentabromobiphenyl	$C_{12}H_5Br_5$	548.5
Hexabromobiphenyl	$C_{12}H_4Br_6$	627.4
Heptabromobiphenyl	$C_{12}H_3Br_7$	706.3
Octabromobiphenyl	$C_{12}H_2Br_8$	785.2
Nonabromobiphenyl	$C_{12}HBr_9$	864.1
Decabromobiphenyl	$C_{12}Br_{10}$	943.0

Table 2. Multiplicity of PBB isomers and congeners[a]

Number of Br Substituent	1	2	3	4	5	6	7	8	9	10
Number of Isomers	3	12	24	42	46	42	24	12	3	1

[a] Modified from: Safe (1984).

The synthesis of pure congeners for use as standards is a prerequisite for advances in chemical analysis, as well as research into the toxicological and biological effects of PBBs. Some routes for the synthesis of PBB congeners have been described by Sundström et al. (1976b), Robertson et al. (1980, 1982a, 1984a), Höfler et al. (1988), and Kubiczak et al. (1989).

Table 3 gives a list of all 209 possible congeners and their CAS numbers, if already designated. The CAS names are designated as follows:

1,1′-Biphenyl, ... bromo-
e.g., 1,1′-Biphenyl, 2,2′,4,4′,5,5′-hexabromo- or
2,2′,4,4′,5,5′-hexabromo-1,1′-biphenyl (BB-153).

2.1.2 Technical products

2.1.2.1 Major trade names

The PBBs produced for commercial use include mixtures mainly containing hexa-, octa-/nona-, and decabromobiphenyls. Data on past and present trade names and manufacturers are summarized in Table 4 (for further details see section 3.2.1).

2.1.2.2 Composition of the technical products

Commercial PBB products are mixtures of various brominated biphenyls. Several structural isomers of each of these brominated compounds are possible and may be present in the product. All mixtures are relatively highly brominated, with bromine contents ranging from about 76% for hexabromobiphenyls to 81-85% for octa- to decabromobiphenyl mixtures (Brinkman & de Kok, 1980).

Data on the composition of PBB mixtures are given in Table 5. As shown in Table 5, the analytical results concerning the various products are rather divergent. It indicates that the exact composition of the mixtures varies between batches, and also within each batch according to the sampling and analytical method. It can be seen that samples of "octabromobiphenyl" often contained a larger proportion of nona- than of octa-substituted PBBs. In this monograph, these compounds are also referred to as "octa/nona" bromobiphenyls.

Information on the isomeric composition of the octa- to deca-mixtures is scarce. In an analysis of Bromkal 80, three isomers of octabromobiphenyl were found to be present at 14, 16, and 42% (Norström et al., 1976). A comparison of the isomeric composition of an "octabromobiphenyl"-mixture with the FireMaster®-mixture has been given by Moore & Aust (1978). De Kok et al. (1977) analysed various "octabromobiphenyl"-mixtures and Bromkal 80-9D and discussed the structures of isomers. Furthermore, two isomeric octa- and three hexa-bromobiphenyls of a commercial decabromobiphenyl mixture (RFR) have been reported (de Kok et al., 1977).

Table 3. Systematic numbering of PBB compounds and their CAS numbers

BB-No.[a]	Structure	CAS No.	BB-No.[a]	Structure	CAS No.
Monobromobiphenyls		(26264-10-8)	17	2,2′,4	
			18	2,2′,5	59080-34-1
1	2	2052-07-7	19	2,2′,6	
2	3	2113-57-7	20	2,3,3′	
3	4	92-66-0	21	2,3,4	
			22	2,3,4′	
Dibromobiphenyls		(27479-65-8)	23	2,3,5	
			24	2,3,6	
4	2,2′	13029-09-9	25	2,3′,4	
5	2,3	115245-06-2	26	2,3′,5	59080-35-2
6	2,3′	49602-90-6	27	2,3′,6	
7	2,4	53592-10-2	28	2,4,4′	6430-90-6
8	2,4	49602-91-7	29	2,4,5	115245-07-3
9	2,5	57422-77-2	30	2,4,6	59080-33-0
10	2,6	59080-32-9	31	2,4′,5	59080-36-3
11	3,3′	16400-51-4	32	2,4′,6	64258-03-3
12	3,4	60108-72-7	33	2′,3,4	
13	3,4′	57186-90-0	34	2′,3,5	
14	3,5	16372-96-6	35	3,3′,4	
15	4,4′	92-86-4	36	3,3′,5	
			37	3,4,4′	6683-35-8
Tribromobiphenyls		(51202-79-0)	38	3,4,5	115245-08-4
			39	3,4′,5	72416-87-6
16	2,2′,3				

Table 3 (contd).

Tetrabromobiphenyls		40088-45-7
40	2,2',3,3'	
41	2,2',3,4	
43	2,2',3,5	
44	2,2',3,5'	
45	2,2',3,6	
46	2,2',3,6'	
47	2,2',4,4'	66115-57-9
48	2,2',4,5	
49	2,2',4,5'	60044-24-8
50	2,2',4,6	
51	2,2',4,6'	97038-95-4
52	2,2',5,5'	59080-37-4
53	2,2',5,6'	60044-25-9
54	2,2',6,6'	97038-96-5
55	2,3,3',4	97038-99-8
56	2,3,3',4'	
57	2,3,3',5	
58	2,3,3',5'	
59	2,3,3',6	
60	2,3,4,4'	
61	2,3,4,5	115245-09-5
62	2,3,4,6	115245-10-8
63	2,3,4',5	
64	2,3,4',6	
65	2,3,5,6	
66	2,3',4,4'	84303-45-7
67	2,3',4,5	
68	2,3',4,5'	
69	2,3',4,6	
70	2,3',4',5	59080-38-5
71	2,3',4',6	
72	2,3',5,5'	
73	2,3',5',6	
74	2,4,4',5	
75	2,4,4',6	64258-02-2
76	2',3,4,5	
77	3,3',4,4'	77102-82-0
78	3,3',4,5	
79	3,3',4,5'	97038-98-7
80	3,3',5,5'	16400-50-3
81	3,4,4',5	59589-92-3
Pentabromobiphenyls		(56307-79-0)
82	2,2',3,3',4	
83	2,2',3,3',5	
84	2,2',3,3',6	
85	2,2',3,4,4'	
86	2,2',3,4,5	
87	2,2',3,4,5'	

Table 3 (contd).

BB-No.[a]	Structure	CAS No.	BB-No.[a]	Structure	CAS No.
88	2,2',3,4,6	77910-04-4	111	2,3,3',5,5'	
89	2,2',3,4,6'		112	2,3,3',5,6	
90	2,2',3,4',5		113	2,3,3',5',6	
91	2,2',3,4',6		114	2,3,4,4',5	96551-70-1
92	2,2',3,5,5'		115	2,3,4,4',6	
93	2,2',3,5,6		116	2,3,4,5,6	38421-62-4
94	2,2',3,5,6'		117	2,3,4',5,6	
95	2,2',3,5',6	88700-05-4	118	2,3',4,4',5	67888-97-5
96	2,2',3,6,6'		119	2,3',4,4',6	86029-64-3
97	2,2',3',4,5		120	2,3',4,5,5'	80407-70-1
98	2,2',3',4,6		121	2,3',4,5',6	
99	2,2',4,4',5	81397-99-1	122	2',3,3',4,5	
100	2,2',4,4',6	97038-97-6	123	2',3,4,4',5	74114-77-5
101	2,2',4,5,5'	67888-96-4	124	2',3,4,5,5'	
102	2,2',4,5,6'	80274-92-6	125	2',3,4,5,6'	
103	2,2',4,5',6	59080-39-6	126	3,3',4,4',5	84303-46-8
104	2,2',4,6,6'	97063-75-7	127	3,3',4,5,5'	81902-33-2
105	2,3,3',4,4'				
106	2,3,3',4,5		Hexabromobiphenyls		(36355-01-8)
107	2,3,3',4',5				
108	2,3,3',4,5'		128	2,2',3,3',4,4'	82865-89-2
109	2,3,3',4,6		129	2,2',3,3',4,5	
110	2,3,3',4',6		130	2,2',3,3',4,5'	82865-90-5

Table 3 (contd).

131	2,2',3,3',4,6	
132	2,2',3,3',4,6'	119264-50-5
133	2,2',3,3',5,5'	55066-76-7
134	2,2',3,3',5,6	
135	2,2',3,3',5,6'	119264-51-6
136	2,2',3,3',6,6'	
137	2,2',3,4,4',5	81381-52-4
138	2,2',3,4,4',5'	67888-98-6
139	2,2'3,4,4',6	
140	2,2',3,4,4',6	
141	2,2',3,4,5,5'	120991-47-1
142	2,2',3,4,5,6	
143	2,2',3,4,5,6'	
144	2,2',3,4,5',6	119264-52-7
145	2,2',3,4,6,6'	
146	2,2',3,4',5,5'	
147	2,2',3,4',5,6	
148	2,2',3,4',5,6'	
149	2,2',3,4',5',6	69278-59-7
150	2,2',3,4',6,6'	93261-83-7
151	2,2',3,5,5',6	119264-53-8
152	2,2',3,5,6,6'	
153	2,2',4,4',5,5'	59080-40-9
154	2,2',4,4',5,6'	36402-15-0
155	2,2',4,4',6,6'	59261-08-4
156	2,3,3',4,4',5	77607-09-1
157	2,3,3',4,4',5'	84303-47-9
158	2,3,3',4,4',6	
159	2,3,3',4,5,5'	120991-48-2
160	2,3,3',4,5,6	
161	2,3,3',4,5',6	
162	2,3,3',4',5,5'	
163	2,3,3',4',5,6	
164	2,3,3',4',5',6	82865-91-6
165	2,3,3',5,5',6	
166	2,3,4,4',5,6	
167	2,3',4,4',5,5'	67888-99-7
168	2,3',4,4',5',6	84303-48-0
169	3,3',4,4',5,5'	60044-26-0
	Heptabromobiphenyl	(35194-78-6)
170	2,2',3,3',4,4',5	69278-60-0
171	2,2',3,3',4,4',6	
172	2,2',3,3',4,5,5'	82865-92-7
173	2,2',3,3',4,5,6	
174	2,2',3,3',4,5,6'	88700-04-3
175	2,2',3,3',4,5',6	

Table 3 (contd).

BB-No.[a]	Structure	CAS No.	BB-No.[a]	Structure	CAS No.
176	2,2',3,3',4,6,6'		195	2,2',3,3',4,4',5,6	
177	2,2',3,3',4,5,6'		196	2,2',3,3',4,4',5',6	
178	2,2',3,3',5,5',6	119264-54-9	197	2,2',3,3',4,4',6,6'	119264-59-4
179	2,2',3,3',5,6,6'		198	2,2',3,3',4,5,5',6	
180	2,2',3,4,4',5,5'	67733-52-2	199	2,2',3,3',4,5,6,6'	
181	2,2',3,4,4',5,6		200	2,2',3,3'4,5',6,6'	119264-60-7
182	2,2',3,4,4',5,6'	119264-55-0	201	2,2',3,3',4',5,5',6	69887-11-2
183	2,2',3,4,4',5',6		202	2,2',3,3',5,5',6,6'	59080-41-0
184	2,2',3,4,4',6,6'	119264-56-1	203	2,2',3,4,4',5,5',6	
185	2,2',3,4,5,5',6		204	2,2',3,4,4',5,6,6'	119264-61-8
186	2,2',3,4,5,6,6'	119264-57-2	205	2,3,3',4,4',5,5',6	
187	2,2',3,4',5,5',6	84303-49-1			
188	2,3',3,4',5,6,6'	119264-58-3	Nonabromobiphenyls		(27753-52-2)
189	2,3,3',4,4',5,5'	88700-06-5			
190	2,3,3',4,4',5,6	79682-25-0	206	2,2',3,3',4,4',5,5',6	69278-62-2
191	2,3,3',4,4',5',6		207	2,2',3,3',4,4',5,6,6'	119264-62-9
192	2,3,3',4,5,5',6		208	2,2',3,3',4,5,5',6,6'	119264-63-0
193	2,3,3',4',5,5',6				
			Decabromobiphenyl		
Octabromobiphenyls		(27858-07-7)			
			209	2,2',3,3',4,4',5,5',6,6'	13654-09-6
194	2,2',3,3',4,4',5,5'	67889-00-3			

[a] The Nos 1-209 correspond to those used by Ballschmiter & Zell (1980) for PCBs (January 1990).

Table 4. Major trade names and manufacturers of technical-grade PBBs and commercial PBB mixtures[a]

PBB mixture	Manufacturer	CAS No.
Hexa-PBBs		
FireMaster® BP-6	Michigan Chemical Corp. (St. Louis, Mich.)	59536-65-1
FireMaster® FF-1[b]	Michigan Chemical Corp. (St. Louis, Mich.)	67774-32-7
Octa/nona-PBBs		
Bromkal 80-9D	Chemische Fabrik Kalk (Cologne, Germany)	61288-13-9
Technical octabromobiphenyl	White Chemical Corp. (Bayonne, New Jersey)	
Octabromobiphenyl FR 250 13A	Dow Chemical Co. (Midland, Mich.)	
Deca-PBB		
Adine 0102	Ugine Kuhlmann now Atochem (Paris, France)	13654-09-6
Berkflam B 10	Berk (London, United Kingdom)	
Flammex B-10	Berk (London, United Kingdom)	
Technical decabromobiphenyl	White Chemical Corp. (Bayonne, New Jersey)	
HFO 101	Hexcel (Basildon, United Kingdom)	

[a] Adapted from: Brinkman & de Kok (1980).

[b] A pulverized form of FireMaster BP-6 containing 2% calcium polysilicate to prevent caking. It was produced in limited quantities as a development-product in 1971 and 1972.

Most research has been conducted with the hexabromobiphenyl mixture FireMaster®, which accounts for most of the manufactured products and most of the environmental contamination (Di Carlo et al., 1978). The main constituent of FireMaster® is 2,2′,4,4′,5,5′-hexabromobiphenyl. Its identification was reported by Andersson et al. (1975), Jacobs et al. (1976), and Sundström et al. (1976a). The second major component is heptabromobiphenyl containing bromine at positions 2,2′,3,4,4′,5,5′ (Hass et al., 1978; Moore et al., 1978c). Accordingly, these two congeners account for about 75% of the mixture (e.g., Dannan et al., 1982d). Data on the isomeric composition of FireMaster® found in the literature are given in Table 6. The ranges of relative abundances of some FireMaster® constituents are compiled in Table 7. Altogether at least sixty compounds have been detected in FireMaster® (Orti et al., 1983). About twelve of them are major PBB-components (Aust et al., 1981), the others belong to the minor components (< 1%).

Table 5. Survey of literature on the composition of PBB mixtures[a]

PBB mixture (manufacturer)	Weight of bromine (%)	Weight of different homologus groups							Reference
		Br_{10}	Br_9	Br_8	Br_7	Br_6	Br_5	Br_4	
"Hexabromobiphenyl"									
FM BP-6 (Michigan Chemical)	75				13.8	62.8	10.6	2	de Kok et al. (1977)[c]
" [Lot RP-158 (1971)]					12.5	72.5	9	4	Willett & Irving (1976)
" [Lot 6244A (1974)]					13	77.5	5	4.5	Willett & Irving (1976)
"						90	10		Norström et al. (1976)
"				1	18	73	8		de Kok et al. (1977)
"					33	63	4		Hass et al. (1978)
"					7.7	74.5	5.6		Robertson et al. (1984b)
"					24.5	79	6		Krüger (1988)
2,2',4,4',6,6' (RFR)					12	84	1		de Kok et al. (1977)
2,2',4,4',6,6' (Aldrich)				2	24	70	4		de Kok et al. (1977)
"Hexabromobiphenyl" (RFR)					25	67	4		
					(12-25)	(60-80)	(1-11)	(2-5)[b]	de Kok et al. (1977)
Octanonabromobiphenyl									
Bromkal 80-9D (Kalk)	81-82.5	9	65	25	1				de Kok et al. (1977)

Table 5 (contd).

Octanonabromobiphenyl (contd)							
Bromkal 80				72	27	1	Norström et al. (1976)
XN-1902 (Dow Chemical)[c]	82	6	47	45	2		Norris et al. (1973)
XN-1902 (Dow Chemical)[c]		2	34	57	7		de Kok et al. (1977)
Lot 102-7-72 (Dow Chemical)[c]		6	60	33	1		Waritz et al. (1977)
"Octabromobiphenyl" (RFR)		4	54	38	2		de Kok et al. (1977)
2,2',3,3',5,5',6,6' (RFR)		1	28	46	23	2	de Kok et al. (1977)
FR 250 13A (Dow Chemical)		8	49	31	1		Krüger (1988)
Decabromobiphenyl							
HFO 101 (Hexcel)	84	96	2				de Kok et al. (1977)
Adine 0102 (Ugine Kuhlmann)	83-85	96	4				de Kok et al. (1977)
Adine 0102 (Ugine Kuhlmann)		96.8	2.9	0.3			Millischer et al. (1979)
"Decabromobiphenyl" (RFR)		71	11	7	4	4	de Kok et al. (1977)
"DBB"; Flammex B 10 (Berk)[c]		96.8	2.9	0.3			Di Carlo et al. (1978)

[a] Adapted from: Brinkman & de Kok (1980).
[b] Range of above readings with the exception of that of Norström et al. (1976), which differs greatly from the others.
[c] According to de Kok et al. (1977), these have never been marked.

Table 6. Identified PBB congeners in FireMaster®

BB No.[a]	Structure	% Composition of FM BP-6	FF-1	References
Dibromobiphenyls				
4	2,2'-	0.02		Moore et al. (1979a)
Tribromobiphenyls				
18	2,2'5-	0.050		Robertson et al. (1984b)
26	2,2',5-	0.024		
31	2,4',5-	0.015		
37	3,4,4'-	0.021		
Tetrabromobiphenyls				
49	2,2',4,5'-	0.025		
52	2,2',5,5'-	0.052		
66	2,3',4,4'-	0.028		
70	2,3',4',5-	0.017		
77[b]	3,3',4,4'-		< 0.08	Orti et al. (1983)
		0.159		Robertson et al. (1984b)
Pentabromobiphenyls				
95	2,2',3,5',6-	0.02		Orti et al. (1983)
99	2,2'4,4',5-		< 0.08	
101	2,2',4,5,5'-	2.69		Robertson et al. (1984b)
		4.5	3.7	Aust et al. (1981)
			1.54	Orti et al. (1983)
		2.6		Krüger (1988)
118	2,3',4,4',5-	2.94		Robertson et al. (1984b)
			0.7	Aust et al. (1981)
		3.2		Krüger (1988)
			0.8	Orti et al. (1983)
126[b]	3,3',4,4',5-		< 0.01	
		0.079		Robertson et al. (1984b)
Hexabromobiphenyls				
132	2,2',3,3',4,6'-	1		Krüger (1988)
138	2,2',3,4,4',5'-	12.3		Robertson et al. (1984b)
		12	8.6	Aust et al. (1981)
			5.23	Orti et al. (1983)
		10.6		Krüger (1988)
149	2,2',3,4',5',6-	2.24		Robertson et al. (1984b)
		1.4	1.3	Aust et al. (1981)
			0.78	Orti et al. (1983)
153	2,2'4,4',5,5'-	53.9		Robertson et al. (1984b)
		47.8	47.1	Aust et al. (1981)
		55.2		Orti et al. (1983)
		58.5		Krüger (1988)
155	2,2',4,4',6,6'-	0.5		

Table 6 (contd).

BB No.[a]	Structure	% Composition of FM BP-6	% Composition of FF-1	References
156	2,3,3',4,4',5-	0.980		Robertson et al. (1984b)
		5.0		Aust et al. (1981)
			0.37	Orti et al. (1983)
		1.0		Krüger (1988)
157	2,3,3',4,4',5'-		0.05	Orti et al. (1983)
		0.526		Robertson et al. (1984b)
		0.5		Krüger (1988)
167	2,3',4,4',5,5'-	5.5	3.3	Aust et al. (1981)
			3.37	Orti et al. (1983)
		< 0.3		
		7.95		Robertson et al. (1984b)
		5.5		Krüger (1988)
169[b]	3,3',4,4',5,5'-	0.294		Robertson et al. (1984b)
Heptabromobiphenyls				
170	2,2',3,3',4,4',5-	0.256		
		1.1	1.5	Aust et al. (1981)
			1.66	Orti et al. (1983)
		2.4		Krüger (1988)
180	2,2',3,4,4',5,5'-	6.97		Robertson et al. (1984b)
			24.7	Aust et al. (1981)
			23.5	Orti et al. (1983)
		20.8		Krüger (1988)
172	2,2',3,3',4,5,5'-		< 0.30	Orti et al. (1983)
174	2,2',3,3',4,5,6'-		0.24	
178	2,2',3,3',5,5',6-	0.3		Krüger (1988)
187	2,2',3,4',5,5',6-	0.392		Robertson et al. (1984b)
			1.0	Krüger (1988)
189	2,3,3',4,4',5,5'-		0.51	Orti et al. (1983)
Octabromobiphenyls				
194	2,2',3,3',4,4',5,5'-	0.9	2.4	Aust et al. (1981)
			1.65	Orti et al. (1983)
possible structures for two minor Br_8 peaks:				
196	2,2',3,3',4,4',5,6'-			Moore et al. (1980);
201	2,2',3,3',4,5,5',6'-			Orti et al. (1983)
203	2,2',3,4,4',5,5'6-			

[a] From: Ballschmiter & Zell (1980).

[b] These coplanar congeners are the most toxic congeners identified in FireMaster BP-6 (Robertson et al., 1984b).

Table 7. Range of relative abundance of some PBB constituents of Firemaster® FF-1 and BP-6[a]

Structure	No.[b]	BB No.[c]	Abundance (%)
2,2',4',5,5'-	1	101	1.5-4.5
2,3',4,4',5,-	2	118	0.7-4.2
2,2',3,4',5',6-	3	149	0.8-2.2
2,2',4,4',5,5'-	4	153	47.1-59
2,2',3,4,4',5'-	5	138	5.2-12.3
2,3',4,4',5,5'-	6	167	3.3-8.0
2,3,3',4,4',5-	7	168	0.4-5.0
2,2',3,4,4',5,5'-	8	180	7.0-24.7
2,2',3,3',4,4',5-	9	170	0.3-2.4
2,2',3,3',4,4',5,5'-	12	194	0.9-2.4

[a] For references, see Table 6.
[b] Congener designation made on the basis of the gas chromatographic elution sequence of the FireMaster® mixture.
[c] Congener designation according to Ballschmiter & Zall (1980).

Variations are due to differences in batches and analytical techniques. In many cases, the differing electron capture responses of the various congeners within the mixture were not taken into account. Thus, values in Table 7 only give an approximate range of composition and it is not possible to provide a precise composition for the material that was introduced into the Michigan environment (Fries, 1985b).

Both formulations of FireMaster® mixture, BP-6 and FF-1 have a similar isomeric composition. However, FireMaster BP-6 contains roughly 10% more of the relatively minor congeners (Dannan et al., 1982b).

As can be concluded from the composition of the commercial mixtures (Table 5), the major source of impurity that occurs in PBBs results from the spread in the degree of bromination. For example, FireMaster® BP-6 has been marketed as a hexabrominated biphenyl, but more than one quarter of the product consists of lower brominated biphenyls because of incomplete bromination reaction (Neufeld et al., 1977).

However, a producer of decabromobiphenyl has reported that their material has a degree of purity of more than 98%, the

remaining 2% being nonabromobiphenyl. It is manufactured by a special proprietary process rendering no brominated by-products (Neufeld et al., 1977).

It is noteworthy that mixed polybromochlorobiphenyls (PCBs) have been observed as minor contaminants in FireMaster®. For example, monochloropentabromobiphenyl (CAS No. 88703-30-4) was added to the list of detected impurities (Domino & Domino, 1980; Tondeur et al., 1984). Such compounds probably result from contamination of commercial bromine by chlorine (Domino & Domino, 1980).

Polybrominated naphthalenes (PBNs) (Fig. 2) have been identified as minor components in commercial PBB mixtures (see Table 8). The isomeric composition of PBNs in FireMaster® is unknown, but studies on this subject have been started (Robertson et al., 1984a). It is assumed that naphthalene, present as an impurity in industrial-grade biphenyl, is brominated during the production of FireMaster®, and that the presence of numerous isomers and congeners of PBNs in FireMaster® is possible (Robertson et al., 1984b).

Table 8. Occurrence of polybrominated naphthalenes (PBNs) in FireMaster®-mixtures

PBN	CAS-Registry Number	FireMaster® mixture	Concentration	Reference
Tetrabromo-naphthalene	88703-31-5	BP-6 or FF-1	no information available	Tondeur et al. (1984)
Pentabromo-naphthalene	56448-55-6	BP-6 or FF-1	no information available	Tondeur et al. (1984)
		FF-1	1 mg/kg	O'Keefe (1979)
		BP-6	150 mg/kg	Hass et al. (1978)
Hexabromo-naphthalene	56480-06-9	BP-6 or FF-1	no information available	Tondeur et al. (1984)
		FF-1	25 mg/kg	O'Keefe (1979)
		BP-6	70 mg/kg	Hass et al. (1978)

It has been shown that synthesis of hexa-bromonaphthalenes by direct bromination results in a mixture of two isomers

(Birnbaum et al., 1983; Birnbaum & McKinney, 1985). The major isomer, 1,2,3,4,6,7-HBN, can be metabolized and excreted, while the minor isomer, 2,3,4,5,6,7-HBN, is extremely persistent (Birnbaum & McKinney, 1985).

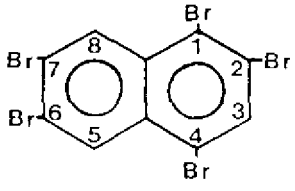


Fig. 2. Structure of a representative polybrominated naphthalene (From: Damstra et al., 1982).

Polybrominated benzenes and a possible methylbrominated furan have also been reported to occur in FireMaster® (Brinkman & de Kok, 1980).

Approximately 20 compounds, other than PBBs, were either tentatively identified in FireMaster® or partially characterized by Hass et al. (1978).

Polybromodibenzo-*p*-dioxins and polybromodibenzofurans were searched for, because of their extreme toxicity and because chlorinated dibenzofurans had been detected in commercial PCBs (Nagayama et al., 1976). If present, their concentrations did not exceed 0.5 mg/kg (Hass et al., 1978, O'Keefe, 1979). Polybromodibenzodioxins and polybromodibenzofurans were determined in a sample of Adine 0102 (decabromobiphenyl). Monobromobenzodifurans were present at a level of 1 mg/kg (1 ppm), otherwise all other polybromodibenzodioxins and polybromodibenzofurans were present only at less than 0.01 mg/kg (Atochem, 1990).

So far, phenoxyphenols and hydroxybiphenyls, which might be intermediates in the formation of brominated dibenzo-*p*-dioxins and brominated dibenzofurans, respectively, have not been identified (O'Keefe, 1979).

Some impurities in PBBs result from impurities in the original biphenyl material. According to two major manufacturers, their biphenyl grade used for bromination contained less than 5 mg/kg

and 5000 mg/kg, respectively, of impurities, e.g., toluene, naphthalene, methylene biphenyl (fluorene), and various methyl biphenyls (Neufeld et al., 1977).

2.2 Physical and chemical properties

In general, PBBs show an unusual chemical stability and resistance to breakdown by acids, bases, heat, and reducing and oxidizing agents (Safe, 1984).

PBBs can be compared chemically to the PCBs. Bromine, however, is a better leaving group in chemical reactions than chlorine. Unlike PCBs, the reactivity of PBBs has not been well studied and documented in the literature (Pomerantz et al., 1978). Like PCBs their chemical stability is dependent, in part, on the degree of bromination and the specific substitution patterns (Safe, 1984). All highly brominated PBB-mixtures are known to degrade rather rapidly with UV irradiation (Brinkman & de Kok, 1980).

The technical mixtures typically are white, off-white, or beige powdered solids. Some physical data on commercial PBB mixtures are given in Table 9. It can be seen that there are discrepancies in the values for the solubility of commercial PBBs in water (given in Table 9) as well as those calculated for various PBB congeners (Table 10). The source and quality of the water is important. Determinations of water solubility of these very hydrophobic compounds are also difficult to perform. Adsorption effects on particles and glass surfaces may influence the results. PBBs were found to be 200 times more soluble in landfill leachate than in distilled water (Griffin & Chou, 1981a). In general, it can be said that PBBs are only slightly soluble in water and that the solubility decreases with increasing bromination.

For details of thermal decomposition, see section 4.3.2.

2.2.1 Physical and chemical properties of individual congeners

PBBs show a wide range of volatility (Farrell, 1980). Partition coefficients between water/*n*-hexane and water/1-octanol, as well as aqueous solubilities for some individual PBB congeners are given in Table 10. Correlations for predicting aqueous solubility and partition coefficients for PBBs based on molecular structure have been proposed (Patil, 1991). The solubility of PBBs in *n*-hexane decreases rapidly with increasing bromine content (de Kok et al., 1977).

Table 9. Some physical data on commercial PBB mixtures[a]

	"Hexabromobiphenyl" (Firemaster BP-6)	"Octabromobiphenyl" (Dow XN 1902)	"Nonabromobiphenyl" (Bromkal 80-9D)[c]	"Decabromobiphenyl" (Adine 0102)[d]
Melting point (°C)	72	200-250	220-290 360-380 385	380-386[b]
Lambda max (nm)	219[e]	225[e]	224[e]	227[e]
Density (g/cm^3) at room temperature	2.6	-	3.2	3.2
Solubility in water (μg/litre) at 25 °C	11[f] 30[f] (pure 2,2', 4,4', 5,5'-) 610[f] 0.06[g] (deionized) 0.32[g] (distilled)	20-30	insoluble	< 30
Solubility in organic solvents (g/kg solvent) at 28 °C				
petroleum ether	20	18	insoluble in common organic solvents	
acetone	60			10[e]
carbon tetrachloride	300			
chloroform	400			
benzene	750	81		
toluene	970			
dioxane	1150			
copra oil (37 °C)				0.8

Table 9 (contd).

Vapour pressure (Pa)				
25 °C	0.000007[h]			< 0.000006
90 °C	0.01			(temperature not given)
140 °C	1			
220 °C	100			
Volatility (% weight loss)		< 1% at 250 °C < 10% at 330 °C < 50% at 350 °C	1-2% at 300 °C	< 5% at 341 °C < 10% at 363 °C < 25% at 388 °C
log P_{ow}	< 7 (calculated)[d]			8.6 (calculated)
Decomposition temperature	300-400 °C	435 °C	435 °C	395 °C > 400° C

[a] Mumma & Wallace 1975).
[b] Norris et al. (1973).
[c] Kerscher (1979); CFK (1982).
[d] Atochem (1990).
[e] Brinkman & de Kok (1980).
[f] Filonow et al. (1976).
[g] Griffin & Chou (1981a,b).
[h] Jacobs et al. (1976).

Table 10. Partition coefficients between water and *n*-hexane (K_{HW}) and 1-octanol (K_{OW}) and aqueous solubilities (S_w) for some individual PBB congeners (all aqueous solubility measurements were carried out by the generator method)

	Log K_{HW}	Log K_{OW}	S_w mol per litre x 10^{-9} (25 °C)	S_w µg/litre[d] (25 °C)
2-bromobiphenyl		4.59[a]		
3-bromobiphenyl		4.85[a]		
4-bromobiphenyl		4.96[a]	2800	650
3,5-dibromobiphenyl		5.78[c]		
4,4′-dibromobiphneyl	5.61	5.72	18.4	5.7
2,4,6-tribromobiphenyl	6.21	6.03	41.1	16
3,4′,5-tribromobiphenyl		6.42[c]		
2,2′,5,5′,tetrabromobiphenyl	6.72	6.50	8.6	4
3,3′,5,5′-tetrabromobiphenyl		7.42[c]		
2,2′,4,5,5′-pentabromobiphenyl		7.10[a]	0.8[b]	0.4
2,2′,4,4′,6,6′-hexabromobiphenyl	7.52	7.20	0.9	0.56
decabromobiphenyl		8.58[a]		

Values from Gobas et al. (1988) with the exception of:

[a] From: Doucette & Andren (1987).
[b] From: Doucette & Andren (1988).
[c] From: Sugiura et al. (1978).
[d] calculated.

Data on the melting points and UV absorption of individual PBB congeners are summarized in Table 11. The main band in these spectra is caused by $\pi \rightarrow \pi^*$ electron transitions, while the k band is generally attributed to the conjugated biphenyl system with the contribution of both biphenyl rings. With the k band, the introduction of bromine atoms in positions meta or para to the phenyl-phenyl bond induces a shift in k_{max} towards the visible region, as is illustrated by 3,3′,5,5′-tetra- and 3,3′,4,4′,5,5′-hexabromobiphenyl. On the other hand, ortho substitution, which causes a considerable hindrance for free rotation of the rings and, thus, a loss in coplanarity, effects a sharp decrease in the extinction coefficient of the k band (de Kok et al., 1977).

Table 11. Melting points and UV spectral data for some PBB congeners[a]
UV conditions: solutions in *n*-hexane; Beckman Acta CIII spectrometer

No.[c]	PBB-isomer	Melting point (°C)[d]	Main band		k band	
			λ maximum (nm)	Log ε ($l.mol^{-1}.cm^{-1}$)	λ maximum (nm)	Log ε ($l.mol^{-1}.cm^{-1}$)
	Biphenyl	71	201	4.66	246	4.26
1	2-	[e]	201	4.51	240	3.90
2	3-	[e]	205	4.60	248	4.21
3	4-	[e]	200	4.67	254	4.38
4	2,2'-	81	198	4.64	220-230	[e]
9	2,5-	[e]	203	4.49	226	4.38
15	4,4'-	164	201	4.64	261	4.43
20	2,4,6-	65-66	213	4.70	220-230	[e]
21	2,2',5-	78	200	4.66	235-245	[e]
26	2,3',5-	[e]	213	4.57	[e]	[e]
31	2,4',5-	78	205	4.60	245-255	[e]
49	2,2',4,5'-	84	207	4.66	235-245	[e]
52	2,2',5,5'-	143	204	4.67	235-240	[e]
80	3,3',5,5'-	188	220	4.76	255	4.18
114[b]	2,3,4,4',5-	128	222.6	(54.8)	258	[e]
137[b]	2,2',3,4,4',5-	124	223.1	(35.4)	[e]	[e]
141[b]	2,2',3,4,5,5'-	127	223.4	(191)	[e]	[e]
153	2,2',4,4',5,5'-	(159-160)[f]	216	4.66	[e]	[e]

Table 11 (contd).

No.[c]	PBB-isomer	Melting point (°C)[d]	Main band λ maximum (nm)	Main band Log ε (1.mol-^{1}.cm-^{1})	k band λ maximum (nm)	k band Log ε (1.mol-^{1}.cm-^{1})
156[b]	2,3,3',4,4',5-	178	224.9	(229)	259	[e]
159[b]	2,3,3',4,5,5'-	195	226.1	(61.4)	258	[e]
167	2,3',4,4',5,5'-	(165-166)[f]	[e]	[e]	[e]	[e]
169	3,3',4,4',5,5'-	248	227	4.76	272	4.34
180[b]	2,2',3,4,4',5,5'-	166 (165-166)[f]	224.1	(62.4)	[e]	[e]
189[b]	2,3,3',4,4',5,5'-	219	230.7	(102)	265	[e]
194[b]	2,2',3,3',4,4',5,5'-	235 (232-233)[f]	223.7	(51.6)	[e]	[e]
202	2,2',3,3',5,5',6,6'-	[e]	224	4.85	[e]	[e]
206[b]	2,2',3,3',4,4',5,5',6-	262 (263-264)[f,g]	225.2	(131)	[e]	[e]
	Nona-(unidentified)	[e]	225	5.18	[e]	[e]
	Deca-	378	227	5.11	[e]	[e]

[a] Adapted from: de Kok et al. (1977), with the exception of the congeners marked with [b].
[b] Congener data, including melting points are taken from Kubiczak et al. (1989). UV measurements: in *n*-heptane.
[c] No. according to Ballschmiter & Zell (1980).
[d] Melting points from Sundström et al. (1976b) but confirmed by de Kok et al. (1977), unless otherwise stated.
[e] No data available.
[f] From: Moore & Aust (1978).

Data on NMR spectra are given by Orti et al. (1983), Robertson et al. (1984b), and Kubiczak et al. (1989), and on mass spectrometry (MS) by Erickson et al. (1980), Roboz et al. (1980), Buser (1986), and Sovocool et al. (1987a,b). The "ortho" effect, observed for PBBs and PCBs having 2,2′-; 2,2′,6- or 2,2′,6,6′-halogens can be combined with GC retention index for isomer specific identifications by gas chromatography and mass spectrometry (GC/MS) (Sovocool et al., 1987a).

2.3 Conversion factors for PBB in air

1 ppm = 26.1 mg/m^3 for hexabromobiphenyl at 20 °C and 101.3 kPa.
1 mg/m^3 = 0.038 ppm.

2.4 Analytical methods

Analytical methods for the determination of PBBs, which have been reviewed by de Kok et al. (1977), Pomerantz et al. (1978), and Fries (1985b), were adapted from established methods for chlorinated hydrocarbon insecticides and PCBs (AOAC, 1975). The chronological development of analytical methods for the detection and quantification of PBB mixtures and congeners is summarized in Table 12. In the wake of the Michigan disaster, methods were described for the analysis of: contaminated feed, milk, and milk products (Fehringer, 1975a,b); animal blood plasma, faeces, milk, and bile (Willett et al., 1978) and liver and fat (Fawkes et al., 1982). The methods were developed using tissue from animals fed with PBBs of known composition. Needham and coworkers developed a method to determine PBBs in human blood serum (Burse et al., 1980; Needham et al., 1981) which was thoroughly tested in several laboratories, but, even here, only the main components of FireMaster® were determined. Similarly, the investigation by Eyster et al. (1983) into the levels of PBBs in fat, serum, faeces, milk, and placenta were not isomer specific. Thus, reported values may not reflect the hazard of the residue because, for example, some congeners are more toxic than the prominent 2,2′,4,4′,5,5′-HBB. Most samples of biological origin have congener distributions that differ from those of the original material (Fries, 1985b).

Concentrations of PBBs as low as 10 μg/kg in fatty foods (Fehringer, 1975a), 3 μg/kg in dry feeds (Fehringer, 1975b) and 1 μg/litre in blood serum (Needham et al., 1981) can be detected and quantified using routine methods. Coefficients of variation

Table 12. Analysis of commercial mixtures and individual PBB congeners: A chronological survey[a]

Sample	Solvent	Analytical method	Detection	Detection limit	Comment	Reference
FireMaster® BP-6	recrystallization from ethanol/isopropanol	GC	FID	no data given	identification of BB 153 and a HpBB as major components	Sundström et al. (1976a)
PBB congeners	no data given	GC	ECD	no data given	routes of synthesis, melting points, relative retention times, electron capture responses for some PBB congeners	Sundström et al. (1976b)
Commercial mixtures FR 250 13A (octabromobipheyl) FireMaster® BP-6 and PBB congeners	solubility of PBBs in *n*-hexane decreases rapidly with increasing bromine content; PBBs dissolved in warm CCl_4	HPLC, TLC, UV, GC ^{1}H- & ^{13}C-NMR	MS	no data given	survey of analysis for PBBs	de Kok et al. (1977)
Commercial sample of octabromobiphenyl	hexane	GC, ^{13}C-NMR, ^{1}H-NMR, IR	ECD	no data given	identification of BB 180 heptabromobiphenyl	Moore et al. (1978)
FireMaster® BP-6	methylene chloride; hexane	GC, NMR, HPLC	MS SIM	0.5 mg/kg	contains at least 13 different PBBs and bromonaphthalene (no bromodibenzofurans or bromodibenzo-*p*-dioxins found)	Hass et al. (1978)

Table 12 (contd).

FireMaster® FF-1 or BP-6 and octabromobiphenyl	hexane	GC, NMR	MS	no data given	purification and structural characterization of 6 further PBB congeners	Moore & Aust (1978)
FireMaster® FF-1	hexane	GC	ECD	0.03 ng	absolute and relative retention times of the 8 major constituents using tetrabromobiphenyl as an internal standard	Domino et al. (1980a)
FireMaster® FF-1	hexane	GC	MS	no data given	mass spectra of major PBBs in FireMaster®; mixed polybromo and chlorobiphenyls detected	Domino & Domino (1980)
FireMaster® BP-6		GC	ECD	no data given	comparison of packed and capillary columns; solves some problems with lower brominated biphenyls, but has no great advantages over packed columns for more highly substituted biphenyls	Farrel (1980)
FireMaster® BP-6	no data given	GC	PED	2.8 mg (cf 1.5 ng ECD)	comparison with ECD; not quite so sensitive, but is selective	Mulligan et al. (1980)

Table 12 (contd).

Sample	Solvent	Analytical method	Detection	Detection limit	Comment	Reference
Individual PBB congeners	toluene	GC	MS, SIM	< 1 ng	mono-deca PBB congeners	Erickson et al. (1980)
22 individual PBBs FireMaster® FF-1	hexane	GC (preceeded by HPLC)	ECD, micro-coulometric GC-detector MS	40 pg	retention times given for 23 congeners response increases with degree of bromination, increased detection temperature gives improved sensitivity	Sweetman & Boettner (1982)
FireMaster® FF-1	carbon tetrachloride; hexane	preparative HPLC and GC ^{1}H-NMR	FID, MS		polar and unpolar hexane fractions were also tested for hyperkeratotic activity	Needham et al. (1982)
FireMaster® BP-6	hexane	GC	NCI, SIM	0.6 ng	evaluation of halogen anion formation by polybrominated compounds in NCI-MS; SIM of bromine anions has greater specificity than ECD	Greaves et al. (1982)
FireMaster® BP-6	fractionation by preferential acetone solubilization, repeated crystallization, alumina adsorption column chromatography, reversed phase Lipidex-500	GC	ECD, MS	no data given	seven congeners were purified	Dannan et al. (1982d)

Table 12 (contd).

FireMaster® FF-1 lot FH 7042	see Needham et al. (1982)	preparative HPLC, GC, GC ^{1}H-NMR	FID, MS	at least 60 components observed; isolated/determined structure of 10 minor components of FireMaster (most are very polar, later eluting fractions)	Orti et al. (1983)
PBB (unspecified)	hexane	GC	helium plasma atomic emission spectrometric detection 230 pg	simultaneous monitoring of 4 atomic emission wave-lengths; PBB mentioned	Eckhoff et al. (1983)
FireMaster® BP-6	no data given	GC 1H-NMR	MS, ECD	identity of over 91% of PBB components in FireMaster using 22 individual PBB congeners as standards; identification of 7 additional PBBs including 3 very toxic coplanar PBBs	Robertson et al. (1984b)
FireMaster® BP-6	hexane	GC	PED, rapid scanning plasma emission	multi-element quantification	Zerezghi et al. (1984)
FireMaster® FF-1	hexane	GC	SIM, MS	determination of suspected toxic impurities	Tondeur et al. (1984)

Table 12 (contd).

Sample	Solvent	Analytical method	Detection	Detection limit	Comment	Reference
PBB photolysis mixture	hexane	GC	FID, ECD, MS		purification of PBB congener 2 using charcoal pretreatment and RPLC	Barnhart et al. (1984)
Benzenes, biphenyls dibenzo-dioxins, dibenzofurans, diphenylethers, benzofurans, phenols	hexane	GC	NCI-MS	0.1 pg	especially valuable for measuring trace levels in biological and environmental samples; must be two Br; structural information is partly lost	Buser (1986)
PBB congeners	no data given	GC	MS	no data given	use of '*ortho*' effect for PBB and isomer identification; accurate structure assignments without use of multiple GC determinations	Sovocool & Wilson (1982); Sovocool et al. (1987a)
Various PBB congeners	hexane	GC, HPLC	FID	no data given	relationship between recorded retention data from HPLC and GC and molecular surface area	Höfler et al. (1988)

Table 12 (contd).

Nine synthetic PBBs; FireMaster® FF-1 and BP-6	products purified by alumina/Florisil; recrystallization from methanol or methylene chloride	GC	MS	1 ng	synthesis of 2,3,4,5-substituted PBBs and characterization	Kubiczak et al. (1989)
Mono- and polybrominated biphenyls	no data given	^{1}H-NMR, ^{13}C-NMR	no data given	no data given		Anklam (1989)

[a] Abbreviations used:

ECD = Pulsed ^{63}Ni electron capture detector.
FID = Flame ionization detector.
GC = Gas chromatography.
GPC = Gel permeation chromatography.
HPLC = High pressure liquid chromatography.
IR = Infrared radiation.
MS = Mass spectrometry.
NAA = Neutron activation analysis.
NCI = Negative ion chemical ionization mass spectrometry.
NMR = Nuclear magnetic resonance.
PED = Microwave-induced plasma emission detector.
PPINICI = Pulsed positive ion-negative ion chemical ionization.
RPLC = Reverse-phase liquid chromatography.
SIM = Selected ion monitoring.
TLC = Thin layer chromatograpy.
Unitrex = Universal Trace Residue Extractor.
UV = Ultraviolet.

become large as concentrations approach the limits of sensitivity of the method; thus, values near the limit must be treated with caution (Fries, 1985b). PBBs adsorb to glass more tenaciously than other halogenated hydrocarbons, and are not easy to remove by the usual cleaning methods (Willett et al., 1978). This can lead to erroneous values, particularly when concentrations in samples are low and there is a carry over from samples of high concentration. This problem can be solved by using disposable glassware (Willett et al., 1978).

Recovery of PBBs using established methods is in the range of 80-90% (Fries, 1985b). The solvent system that is used for sample extraction can affect recovery. Poor recoveries were often found with hexane but the optimal solvent conditions depend on the source of the medium sample.

For extraction conditions see Table 13 (environmental samples), Table 14 (food/feed), Table 15 (biological tissues and fluids (a) serum/blood (b) adipose and other tissues).

In soil, Griffin & Chou (1981a) found that a polar organic solvent was important and obtained the best results with hexane/acetone (9:1).

For serum and blood, the standard extraction method given by Burse et al. (1980) has been used by most workers.

Extraction of PBBs from adipose and other tissues presents greater problems. PBBs are readily soluble in fat. They can therefore be extracted with the fat out of the tissue/sample but, afterwards, an intensive clean-up procedure for PBBs is necessary. Various methods, such as adsorption chromatography with Florisil, gel permeation chromatography, Florisil cartridges (Chiang et al., 1987), and Unitrex (Head & Burse, 1987) have been proposed.

The sample extraction and clean-up techniques for the determination of PBBs are similar to those used for PCBs (Krüger et al., 1988; Jansson et al., 1991). The lipids can be removed from the extract by gel permeation (Krüger, 1988) or by hydrolysis (Jansson et al., 1991). Usually PBBs and PCBs are separated from more polar compounds by adsorption chromatography on silica gel or Florisil. If the coplanar compounds are to be determined, they have to be isolated from the major compounds in the extract. This can be done using activated charcoal, which adsorbs the planar molecules more strongly than the non-planar. Brominated

Table 13. Determination of PBBs in environmental samples[a]

Matrix	Extraction	Clean up	Analytical method	Detection	Detection limit	Comment	References
Soil, grass, carrots	benzene/ 2-propanol	Florisil	GC	ECD, FID MS ^{13}C-NMR	0.1 µg/kg dry weight (soil) 10 µg/kg wet weight (plant)	BB 153, two PeBB isomers, three additional HxBB isomers, two HpBB isomers detected	Jacobs et al. (1976)
Soil leachate	benzene/ 2-propanol		GC	ECD	0.1 µg/kg dry weight	laboratory experiments	Filonow et al. (1976)
Soil, plant samples	hexane/ acetone	Florisil	GC	ECD	0.1 µg/kg dry weight (soil)	field and laboratory experiments; no significant degradation of PBBs after 1 year	Jacobs et al. (1978)
			TLC	ECD	0.3 µg/kg wet weight (plant)		
Effluent river water	hexane/ diethyl ether	no data given	GC	ECD	0.1 µg/litre (later 0.01 µg/litre)	environmental samples	Hesse (1975) Hesse & Powers (1978)
Sediment	hexane/ acetone	no data given	GC	ECD	100 µg/kg	environmental samples	Hesse & Powers (1978)
Soil	hexane/ acetone 9:1	no data given	GC	ECD, FID, MS		separation of 30 PBB congeners tested optimum conditions for extraction of PBBs from soil; polar organic solvent important	Stratton & Whitlock (1979)

Table 13 (contd).

Matrix	Extraction	Clean up	Analytical method	Detection	Detection limit	Comment	References
98 environmental samples (fish, sediment, soils, vegetation)	hexane, Soxhlet	Florisil	GC	MS	0.2 µg/kg	analysed for hexa-, hepta-, octa-, nona-, decabromobiphenyls; HxBB in 84% of samples	Stratton et al. (1979)
Soil, sediment, sludge, vegetation	hexane	Florisil	GC	MS (SIM)	0.2 µg/kg	congeners detected	Griffin & Chou (1981a)
Soil	hexane/ acetone 1:1	Florisil	GC	FID, ECD		degradation of PBBs in soil	Hill et al. (1982)
Sewage sludge	hexane/methanol Soxhlet extraction		TLC GC	IR, NMR, MS	10 ng/kg	no PBBs found	Strachan et al. (1983)
Plants	cut, extracted with hexane/ acetone	Florisil	GC	ECD	0.3 µg/kg wet basis	no translocation in plants	Chou et al. (1978)

[a] Abbreviations used:

ECD = Pulsed ^{63}Ni electron capture detector.
FID = Flame ionization detector.
GC = Gas chromatography.
IR = Infrared radiation.
MS = Mass spectrometry.
NMR = Nuclear magnetic resonance.
SIM = Selected ion monitoring.
TLC = Thin layer chromatography.

Table 14. Determination of PBBs in food/feed[a]

Matrix	Extraction	Clean up	Analytical method	Detection	Detection limit	Comment	References
Dairy products	fat extracted by AOAC (1975) methods (methanol/ether)	GPC, 25% toluene in ethyl acetate	GC	ECD	7 µg/kg	comparison of methods	Fehringer (1975a)
		Florisil/pet ether	TLC		0.2 mg/kg		
Dry animal feeds	finely ground feed packed into a column containing celite, elution with methylene chloride	Florisil/pet ether	GC, TLC	ECD	8 µg/kg 30 µg/kg	hexabromo isomer measured	Fehringer (1975b)
Feeds and dairy products	see Fehringer (1975a,b)		GC before and after UV irradiation to determine background	ECD	5 µg/kg	confirmation of PBB residues using UV irradiation	Erney (1975)

[a] Abbreviations used:

ECD = Pulsed ^{63}Ni electron capture detector.
GC = Gas chromatography.
GPC = Gel permeation chromatography.
TLC = Thin layer chromatography.
UV = Ultraviolet.

Table 15. Determination of PBBs in biological tissues and fluids[a]

Matrix	Extraction	Clean up	Detection	Detection limit	Comment	References
a) Serum/blood						
Human serum	methanol-treated serum, extraction with hexane	Florisil	ECD	5 pg	analysis based on HxBB peak	Bekesi et al. (1978)
Human serum	methanol-treated serum, extraction with hexane/ether	Florisil	ECD	0.2 µg/litre		Wolff et al. (1978)
Human/rat serum	methanol-treated serum, extraction with hexane/ether	Florisil	ECD	0.2 µg/litre	PBB homologues as % HxBB peak	Wolff & Aubrey (1978)
	methanol-treated serum, extraction with hexane/ether	Florisil	ECD, MS	< 1 mg/ml		Wolff et al. (1979a)
Plasma from PBB-fed cows	multiple extraction with mixture of diethyl and pet. ethers	Florisil	ECD	0.001 µg/litre	recovery 96%	Willett et al. (1978)

Table 15 (contd).

Human serum	methanol-treated serum; extraction with hexane/ether	Florisil	ECD	0.1 µg/litre	interlaboratory comparison	Burse et al. (1980)
Plasma, white cell fraction erythrocytes β-lipoprotein	methanol; precipitated protein removed; extraction with hexane/ether (1:1)	Florisil	MS-SIM NCI	0.1 µg/mg protein	very exact details with spectra review	Roboz et al. (1980)
Human serum	methanol; hexane/diethyl-ether (1:1)	silica gel	ECD	1 µg/litre		Needham et al. (1981)
Human serum	+ methanol precipitated protein *not* removed + hexane/diethylether (1:1)	Florisil	ECD MS-NCI	< 1 µg/litre	serum protein precipitated with methanol should not be removed from sample	Roboz et al. (1982)
Human serum	see Burse et al. (1980)		ECD	1 µg/litre		Eyster et al. (1983)
Blood (*in vitro* experimental)	see Roboz et al. (1982)		MS-(PPINCI)		*in vitro*	Roboz et al. (1985a)
Human blood (model and environmentally exposed)	see Roboz et al. (1982)		ECD, SIM, NCI	10-35 ng individual serum	distribution of PBBs among blood components congener/litre	Roboz et al. (1985b)

Table 15 (contd).

Matrix	Extraction	Clean up	Detection	Detection limit	Comment	References
b) Adipose and other tissues						
Adipose tissue from exposed workers	toluene/ethyl acetate (1+3)	GPC (Bio Beads toluene/ethyl acetate (1+3)	ECD	0.5 µg/kg	major HxBB peak determined	Wolff et al. (1979a)
Various rat tissues and serum	Burse et al. (1980)		ECD	10 µg/kg	comparison of concentrations of PBBs in various tissues with time	Miceli & Marks (1981)
Liver and perirenal adipose tissue from dosed rats	1) hexane (liver and adipose)	1) Florisil	ECD, NAA		comparison of extraction methods (showed PBB extraction with hexane leads to erratic recoveries and results) increase in detection limits over ECD (2 pg FireMaster®); 1 µg/litre or less of hexa congener)	Fawkes et al. (1982)
	2) chloroform: methanol (liver)	2) acidic alumina				
	3) methylene chloride chloroform (adipose)					

Table 15 (contd).

Human adipose tissue	15% diethyl ether in hexane	Florisil/GPC	ECD MS		GPC clean-up tested (85% recovery); MS free of serious interference from 46 to 500 m/z	MacLeod et al. (1982)
Adipose tissue from general population	6% diethyl ether in hexane	Florisil/GPC	MS	1-2 µg/kg	HxBB peak	Lewis & Sovocool (1982)
Human adipose tissue, placenta, cord blood, biliary fluid, faeces	hexane/diethylether	silica gel	ECD	1 µg/kg		Eyster et al. (1983)
Human post-mortem tissue		Chromaflex adsorption column with 5% silica gel + sodium sulfate/ hexane	ECD	0.5 µg/kg	HxBB peak	Miceli et al. (1985)
Adipose tissue (bovine), spiked for model system	hexane Florisil cartridges	solid phase	ECD		1-14 ng/kg Florisil cartridges to separate fat; 116% recovery	Chiang et al. (1987)

Table 15 (contd).

Matrix	Extraction	Clean up	Detection	Detection limit	Comment	References
c) Milk						
Human milk	potassium oxalate, ethanol/diethyl ether; hexane		ECD	1 µg/kg		Eyster et al. (1983)
Human milk	potassium oxalate, ethanol/diethyl ether	Bio Beads/ Florisil/acti-vated charcoal	MS (NCI, SIM)	1 ng/kg	separation of coplanar and planar isomers with charcoal	Krüger (1988)
d) Biological samples from the environment						
Fish, seal	freeze, pulverize, pet. ether	Bio Beads/ Florisil/acti-vated charcoal	MS (NCI, SIM)	10 ng/kg		Krüger (1988)

Table 15 (contd).

Matrix	Extraction	Clean up	Detection	Detection limit	Comment	References
Dolphin fat/ organ tissue	Soxhlet; hexane, methylene chloride	GPC; silica gel	MS	no data given	lowest value given: 40 µg/kg	Kuehl et al. (1991)
Terrestrial, freshwater and marine samples	diethyl ether/hexane	hydrolysis with 98% H_2SO_4/Bio Beads/ silica gel/activated charcoal	MS (NCI)	no data given	lowest value given: 40 ng/kg	Jansson et. al. (1991, 1992)

[a] Analytical method used was gas chromatography.
Abbreviations used:

ECD = Pulsed ^{63}Ni electron capture detector.
GPC = Gel permeation chromatography.
MS = Mass spectrometry.
NAA = Neutron activation analysis.
NCI = Negative ion chemical ionization mass spectrometry.
PPINICI = Pulsed positive ion-negative ion chemical ionization.
SIM = Selected ion monitoring.

naphthalenes, dioxins, and furans will also be separated from the major PBB components in this step. HPLC methods are now being adopted for these separations and both charcoal and modified silica gel columns are available for HPLC separations of coplanar compounds.

Using negative ion chemical ionization mass spectrometry (MS-NCI), the bromide ions can be used to detect brominated compounds with high sensitivity and selectivity. However, using this detection method (or ECD), interference between congeners of PBB and polybrominated diphenyl ethers is possible.

The 209 possible PBB congeners have a wide range of volatility, which causes very difficult separation problems (Farrell, 1980). In earlier studies, gas chromatography (GC) with packed columns, e.g., 3% OV-1 on 80/100 mesh Chromosorb W(HP) was used (Fehringer, 1975a,b). Capillary columns enable a good separation with lower brominated biphenyls but do not have any great advantages over packed columns for more highly substituted biphenyls (Farrell, 1980; Orti et al., 1983; Robertson et al., 1984b).

The detection method most frequently used is that of pulsed ^{63}Ni electron capture detection (ECD). In general, retention times and electron capture responses increase with increasing bromination. This is a sensitive method, but has some shortcomings. ECD is a group selective detector that responds to halogens and other electronegative groups. This places stringent requirements on chromatographic separation. Moreover, ECD responds differently to different compounds, depending on the molecular structure. The response or sensitivity of the ECD depends on the position of the halogen on the biphenyl nucleus as well as the number of halogens. This necessitates running a standard for each compound to be determined (Zerezghi et al., 1984). Sweetman & Boettner (1982) analysed the structure-sensitivity of PBBs using ECD (see Table 12).

Flame ionisation detection (FID) can only be used for the analysis of standard substances because of its low specificity (Krüger, 1988).

A microwave-induced plasma emission detector has been used as a specific method of detection for bromine (Mulligan et al., 1980; Zerezghi et al., 1984). However, the method is not sensitive enough for environmental samples.

Some authors have confirmed their results by GC/ECD determination before, and after, exposure to UVR. The PBBs present are photolyzed and, in this way, the background values can be eliminated (Erney, 1975; Trotter, 1977).

Very often, the presence of PBBs is confirmed using mass spectrometry (MS) together with gas chromatography. The purity of the sample can be verified by comparison with known standards. Negative chemical ionization (NCI) mass spectrometry has a sensitivity comparable with, and somewhat better than, GC/ECD analysis. The detection level for hexabromobiphenyl standards is lower by a factor of 20 to 10-35 ng/ml in comparison with GC/ECD analyses (Roboz et al., 1982). This relatively new method has also been used to detect polychlorinated and polybrominated dioxins and furans (see section 4.3).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

PBBs are not known to occur naturally.

3.2 Man-made sources

3.2.1 Production levels and processes

3.2.1.1 World production figures

1) United States of America

The commercial production of PBBs in the USA commenced in 1970 (Neufeld et al., 1977). Several US producers of commercial quantities have been identified (Mumma & Wallace, 1975; Neufeld et al., 1977; Di Carlo et al., 1978; Brinkman & de Kok, 1980).

In 1976, a US firm had a combined production of about 0.45 million kg of PBBs for export to Europe (Anon., 1977).

A list of suppliers of laboratory quantities (with a maximum production or importation of about 2 kg/year) is presented by Mumma & Wallace (1975) and Neufeld et al. (1977).

As a result of the Michigan catastrophe of mid-1973, the sole US manufacturer of hexabromobiphenyl ceased production in November 1974. It is not clear, whether the production of bromine-based fire retardants was resumed by another US company in 1978 (Brinkman & de Kok, 1980). Two other companies continued their production of octa- and deca-PBB until 1977 (Di Carlo et al., 1978). According to the German "Umweltbundesamt" (UBA, 1989), decabromobiphenyl was produced in the USA until 1979.

There are repeated statements that all PBBs manufactured in the USA since 1975-76 have been exported, mainly to Europe, and that there is no importation of any PBB mixtures into the USA (Brinkman & de Kok, 1980).

Relevant production data for the period 1970-76 are presented in Table 16.

Table 16. Commercial production of polybrominated biphenyls in the USA, 1970-76[a]

Product	Estimated production in thousand kg							
	1970	1971	1972	1973	1974	1975	1976	1970-76
Hexabromobiphenyl	9.5	84.2	1011	1770	2221	0	0	5369
Octabromobiphenyl and decabromobiphenyl[b]	14.1	14.1	14.6	163	48	77.3	366	702
Total PBBs	23.6	98.3	1025	1933	2269	77.3	366	6071

[a] From: Di Carlo et al. (1978).
[b] Manufacture was continued in 1977, but production figures are not available.

Hexabrominated biphenyl forms the major part (about 5.4 million kg FireMaster® BP-6 plus some 68 300 kg FireMaster® FF-1) of the estimated total production of 6.1 million kg (Neufeld et al., 1977). The remaining 0.7 million kg are accounted for by the higher brominated biphenyls. In 1976, for example, 0.35 million kg of decabromobiphenyl and 13 600 kg of octabromobiphenyl were manufactured (Neufeld et al., 1977). No production figures are available for 1977 (Di Carlo et al., 1978).

2) Japan

According to IARC (1978), PBBs have never been produced in Japan, but, up to 1978, some were imported.

3) Europe

a) Germany

A German firm produced a mixture of highly brominated PBBs, called Bromkal 80-9D until mid-1985, when the activities concerning bromine-based fire retardants were shifted to the USA. No production figures are available.

b) France

A French firm manufactures a technical-grade decabromobiphenyl, sold as Adine 0102, production being a few hundred thousand kg/year (Atochem, 1988). It is marketed in France, Great Britain, Spain and the Netherlands (Atochem, 1988; UBA, 1989). More than 200 tonnes decabromobiphenyl/year were used in the Netherlands for incorporation into polybutylenterephthalate plastics (UBA, 1989).

c) United Kingdom

Two companies are reported to have marketed or produced technical-grade decabromobiphenyl in the United Kingdom (Brinkman & de Kok, 1980). In 1977, the production of PBBs was discontinued (Neufeld et al., 1977).

No production or sales data are available.

d) Netherlands

No domestic producer has been identified. An Israeli company with two bromine plants in Holland denied the production of PBBs

(Neufeld et al., 1977). However, the amount of decabromobiphenyl sold annually in the Netherlands was estimated to be of the order of 91 000 kg (Brinkman & de Kok, 1980).

No information is available on production in other parts of the world.

3.2.1.2 Manufacturing processes

The process of manufacturing PBBs consists of a Friedel-Crafts type reaction in which biphenyl is reacted with bromine in the presence of chloride in an organic solvent, using aluminium chloride, aluminium bromide, or iron as catalyst (Brinkman & de Kok, 1980). In the Atochem decabromobiphenyl manufacturing process, biphenyl is directly brominated in a large excess of bromine, used as reactant and solvent in the presence of a Lewis acid catalyst (aluminium type). Decabromobiphenyl is further purified by distillation of the excess bromine in the presence of a brominated solvent (Atochem, 1992).

3.2.1.3 Loss into the environment during normal production

Data are published only for the USA. The following information refers to reviews by Neufeld et al. (1977) and Di Carlo et al. (1978).

Losses of PBBs to the environment at sites of its manufacture can total 51 kg/1000 kg of product. These losses occur through:

1) Emission into the air

In 1977, the maximum air losses as particulate matter at production sites were estimated to total 1.1 kg of PBBs/1000 kg manufactured.

(a) Emission to the air from the vents of the hydrogen bromide recovery system:

Total emission of FireMaster® PB-6 was estimated to amount to 70 mg/1000 kg produced.

(b) Loss of particulate PBB to the atmosphere during centrifugation (which was carried out to separate the solid reaction products from the organic solvent).

A New Jersey permit application by Hexcel Corp. plant (1976) indicated a loss of less than 0.05% of the product.

(c) Loss of dust from drying and pulverizing PBBs to a fine powder (dust from this operation was removed by a bag type filter).

In 1974, atmospheric levels of PB-6 in the Michigan Chemical Corp. bagger area were 16-32 mg/m^3 during the bagging operation and 3 mg/m^3 after bagging was completed. Lower levels were detected in other areas of the plant.

(d) Emission of hexabromobiphenyl as a vapour contaminant in vapour streams leaving scrubbers or equivalent equipment was calculated to be less than 25 μg/m^3 (1 ppb) at ambient temperature (Neufeld et al., 1977).

2) Losses in waste waters resulting from the quenching and washing of the PBBs as they are recovered from the reaction mass:

The losses of PBBs to sewers at manufacturing sites were estimated, in 1977, to be 4.6 μg/kg of product.

- In 1972, samples of the Michigan Chemical Corp. effluent discharges were found to contain PBB levels of 98-503 μg/litre (Hesse, 1975);

- The total quantity of PBBs being discharged to the Pine River was estimated as 0.11 kg daily.

- Unfiltered water from an industrial storm sewer at the Hexcel Corp. plant contained 92 μg/litre, mainly as decabromobiphenyl (hexa-, octa-, and nonabromobiphenyls levels were also measurable).

- Liquid effluents, diluted by canal water, from the White Chemical Co. plant showed values of up to 31 μg PBBs/litre.

3) Solid losses to landfills resulting from drying, handling, shipping and transportation.

An estimate of PBB losses as solid waste to landfills was 50 g/kg of product.

According to a report of the Michigan Chemical Corp., their solid waste included approximately 5% of the BP-6 produced.

4) Losses to the soil

Soil samples from the bagging and loading areas of the Michigan Chemical corp. contained PBBs at concentrations of 3500 and 2500 mg/kg, respectively.

Losses of other compounds:

The following typical air contaminants released during PBB-manufacture were reported: hydrogen chloride, bromine, ethylene dichloride, aluminium chloride, and biphenyls. The total quantity emitted was stated to be less than 5.5 kg/day.

3.2.1.4 Methods of transport, accidental release, and disposal of production wastes

Details of present-day labelling and transport regulations are given in the Health and Safety Guide for PBBs (WHO, 1993).

In 1973, an accidental release of PBBs occurred in Michigan ("Michigan disaster"), when two products manufactured by the Michigan Chemical Company were inadvertently confused, i.e., 250-500 kg (Di Carlo et al., 1978) of FireMaster®, instead of NutriMaster®, a magnesium oxide-based cattle feed supplement, were added to animal feed and distributed to farms within the state. The compound is believed to have been FireMaster® FF-1 (e.g., Fries, 1985b), even if in some publications the name FireMaster® BP-6 is used (e.g., Neufeld et al., 1977; Di Carlo et al., 1978). This accidental mix up resulted in widespread contamination by PBBs (see section 5). As a result of this incident, the production of FireMaster® BP-6 by Michigan Chemical Corp. was stopped in 1974 (Di Carlo et al., 1978). Chronological reports or reviews of the PBB disaster are given by Carter (1976), Getty et al. (1977), Kay (1977), Di Carlo et al. (1978), Damstra et al. (1982), Zabik (1982), and Fries (1985b).

Details of the disposal of manufacturing waste during present production are not available. In a report by Neufeld et al. (1977), solids from manufacturing operations were disposed of in landfills. Waste waters containing small amounts of PBBs were discharged into the chemical sewer.

3.2.2 Uses

Commercially manufactured PBBs are processed by industrial users, primarily as flame retardants in polymeric materials. PBBs were developed for this major application, because: they are able to meet the flame-resistance performance requirements, they are economically feasible, and they have little effect on the flexibility of the base compounds (Mumma & Wallace, 1975).

The process of application is basically one of physical blending: the PBBs are not functional additives, and on blending with the dry solid or liquid polymeric material, provide filter-type flame retardant action with the chemical release of hydrogen bromide if ignited (Neufeld et al., 1977).

Neufeld et al. (1977) list 34 applications of PBBs found in patent and technical literature. The majority are related to the use of the PBBs as flame retardants in polymeric materials, other claims include self-extinguishing properties and improved wearability and machinability. Further potential uses of PBBs are: in the synthesis of biphenyl esters or in a modified Wurtz-Fittig-synthesis; in light sensitive compositions to act as colour activators; as relative molecular mass control agents for polybutadiene; as wood preservatives; as voltage stabilizing agents in electrical insulation; as functional fluids, such as dielectric media (Neufeld et al., 1977). In the USA and Canada, hexabromobiphenyl (FireMaster®) was the principal PBB product. It was used as a fire retardant in three main commercial products: acrylonitrile-butadiene-styrene (ABS) plastics; coatings and lacquers; and polyurethane foam (Neufeld et al., 1977).

The types of ABS plastic products in which FireMaster® BP-6 was used are compiled in Table 17.

According to Neufeld et al. (1977), the use of FireMaster® BP-6 as a flame retardant in thermoplastic resins was confined to products that do not come into contact with food or feed and are not used in fabrics to which humans are exposed.

Although more than 130 companies in the USA used PBBs prior to 1976 (Di Carlo et al., 1978), only a limited number seems to have been the major users of PBBs. For example, in 1974, the final year of US production, Borg Warner Corp. (Parkersburg, W.Va.; using FireMaster® in ABS plastics) and Standard T Chemical Co. (Staten Island, New York; using FireMaster® in fire

retardant coatings for industry) consumed over 50% of the total US yearly production (Mumma & Wallace, 1975; Jamieson, 1977; Neufeld et al., 1977; Brinkman & de Kok, 1980).

Table 17. Uses of FireMaster® BP-6 in ABS plastics in the USA[a]

Industry	Approximate % of total use	Examples
Business machines and industrial equipment	48	Typewriter, calculator and microfilm-reader housings; business machine housings
Electrical	35	Radio and TV parts, thermostats, shaver and hand-tool housings
Fabricated products	12	Projector housings, movie equipment cases
Transportation	1	Miscellaneous small automotive parts; electrical-wireconnectors,switchconnectors, speaker grills
Miscellaneous	4	Small parts for electrical applications, motor housings; components for industrial equipment

[a] From: Brinkman & de Kok (1980).

Of the estimated 2200 tonnes hexabromobiphenyl produced in 1974 (IARC, 1978), about 900 tonnes (Mumma & Wallace, 1975; Neufeld et al., 1977; IARC, 1978) were used in ABS plastic products and about 34 000 tonnes (Mumma & Wallace, 1975; Neufeld et al., 1977; IARC, 1978) in cable coatings.

The exact quantity of FireMaster® used in polyurethane foam for automobile upholstery was not published. The two larger consumers ceased using hexabromobiphenyl (one of these in 1972) because PBBs did not decompose in the ultimate incineration of scrapped automobiles (Neufeld et al., 1977).

No current users of hexabromobiphenyl have been identified (Neufeld et al., 1977; Di Carlo et al., 1978; Brinkman & de Kok, 1980). As regards octa- and decabromobiphenyl, no commercial use was reported in the USA during 1970-74 (Neufeld et al., 1977). In Western Europe, the use of higher brominated PBBs

seems to be dominant. The decabromobiphenyl Adine 0102® (in the past manufactured by Ugine Kuhlmann, at present by Atochem) is used as a flame retardant for thermoplastics and thermosets (e.g., in polyesters, epoxy resins, polystyrene, ABS, polyolefines, and PVC), for elastomers (e.g., in PU-elastomers and india rubber) and for cellulosics (e.g., chip-board). It is applied frequently in association with antimony trioxide (Sb_2O_3) (Atochem, 1984a). Its use in paints and varnishes has also been reported (Brinkman & de Kok, 1980).

Losses of PBBs to the environment from processing plants are possible, but little information is available about this.

Although decabromobiphenyl and, possibly, other PBBs are still produced commercially, alternative chemicals have been introduced to replace them as flame retardants, in particular polybrominated biphenyl ethers (oxides) (PBBO), e.g., decabromobiphenyl ether (Adine 505; Bromkal 82-0 DE; Great Lakes DE-83™ and DE 83R™), octabromobiphenyl ether (Bromkal 79-8 DE; Great Lakes DE 79), and pentabromobiphenyl ether (Bromkal 70-5 DE; Great Lakes DE-71™: Atochem, 1984b; Great Lakes Chemical Corp., 1986).

Decabromobiphenyl ether (DBBO) for example, appears to be a much less toxic material than PBBs. However, DBBO is said to have a tendency to degrade to lower brominated biphenyl oxides. It is possible that these lower order compounds may pose environmental problems similar to those of the lower brominated PBBs (Mumma & Wallace, 1975). In addition, on pyrolysis, PBBOs produce larger amounts of dioxins and furans than PBBs and so may themselves have to be replaced by other compounds.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 Air

The commercial PBB-mixtures are solids at room temperature. Despite their low vapour pressure, air pollution by PBBs can occur as follows:

- PBBs may be released into the atmosphere as vapour or dust from production and processing plants. Stratton & Whitlock (1979) found indirect evidence of airborne discharges of PBBs near two out of three chosen industrial sites in north-eastern New Jersey and Staten Island, New York, where these materials had been manufactured or used in product formulations.

- Further air contamination may occur during the incineration of industrial and municipal wastes. Most municipal incinerators are not very effective in destroying halogenated biphenyls. Like PCBs, PBBs do not burn readily and incinerating conditions must be carefully controlled, otherwise these compounds will reenter the environment in the stack gases (Griffin & Chou, 1981a) or may be transformed to polybrominated dibenzofurans.

Flameless combustion of the consumer products causes volatilization of intact PBBs (Benbow & Cullis, 1975).

An appreciable loss of PBBs during the lifetime of PBB-containing products is unlikely.

Secondary ways of entrance of PBBs into the atmosphere, e.g., through evaporation from contaminated soils, are thought to be negligible, though small losses of PBBs from soil during long-term (6 months) incubation studies were observed, which were associated with volatilization rather than sorption or masking (Griffin & Chou, 1981a).

The ability of PBBs to co-distil from landfills or from the surface layer of water bodies, as reported for PCBs (Kalmaz & Kalmaz, 1979), has not yet been examined.

By analogy with PCBs, it might be expected that PBBs entering the atmosphere in the vapour phase would be adsorbed rapidly onto particles, which would then be deposited by particle sedimentation, depending on micro- and macrometeorological conditions.

According to Eisenreich et al. (1981) organic compounds having a vapour pressure $\geq 10^{-5}$ kPa should exist almost entirely in the vapour phase, and those having a vapour pressure $\geq 10^{-9}$ kPa should exist almost entirely in the particulate phase.

PBBs, e.g., hexabromobiphenyl or FireMaster with a vapour pressure of 6.9×10^{-9} kPa (Jacobs et al., 1976), belong to the latter. In reality, distribution and atmospheric lifetimes of organic compounds with a high relative molecular mass depend largely on the particle concentration and composition in the atmosphere (Eisenreich et al., 1981). Gas-phase reactions with hydroxyl (OH) radicals also influence the lifetimes of organic compounds emitted into the atmosphere. Atkinson et al. (1984) determined rate constants for the gas-phase reaction of OH radicals with biphenyl and predicted, from their findings, that the chlorine - and bromine-substituted biphenyls would have OH radical rate constants of $< 8 \times 10^{-12}$ cm^3/molecule per second at room temperature.

4.1.2 Water

The principal route of entrance of PBBs into aquatic environments is from industrial waste streams into receiving waters. Further potential routes (of minor relevance) are atmospheric deposition and erosion of polluted soils. Groundwater contamination is possible, if these compounds are leached from landfills (Shah, 1978).

Because compounds like PBB are very poorly soluble, they are primarily found in sediments of polluted lakes and rivers (Kimbrough, 1980a). In laboratory experiments, Simmons & Kotz (1982) determined the "percent adsorption" of PBBs in sediments from sites at Lake Michigan and the Huron River and concluded from values ranging from 9 to 32% that the capacity of the sediments for PBB was small to moderate.

PBBs in water are mainly adsorbed on particulate matter followed by sedimentation at a rate that depends on several factors, such as the size and type of the sediment and/or the

organic contents of both the sediment and the overlying water mass. The relative importance of these parameters is controversial (Simmons & Kotz, 1982). Laboratory results concerning PCBs (Jensen et al., 1973) led to the assumption that the kinetics of the sorption reaction may vary inversely with particle size (because smaller particles have a larger surface area for surface adsorption). Leland et al. (1973), Choi & Chen (1976), and Simmons et al. (1980) have shown that the organic content of the sediment is directly related to its adsorptive capacity for a specific contaminant. According to Schwarzenbach & Westall (1981), adsorption of non-polar compounds is highly correlated with the organic carbon content of sorbents containing more than 0.1% organic carbon. Simmons & Kotz (1982) found strong correlations between the adsorptive capacity of the sediments for PBBs and TOC (total organic carbon) and the % silt/clay fraction.

Sediments are potential sources as well as sinks for most chemicals (Simmons & Kotz, 1982). Desorption of a contaminant from the sediments is favoured where a high concentration of organic matter exists in the water column (Huang, 1971). The presence of organic matter may also enhance the partitioning of the contaminant in the water phase and, thus, facilitate further movement with the water mass (Hassett & Anderson, 1979). Laboratory studies on the mode of action that PBBs may take in their movement through the water column have verified that the total organic content of the natural water will decrease the adsorption of PBB onto sediment and therefore keep the PBB in the water phase. For example, comparing the distilled water versus natural water systems, in river water with an organic content of 11-12 mg C/litre, the % PBB-adsorption was decreased by 33-43%; for lake water with an organic content of 3.8 mg/litre, the % PBB-adsorption was reduced by about 12% (Simmons & Kotz, 1982). Another investigation indicated that the solubilities of PBBs were directly correlated with the levels of dissolved organics in the water (Griffin & Chou, 1981a) (see also section 4.1.3).

However, in the natural environment, upon settling out, the association of the contaminant with the sediment may become the dominant process in the water/sediment system (Simmons & Kotz, 1982). Transport of PBBs is thought to take place, when mixing or bioturbation of sediments causes redistribution of the contaminant in the water column (Simmons & Kotz, 1982), and through transport of the sediment itself.

4.1.3 Soil

Pollution of soils can originate from point sources such as PBB plant areas and waste dumps. Very few data are available on the deposition of PBBs on soil via the atmosphere, sewage sludge from municipal sewage treatment systems, and the dredging of sludge from contaminated waters.

Other possible sources are illicit, or improper, disposal of such chemicals (Kimbrough, 1980a) and incidents. For example, as a consequence of an incident in 1973, Michigan soils have been contaminated by manure from PBB-fed animals and by the disposal of contaminated feed, milk, carcasses, etc. (Getty et al., 1977; Chou et al., 1978; Damstra et al., 1982; Fries, 1985b). Once PBBs have been introduced into the soil, they appear to have little tendency to translocate (Damstra et al., 1982).

The ability of rainfall to carry PBBs through the soil was tested in a laboratory simulation. Filonow et al. (1976) percolated water through columns of 4 Michigan soils containing 100 mg 2,2',4,4',5,5'-hexabromobiphenyl/kg. They found a loss of less than 0.6% of the hexabromobiphenyl congener from each soil, even with leachate quantities equivalent to 20 times the average annual rainfall in Michigan.

Field investigations also indicated that PBBs were retained in the top soil. Results of subsequent studies on highly contaminated farm soils showed that PBBs did not move below the 15 cm level, except where there was a history of physical mixing of the soil (Fries, 1985b).

The mobility in soils of a chemical like PBBs will largely be governed by its solubility in water and its adsorption, or interaction, with soil particles (Jacobs et al., 1978).

As already mentioned, PBBs have a very low solubility in water. However, studies with distilled, tap, river, and soil waters showed that their solubility was markedly influenced by water purity (Jacobs et al., 1978). Griffin & Chou (1981a) ascertained, under well defined conditions, the following average solubilities of PBBs: 0.06 μg/litre in distilled water, 0.3 μg/litre in deionized water, 0.5 μg/litre in creek water, 8.9 μg/litre in Du Page leachate, and 16.9 μg/litre in Blackwell leachate.

Hence, PBBs were more than 200 times more soluble in landfill leachate than in distilled water; the solubilities of PBBs were also higher in creek water than in distilled water. As shown by the TOC (total organic carbon) values for the waters, the higher solubilities of PBBs were directly correlated with the level of dissolved organic compounds in the waters. The type of dissolved organic matter may also influence the solubility (Griffin & Chou, 1981a).

PBBs are quite soluble in organic solvents, such as dioxane, carbon tetrachloride, acetone, and methanol. This could play a major role in soil environments where leachates from chemical waste disposal sites are percolating.

The other important factor affecting the migration of PBBs, i.e., their adsorption by soils, was also studied under laboratory conditions. The hydrophobic properties of PBBs make them easily adsorbed from aqueous solutions onto soils. Filonow et al. (1976) examined the adsorption of purified 2,2',4,4', 5,5'-hexabromobiphenyl (BB153) on four soil types. They found that the adsorption of 2,2',4,4',5,5'-hexabromobiphenyl conformed well to Freundlich adsorption isotherms, and that 2-19% of the available HBB was adsorbed. Adsorption of HBB was influenced primarily by the organic content of the soils. An increase in the organic matter content of soils enhanced their adsorption capacity.

Neither percentage clay nor pH correlated well with BB153 adsorption. Any effect that the clay contents may have had, was apparently masked by the effect of the organic contents on adsorption (Filonow et al., 1976).

Griffin & Chou (1981a,b), using the PBB-mixture FireMaster® BP-6 or ^{14}C-labelled-PBB, also confirmed the strong adsorption of PBBs on soils and indicated a very high direct correlation between the total organic carbon content (TOC) of three different soils and the amounts of PBBs adsorbed. However, they pointed out that, in soils with a low TOC, the mineral fraction may contribute markedly to the adsorption capacity.

Furthermore, preferential adsorption of PBB congeners and isomers was noted, depending on the characteristics of the adsorbent, e.g., organic content (Griffin & Chou, 1981a), as well as on the degree and position of bromine substitution (Griffin & Chou, 1980, 1981b).

No measurable adsorption on soils occurred of PBBs from organic solvents (Griffin & Chou, 1981a).

The results of migration studies were in agreement with the findings discussed above. The mobility of PBBs in five soils was measured with several leaching solvents, using a thin-layer chromatography technique and column leaching studies (Griffin & Chou, 1981a,b). PBBs remained immobile in the soils when leached with water or landfill leachate, but were highly mobile when leached with organic solvents. Mobility was directly proportional to the solubility in the leaching solvents and inversely proportional to the soil total organic content.

On the other hand, because PBBs are bound to soil, wherever contaminated soil moves, whether through wind or water erosion or animal ingestion and migration, traces of PBBs (if present) can be expected to be found (Jacobs et al., 1978).

4.1.4 Biota

PBBs are stable and persistent, lipophilic, and only very slightly soluble in water; they are poorly metabolized, and therefore accumulate in lipid compartments of biota. Once they have been released into the environment they will reach the food chain, where they are concentrated. Fish and wildlife are the most consistent targets for such contamination, but livestock and humans may also become contaminated (Kimbrough, 1980a). The precise routes and transport mechanisms of PBBs travelling through biota have not been thoroughly investigated as pointed out below.

4.1.4.1 Terrestrial ecosystems

Several studies have been concerned with whether plants in terrestrial ecosystems would take up, translocate, and introduce PBBs into the food chain. Jacobs et al. (1976) selected orchard grass (*Dactylus glomerata*) as test plants in their greenhouse studies because of its extensive root mass, and carrots (*Daucus carota*), which, according to Iwata et al. (1974), have an outstanding ability to absorb pesticide residues from the soil. They did not detect any PBBs in the tops of either species grown in soils supplied with high levels of PBBs (10 or 100 mg/kg of FireMaster® BP-6). However, they did find traces of PBBs (20-40 µg/kg) associated with carrot roots. ^{14}C-uptake studies (autoradiography and GC-analysis) on corn and soybean seedlings grown in hydroponic

solutions and on three root crops (radishes, carrots, and onions) grown in two different soils, also showed no translocation of PBBs into plant tops (Chou et al., 1978). In addition, these authors found that the amount of PBBs associated with roots depended on plant species and the clay and organic matter contents of the soil. Roots of carrots contained more PBBs than those of radish or onion bulbs; all roots had higher levels of PBBs (50-500 μg/kg tissue) when grown in a high-PBB treatment soil (100 mg/kg) with lower clay and organic content, than they did (30-120 ng/g plant tissue) in a soil containing more clay and organic matter. Furthermore, PBBs seem to be localized on the surfaces of roots, because a significant portion of ^{14}C-PBBs was removed, when the roots were dipped in acetone.

Analyses of field samples from plant tissues of corn, alfalfa, and sudax, grown on Michigan fields with soil PBB levels ranging from 9 to 371 μg/kg, resulted in no detectable (detection limit: 0.3 μg/kg) PBB (Jacobs et al., 1978). The same was true for washed radishes from a garden with an estimated PBB concentration of 500-1000 μg/kg and for corn leaf whorls containing dust from a PBB contaminated soil (102 μg/kg) (Chou et al., 1978).

However, Stratton & Whitlock (1979), who conducted a field screening survey near sites of manufacture and use of PBBs, found high surface contamination of lichens and reeds.

The salt marsh cordgrass (*Spartina alterniflora*) is reported to take up, accumulate, and transfer effectively PCB from contaminated sediments to food chains (Mrozek et al., 1982). No data are available with regard to PBBs.

So far, except for the surface contamination of roots from contaminated soils and of foliage via air deposition processes, plants are generally free of significant amounts of residue. Thus, vegetation on PBB-contaminated soils is a less likely source of contamination of animals (Damstra et al., 1982; Fries, 1985a,b).

In contrast, a major route of residue transmission from soils to animals is the direct ingestion of soil (Fries 1982; 1985a). The degree of contamination depends on the amount of soil ingested and the bioavailability of the residues.

Quantitative data on soil ingestion by farm animals are given by several authors (Healy et al., 1967; Healy, 1968; Fries, 1982; Fries et al., 1982a,b) and range from 2 to 15% of the intake of dry matter.

Fries (1985a) determined the bioavailability of soil-borne PBBs in sheep, under controlled feeding conditions, using diets containing 5% PBB-contaminated soil, and found 65% PBB absorption from this diet, which contained 9 μg PBB/kg. Addition of activated carbon to soil had only little effect on bioavailability of PBB.

The same author recorded PBBs in the fat of beef cows, beef calves, ewes, and pigs from several farms on which soil-borne PBBs in confinement areas was the only source of PBBs. It can also be concluded from these results that the animals consumed soil, and that soil-borne PBB was bioavailable. As might be expected, pigs accumulated higher PBB concentrations from a soil environment than ruminants (Fries, 1985a). Recontamination of soil by animal excreta (Getty et al., 1977; Fries, 1985a) or carcasses (Shah, 1978) also occurred.

Recently, PBBs have been detected in European herbivorous mammals (Swedish reindeers: Jansson et al., 1992; German cows (milk): Krüger, 1988) (see also sections 5.1.4 and 5.1.6).

Despite the affinity of PBBs for soil, there are no investigations on the role of the soil fauna in the transfer of PBBs. Earthworms are of great ecological importance and might be expected to take up and accumulate PBBs as has been ascertained for PCBs (Diercxsens et al., 1985) and, thus, introduce them into the food chain.

4.1.4.2 *Aquatic ecosystems*

PBBs enter the aquatic food chains via water and food. Bacteria and plankton play an important role in the accumulation and translocation of PCBs to higher trophic levels (Kalmaz & Kalmaz, 1979; Lorenz & Neumeier, 1983). According to Falkner & Simonis (1982), sorption processes probably control uptake and accumulation of PCBs by phytoplankton, because of its high surface-volume ratio. These mechanisms could also be valid for PBBs. However, Stratton & Whitlock (1979) did not find PBBs in algae collected in the vicinity of industrial sites, where PBB concentrations of sediments ranged from 20 to 60 μg/kg and where captured fish contained 220-230 μg PBB/kg (detection limit: not given).

No information on the uptake of PBBs from sediment through bottom living organisms (e.g., mollusca or oligochaete worms) is available.

In contrast, several laboratory (Norris et al., 1973; Zitko & Hutzinger, 1976; Zitko, 1977; Sugiura et al., 1978) and field (Hesse & Powers, 1978; Stratton & Whitlock, 1979; Jaffe et al., 1985) studies on fish have been conducted. They confirm PBB uptake from water and food, with the exception of hepta- and octabromobiphenyl (Norris et al., 1973; Zitko, 1977), which were not taken up from water.

Consequently, ingestion of fish is a source of PBB transfer to mammals and birds. Because of the possible selective accumulation and metabolism of PBB congeners in prey, it can be expected that predators will be subjected to a somewhat different PBB congener composition than that found in the surrounding media (sediment, water, etc.).

In natural situations, food chains become linked together in complex food webs, and PBBs are distributed in the corresponding manner.

PBBs have been detected in other species of wildlife besides fish, e.g., in ducks living near contaminated waters (Hesse & Powers, 1978), in a turtle (Stratton & Whitlock, 1979), in the eggs of waterbirds (Haseltine et al., 1981; Heinz et al., 1983, 1985), in eagles (Kaiser et al., 1980), and in marine mammals (Jansson et al., 1987, 1992; Krüger, 1988; Kuehl et al., 1991) (see also section 5.1.6).

4.1.4.3 *Accidental contamination of the food chain*

A special case of entrance of PBBs into the food chain occurred accidentally in 1973 in Michigan, when FireMaster® FF-1 was inadvertently substituted for magnesium oxide as a supplement in the formulation of cattle feed (Damstra et al., 1982). Ten to twenty bags, 22.8 kg each, of PBBs (Carter, 1976) were mixed into feeds, that were widely distributed to Michigan farmers.

In addition, feeds not formulated to contain magnesium oxide also became contaminated (with relatively low concentrations) because of carryover of PBBs from batch to batch in the mixing equipment (Dunckel, 1975) and, on farms, through the recycling of contaminated products (Kay, 1977). Distribution of contaminated antibiotics, e.g., aureomycin, also contributed to the introduction of PBBs into farm animals (Di Carlo et al., 1978).

The mixing error was not discovered immediately, and it was almost a year before analyses indicated that a compound of PBB was involved in the illness or death of farm animals (Getty et al., 1977). During this time (IARC, 1978; Zabik, 1982), contaminated animals and their produce entered the human food supply and the environment of the state of Michigan. Hundreds of farms were affected. Altogether, at least 29 800 cattle, 5920 pigs, 1470 sheep, and 1.5 million chickens had been killed and buried by the end of 1975 (Robertson & Chynoweth, 1975; Carter, 1976), in order to minimize further human exposure. In addition, at least 785 thousand kg of feed, 8185 kg of cheese, 1197 kg of butter, 15 500 kg of dried milk products, and nearly 5 million eggs were destroyed (Carter, 1976). The number of animals quarantined or contaminated below quarantine level was estimated to be several thousands (Isleib & Whitehead, 1975). Although the Michigan PBB episode was primarily an incident of feed contamination, it also resulted in secondary contamination of animals from contaminated soil (Fries, 1985a).

4.2 Degradation

Compounds like PBBs are very stable to hydrolysis, chemical oxidation, and thermal decomposition. Degradation by purely abiotic chemical reactions (excluding photochemical reactions) is therefore considered an unlikely environmental sink (Pomerantz et al., 1978; Pearson, 1982).

The persistence of PBBs under actual field conditions is reported in some publications. Jacobs et al. (1976) detected PBBs in soils from a field that had received manure from a FireMaster®-contaminated dairy herd 10 months earlier.

Follow-up surveys over a three-year period following the termination of PBB production showed no significant decline in PBB levels in sediments from the Pine River (Hesse & Powers, 1978). Soil samples from the former PBB-manufacturing site in St. Louis, Michigan, analysed several years (nearly ten years?) after contamination (during the early 1970s) still contained PBBs. However, the PBB congener composition differed from that of the original FireMaster® mixture, indicating a partial degradation of the PBB residue in the soil sample (Hill et al., 1982).

The chemical Inspection and Testing Institute, Japan (1987) has listed decabromobiphenyl as non-biodegradable.

The most probable degradation mechanisms of PBBs in the environment, if there is any degradation at all, are photodecomposition and microbial degradation.

4.2.1 Photolytic degradation

Under laboratory conditions, PBBs were easily degraded by UVR. The photoreactivity of PBBs has been used to confirm PBB residues (Erney, 1975; Trotter, 1977). The predominant photochemical reaction of PBBs in organic solvents was a reductive debromination. Irradiation of 4-monobromobiphenyl at 300 nm in various polar and nonpolar solvents led to the formation of biphenyl as the sole product (Freeman et al., 1991). Earlier studies using lower brominated PBB congeners (i.e., tetra and lower) reported a preferential loss of *ortho* bromines (Bunce et al., 1975; Ruzo et al., 1976). Irradiation of higher brominated congeners yielded a series of photoproducts (Table 18), but a stepwise cleavage of *ortho*bromines did not appear to be preferred to *meta* or *para* debromination (Patterson et al., 1980; Millis & Aust, 1985).

The photoreactivity of 2,2′,4,4′,5,5′-hexabromobiphenyl, the main component of FireMaster®, was consistently found to be relatively high (Andersson et al., 1975; Ruzo et al., 1976; Robertson et al., 1983a; Millis & Aust, 1985), and degradation occurred more rapid than with the hexachloro analogue (Andersson et al., 1975; Ruzo & Zabik, 1975).

Consistent with the dehalogenation pathway, photodegradation of the commercial FireMaster® mixture led to reduced concentrations of the more highly substituted PBB congeners (De Kok et al., 1977; Robertson et al., 1981b, 1983; Epling et al., 1987). Robertson et al. (1983a) examined changes in the composition of FireMaster® BP-6 during photolysis (300 nm for 2-12 h; solvent: cyclohexane) by monitoring 25 individual PBB congeners; they also did not find a preferential loss of *ortho* bromines. Nevertheless, the photoproducts of FireMaster® did contain increased concentrations of congeners possessing no *ortho* bromines (e.g., 3,4,4′-tri-, 3,3′,4,4′-tetra-, 3,3′,4,4′,5-pentabromobiphenyl). Moreover, other congeners, known as relatively toxic (e.g., 2,3′,4,4′,5-pentabromobiphenyl), were enriched (Robertson et al., 1983). Biphenyl, the ultimate product of the debromination pathway, was found only to a small extent after the photolysis of FireMaster® BP-6 (Epling et al., 1987).

Table 18. Photodegradation of higher brominated PBB congeners under laboratory conditions

PBB	Irradiation (duration)	Solvent	Initial rate of photolysis (nmol/min)	Primary products of photolysis identified	Remarks	References
2,2',4,5,5'-penta	254 nm (up to 100 min)	hexane	43.4[a]	2,3',4',5-tetra (minor product) 2,2',4,5'-tetra 2,2',5,5'-tetra (major product)	*ortho*-debromination *meta*-debromination *para*-debromination (additional production of a yellow gum)	Millis & Aust (1985)
2,3',4,4',5-penta	254 nm (up to 90 min)	hexane	50[a]	2,3',4',5-tetra 3,3',4',4'-tetra	*para*-debromination *ortho*-debromination	Millis & Aust (1985)
2,2',4,4',5,5'-hexa BB 153	366 nm	methanol	not specified	lower brominated PBBs (main products) methoxy-PBBs (minor products)	degradation (90% after 9 min) more rapid than with the hexachloro analogue	Andersson et al. (1975)
	> 300 nm (0.5-2 h)	hexane	not specified	lower brominated PBBs quaterphenyls (< 5%)	BB 153 was 24.4 times more reactive than 4,4'-dibromobiphenyl	Ruzo et al. (1976)

Table 18 (contd).

2,2',4,4',5,5'-hexa	254 nm (up to 100 min)	hexane	53[a]	2,2',4,5,5'-penta (major product) 2,3',4,4',5-penta 2,2',4,4',5-penta	*para*-debromination *ortho*-debromination *meta*-debromination	Millis & Aust (1985)
2,2',4,4',5,5'-hexa	254 nm (up to 100 min)	hexane	53[a]	2,2',4,5.5'-penta (major product) 2,3',4,4',5-penta 2,2',4,4',5-penta	*para*-debromination *ortho*-debromination *meta*-debromination secondary photoproduct: 3,3',4,4'-tetra formation of yellow gum at 25 min	Millis & Aust (1985)
2,2',3,4,4',5,5'-hepta	sunlight (390 min)	not specified	not specified	2,2',4,4',5,5'-hexa (major product) 2,3',4,4',5,5'-hexa	*meta*-debromination *ortho*-debromination	Patterson et al. (1980)
2,2',3,3',4,4',5,5'-octa	sunlight (300 min)	not specified	not specified	unidentified hexa-PBB (major product) 2,3',4,4',5,5'-hexa	*ortho*- and *meta*-debromination	Patterson et al. (1980)
2,2',3,3',5,5',6,6'-octa	300 nm (0.5-2 h)	hexane	not specified	di- to heptabromobiphenyls, e.g., 3,3',5,5'-tetra	*ortho* debromination	Ruzo et al. (1976)

[a] Original PBB concentration = 1.59 mmol/litre.

Technical octabromobiphenyl has been reported to photodegrade in xylene by reductive debromination with a half-life of 40 h (Norris et al., 1973).

There were investigations to enhance the photochemical process aiming at a potential technique for the breakdown and removal of PBBs from the environment. In laboratory testing, photodegradation of PBBs was accelerated in the presence of ethylenediamine and tertbutylamine (Christensen & Weimer, 1979) and in the presence of sodium borohydride (Epling et al., 1987).

Epling et al. (1987) obtained high yields of biphenyl during borohydride enhanced photolysis of FireMaster® BP-6 (irradiation under nitrogen at 254 nm; solvent: 90% acetonitrile/water).

The rates and extent of photolytic reactions of PBBs in the environment have not been determined in detail. However, the few field observations available indicate a high persistence of the original PBBs (Jacobs et al., 1978) or a partial degradation to less brominated (and often more toxic) photoproducts (Hill et al., 1982). Jacobs et al. (1978) examined field soil that had received manure from FireMaster®-contaminated cattle, for the first time, 2-3 years earlier. They did not detect any significant changes in the relative concentrations of the major PBB peaks (Br_5, Br_6, Br_7) compared with the FireMaster® standard. In contrast, soil samples, obtained from the former FireMaster® manufacturing site in Michigan and analysed several years (approximately 10 years?) after contamination, contained enhanced concentrations of possible photodegradation products including 2,3',4,4',5-pentabromobiphenyl, 2,2',4,4',5-pentabromobiphenyl, and two unidentified tetrabromobiphenyls (Hill et al., 1982).

Considering the diversity of microenvironments, both laboratory and field data on photo alteration of PBBs are incomplete; there is a lack of studies on the photochemistry of PBBs in water, or in the vapour or solid states.

4.2.2 *Microbial degradation*

In laboratory investigations, mixtures of PBBs appear to be fairly resistant to microbial degradation. Soil incubation studies using FireMaster® BP-6 (lot no. 6244A) and ^{14}C-PBB (lot 872-244) showed a little, but not significant, degradation of the major hexa- and heptabromobiphenyl congeners after 6 months or 1 year; only pentabromobiphenyl was assumed to degrade slowly (Jacobs et al.,

1976, 1978). These results were deduced from recovery rates of PBBs from soil, $^{14}CO_2$ production, and the lack of ^{14}C-PBB intermediates.

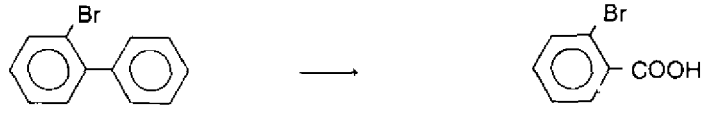
Soils incubated with photodecomposition products of ^{14}C-hexa and heptabromobiphenyl caused enhanced, but still minor, degradation (ca. 3%) as measured by $^{14}CO_2$ production (Jacobs et al., 1978). These findings are consistent with observations according to which degradation of PCBs by bacteria increases with decreasing chlorination (Kalmaz & Kalmaz, 1979; Fries, 1982).

In further incubation experiments with FireMaster® BP-6 (lot no. 6244A) in sterilized and nonsterilized Catlin-soil, Griffin & Chou (1981a) measured the recoveries of penta-, hexa-, and heptabromobiphenyls and found that all PBBs persisted for 6 months with no significant microbial degradation. They observed the same kind of persistence over a period of 4 weeks in PBB incubations with mixed cultures of microorganisms (predominantly *Alkaligenes odorans*, *A. denitrificans*, and an unidentified bacterium). This culture had been isolated previously and was known to degrade water-soluble PCBs (Clark et al., 1979). No PBB metabolites were found in the PBB-saturated mineral solution after 4 weeks of incubation (Griffin & Chou, 1981a).

As with PCBs, the high degree (penta or greater) of halogen substitution of its major components probably accounts for the lack of degradation of the FireMaster®-mixture (Griffin & Chou, 1981a). Congruently, biodegradation of monobrominated biphenyls has recently been reported.

A soil isolate, strain S93B1, identified as *Pseudomonas cruciviae*, could grow on more than ten biphenyl-related compounds including *o*-bromobiphenyl (Takase et al., 1986). *O*-bromobiphenyl was converted to *o*-bromobenzoic acid (Fig. 3) (identified by IR-spectrum). This is analogous with some PCBs showing chlorinated benzoates as metabolites (Ballschmiter et al., 1977). In these experiments, biphenyl-related compounds 0.2-0.5% (w/v) were added as the sole sources of carbon to the liquid artificial medium.

However, this pathway is also realized under simulated natural conditions (aquatic environments), as reported by Kong & Sayler (1983). They used river water as supportive culture medium and "mixed bacterial cultures" (not identified), which were obtained from PCB-contaminated river sediments. This mixed bacterial culture was capable of degrading monohalogenated biphenyls.



o-bromobiphenyl o-bromobenzoic acid

Fig. 3. Isolated microbial degradation product from monobromobiphenyl.

The degradation rates of 2-, 3-, and 4-bromobiphenyl, at 30 μg/ml, were 2.3, 4.2, and 1.4 μg/ml per day, respectively, and were comparable with those of monochlorinated biphenyls. Degradation occurred when the substrates were supplied as the sole carbon source or when added in combination with glucose. The major metabolite of 4-bromobiphenyl (*para*) was 4-bromobenzoate, identified by means of cochromatography with an authentic compound in HPLC. Two bacterial strains of the genus *Pseudomonas*, isolated from a lake sediment by using *p*-chlorobiphenyl as a sole carbon source, were capable of degrading 2-, and 4-bromobiphenyl, but they did not degrade 4,4'-dibromobiphenyl (Sugiura, 1992).

In contrast to several reports indicating that chlorobenzoates are the principal stable metabolites of PCBs (Furukawa & Matsumara, 1976; Furukawa et al., 1979; Yagi & Sudo, 1980; Reichardt et al., 1981), 4-bromobenzoate as well as 4-chlorobenzoate appeared transient. For, when tested with the same bacterial consortium, 4-bromobenzoate at 30 mg/kg was readily degraded at the rate of 4 μg/ml per day (Kong & Sayler, 1983). The terminal decomposition product is assumed to be CO_2 (Kong & Sayler, 1983), i.e., 4-bromobiphenyl can most likely be completely mineralized by this bacterial culture. Suflita et al. (1982) also observed degradation of bromobenzoates. They reported the reductive dehalogenation of halobenzoates, including 2-, 3-, or 4-bromobenzoate by microorganisms of lake sediment and sewage sludge. Dehalogenation required strict anaerobic conditions. The primary degradative event was loss of the aryl halide without the alteration of the aromatic ring, the end products were CH_4 and CO_2. The stable bacterial consortium enriched from sludge consisted of both chemolithotrophic and heterotrophic methanogens as well as three, unidentified, non-motile Gram-negative rods.

Recently, there was a brief report on the reductive debromination of the FireMaster® mixture (rate and extent of debromination reaction not given) by anaerobic microorganisms eluted from PCB-contaminated river sediments (Quensen et al., 1990; abstract only).

4.2.3 Degradation by plants and animals

No degradation of PBBs by plants has been recorded. In contrast to plants, animals can easily absorb PBBs and, though they have been found to be very persistent in animals, small amounts of PBB metabolites have been detected. The main metabolic products were hydroxy-derivatives and, in some cases, there was evidence of partially debrominated PBBs (cf. also section 6.3).

The metabolism of crude FireMaster® BP-6 by a pig gave a monohydroxypentabromobiphenyl (Kohli & Safe, 1976). The faeces of dogs fed FireMaster BP-6 contained a metabolite identified as 6-hydroxy-2,2′,4,4′,5,5′-hexabromobiphenyl (Gardner et al., 1979). However, the authors do not exclude microbial metabolism of PBB in the dog's gut followed by excretion into the faeces. Doses of 2,2′,4,4′,5,5′-[^{14}C]-hexabromobiphenyl given intravenously or orally to male rats were not subject to appreciable metabolism (Matthews et al., 1977). Metabolites were not detected in tissue extracts. A trace of radioactivity, which may have represented a PBB-metabolite, was found in bile and faeces, but the quantity was too small to be isolated and identified.

Some investigations imply that fish may debrominate the more highly brominated components of PBB-mixtures. Fish (juvenile *Salmo salar*), exposed in laboratory studies to FireMaster® BP-6 in water, contained several mono to pentabromobiphenyls that were not present in BP-6. Several additional pentabromobiphenyls were detected in fish fed FireMaster® BP-6-contaminated food. Fish fed octabromobiphenyl contaminated food contained unidentified penta-, hexa-, and heptabromobiphenyls in addition to the octabromobiphenyls (Zitko, 1977). It was not known whether the partially debrominated biphenyls were generated by the fish, or by the associated microflora.

Because the carbon-bromine bond is less stable than the carbon-chlorine bond, reductive debromination may be a degradative pathway of bromobiphenyls, and this reaction may have toxicological consequences not encountered with PCBs (Zitko & Hutzinger, 1976; Zitko, 1977).

4.2.4 Bioaccumulation

As expected from their high lipophilicity, PBBs show a marked tendency to accumulate in animals. However, data are available only on single links of food chains. It has been reported that similar compounds, e.g., PCBs, which are more widely spread in the environment, may have bioconcentration factors of 3-4 orders of magnitude between water and fish, with a further 1-2 orders of magnitude between whole fish and the fat storage tissues of fish predators, such as cormorant, heron, and seal (Pearson, 1982).

4.2.4.1 Aquatic organisms

Fish are the only aquatic organisms for which the bioaccumulation of PBBs has been investigated intensively. They serve as an example for the efficiency of such bioaccumulation (Damstra et al., 1982).

Fathead minnows (*Pimephales promelas*) caged in a river, where water levels of PBB (Firemaster® BP-6; probably measured as concentration of the main peak, 2,2′,4,4′,5,5′-hexabromobiphenyl) remained consistently at less than 0.1 μg/litre, concentrated these contaminants in their bodies more than 10 000 fold in two weeks of exposure (Hesse & Powers, 1978). In laboratory studies, accumulation coefficients of FireMaster® BP-6 and technical octabromobiphenyl from water (A = concentration in fish, μg/g wet weight/concentration in water, μg/ml) and from food (B = concentration in fish, μg/g wet weight/concentration in fish-food, μg/g) were determined. FireMaster® BP-6 reached values of A = 48 (after an exposure of 48 h) and B = 1.0 (in equilibrium) in juvenile Atlantic salmon (*Salmo salar*). The main component accumulated was 2,2′4,4′,5,5′-hexabromobiphenyl (Zitko, 1977). In contrast, octabromobiphenyl, as such, was not concentrated from water by Atlantic salmon (Zitko, 1977) and by rainbow trout (Norris et al., 1973), but a little uptake (B = 0.023) was observed from suspended food (Zitko, 1977). Instead of octabromobiphenyl, an unidentified hexabromobiphenyl was mainly accumulated (A = 1.73; B = 0.114; Zitko, 1977). In comparison with Aroclor 1254, the accumulation of FireMaster® BP-6 from water was less, but accumulation from food was a little higher than that of the corresponding PCB mixture (A = 282; B = 0.358; Zitko, 1977).

There are some differences in the accumulation of different congeners. Zitko & Hutzinger (1976) determined accumulation

coefficients of di-, tri-, and tetrabromobiphenyls in *Salmo salar*. The coefficients were calculated on the basis of accumulation from water after a 48-h exposure, and of the extrapolated equilibrium levels in fish fed contaminated food. The accumulation coefficients generally decreased with increasing degree of substitution during the uptake from water, and increased, when taken up from food. Of the dibromobiphenyls, the 3,4-isomer accumulated from water much less than the 2,6- and 2,4-isomer, and did not accumulate from food (Zitko & Hutzinger, 1976). Sugiura et al. (1978) dealing with the accumulation of lower substituted halobiphenyls (di-, tri- and tetra-) in killifish (*Oryzias latipes*) found that equilibrium accumulation from water was not reached during a period of 20 days. Their data, derived from a flow through test using PBB concentrations of 0.5–50 μg/litre, resulted in bioaccumulation factors (equilibrium extrapolated) ranging from 340 to 7340. They also found that accumulation factors were proportional to partition coefficients (*n*-octanol/water), when the coefficients were below 10^6, but not when the coefficients were above 10^6.

It is obviously important to note the lipid contents of test animals in bioaccumulation studies. For example, the bioconcentration factors of PCB congeners for whole fish tissue were proportional to the lipid content of the different species, which can range from 3 to nearly 20% (Sugiura et al., 1979). Gobas et al. (1989) reported lipid weight-based bioconcentration factors, log K_L ranging from 5.06 to 6.16, for some PBBs (di- to hexa-) in the guppy (*Poecilia reticulata*).

4.2.4.2 *Terrestrial organisms*

Bioaccumulation of PBBs in terrestrial organisms has been considered only for avian and mammalian species of farm and laboratory animals. Data were obtained through field observations (accumulation from soil), evaluation of an accident, and through controlled feeding studies.

Accumulation of soilborne PBBs has been studied in Michigan farms that were contaminated accidentally by FireMaster® FF-1 (Fries, 1985a). Ratios of PBB concentrations between the fat of farm animals (cows, sheep, pigs) and soil ranged from 0.10 to 1.86. Multiparous dairy cows had lower ratios, because of the excretion of PBB in milk during long-term lactation, and swine had higher ratios, because they ingest greater amounts of soil than other species (Fries, 1985a). In another study, PBB (FireMaster® FF-1)

was applied to the soil surface for experimental purposes. Sheep grazing for 180 days on these plots containing 33 mg PBB/m^2 (plot 1) and 48 mg/m^2 (plot 2) reached average residue levels in body fat of 0.30 and 0.79 μg PBB/g fat (quantified as concentrations of 2,2',4,4',5,5'-hexabromobiphenyl), respectively. Average residue concentrations in ewes that grazed for 60 days were nearly as great (Fries & Marrow, 1982). A second trial, conducted 3 years later after ploughing and reseeding the plots, showed that PBBs were distributed throughout the top 16 cm of soil with an average concentration of 0.14 μg 2,2',4,4',5,5'-hexabromobiphenyl/g soil in plot 2. Sheep grazing here for 136 days had average concentrations of 0.032 μg PBB/g body fat (Fries & Marrow, 1982).

The accidental ingestion of FireMaster® FF-1 by cattle on Michigan farms, first described by Jackson & Halbert (1974), resulted in high body burdens of PBBs. There were tissue levels of 2,2',4,4',5,5'-hexabromobiphenyl in the fat of cows of up to approximately 4000 mg/kg, nearly one year after high exposure (estimated total dose: 150-400 g of FireMaster® FF-1/cow over 14 days). Low exposure from cross contamination produced PBB concentrations in fat of less than 0.3 μg/g (Fries et al., 1978a,b; Fries, 1983).

Laboratory data for the accumulation of PBBs from known diets are given in Table 19 (diets supplemented with FireMaster®) and in Table 20 (diets supplemented with single PBB congeners). PBB levels in tissues of FireMaster®-exposed animals were expressed as the concentration of the most abundant constituent of the mixture, namely 2,2',4,4',5,5'-hexabromobiphenyl. Fries et al. (1976) additionally reported the concentration of a heptabromobiphenyl component (not the pure isomer). They found 31.4 mg/kg of this component in the body fat of hens fed diets containing 20 mg FireMaster®/kg feed for 63 days. The fate of minor constituents of the FireMaster® mixture is not evident from the studies compiled in Table 19.

Generally, accumulation of PBBs in body fat depended on dosage and duration of exposure. The highest accumulation coefficients (mg PBB/kg of tissue divided by mg PBB/kg feed) were found in minks (Table 19). PBB residue levels in the adipose tissue of treated minks were 60 times the amount in the diet (Aulerich & Ringer, 1979). According to the authors, the high diet-to-fat residue accumulations in the minks may be due, in part, to the relatively small subcutaneous fat deposits of the test

Table 19. Accumulation of PBBs in feeding studies on mammals and birds
a) Feeding of FireMaster®

Species	FireMaster®	Dietary concentration (mg/kg)	Feed intake (g/day)	Feeding period	Residue level (mg/kg)[a]			Weight basis	References
					Adipose	Liver tissue	Others		
Rat (male)	BP-6	0.1	20.9[c]	9 days	0.3	1.5	brain: 0.5	lipid	Render et al. (1982)
Rat (male)	BP-6	1	23.3[b]	9 days	1.7	8.3	brain: 1.8	lipid	
Rat (male)	BP-6	1	not specified	2-3 weeks	-	2.7	-	dry	Babish & Stoewsand (1977)
Rat (male)	BP-6	1	not specified	30 days	7.8	22.3	thymus: 21	lipid	Akoso et al. (1982a)
Rat (male)	BP-6	10	22.9[b]	9 days	27	135	brain: 12.3	lipid	Render et al. (1982)
Rat (male)	BP-6	10	not specified	30 days	61.6	310	kidney: 147	lipid	Akoso et al. (1982a)
Rat (male)	BP-6	50	not specified	2-3 week	-	341	-	dry	Babish & Stoewsand (1977)
Rat (male)	BP-6	50	26[b]	10 weeks	864	55	-	wet	Harris et al. (1978b)
Rat (male)	BP-6	100	22[b]	9 days	251	1213	brain: 103	lipid	Render et al. (1982)
Rat (male)	BP-6	100	not specified	30 days	1535	2507	thymus: 1044	lipid	Akoso et al. (1982a)
Rat (male)	BP-6	100	27[b]	10 weeks	3460	107	-	wet	Harris et al. (1978b)
Rat (male)	BP-6	150	26[b]	10 weeks	3574	295	-	wet	
Rat (male)	BP-6	200	26[b]	10 weeks	3242	245	-	wet	

Table 19 (contd).

Species	FireMaster®	Dietary concentration (mg/kg)	Feed intake (g/day)	Feeding period	Residue level (mg/kg)[a]			Weight basis	References
					Adipose	Liver tissue	Others		
Mouse (male)	BP-6	100	not specified	14 days	223	33.2	thymus: 391	wet	Corbett et al. (1978a)
Mouse (male)	BP-6	1000	not specified	11 days	39.5	2.5	-	wet	Corbett et al. (1975)
Mouse (male)	FF-1	5	not specified	3 weeks	-	7	thymus: 20	wet	Loose et al. (1981)
Mouse (male)	FF-1	5	not specified	6 weeks	-	15	thymus: 37.8	wet	
Mouse (male)	FF-1	167	not specified	3 weeks	-	154	thymus: 109	wet	
Mouse (male)	FF-1	167	not specified	6 weeks	-	623	thymus: 3088	wet	
Sheep (male)	BP-6	50	1000	30 days	25 (omental fat) 42 (renal fat) 17 (brisket fat)	12	heart: 4.3	wet	Gutenmann & Lisk (1975)
Pig	BP-6	20	1880[c]	4 weeks	0.33 (back fat)	-	-	wet	Ku et al. (1978)
Pig	BP-6	20	1880[c]	16 weeks	64 (back fat) 42.9 (leaf fat)	8.5	muscle: 6.6	wet	

Table 19 (contd).

Pig	BP-6	200	1230[c]	4 weeks	6.7 (back fat)	-	-	wet	Ku et al. (1978)
Pig	BP-6	200	1230[c]	16 weeks	503 (back fat) 459 (leaf fat)	17.2	muscle: 18.4	wet	
Mink	FF-1	2.5	not specified	136 days	149	-	muscle: 7.3	wet	Aulerich & Ringer (1979)
		6.25		172 days	-	-	brain: 66	wet	
		15.6		72-93 days	986	-	muscle: 70	wet	
Japanese quail (male)	not specified	10	-[b]	9 weeks	-	48	heart: 78	dry	Babish et al. (1975a)
		20	-[b]	9 weeks	-	374	kidney: 105	dry	
		100	-[b]	9 weeks	-	642	kidney: 725	dry	
Japanese quail (female)	not specified	10	-[b]	9 weeks	-	99	heart: 48	dry	
		20	-[b]	9 weeks	-	225	heart: 50	dry	
		100	-[b]	9 weeks	-	503	kidney: 428	dry	
Chicken (White leghorn hens)	BP-6	20	not specified	63 days	79.8	-	egg: 20	wet	Fries et al. (1976)
	BP-6	20	-[b]	4-8 weeks	-	-	egg: 30	wet	Cecil & Bitman (1978)
	BP-6	64	-[b]	4-8 weeks	-	-	egg: 100	wet	
	not specified	1	106[b]	5 weeks		0.6	egg: 1.5	wet	Ringer & Polin (1977)

Table 19 (contd).

Species	FireMaster®	Dietary concentration (mg/kg)	Feed intake (g/day)	Feeding period	Residue level (mg/kg)[a]			Weight basis	References
					Adipose	Liver tissue	Others		
	not specified	125	94[c]	5 weeks	-	-	egg: 209	wet	Ringer & Polin (1977)
	not specified	625	28.4[c]	5 weeks	-	80	-	wet	
Chicken (White leghorn hens)	FF-1	0.2	99[b]	5 weeks	(-)[d]	(-)[d]	egg: 0.3	wet	Polin & Ringer (1978a,b)
	FF-1	1	106[b]	5 weeks	(-)[d]	(-)[d]	egg: 1.5	wet	Polin & Ringer (1978a,b)
	FF-1	5	100[b]	5 weeks	(-)[d]	(-)[d]	egg: 7.4	wet	Polin & Ringer (1978a,b)
	FF-1	25	99[b]	5 weeks	(-)[d]	(-)[d]	egg: 43.4	wet	Polin & Ringer (1978a,b)
	FF-1	125	94[c]	5 weeks	(-)[d]	(-)[d]	egg: 215	wet	Polin & Ringer (1978a,b)
Chicken (White leghorn cockerels)	FF-1	0.1	35	2 weeks	-	-	carcass: 0.11	wet	Polin & Leavitt (1984)
	FF-1	1	35	2 weeks	-	-	carcass: 0.87	wet	Polin & Leavitt (1984)
	FF-1	10	-[b]	28 days	-	83.8	-	lipid	Dharma et al. (1982)
	FF-1	100	-[b]	28 days	-	752	-	lipid	Dharma et al. (1982)

[a] Measured as the concentration of 2,2',4,4',5,5'-hexabromobiphenyl.
[b] Values not significantly different from control values.
[c] Values significantly different from control values.
[d] Diagrams only, generally, the ratios of tissue PBB: diet PBB averaged 3:1 for adipose tissue, 0.8:1 for liver, and 1.5:1 for whole egg.

Table 20. Accumulation of PBBs in feeding studies on mammals and birds
b) Feeding of individual PBB congeners

Species	Species (sex)	Dietary concentration (mg/kg)	Feed intake (g/day)	Feeding period	Residue level (mg/kg lipid)			References
					Adipose tissue	Liver	Others	
2,2',4,4',5,5'-Hexabromobiphenyl	rat (male)	0.1	23.8[a]	9 days	0.2	1.7	brain: 0.3	Render et al. (1982)
		1	26.2[b]	9 days	3.1	11.4	brain: 1.1	
	rat (male)	1	not specified	30 days	16	68.6	kidney: 38.7	Akoso et al. (1982a)
	rat (male)	10	25.5[b]	9 days	31.2	181	brain: 11.5	Render et al. (1982)
	rat (male)	10	not specified	30 days	149	693	kidney: 373	Akoso et al. (1982a)
	rat (male)	100	23.2[a]	9 days	436	2558	brain: 143	Render et al. (1982)

Table 20 (contd).

Species	Species (sex)	Dietary concentration (mg/kg)	Feed intake (g/day)	Feeding period	Residue level (mg/kg lipid)			References
					Adipose tissue	Liver	Others	
	rat (male)	100	not specified	30 days	992	6062	thymus: 3841	Akoso et al. (1982a)
	chicken (male)	10	-[a]	28 days	-	105	-	Dharma et al. (1982)
		62	-[a]	28 days	-	751	-	
2,3',4,4',5,5'-Hexabromobiphenyl	rat (male)	1	not specified	30 days	9.1	23.5	kidney: 13.9	Akoso et al. (1982a)
	rat (male)	10	not specified	30 days (1982a)	69.1	242	thymus: 211	Akoso et al. (1982a)
	rat (male)	100	not specified	30 days	648	4340	thymus: 1639	Akoso et al. (1982a)
	chicken (male)	4	-[a]	28 days	-	32.5	-	Dharma et al. (1982)

Table 20 (contd).

	chicken (male)	10	-[a]	28 days	-	132	-	Dharma et al. (1982)
3,3',4,4',5,5'-Hexabromobiphenyl	rat (male)	0.1	23.6[a]	9 days	0	3.3	brain: 0	Render et al. (1982)
		1	24.7[a]	9 days	0.4	101	brain: 0	
	rat (male)	1	24.7[b]	30 days	0.6	125	thymus: 0	Akoso et al. (1982a)
	rat (male)	10	20.2[b]	9 days	1.9	-	brain: 0	Render et al. (1982)
	rat (male)	10	21.3[b]	30 days	6.9	448	thymus: 20.4	Akoso et al. (1982a)
	rat (male)	100	13.7[b]	9 days	22.5	1098	brain: 0	Render et al. (1982)

[a] Values not significantly different from control values.
[b] Values significantly different from control values.

animals, most of which were extremely emaciated at the time of death. Technical octabromobiphenyl was also accumulated from the diet, as shown by analyses of the bromine contents of the tissues (Norris et al., 1973; Lee et al., 1975a; Waritz et al., 1977). There was a dose-related build-up of bromine, predominantly in the fat, as well as in the liver, of rats fed octabromobiphenyl. For example, after 4 weeks of feeding 1, 10, 100, or 1000 mg octabromobiphenyl/kg feed, the bromine concentrations in adipose tissue were 2, 12, 120, and 600 times, respectively, greater than those of the controls (Lee et al., 1975a).

Data on accumulation of technical decabromobiphenyl have not been found in the literature.

Isomer specific accumulation has been studied for three hexabromobiphenyl congeners. The residue levels in rats and chickens fed with 2,2′4,4′,5,5′-; 2,3′,4,4′,5,5′- or 3,3′,4,4′,5,5′-hexabromobiphenyl are listed in Table 20. In many cases, the lowest concentrations in tissues were found with 3,3′,4,4′,5,5′-hexabromobiphenyl and the highest, with 2,2′,4,4′,5,5′-hexabromobiphenyl.

4.3 Ultimate fate following use

4.3.1 Disposal of PBB-contaminated animals and wastes from the Michigan disaster

Accidental contamination of livestock feed in 1973 by PBBs led to the destruction of over 30 000 animals in Michigan. As the toxicity and other physical and chemical properties of PBBs were at that time not so well known, the State of Michigan decided to locate an environmentally safe site for the burial of contaminated carcasses (Shah, 1978). A site in Kalkaska County was chosen and test drilled in order to determine the long-range protection for groundwaters in the area. The Kalkaska disposal site received over 10 000 animal carcasses most of which contained PBB levels above 1 mg/kg fat, and close to 20 000 carcasses with PBB levels ranging from 0.3 to 1 mg/kg. This animal disposal site contains approximately 45 kg of PBBs in all buried carcasses (Shah, 1978; see section 5.1.2.3. for groundwater studies).

The Gratiot County landfill near St. Louis became operational in late 1970, and it was designed only for general municipal solid waste disposal. According to the Michigan Chemical Corporation report to the Environmental Protection Agency, PBB wastes were

disposed of in the landfill between 1971 and 1973. Wastes containing large amounts of PBBs (60–70%) were received in the landfill before any information about the toxic effects of PBBs on animals was publicly known (Shah, 1978).

The Forest Waste Disposal site consists of an 11-acre, abandoned, municipal and industrial waste landfill and 9 surface impoundments. It is located in Genesee County, Michigan, and is surrounded by agricultural land and undeveloped woodlands and wetlands. Forest Waste Disposal conducted landfill operations from 1972 to 1978. PBB-contaminated feed has recently been found in the landfill. A decontamination programme has been recommended (Anon., 1988).

The Michigan Chemical Corporation stated that, in their opinion, PBBs would eventually undergo oxidative/biological degradation forming carbon dioxide, water, and bromide ion (Cordle et al., 1978). However, studies on PBBs in soil indicate that they may remain in soils for many years, because of their resistance to degradation (Jacobs et al., 1976).

4.3.2 *Thermal decomposition of PBBs*

There is little information on the pyrolysis of PBBs. The products of the thermal decomposition of PBBs depend on the temperature as well as on the amount of oxygen present.

Norris et al. (1973) constructed a special apparatus to measure the relative amounts of bromine from octabromobiphenyl converted during combustion, when these materials were used as additives in thermoplastic resins. An exact temperature is not given. Hydrogen bromide and bromine were not detected.

Waritz et al. (1977) carried out experiments to determine the approximate lethal temperature of hexa- and octobromobiphenyl. The dense clouds of fumes obtained at 350 °C were lethal to rats whereas those produced at 290 °C were not. The fumes were not analysed.

Earlier experiments by Benbow & Cullis (1975) on the pyrolysis of decabromobiphenyl pressed together at 160 °C with polystyrene and polypropylene, respectively, showed that, during flameless combustion, decabromobiphenyl appeared to be volatilized virtually unchanged from the polymer, whereas when the polymer burned, the decabromobiphenyl was converted quantitatively to hydrogen bromide.

In these early experiments, the analytical methods were not so refined that it was possible to detect furans and dioxins. O'Keefe (1978) pyrolyzed samples of FireMaster FF-1 at 380-400 °C in open glass tubes and in tubes sealed after nitrogen flushing. Analysis by low resolution direct probe mass spectrometry showed the presence of tetra- and pentabrominated dibenzofurans in extracts of the open tube pyrolyzed material and trace levels of tetrabromodibenzofuran in those from PBB pyrolyzed under nitrogen.

Buser et al. (1978) studied the pyrolysis of FireMaster BP-6 with oxygen in sealed tubes. The flame retardant was completely destroyed at 700 °C, but, at 600 °C, new compounds were formed, one of which was probably tetrabromodibenzofuran.

The diversity of possible brominated and mixed brominated furans and their toxicological implications led to further refinements in analytical methods (Buser, 1986) and to the demand for, and synthesis of, suitable standard isomers (Mason et al., 1987a; Sovocool et al., 1987a; Munslow et al., 1989). There are over 5000 halogenated dibenzodioxins and dibenzofurans containing chlorine and/or bromine, over 400 of which are 2,3,7,8-substituted tetra-, penta- and hexahalo congeners suspected to be of high toxicity (Buser 1987). These mixed congeners are of particular importance with regard to chemical waste burning (Schäfer & Ballschmiter, 1986).

Investigations into the pyrolysis of FireMaster BP-6 in the absence of oxygen have shown that small amounts of bromobenzenes and lower brominated biphenyls are formed (600-900 °C), but no furans (Thoma et al., 1987a; Thoma & Hutzinger, 1989).

In contrast, the pyrolysis of FireMaster BP-6 in an open quartz tube (700-900 °C) in the presence of oxygen yielded over 3 mg/kg (ppm) of di- to heptabrominated dibenzofurans, though the pyrolysis of pentabromodiphenyl ethers yielded brominated dibenzofurans at over 300 times this level (Thoma et al., 1987a). In the presence of polystyrene and polyethylene, higher levels of brominated (mona-tetra) dibenzofurans (over 8 and 51 mg/kg (ppm), respectively) were found (Thoma et al., 1987a). Pyrolysis of FireMaster BP-6 with PVC at 800 °C yielded mixed bromide/chloride biphenyls, the bromine atoms being substituted by the chlorine. No ring closure to dioxins and furans occurred (Thoma et al., 1987b).

Decabromobiphenyl was pyrolyzed for 10 min at 800 °C in a loosely plugged quartz tube. The pyrolysates were extracted with toluene and after clean-up, analysed using GC/MS. No brominated dioxins or dibenzofurans were detected (detection limits 0.2-0.8 μg/g). The clean-up was said to be very difficult because of the formation of a large number of brominated compounds that were not dioxins or furans. Debromination of decabromobiphenyl appeared to be the main reaction, but no details were given (Atochem, 1987).

Zacharewski et al. (1988) pyrolyzed samples of FireMaster® BP-6 in open quartz tubes at 800 °C for 10 min. The resulting products, mainly tetrabromodibenzofurans (1183 μg/g) but also tribromo-, pentabromo-, hexabromo-, and heptabromodibenzofurans (187, 584, 107, and 11 μg/g, respectively), were tested for toxicity (see section 8.12.3.2). Very little is known about the toxicities of brominated and brominated/chlorinated dioxins and furans, but they are estimated to be of the same order as those of PCDD and PCDF (Mason et al., 1987a; Safe, 1987).

Analysis of actual environmental samples has also been carried out. Monobromo-polychloro substituted benzenes, biphenyls, dibenzodioxins, and dibenzofurans have been detected in solid material collected from a chimney of an industrial waste incinerator (Schäfer & Ballschmiter, 1986). Brominated dibenzofurans with a very small amount of mixed brominated/chlorinated compounds were detected in soot from an accidental fire at a bowling alley (Buser, 1986). Schwind et al. (1988; 1989) analysed samples from a municipal waste incinerator and detected for the first time a complete series of tetrahalogenated dibenzofurans (Cl_4DF, Br_1Cl_3DF, Br_2Cl_2DF, Br_3Cl_1DF and Br_4DF). It is possible that PBCDD/F could occur during the incineration of flame retardant-treated plastic material, which produces PBDD and PBDF. These could react with PVC via the mixed brominated/chlorinated dioxins and furans to PCDD and PCDF (Schwind et al., 1988).

As with PCB disposal, the destruction of PCB-contaminated waste should be carefully controlled. For PCBs, a burning temperature above 1000 °C for 2 seconds is recommended (WHO/EURO, 1987).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 Air

Only one report is available on PBB levels in air. It refers to air samples taken in the vicinity of three PBB-manufacturing or -processing plants in the USA (Stratton & Whitlock, 1979). Traces of hexabromobiphenyl (0.06-0.10 ng/m^3) were found at two of the three industrial sites examined.

Further information on PBB levels in ambient air, e.g., near municipal incinerators, is lacking.

5.1.2 Water and sediments

5.1.2.1 Surface waters

Surface waters have been monitored in the vicinity of PBB-producing or -processing industrial sites in the USA and in the vicinity of the Gratiot County landfill (Michigan, USA), which had received 122 000 kg of wastes containing 60-70% PBBs between 1971 and 1973. The results are summarized in Table 21.

Depending on the sources, the predominant PBB compounds detected in surface waters were hexabromobiphenyl and decabromobiphenyl. However, only Stratton & Whitlock (1979) determined all PBB homologues from Br_1 to Br_{10}, the percentage composition of some of which is given in Table 22.

5.1.2.2 Sediments

Generally, PBBs reach higher concentrations in sediments (Table 23) than in the associated waters (Table 21).

PBB concentrations in sediments of the Pine River were as high as 77 mg/kg near the Michigan Chemical Corp. plant. The assays conducted from July 1974 to April 1975, upstream and downstream of the plant, showed a decline in sediment PBB content to 6.2 mg/kg, half a mile downstream, and to 0.1 mg/kg, 24 miles or 29 miles downstream (Hesse & Powers, 1978).

Table 21. PBB levels in surface waters near sites of manufacture, use, or disposal in the USA

Site	Date of sampling	No. of samples	PBB compound examined	PBB concentration (μg/litre)	References
Pine River (downstream from the Michigan Chemical Co., St. Louis)	1974	8	HxBB	0.01-3.2	Hesse (1975)
Tittabawassee River[a]	1974	2	HxBB	< 0.01	
Canal (called Platti Kill) in the vicinity of White Chemical Co., Bayonne, New Jersey	1977	3	total PBB (MoBB-DeBB)	not detected-46	Stratton & Whitlock (1979); DeCarlo (1979)
Canal (discharging into Kill van Kull River) in the vicinity of Standard T Chemical Co., Staten Island, New York	1977	1	total PBB (HxBB-DeBB)	< 0.2	Stratton & Whitlock (1979)

Table 21 (contd).

Site	Date of sampling	No. of samples	PBB compound examined	PBB concentration (μg/litre)	References
Storm sewer, receiving swamp, etc. in the vicinity of Hexcel Fine Organics Sayreville, New Jersey	1977	5	total PBB (HxBB-DeBB)	< 0.2-210	Stratton & Whitlock (1979); DeCarlo (1979)
Drain waters at or near the margin of the Gratiot County landfill, Michigan	1977	not specified	HxBB	0.1-14	Shah (1978); Rosenblatt et al. (1982)

[a] Note that PBBs were not detected in fish from the Tittabawassee River in 1974 but were detected in 1983 (see Table 30).

Table 22. Percentage of different PBB homologues detected in surface water samples taken in the vicinity of PBB-producing plants[a]

PBB homologues	Bayonne, New Jersey (White Chemical Corp.)[b]		Sayreville, New Jersey (Hexcel Corp.)[c]	
	Sample 1	Sample 2	Sample 1	Sample 2
PeBB	1	0	-	-
HxBB	4	2	5	< 1
HpBB	2	2	1.6	< 1
OcBB	2	17	1	1
NoBB	15	20	1	2.6
DeBB	76	58	91	96

[a] From: Stratton & Whitlock (1979).
[b] Producer of octa- and decabromobiphenyl along with bromobiphenyl ethers.
[c] Producer of laboratory quantities of various PBBs.

Concentrations measured upstream were all less than the sensitivity limit of 30 μg/kg with the exception of one sample collected a quarter of a mile upstream of the plant, which contained 60 μg/kg (Hesse, 1975). This latter analysis was repeated in 1977 (Hesse & Powers, 1978) giving 350 μg/kg (detection limit 100 μg/kg).

Hesse & Powers (1978) compared the PBB levels of Pine River sediments from the same locations over a period of time after the termination of FireMaster® BP-6 production. The results of the 1976 and 1977 analyses showed that PBB distributions and concentrations in the sediments had not changed significantly in the three years after PBB manufacture stopped.

Various PBB homologues were identified again only by Stratton & Whitlock (1979) who examined aquatic sediments, sludge deposits, and marsh soils near the sites of manufacture and use of PBBs in New Jersey and New York (see Table 24).

More recently, sewage sludge has been analysed for PBBs (Strachan et al., 1983). The authors did not detect any PBBs, PCBs, or chlorinated hydrocarbon pesticides in the three sludge samples obtained from sewage treatment plants in three Indiana cities (USA). However, the detection limit for PCBs and PBBs

Table 23. PBB levels in sediments and sludge from surface waters near sites of manufacture, use, or disposal in the USA

Site	Date of sampling	No. of samples	PBB compound examined	PBB concentration (µg/kg dry weight)	References
Near Michigan	1974/75	19	HxBB	< 30-77 000	Hesse (1975)
Chemical Co.	1974	9		< 100-9200	Hesse & Powers (1978)
Pine River	1976	9		< 100-1200	
	1977	8		< 100-500	
Tittibawassee River	1974	2		tr-16	Hesse (1975)
Near White Chemical Co., Bayonne, New Jersey: Sediments from Platti Kill Canal and Kill van Kall River	1977	3	total PBB (MoBB-DeBB)	< 10-20	Stratton & Whitlock (1979)
Sludge from Platti Kill Canal		1		431 000	

Table 23 (contd).

Site	Date of sampling	No. of samples	PBB compound examined	PBB concentration (μg/kg dry weight)	References
Near Standard T Chemical Co., Staten Island, New York Sediment from Kill van Kull River (at discharge site)	1977	1		60	
Near Hexcel Fine Organics, Sayreville, New Jersey Marsh Soil	1977	1	total PBB (MoBB-DeBB)	4600	Stratton & Whitlock (1979) DeCarlo (1979)
Gratiot County landfill, Michigan Associated sediments of surface drain waters	1977	not specified	HxBB	up to 17 000	Shah (1978) Rosenblatt et al. (1982)

Table 24. Concentration of PBB-homologues in aquatic sediment, sludge deposit, or marsh soil samples taken in the vicinity of PBB-producing or -processing plants[a] (μg/kg dry weight)

PBB	Bayonne, New Jersey (White Chem. Corp.)[b]			Staten Island, New Jersey (Standard T Chem Corp.)[c]	Sayreville, New Jersey (Hexcel Corp.)[d]
	Sediment samples:[e] 1 + 2	3	Sludge	Sediment[e]	Marsh soil[e]
MoBB	-	n.d.	540	n.d.	n.d.
DiBB	-	n.d.	2200	n.d.	n.d.
TrBB	-	n.d.	4300	n.d.	n.d.
TeBB	-	n.d.	n.d.	n.d.	n.d.
PeBB	-	n.d.	590	n.d.	n.d.
HxBB	n.d.	10	3800	40	30
HpBB	n.d.	10	3300	20	n.d.
OcBB	n.d.	n.d.	3600	n.d.	n.d.
NoBB	n.d.	n.d.	22 500	n.d.	80
DeBB	n.d.	n.d.	390 000	n.d.	4500

[a] From: Stratton & Whitlock (1979).
[b] Producer of octa- and decabromobiphenyl along with bromobiphenyl ethers.
[c] Major user of FireMaster® BP-6.
[d] Producer of laboratory quantities of various PBBs.
[e] n.d. = Not detected (detection limit = < 10 μg/kg).

with the GC-MS system used was about 10 μg/g, and this apparently is not sensitive enough, even for PCBs. For example, the amounts of PCBs found in sewage sludge of German (Lorenz, 1983) and Canadian (Webber et al., 1983) cities ranged from 1.8 to 2.5 μg/g (dry weight) and from 0.13 to 1.61 μg/g (dry weight), respectively. Values for PBBs have not been reported in these investigations.

Surficial sediments from the St. Lawrence River (USA/Canada) were analysed for HxBB, but the compound was not detected (estimated detection limit: 1 ng/g) at the ten stations surveyed (Sloterdijk, 1991).

5.1.2.3 Groundwater

Groundwater monitoring data from the Gratiot County landfill (Michigan, USA) mentioned above, have shown trace levels of PBBs, even outside the landfill area (see Table 25). However, so far, domestic drinking-water wells have not shown any traces of PBBs (Shah, 1978). Groundwater near the disposal site of PBB-contaminated animals and other products (see section 4.3.1) in Kalkaska County (Michigan, USA) is reported not to be contaminated by PBBs (Shah, 1978).

Table 25. PBB levels in groundwater from Gratiot County landfill, 1977[a]

Site	No. of samples	PBB compound examined range (μg/litre)	PBB concentration
Test wells within the landfill site	4	HxBB	0.5-26
Observation wells outside the landfill area	11		0.1-4.4
Domestic drinking-water wells near the landfill	not specified		not detected

[a] From: Shah (1978).

5.1.3 Soil

Data on soil pollution by PBBs are available for areas of manufacture, use, or disposal of PBBs (Table 26), and for soils from fields, etc. of the PBB-contaminated Michigan farms (Tables 27 and 28).

Concentrations of PBBs in soils from industrial sites were highest (more than 2000 mg/kg) in areas around the Michigan Chemical Company (see Table 26). Although such highly contaminated soils were removed (Hesse & Powers, 1978), Hill et al. (1982) still found, some years later, PBB levels up to 2130 mg/kg in soils of the former manufacturing site. Various PBB

Table 26. PBB levels in soils near sites of manufacture, use, or disposal in the USA

Site	Date of sampling	No. of samples	PBB compound examined	PBB concentration (range) dry weight	References
Michigan Chemical Co., St. Louis, Michigan					
bagging area	not specified	1	HxBB	3500 mg/kg	Hesse (1975); Hess & Powers (1978)
loading area of the plant	not specified	1	HxBB	2500 mg/kg	
"former manufacturing site"	not specified	3	PBB ($C_{12}H_6Br_4$-$C_{12}H_3Br_7$)	16-2130 mg/kg	Hill et al. (1982)
Vicinity of White Chemical Co., Bayonne, New Jersey					
150 m east	1977	1	total PBB	4.250 mg/kg	Stratton & Whitlock (1979)
150 m west of the plant	1977	1	($C_{12}H_9Br_1$-$C_{12}Br_{10}$)	1.135 mg/kg	DeCarlo (1979)
not specified	not specified		PBB	0.75-2.8 mg/kg	Di Carlo et al. (1978)

Table 26 (contd).

Vicinity of Standard T Chemical Co., Staten Island, New York	1977	4	total PBB (MoBB-DeBB)	10-100 µg/kg	Stratton & Whitlock (1979)
75 m south west				30	
900 m west				10	
1500 m south				10	
700 m east (prevailing down- wind direction)				100	
Vicinity of Hexcel Fine Organics, Sayreville, New Jersey	1977		total PBB (MoBB-DeBB)		Stratton & Whitlock (1979); DeCarlo (1979)
75 m southeast		1		40 µg/kg	
Soil in roadside ditch		1		3400 µg/kg	

Table 26 (contd).

Site	Date of sampling	No. of samples	PBB compound examined	PBB concentration (range) dry weight	References
Gratiot County landfill, St. Louis, Michigan					
Samples inside of the landfill from the uppermost 2.5 cm (after capping of the landfill)	not specified	not specified	"PBB" HxBB	12 (16) mg/kg	Rosenblatt et al. (1982)
Sample somewhat distant from the landfill, in the area of the Michigan Chemical plant			"PBB" (HxBB)	61 µg/kg	

Table 27. Concentration of PBB homologues detected in soil samples taken in the vicinity of PBB-producing or processing plants (μg/kg dry weight)

PBB	Bayonne, New Jersey[a] (White Chemical Corp.)[c]	Staten Island, New York[a] (Standard T-Chemical Corp.)[d]	Sayreville, New York[a] (Hexcel Corp.)[e]	Michigan[b] (Michigan Chemical Corp.)[f]
MoBB	n.d.[g]	n.d.[g]	n.d.[g]	-
DiBB	n.d.[g]	n.d.[g]	n.d.[g]	-
TrBB	n.d.[g]	n.d.[g]	n.d.[g]	-
TeBB	n.d.[g]	n.d.[g]	n.d.[g]	< 1000-510 000
PeBB	n.d.[g]	n.d.-100	n.d.[g]	4000-60 000
HxBB	15-30	n.d.-10	40-90	12 000-670 000
HpBB	30-110	n.d.-10	n.d.-90	< 1000-190 000
OcBB	90-150	n.d.	n.d.-170	-
NoBB	330-2200	n.d.	n.d.-440	-
DeBB	530-2100	n.d.-10	n.d.-2600	-

[a] Data from: Stratton & Whitlock (1979); No. of samples = 2, 4, 2 respectively.
[b] Data from: Hill et al. (1982); No. of samples = 3.
[c] Producer of octa- and decabromobiphenyl along with bromobiphenyl ethers.
[d] Major user of FireMaster® BP-6.
[e] Producer of laboratory quantities of various PBBs.
[f] Producer of FireMaster® BP-6.
[g] n.d. = Not detected (detection limit = < 10 μg/kg).

Table 28. Composition and concentration of PBBs in soil samples from former FireMaster® manufacturing plant site (St. Louis, Michigan)[a]

Compound	% Composition (concentration in mg/kg)			
	FireMaster® Lot #5143	Soil 1	Soil 2	Soil 3
Tetrabromobiphenyls	< 0.1	23.9 (510)	11.3 (6)	(< 1)
Pentabromobiphenyls				
2,2',4,5,5'-	3.9	2.8 (60)	9.4 (5)	12.5 (2)
2,2',4,4',5-	< 0.1	5.2 (110)	(< 1)	(< 1)
2,3',4,4',5-	5.7	27.7 (590)	9.4 (5)	12.5 (2)
Hexabromobiphenyls				
2,2',4,4',5,5'-	54.9	24.4 (520)	56.6 (30)	62.5 (10)
2,2',3',4,4',5-	10.3	4.7 (100)	7.5 (4)	6.2 (1)
2,3',4,4',5,5'-	5.0	1.9 (40)	5.7 (3)	6.2 (1)
2,3,3',4,4',5-	2.1	0.5 (10)	(< 1)	(< 1)
Heptabromobiphenyls				
2,2',3,4,4',5,5'-	12.8	5.2 (110)	(< 1)	(< 1)
2,2',3,3',4,4',5-	1.7	3.8 (80)	(< 1)	(< 1)
(Total PBBs)		(2130)	(53)	(16)

[a] Adapted from: Hill et al. (1982).

homologues from Br_4 to Br_{10} were present in the industrial soil samples (see Table 27).

Hill et al. (1982) identified not only PBB homologues, but also the isomeric composition of PBBs in the soil samples from the Michigan Chemical Corp. plant (Table 28). Thus, they provided more exact analytical data and were able to make an interesting comparison with the original FireMaster® mixture; conclusions could then be drawn on the environmental fate of PBBs (section 4.2). According to Shah (1978), test samples of the Gratiot County landfill showed that, in general, the concentrations of PBBs in the fill increased with depth and were highest at a depth of 3 to 7.6 m below the top of the refuse.

As a consequence of the Michigan cattle food mixing error, the soils of the farms involved have been contaminated by PBBs, mainly through the faeces of the exposed animals. Fries (1985b)

calculated that about 145 kg of PBBs were distributed in this way, and that most of this was located on 20-25 farms. (The total number of quarantined farms was over 500; Robertson & Chynoweth, 1975).

Concentrations of PBBs in soil samples from fields that had received PBB-contaminated manure were as high as 371 μg/kg (dry weight), whereas levels in samples from manure piles and from dirt exercise lots were as high as 2000 μg/kg (Jacobs et al., 1978; Fries, 1985b).

Soil contamination by PBBs can result in PBB accumulation in animals, when they have direct access to the contaminated soil. This is most likely to occur when animals are confined to dirt lots on which manure-containing PBB has been deposited. Crops grown on PBB-contaminated soils are not considered an important source of PBB contamination in animals (Fries & Jacobs, 1986).

Soils from industrial sites have, in general, been more heavily contaminated than Michigan soils.

5.1.4 *Feed and food*

5.1.4.1 *Feed*

Contamination of feed by PBBs has been reported only in connection with the Michigan PBB incident.

In 1973, about 290 kg (Fries, 1985b) - 1000 kg (IARC, 1978) of FireMaster® FF-1 was inadvertently mixed in cattle feeds and delivered to Michigan farms.

Three feed preparations appeared initially to be involved in the Michigan episode with PBB levels as follows:

Feed No. 405, 2.4 mg PBB/kg,
Feed No. 410, 1790 mg PBB/kg,
Feed No. 407, 4300 mg PBB/kg
(Cordle et al., 1978).

A concentration as high as 13 500 mg PBB/kg was also cited (Kay, 1977; Di Carlo et al., 1978; Damstra et al., 1982). Feed of one highly contaminated farm (Halbert farm) is reported to have contained 2900 mg PBB/kg (Fries, 1985b).

In 1974, 68% of 1770 feed samples collected in Michigan contained PBB residues: 60% in the range of trace to 0.99 mg/kg, and 8% over 1 mg/kg. Resampling in 1975 revealed that 6% of 1208 feed samples were contaminated and that fewer than 0.16% contained more than 1 mg PBB/kg. In 1976, only 0.3% of 663 samples analysed were contaminated: no samples contained more than 0.1 mg/kg (Di Carlo et al., 1978).

PBB residues were not detected in harvested forages grown on soils with residue levels as high as 0.3 mg/kg (Fries & Jacobs, 1980).

In 1974 and 1975, low-level feed contamination with PBBs was detected in Indiana and Illinois, which are neighbours of Michigan (Di Carlo et al., 1978).

5.1.4.2 *Food*

Again, almost all the data available on PBB residues in food are derived from the Michigan cattle food contamination incident in 1973.

The extent to which the general population was exposed depended on where they obtained their milk, dairy products, and eggs, i.e., direct from the contaminated farms or from sources where contaminated products had been mixed with non-contaminated samples. Table 29 shows examples of some PBB levels in Michigan foods. Whereas in 1974 milk from some highly contaminated cows contained PBB concentrations of up to 900 mg/kg fat (Robertson & Chynoweth, 1975), canned milk samples contained concentrations of up to 1.6 mg/kg fat (Cordle et al., 1978). The most highly contaminated milk (1 to > 100 mg PBB/kg milk fat) originated from a total of 40 herds with different levels of PBBs at the time of detection (Fries, 1985b). In 1975, PBBs were still detected in milk from some herds (Kay, 1977).

Data on meat can be derived from Table 33, which shows PBB levels in Michigan farm animals.

Milk contains far less fat than meat (about 4% versus 30%), and butterfat contains only 40% of the PBB concentration found in the animal from which it comes (Fries et al., 1978b; Rosenblatt et al., 1982). Among the dairy products, PBBs are again concentrated in the high-fat products (Murata et al., 1977; Zabik et al., 1978).

Table 29. Some examples of PBB levels in food (contaminated as a consequence of the Michigan PBB incident in 1973)

Product	Year of sampling	PBB concentration (mg/kg)	References
Milk[a]	1974	2.8-270.5[h]	Cordle et al. (1978)
Milk[b]	1974	44-900[h]	Robertson & Chynoweth (1975)
Milk[c]	1974	43-56[h]	Jackson & Halbert (1974)
Milk[d]	1974	up to 595	Kay (1977); IARC (1978)
Milk[e]	1974	1-> 100[h]	Fries (1985b)
Canned milk	1974	1.15-1.62[h]	Cordle et al. (1978)
Dry skimmed milk[f]	1974	0.75-1.5	Isleib & Whitehead (1975)
Fluid milk processors' products	1974	< 0.02-1.15	
Butter	1974	1-2[h]	Cordle et al. (1978)
Cheese	1974	1.4-15.0[h]	
Milk[g]	1975	1-13[h]	Kay (1977); IARC (1978)
Eggs	1974	up to 59.7	

[a] = Collected from individual farms.
[b] = Collected from 21 cows.
[c] = Collected from 2 cows (having 174 and 200 mg PBBs/kg in body fat, respectively).
[d] = Collected from 22 farms.
[e] = Collected from 28 herds.
[f] = From one dairy plant.
[g] = Collected from 16 herds.
[h] = On a fat basis.

In May 1974, the US Food and Drug Administration (FDA) established the following enforcement limits for unavoidable residues of PBBs in foods: 1 mg/kg in the fat of meat, milk, and dairy products, 0.3 mg/kg in animal feeds, 0.1 mg/kg in eggs. These enforcement guidelines were reduced in November 1974 to 0.3 mg/kg in the fat of meat, milk, and dairy products, and 0.5 mg/kg in eggs and animal feeds. In February 1977, the FDA rejected a petition to lower the enforcement guideline level to 0.02 mg/kg for all food products (IARC, 1978). However, according to Fries (1985b), final legislation, Act 77, lowered the tolerance to 0.02 mg/kg in the body fat of all cull dairy cows offered for slaughter. (Unlike the situation under the previous regulations, the finding of a single animal with a higher than legal body fat level did not lead to quarantine and the disposal of the whole herd.) As

a result of the rigid quarantine policy, the food levels of PBBs decreased in Michigan. In 1975, none of 18 milk samples, 3 out of 14 butter samples, and none of 13 cheese samples exceeded FDA guidelines (0.3 mg/kg). Also in 1975, 245 of 2040 meat samples were contaminated with PBBs: 24 contained more than 0.3 mg/kg. None of the meat specimens collected in 1976 exceeded FDA guidelines: 96% of 1430 samples were contaminated, but only 1 sample contained more than 0.6 mg/kg of PBBs. A market basket survey of meat in 1976 revealed detectable PBBs in only 1 out of 102 samples in Michigan (Di Carlo et al., 1978).

Additional information on PBB findings is presented in several government reports, which are cited by Di Carlo et al. (1978). According to these reports 29 170 products had been assayed. In 1974, 14 out of 16 milk samples, 4 out of 34 butter samples and 11 out of 23 cheese samples, collected in Michigan, were found to exceed FDA guidelines for PBBs. Another survey showed that 24.9% of 272 finished product samples, collected from May to October 1974, were contaminated with PBBs and that 15.8% contained more than 0.3 mg/kg (Di Carlo et al., 1978).

PBBs were also detected in other states in the USA, for example in beef in Iowa, duck in Wisconsin, chicken in Alabama, Mississippi, New York, and Texas, and turkey in Indiana: the levels were extremely low. During 1975 and 1976, PBBs were found in 9 out of 597 food samples outside of Michigan (Di Carlo et al., 1978).

Food contamination, not derived from the Michigan PBB-incident, becomes evident, when looking at PBB levels in fish (see Table 30) some of which are used for human consumption. For example, skinless fillets of carp from the Pine River, captured in the vicinity of Michigan Chemical Company, contained 1.33 mg PBBs/kg (wet weight basis) which is approximately equivalent to 30 mg/kg on a fat weight basis (Hesse & Powers, 1978). This was obviously greatly in excess of the US FDA tolerance limit for beef, a tolerance limit for fish has not been established (Hesse & Powers, 1978).

More recent information on "background" PBB levels in food may be expected in future via a USA data collection programme (Foodcontam) initiated by the US Food and Drug Administration which includes PBBs besides other chemicals (Minyard et al., 1989).

Table 30. PBB levels in fish

Year	Region	Species	Type of sample	PBB concentration (μg/kg)	Weight basis	PBB examined	References
1974	Pine River, downstream from St. Louis (vicinity of Michigan Chemical Co.)	Carp (*Cyprimus carpio*)	skinless fillets	not detected-1330	wet	HxBB	Hesse & Powers (1978)
		White sucker		670			
		Northern pike		540			
		Bullhead		450-780			
1974	Tittabawassee River	Carp (*Cyprimus carpio*)		not detected			
		Freshwater drum (*Aplodinotus grunniens*		not detected			
1976	Pine River, downstream from St. Louis (vicinity of Michigan Chemical Co.)	Carp (*Cyprimus carpio*)		60-750			
		Northern pike		180-230			

Table 30 (contd).

Year	Region	Species	Type of sample	PBB concentration (μg/kg)	Weight basis	PBB examined	References
1976	Pine River, downstream from St. Louis (vicinity of Michigan Chemical Co.)	Largemouth bass	skinless fillets	not detected-740	wet	HxBB	Hesse & Powers (1978)
		Smallmouth bass		130			
		Rockbass		320-700			
1977	Kill van Kull River (vicinity of White Chemical Co., Bayonne, New Jersey); Port Johnson	Killifish	whole	220	dry	total PBB HxBB-DeBB	Stratton & Whitlock (1979)
1977	Kill van Kull River (vicinity of Standarad T Chemical, Staten Island, New York); canal at discharge site	Killifish	whole	230	dry	total PBB HxBB-DeBB	
Not specified	Lake Huron (Saginaw Bay)	Yellow perch		0.3-0.8			Kreis & Rice (1985)
	Saginaw Bay	Catfish		21.0			

Table 30 (contd).

1983	Pine River	Hogsucker	whole	6000	fat	most abundant congeners	Jaffe et al. (1985)
1983	Chippewa River	Carp		5300-15 000			
1983	Tittabawassee River			140-160			
1983	Shiawassee River			120			
1983	Flint River			15-32			
1983	Saginaw River			80-200			
1983	Saginaw Bay			110-1100			

Four samples of cow's milk from Germany have been analysed for PBBs (Krüger, 1988). Three congeners were detected; BB 153 (0.025-0.053 μg/kg milk fat), BB 180 (0.001-0.007 μg/kg) and BB 187 (0.005-0.014 μg/kg). The other 30 congeners covered by the method were not detected with detection limits ranging from 0.001 to 0.003 μg/kg milk fat (see Table 33).

The processing and cooking of contaminated food have been found to have some potential for reducing PBB levels. Spray-drying appeared to reduce the contents of PBBs in whole milk and skim milk by 30-36% and 61-69%, respectively (Murata et al., 1977; Zabik et al., 1978). Pressure cooking of chicken pieces also resulted in a loss of PBBs, however, part of the PBBs lost were found in the drip (Zabik et al., 1978).

5.1.5 Other products

Antibiotics used for attending farm animals were also found to be contaminated: Levels of PBBs in aureomycin, which was distributed by the Michigan Farm Bureau, were as high as 70 mg/kg (Di Carlo et al., 1978).

5.1.6 Terrestrial and aquatic organisms

5.1.6.1 Aquatic and terrestrial plants

Only few data on PBB contamination of aquatic and terrestrial plants are available. Stratton & Whitlock (1979) analysed algae (e.g., filamentous green algae) from surface waters in the vicinity of White Chemical (Bayonne, New Jersey) and near Standard T Chemical Company (Staten Island, New York) for PBBs (MoBB through DeBB). The two samples did not contain detectable levels of PBBs (detection limit: 10 μg/kg, dry weight). However, bottom sediments taken in the same location contained hexa- and heptabromobiphenyl.

Surface contamination was observed on terrestrial vegetation in the vicinity of PBB facilities (up to 92 mg/kg dry weight; Stratton & Whitlock, 1979). As Chou et al. (1978) reported, the PBB contamination of field soils in Michigan (USA) did not result in any detectable surface contamination of field crops.

5.1.6.2 Animals

a) Wildlife

Most earlier data available on PBB contamination of wildlife refer to freshwater fish (Table 30) and birds (Tables 31 and 32), primarily waterfowl in the USA. Recent reports refer to PBB contamination of fish-eating mammals and birds from marine environments in the USA (Kuehl et al., 1991) and in Europe (Jansson et al., 1987, 1992; Krüger, 1988). Residues were found also in terrestrial mammals (Jansson et al., 1992) and in freshwater and marine fish in Europe (Krüger, 1988; Jansson et al., 1992).

Table 30 gives PBB levels in fish captured for analysis in industrialized areas of the USA, at various distances from PBB-containing or -using facilities. PBBs were detected in several fish species from all rivers or bays examined. The PBB levels ranged up to a maximum of 1.33 mg/kg wet weight (approximately equivalent to 30 mg/kg on a fat basis) found in carp from the Pine River near Michigan Chemical Company (Hesse & Powers, 1978).

No apparent change in PBB concentrations was observed in Pine River fish between 1974 and 1976 (Hesse & Powers, 1978; see also Table 30). Although Michigan Chemical Co. had terminated PBB production in 1974, even in 1983, Jaffe et al. (1985) detected PBB in fish from the Saginaw River system, with highest concentrations in fish from Pine and Chippewa Rivers (Table 30). While carp from Tittabawassee River, to which Pine River joins, did not contain any detectable PBBs in 1974, PBB-residues were detected (approximately 150 μg/kg on a fat basis) in 1983 (Table 30).

Various PBB homologues were examined in killifish (*Oryzias latipes*) from Kill van Kull River near White Chemical Co. (Bayonne, New Jersey). The main component found was NoBB. In the vicinity of a FireMaster®-using facility (Staten Island, New York), killifish samples contained only HxBB (Stratton & Whitlock, 1979).

PBB contamination has been reported in wild ducks collected within two miles of the Michigan Chemical Corporation plant (Table 31), in eggs of waterfowl nesting around Green Bay and other areas of Lake Michigan and on Lake Michigan island (Table 32), and, in bald eagles found moribund or dead in 13 US states (Table 31).

Table 31. PBB residues in birds (ducks and bald eagles)

Year	Region	Species	Type of sample	No. of samples[a]	PBB concentration[b] (mg/kg wet weight) mean	range	median	References
1974	Pine River within two miles downstream from St. Louis	Mallard	breast tissue (skinless)	3	0.25			Hesse & Powers (1978)
		Wood duck			0.29			
		Teal			1.8			
1976		Mallard	breast tissue:					
			skinless	3[c]	0.24			
			with skin	3[c]	2.00			
		Wood duck						
				4[c]	0.17			
				4[c]	2.70			
1977		Wood duck	breast tissue:					
			skinless	4[c]	0.08			
			with skin	4[c]	0.23			

Table 31 (contd).

Year	Region	Species	Type of sample	No. of samples[a]	PBB concentration[b] (mg/kg wet weight) mean	range	median	References
1977		Teal	breast tissue:					
			skinless	0[c] (1)	not detected			
			with skin	0[c] (1)	not detected			
	13 US states	Bald eagle (*Haliaeetus leucocephalus*)	found moribund or dead;					Kaiser et al. (1980)
			carcass	10 (32)[d]		0.03-0.27	0.07	
			brain	7		0.03-0.17	0.05	

[a] Number of samples containing residues; median is based on this number. Total number of samples in parentheses.
[b] PBB values were based on the major hexabromobiphenyl peak (BB 153).
[c] Paired samples.
[d] Detection limit: 0.02 mg PBBs/kg.

Table 32. PBB residues in eggs of fish-eating and non-fish-eating waterbirds from Green Bay and Lake Michigan (USA)

Year	Collection site	Species	No. of eggs[a]	PBB concentration[b] (mg/kg wet weight) geometric mean	range	References
		Fish eater				
1975	Green Bay (Sensila Wildlife Area)	Little gull (*Larus minutus*)	1	n.d.		Heinz et al. (1985)
1977	three Lake Michigan islands off the tip of Door County, Wisconsin	Red-breasted merganser (*Mergus serrator*)	114 (109)	0.06	n.d.-0.13	Haseltine et al. (1981)
1977	islands in north-western Lake Michigan	Red-breasted merganser (*Mergus serrator*): eggs from the same nests				Heinz et al. (1983)
		randomly selected	49	0.05		
		unhatched	49	0.04		
1977	Lake Michigan (Gravel Island)	Herring gull (*Larus argentatus*)	9 (9)	0.18	0.11-0.25	Heinz et al. (1985)

Table 32 (contd).

Year	Collection site	Species	No. of eggs[a]	PBB concentration[b] (mg/kg wet weight) geometric mean	range	References
1977	Green Bay (Lone Tree Island)	Common tern (*Sterna hirundo*)	10 (10)	0.06	0.02-0.22	Heinz et al. (1985)
	Green Bay (St. Vital Island)	Common tern (*Sterna hirundo*)	2 (2)	0.03	0.03-0.04	
	Green Bay (Portage Point)		2 (2)	0.03	0.02-0.06	
	Green Bay (Cat Island)	Double-crested cormorant (*Phalocrocorax auritus*)	4 (3)	0.01	n.d.-0.02	
	Lake Michigan (Fish Island)		6 (3)	0.02	n.d.-0.05	
	Green Bay (Oconto Marsh)	Black-crowned night-heron (*Nycticorax nycticorax*)	1 (1)	0.02		
	Green Bay (Oconto Marsh)	Green-backed heron (*Butorides striatus*)	1	n.d.		

Table 32 (contd).

Year	Collection site	Species	No. of eggs[a]	PBB concentration[b] (mg/kg wet weight) geometric mean	range	References
		Non-fish eater				
1977	Three Lake Michigan islands off the tip of Door County, Wisconsin	Mallard (*Anas platyrhynchos*)	22	n.d.		Haseltine et al. (1981)
1977	Lake Michigan (three islands off the tip of Door County, Wisconsin)	Gadwall (*Anas strepera*)	4	n.d.		
		Black duck (*Anas rubripes*)	3	n.d.		

[a] Number of collected eggs (in parentheses: number of eggs with quantifiable levels of PBBs).
[b] PBB values were based on hexabromobiphenyl;
n.d. = No residue of quantifiable level. Level over which quantification was possible: 0.02 mg/kg.
Samples with no detectable residues were calculated in the means as one-half the quantification level.

Approximately one third of bald eagles examined contained PBB residues (see Table 31).

Concentrations of PBBs in duck samples with skin left on were considerably higher than those in skinless samples (see Table 31) indicating that much of the PBBs is associated with the skin or fat layer between the skin and muscle (Hesse & Powers, 1978).

While the majority of ducks analysed from the Pine River contained measurable concentrations of PBBs (Table 31), the eggs of ducks from Lake Michigan islands did not contain detectable PBB residues (Table 32). In contrast, most eggs of fish-eating waterbirds from Green Bay and Lake Michigan showed PBB residues (Table 32). Highest concentrations were detected in herring gull eggs (0.18 mg/kg wet weight), perhaps reflecting their year round residence on the Great Lakes (Heinz et al., 1985).

Stratton & Whitlock (1979) analysed a snapping turtle captured in the vicinity of Hexcel Fine Organics Division (Sayreville, New Jersey) for hexa- to decabromobiphenyls and found a tissue concentration of 20 μg hexabromobiphenyl/kg (dry weight).

Di Carlo et al. (1978) reported on PBB contamination of miscellaneous wildlife, such as deer, rabbits, coyotes, and ravens, without, however, specifying the sampling locations and the levels of contamination.

In Europe, 2,2',4,4',5,5'-hexabromobiphenyl (BB 153) was found in fish from German and Swedish rivers at concentrations ranging from 0.3 to 0.6 μg/kg lipid (Krüger, 1988; Jansson et al., 1992; see also Tables 33 and 34). A trout sample from a breeding farm contained much lower levels of PBBs than the fish samples from the rivers (Krüger, 1988).

A residue of 22 μg BB 153/kg lipid was observed in pooled samples of osprey specimens found dead in various parts of Sweden (Jansson et al., 1992; Table 34).

Swedish reindeers (pooled samples) showed BB 153 levels as low as 0.04 μg/kg lipid (Jansson et al., 1992; Table 34).

PBBs (as a group) were not found in otters (*Lutra canadensis*) from a region relatively remote from industrial sites in north-eastern Alberta (Canada) (Somers et al., 1987).

Table 33. Average concentrations (μg/kg lipid) of PBB congeners in fish, seals, cows, and human milk samples

Congener	River fish (Germany) (No. = 17)	Baltic fish (No. = 6)	North Sea fish (No. = 11)	Spitbergen seal (No. = 5)	Cow's milk (Germany) (No. = 4)	Human milk (Germany) (No. = 25)
BB 103	0.02	0.12	0.10	< 0.02	< 0.02	not analysed
BB 131 + 142/146	0.30	0.62	0.25	0.03	< 0.02	< 0.01
BB 132	0.33	1.25	0.62	0.15	< 0.02	0.05
BB 135 + 144/151	0.69	4.10	1.48	0.46	< 0.02	0.12
BB 147/135 + 144	0.21	0.31	0.25	< 0.02	< 0.02	< 0.01
BB 148/136	0.10	0.13	0.11	< 0.02	< 0.02	< 0.01
BB 149	0.26	0.45	0.53	< 0.02	< 0.02	< 0.01
BB 153	0.60	2.39	1.31	0.81	0.04	1.03
BB 154/151	0.22	0.54	0.37	< 0.02	< 0.02	0.01
BB 155	0.66	2.64	1.11	0.40	< 0.03	0.05
BB 169	< 0.01	15.16	< 0.01	< 0.01	< 0.01	0.05
BB 176	0.03	< 0.01	0.02	< 0.01	< 0.01	< 0.05
BB 178	0.18	0.87	0.36	0.03	< 0.01	0.09
BB 179	0.08	0.04	0.04	< 0.01	< 0.01	< 0.05
BB 180	0.02	< 0.01	0.02	< 0.01	< 0.04	0.02
BB 181 + 174	0.01	0.01	0.01	< 0.01	< 0.01	< 0.05
BB 184	0.05	0.09	0.03	< 0.01	< 0.01	0.01
BB 185	0.03	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05

Table 33 (contd).

Congener	River fish (Germany) (No. = 17)	Baltic fish (No. = 6)	North Sea fish (No. = 11)	Spitbergen seal (No. = 5)	Cow's milk (Germany) (No. = 4)	Human milk (Germany) (No. = 25)
BB 186	0.30	0.40	0.16	0.01	< 0.01	0.02
BB 187 + 182	0.03	0.05	0.04	0.03	0.01	0.33
BB 188	0.11	0.28	0.11	< 0.01	< 0.01	0.01
BB 192	0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05
BB 194	0.07	< 0.02	0.04	< 0.02	< 0.02	< 0.05
BB 197	0.11	0.11	0.08	< 0.02	< 0.02	0.04
BB 198	0.27	0.14	0.12	< 0.02	< 0.02	< 0.05
BB 200 + 204	0.41	0.36	0.24	< 0.02	< 0.02	0.02
BB 201	0.09	< 0.02	0.03	< 0.02	< 0.02	< 0.05
BB 202	0.87	0.42	0.36	< 0.02	< 0.02	0.01
BB 206	0.05	< 0.03	0.04	< 0.03	< 0.03	< 0.01
BB 207	0.06	< 0.03	0.02	< 0.03	< 0.03	< 0.01
BB 208	0.16	0.04	0.04	< 0.03	< 0.03	< 0.01
PBB	6.3	30.5	7.9	1.9	0.05	2.0

From: Krüger (1988).

Table 34. Concentrations (μg/kg lipid) of 2,2',4,4',5,5'-HxBB (BB 153) in pooled biological samples[a]

Species	Number of specimens in the homogenate	Sampling site	Concentration of BB 153
Rabbit (*Oryctlagus cuniculus*)	15	S. Sweden	not detected
Moose (*Alces alces*)	13		not detected
Reindeer (*Rangifer tarandus*)	31	N. Sweden	0.037
White fish (*Coregonus* sp.)	35		0.29
Arctic char (*Salvelinus alpinus*)	15	S. Sweden	0.42
Herring (*Clupea harengus*)	100	Bothnian Bay	0.092
Herring (*Clupea harengus*)	60	Baltic Proper	0.16
Herring (*Clupea harengus*)	100	Skagerrak	0.27
Ringed seal (*Pusa hispida*)	7	Svalbard	0.42
Grey seal (*Halichoerus grypus*)	8	Baltic Sea	26
Osprey (*Pandion haliaetus*)	35	S. Sweden	22

[a] From: Jansson et al. (1992).

Fish samples (freshwater and marine species) collected in 1983 from an industrial area of Japan (Osaka) did not contain "PBBs" (not specified) (Watanabe & Tatsukawa, 1990).

Recently, PBBs have been identified in bottlenose dolphins (*Tursiops truncatus*) collected during the 1987/88 mass mortality event along the Atlantic Coast of the USA. All three animals (females), analysed for PBBs (tetrabromo- to hexabromobiphenyl congeners) within a subset of the screening programme for anthropogenic contaminants, contained PBBs at concentrations ranging from 14 to 20 ng/g lipid (Kuehl et al., 1991).

In Europe, PBBs have been detected in seals (*Phoca vitulina; Pusa hispida*), guillemots (*Uria aalge; U. lomvi*), and white-tailed sea eagles (*Haliaeetus albicilla*). The concentrations (estimated by comparison with the technical product FM BP-6) ranged from 3 to 280 μg/kg lipid (Jansson et al., 1987). The concentrations of PBBs in comparable samples from the Baltic Ocean were all higher than concentrations in samples from the Arctic Ocean. The same was true for polybrominated biphenyl ethers and PCBs (Jansson et al., 1987).

Concentrations of BB 153 determined in marine fish ranged from 0.2 to 2.4 μg/kg lipid (Krüger, 1988; Jansson et al., 1992; see

also Tables 33 and 34). BB 153 levels of 0.4-26 μg/kg lipid were found in seals (Krüger, 1988; Jansson et al., 1992; see also Tables 33 and 34).

Detailed isomer-specific PBB analyses were carried out by Krüger (1988) in fish (several species) from the Baltic and North Seas and from sections of the Lippe and Rur rivers in North Rhine-Westphalia, Germany. Seal samples from Spitsbergen (Norway) were also included in this investigation (Table 33). All samples contained PBBs. The smallest number of PBB congeners was found in seals (n = 5) from an area remote from industrial sites. The main components were different hexabrominated isomers with 2,2',4,4',5,5'-hexabromobiphenyl reaching a mean concentration of 0.8 μg/kg fat. The mean concentrations of several PBB congeners and isomers (penta- to nonabrominated biphenyls) measured in fish (n = 35) ranged, mostly, between 0.01 and 2 μg/kg fat. The pattern of PBB congeners found in fish differed in a characteristic manner, depending on the different capture sites. While relatively high amounts of nona- and octabromobiphenyls (besides polybrominated biphenyl ethers) were present in fish from German rivers (n = 17; several species), hexabrominated biphenyls were predominant in fish from the North Sea and the Baltic Sea (n = 17; several species). In all samples from the Baltic Sea (n = 6), 3,3',4,4',5,5'-hexabromobiphenyl was found in relatively high concentrations (maximum concentration: 36 μg/kg fat), but it was not detected in samples from the North Sea and from rivers. The concentrations of the other hexabrominated biphenyls were mostly higher in fish from the Baltic Sea than in fish from the North Sea.

b) Farm animals

Farm animals in Michigan were contaminated by PBBs, when FireMaster® FF-1 was accidentally mixed with animal feed in mid-1973 (see section 4.1). The PBB levels resulting from this event varied greatly with the extent of exposure. Data reported in the literature are compiled in Table 35. The extent of contamination can be seen from the fact that, during the months following the event, 172 dairy and beef herds (18 000 animals), 32 swine herds (3500 animals), 16 sheep flocks (1200 animals), and 92 chicken flocks (1.5 million birds) were destroyed (Isleib & Whitehead, 1975; Robertson & Chynoweth, 1975; Mercer et al., 1976). In relation to these great numbers, the portion of highly contaminated animals was small (e.g., 40 herds of cattle, as can be derived from contamination values measured in milk (section 5.1.4.2).

Table 35. PBB levels in farm animals (derived from the Michigan cattle food contamination incident in 1973)

Year	Animal (Type of sample)	PBB concentration[a] (mg/kg)	References
1974	Poultry[b] (tissue)	4600	Kay (1977); IARC (1978)
Not specified	Cattle (fat)	up to 200	Pearson (1982)
Not specified	Aborted calves	120-400	Kay (1977)
1974	Cattle[c] (body fat)	110-2480	Robertson & Chynoweth (1975); Mercer et al. (1976)
1974-75	Cattle[d] (fat)	9-4100	Fries et al. (1978b)
1974	Cattle[b] (tissue)	up to 2700	Kay (1977); IARC (1978)
1974	Cattle[j] (body fat)	174-200	Jackson & Halbert (1974)
March (1975)	Dairy cattle[e]	1-12	Kay (1977)
1975	Cows[f] (tissue-fat)	not detected-1.69	Isleib & Whitehead (1975)
1975	Steers and heifers[g] (tissue-fat)	not detected-2.27	
1975	Pigs[h] (tissue-fat)	not detected-0.58	
1975-76	Cattle[i] (male and female) (eye fat)	not detected-0.13	Cook et al. (1978a)
Not specified	Cattle[k] (body fat)	not detected-3.8	Mercer et al. (1976)

[a] PBB values were based on 2,2',4,4',5,5'-hexabromobiphenyl.
[b] From 22 farm premises.
[c] 21 highly exposed cows.
[d] 32 cows from one herd heavily contaminated during September/October 1973, and 9 calves borne to these cows in 1974.
[e] 16 herds of dairy cattle with a history of feed levels from 1 to 14 mg/kg PBB.
[f-h] Slaughter house survey during a 3-month period (January-April 1975).
[f] Number of samples: 216; mean-PBB: 0.018 mg/kg.
[g] Number of samples: 247; mean-PBB: 0.030 mg/kg.
[h] Number of samples: 213; mean-PBB: 0.017 mg/kg.
[i] Cattle of 5 affected herds.
[j] 2 cows of the Halbert farm.
[k] Cattle of 12 affected herds.

5.2 General population exposure

Apart from data collected after the Michigan disaster, there is only limited information on exposure of the general public. PBBs have been detected in humans in the vicinity of manufacturing

premises and in a few sites in the USA and Europe, not directly connected with PBB contamination.

5.2.1 Quantified data on human exposure

5.2.1.1 Worldwide

For most human populations, direct data on exposure to PBBs from various sources have never been documented. This is true also for the possible exposure of the general population from the use of PBB-containing plastic products, and from fumes, generated in the combustion of these products inadvertently in fires, or from burning in dumps (Kay, 1977), and, additionally, from sources such as PBB-containing landfills or PBB-manufacturing and processing plants.

5.2.1.2 The Michigan Accident

Widespread human exposure resulting from direct contact with contaminated feed, and, primarily, from the consumption of PBBs in meat, eggs, and dairy products has been reported from the state of Michigan, USA (Kay, 1977; Landrigan, 1980; Fries, 1985b; Table 36). Many Michigan residents were exposed to PBBs between the onset of contamination in the autumn of 1973 and the establishment of the quarantine of affected farm animals in the spring of 1974. There was considerable variation in both lengths and levels of exposure. At least 2000 families (primarily farmers and their neighbours) received the heaviest exposure (Meester & McCoy, 1976; IARC, 1978).

Brilliant et al. (1978) concluded from their results of human milk analyses, conducted in 1976, that about 8 million of the 9.1 million residents of Michigan have detectable body burdens of PBBs. Further studies (see Table 37) confirmed this widespread distribution of PBBs.

The amount of PBBs consumed or absorbed by the various groups in Michigan cannot be determined accurately (Safe, 1984). However, there have been some trials to estimate the possible exposure to PBBs of farm families and other people. The estimates were based on kinetic data and other observations, e.g., time and level of animal exposure, residue levels in herds at the time of the contamination, and serum levels of exposed people.

Table 36. Approximate distribution of PBBs in the Michigan episode[a]

Item	Amount (kg)
Total released	295
Not fed to livestock	45
Fed to livestock	250
Eliminated in faeces	125
Absorbed by animals	125
In human foods before regulation	94

[a] Modified from: Fries (1985b).

In this way, Fries et al. (1978a) estimated (assumptions: see Fig. 4), that the total exposure of an individual in a farm family consuming its own milk was, for example, 9.8 g over the 230-day period, during which the contamination was undetected. The cumulative intake over time is shown in Fig. 4. In addition, the authors concluded that the most highly exposed people consumed from 5 to 15 g PBBs over a 230-day period via milk. The projected intake of PBB via the meat of cows slaughtered for home consumption would have exceeded the projected intake from milk.

Application of a pharmacokinetic model (Tuey & Matthews, 1980) to the mean serum concentrations for residents of quarantined farms resulted in similar values, e.g., about 170 mg mean total exposure per individual and 11.7 g highest exposure to PBBs (Fries, 1985b; Brown & Nixon, 1979) supposed a consumption of 1-20 g of PBB by families on the most contaminated farms.

The exposure of an individual in the general population would have a pattern over time as projected above for the farm family (Fries et al., 1978a). However, the exposure level would have been much less, because of dilution in the normal marketing channels (the mixing of milk from a large number of producers; the use of meat of cull dairy cattle for hamburger and processed meat products). The calculations of Fries (1985b) indicate that total exposure was about 9-10 mg for an average male with an average adipose content. However, the individual with the highest PBB serum concentration was projected to have had a total exposure of about 800-900 mg.

Table 37. Distribution of serum levels of PBBs, Michigan, 1974[a]

Serum PBBs (μg/litre)	Quarantined farms				Non-quarantined farms			
	Adults		Children		Adults		Children	
	(Number)	(%)	Number	(%)	Number	%	Number	%
0	3	3.7	-	-	21	28.4	-	-
2-19	43	52.4	8	28.6	52	70.3	29	96.7
20-90	19	23.2	10	35.7	1	1.4	1	3.3
100-490	11	13.4	3	10.7	0	0	0	0
500-2260	6	7.3	7	25.0	0	0	0	0
Total	82	100.0	28	100.0	74	100.1	30	100.0

[a] From: Humphrey & Hayner (1975).

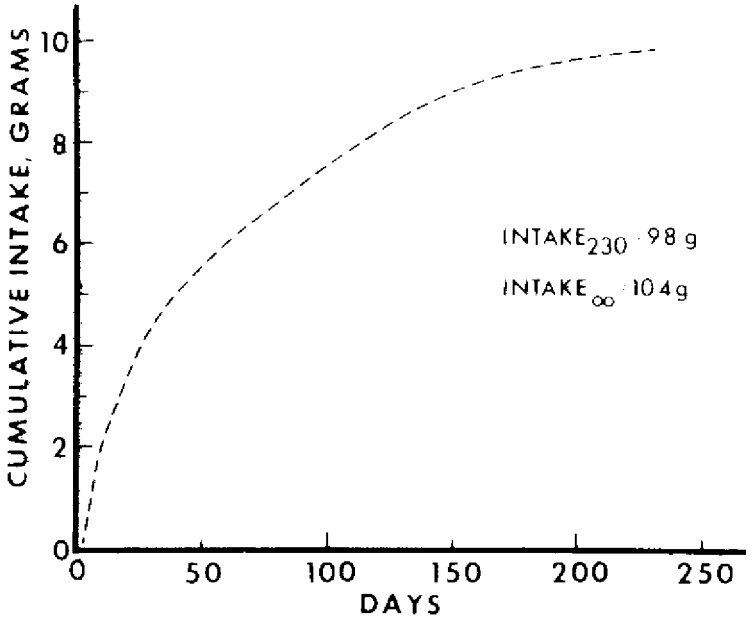


Fig. 4. Estimated cumulative intake of polybrominated biphenyls by an individual drinking one litre of milk per day from cows that ate 28 g of polybrominated biphenyl per day for 15 days. From: Fries et al. (1978a).

People who bought food primarily from quarantined farms were thought to have been exposed 10 to 100 times more than the typical retail store customer (Schwartz & Rae, 1983): ca. 100 mg of PBBs versus 1-10 mg (Brown & Nixon, 1979).

While many dust and cobweb samples found in the buildings of some PBB-contaminated farms had very high residue levels, the amount of PBB residue involved is said not to be sufficient to be an important contributor to animal residues (Fries & Jacobs, 1980) and, possibly to human exposure.

5.2.2 *Human monitoring methods for PBBs*

Usually, suitable human monitoring data, as such, are used to describe the real exposure to a toxic chemical. As an indicator of human exposure to PBBs, the presence of PBBs in adipose tissue, breast-milk, whole blood, serum, red and white blood cells (Bekesi et al., 1979a,b), and human hair oils (Stratton & Whitlock, 1979) has been assessed. The most commonly used specimens were serum, breast-milk, and adipose tissue (see Tables 38-40).

Table 38. Human monitoring data: PBB levels in the Michigan population (USA)

Year	Number of specimens	Positive findings (%)	Specimen (tissue, etc.)	Group	PBB-concentration[a] Range	Arithmetic mean	Geometric mean	Median	Detection limit	References
1974	82	96.3	serum	adults from quarantined farms	not detected-2260			14	not specified	Humphrey & Hayner (1975)
	28	100	serum	children from quarantined farms	2-2260			35	not specified	
	5	100	serum	lactating females from quarantined farms	3-1068					
1976	524		serum	Michigan farmers		23.7		2.6	0.2 µg/litre	Wolff et al. (1978a); Lilis et al. (1978)
	283		serum	residents on quarantined farms	0.2-> 1000	33.9		3.9		
	153		serum	residents of non-quarantined farms	0.2-50	2.9		1.4		
	40		serum	consumers of products from quarantined farms	0.3-1000	56.6		4.2		

Table 38 (contd).

Year	Number of specimens	Positive findings (%)	Specimen (tissue, etc.)	Group	Range	PBB-concentration[a] Arithmetic mean	Geometric mean	Median	Detection limit	References
	28		serum	consumers of products from non-quarantined farms	0-50	3.4		2.2		
				consumers and residents: quarantined farms:						Wolff et al. (1978)
	40		serum	females < 18 years		28.0		2.3	0.2 µg/litre	
	102		serum	females > 18 years		18.2		2.5		
	51		serum	males < 18 years		67.7		7.3		
	129		serum	males > 18 years		28.2		4.4		
				consumers and residents: non-quarantined farms:						
	37		serum	females < 18 years		3.1		1.3		
	57		serum	females > 18 years		1.7		0.9		
	35		serum	males < 18 years		4.8		1.7		
	51		serum	males > 18 years		3.1		2.2		

Table 38 (contd).

1976	485	serum	consumers and residents: quarantined farms:					Chanda et al. (1982)
	27	serum	0-5 years	0.2-64.2	10.15		not specified	
	137		6-18 years	0.0-962.4	27.22		not specified	
	321		> 18 years	0.2-1778.0	24.42			
1976	321	serum	consumers and residents: non-quarantined farms:					Chanda et al. (1982)
	18		0-5 years	0.2-37.4	6.42		not specified	
	104		6-18 years	0.0-42.6	3.25		not specified	
	177		> 18 years	0.0-94.0	3.03		not specified	
1976	292	serum	Michigan children			3.41	not specified	Barr (1980)
	143		females			2.72	not specified	
	149		males			4.23	not specified	
	33		0-4 years			2.75	not specified	
	77		5-8 years			5.59	not specified	
	81		9-12 years			3.18	not specified	
	101		13-16 years			2.65	not specified	
1976-77	3639	serum	Michigan residents with various degrees of exposure	0-1900	21.2	3.0	1 µg/litre	Landrigan et al. (1979); Landrigan (1980)

Table 38 (contd).

Year	Number of specimens	Positive findings (%)	Specimen (tissue, etc.)	Group	Range	PBB-concentration[a] Arithmetic mean	Geometric mean	Median	Detection limit	References
1976-77	1750		serum	contaminated farm residents	0-1900	26.9		4.0	1 μg/litre	Landrigan et al. (1979); Landrigan (1980)
	1114			farm product recipients	0-659	17.1		3.0		
	216			chemical workers and families	0-1240	43.0		4.5		
	559			volunteers	0-111	3.4		2.0		
1976-77	52		serum	women at the time of delivery	not detected-1150	26.2		2.5	1 μg/litre	Landrigan et al. (1979)
1977	3683		serum	Michigan PBB cohort	< 1-3150	23.2	4.1	3	not specified	Kreiss et al. (1982)
	1888			males			5.8			
	1795			females			2.8			
1978	1681		serum	Michigan residents (randomly selected)						Wolff et al. (1982)
	1120	68.9		adults	0.2-120.5	1.3		0.6	0.2 μg/litre	
	461	72.7		children	0.2-37.2	1.8		0.8		
	232			Upper Peninsula				0.2		
				Lower Peninsula:						
	467			Detroit Area				0.5		
	191			Muskegon Area				1.7		
	791			remainder of state				0.9		

Table 38 (contd).

				Muskegon County:					
	54		serum	male adults		4.0	2.6	0.2 μg/litre	Wolff et al. (1982)
	74			female adults		2.1	1.4		
	36			male children		4.9	3.4		
	27			female children		3.8	2.0		
1975-80			serum	Michigan PBB cohort:					Eyster et al. (1983)
	61			pregnant females	not detected-1068		3.5	3	1 μg/litre
	56			non-pregnant females	not detected-873		3.1	2	
	29			male chemical workers	1-1200		25.4	20	
	83			male farm and other workers	not detected-1515		5.4	4	
1974-75	5	100	milk	women from quarantined farms	0.21-92 660			not specified	Humphrey & Hayner (1975)
1976			milk (fat)	lactating women (randomly selected from Michigan:					Brilliant et al. (1978)
	53	96		Lower Peninsula	not detected-1.2			0.068	0.1 mg/kg
	42	43		Upper Peninsula	not detected-0.320				

Table 38 (contd).

Year	Number of specimens	Positive findings (%)	Specimen (tissue, etc.)	Group	Range	PBB-concentration[a] Arithmetic mean	Geometric mean	Median	Detection limit	References
1976-77	32	100	milk (fat)	women at the time of delivery (Michigan PBB cohort)	0.032-93	3.61[b]		0.225[b]		Landrigan et al. (1979)
1976-78	2986	88.5 milk	milk	lactating women (self-selected)	not detected-2	0.097	0.1	0.06	< 0.05 mg/kg	Miller et al. (1984)
1975-80				Michigan PBB cohort						Eyster et al. (1983)
	47		milk (fat)	pregnant females	not detected-92.7		0.312[b]	0.250[b]	0.001 mg/kg	
1974-75	15	100	adipose	persons from quarantined farms	0.104-175[c]					Humphrey & Hayner (1975)
1975-76	53		adipose	quarantined farmers		1.965				Meester & McCoy (1976)
	29	100		non-quarantined farmers		0.516				
	9	100		city residents		0.226				

Table 38 (contd).

	116		fat	members of farm families	0.58-273.0					
1977	19		subcu-taneous fat	children with known exposure to PBBs *in utero* and/or through breast milk						Weil et al. (1981); Schwartz & Rae (1983); Seagull (1983)
	10	100		"high exposure"	0.116-20.960		4.218			
	9	100		"low exposure"	0.010-0.074		0.050			
1978	844	97.3	adipose	Michigan residents (randomly selected)	< 0.002-36.7	0.4		0.199	0.002 mg/kg	Wolff et al. (1982)
	87			Upper Peninsula				0.015		
				Lower Peninsula:						
	255			Detroit Area				0.16		
	84			Muskegon Area				0.50		
	418			remainder of state		0.24	0.050			
1975-80	32		adipose lipid	Michigan PBB-cohort: pregnant females	not detected-174		0.330	0.540	0.001 mg/kg	Eyster et al. (1983)
	56			non-pregnant females	not detected-0.619		0.00057	0.460		

Table 38 (contd).

Year	Number of specimens	Positive findings (%)	Specimen (tissue, etc.)	Group	Range	PBB-concentration[a] Arithmetic mean	Geometric mean	Median	Detection limit	References
	29			male chemical workers	0.4-350		5.29	6.0		
	83			male farm and other workers healthy male	70-350		1.65	1.05		
Not specified	7	100	adipose lipid (subcutaneous)	volunteers, aged 20-30 years	0.01-2.72				0.001 mg/kg	Schnare et al. (1984)
1983	15	100	perirenal post-mortem adipose tissue (wet wt)	autopsy cases from the "high" exposure area of Michigan (Grand Rapids)	0.032-1.65	0.475		0.32	0.0005 mg/kg	Miceli et al. (1985)

[a] Expressed as the concentration of the major hexabromobiphenyl component (BB 153) in µg/litre serum or mg/kg milk, or adipose tissue, respectively.

[b] The sample measuring 93 mg/kg was excluded from statistical analysis.

[c] Most in the order of 1 mg/kg.

The last one has been preferred for analysis, since depot fat is the predominant storage site of PBBs (and other persistent halogenated hydrocarbons), and, therefore, allows an increased detectability of body burden. For example, had serum PBBs been used alone as an indicator of exposure in the PBB survey of the general population of Michigan (Table 38), only 70% of the 839 individuals would have been considered exposed. When adipose tissue results are added, an additional 24% indicate exposure, raising the positive rate to 94%. Even though the limit of detection was an order of magnitude higher (2.0 μg/litre in adipose tissue vs. 0.2 μg/litre in serum), the partition ratio of approximately 300:1 made the adipose limit of detection a more sensitive indicator of exposure (Wolff et al., 1982; Anderson, 1985).

On the other hand, collection of hair, blood, and breast-milk samples is simpler and less invasive than adipose tissue biopsy. Moreover, with some exceptions, significant correlations between adipose tissue and blood serum or breast-milk PBB levels were found (section 6.2). Further advantages and limitations of these techniques are discussed in detail by Anderson (1985) and Fries (1985b).

It should be noted that levels of PBBs in breast-milk may not be comparable between studies unless the concentration is adjusted for fat content, because the fat content of breast-milk varies widely from woman to woman, and the value increases during feeding (Rogan et al., 1980).

Although the accurate relationship between observed body levels of PBBs and individual exposure to PBBs is not clear (Safe, 1984), PBB concentrations in human tissues can give some idea of the levels of exposure (Kimbrough, 1980a).

5.2.3 *Human monitoring data*

In the following subsection, human monitoring data are presented from contaminated farms in Michigan, from Michigan state, and from other countries.

Most data available refer to the Michigan PBB incident in 1973-74 (Tables 38 and 39). Because, in this case, the spilling of PBBs started from farms, the Michigan Department of Public Health (MDPH) undertook a series of studies on farm families as a high-risk group in the summer and autumn of 1974.

Serum samples were obtained from 110 persons in the exposed group (had been working or living in the quarantined farms for six months or more since the accident) and for 104 persons from the control group (randomly selected from a list of dairy producers in the same geographical area, where farms had not been quarantined). As shown in Tables 37 and 38, serum levels of PBBs were significantly higher in the people from quarantined farms compared with those from non-quarantined farms, though low levels were also observed in the control group (Cordle et al., 1978). In 1976, the MDPH, together with the Centre for Disease Control, the FDA, NIH, and EPA, established a cohort of 4545 people in Michigan to be examined at regular intervals over several decades (Barlow & Sullivan, 1982) to evaluate the long-term effects of PBB exposure. Four groups were included (Landrigan, 1980): Quarantined farm residents, direct recipients of farm produce, chemical workers and their families, and persons who either volunteered for the study or who had participated as control subjects in an earlier pilot study (Humphrey & Hayner, 1975). The first report was published by Landrigan et al. (1979) followed by several reports on subgroups of this population (e.g., Kreiss et al., 1982; Eyster et al., 1983).

Study groups of the Mount Sinai School of Medicine have also conducted comprehensive examinations on similarly categorized groups, e.g., residents of quarantined farms, residents of non-quarantined farms, consumers of products directly from quarantined or non-quarantined farms, and Michigan Chemical Company workers; residents of the state of Wisconsin were used as a control group.

It can be seen from Table 38 that nearly 100% of the adipose samples randomly selected throughout the state had detectable PBB concentrations. Thus, statewide exposure of Michigan residents to PBBs can be demonstrated.

Levels of PBBs in serum (Landrigan, 1980; Wolff et al., 1982), breast-milk (Brilliant et al., 1978; Miller et al., 1984), and adipose tissue (Wolff et al., 1982) were highest in the area of the accident (lower peninsula), and lowest in the upper peninsula, farthest from the source.

Compared with residents of quarantined farms, direct consumers of products from quarantined farms, and PBB-production workers, the tissue burdens among the general population of Michigan were 1-3 orders of magnitude lower.

Moreover, for example, only 36% of the general population had serum PBB concentrations greater than 1 μg/litre, compared with 78% among farmers (Anderson et al., 1979; Wolff et al., 1982).

PBB levels appear to be higher in males than females (Meester & McCoy, 1976; Landrigan et al., 1979; Landrigan, 1980; Wolff et al., 1978; 1980; Kreiss et al., 1982; Eyster et al., 1983) and higher in children (below the age of 10 years) than in adults (Humphrey & Hayner, 1975; Landrigan et al., 1979; Landrigan, 1980; Barr, 1980; Wolff et al., 1982).

A later study (Schnare et al., 1984) recorded not only the concentration of the most abundant congener of the FireMaster®-mixture (2,2′,4,4′,5,5′-hexabromobiphenyl) but also the concentrations of other PBB congeners detected in subcutaneous adipose tissue samples of 7 former participants of the Michigan PBB studies (Table 39).

Table 39. Range of adipose tissue concentrations of various PBBs in 7 persons[a] (mg/kg on a lipid weight basis)[b]

PBB	Range[c] (mg/kg)
2,3′,4,4′,5-penta	nd-0.16
2,2′,4,4′,5,5′-hexa	0.01-2.72
2,2′,3,4,4′,5′-hexa	nd-0.22
2,3′,4,4′,5,5′-hexa	nd-0.09
2,2′,3,3′,4,4′,5-hepta	nd-0.26
2,2′,3,4,4′,5,5′-hepta	nd-0.01

[a] 7 healthy male volunteers, aged 20-30 years, having been exposed to PBBs some years earlier, as a consequence of the Michigan PBB incident in 1973.
[b] From: Schnare et al. (1984).
[c] nd = Not detectable; detection limit = 0.001 mg/kg.

In most cases, PBB concentrations did not appear to be decreasing significantly over time. Wolff et al. (1979b) did not find any significant variation in the serum PBB levels of nine dairy farm residents during 18 month of observation.

Paired serum samples, one collected in 1974 and the other in 1977, were also available for 148 members of the Michigan PBB cohort. The data indicate that levels were generally stable over the 3-year period with a mean change of 16 μg/litre (Landrigan et al., 1979). In another study of the Michigan PBB-cohort, the decrements in median serum levels of PBBs between matched pairs over one - (1977-78) and two - (1977-79) year intervals were both only 1 μg/litre (Kreiss et al., 1982). No significant change in blood plasma PBB levels was observed over a 5-month period in 41 residents of quarantined farms (Humphrey & Hayner, 1975). In contrast, Meester & McCoy (1976) reported a marked decline over 3 years (1974-76) in serum levels of PBBs. These authors also found that the average decrease in PBB concentrations in the fat of 16 individuals was about 40%, in a period of 6 months. No changes in PBB levels were seen over an 11-year period (1976-87) in fat samples from a patient with long-term exposure to PBBs from the early 1970s as a result of the Michigan PBBs accident. The average fat level of PBBs was 0.8 mg/kg (Sherman, 1991).

In 1981, PBBs were found in 13-21% of serum samples from 4-year-old Michigan children. Their mothers belonged to a group that was surveyed either with regard to the consumption of Lake Michigan sport fish (mean PBB level detected in children: 2.4 ng/ml) or with regard to former exposure to quarantined farm products (mean PBB level detected in children: 3.0 ng/ml) (Jacobson et al., 1989).

Few human monitoring data are available for the US population outside of Michigan. They are summarized in Table 40. One study deals with the population in the vicinity of industrial areas involved in PBB production or use (Stratton & Whitlock, 1979), the other with farmers of the state of Wisconsin who were examined as control group in connection with the Michigan PBB studies (Wolff et al., 1978).

PBBs were found in all studies, but, because of the limited data, the significance is unclear. The highest PBB levels were found in the hair of humans living near PBB industry. Of the nine samples analysed, five had detectable PBB levels. Both male and female hair samples contained PBBs (Stratton & Whitlock, 1979).

In contrast to the other surveys, which had regard only to the major PBBs component (hexabromobiphenyl), Stratton & Whitlock (1979) identified the different PBB homologues in the extracted oils of the human hair, collected from barbershops and beauty

Table 40. Human monitoring data: PBB levels in the US population (outside of Michigan)

Year	No. of specimens	% of positive findings	Specimen tissue	Specimen group/area	PBB concentration[a] range	PBB examined	Detecion limit[a]	Remarks	References
1977	56	3.6	serum	Wisconsin farmers	not detected-1.1[b]	$C_{12}H_4Br_6$		examined as a control population	Wolff et al. (1978)
1977	3	33	hair (from barber-shops)	males and females, Bayonne New Jersey, Vicinity of White Chemical	< 100-8100	total PBBs	100	reported as µg/kg in oil	Stratton & Whitlock (1979)
	3	100	hair (from barber-shops)	males and females, Staten Island, New York, Vicinity of Standard T Chemical Co.	440-26 600	total PBBs	100	reported as µg/kg in oil	
	3	33	hair (from barber-shops)	males and females, Sayreville New Jersey, Vicinity of Hexcel Fine Organics	< 100-310 000	total PBBs	100	reported as& µg/kg in oil	

[a] (µg/litre or µg/kg).

[b] PBBs not detected in 54/56 persons. PBBs observed at 1.1 µg/litre in one person, identified as recently moved from a Michigan farm, and at 0.5 µg/litre in another person.

parlours (Table 41). There were identifiable differences in the composition of PBB congeners found in hair from the three locations.

Table 41. Concentration (range) of different PBB congeners in human hair samples taken in the vicinity of three industrial sites in the USA, reported as μg/kg in oil[a]

PBB-congeners	Bayonne, New Jersey (White Chemical Corp.)[b]	Staten Island, New York (Standard T Chemical Comp.)[c]	Sayreville, New Jersey (Hexcel Corp.)[d]
MoBB	nd[e]	nd[e]	nd[e]
DiBB	nd-8100	nd	nd
TrBB	nd	nd	nd
TeBB	nd	nd	nd
PeBB	nd	nd	nd
HxBB	nd	440-740	nd-480
HpBB	nd	nd-890	nd
OcBB	nd	nd-1100	nd
NoBB	nd	nd-3600	nd-22 500
DeBB	nd	nd-20 000	nd-285 000

[a] Data from: Stratton & Whitlock (1979).
[b] Having manufactured octa- and decabromobiphenyl along with bromobiphenyl ethers.
[c] Major user of FireMaster BP-6.
[d] Producer of laboratory quantities of various PBBs.
[e] nd = Not detected (detection limit = 100 μg/kg).

The samples with the highest concentrations contained relatively large amounts of decabromobiphenyl, while the samples with lower concentrations contained only hexabromobiphenyl (Stratton & Whitlock, 1979). One sample was different from the others because it contained dibromobiphenyl (see Table 41). As a result of the sampling method, it was impossible to ascertain whether the exposure was related to the workplace or to the ambient environment.

In a report by Lewis & Sovocool (1982), pooled adipose tissue samples from 202 individuals from nine census regions in the USA

were analysed for HxBB. Although the average concentration was 1-2 μg/kg, it cannot be excluded that this was because of the inclusion of a few samples with high PBB concentrations.

There is very little human monitoring data on PBBs in the populations of countries other than the USA. Krüger et al. (1988) reported PBB contamination of breast-milk from European women in a survey from North Rhine-Westphalia, Germany (Table 33). The milk samples (n=25) contained a typical pattern of certain PBB congeners. It included penta- to octabromobiphenyls in concentrations ranging from 0.002 to 28 μg/kg, based on milk fat. The most abundant component was 2,2'4,4',5,5'-hexabromobiphenyl (BB 153) followed by a peak consisting of two heptabromobiphenyl isomers (2,2',3,4',5,5',6- and 2,2',3,4,4',5,6'-heptabromobiphenyl BB 187 and 182). Differences in the pattern were only found in the milk given by a Chinese woman and in that given by a woman having been exposed to several fires in industry.

Concentrations of BB 153 in human and cow's milk, both collected from the same region (North Rhine-Westphalia), were 1 μg/kg and 0.03 μg/kg, respectively, measured on a fat basis (Krüger, 1988).

5.2.4 *Subpopulations at special risk*

Children are at risk from exposure to PBBs in different ways.

Studies on the Michigan population indicated a significant PBB transfer to the fetus (Landrigan et al., 1979; Eyster et al., 1983; Jacobson et al., 1984) and to breast-milk (Brilliant et al., 1978; Landrigan et al., 1979; Eyster et al., 1983; Jacobson et al., 1984, 1989; Miller et al., 1984). PBB levels to which fetuses and newborn infants were exposed in the Michigan accident are shown in Table 42. Because the placenta acts only as a partial barrier to PBBs, a newborn baby has a body burden, even before breast feeding. Placental and cord serum levels are much lower than levels in breast-milk. However, even at low concentrations, intrauterine exposure may be significant, for several reasons, as pointed out in detail by Jacobson et al. (1984).

Infants are not only exposed to PBBs through their mothers and through consumption of contaminated food, but they also through contact with PBBs from the environment. Young crawling children are known to ingest accidentally soil or dust to an extent of up to 0.1 g/day.

Table 42. PBB[b] concentrations in maternal serum, adipose lipid, and milk lipid, and in the cord serum and placenta of Michigan women (Michigan PBB-cohort) at the time of parturition (1975-80)[a]

Paired specimen	No.	Range[c]	Median	Geometric mean	Measure
Maternal serum	61	nd-1068	3	3.5	µg/litre
Placenta		nd-370	< 1	-	µg/kg
Maternal serum	60	nd-1068	3	3.2	µg/litre
Cord serum		nd-104	< 1	-	µg/litre
Maternal serum	47	nd-1068	3	3.0	µg/litre
Milk lipid		nd-92 667	250	312	µg/kg
Milk lipid	27	52-92 667	384	472	µg/kg
Adipose lipid		nd-174 000	522	82	µg/kg

[a] From: Eyster et al. (1983).
[b] Concentrations expressed as concentrations of hexabromobiphenyl.
[c] nd = Not detected (detection limit: 1 µg/litre or kg).

5.3 Occupational exposure during manufacture, formulation, or use

In general, occupational exposure is to be expected in PBB manufacturing and processing plants. In Michigan, as a result of the PBB incident, farmers, and possibly dairymen, elevator, mill personnel etc. were occupationally exposed (Kay, 1977).

Bialik (1982) reported the following contaminant levels of decabromobiphenyl measured in 1977 in the manufacturing area of Hexcel/Fine Organics and Saytech, Inc. (Sayreville; USA):

- Plant air samples: 0.18 and 0.23 mg/m^3 8 h TWA (time-weighted average);
- Wipe tests, unspecified: up to 8 mg/100 cm^2;
- Wipe tests, eating Table: 0.1 mg/100 cm^2.

At this time, 95% of the plant production consisted of decabromobiphenyl (18%) and decabromobiphenyl oxide (77%).

About 2000 tonnes of decabromobiphenyl were manufactured during 1973-77 (Bialik, 1982).

Employees of chemical plants may be exposed directly to PBBs (in most cases along with other chemicals) through contact, inhalation, or ingestion (Wolff et al., 1979a). As an index of individual exposure, PBB levels in the serum and adipose tissue of chemical workers have been recorded. The results of several authors are compiled in Table 43.

Most data refer to the Michigan Chemical Corp., St. Louis (Michigan), which produced several brominated organic compounds and manufactured over 5000 tonnes of PBBs, predominantly hexabromobiphenyl, from 1970 to 1974. Some additional general exposure from contaminated food can also be included for the workers of Michigan Chemical.

To summarize, median serum and adipose tissue PBB levels were higher among chemical workers than among male residents of quarantined farms.

Non-production workers at the Michigan Chemical plant showed significantly lower levels than workers involved in PBB production; for example, median adipose tissue concentrations of PBBs were 2.49 mg/kg and 46.94 mg/kg, respectively.

In another study on workers at a PBB plant in New Jersey, Bahn et al. (1980b) presented a detailed comparison of serum PBB levels in various occupational groups. A significantly higher number of PBB workers had detectable levels of PBBs, compared with other workers in the study (35.9% compared with 12.2%). Among workers with detectable PBB levels, the PBB workers had significantly higher serum levels than workers from neighbourhood industries not using PBBs.

Although this factory concentrated on manufacturing decabromobiphenyl and decabromobiphenyl oxide (ether), there was no positive identification of $C_{12}Br_{10}$ (Table 44) or $C_{12}Br_{14}O$ (Bahn et al., 1980b).

No data are available about occupationally exposed women.

Family members of chemical workers have also been found to have a body burden of PBBs (Landrigan, 1980).

Table 43. Occupational exposure: PBB levels in chemical workers (USA)

Year	Plant	Group (number)	Sample	PBB concentration[a] range	Mean (geometric mean)	Median	PBB examined	Detection limit[a]	References
1975	Michigan Chemical Corp. (MCC) (St. Louis, Michigan)	workers (8-36 months exposure (7)	serum	6-85			HxBB		Kay (1977)
1976	MCC (St. Louis, Michigan)	employees (55)	serum	1.1-1729	123	9.3	HxBB		Wolff et al. (1978, 1979a)
		production workers (10)	serum		603.9	108.4	HxBB	1	Wolff et al. (1979a)
		non-production workers (45)	serum		16.5	6.1	HxBB	1	
		workers (14)	serum	1-1530			HxBB	< 0.2	Wolff et al. (1979b)
1978		workers (14) (matched pairs)		1-1363			HxBB	< 0.2	

Table 43 (contd).

1976-77	MCC (St. Louis, Michigan)	workers and families (216)	serum	not detected-1240	43.0	4.5	$C_{12}H_4Br_6$	1	Landrigan et al. (1979)
1975-80	MCC (St. Louis, Michigan)	workers (male) (29)	serum	1-2000	(25.4)	20	$C_{12}H_4Br_6$	1	Eyster et al. (1983)
1978	Hexcel/Fine Organics and Saytech, Inc. (Sayreville New Jersey)	PBB workers (exposure to PBBs (and PBBOs) for at least 6 weeks between January 1973 and August 1978) (39)	serum	not detected-1340			MoBB DeBB		Bahn et al. (1980b)
1976	Michigan	production workers (7)	adipose tissue	5000-581 000	196 490	46 940	HxBB	500	Wolff et al. (1979a)
		non-production workers		500-10 000	3880	2490			
1975-80	Michigan	workers (male) (29)	adipose tissue	400-350 000	5290	6000	HxBB	1	Eyster et al. (1983)

[a] In μg/litre or μg/kg.

Table 44. Detectable[a] serum levels (μg/litre) of PBB homologues in workers at a plant producing decabromobiphenyl and decabromobiphenyl oxide[b]

PBB homologue	Number of cases	Range
$C_{12}H_9Br$	14	0.3-5.5
$C_{12}H_8Br_2$	1	6.9
$C_{12}H_7Br_3$	1	0.9
$C_{12}H_6Br_4$	0	-
$C_{12}H_5Br_5$	2	1.6-13.0
$C_{12}H_4Br_6$	2	0.4-6.0
$C_{12}H_3Br_7$	7	9.0-40.0
$C_{12}H_2Br_8$	9	20.0-800.0
$C_{12}H\ Br_9$	1	500
$C_{12}Br_{10}$	0	-
Total PBBs	26	0.3-1340

[a] Excludes cases with "trace", "not confirmed" and "not detectable" levels.
[b] From: Bahn et al. (1980b).

Bekesi et al. (1979b) determined the distribution of PBBs in the blood compartments of 4 Michigan Chemical plant workers (Table 45) and suggested that the PBB level of the white cell fraction may be a better indicator for risk potential than the total plasma PBB concentration.

Despite its significance for toxicological assessment, the content of minor constituents of FireMaster® in the body burden was rarely investigated. For example, Wolff & Aubrey (1978) examined other PBB congeners, which are identifiable as peaks by GC/MS (2 pentabromobiphenyl peaks, and 2 heptabromobiphenyl peaks), in the serum of Michigan Chemical workers (n = 24) and Michigan dairy farmers (n = 37), besides the major component (2,2′,4,4′,5,5′-hexabromobiphenyl) of FireMaster®. The relative concentrations, with respect to the major hexabromobiphenyl peak, of these PBB components were somewhat different for chemical workers and for farmers, i.e., the two pentabromobiphenyl values (peak area ratios) were significantly higher in the serum from chemical workers.

Table 45. Distribution of PBBs in blood compartments of Michigan Chemical Workers[a]

	Polybrominated biphenyls					
	ng/mg Protein			Ratio[b]		
	RBC	plasma	WBC	RBC	plasma	WBC
Michigan Chemical Workers;						
not directly involved in	0.07	0.13	3.9	1	: 2	: 56
the production of PBB	0.03	0.23	1.8	1	: 8	: 60
directly involved in	0.67	10.0	57.3	1	: 15	: 86
the production of PBB	0.63	10.2	32.0	1	: 16	: 51

[a] From: Bekesi et al. (1979b).
[b] RBC = Red blood cells; WBC = white blood cells.

This variation might be attributed to the different routes (skin contact, inhalation, direct ingestion versus, primarily, ingestion of animal foodstuff) and to the different composition (unchanged versus animal-mediated material) of exposure in chemical workers versus farmers. Further reasons might be the earlier initial onset of contamination in workers and slight variations in the composition (section 2.1.2) of several lots of FireMaster® BP-6 (the main product of Michigan Chemical) and FireMaster® FF-1, which caused contamination of livestock feed (Anderson et al., 1978a; Wolff & Aubrey, 1978; Wolff et al., 1979a).

The change in serum PBB levels over time was investigated in chemical workers at two facilities. Wolff et al. (1979b) reexamined serum PBB concentrations (determined as the major hexabromobiphenyl peak) in 1978 from 14 workers of the Michigan Chemical Corp., who had also been tested 18 months earlier. They found PBB levels of a comparable order. In contrast, no subject (n=109) in a study on chemical workers of Hexcel/Fine Organics and Saytech Inc. (manufacturing decabromobiphenyl and decabromobiphenyl oxide) showed any detectable serum level of PBBs (different congeners) in 1981 (Bialik, 1982), which was true, even for the two persons who had shown high levels of serum PBBs in the previous study of 1978 (Bahn et al., 1980b; Table 43). However, the results of PBB determination in the fat of these two cases were positive in 1981.

The negative results of the determination of PBBs in serum were not expected, and the authors suggested further studies.

6. KINETICS AND METABOLISM

6.1 Absorption

6.1.1 Animal studies

6.1.1.1 Gastrointestinal absorption

Studies have been performed only on the gastrointestinal absorption of PBBs. Some studies indicate that PBBs are rapidly and efficiently absorbed, other studies indicate a much lower efficiency of absorption (see Table 46). No information is available on the extent of absorption of decabromobiphenyl.

Absorption can be strongly influenced by the vehicle in which the compound is administered (Birnbaum, 1985). Administration of hexabromobiphenyl in mineral oil or olive oil solution resulted in higher absorption than administration in a methyl cellulose suspension (see Table 46: Rozman et al., 1982). The degree of halogenation also appeared to influence the absorption of PBB. For example, less than 10% of ^{14}C-labelled hexabromobiphenyl, but 62% of a dose of ^{14}C-labelled octabromobiphenyl were eliminated in the faeces of rats in 24 h, though both compounds had been administered in corn oil (see Table 46).

The conclusion that more brominated biphenyls are absorbed less efficiently than less brominated biphenyls can, possibly, be drawn from other findings. Willett & Durst (1978) observed that, during feeding of FireMaster® BP-6, the relative concentration of pentabromobiphenyl in the faeces of cows was decreased, and that of heptabromobiphenyl was elevated compared with the FireMaster®-standard. Similarly, faecal concentrations of heptabromobiphenyl were enhanced relative to concentrations of hexabromobiphenyl in the faeces of hens, when FireMaster® BP-6 was fed (Fries et al., 1976). However, Polin & Leavitt (1984) found that the ratio of 3.5 for hexa- to heptabromobiphenyl in the chemical sample of FireMaster® FF-1 shifted to an average ratio value of 2.5 in the whole carcasses of chickens analysed on days 0, 21, and 42 of withdrawal, inferring a better absorption of hepta-bromobiphenyl.

Generally, it should be noted that faecal elimination during the first few days following dosing might be an indicator, but is not a measure, of lack of absorption, because some absorbed PBB is

Table 46. Absorption of PBBs after oral administration

PBB compound	Species (sex)	Vehicle	Absorption parameter[a]	Methods	Comments	References
[^{14}C-]2,2',4,4',5,5'-hexabromobiphenyl	rat (male)	emulphor-EL 620: ethanol: water (1 : 1 : 8)	90%, 24 h	faeces analysis gut content	single dose	Matthews et al. (1977)
		corn oil	90%		multiple doses (4)	
[^{14}C-] octabromobiphenyl (technical mixture)	rat (male, female)	corn oil	38%, 24 h	faeces analysis	single dose	Norris et al. (1973)
[^{14}C-]2,2'4,4',5,5'-hexabromobiphenyl	rhesus monkey (male)	1% methyl cellulose mineral oil olive oil	40%, 10 days 62%, 5 days 66%, 5 days	faeces analysis faeces analysis faeces analysis	two doses single dose repeated doses (4)	Rozman et al. (1982)
FireMaster® BP-6	cow (female)	crystalline PBB in gelatin capsules	50%, 168 h (7 days)	faeces analysis	single dose	Willett & Irving (1976)
	calf (male)	crystalline PBB in gelatin capsules	95%, (9 days)	faeces analysis	daily feeding	

[a] Values based on concentrations of 2,2',4,4',5,5'-hexabromobiphenyl (FireMaster® BP-6 sample) or on [^{14}C-]activity.

eliminated and recycled into the faeces in bile and by diffusion across intestinal membranes (Rozman et al., 1982; Fries, 1985b).

6.1.1.2 Dermal and inhalation absorption

No quantitative information is available on skin absorption and intake through inhalation.

6.1.2 Human studies

It is plausible that inhalation and dermal contact are the main routes of exposure to PBBs for chemical plant workers (Wolff et al., 1979a), while the main route for Michigan people was the ingestion of PBBs dissolved in the fat of meat and milk (Di Carlo et al., 1978). An appropriate model for assessing the latter kind of absorption is thought to be the rat-corn oil model (Fries, 1985b).

No quantitative data are available on PBB absorption in humans.

6.2 Distribution

6.2.1 Animal studies

6.2.1.1 Levels in organs and blood

As can be seen from Tables 47, 48, and 49, most studies on the distribution of PBBs have been conducted with the FireMaster®-mixture. A few earlier publications refer to technical octabromobiphenyl. No experimental data are available on tissue distribution of decabromobiphenyl. When FireMaster® was administered, the distribution process was studied predominantly as the distribution of 2,2',4,4',5,5'-hexabromobiphenyl, and, with far less emphasis, on the distribution of the minor components of the mixture. Little information is available on the distribution of PBB congeners, when administered individually.

Investigations on rats, mice, cows, sheep, pigs, and avian species demonstrated that PBBs were distributed widely throughout the body tissues in all species. Highest (equilibrium) concentrations on a wet tissue basis were found in adipose tissues, consistent with the solubility characteristics of PBBs. Adipose concentrations are usually an order of magnitude higher than those of most muscle and organ tissues (see Tables 47, 48, 49, and 50).

Table 47. Distribution of PBBs in mammals after the administration of a single dose of PBBs

PBB	Species (sex)	Administration (dose in mg/kg body weight)	Time after dosing	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre, unless otherwise specified)	References
FireMaster® FF-1 (lot No. 7042)	rat (male)	oral 1000 in corn oil	10 months[b]	adipose tissue (714) > liver (60) > blood (0.94)	Kimbrough et al. (1978)
	rat (female)		10 months[b]	adipose tissue (1202) > liver (37) > blood (2.9)	
FireMaster® FF-1	rat (male)	oral 80 in corn oil	42 days	fat (295) > blood (0.38)	Wolff & Selikoff (1979)
FireMaster® FF-1 (lot No: 7042)	rat (male)	oral 500 in corn oil	4 months	adipose tissue (1008) > liver (50) > blood (2.1)	Kimbrough et al. (1980)
FireMaster® FF-1 (lot No: FF-1312-FT)	rat (male)	oral 10	24 h[b]	sc fat I (61 500) > sc fat II (38 700) > liver (20 900) > lung (7650) > kidney (7310) > heart (6470) > jejunum (4860) > spleen (3530) > cerebellum (2990) > grey matter (2850) > white matter (2750) > testes (2380) > blood (945)	Domino et al. (1980b)

Table 47 (contd).

			4 weeks[b]	sc fat (19 200) > jejunum (3170) > lung (1240) > liver (690) > kidney (650) > spleen (520) > heart, testes (both 240) > grey matter (210) > cerebellum (200) > white matter (170) > blood (56.9)	Domino et al. (1980b)
FireMaster® BP-6	rat (male)	intraperitoneal 10 in corn oil	12 weeks	serum (46.80 ng/ml)	Miceli & Marks (1981)
				fat (21.90) > adrenal (3.64) > lung (0.98) > liver (0.59) > pituitary (0.91) > gonad (0.33) > kidney (0.22) > heart (0.20) > spleen (0.17) > brain (0.13)	
			36 weeks[b]	serum (23 ng/ml)	
				fat (16.62) > adrenal (2.67) > lung (0.51) > pituitary (0.29) > liver (0.20) > kidney (0.14) > gonad, brain (both 0.10) > heart (0.08) > spleen (0.05)	
2,2',4,4',5,5'-[^{14}C]-hexabromobiphenyl	rat (male)	oral 1 in: Emulphor EL 600: ethanol: water (1:1:8)	1 day	muscle (29.9) > adipose (25.5) > skin (17.9) > liver (9.0) > blood (0.90)[c]	Matthews et al. (1977)

Table 47 (contd).

PBB	Species (sex)	Administration (dose in mg/kg body weight)	Time after dosing	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre, unless otherwise specified)	References
^{14}C-PBB	rat (male and female pups)	intraperitoneal 150 in: peanut oil	28 days	ovaries (130) > skin (15.1) > testicles (13.3) > intestine (11.7) > lung (7.3) > liver (4.7) > muscle, heart (1.9) > fat (1.8) > brain (0.9)[d]	McCormack et al. (1979b)
FireMaster® BP-6 (lot No. RP-158)	cow (female)	oral 5.95 in: gelatin capsule	10 days	liver (1.35) > fat (sc: 1.15; perirenal: 1.09; pericardiac: 0.97; intermuscular: 0.81; omental: 0.78) > brain (pons: 0.27; cortex: 0.08) > mammary gland (0.25) > kidney (0.12) > heart (0.11) > lung, muscle (0.08) > ovaries, uterus (0.06) > plasma, rumen wall (0.04) > bile (0.02) > synovial fluid (0.01)	Willett & Irving (1976)
[^{14}C-]octabromobiphenyl (technical mixture)	rat (male)	oral 1 in: corn oil	16 days	adrenal, adipose, heart, skin > liver, pancreas, spleen	Norris et al. (1973)

[a] Measured as concentration of 2,2',4,4',5,5'-hexabromobiphenyl or [^{14}C-]activity; (in parentheses: values measured - referring to various measures).

[b] For additional time points: see original reference.

[c] Values in average % total PBB dose.

[d] Values in µg-equivalents/g wet weight.

sc. = Subcutaneous.

Table 48. Studies on the distribution of PBBs in animals following dietary or repeated oral intake of the FireMaster® mixtures or 2,2',4,4',5,5'-[^{14}C]-hexabromobiphenyl

PBB	Species	Exposure		Duration of recovery	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre wet weight, unless otherwise specified)	References
		Dietary concentration or dose	Duration			
FireMaster® BP-6	rat (pregnant)	50 mg/kg feed	day 8 of gestation until day 21 of gestation	0	fat (330) > mammary gland (318) > kidney (30) > skin (22) > liver, lung, brain, heart, small intestine, placenta, uterus (all < 5)	Rickert et al. (1978)
FireMaster® BP-6	rat (maternal)	50 mg/kg feed	day 8 of gestation to 14 days postpartum	0	mammary gland (117) > liver (4)	Dent et al. (1977b)
FireMaster® BP-6	rat (maternal)	25 mg/kg feed	day 8 of pregnancy to 14 days postpartum	0	fat (74) > mammary > liver > kidney > lung (6)	McCormack et al. (1979a)
		50 mg/kg feed		0	fat (483) > mammary > kidney > lung (13)	
		200 mg/kg feed		0	fat (966) > mammary > kidney > lung (21)	

Table 48 (contd).

PBB	Species	Exposure		Duration of recovery	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre wet weight, unless otherwise specified)	References
		Dietary concentration or dose	Duration			
FireMaster® BP-6	rat (maternal)	100 mg/kg feed	day 8 of pregnancy to 28 days postpartum	0	fat (813) > liver (54) > mammary (43)	McCormack & Hook (1982)
				14 weeks (after first and only litter was weaned)	fat (459) > mammary (225) > liver (12)	
				> 10 weeks and after weaning their second litter	fat (77) > mammary (19) > liver (3)	
2,2'4,4',5,5'-hexabromobiphenyl	rat (male)	1 mg/kg body weight per day	4 days	3 days	adipose (41.1) > skin > muscle > liver > blood (0.32)[b]	Matthews et al. (1977)

Table 48 (contd).

FireMaster® BP-6 (Lot 6224A)	rat (male)	0.1 mg/kg feed	9 days	0	liver (1.5) > brain (0.5), adipose (0.3)[c]	Render et al. (1982)
		1 mg/kg feed	9 days	0	liver (8.3) > brain (1.8), adipose (1.7)[c]	
		10 mg/kg feed	9 days	0	liver (135) > adipose (27) > brain (12)[c]	
		100 mg/kg feed	9 days	0	liver (1213) > adipose (251) > brain (103)[c]	
FireMaster® FF-1 (Lot No. FF-1312-FT-3)	rat (male)	3 mg/kg body weight per day (in lecithin liposomes)	20 days	0	adrenal (93.7) > thyroid (> 20) > testes (8.7)	Allen-Rowlands et al. (1981); Castracane et al. (1982)
			20 days	5 months (plus dietary restriction)	adrenal (481)	Castracane et al. (1982)
FireMaster® BP-6	mouse	100 mg/kg feed	14 days	6 h	thymus (391) > fat > liver > brain > pancreas > testicles > spleen (2.7)	Corbett et al. (1978a)
				14 weeks	thymus (50) > adrenals = fat > liver > testicles > spleen > brain > pancreas (n.d.)	

Table 48 (contd).

PBB	Species	Exposure		Duration of recovery	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre wet weight, unless otherwise specified)	References
		Dietary concentration or dose	Duration			
				12 weeks	perithymic fat (96) > perirenal fat > adrenal glands > thymus gland (5.5)	
FireMaster® FF-1 (lot No. 7042)	mouse	5 mg/kg feed	3 weeks	0	thymus (20) > lung, liver > spleen > serum (< 0.002)	Loose et al. (1981)
			8 weeks	0	thymus (24) > liver, lung > spleen > serum (0.019)	
FireMaster® (lot No. 7042)	mouse	167 mg/kg feed	3 weeks	0	thymus (109) > liver > lung > spleen > serum (1.22)	Loose et al. (1981)
			6 weeks	0	thymus (3088) > liver > spleen > lung > serum (4.75)	
			8 weeks	0	thymus (2426) > liver > lung > spleen > serum, (11)	

Table 48 (contd).

			8 weeks	0	thymus (2426) > liver > lung > spleen > serum (11)	
FireMaster® BP-6	cow (lactating)	50 mg/kg feed	15 days	15 days	renal fat (10) > omental fat > brisket fat > liver = thyroid > mammary = chuck muscle > loin muscle > heart > kidney = brain > adrenal = spleen (0.4)	Gutenmann & Lisk (1975)
FireMaster® BP-6 (lot 6244 A)	calf	25 g daily (in gelatin capsules)	9 days	0	rumen contents (14257) > feces > rumen wall > bile > marrow > perirenal fat (441) > kidney > testes > liver > thymus > heart > brain, pons > lymph nodes > tongue > spinal cord > brain, cortex > plasma > small intestine > lung > spleen > thyroid > muscle (25)	Willett & Irving (1976)
FireMaster® BP-6 (lot 6244 A)	cow (heifer)	250 mg daily (in gelatin capsules)	60 days	0	fat (25) > liver > glands > nervous > bile > contractiles > plasma > liquids (0.0198)	Willett & Durst (1978)

Table 48 (contd).

PBB	Species	Exposure		Duration of recovery	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre wet weight, unless otherwise specified)	References
		Dietary concentration or dose	Duration			
FireMaster® FF-1	cow	environmentally contaminated (Michigan PBB incident) ca. 200-400 g	ca. 14 days	9 months	perirenal fat (380*) > omental fat > subcutaneous fat > kidney > liver > skeletal muscle > cardiac muscle > lung > brain (10.5*)	Fries et al. (1978b)
				9-12 months (killed in extremis)	perirenal fat (1224*) > omental fat > subcutaneous fat > skeletal muscle > liver > cardiac muscle > kidney > lung > brain (57*)	
FireMaster® FF-1	calf (female)	10 mg/kg body weight per day in gelatin capsules	4 weeks	0	fat (378) > kidney > liver > muscle (1.26)	Robl et al. (1978)
	calf (male)	100 mg/kg body weight per day	6 weeks	0	fat (6080) > kidney > liver > muscle (34)	

Table 48 (contd).

	cow	1	158 days	182 days	brisket fat (4.5) > bone marrow > stomach fat > tail fat (3.3)	
FireMaster® BP-6	sheep	50 mg/kg feed per day (complete ration)	30 days	0	renal fat (42) > omental fat > brisket fat > liver > chuck muscle > loin muscle > heart > thyroid > brain > adrenal > kidney = spleen (0.9)	Gutenmann & Lisk (1975)
FireMaster® BP-6	pig	20 mg/kg feed	16 weeks	0	back fat (64) > leaf fat > liver > muscle > kidney (0.9)	Ku et al. (1978)
		200 mg/kg feed	16 weeks	0	back fat (503) > leaf fat > muscle > liver > kidney (13.5)	
FireMaster® BP-6	pig (lactating sow)	100 mg/kg feed 200 mg/kg feed	during 2nd half gestation and during lactation	0	adipose tissue > liver > kidney > > brain[d]	Werner & Sleight (1981)

Table 48 (contd).

PBB	Species	Exposure		Duration of recovery	Tissues, organs, under study - ranked in order of decreasing PBB concentrations[a] (mg/kg or mg/litre wet weight, unless otherwise specified)	References
		Dietary concentration or dose	Duration			
"PBB" (ca 75% hexabromobiphenyl)	Japanese quail male	20 mg/kg feed	9 weeks	0	liver (374) > kidney > muscle > heart > brain (40)[e]	Babish et al. (1975a)
	female			0	liver (225) > heart > kidney > > muscle > brain (26)[e]	
FireMaster® FF-1	chicken (White Leghorn hens)	various concentrations	5 weeks	0	adipose tissue (3:1) > whole egg > liver > muscle (0.008:1)[f]	Polin & Ringer (1978a)

[a] Measured as concentrations of 2,2',4,4',5,5'-hexabromobiphenyl (in parentheses: values measured - referring to various measures).
[b] Values in average % total PBB dose.
[c] Values on a fat basis.
[d] Concentrations are listed in Table 53.
[e] Values in mg/kg dry weight.
[f] Values as ratios of tissue PBBs: diet PBBs.
* = Geometric mean.

Table 49. Studies on distribution of the following continuous exposure to octabromobiphenyl

Species	Exposure: Route, concentration	Duration	Duration of recovery	Tissues and organs under study, ranked in order of decreasing concentrations (average bromine content: μg/g wet weight)	References
Rat (male)	in diet				Lee et al. (1975a)
	0 mg/kg feed (control)	2 weeks		liver (3.4) > fat (1.7) > muscle (1.6)	
	100 mg/kg feed	2 weeks	-	liver (83) > fat (73) > muscle (14)	
	1000 mg/kg feed	2 weeks	-	fat (333) > liver (319) > muscle (77)	
	100 mg/kg feed	4 weeks	0,2,6 weeks	fat > liver > muscle	
	100 mg/kg feed	4 weeks	18 weeks	fat > muscle > liver	
Rat	inhalation (OcBB vapour)[a]	23 h/day, 7 days per week, 15 weeks			Waritz et al. (1977)
	0 pg/litre air (control)			liver (3) > muscle (1.6) > fat (1.5)	
	3.5 pg/litre air		-	liver (4.2) > fat (3.0) > muscle (1.5)	

[a] OcBB = Octabromobiphenyl, Dow, Lot 102-7-72.

Table 50. Tissue: blood ratios of PBBs estimated in a standard 250-g rat[a]

Compartment	Ratio
Liver	17:1
Muscle	5:1
Skin	56.5:1
Adipose	340:1
Intestine tissue	1:1

[a] From: Tuey & Matthews (1980).

Much of the variation in concentrations among tissues can be accounted for by variations in the fat concentrations in these tissues (Willett & Durst, 1978; Fries et al., 1978b; Fries, 1985b).

However, even when concentrations are expressed on a fat basis rather than a wet tissue basis, there are some deviations from uniform concentrations among tissues (Fries, 1985b). PBB concentrations, for example, were low in nervous tissue, despite its high lipid content and often disproportionally high in liver, considering its relatively low lipid content (see Tables 47, 48, and 49; additional information on fat content percentage, e.g., by Willett & Irving, 1976; Fries et al., 1978a,b; Kimbrough et al., 1978; Werner & Sleight, 1981).

The ratios between the PBB concentrations of adipose tissue, blood, and vital organs are different when animals are not at equilibrium (see also section 6.5) with respect to dosing regimen or body condition. Usually, concentrations in liver are very high compared with those in other tissues, immediately after dosing, and decline relatively as equilibrium concentrations are established (e.g., Lee et al., 1975a; Matthews et al., 1977; Miceli & Marks, 1981; Fries, 1985b). Generally, this phenomenon is most pronounced in tissues that have high blood flow rates relative to tissue mass (Tuey & Matthews, 1980). As an exception, livers of mice, tested in a small series, appeared to have relatively concentrated the PBB with passing time (Corbett et al., 1978a).

On the other hand, body weight changes, pregnancy, parturition, and lactation can affect the concentration relationships until equilibrium is reestablished (e.g., Rickert et al., 1978; Willett & Durst, 1978; McCormack & Hook, 1982).

The route of exposure (oral or intravenous administration) had no effect on the tissue distribution (blood, liver, muscle, adipose, skin) of ^{14}C-labelled 2,2',4,4',5,5'-hexabromobiphenyl (dose = 1 mg/kg body weight) in rats (Matthews et al., 1977).

Kimbrough et al. (1980) studied the effects of different diets and of mineral oil on the HxBB concentration in rats that had received a single oral dose of FireMaster® FF-1 (500 mg/kg body weight, in corn oil). After 3 months of feeding, GC-analysis of blood, liver, and adipose tissue showed no statistically significant differences in PBB concentrations among the differently fed groups, when concentrations were calculated on a lipid weight basis. On a wet weight basis, however, the PBB concentrations were significantly increased in the livers of rats on the experimental diets (Teklad-4% and -20% fibre) and on mineral oil compared with those of rats on the basal diet (Purina Chow).

In another study, McCormack et al. (1979a) examined the consequences of simultaneous exposure to PCBs and PBBs in (lactating) rats, because human populations that have been exposed to PBBs are also likely to have been exposed to PCBs. The extrahepatic tissue (kidney, mammary, lung, fat) concentrations of PCBs and PBBs were similar, regardless of whether the agents were administered together or alone. Liver, however, contained lower concentrations of PBBs after treatment with an equal mixture of PCBs and PBBs than when PBBs were administered alone. (None of the tissues had higher concentrations of PBBs than PCBs after concomitant administration. The reasons for this were not clear).

The distribution of PBB (hexa) among blood compartments (plasma, red cells) has been studied in rats (Domino et al., 1980b). It was found that plasma levels of 2,2',4,4',5,5'-hexabromobiphenyl were generally four times greater than red cell levels.

Matthews et al. (1984) reported that 81% of plasma PBB (hexa) was associated with the total lipoprotein fraction. In another study (Kraus & Bernstein, 1986), approximately 65% of all radiolabelled HxBB incubated with human serum *in vitro* was recovered in the lipoprotein fraction. Of the HxBB in the lipoprotein fractions, 40% was recovered in low-density lipoproteins (LDL), 33% in very-low-density lipoproteins (VLDL), and 23% in high-density lipoproteins (HDL). Addition of human lipoprotein to a culture medium influenced the partition of HxBB between adipocytes and culture medium (Kraus & Bernstein, 1989).

Some data are available on the tissue distribution of the minor components of FireMaster®-mixture (see also section 6.5). Domino et al. (1980b) analysed the relative percentages of various PBB congeners (two penta-, three hexa-, and three heptabromobiphenyls) in several tissues of rats given FireMaster® FF-1. From their list, it was evident that each of the PBB analogues was found in all tissues examined (liver, lung, testes, fat; blood, brain) but their partitioning ratios differed. Distribution has been recorded also after exposure to single PBB congeners, e.g., tetra-, penta-, and hexa-isomers (Akoso et al., 1982a; Dharma et al., 1982; Domino et al., 1982; Render et al., 1982; Millis et al., 1985a). In some cases, it was not clear whether the differences in partitioning between congeners were real or were caused by analytical problems (Render et al., 1982).

6.2.1.2 *Transfer to offspring*

1) Mammals

Placental transfer

PBBs are capable of passing through the placental barrier into the developing fetuses. This has been demonstrated in mice (Corbett et al., 1978a; Welsch & Morgan, 1985), rats (Beaudoin, 1977; Rickert et al., 1978), guinea-pigs (Ecobichon et al., 1983), minks and ferrets (Bleavins et al., 1981), cows (Detering et al., 1975; Fries et al., 1978a,b), and pigs (Werner & Sleight, 1981) by administering the Fire-Master®-mixture or individual PBBs, or by using technical octabromobiphenyl in rats (Aftosmis et al., 1972a; Waritz et al., 1977).

The studies compiled in Table 51 are rarely intercomparable. However, it is obvious that PBBs are readily transferred across placental membranes, the concentrations among fetal tissues being highest in the liver. The limited data on the distribution of PBBs in fetal tissues showed often, but not always (Ecobichon et al., 1983; Welsch & Morgan, 1985), lower PBB residues in fetal than in maternal tissues (see Table 51). In cows, the average ratio of PBB concentrations in fetal or calf tissue to PBB concentrations in dam tissue was 0.36 : 1 for fat and 0.37 : 1 for blood (Fries et al., 1978a,b). In contrast, the concentration ratio between the fetal and maternal liver of mice ranged from 3.5:1 to 10:1 (Welsch & Morgan, 1985).

Species-dependent differences in the amounts of PBBs transferred have been demonstrated for two mustelids, the mink

Table 51. Placental transfer: PBB concentrations in the fetus and the mother

Species	Dosing regimen[a]	PBB concentrations							Concentration expressed as:[c]	References
		Maternal adipose	Maternal liver	Maternal others	Whole fetus	Fetal[b] adipose	Fetal[b] liver	Fetal[b] others		
Mouse	FireMaster® BP-6; 1000 mg/kg diet on days 7-18 of pregnancy	39.52	2.51	-	0.53				[HxBB] (mg/kg)	Corbett et al. (1975)
	0 mg/kg (control)		0.04		0.05					
Mouse	FireMaster® BP-6; 100 mg/kg diet on days 7-18 of pregnancy	112.74	12.02	-	0.95	-	5.86	-	[HxBB] (mg/kg)	Corbett et al. (1978a)
Mouse	2,2',4,4',5,5'-hexabromobiphenyl (purity: > 99%)								[HxBB] (mg/kg)	Welsch & Morgan (1985)

Table 51 (contd).

Species	Dosing regimen[a]	PBB concentrations: Maternal adipose	Maternal liver	Maternal others	Whole fetus	Fetal[b] adipose	Fetal[b] liver	Fetal[b] others	Concentration expressed as:[c]	References
	dietary intake from day 6-15 of pregnancy; sacrifice on day 17			placenta:						
	100 mg/kg feed	9.08	17.26	3.79	3.06		182.88			
	300 mg/kg feed	17.30	39.84	8.23	4.56		217.48			
	500 mg/kg feed	69.13	89.47	24.58	17.64		316.79			
	750 mg/kg feed	95.36	103.70	54.33	18.64		453.12			
Rat	FireMaster® BP-6								[HxBB] (mg/kg)	Beaudoin (1977)
	single oral dose of 800 mg/kg body weight (in sesame oil) at day 12 of pregnancy; killing: 24 h later	51	267		13				(pooled samples from 4 rats)	
	48 h later	250	248		6					

Table 51 (contd).

Rat	FireMaster® BP-6; 50 mg/kg diet from day 8-21 of pregnancy	330	4.2	-	1.6		0.2	GI tract: 0.1	[HxBB] (mg/kg)	Rickert et al. (1978)
Rat	Octabromobiphenyl (technical); dietary intake from day 8-15 of pregnancy; sacrifice on day 20;									Waritz et al. (1977)
	0 mg/kg (control)	1.43	3.56		4.38				[Br] (mg/kg)	
	100 mg/kg	70.4	16.1		7.62					
	1000 mg/kg	326	79.8		21.2					
	10 000 mg/kg	590	158		30.1					
Mink	[^{14}C-]-PBBs (HxBB and HpBB); iv injection (1 μCi) in the final trimester of gestation; killed 2 h later	0.031	1.622	plasma: 0.04	0.002	0	0.005	kidney: 0.003; brain: 0; intestine: 0.001	% of the initial dose per g of tissue or ml of fluid	Bleavins et al. (1981)

Table 51 (contd).

Species	Dosing regimen[a]	PBB concentrations: Maternal adipose	Maternal liver	Maternal others	Whole fetus	Fetal[b] adipose	Fetal[b] liver	Fetal[b] others	Concentration expressed as:[c]	References
Ferret	see above	0.124	1.525	plasma: 0.07	0.005	0.004	0.013	kidney: 0.010 brain: 0.003 intestine: 0.005	see above	
Guinea-pig	FireMaster® FF-1; single oral dose of 50 mg/kg body weight at approximately 65 days of gestation; killed 2 days later	45	7	kidney: 4.5; lung: 7		45	45	kidney: 1 lung: 1.5	[HxBB] (mg/kg)	Ecobichon et al. (1983)

Table 51 (contd).

Pig	FireMaster® BP-6; dietary intake during 2nd half of gestation					Werner & Sleight (1981)
	10 mg/kg feed	0.4	1.0	kidney: nd; brain: nd	[HxBB] (mg/kg)	
	100 mg/kg feed	4.9	11.5	kidney: nd; brain: nd		
	200 mg/kg feed	40.3	24.2	kidney: 1.5 brain: 1.8		

[a] HpBB = 2,2',3,4,4',5,5'-heptabromobiphenyl.
[b] nd = Not detected.
[c] [HxBB] = Concentration of 2,2',4,4',5,5'-hexabromobiphenyl; [Br] = Concentration of bromide.

and the European ferret. PBB levels in the ferret kit were significantly greater than those in the mink kit (see Table 51: Bleavins et al., 1981).

Milk transfer

In mammals, the second route of PBB transfer from the mother to the offspring is nursing. The efficiency of this way has been shown through determining the PBB content in milk in relation to the body burden or in relation to exposure levels of contaminated dams, and through measuring PBB levels in kits that have been exposed to PBBs only from suckling. The FireMaster® mixture was used in all studies. Mammary transfer of technical octa- or decabromobiphenyl has not (yet) been assayed.

Most investigations on the PBB contents of milk from contaminated animals have been conducted on cows (Fries & Marrow, 1975; Willett & Irving, 1976; Robl et al., 1978; Fries et al., 1978a,b; Willett & Durst, 1978). The ratios of concentrations in milk fat to body fat in cows no longer receiving PBBs averaged about 0.4 :1 (Willett & Durst, 1978; Fries et al., 1978a,b; see also Fig. 5). This ratio is much lower than the ratio in humans (see section 6.2.2).

For other species (guinea-pig, rat, mink, pig) only single data can be found in the literature. When (lactating) guinea-pigs received a single oral dose of FireMaster® FF-1 (50 mg/kg body weight) within 6-12 h of parturition, levels of HxBB in breast milk (and in perirenal adipose tissue) were of the order of 22 μg/g (and 17 μg/g), respectively, 2 days after treatment (Ecobichon et al., 1983). Rats fed 50 mg FireMaster® BP-6/kg in their diet from day 8 of pregnancy until 14 days after delivery showed, on day 14 postpartum, HxBB concentrations of about 51 μg/ml in the milk and about 483 μg/g wet weight in their body fat (McCormack et al., 1979a). In the same study, milk transfer of PBBs and PCBs was compared. Milk usually contained higher concentrations of PCBs than of PBBs, after simultaneous or separate exposure.

Contrary results were obtained with minks, intraperitoneally injected with either 3 μCi of ^{14}C-labelled PCB or 3 μCi of ^{14}C-labelled PBB on the approximate date at which the embryos would have been implanted (Bleavins et al., 1981). Two weeks postpartum, milk levels of PBBs were determined to be four times those of PCBs (0.105% versus 0.025% of the initial maternal dose per gram of tissue). Werner & Sleight (1981) determined PBB concentrations in the tissues and milk of sows fed various amounts

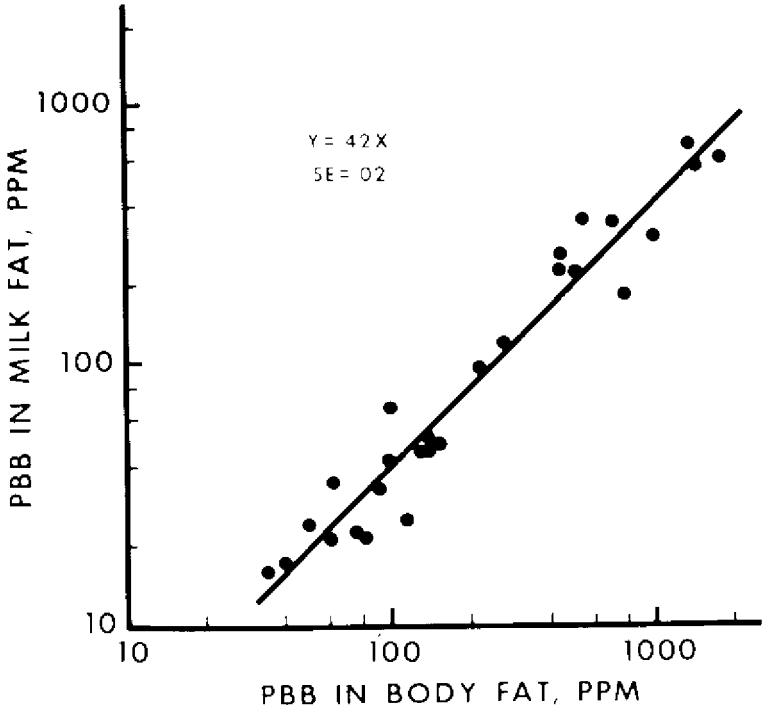


Fig. 5. Relationship between the concentration of hexabrominated biphenyl in milk and subcutaneous body fat of cows (Fries et al., 1978a).

of FireMaster® BP-6 (Table 53). At the end of lactation (4th week), the adipose tissue and milk of sows, fed daily with 200 mg PBB/kg feed, had HxBB concentrations of 194 μg/g tissue (wet weight) and of 22 μg/ml whole milk, respectively. The authors calculated that, on a body weight basis, nursing pigs consumed PBBs in concentrations similar to the concentration given to the sows. Tissue levels of young exposed to PBBs only via nursing have been determined for rats (Rickert et al., 1978) and for guinea-pigs (Ecobichon et al., 1983). When pups of non-treated female rats were nursed by dams fed FireMaster® BP-6 (50 mg/kg body weight) on days 1-14 postpartum, hepatic HxBB-concentrations were on average approximately eight times higher than those in the dams on day 14 postpartum (Rickert et al., 1978).

When dams of guinea-pigs received a dose of FireMaster® FF-1 on day 1 after delivery, the concentrations of 2,2',4,4',5,5'-

HxBB in the lungs, livers, kidneys, and fat of the pups were similar to those of the dams for 4-60 days after treatment (Ecobichon et al., 1983).

Combined placental and milk transfer

Rickert et al. (1978), Bleavins et al. (1981), and Werner & Sleight (1981) concluded from their studies on rats, minks, and pigs, respectively, that milk transfer is far more important than placental transfer; studies on guinea-pigs (Ecobichon et al., 1983) did not confirm this observation. However, under less controlled conditions, perinatal exposure (both placental and milk transfer) occurs and results in a marked body burden in the offspring, as has been shown in studies on rats (Table 52 and McDaniel & Lucier, 1979) and pigs (Table 53). From minks, it has been reported that 14-day-old kits of dams that had received a single intraperitoneal dose of ^{14}C-PBB at an early stage of pregnancy, contained about 3% of the initial maternal dose (Bleavins et al., 1981). PBB body burdens in the offspring of rats were still measurable at 328 days of age and at the end of their life span (see Table 52).

Moreover, a multigeneration study on rats (McCormack et al., 1981) demonstrated that administration of PBBs to a single generation resulted in detectable residues in two subsequent generations (Table 54). The concentrations of PBBs measured in the tissues of F_1-animals were approximately 5-30 times higher than those in tissues from F_2-animals and approximately 50-1000 times higher than those in tissues from F_3-animals (see Table 54).

2) Birds

In birds, eggs are the medium of PBB transfer to the offspring. The ratio of egg PBB contents to dietary level has been reported to be 1 : 1 (Fries et al., 1976) and 1.3 - 1.5 : 1 (Babish et al., 1975a; Ringer & Polin, 1977; Cecil & Bitman, 1978; Polin & Ringer, 1978a) in chickens (White Leghorn hens) and Japanese quail, respectively. After 63 days of feeding FireMaster® BP-6 in the diet, the PBB level in body fat of White Leghorn hens was about 4 times the level in eggs (Fries et al., 1976).

6.2.2 Human studies

Studies on the distribution of PBBs in humans refer only to people having been exposed in a direct or indirect way to the FireMaster®-mixture.

Table 52. Tissue concentrations of PBBs in rats following perinatal exposure to PBBs (FireMaster®-mixture BP-6 or FF-1)

Dosing regimen to dams	Age of offspring	Tissue concentrations of PBBs[a] (mg/kg wet weight)					References
		Offspring				Dams	
50 mg BP-6/kg diet: day 8 of gestation through day 14 postpartum	14 days	liver 9.5			carcass 149.7	liver 4.0	Rickert et al. (1978)
100 mg PB-6/kg diet: day 8 of pregnancy through 28 days postpartum	 28 days 328 days	liver 397 17		kidney 96 11	fat 1693 387	[b]	McCormack et al. (1980)
BP-6 (lot 6244 A) in the diet: day 8 of pregnancy through 28 days postpartum:	28 days	lung	liver	kidney	fat	[b]	McCormack et al. (1982a)
10 mg/kg		5	18	8	162		
100 mg/kg		32	410	109	1693		
200 mg FF-1/kg body weight (in corn oil; by stomach tube): day 7 and 14 of pregnancy (weaning at day 21 of age)	 2 months 2 years	liver: (female) 2.4 (218)[c] 0.8 (107)[c]	liver: (male) 3.0 (280)[c] 0.6 (58)[c]			liver 7.8 (542)[c]	Groce & Kimbrough (1984)

[a] Concentration expressed as the concentrations of 2,2',4,4',5,5'-hexabromobiphenyl.
[b] See McCormack & Hook (1982) and Table 48.
[c] Values calculated on a lipid basis.

Table 53. Mean concentrations of PBBs (mg/kg of tissue, wet weight) in tissues of sows and 4-week-old nursing pigs following perinatal exposure to PBBs[a]

PBBs[b] (mg/kg feed)	Liver		Adipose tissue		Kidney		Brain	
	Sows	Pigs	Sows	Pigs	Sows	Pigs[c]	Sows	Pigs[c]
10	1.0	2.4	15.2	14.8	0.6	nd	0.2	nd
100	45.8	30.2	96.3	96.7	2.3	nd	1.7	nd
200	92.6	41.3	194.2	222.5	3.7	4.1	2.7	4.2

[a] From: Werner & Sleight (1981).
[b] FireMaster® BP-6 fed to the sows during the second half of gestation and during lactation.
[c] nd = Not detected.

Table 54. Tissue concentrations of PBBs in several generations of rats following perinatal exposure to PBBs[a,b,c]

Treatment	Liver	Kidney	Lung	Thyroid	Testis	Ovary	Fat
Control	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
F_1-10	17.1 ± 3.6	7.5 ± 0.6	5.1 ± 0.8	4.4 ± 1.0	8.2 ± 5.3	24.0 ± 1.6	161.7 ± 24.2
F_2-10	0.4 ± 0.1	0.6 ± 0.2	0.9 ± 0.1	0.5 ± 0.1	0.2 ± 0.1	3.0 ± 0.5	6.7 ± 1.9
F_1-100	410.2 ± 40.6	108.6 ± 11.2	32.4 ± 2.0	162.6 ± 20.8	-[d]	-[d]	1693.2 ± 250.4
F_2-100	21.8 ± 3.2	7.2 ± 1.3	8.7 ± 1.0	2.7 ± 0.6	1.8 ± 0.1	16.5 ± 2.6	159.5 ± 16.9
F_3-100	0.4 ± 0.1	0.8 ± 0.4	0.6 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.6 ± 0.1	4.9 ± 0.8

[a] From: McCormack et al. (1981).

[b] Rats were fed 0,10, or 100 mg PBBs (FireMaster® BP-6)/kg from day 8 of pregnancy until 28 days postpartum at which time all offspring (F_1-10 and F_1-100) were weaned on to a control diet, allowed to mature sexually, and bred with littermates to produce the F_2-generation (F_2-10 and F_2-100). F_2-100 littermates were bred to produce F_3-100 animals.

[c] Values are means in mg 2,2',4,4',5,5'-hexabromobiphenyl/kg wet tissue ± SE for at least three animals at 28 days of age.

[d] Sample not available.

As can be seen from a post-mortem study on people from a "high" exposure area of the State of Michigan (USA), PBBs are distributed throughout the entire human body (Table 55). Moreover, it was found that fat and fat-rich tissue had the highest HxBB concentrations. Perirenal fat had the highest mean concentration (475 ng/g). Adrenal, atheromatus aorta, and thymus had mean concentrations of about half that of perirenal fat; all other tissues had mean concentrations of only one-tenth or less of that of perirenal fat (Miceli et al., 1985).

Most of the distribution studies performed with living subjects used paired samples of serum, adipose tissue (fat biopsy technique, e.g., Daum et al., 1978), and breast-milk (see Tables 56, 57 and 58). Other tissues or fluids have rarely been analysed for PBB content, e.g., there is one report on liver biopsy tissue (300 μg HxBB/kg), fat (1069 μg/kg), bone marrow (3.5 μg/kg) and synovial fluid (twice the amount present in serum) of a single person (Meester & McCoy, 1976).

In some early investigations, serum (plasma, resp.) and adipose tissue levels (Table 56) or serum (plasma, resp.) and breast-milk levels (Table 57) did not seem to correlate well with each other. Later studies, performed when continuing exposure had ceased (Anderson, 1985), did reveal good correlations between serum and adipose levels (Table 56) and between breast-milk and serum or adipose tissue levels (Tables 57 and 58). The PBB concentrations measured are compiled in section 5.2 and 5.3.

Different groups of the population can differ in their ratios. For example, lowest adipose to serum ratios were found in lactating and pregnant females (see Table 56). Eyster et al. (1983) found statistically different ratios for females and male chemical workers versus farm workers and other males. The adipose to serum ratio of 340:1, theoretically predicted by Tuey & Matthews (1980) was between the values reported for the Michigan general population (see Table 56). Factors that appear to affect the partitioning ratios are sex, pregnancy, occupational status, the total amount of PBBs present, and whether samples were collected during exposure or during the recovery phase (Eyster et al., 1983; Anderson, 1985). Generally, the stability of a ratio would depend on a person being at equilibrium with respect to PBB intake and fat mobilization (Fries, 1985b).

Transfer of PBBs to offspring occurs via transplacental passage and via breast-milk (see also section 5.2.4). Breast-milk had levels of more than 100 times the maternal serum levels (Table 57). The

Table 55. PBB postmortem study: autopsied tissue samples from humans in the Grand Rapids area (Michigan, USA)[a]

PBBs[b] in tissue (μg/kg wet weight)

Subject No.	Adrenal	Aorta	Brain	Heart l. vent.	Kidney Cortex	Kidney Medulla	Liver	Lung	Pancreas	Renal fat	Skeletal muscle	Spleen	Thymus	Thyroid
1	40	-	2	6	2	4	9	2	4	80	8	3	-	3
2	407	118	1	15	4	15	17	2	43	457	10	9	295	9
3	242	247	16	21	18	61	0	63	51	320	42	2	-	80
4	148	294	103	36	32	30	147	73	653	430	84	123	-	-
5	43	18	3	4	3	6	39	4	135	134	7	1	-	5
6	98	64	24	126	53	77	104	14	130	110	45	64	29	12
7	35	6	1	52	5	6	5	2	9	32	2	2	0	5
8	868	1011	142	233	61	100	259	93	188	1650	22	69	-	-
9	-	75	16	15	6	2	59	6	158	94	11	0	-	12
10	110	285	-	110	95	81	31	62	170	1110	57	312	-	40
11	602	107	0	21	29	38	37	11	148	607	33	15	617	41
12	196	29	11	4	17	31	30	80	92	322	13	4	30	22

Table 55 (contd).

PBBs[b] in tissue (μg/kg wet weight)

Subject No.	Adrenal	Aorta	Brain	Heart l. vent.	Kidney Cortex	Kidney Medulla	Liver	Lung	Pancreas	Renal fat	Skeletal muscle	Spleen	Thymus	Thyroid
13	17	44	9	4	2	3	22	4	20	205	14	2	-	6
14	48	-	5	6	10	5	15	4	17	167	8	4	-	8
15	850	514	13	37	42	67	143	43	146	1390	53	36	-	37
Mean	265	216	27	46	25	35	61	31	131	475	27	43	243	22
SEM	80	77	12	16	7	9	18	9	41	131	6	21	140	6
Range	17-850	6-1011	1-103	2-95	2-100	0-259	2-93	4-653	32-1650	2-84	2-84	0-312	29-617	3-80
Tissue/ renal fat: mean ratio	0.56	0.45	0.06	0.10	0.05	0.07	0.15	0.07	0.28	1.0	0.06	0.09	0.51	0.06

[a] From: Miceli et al. (1985).
[b] Measured (by GC) as the concentration of 2,2',4,4',5,5'-hexabromobiphenyl; limit of detection: 0.5 μg/kg.

Table 56. Adipose tissue and serum partitioning ratios of 2,2'4,4',5,5'-hexabromobiphenyl

Exposed group collected[a]	Year	Partition coefficient ratios	Correlation	Reference
Male chemical workers				
(No. = 27)	1976	287:1	0.96	Wolff et al. (1979a)
(No. = 22)	1975-80	190-260:1	0.89	Eyster et al. (1983)
Farm residents, etc.				
Mixed sexes (No. = 13)	1974-75	175:1 (range: 61-370:1)		Humphrey & Hayner (1975)[b]
Mixed sexes (No. = 116)	1975-76	4752 (± 793):1 (range: 27-14 850:1)		Meester & McCoy (1976)
Mixed sexes (No. = 132)	1976-77	363:1	0.96	Landrigan et al. (1979)
Mixed sexes	1976	370:1	0.94	Wolff et al. (1979b)
(No. = 31)	1976-77	300:1		
(No. > 31)	not specified	320:1		
Mixed sexes (No. = 197)	1974-77	358:1	0.81[d]	Tuey & Matthews (1980)[b,c]

Table 56 (contd).

Exposed group collected[a]	Year	Partition coefficient ratios	Correlation	Reference
Pregnant females (No. = 30)	1975-80	140-180:1	0.91	Eyster et al. (1983)
Non-pregnant females (No. = 51)	1975-80	193-230:1	0.84	Eyster et al. (1983)
Males (No. 75)		325-329:1	0.95	Eyster et al. (1983)
Lactating women throughout Michigan (No. = 8)	1976	100:1	0.72	Brilliant et al. (1978)
Michigan general population (No. = 396)	1978-79	370:1	"high"	Selikoff & Anderson (1979)
Michigan general population (No. = 588)	1978	300:1	0.96	Wolff et al. (1982)

[a] No. = Number of paired samples.
[b] Use of "plasma" (instead of "serum").
[c] Values based on data of Gladen & Rogan (1979).
[d] Spearman correlation coefficient.

Table 57. Breast-milk (fat) and serum, partitioning ratios of 2,2′,4,4′,5,5′-hexabromobiphenyl in Michigan women

Year collected	Number of paired samples	Partition ratios	Correlation coefficient	Reference
1974-75	5	70-132:1	0.78	Humphrey & Hayner (1975)
1976			0.81	Brilliant et al. (1978)
1976-77	21	122:1 (62-257:1)		Landrigan et al. (1979)
1975-80	46	107-119:1	0.95	Eyster et al. (1983)
Not specified	92		0.71[a]	Jacobson et al. (1984)

[a] Pearson product moment correlation.

Table 58. Adipose tissue and breast-milk (fat) partitioning ratios of 2,2′,4,4′,5,5′-hexabromobiphenyl in Michigan women

Year collected	Number of paired samples	Partition ratios	Correlation coefficient	Reference
1976	10	1.07:1	0.88	Brilliant et al. (1978)
1975-80	24	1.1-1.5 :1	0.97	Eyster et al. (1983)

ratios of 2,2′,4,4′,5,5′-HxBB concentrations in milk fat to maternal body fat were found to be in the range of 0.7-0.9 : 1 (Table 58). Placental tissue and cord or fetal serum levels were 1/6 to 1/10 the maternal serum levels (see Tables 59 and 60).

According to Jacobson et al. (1984), the higher maternal serum levels were, in part, reflecting the greater concentration of lipids found in maternal serum (Table 60). Nevertheless, even when calculated on a fat basis, PBB concentrations in maternal serum were still about three times higher than those in cord serum (Jacobson et al., 1984).

Table 59. Placental transfer of PBB; partitioning ratios of 2,2',4,4',5,5'-hexabromobiphenyl between fetal and maternal tissues

Year collected	No.[a]	Paired tissues	Ratios	Correlation coefficient	Reference
1976-77	13	maternal serum/ cord serum	7.04:1 (1.5-10.3:1)		Landrigan et al. (1979)
1975-80	58	cord serum/ maternal serum	0.10-0.14:1	0.88	Eyster et al. (1983)
1975-80	56	placenta/ maternal serum	0.10-0.17:1	0.85	Eyster et al. (1983)
Not specified	153	maternal serum/ cord serum		0.81[b]	Jacobson et al. (1984)
Not specified	107	maternal milk/ cord serum		0.39[b]	Jacobson et al. (1984)

[a] No. = Number of paired samples.
[b] Pearson product moment correlation.

Table 60. Mean PBB and lipid levels in cord serum and maternal serum and milk[a]

	No.	Mean PBB[b] levels	Mean lipid levels
Cord serum	230	0.3 µg/litre	3.24 g/litre
Maternal serum	205	1.7 µg/litre	
	206		6.181 g/litre
Maternal milk	138	3.6 µg/litre	0.029%
Maternal milk-fat	138	105.1 µg/kg	

[a] From: Jacobson et al. (1984).
[b] Probably measured as concentration of 2,2',4,4',5,5'-hexabromobiphenyl.

Incidentally, in contrast to PBBs, PCB levels (examined additionally) were not significantly different in the maternal and cord serum when compared on a fat basis (Jacobson et al., 1984).

PBB levels measured in children with known exposure to PBB *in utero* and/or through breast-milk (see Table 38: Weil et al., 1981) also indicate significant PBB transfer.

The results of analysis of fat and thymus specimens from 2 infants, taken at autopsy, are shown in Table 61. The ratio of thymus/fat "hexabromobiphenyl" concentrations, expressed as percentage, were 13 and 37% (Corbett et al., 1978a).

Table 61. Fat and thymus concentrations of hexabromobiphenyl (HBB) in 3-day-old infants

	HxBB concentration (mg/kg)	
	Fat	Thymus
Patient I	0.091	0.012 (13.2%)
Patient II	0.062	0.023 (37.1%)

[a] From: Corbett et al. (1978a).

The distribution pattern of PBB congeners, other than 2,2'4,4',5'5-hexabromobiphenyl (BB 153), has been studied by Wolff et al. (1979a). They examined the relative (to BB 153) distribution of PBB congeners (penta- to heptabromobiphenyls) in the fat and serum of Michigan chemical workers and farm residents, and found different partition ratios for different homologues.

The distribution of PBBs among blood compartments was studied by Bekesi et al. (1979a,b), Greaves et al. (1984), and Roboz et al. (1980, 1985a,b). In *in vitro* models (PBBs added to blood), the distribution of PBBs among plasma, erythrocytes, mononucleocytes (white cell fraction) and polymorphonucleocytes (white cell fraction) was found to be 89:9:< 1:< 1 (Roboz et al., 1985a,b). When, however, the amount of PBBs per cell was considered, there was an approximately 100-fold excess of PBBs in the white cell fractions compared with the erythrocyte fraction (Roboz et al., 1985b). In environmentally contaminated human blood, PBBs

were also present in higher concentrations per mg protein in lymphocytes than in erythrocytes (Bekesi et al., 1979a,b,; Roboz et al., 1980; see also Table 45).

It is thought that the relatively large amounts of PBBs associated with the white blood cells are possibly the cause of the immunological dysfunctions that result from exposure to PBBs (Roboz et al., 1985b).

In serum, 20% of the PBBs were not bound to protein. The remaining 80% were bound to apolipoproteins B and A in a 3:1 ratio (Greaves et al., 1984). Roboz et al. (1985b) reported a ratio of 4:1, which was close to the ratio (by weight) of the lipid content of these apolipoproteins. For comparison: the ratio between their amino acid content was 1.6:1 (Roboz et al., 1985b). There was no evidence of differential binding of various PBB congeners (penta-, hexa-, heptabromobiphenyls) to any of the serum fractions (Greaves et al., 1984; Roboz et al., 1985a,b).

6.3 Metabolic transformation

Indirect evidence for vertebrate metabolism of some PBB congeners has been obtained by analysis of tissues from experimentally and environmentally exposed animals and humans (see section 6.5). While many PBB congeners tended to be persistent, others were frequently absent or diminished. However, the changes in the relative abundances can reflect differences in uptake, distribution, and excretion among the congeners, as well as differences in the metabolism (Moore et al., 1980).

There are several *in vitro* and *in vivo* methods for studying the metabolism of PBB congeners and mixtures.

6.3.1 In vitro studies

Using *in vitro* techniques, hepatic microsomes from rats (or rabbits: Kohli et al., 1978) were incubated with individual PBB congeners or a PBB mixture, in the presence of nicotinamide adenine dinucleotide phosphate (reduced) (NADPH) and atmospheric oxygen. Most of the authors measured rates of disappearance of congeners (Dannan et al., 1978b; Moore et al., 1980; Parkinson & Safe, 1982; Millis et al., 1985a,b; Mills et al., 1985). A second approach was to examine the incubation mixture for metabolites (Kohli et al., 1978; Purdy & Safe, 1980; Safe et al., 1980; Sparling et al., 1980). The initial studies (Dannan et al.,

1978b; Moore et al., 1980) revealed that only two of twelve PBB congeners from FireMaster® were metabolized when incubated with microsomes isolated from rats, pretreated with phenobarbital (PB) or PBB, namely 2,4,5,2′,5′-pentabromobiphenyl and 2,3,6,2′,4′,5′-hexabromobiphenyl. No metabolism could be observed with control microsomes or microsomes from 3-methylcholanthrene (MC)-treated rats. These and other investigations performed with a number of PBB congeners (Br_1-Br_7 = model congeners, FireMaster® components, photolysis products of several hexabromobiphenyls) and with liver microsomal enzymes induced by either PB or MC are summarized in Table 62.

The results suggest that the rates of metabolism of PBB congeners are dependent upon the positions of bromine and the type of cytochrome induced (P-450:PB-induced; P-448:MC-induced).

The following structure-activity relationships have been derived: PBB congeners that possessed adjacent non-brominated carbons *meta* and *para* to the biphenyl bridge on at least one ring were metabolized by PB-induced microsomes (Dannan et al., 1978b; Moore et al., 1980; Mills et al., 1985). In one case, even one free *para* position was reportedly sufficient for PB-induced metabolism (Moore et al., 1980). Increasing bromination of PBB congeners did not appear to prevent their metabolism (Moore et al., 1980; Mills et al., 1985). Significant metabolism by MC-pretreated microsomes required adjacent *ortho* and *meta* positions free of bromines on at least one ring of lower substituted congeners (up to Br_4). Higher substituted congeners (Br_5, Br_6) were not metabolized, though they fulfilled this criterion (Mills et al., 1985).

In contrast to the studies mentioned above, Purdy & Safe (1980) found that radiolabelled [^{3}H]-2,2′,4,4′,5,5′-hexabromobiphenyl (purity: > 98%) was metabolized *in vitro* by rat liver microsomal enzymes. They determined polar, lipophilic metabolites after incubation with control and PBB-induced microsomes, however, in quantities that were much smaller than those yielded from [^{3}H]-4-bromobiphenyl.

Mono- and dihydroxylated derivatives have been identified as major *in vitro* metabolism products of lower brominated PBBs (Kohli et al., 1978; Purdy & Safe, 1980; Safe et al., 1980, Sparling et al., 1980; Parkinson & Safe, 1982).

Table 62. Metabolism of PBB congeners with rat liver microsomes

	Evidence for metabolism[a]			
PBB congener[b]	MC microsomes[c]	Reference	PB microsomes[d]	Reference
4-MoBB	Yes (172)		Yes (53.1)	Parkinson & Safe (1982)
2,2'-DiBB	Yes (0.33)		Yes (201.7)	Mills et al. (1985)
			Yes (> 2100)	Moore et al. (1980) Dannan et al. (1978b)
4,4'-DiBB	-		No (< 0.02)	Moore et al. (1980) Dannan et al. (1978b)
3,4,4'-TrBB	Yes (100.7)		No (0.02)	Mills et al. (1985)
2,4,2',4'-TeBB	Yes		No	Mills et al. (1985)
2,4,2',5'-TeBB	Yes (43.5)		Yes (184.6)	Mills et al. (1985)
			Yes (24)	Moore et al. (1980)
2,4,2',6'-TeBB	Yes		Yes	Mills et al. (1985)
2,5,2',5'-TeBB	No (0.0)		Yes (66.2)	Mills et al. (1985)
			Yes (27)	Moore et al. (1980)
2,6,2',6'-TeBB	No		Yes	Mills et al. (1985)
2,3,3',4'-TeBB	Yes (57.6)		Yes (52.8)	Mills et al. (1985)
2,5,3',4'-TeBB	Yes (49.7)		Yes (47.5)	Mills et al. (1985)
3,4,3',4'-TeBB	Yes (58.8)		No (0.01)	Mills et al. (1985)
3,4,3',5'-TeBB	Yes		No	Mills et al. (1985)
3,5,3',5'-TeBB	No (0.06)		No (0.0)	Mills et al. (1985)
			Yes	Moore et al. (1980)
2,4,6,2',4'-PeBB	No		No	Mills et al. (1985)

Table 62 (contd).

PBB congener[b]	Evidence for metabolism[a]			
	MC microsomes[c]	Reference	PB microsomes[d]	Reference
2,4,5,2′,5′-PeBB	No (0.02)		Yes (23.7)	Mills et al. (1985)
	No	Dannan et al. (1978b)	Yes (13)	Moore et al. (1980) Dannan et al. (1978b)
2,4,6,2′,6′-PeBB	No		Yes	Mills et al. (1985)
2,4,5,3′,4′-PeBB	No (0.05)		No (0.03)	Mills et al. (1985)
	No	Dannan et al. (1978b)	No (< 0.06)	Moore et al. (1980) Dannan et al. (1978b)
3,4,5,3′,4′-PeBB	No	Dannan et al. (1978b)	No	Mills et al. (1985)
3,4,5,3′,5′-PeBB	No	Dannan et al. (1978b)	No	Mills et al. (1985)
2,3,4,2′,4′,5′-HxBBB	No (0.16)		No (0.0)	Mills et al. (1985)
	No	Dannan et al. (1978b)	No (< 0.3)	Moore et al. (1980) Dannan et al. (1978b)
2,3,6,2′,4′,5′-HxBBB	No	Dannan et al. (1978b)	Yes (19)	Moore et al. (1980) Dannan et al. (1978b)
2,4,5,2′,4′,5′-HxBBB	No	Dannan et al. (1978b)	No (< 0.3)	Moore et al. (1980) Dannan et al. (1978b)
2,3,4,5,3′,4′-HxBBB	No (0.11)		No (0.0)	Mills et al. (1985)
	No		No	Dannan et al. (1978b)
2,4,5,3′,4′,5′-HxBBB	No		No	Dannan et al. (1978b)
3,4,5,3′,4′,5′-HxBBB	No (0.20)		No (0.0)	Mills et al. (1985)
2,3,4,5,2′,4′,5′-HpBB	No	Dannan et al. (1978b)	No (< 0.3)	Moore et al. (1980) Dannan et al. (1978b)

[a] Measured as the rate of substrate disappearance (in parentheses: values measured in pmol/min per mg protein).
[b] For expediency, a trivial numbering system was used.
[c] MC microsomes = 3-methylcholanthrene-induced microsomes.
[d] PB microsomes = phenobarbital-induced microsomes.

Some PBB congeners may induce their own metabolism (Aust et al., 1983), and some PBB congeners may influence the metabolism of other PBB congeners (Purdy & Safe, 1980; Mills et al., 1985). However, it should be noted that PBB congeners that induce microsomal enzymes (see also section 8.8.1) are not necessarily metabolized (Aust et al., 1983).

Some studies were carried out using AHH, specific DNA binding, and 7-ethoxyresorufin assays. The results showed that PBBs (FM FF-1) can induce *in vitro* cytochromes P450 IA (P448) in the primary cultures of human, and newly-born rat, epidermal keratinocytes, and of a rat hepatoma cell-line (Yao et al., 1991).

6.3.2 In vivo studies

In vivo metabolism studies included attempts to find and identify PBB metabolites from intact animals. Hydroxylated derivatives have been reported most commonly as metabolites of vertebrates.

As can be seen from Table 63, administration of lower brominated congeners resulted in low yields of, mainly, mono- or dihydroxy metabolites. However, most of the studies compiled suffered from the fact that the purities of the congeners used in these studies were not determined (Moore et al., 1980). The two studies with 2,2′,4,4′,5,5′-HxBB did not provide evidence of significant metabolism (Table 63).

Various results were obtained after administering commercial PBB mixtures. No hydroxylated PBBs could be detected in the urine of cows given single 3-g doses of FireMaster® BP-6 (Willett & Irving, 1976) or in the milk of cows (accidentally contaminated by FireMaster® FF-1) with PBB residues as high as 900 μg/kg, on a whole milk basis (Gardner et al., 1976). Approximately 1% of the FireMaster® BP-6 administered to a pig was eliminated as an unidentified pentabromobiphenylol (Kohli & Safe, 1976). It is not clear whether this metabolite was formed from hexabromobiphenyl (by reductive debromination followed by hydroxylation) or directly from pentabromobiphenyl (by hydroxylation).

The faeces of dogs fed FireMaster® BP-6 contained a metabolite identified as 6-hydroxy-2,2′,4,4′,5,5′-hexabromobiphenyl (Gardner et al., 1979). However, the authors did not exclude microbial metabolism in the dog's gut, because no hydroxyhexabromobiphenyl was found in the liver of the dog,

Table 63. PBB *in vivo* metabolites reported in the literature

Parent compound	Species (tissue, etc.)	Yield[a]	Reported metabolites	References
Monobromobiphenyls				
2-bromobiphenyl	rabbit (urine)	1%	2'-bromo-4-biphenylol	Kohli et al. (1978)
		traces	mono-hycroxybromobiphenyl	
	rat	(>)	2-bromo-4-4'-biphenyldiol	Sparling et al. (1980)
		(>)	2-bromo-4-4'-biphenyldiol	
		(<)	2-bromo-4-biphenylol	
3-bromobiphenyl	rabbit (urine)	4%	3-bromo-4-biphenylol or 5-bromo-2-biphenylol	Kohli et al. (1978)
		< 1%	dihydroxybromobiphenyl	
	rat (urine)	(>)	3-bromo-4,4'biphenyldiol and an unidentified diol	Sparling et (1980)
		(<)	monohydroxybromobiphenyls	
4-bromobiphenyl	rabbit (urine)	4%	4'-bromo-4-biphenylol	Kohli et al. (1978)
		1.5%	4'-bromo-3,4-biphenyldiol	
	rat (urine)	(>)	4'-bromo-4-biphenylos	Sparling et (1980)
		(<)	mono- and dihydroxylated species	
	pig (urine)	3%	4'-bromo-4-biphenylol	Kohli & Safe (1976)
		traces	monohydroxybromobiphenyl	
		0.5%	4'-bromo-3-methoxy-4-biphenylol	

Table 63 (contd).

Parent compound	Species (tissue, etc.)	Yield[a]	Reported metabolites	References
	chicken (excreta)	12.2% 9.8%	4′-bromo-4-biphenylol 4′-bromo-3,4-biphenyldiol	Jones et al. (1979)
	(eggs)	0%	no metabolites	
Dibromobiphenyls				
4,4′-dibromobiphenyl	rabbit (urine)	10% 1% 2%	4,4′-dibromo-3-biphenylol 3,4′-dibromo-4-biphenylol 4′-bromo-4-biphenylol	Safe et al. (1976)
	pig (urine)	5% 1% traces 1%	4,4′dibromo-3-biphenylol 3,4′-dibromo-4-biphenylol dibromomethoxybiphenylol 4′-bromo-3-methoxy-4-biphenylol	Kohli & Safe (1976)
		traces	dibromomethoxybiphenyl	
Mixture of di-, tri-, and tetrabromobiphenyls	fish *Salmo salar* (whole animal)		dibromobiphenylol	Zitko & Hutzinger (1976)
Hexabromobiphenyls				
2,2′,4,4′,5,5′-hexabromobiphenyl (purity: 95%)	rat (urine and faeces)	traces	"metabolites"	Safe et al. (1978)
2,2′,4,4′,5,5′-hexabromobiphenyl (purity: 99%)	rat (tissues)	0%	no metabolites	Matthews et al. (1977)
	(bile and faeces)	traces (1-4%)	may be metabolites	

[a] (>) and (<) = major and minor components (no further quantitative information).

though PBB was present. Matthews et al. (1979) mentioned that dogs were able to metabolize 2,2',4,4',5,5'-hexachlorinated biphenyl, but were unable to metabolize the analogous PBB at an appreciable rate.

Some investigations implied that fish may debrominate the more highly brominated components of PBB mixtures. Juvenile Atlantic salmon (*Salmo salar*) experimentally exposed to FireMaster® BP-6, in water or in food, contained several mono- to pentabromobiphenyls, not present in FireMaster® BP-6 (Zitko, 1977). Fish (*Salmo salar*) fed octabromobiphenyl (Dow Chemical)-contaminated food contained unidentified penta-, hexa-, and heptabromobiphenyls in addition to the octabromobiphenyls. It was not known whether the partially debrominated biphenyls were generated by the fish, or by the associated microflora (Zitko, 1977). Analyses of fish captured from natural waters may also indicate the possibility of the debromination reaction in fish, unless selective accumulation or elimination takes place (Stratton & Whitlock, 1979). In fish from water mainly contaminated with decabromobiphenyl, only the nona- and hexabromobiphenyl congeners were present. However, in fish from FireMaster® BP-6-contaminated waters, only hexabromobiphenyl was detected.

6.3.3 Metabolic pathway

The most frequently reported route of PBB metabolism was hydroxylation. However, according to Zitko & Hutzinger (1976), a reductive debromination may be a degradative pathway of higher brominated biphenyls, because the carbon-bromine bond is less stable than, e.g., the carbon-chlorine bond.

The hydroxylation reaction probably proceeds via both arene oxide intermediates (Safe et al., 1976, 1978, 1980; Kohli et al., 1978; Moore et al., 1980) and by direct hydroxylation (Kohli et al., 1978; Sparling et al., 1980; Moore et al., 1980). Schemes of possible metabolic routes have been published by Matthews (1982) and Safe (1989). The most important enzyme involved in the oxidation of xenobiotics, such as PBBs, is aryl hydrocarbon hydroxylase. It is a highly inducible, haem-containing monooxygenase belonging to the family of cytochromes P-450 (e.g., Safe et al., 1980). A (partial) summary of the AHH-mediated metabolism is given by Safe et al. (1978).

The formation of covalently bound macromolecular adducts has been reported. Less than 10% of the metabolites were present in

the urine of rabbits in a bound form, e.g., as glucuronides (Safe et al., 1976). *In vitro* metabolism also resulted in macromolecular conjugates (Kohli et al., 1978; Purdy & Safe, 1980; Safe et al., 1980; see also section 6.6). In general, the biotransformation of PBBs is a slow process, but the stereochemistry and molecular size vary so widely among PBBs that there are great differences in their metabolic activity.

6.4 Elimination and excretion in expired air, faeces, urine

6.4.1 Animal studies

Elimination of PBBs from the body has been studied using hexa- and octabromobiphenyl. No information is available on decabromobiphenyl. Some data found in the literature (see also section 6.1) are compiled in Table 64 (^{14}C-labelled single doses), Table 65 (^{14}C-labelled multiple doses), and Table 66 (daily feeding).

The only study conducted with octabromobiphenyl resulted in a much higher elimination from rats than was found for HxBB in another study on rats (Table 64). However, there are also reports on the rapid elimination of HxBB, e.g., by Willett & Irving (1976), who found a 50% recovery of HxBB after 168 h in the faeces of two cows given single intraruminal doses (3 g) of FireMaster® BP-6. However, relatively high concentrations of radioactivity or of HxBB, found, in some cases, in the faeces during the first few days after dosing or during daily dosing, may have been due to incomplete absorption (Tuey & Matthews, 1980). Approximately 60% of the total dose was also recovered in the faeces of rhesus monkeys (Rozman et al., 1982: Table 64).

Elimination of PBBs was primarily via the bile and the intestine into the faeces and, in general, was found to be a slow process.

Biliary concentrations have been measured in a Rhesus monkey (Rozman et al., 1982), in rats (Matthews et al., 1977) and in cattle (Willett & Irving, 1976; Willett & Durst, 1978). In rats, excretion of HxBB in the bile accounted for 0.68% of the total PBB dose between 0 and 4 h after intravenous (iv) administration. Twenty-four hours after an iv dose, 0.032% of the total dose was excreted in the bile in 1 h, and, 7 or 42 days after dosing concentrations were too low to quantify (Matthews et al., 1977). Because of this small amount cleared with the bile, enterohepatic recirculation of HxBB in rats is not important (Tuey & Matthews, 1980). Concentrations of HxBB in the bile of cattle were two-three times greater

Table 64. Faecal, urinary, and exhalative elimination of ^{14}C activity as a percentage of a single dose of [^{14}C-]PBB

Species	Agent; solvent; dose (mg/kg body weight); route	Time	% recovery in: faeces	urine	expired air	Reference
Rhesus monkey (male)	[^{14}C-]HxBB in mineral oil; 2, oral	5 days	38	(0.18)	-	Rozman et al. (1982)
Rat (male)	[^{14}C-]HxBB in Emulphor EL-620: ethanol: water (1:1:8)				-	Matthews et al. (1977); Tuey & Matthews (1978, 1980)
	1, oral	24 h	7.9			
	1, intravenous	24 h	0.96			
	1, intravenous	7 days	3.28	< 0.1		
		42 days	6.6	not detected		
Rat (male and female)	[^{14}C-]OcBB[a] in corn oil; 1, oral	24 h	62			Norris et al. (1973)
		48 h	69			
		16 days	73	< 1	< 1	
Mink (*Mustela vison*) (pregnant female)	[^{14}C-]PBB[b] in propylene glycol (1 µCi in 0.1 ml) intravenous	2 h	-	0.003	-	Bleavins et al. (1981)
Ferret (*Mustela puttorius (furo)* (pregnant female)		2 h	-	0.004		
Dog	[^{14}C-]2,2',4,4',5,5'-hexabromo biphenyl (solvent not specified) 0.6, intravenous	25 days	8			Sipes et al. (1979)

[a] OcBB = technical octabromobiphenyl.
[b] Consisted of 2,2', 4,4', 5,5'-HxBB and 2,2', 3, 4,4', 5,5'-HpBB.

Table 65. Urinary and faecal elimination of HxBB and/or metabolites in male Rhesus monkeys and male rats, dosed repeatedly with [^{14}C-]HxBB

Species	Dose (mg/kg body weight)	Days after first dose	Urine (µg/kg per day)	Faeces (µg/kg per day)	Cumulative % recovery of total dose in faeces	Reference
Monkey (No. = 2)	50 in methyl cellulose; oral on days 1 and 5	1-10 11-17 203-209	3.2 2.5 not detectable	5890 5.0 3.5	ca 60%	Rozman et al. (1982)
Rat (No. = 3)	1 in corn oil; oral on days 1, 2, 3, and 4	7			ca 14%	Matthews et al. (1977)

Table 66. Elimination of HxBB (2,2',4,4',5,5'-hexabromobiphenyl) in faeces and urine during the feeding of FireMaster®-mixtures

Species (sex)	Intake of FireMaster® BP-6 or FF-1	Sampling time	Concentration in: (mg/kg) Faeces	Urine	Approximate % recovery in faeces	Reference
Dog (female)	BP-6: in corn oil (capsule) 1 mg/kg body weight per day for 6 weeks	last day of dosing	7			Gardner et al. (1979)
Pig	BP-6: in corn oil 20 mg/kg diet 200 mg/kg diet (ad libitum) for > 4 weeks	at week 4	 21.3[a] 182.0[a]	 0.015 0.07		Ku et al. (1978)
Cow	FF-1: in gelatin capsules; for 90 days 0.1 mg/kg diet 1.0 mg/kg diet 10 mg/kg diet	weekly	 0.02 0.15 1.5	 mostly n.d.[b]	 15% of ingested dose	Robl et al. (1978)

Table 66 (contd).

Species (sex)	Intake of FireMaster® BP-6 or FF-1	Sampling time	Concentration in: (mg/kg) Faeces	Urine	Approximate % recovery in faeces	Reference
Calf (male)	BP-6:(capsule); 25 g daily for 9 days	total collection	8045		5% of total dose	Willet & Irving (1976)
Hen	BP-6; 20 mg/kg in the diet for 63 days	weekly			9% of daily dose	Fries et al. (1976)
Hen	FF-1: not specified	not specified			11% of daily dose	Ringer & Polin (1977)

[a] Faecal samples oven-dried.
[b] nd = Not detected (detection limit = 0.005 mg/kg).

than the concentration in the plasma (Willett & Irving, 1976; Willett & Durst, 1978).

According to Fries (1985b), excretion of PBB in the urine is not expected, because of the insolubility of PBBs in water. He attributed the few instances in which low concentrations of PBBs were reported to cross-contamination with faeces. On the other hand, this route of excretion may account for minor or metabolized biphenyls (Damstra et al., 1982; see also Table 63). However, excretion of PBB metabolites may be of minor relevance, since the more abundant PBB congeners are not, or only slightly, metabolized (see also section 6.3). The amounts of urinary or faecal metabolites were low. A study on a pig that received a single intraperitoneal (ip) dose of FireMaster® BP-6 (100 mg/kg body weight) reported a yield of about 1% of pentabromobiphenylol in the urine and faeces, collected for 7 days (Kohli & Safe, 1976). The level of a hydroxy metabolite detected in the faeces of dogs fed FireMaster® BP-6 was about an order of magnitude less than the PBB levels (Gardner et al., 1979). Yields of lower brominated urinary PBB metabolites are compiled in Table 63.

In their study on cows, Willett & Durst (1978) did not find any direct relationships between the amount of PBBs fed and the concentration in the faeces. In contrast, Babish et al. (1975a) did find a linear correlation ($r > 0.97$) of dietary PBBs with excreta residues in Japanese quails. In another study on cows, it was also reported that relationships were approximately constant (Robl et al., 1978: Table 66).

Following withdrawal of PBBs (FireMaster® BP-6) from the diet of cows, the faecal concentrations of HxBB declined to 1-2% of faecal levels during dosing (Willett & Durst, 1978) and to less than 5% in hens (Fries et al., 1976). Faecal concentrations were small in relation to body burden. Cows that received 250 mg FireMaster® BP-6 daily had HxBB concentration ratios in body fat to faeces of about 750 : 1. Their faeces to plasma ratio was 0.7 :1 (Willett & Durst, 1978). Cows environmentally contaminated (FireMaster® FF-1) 7-9 months before examination had comparable body fat to faeces ratios, but a different faeces to blood ratio of 4.2 : 1 (Detering et al., 1975; Cook et al., 1978b; Fries et al., 1978a). Post-exposure lactating cows eliminated via milk fat three times the quantity of HxBB cleared in faeces (Willett & Durst, 1978).

There have been some studies on the means to enhance the elimination of PBBs. PBBs used were: FireMaster® FF-1 (Cook et al., 1978b; Kimbrough et al., 1980; McConnell et al., 1980; Polin & Leavitt, 1984; Polin et al., 1985) and [^{14}C-]HxBB (Rozman et al., 1982). The treatments included activated carbon in rats (McConnell et al., 1980) and cows (Cook et al., 1978b), cholestyramine in rats (McConnell et al., 1980) and monkeys (Rozman et al., 1982), colestipol in chickens (Polin & Leavitt, 1984; Polin et al., 1985), mineral oil in rats (Kimbrough et al., 1980), monkeys (Rozman et al., 1982), and chickens (Polin et al., 1985), high-fibre diets in rats (Kimbrough et al., 1980), and phenobarbital in cows (Cook et al., 1978b). The effects of restricted caloric intake, alone, or in combination with other treatments, was investigated in rats (McConnell et al., 1980) and chickens (Polin & Leavitt, 1984; Polin et al., 1985). The procedures were found not to be (Cook et al., 1978b; Kimbrough et al., 1980; McConnell et al., 1980), or to be only partially, effective (Rozman et al., 1982; Polin & Leavitt, 1984; Polin et al., 1985) in reducing the body burden of PBBs (measured as concentrations of HxBB, total bromine levels, or ^{14}C-activity).

6.4.2 Human studies

The concentrations of PBBs in human bile and faeces represent a minor proportion of the total body burden, as has been demonstrated by Eyster et al. (1983), who determined HxBB levels in Michigan farm and chemical workers in 1975-80. Concentrations of HxBB observed in the bile and faeces were about 1/2 to 7/10 of the serum levels (on a whole-weight basis) and were estimated to be approximately 0.5% of the adipose tissue levels (Table 67).

These findings are consistent with the theoretical predictions of Tuey & Matthews (1980), who calculated slow rates of faecal excretion in humans. In addition, these authors showed that the excretion rate in lean individuals exposed to HxBB would be higher than those in overweight individuals.

6.5 Retention and turnover

6.5.1 Animal studies

The time course of PBB tissue concentrations has been studied predominantly in rats, and, to a lesser extent, in cattle, chickens, and guinea-pigs (Table 68). Incomplete data are available for

Table 67. Medians, range, and geometric means of 2,2',4,4',5,5'-hexabromobiphenyl (HxBB) for paired specimens of serum, faeces, and bile obtained from farm and chemical workers[a]

Number	Paired specimen	Median	Range[b]	Geometric mean
51	serum	7 µg/litre	1-1540 µg/litre	14.4 µg/litre
	faeces	5 µg/kg	nd-862 µg/kg	9.0 µg/kg
20	serum	3.5 µg/litre	1-153 µg/litre	4.2 µg/litre
	biliary fluid	2 µg/litre	nd-70 µg/litre	2.7 µg/litre

[a] From: Eyster et al. (1983).
[b] nd = Not detectable (detection limit: 1 µg/kg or µg/litre).

mice, pigs, and monkeys. With the exception of 3 older studies (Norris et al., 1973; Lee et al., 1975a; Waritz et al., 1977), in which the behaviour of technical octabromobiphenyl in rats was observed, the majority of investigators used the FireMaster®-mixture (BP-6 or FF-1). Of the individual PBB congeners, 2,2',4,4',5,5'-hexabromobiphenyl (Matthews et al., 1977; Millis et al., 1985b) and 3,3',4,4'-tetrabromobiphenyl (Millis et al., 1985b) were administered.

Complex and varied relationships were found in tissue concentrations with time after PBB administration (see also Tables 47, 48, and 49).

6.5.1.1 Time trends, retention: 2,2',4,4',5,5'-hexabromobiphenyl (BB 153)

a) Rat

When rats dosed with 2,2',4,4',5,5'-hexabromobiphenyl (Matthews et al., 1977; Tuey & Matthews, 1980) or with FireMaster® FF-1 (Kimbrough et al., 1978; Domino et al., 1980b; 1982), BB 153 concentrations in the blood were highest immediately after dosing, but fell rapidly during the first day (as PBBs are taken up from blood by the liver and muscle tissues, which are highly perfused tissues). Then, concentrations in the blood, liver, and muscle declined less quickly (as the dose was redistributed to the adipose tissue; Tuey & Matthews, 1980; Fries,

Table 68. Reported biological half-lifes of PBBs in mammals and birds, after single or repeated exposure

Species (sex)	PBB[a] (Dosing regimen) Observation period	Elimination from:	Calculated half-life[b] (Kinetic phases)	References
Rhesus Monkey (male)	[^{14}C-]HxBB (50 mg/kg body weight on days 1 and 5; oral) 209 days	body	> 4 years	Rozman et al. (1982)
Rat (male)	[^{14}C-]OcBB (1 mg/kg body weight; single dose; oral) 16 days	faeces	< 24 h (1st phase) > 16 days (2nd phase)	Norris et al. (1973)
Rat	[^{14}C-]HxBB (1 mg/kg body weight; single iv dose) 42 days	faeces	2 days (1st phase)[c]	Birnbaum (1985)
		"tissues" (blood, liver muscle, skin)	ca 24 days[c]	Ecobichon et al. (1983)
Rat (male)	FM BP-6 (1 mg/100 g body weight; single ip dose; 36 weeks	serum	23.1 weeks	Miceli & Marks (1981)
		fat	69.3 weeks	
		adrenal	43.3 weeks	
		brain	63.0 weeks (2nd phase)	
		liver	11.5 weeks (2nd phase)	
		lung	11.2 weeks	
		spleen	9.0 weeks	

Table 68 (contd).

Rat (male)	FM FF-1 (10 mg/kg body weight; single dose; oral) 112 days	whole blood	3.27 h (β) 33.3 h (α) 145 days (β)	Domino et al. (1982)
Guinea-pig (lactating females and pups)	FM FF-1 (50 mg/kg body weight; single dose; oral) 60 days	tissues (fat, liver, kidney, lung) of both	ca 22 days	Ecobichon et al. (1983)
Cow	FM BP-6 (fed 1.13 g/day for 15 days; = 50 mg/kg in the diet) 15 days (of withdrawal)	milk	10.5 days	Gutenmann & Lisk (1975)
Cow	FM BP-6 (fed 10 mg/day for 60 days) 60 days (of withdrawal)	milk fat	ca 58 days (2nd phase)	Fries & Marrow (1975)
Cow	FM FF-1 (environmentally contaminated 1 year earlier; 6 months of observation)	milk fat	ca 60 days (range: 36-301 days)	Fries et al. (1978a); Cook et al. (1978b)
Cow	FM BP-6 (fed 0.25 mg-25 g/day for various periods) up to 3 years of observation	milk fat (body)	> 6 months[d]	Fries (1985b)

Table 68 (contd).

Species (sex)	PBB[a] (Dosing regimen) Observation period	Elimination from:	Calculated half-life[b] (Kinetic phases)	References
Chicken (White Leghorn hens)	FM FF-1 (fed in the diet) 28 days (of withdrawal)	egg	17 days	Ringer & Polin (1977)
Chicken (White Leghorn hens)	FM FF-1 (fed 0.2-125 mg/kg in the diet for 5 weeks) 56 days (of withdrawal)	egg	17 days	Polin & Ringer (1978a)
	(fed 1125 and 625 mg/kg in the diet for 5 weeks) 56 days (of withdrawal)	liver	31 days	
	(fed 5-625 mg/kg in the diet for 5 weeks) 56 days (of withdrawal)	muscle	17 days	

Table 68 (contd).

Chicken (White Leghorn hens)	FM BP-6 (fed 20 mg/kg in the diet for 63 days) 49 days (of withdrawal)	egg	28 days (2nd phase)	Fries et al. (1976)
Chicken (White Leghorn hens)	FM BP-6 (fed 20 and 64 mg/kg in the diet for 8 weeks) 266 days (of withdrawal)	egg	112 days (late phase)	Cecil & Bitman (1978)
Chicken (White Leghorn hens)	FM BP-6 (fed 20 and 64 mg/kg in the diet for 8 weeks) 266 days (of withdrawal)	excreta	4-5 days[e]	Polin & Leavitt (1984)

[a] HxBB = 2,2',4,4',5,5'-hexabromobiphenyl; OcBB = octobromobiphenyl (technical mixture); FM BP-6 = FireMaster® BP-6; FM FF-1 = FireMaster® FF-1.

[b] Referring to 2,2',4,4',5,5'-hexabromobiphenyl or [^{14}C-]activity.

[c] Half-life calculated from data of Matthews et al. (1978); see also Fig. 6.

[d] Half-life calculated from data of Willett & Durst (1978).

[e] Half-life calculated from data of Fries et al. (1976).

1985b), finally decreasing only very slowly. After a single intravenous dose of BB 153 (1 mg/kg body weight), adipose tissue contained more than 60% of the total body burden within four days (Tuey & Matthews, 1980; see Table 50).

BB 153 concentrations in the adipose tissue peaked later than in other tissues and remained high throughout the period of observation (6 weeks: Matthews et al., 1977; 16 weeks; Domino et al., 1980b; 36 weeks: Miceli & Marks, 1981). For example, ratios between fat and serum levels in rats rose from 221 : 1 to 722 : 1 between 6 and 36 weeks after a single dose exposure (Miceli & Marks, 1981), reflecting the much more rapid clearance of BB 153 from serum than from fat.

Kinetic models to describe the principal toxicokinetics of BB 153 in the rat were constructed by Tuey & Matthews (1980; a blood flow-limited physiological compartmental model) and by Domino et al. (1982). The latter developed a three-compartment model. Tissues within a compartment showed similar kinetic characteristics, but concentrations could vary widely. Compartment 1 consisted of whole blood, spleen, kidney, and heart. Compartment 2 included liver, lung, cerebral grey and white matter, cerebellum, and testes, and compartment 3 consisted of subcutaneous fat. Jejunum could not be classified.

However, results of Miceli & Marks (1981) (PBB levels monitored over longer periods) do not fit in well with this scheme. For example, these authors observed typical first-order-elimination kinetics of BB 153 in the serum of rats, but kinetics of disappearance from heart and kidney (and pituitary) do not appear to be first order, though belonging to the same compartment (according to Domino et al., 1982). BB 153 concentrations in the brain and liver (both "compartment 2") declined rapidly during the interval from 6-12 weeks after exposure, but, thereafter, (from week 12 to 36) brain concentrations fell far more slowly than those of the liver. The study of Miceli & Marks (1981) showed that the (long-term) retention, but not always the concentration, of BB 153 in lipid-rich tissues (brain, adrenal, adipose) was much greater than in most other tissues (see also Table 68).

Corresponding to the small decline in BB 153 from the tissues of rats, the elimination rates in the faeces were slow (see Fig. 6). Less than 7% of the dose was eliminated 42 days after a single iv dose, most, during the first 3-4 days (Tuey & Matthews, 1980).

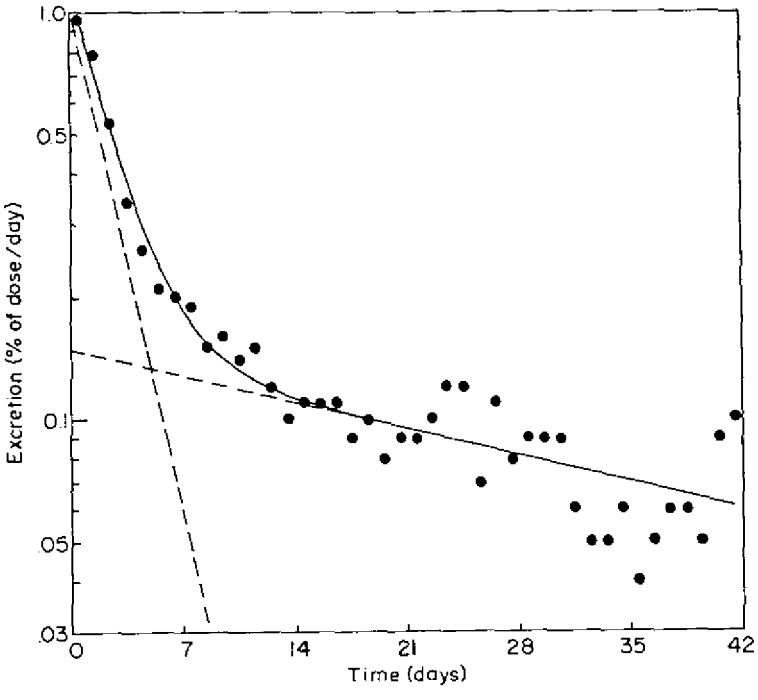


Fig. 6. Daily elimination of PBBs in faeces. Each point represents the average obtained with three animals that received a single iv dose of BB 153 (1 mg/kg body weight). The solid line represents the rate of elimination determined by non-linear regression analysis and the dashed lines represent the biphasic decay components (From: Matthews et al., 1977).

The kinetic models or calculations for BB 153 were based on the results of studies on adult male rats. In maternal rats the situation is more complex, and only a little information is available. For example, BB 153 levels in the liver and fat of maternal rats decreased during a period from the end of lactation (and exposure) until 14 weeks later (decline in fat: 50%), but BB 153-concentrations in the mammary glands increased (5 times higher) during the same period (see also Table 48), indicating redistribution of BB 153 during the recovery period following lactation (McCormack & Hook, 1982).

During continued exposure to FireMaster® BP-6, BB 153 concentrations in the milk of lactating rats were determined 0, 3,

5, 7, and 14 days following parturition and showed a decline from 180 mg/litre (via 115, 89, 63 mg/litre) to 50 mg/litre (McCormack et al., 1979a).

The kinetics of BB 153 in growing animals have not been frequently investigated. The differences in BB 153 levels and organ weights have been reported only between two ages. McCormack et al. (1980) showed that at 328 days of age, the concentrations of BB 153 in the liver, kidney, and fat of rats were approximately 5, 10, and 25% of the respective tissue concentrations at weaning (28 days of age; cessation of exposure). Another long-term study (Groce & Kimbrough, 1984) compared BB 153 levels in the livers of perinatally exposed rats at the age of 2 months and 2 years and also found diminished values (see Table 52).

Comparing BB 153 concentrations in the blood and adipose tissue of rats after 10 and 14 months recovery resulted in no "true" decrease (Kimbrough et al., 1978). Other studies also indicated a long retention of PBBs in the brain (Geller et al., 1979), thyroid, and liver (Allen-Rowlands et al., 1981), and in the adrenal glands (Castracane et al., 1982).

b) Other species

The species, the second most often examined, was cattle, but the kinetic models used for cattle (e.g., Fries et al., 1978a) were less sophisticated than those described for rats (Fries, 1985b).

In cows given FireMaster® BP-6, the BB 153 concentration in blood plasma was maximal 24 h after exposure (Willett & Irving, 1976; Willett & Durst, 1978). When multiple doses were administered, plasma concentrations were at equilibrium by 15 days. When dosing was terminated, concentrations declined approximately 50% in 10 days and 66% by day 20. Thereafter, plasma residues did not fit a consistent decline model (Willett & Durst, 1978).

While BB 153 was detectable in plasma within 2-4 h of exposure (Willett & Durst, 1978), it was detected in the milk of cows 13 h after exposure (Willett & Irving, 1976). With continued exposure, a steady state of BB 153 concentrations in milk fat was reached after 20-40 days (Fries & Marrow, 1975; Willett & Durst, 1978; Fries et al., 1978a; Robl et al., 1978). When the feeding of PBBs was stopped, concentrations in milk fat declined rapidly for a short time (Fries & Marrow, 1975). When a new equilibrium was established, milk fat and body fat concentrations declined in a

parallel manner (Fries, 1985b). An example of the biphasic decline is given in Fig. 7. However, as Fries et al. (1978a) observed, the stage of lactation influenced the rate of elimination, and, in some cases, BB 153 levels in milk increased shortly after calving.

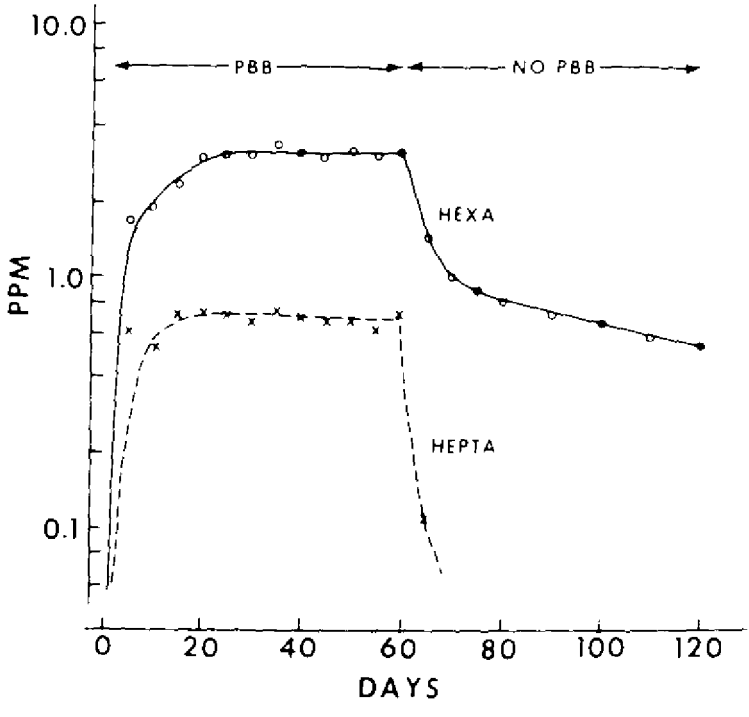


Fig. 7. Concentrations of polybrominated biphenyl in the milk fat of cows fed 10 mg/day. Each point is an average of four cows. Calculations of the concentrations of each component were based on the assumption that each was fed at 10 mg/day (From: Fries et al., 1978a).

Data from Detering et al. (1975) indicated that BB 153 levels in cow's milk would decrease from 200-400 mg/kg in fat to 0.3 mg/kg in 120 weeks.

Information on a time course of PBB levels in the body fat of cows is limited. According to Willett & Durst (1978), e.g., BB 153 concentrations in the subcutaneous fat of cows had declined by 40%, 20 days after exposure. Two measurements, one at parturition (ca. 150 days later) and one after heavy lactation (ca.

200 days later) showed an increase in residues. During late lactation, significant declines occurred.

Probably, a multicompartment system is necessary to describe the long-term behaviour of PBBs in lactating cows, with special trends when pregnancy, parturition, etc. occur (Willett & Durst, 1978; Fries et al., 1978a; Fries, 1985b).

The appearance and decline of BB 153 in faeces were reported for two cows given a single intraruminal dose of FireMaster® BP-6 (Willett & Irving, 1976) and for cows fed BP-6 daily for 60 days (Willett & Durst, 1978). In the first case, BB 153 was detected 12 h after administration, peaked between 20 and 36 h, and declined to about 2% of the peak concentration during the subsequent 48 h. By day 8, approximately 50% of the dose was detectable in the faeces (Willett & Irving, 1976). During daily exposure, BB 153 concentrations in the faeces reached a steady state by day 10. After withdrawal of the PBBs, the levels of BB 153 declined within 10 days to approximately 1% of the concentration present during exposure (Willett & Durst, 1978). Fries (1985b) inferred low rates of elimination in faeces, because faecal BB 153 concentrations in cattle that were no longer being exposed to PBBs were relatively low (Willett & Durst, 1978; Fries et al., 1978a).

Another domestic species in which the kinetics have been examined is the chicken. Whole carcass analysis of male White leghorn chickens showed that, during the 2 weeks that FireMaster® FF-1 was fed at 0.1 or 1.0 mg/kg, the chickens retained 88 and 69%, respectively, of the FF-1 that was consumed (Polin & Leavitt, 1984). Withdrawal rates were determined in a similar study on egg- and meat-type chickens fed diets containing 1 or 10 mg FF-1/kg. Body burdens of BB 153 in chickens, previously fed 10 mg/kg, did not decrease significantly during a withdrawal period of 42 days (e.g., 3% loss by day 21 of withdrawal). In contrast, chickens, previously fed 1 mg/kg, eliminated up to 40% of the BB 153 (Polin et al., 1985).

Withdrawal of PBBs from the adipose tissue of laying hens fed FireMaster® FF-1 at different dietary levels (0.2, 1, 5, 25, 125, or 625 mg/kg) has been followed by Polin & Ringer (1978a). BB 153 levels remained unchanged over the 56 days of withdrawal. Lillie et al. (1975) calculated a 50% reduction after more than 16 weeks. Withdrawal from other tissues and from eggs was more rapid (Ringer & Polin, 1977; Polin & Ringer, 1978b).

BB 153 levels in eggs laid by hens fed 20 or 64 mg FireMaster® BP-6/kg diet for 8-9 weeks reached a plateau by the third or fourth week of feeding. When feeding of BP-6 stopped, residues decreased in a two-phase rate pattern with a phase of rapid decline shortly after exposure had ceased and a late phase of slow decrease (Fries et al., 1976; Cecil & Bitman, 1978). In one study (Fries et al., 1976), the levels after 49 days were approximately 10% of the values on day 0 of cessation; in the other study by Cecil & Bitman (1978), detectable amounts were still present 33 weeks after withdrawal of BP-6 from the diet.

Excreta were analysed from hens fed 20 mg FireMaster® BP-6/kg for 63 days (Fries et al., 1976). After an initial rise and decline, the BB 153 levels remained fairly constant (at about 2 mg/kg on a wet weight basis) during the feeding of PBBs. After withdrawal of PBBs, the residues dropped to a negligible level (< 0.1 mg/kg).

Only some milk data during continued exposure are available for pigs. Milk of sows having received 10, 100, or 200 mg of FireMaster® BP-6/kg feed during the second half of gestation and during lactation was monitored until the 4th week. On a fat basis, concentrations of BB 153 were highest in the colostrum and decreased slowly during lactation (Werner & Sleight, 1981).

Disappearance of BB 153 from the tissues of lactating guinea-pigs and of their pups was described by Ecobichon et al. (1983). The maternal animals had received a single oral dose of FireMaster® FF-1 (50 mg/kg body weight) within 6-12 h of parturition, and the residue levels of nursing young and the dams were measured up to 60 days after exposure (at intervals of 2, 4, 7, 14, 28, 42, and 60 days: see Fig. 8). Following the initial 7 days during which there was obvious inter-tissue transportation and sequestration in body fat, a gradual, but similar, linear rate of decline was observed in the livers, kidneys, and lungs of both the young and their dams. A similar rate of reduction was observed in the body fat of both pups and dams.

In a study on mice, BB 153 residue levels were measured 6 h after dietary intake of 100 mg/kg. FireMaster® BP-6 (for 14 days) can be compared with those obtained 14 weeks after feeding. There was a decline in all tissues including fat (see Table 48), however, to a different extent, resulting in changes in the relative BB 153-concentrations between tissues (Corbett et al., 1978a).

BB 153 blood levels of rhesus monkeys, dosed with BB 153, markedly declined over time (day 5: 1.5 mg/kg, day 11: 0.2 mg/kg; day 25 < accurate measurement levels) (Rozman et al., 1982).

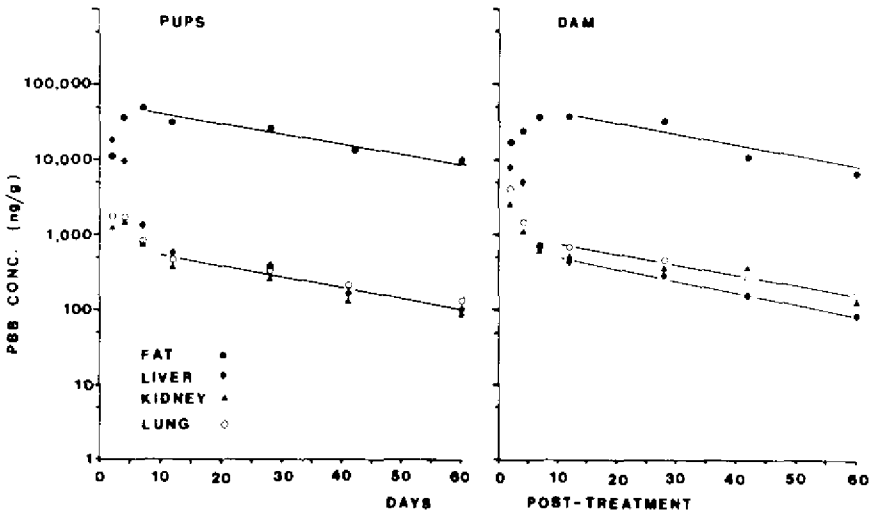


Fig. 8. The distribution and elimination of residues of 2,2',4,4',5,5'-hexabromobiphenyl from the perirenal fat, liver, kidney, and lung of polybrominated biphenyl-treated lactating guinea-pigs and their nursing young, at intervals following the administration of a single dose of FireMaster® FF-1 to the dams within 6-12 h of parturition. The values shown are mean residue concentrations. Lines were fitted to the data by linear regression analysis (From: Ecobichon et al., 1983).

The PBB body burden of juvenile Atlantic salmon (*Salmo salar*), fed for 42 days with FireMaster® BP-6-contaminated food, remained practically constant after 14 days of feeding non-contaminated food (Zitko, 1977).

6.5.1.2 Biological half-lives

The biological half-lives of PBBs reported in the literature for various species have been compiled in Table 68. McDaniel & Lucier (1979) reported a half-life of BB 153 exceeding the lifetime of rats.

In some cases the results obtained by different authors are similar, in other cases, large discrepancies exist. These deviations were, perhaps, caused by measuring the half-lifes under different circumstances of exposure and for different lengths of time (Fries, 1985b). By means of simulation studies, Domino et al. (1982) demonstrated the effects of different amounts of body fat on the half-life of BB 153 in the rat (see Table 69).

Tuey & Matthews (1980) have simulated the effects of a growing animal on the kinetics of BB 153 and found that, though concentrations of BB 153 in fat fell faster than in a stable animal, the "actual" half-life of the substance was proionged, because of an increase in the relative fat proportions.

6.5.1.3 Differences between individual congeners

There are some reports on the differences in turnover and retention of individual PBB congeners. Mostly, they refer to changes in the relative abundances of certain FireMaster® components, namely: 2,2′,4,5,5′-pentabromobiphenyl (BB 101), 2,3′,4,4′,5-pentabromobiphenyl (BB 118), 2,2′,3,4′,5′,6-hexa-bromobiphenyl (BB 149), 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153),2,2′,3,4,4′,5′-hexabromobiphenyl(BB138),2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167), 2,3,3′,4,4′,5-hexabromobiphenyl (BB 156), 2,2′,3,4,4′,5,5′-heptabromobiphenyl (BB 180), and 2,2′,3,3′,4,4′5-heptabromobiphenyl (BB 170). To describe such changes, the GC profile of the original FireMaster® mixture was compared with the GC profile obtained on analysis of tissues from animals treated with this mixture, by measuring either the area (e.g., Wolff & Aubrey, 1978; Domino et al., 1980b) or the height (e.g., McCormack et al., 1982a; Bernert & Groce, 1984; Groce & Kimbrough, 1984) of the GC peaks and by normalizing the values to BB 153 as 100. A few other authors (Fries & Marrow, 1975;

Fries et al., 1976) based their calculations on the assumption that each component (BB 153 and BB 180) was fed at the same rate in the diet. According to Fries (1985b), some differential behaviour may be due to analytical artefacts, introduced by differential recovery of the congeners or by adsorption of congeners on the glassware (Willett et al., 1978), but many changes appear real.

Table 69. Effect of different amounts of body fat on the half-life of 2,2′,4,4′,5,5′-hexabromobiphenyl in the rat[a]

	Amount fat (% normal fat)	Half-life (days)
Emaciated	25	60.5
	50	88.8
	75	117
	90	134
Normal	100	145
	110	156
	125	173
	150	200
	175	228
	200	256
Obese	250	311

[a] From: Domino et al. (1982).

The trends reported in the literature include the selective retention of 5 minor components of the FireMaster® mixture in the tissues of rats, pigs, cows, and chickens (Fries & Marrow, 1975; Fries et al., 1976, 1978a; Dannan et al., 1978b; Willett & Durst, 1978; Wolff & Aubrey, 1978; Wolff & Selikoff, 1979; Domino et al., 1980b; McCormack et al., 1980, 1982a; Werner & Sleight, 1981; Groce & Kimbrough, 1984; Polin & Leavitt, 1984). They can be summarized, as follows.

With some exceptions, the concentrations of 2,2′,4,5,5′-pentabromobiphenyl (BB 101) and 2,2′,3,4,4′,5,5′-heptabromobiphenyl (BB 180) relative to BB 153 appeared to be lower in tissues from treated animals than in those fed FireMaster® mixture. The relative concentrations of 2,3′,4,4′,5-pentabromobiphenyl (BB 118) and 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167) appeared to be

higher or unchanged in many cases. 2,2′,3,4′,5′,6-Hexabromobiphenyl (BB 149) was barely, or not, detected in the tissues of any animals.

The results of a multigeneration study on rats also reflected the differential behaviour of certain PBB congeners (McCormack et al., 1981). Of the first eight peaks (penta- to heptabromobiphenyls) in the GC profile of FireMaster®, all except peak 3 (BB 149) were detected in the livers of rats in the F_1, F_2, and F_3 generations (experimental design: see Table 54). For example, the concentration of 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167) relative to BB 153 was higher in the livers of animals in the F_1 generation than in the FireMaster® BP-6 standard, but decreased with each subsequent generation. Although F_2-10 and F_3-100 animals (10 and 100 mg/kg treatment, respectively; see Table 54) had similar hepatic concentrations of BB 153, the relative concentrations of other PBB congeners, including BB 167 appeared to be lower in the livers from F_3-100 than F_2-10 animals (McCormack et al., 1981).

Domino et al. (1980b) found that 2,2′,4,5,5′-pentabromobiphenyl (BB 101) penetrated the brain of rats more rapidly than 2,3′,4,4′,5-pentabromobiphenyl (BB 118) or any of the higher relative molecular mass homologues. Fries et al. (1976) reported a faster clearance of 2,2′,3,4,4′,5,5′-heptabromobiphenyl (BB 180) (half-time = approximately 20 days) than of BB 153 (half-time = approximately 28 days) from eggs of hens after feeding stopped. However, analyses of whole chicken carcasses resulted in unchanged ratios of BB 153/BB 180 on days 0, 21, and 42 of withdrawal (Polin & Leavitt, 1984). The authors judged that the dynamics for withdrawal of these two congeners from tissues of chickens were parallel. The withdrawal from milk of dairy cows was found to be more rapid for BB 180 than for BB 153 (Fries & Marrow, 1975; Fries et al., 1978a; see also Fig. 7).

In just one study (Millis et al., 1985b), equimolar doses of individual PBB congeners were administered to the test animals. Immature male rats received a single oral dose (21.3 μmol/kg body weight) of 3,3′,4,4′,5,5′-hexabromobiphenyl or 3,3′,4,4′-tetrabromobiphenyl and were analysed at various times up to 14 days after treatment. Adipose tissue and liver concentrations of 3,3′,4,4′,5,5′-hexabromobiphenyl appeared unchanged over time whereas the tissue concentrations of 3,3′,4,4′-tetrabromobiphenyl decreased in a biphasic manner.

6.5.1.4 Octabromobiphenyl

Some kinetic data are available for technical octabromobiphenyl. Bromine levels in the adipose tissue of rats dosed with octabromobiphenyl did not decrease during a period of 90 days (Norris et al., 1973) or 18 weeks (Aftosmis et al., 1972a; Waritz et al., 1977) after cessation of dosing, or, according to Lee et al. (1975a), levels even increased 18 weeks after exposure. A partial elimination of bromine was observed from the livers of these rats after recovery (Norris et al., 1973; Lee et al., 1975a; Waritz et al., 1977).

The contents of total PBB (octabromobiphenyl plus an unidentified hexabromobiphenyl) in juvenile Atlantic salmon (*Salmo salar*), fed 90 days with octabromobiphenyl (Dow Chemical)-contaminated food, also remained fairly constant after 28 days of withdrawal (Zitko, 1977).

6.5.2 Human studies

Information on the time trends of BB 153 distribution or retention in humans is limited. As with animals, BB 153 seems to be highly persistent in humans. This conclusion has been drawn from monitoring BB 153 levels over time in both individual persons and the Michigan population.

Most paired serial samples exist for serum (or plasma) from farmers, etc. (Humphrey & Hayner, 1975: sampled June/Autumn, 1974; Landrigan et al., 1979: sampled 1974/77; Wolff et al., 1979b: sampled 1976/77/78; Kreiss et al., 1982: sampled 1977/78/79; Sherman, 1991: sampled 1976/80/87) and chemical workers (Wolff et al., 1979b: sampled 1976/78; Bahn et al., 1980b and Bialik, 1982: sampled 1978/1981; Lambert et al., 1990) (in parentheses: references plus year of sampling). The values obtained indicated no, or little, decrease (see sections 5.2 and 5.3, and Table 38) with the exception of the results of Bahn et al. (1980b) and Bialik (1982) (see section 5.3). Paired adipose analyses have been reported only by Meester & McCoy (1976) who found a considerable average decline in HxBB levels over six months (see also section 5.2). However, one of the 16 persons tested had increasing or unchanged fat levels, while serum levels slowly dropped. The significance of these observations and the combined results of Bahn et al. (1980b) and Bialik (1982) are unclear. A most recent case report (Sherman, 1991) showed that "PBB" could be identified in the serum and fat of a cancer patient over an 11-year

period (1976-87). Serial testing of 11 breast-milk samples from one lactating Michigan woman showed that HxBB concentrations varied between 0.1 and 0.2 mg/kg (expressed on a fat basis) during a three-month period, without any significant downward trend (Brilliant et al., 1978).

Comparisons at the population level have been made for serum (Meester & McCoy, 1976), breast-milk (Miller et al., 1984), and adipose tissue (Miceli et al., 1985). Generally, the presence of PBBs in the tissues of Michigan people many years after the spill (1973) may be an indicator for its persistence (see Tables 38 and 39). Meester & McCoy (1976) found that the average HxBB level in the serum of farmers during the first six months of 1976 was ten times lower than that during the last six months of 1975 (0.2 μg/litre versus 2.0 μg/litre). Miller et al. (1984) concluded from their analyses of breast-milk from 2986 lactating women during May 1976 and December 1978 that HxBB levels were not declining. Approximately 5 years after the Michigan PBB incident occurred, adipose tissue from live residents of a "high" exposure area (Muskegon County area) contained median HxBB levels of 500 μg/kg (Wolff et al., 1982). Approximately 10 years after exposure, postmortem adipose tissue contained median HxBB levels of 320 μg/kg (Miceli et al., 1985).

On the basis of the two last values, Miceli et al. (1985) calculated a half-life of 7.8 years for HxBB (BB 153) in human adipose tissue. This prediction was close to the body burden half-time of 6.5 years estimated by Tuey & Matthews (1980) using pharmacokinetic data obtained from rats.

A median serum half-life of BB 153 of 12 years (range: 4.6-94.7 years) has been determined by comparing previous and more recent serum BB 153 levels of Michigan residents (Lambert et al., 1990).

As Tuey & Matthews (1980) explained, the half-life may be longer in growing children or in persons gaining weight. However, calculating the effects of different amounts of body fat on the retention of BB 153, these authors also found that adipose tissue may act as a protective reservoir in mature humans, because the concentration of BB 153 in the blood (and possibly other more critical tissues) of obese persons should be significantly less than those of leaner individuals who received comparable exposures.

There was some evidence for the differential retention of various PBB congeners in humans, when PBB congeners in serum

samples from Michigan subjects were compared with FireMaster® BP-6. The main congeners assayed by using GC-MS analysis (Wolff & Aubrey, 1978; Wolff et al., 1978) or Negative Chemical Ionisation Spectrometry (NCIMS) analysis (Roboz et al., 1982; Greaves et al., 1984) were as follows: 2,2',4,5,5'-pentabromobiphenyl (BB 101), 2,3',4,4',5-pentabromobiphenyl (BB 118), 2,2',3,4',5',6-hexabromobiphenyl (BB 149), 2,2',4,4',5,5'-hexabromobiphenyl (BB 153), 2,2',3,4,4',5'-hexabromobiphenyl (BB 138), 2,3',4,4',5,5'-hexabromobiphenyl (BB 167), 2,2',3,4,4',5,5'-heptabromobiphenyl (BB 180). The most obvious changes refer to the two penta isomers and to the major heptabromobiphenyl. The2,2',3,4,4',5,5'-heptabromobiphenyl was absent (Roboz et al., 1982) or greatly diminished in serum (Wolff & Aubrey, 1978; Wolff et al., 1979a; Greaves et al., 1984) in relation to the concentrations of BB 153 (taken as 100%). The relative amounts of 2,2',4,5,5'-pentabromobiphenyl (BB 101) were also greatly decreased (e.g., 80%: Greaves et al., 1984) in all samples. However, a marked decrease in 2,3',4,4',5-pentabromobiphenyl (BB 118) concentrations was observed only in the serum of farmers, taken several years after exposure (e.g., 60%: Greaves et al., 1984), but not in the serum of chemical workers (Wolff & Aubrey, 1978; Wolff et al., 1979a; Roboz et al., 1982).

6.6 Reaction with body components

6.6.1 *Animal studies*

When a ^{14}C-PBB mixture (FireMaster®) was incubated with rat liver microsomes, no binding to exogenous DNA was detected, and only a small amount of radioactivity was covalently bound to microsomal protein (Dannan et al., 1978b). The formation of low and high relative molecular mass adducts with PBB metabolites has been quoted elsewhere (section 6.3).

6.6.2 *Human studies*

Studies on human serum revealed that lipoproteins are the predominant protein carriers of PBBs in serum (Greaves et al., 1983). 80% of the PBBs were bound to apolipoproteins B and A in a 4 : 1 ratio (Greaves et al., 1984; Roboz et al, 1985a). According to Roboz et al. (1985b), the ratio was 3 : 1. No preferential binding of PBB congeners (2,2',4,4',5,5'-hexa-; 2,2',4,5,5'-penta-; 2,2',4,5',6-pentabromobiphenyl) was found (Roboz et al., 1985a,b).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Only few data are available on effects of PBBs on organisms in the environment. They refer to microorganisms, water fleas, waterbirds, (rodents), and farm animals.

7.1 Microorganisms

The toxicity of technical decabromobiphenyl (Adine 0102) against bacteria (*Pseudomonas putida* M.) was determined by the cell multiplication inhibition test (according to the ISO TC 147/SC 5/WG 1/N 111 standard, and using 0.1-1% DMSO (dimethylsulfoxide) as a solvent. An EC_{10} of 53 mg/litre was found (Atochem, 1990).

7.2 Aquatic organisms

In a short-term test (according to the ISO standard 6341) the immobilization of *Daphnia magna* (Crustacea) by technical decabromobiphenyl (Adine 0102) has been investigated. The following results were obtained after dissolution of the test material in DMSO because of its weak solubility in water:

- EC_{50} (24 h): > 66 mg/litre;
- The maximum concentration resulting in 0% immobilization (24 h): < 2 mg/litre (Atochem, 1990).

7.3 Terrestrial organisms

7.3.1 Wildlife

In 1977 and 1978, Haseltine et al. (1981) and Heinz et al. (1983) studied red-breasted mergansers (*Mergus serrator*) nesting on islands in the northwestern Lake Michigan in order to determine whether environmental contaminants (organochlorines and metals) were producing effects on reproduction. Seventeen contaminants, including PBBs, were measured in randomly chosen eggs from 206 nests under study. Using a variety of statistical approaches, Heinz et al. (1983) looked for effects of individual contaminants and combinations of contaminants on reproductive measurements, such as nest desertion, failure of eggs to hatch, death of newly hatched ducklings, percentage hatching success, number of ducklings leaving the nest, and egg-shell thickness. PBBs and other

chemicals were sometimes negatively correlated with shell thickness or thickness index, but not consistently so, as found for DDE. However, no contaminant or combination of contaminants measured seemed to have a pronounced effect on the aspects of reproduction mentioned above. The hatching success of the mergansers averaged 81.7% in 1977. According to Heinz et al. (1983), the hatching success averaged 85.6% in 1978 (Haseltine et al., 1981).

Although it is not valid to compare reproductive success among different species, it should be noted that dabbling ducks, whose eggs contained only a fraction of the contaminant burdens (e.g., no PBBs: Haseltine et al., 1981; see also Table 32), of the redbreasted mergansers had better hatching success (Heinz et al., 1983).

An interesting observation on rodents living on a PBB-contaminated farm has been reported by Jackson & Halbert (1974). They observed that rats and mice were apparently eradicated when they came into contact with PBB-contaminated cattle feed pellets.

7.3.2 Farm animals

Farm animals in Michigan that ingested feed inadvertently containing PBB (FireMaster® FF-1) in place of magnesium oxide fell sick. First symptoms were observed in the cattle of several dairy herds and revealed this so-called "Michigan PBB incident".

7.3.2.1 Cattle

The exact doses of PBBs to which Michigan cattle were exposed are not known. Fries (1985b) estimated the maximum PBB doses of individual cattle based on milk or tissue fat concentration at the time of detection, which ranged from 9 to 24 months after the cattle had consumed contaminated feed. For example, if PBB were detected 9 months after exposure, PBB concentrations of 0.1 mg/litre of milk and 0.25 mg/kg tissue would indicate that the cow had received a total dose of 1 mg/kg of body weight. Increased PBB concentrations in milk and tissue would indicate a proportionally higher dose. If detection were delayed for as long as 24 months, the above example for milk and tissue concentrations would indicate an exposure of 6 mg/kg of body weight.

a) High-level contamination in cattle

Adverse effects of PBBs in lactating cows were first reported by Jackson & Halbert (1974).

In reconstructing the accident, it was assumed that the cows on this farm (Halbert farm) consumed PBB-contaminated feed (PBB content from 3 to 4 g/kg; Isleib & Whitehead, 1975) over 16 days, and ingested about 20 g PBB/day, initially. The total average exposure of these cows was estimated to be 250 mg/kg body weight (Fries, 1985b). The contaminated feed was also fed to a group of 6- to 18-month-old calves. The dose might have been about 58 mg/kg body weight per day when feeding started, and the total doses may have reached 700 mg/kg body weight over 6 weeks (Fries, 1985b), if feed was consumed at the same rates as in experimental studies (Durst et al., 1977).

The clinical signs of toxicity, described by Jackson & Halbert (1974), were anorexia (50% reduction in feed consumption) and a 40% decrease in milk production a few weeks after ingestion of the contaminated feed. Although the supplemented feed was discontinued within 16 days, milk production was not restored, and the cows continued to lose weight. An unspecified number of cows had increased frequency of urination and lacrimation and developed haematomas, abscesses, abnormal hoof growth, lameness, alopecia, hyperkeratosis, and cachexia, and several died within 6 months. Altogether, the death rate of Halbert cows was about 24/400.

The death rate of the 6- to 18-month-old calves (heifers and bulls) to which the suspected feed was offered, was much higher. About 50% of the calves died within 6 weeks. After 5 months, only two of twelve animals were alive, and they had developed hyperkeratosis over their entire bodies. There were also a variety of reproductive problems including embryo resorption, abortions, stillbirths, deaths shortly after births, delayed deliveries, and enlarged calves. The clinical signs were variable, and, with the exception of decreased milk production and weight loss, no particular symptom was predominant in the affected animals (Jackson & Halbert, 1974; Robertson & Chynoweth, 1975).

Necropsy findings have been reported for some of the 24 mature cows that died during the 6 months following exposure (Jackson & Halbert, 1974). Gross lesions observed included somewhat enlarged livers, haematomas and abscesses in the thoracic and abdominal cavities, abomasal ulcers, necrotic metritis, suppurative bronchopneumonia, and pericarditis. As in all observations without controls, it was difficult to draw definitive conclusions as to which lesions were caused by PBBs and which were unrelated to PBBs (Fries, 1985b). Two of the twelve calves in a calf feeding trial had massive liver abscesses.

Histopathological studies on ten of the cows revealed various liver and kidney changes. Liver lesions were reported in seven animals and included fatty changes and amyloidosis. Renal tubular nephrosis and interstitial nephritis were reported in four of the cows (Jackson & Halbert, 1974; Getty et al., 1977).

Several clinical signs and pathological changes, reported by Jackson & Halbert (1974), were also described in cows in controlled feeding studies (Durst et al., 1977; Durst et al., 1978a,b; Moorhead et al., 1977, 1978; Robl et al., 1978; Willett et al., 1980; see also section 8). These included anorexia, dehydration, excessive lacrimation, emaciation, hyperkeratosis, reproductive difficulties (fetal death, enlarged calves, and difficulty in calving, hypospermatogenesis), and renal damage. Conditions described in the accidentally exposed cows, but not confirmed in the controlled studies, included haematomas, abscesses, abnormal hoof growth, extensive hair loss, liver abscesses, necrosis, and metritis (Fries, 1983, 1985b).

The Halbert herd was one of about 12 "highly" contaminated herds that had PBB concentrations of more than 30 mg/kg in milk fat, when detected. According to Fries (1985b), it is likely that all of these herds had some clinical signs of toxicosis. According to the same author, there was no comprehensive clinical examination of any herd that had milk concentrations in the range of 1-30 mg/litre, but it appears that most animals in these herds did not have clinical signs when the farms were depopulated. A preliminary report (cited by Getty et al., 1977) indicated that cows that had been exposed to PBBs 19 months earlier had levels of up to 80 mg/kg in body fat, but were apparently normal clinically and were producing normal quantities of milk. Gross or microscopic lesions that could be attributed to PBB exposure were not found.

b) Low-level contamination in cattle

Residue concentrations in the body fat or milk fat of cows, classed as having low-level contamination, rarely exceeded 1 mg/kg, and, for the most part, not even 0.3 mg/kg. There were several studies on Michigan cattle with such low exposures.

Results of an evaluation of 72 low-level contaminated herds have been reported by Kay (1977) and Getty et al. (1977). Production drop and sterility were two consistent signs and were regarded as interrelated. The retardation of growth of young stock

was very significant, as it was in the Jackson & Halbert study (1974). Some other findings were not consistent. A mail questionnaire survey (Getty et al., 1977) showed similar observations.

Cows (n = 46) from six herds across Michigan, whose body fat contained a mean concentration of 0.31 mg/kg and a maximum concentration of 1.8 mg/kg, were compared with a group of cows from Wisconsin (n = 40) that had not been exposed to PBB. The two groups were reared together and subjected to the same feeding and management system. There were no significant differences in the animals' milk production, body weight, weight gain, breeding and reproductive performance, incidence of commonly experienced health problems, calving rate, and the health of their calves. Also no pattern of gross or histopathological lesions was seen between test animals and control animals upon necropsy (Wastell et al., 1978).

An epidemiological survey, which compared the health status of 16 herds with low PBB exposure (traces to 1 mg/kg body fat or milk fat) with the status of 15 herds with no PBB exposure, also indicated that productivity and general health conditions between the two groups of herds were similar. Of the biochemical parameters tested (9 urinalyses, 13 serum chemistry parameters), three resulted in significantly different values. Serum concentrations of calcium, glucose, and cholesterol in contaminated herds were significantly lower than those of the control herds. But the relationship to PBB exposure was unknown (Mercer et al., 1976).

Instead of specific clinical conditions, Fries (1983) evaluated the overall performance of exposed herds (residues in tissue or milk fat generally < 0.3 mg/kg) and of "relatively unexposed" herds (residues < 0.02 mg/kg) of comparable size, breed, and location by analysing Dairy Herd Improvement Association records. He found that no productive or reproductive characteristics of the herds were affected by PBB exposure.

It should be noted that the classification of herds as having a high or a low level of contamination refers to PBB levels at the time of detection. Thus, it is sometimes impossible to know whether there was a history of a short-term, high exposure or a long-term, low exposure, which may produce different syndromes. For example, Fries (1985b) pointed out that feed that was contaminated by cross-contamination in the feed mills was being fed at the time of detection, in some cases. Under this circum-

stance, PBB intakes as low as 0.1 mg/kg of body weight per day could produce milk fat residues as high as 20 mg/kg (Fries & Marrow, 1975; Fries 1985b).

7.3.2.2 *Other farm animals*

Although it was cattle feed that was originally involved in the accidental substitution, all other feeds became involved by cross contamination, e.g., in the mixing machinery of feed companies that had been exposed to PBB (Dunckel, 1975). It is likely that other animals were not exposed to the same high levels as cattle.

(i) Poultry

There are no reports of clinical signs or problems associated with the accidental contamination of poultry feed. However, some controlled feeding studies have been published (see section 8).

(ii) Pig

Adverse health effects in pigs, identified as contaminated, were rarely reported. Only one review (Reggiani & Bruppacher, 1985) mentioned that abortions occurred in pigs. Two controlled feeding studies (Ku et al., 1978; Werner & Sleight, 1981) have been conducted (see section 8).

(iii) Horse, rabbit, goat, sheep

Other species of farm animals, including at least 2 horses, 32 rabbits, 2 goats, and 19 flocks of sheep, were identified as contaminated and buried at Kalkaska, but details of ill effects were not recorded (Dunckel, 1975; Getty et al., 1977).

One experimental feeding study on sheep (Gutenmann & Lisk, 1975) is available (see section 8).

7.4 Population and ecosystem effects

No information available.

7.5 Effects on the abiotic environment

No information available.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

Differences in toxic responses between acute, high-level exposures and long-term, low-level exposures to halogenated aromatic compounds are mainly quantitative (McConnell & Moore, 1979). Moreover, the delayed onset of toxic signs and the persistence of PBBs in the body, which may cause long-term exposure of the target organs from a single dose, "tend to blur the usual distinctions that are made between acute and chronic exposure" (Fries, 1985b). For these reasons, symptoms after single and short-term exposures are reviewed together in section 8.2. Another feature of the toxicity of PBBs and related classes of compounds is the latent period between the time of exposure and the time of death, which ranged from several days to weeks (Di Carlo et al., 1978; Safe, 1984; Hutzinger et al., 1985a; McConnell, 1985). Thus, the classical LD_{50} values and other mortality data found are summarized in one section (8.1).

8.1 Lethality

"Acute" toxicity data (LD_{50} and LC_{50} values) of commercial PBB mixtures have been compiled in Table 70. The LD_{50} values of all mixtures show a relatively low order of acute toxicity (LD_{50} > 1 g/kg body weight) in rats, rabbits and quails, regardless of the route of administration, and range from > 1 to 21.5 g/kg body weight. Regarding the LC_{50} values for minks, this species may be highly sensitive to PBBs, but a direct comparison is complicated by differences in the experimental design.

As with TCDD and PCBs (McConnell, 1984; Safe, 1984), the apparent toxicity of PBBs is higher with multiple-dose rather than single-dose administration. For example, the single oral LD_{50} of FireMaster® in rats was quoted to be 21.5 g/kg body weight, but, if given in small repeated doses, the total lethal dose was approximately 1-3 g/kg body weight (see Table 70).

Deaths after exposure to PBBs are delayed (Di Carlo et al., 1978; Tables 71 and 72). Thus, Gupta & Moore (1979) have recommended that the LD_{50} of halogenated aromatic hydrocarbons or chemicals that may have a long-term build-up with delayed toxicity should be determined more accurately after multiple dosing and an extended period of observation.

Table 70. Toxicity of PBB mixtures

PBB	Species	Sex	Route (Strain)	Observation period	Parameter[a]	Dose/ concentration[b]	Details	References
FireMaster®	rat		oral		LD_{50}	21.5	single dose	Di Carlo et al. (1978)
FireMaster® FF1 (Lot No. 1312 FT) (in corn oil)	rat (Fischer-344/N)	female	oral	90 days	LD_{50}	1.43	22 doses (over 30 days)	Gupta & Moore (1979)
		male	oral	90 days	LD_{50}	3.28	22 doses (over 30 days)	
FireMaster® BP-6	rabbit		dermal		LD_{50}	5		Aftosmis et al. (1972b)
FireMaster® (Lot 635-71) (in corn oil)	rabbit (New Zealand, albino)	male	dermal	14 days	ALD	5	24 h of exposure	Waritz et al. (1977)
FireMaster® FF1	mink (*Mustela vison*)	male, female	in feed	313 days	LC_{50}	3.95		Ringer et al. (1981)
FireMaster®	Bobwhite quail (*Colinus virginianus*)		in feed	8 days	LC_{50}	428	5 days of treated diet	Cottrell et al. (1984)

Table 70 (contd).

FireMaster®	Japanese quail		oral	not specified	LD_{50}	> 1		Strik (1973a)
Octabromobiphenyl	rat	male	oral		LD_{50}	2	single dose	Aftosmis et al. (1972a)
Octabromobiphenyl (Dow Lot 102-7-72) (in acetone: corn oil = 15:85)	rat (Sprague-Dawley)	male	oral	7 days	ALD	> 17	single or repeated dose	Waritz et al. (1977)
Octabromobiphenyl	rabbit		dermal		LD_{50}	> 10		Aftosmis et al. (1972b)
Octabromobiphenyl (Dow Lot 102-7-72)	rabbit (New Zealand albino)	male	dermal	14 days	ALD	> 10	24 h of exposure	Waritz et al. (1977)
Octabromobiphenyl	Japanese quail		oral		LD_{50}	> 12.5	single dose	Aftosmis et al. (1972a)
Octabromobiphenyl (Dow Lot 102-7-72) (in corn oil)	Bobwhite quail	male, female	oral	14 days	ALD	> 12.5	single dose	Waritz et al. (1977)

Table 70 (contd).

PBB	Species	Sex	Route (Strain)	Observation period	Parameter[a]	Dose/ concentration[b]	Details	References
Nonabromobiphenyl (Bromkal 80-9D)	mouse ($B_6C_3F_1$)	male, female	oral	14 days	LD_{50}	> 15	single dose	Momma (1986)
Decabromobiphenyl	rat		oral		LD_{50}	> 20	single dose	[c]
Decabromobiphenyl (in corn oil)	rat (Sprague-Dawley CFY)	male, female	oral	14 days	LD_{50}	> 5	single dose	Millischer et al. (1979)
		dermal		14 days	LD_{50}	> 5	single dose	
Decabromobiphenyl	rat	oral			LD_{50}	> 20	single dose	[c]
Decabromobiphenyl	rabbit	dermal			LD_{50}	> 8		[c]

[a] ALD = Approximate lethal dose.
[b] LD_{50} or ALD in g/kg body weight; LC_{50} in mg/kg diet (ppm).
[c] Consumer Product Testing Co. (1977) quoted by Di Carlo et al. (1978).

Table 71. Mortality associated with PBB administration: Commercial mixtures (dosing studies)

PBB[a]	Species	Sex (No.)	Route	Dose[b]	Observation period	Details	Mortality (in percentage or No. dead/No. treated)	Time to death (days)	References
FM FF1 (No. 1312 FT) (in corn oil)	rat	male	oral	0.03-30	60 days	22 doses over 30	no mortality		Luster et al. (1978)
	rat (Fisher)	female	oral	0.1-10	6 months	122 doses over 6 months	no mortality		Luster et al. (1980)
	rat (Fisher 344/N)	female	oral	100	90 days	22 doses over 30 days	100%	41-53	Gupta & Moore (1979)
		male	oral	100	90 days over 30 days	22 doses	38%	50-73	Gupta & Moore (1979)
		female, male	oral	300	90 days	9-21 doses	100%	14-29	Gupta & Moore (1979)
		female, male	oral	1000	90 days	6-10 doses	100%	9-14	Gupta & Moore (1979)
FM BP-6	rat		inhalation	71 mg per litre	not specified	1 h of exposure	no mortality		Di Carlo et al. (1978)

Table 71 (contd).

PBB[a]	Species	Sex (No.)	Route	Dose[b]	Observation period	Details	Mortality (in percentage or No. dead/No. treated)	Time to death (days)	References
FM FF-1 (Lot No. 1312 FT in corn oil)	mouse	female	oral	0.03-30	60 days	22 doses over 30 days	no mortality		Luster et al. (1978)
	mouse	female	oral	0.1-10	6 months	122 doses over 6 months	no mortality		Luster et al. (1980)
FM	guinea-pig (Hartley), albino		oral	50	60 days	single dose	no mortality mentioned		Ecobichon et al. (1983)
FM BP-6 (finely ground)	cattle		oral	25 g/day[c]	60 days	daily doses	100% (animals became moribund and were necropsied)	33-60	Irving et al. (1976); Durst et al. (1977); Moorhead et al. (1977, 1978)
FM BP-6 (finely ground)	cattle	female	oral	250 mg/day	180 days	daily doses	no mortality		Durst et al. (1978b)
	cattle	female	oral	0.3[d]	340 days	daily doses over 158-228 days	no mortality		Robl et al. (1978)

Table 71 (contd).

FM BP-6 (in corn oil)	rainbow trout (*Oncorhynchus mykiss*)		intraperi-toneal	150	15 days	single dose mentioned	no mortality	Elcombe & Lech (1978)
FM BP-6 (in dogfish oil)	brook trout (*Salvelinus fontinalis*)		oral	66.3	18 days	3 doses over 5 days	no mortality mentioned	Law & Addison (1981)
FM FF-1	sheepshead (*Archosargus probato-cephalus*)		intraperi-toneal	15	56 days	single dose	no mortality	James & Little (1981)
				50	4-5 days	single dose	2/5 (remaining 3 moribund)	James & Little
OcBB (in corn oil)	rat Sprague-Dawley)	female	oral	126-2000	14 days	single dose	no mortality	Norris et al. (1973)
OcBB	rat Sprague-Dawley)	male	oral	1000	28 days	single dose	no mortality	Lee et al. (1975b)

Table 71 (contd).

PBB[a]	Species	Sex (No.)	Route	Dose[b]	Observation period	Details	Mortality (in percentage or No. dead/No. treated)	Time to death (days)	References
OcBB (Dow Lot 102-7-72)	rat (Sprague-Dawley)	male	inhalation	0.96 mg/litre air	7 days	4 h of exposure	no mortality		Waritz et al. (1977)
DeBB	rat		inhalation	200 mg/litre air	not specified	1 h of exposure	no mortality		Di Carlo et (1978)
DeBB	rat (Sprague-Dawley)	male,	inhalation	0.05-5 mg/litre air	4 weeks	6 h/day; 5 days/week	no mortality		Millischer et al. (1979)

[a] Commercial mixtures: FM = FireMaster®; OcBB = octabromobiphenyl; DeBB = decabromobiphenyl.
[b] In mg/kg body weight per day, unless otherwise specified.
[c] Initially equivalent to 67.2 mg/kg body weight per day.
[d] Equivalent to 10 mg/kg feed.

Table 72. Mortality associated with PBB administration: Commercial mixtures (feeding studies)

PBB[a]	Species	Sex	Dietary concentration (mg/kg feed)	Period of treatment observation	Mortality (in percentage or No. dead/No. treated)	Time to death	References
FM BP-6	rat (Sprague-Dawley)	female	4.7-300	2/2 weeks mentioned	no mortality		Dent et al. (1976a)
FM	rat (Sprague-Dawley)	male	1-500	30/30 days	no mortality		Sleight & Sanger (1976)
FM BP-6	mouse (BALB/c)	female	1000	9/9 days	70%		Fraker & Aust (1978); Fraker (1980)
FM BP-6 (Lot No. 182 RP)	guinea-pig		50	45/45	7/8		Vos & van Genderen (1974)
FM	guinea-pig		100	30/30 days	4/6		Sleight & Sanger (1976)
	guinea-pig		500	15/15 days	100%		
FM FF-1	mink (*Mustela vison*)	male, female	1	313/313 days	no mortality		Aulerich & Ringer (1979)
			2.5		10%	136 days	
			6.25		90%	63-294 days	Ringer et al. (1981)
			15.6		100%	25-93 days	

Table 72 (contd).

PBB*	Species	Sex	Dietary concentration (mg/kg feed)	Period of treatment observation	Mortality (in percentage or No. dead/No. treated)	Time to death	References
FM	pig		20, 200	16/16 weeks	no mortality mentioned		Ku et al. (1978)
FM FF-1	rhesus monkey (adult)	male	25 (total: 1 g)	25/25 weeks	1/1	25 weeks	Allen et al. (1978)
	(juvenile)	female	300 (total: 6.4 g)	137/137 days	1/1	137 days	Allen et al. (1978)
FM BP-6 (Lot No. 182 RP)	chicks (Hubbard Leghorn)	male	400	15/15 days	37%		Vos & van Genderen (1974)
FM BP-6	chicken (White Leghorn)		20-200	8/16 weeks	no mortality		Cecil & Bitman (1978)
			640	4/4 weeks	60% (control 10%)		Cecil & Bitman (1978)
FM FF-1	chicken (White Leghorn)		3125	4/4 weeks	100%		Polin & Ringer (1978a)

Table 72 (contd).

FM	Japanese quail		10-100		no mortality		Babish et al. (1975a)
			500-1000	"few" days	100%		Babish et al. (1975a)
FM	Bobwhite quail		100	5/8 days	no mortality		Cottrell et al. (1984)
			200	5/8 days	1/10	8 days	Cottrell et al. (1984)
			600	5/8 days	100% (10/10)	5.3 days (mean)	Cottrell et al. (1984)
FM BP-6	Atlantic salmon (*Salmo salar*)		100	42/70 days (in excess of that of control fish)	no mortality		Zitko (1977)
OcBB	rat (Sprague-Dawley)	male	100-10 000	30/30 days	no mortality mentioned		Norris et al. (1973)
OcBB	rat (Sprague-Dawley)	male	1-1000	4/22 weeks	no mortality		Lee et al. (1975a)
OcBB (Dow Chemical)	Atlantic salmon (*Salmo salar*)		100	74/96 days	no mortality (in excess of that of control fish)		Zitko (1977)
DeBB	rat (Sprague-Dawley)	female, male	1-2000	90/90 days	no mortality mentioned		Millischer et al. (1979)

[a] Commercial mixtures: FM = FireMaster®; OcBB = octabromobiphenyl; DeBB = decabromobiphenyl.

Generally, the susceptibility to the toxic effects of aryl hydrocarbons is dependent on the sex, age, species, and strain of the experimental animals (e.g., Safe, 1984; Hutzinger et al., 1985b). In the case of PBBs, female rats dosed with FireMaster® FF-1 showed a lower LD_{50} than male rats (Gupta & Moore, 1979; Table 70).

Although the studies, in most cases, are not directly comparable, species differences in the response to PBBs are reflected, in part, by the mortality data collated in Tables 71 and 72. For example, minks appear to be more sensitive to the FireMaster® mixture than the other species of animals tested. Compared to rats, guinea-pigs were far more susceptible to FireMaster® (Table 72).

The few studies performed with commercial octa- and decabromobiphenyl mixtures did not result in any mortality in rats and fish (Tables 71 and 72). Of individual PBB congeners, only three hexa isomers have been tested. Apparently, 3,3',4,4',5,5'-hexabromobiphenyl is more toxic for rats than 2,2',4,4',5,5'-hexabromobiphenyl (Table 73).

With few exceptions, the cause of death by halogenated aryl hydrocarbons cannot usually be ascribed to pathology in a given organ or system as with most toxicants (McConnell & Moore, 1979; McConnell, 1984). At lethal doses, the affected animals develop, as a first indication of toxicity, a "wasting syndrome", i.e., a progressive loss of body weight, which may not be related simply to decreased food consumption. It is followed by weakness, debilitation, and finally death (Hutzinger et al., 1985a; McConnell, 1985). Some authors (Allen et al., 1978) use the term "metabolic death".

The extended course of the disease can be complicated by other diseases, usually of an infectious etiology (McConnell, 1984). For instance, parasitism, diarrhoea, and pulmonary infections have been observed in PBB-contaminated cattle (Jackson & Halbert, 1974; Willett & Irving, 1976; Moorhead et al., 1978). Many of the pigs that died during lactation after perinatal exposure to PBB had acute suppurative pneumonia (Werner & Sleight, 1981). Severely intoxicated rhesus monkeys may have succumbed finally to gastrointestinal and respiratory infections (Allen et al., 1978). Male rats that were given 100 mg FireMaster® FF-1/kg body weight per day and died after 90 days had liver lesions (Gupta & Moore, 1979). Such overlying disease problems often result in

Table 73. Mortality associated with PBB administration: Individual PBB congeners

PBB	Species	Sex	Exposure	Dose concentration	Mortality (in percentage or No. dead/No. treated)	References
2,2',4,4',5,5'-hexabromobiphenyl	rat (Sprague-Dawley)	male	in diet for 30 days	100[a]	no mortality	Akoso et al. (1982a)
	mouse (B6C3F1) (pregnant)	female	in diet for 10 days	750[a]	2/8	Welsch & Morgan (1985)
	sheepshead (*Archosargus probatocephalus*		intraperitoneal; single or multiple doses; observation: 17-40 days	20[b]	no mortality	James & Little (1981)
3,3',4,4',5,5'-hexabromobiphenyl	rat (Sprague-Dawley)	male	in diet for 20 days	100[a]	1/2 (the remaining rat was moribund)	Render et al. (1982)
2,3',4,4',5,5' hexabromobiphenyl	rat (Sprague-Dawley)	male	in diet for 30 days	100[a]	no mortality	Akoso et al. (1982a)
Mixture of di-, tri-, and tetrabromobiphenyls	Atlantic salmon (Salmo salar)		in diet for 40 days plus additional stress at day 4; observation: 42 days	7.75[a]	(100% mortality)	Zitko & Hutzinger (1976)

[a] In mg/kg feed.
[b] In mg/kg body weight per day.

difficulties in establishing a definitive etiological diagnosis in environmental exposures (McConnell, 1984).

8.2 Single and short-term exposures: general signs of toxicity

8.2.1 PBB mixtures

8.2.1.1 Overt clinical signs, food intake, and body weight changes

In many acute and short-term studies, signs of PBB toxicity include reduction in feed consumption and weight loss or a decreased weight gain (see Tables 74 and 75). Most of the reports refer to the FireMaster® mixture, which was tested in rats, mice, guinea-pigs, pigs, cattle and avian species. From these studies with various protocols, the minimum effective doses of FireMaster® (FM) in the diet or by gavage ranged between 0.3 and 500 mg FM/kg feed or between 4 and 100 mg FM/kg body weight per day, respectively. Only a few studies have been performed with technical octabromobiphenyl and technical decabromobiphenyl; no effects were observed on feed consumption or body weight of rats (Tables 74 and 75).

Weight loss is not necessarily accompanied by decreased food intake (e.g., Allen et al., 1978; Lambrecht et al., 1978; Gupta & Moore, 1979) suggesting that PBBs may cause poor feed utilization. On the other hand, increased efficiency of feed utilization has been reported in growing pigs (Ku et al., 1978) and weight loss in hens was accounted for completely by reductions in feed consumption in paired feeding studies (Cecil & Bitman, 1978; Ringer, 1978). If the concentrations of PBBs are high enough, a total refusal of feed will occur (Babish et al., 1975a; Gutenmann & Lisk, 1975; Ringer & Polin, 1977; Cecil & Bitman, 1978; Polin & Ringer, 1978a; Aulerich & Ringer, 1979). At death, the loss in body weight can be as great as 30-40% (Allen et al., 1978; Aulerich & Ringer, 1979; Durst et al., 1978b).

At sublethal doses, decreased food intake and weight loss may be the only overt signs observed in many species. However, calves (fed 100 mg FireMaster® FF-1/kg body weight per day) also developed keratitis and lacrimation from day 35, and alopecia from day 50 (Robl et al; 1978). During a 16-week test period, some pigs receiving FireMaster® BP-6 at 200 mg/kg in the diet had dermatosis (Ku et al., 1978). Loss of hair (including eye lashes), dry scaly skin, and periorbital oedema were reported in a juvenile female rhesus monkey given 25 mg FireMaster® FF-1/kg

Table 74. Effects on feed consumption and changes in body and organ weights after single or short-term exposure to commercial PBB mixtures (dosing studies)

PBB[a] (carrier)	Species (strain)	Sex	Exposure[b]	Dose[c]	Feed intake[d]	Weight (gain) changes Body[d]	Organ[e]	References
FM FF-1 (in peanut oil)	rat (Sherman)	male, female	oral single dose t.p.: 2 months	1000	n.r.	no effect	liver: increase	Kimbrough et al. (1978)
M BP-6 (Lot No. 5143 in corn oil)	rat (Sherman)	male	oral single dose t.p.: 1-8 weeks	500	n.r.	--	liver: increase	Bernert Jr & Groce (1984)
FM BP-6 (in olive oil)	rat (Sprague-Dawley)	female	oral daily doses (9) during pregnancy t.p.: 13 days (after first dose)	1 (mg/day)	no effect	no effect	liver: increase; spleen kidney, adrenal, ovary gravid uterus, perirenal fat pads: no effect	Harris et al. (1978a)
FM FF-1 (Lot No. 1312 FT) (in corn oil)	rat (Fischer)	male	oral multiple doses (22) over 30 days t.p.: 60 days (after first dose)	3	n.r.	no effect	thymus spleen: decrease	Luster et al. (1978)
				30	n.r.	reduced	thymus, spleen: decrease	
FM FF-1 (Lot No. (1312 FT) (in corn oil)	rat (Fischer 344/N)	male, female	oral multiple doses (22) over 30 days t.p.: up to 90 days	100-1000	reduced (day 10)	reduced	liver, spleen: increase thymus: decrease	Gupta & Moore (1979)

Table 74 (contd).

PBB[a] (carrier)	Species (strain)	Sex	Exposure[b]	Dose[c]	Feed intake[d]	Weight (gain) changes Body[d]	Organ[e]	References
		male		30	no effect	reduced (day 15)	--	Gupta & Moore (1979)
		female		30	variable	reduced (day 10)	--	
		male, female		3 30	-- no effect	-- reduced (3 week)	liver: increase (day 15) thymus: decrease (day 15); lung, heart, spleen, kidney, adrenal, thyroid, testis, ovary, uterus, brain: no effect	Gupta et al. (1981)
FM FF-1 (Lot No. 1312 FT) (in lecithin liposomes)	rat (Sprague-Dawley)	male	oral multiple doses (20) t.p.: 4 weeks (after 1 dose)	1-6	n.r.	no effect	liver, thyroid: increase adrenal, testis: no effect	Allen-Rowlands et al. (1981); Castracane et al. (1982)
FM (in corn oil)	rat		intraperitoneal single dose t.p.: 7 days	1000	n.r.	n.r.	liver: increase	Aftosmis et al. (1972b)

Table 74 (contd).

FM BP-6 (in peanut oil)	rat (Sprague-Dawley)	female	intraperitoneal single dose t.p.: 2 weeks	25, 150	n.r.	no effect	liver: increase	Dent et al. (1976b)
FM FF-1 (in corn oil)	rat (Fischer)	female	intraperitoneal single dose t.p.: 4 days	200-1000 (μmol/kg body weight)	n.r.	no effect	liver: increase	Goldstein et al. (1979)
FM FF-1 (in polyethylene glycol)	rat (Sprague-Dawley)	male	intraperitoneal single dose	90				
			t.p.: 1 week		n.r.	n.r.	liver: increase	Dannan et al. (1978a)
			t.p.: 2 weeks		n.r.	no effect no effect	liver: increase; spleen, thymus:	Dannan et al. (1982c); Millis et al. (1985a)
FM BP-6 (Lot 7062) (in corn oil)	rat (Wistar)	male	intraperitoneal (days 1 and 3) two doses t.p.: 6 days (after 1 dose)	30 75	n.r. n.r.	n.r. n.r.	liver, spleen: increase liver: increase; spleen, thymus: decrease	Robertson et al. (1981b)

Table 74 (contd).

PBB[a] (carrier)	Species (strain)	Sex	Exposure[b]	Dose[c]	Feed intake[d]	Weight (gain) changes Body[d]	Organ[e]	References
FM BP-6 (in peanut oil)	rat (Wistar)	male	intraperitoneal three doses (days 1, 2, 3) t.p.: 7 days (after 1 dose)	0.2 mmol/kg body weight	n.r.	n.r.	liver: increase	Ecobichon et al. (1979)
FM BP-6 (in corn oil)	rat (Wistar)	male	intraperitoneal single or multiple doses (4) t.p.: 15 days	500	n.r.	reduced	liver: increase; thymus, spleen: decrease	Andres et al. (1983)
FM FF-1 (Lot No. 1312 FT) (in corn oil)	mouse ($B_5C_3F_1$)	female	oral multiple doses (22) over 30 days t.p.: 60 days (after 1 dose)	30	n.r.	no effect	spleen: decrease thymus: no effect	Luster et al. (1978)
	mouse ($B_6C_3F_1$) (pregnant)	female	oral multiple doses (22) from gestational day 0 until litters were weaned	30	n.r.	no effect	spleen: increase; thymus: decrease	Luster et al. (1980)

Table 74 (contd).

FM FF-1 (Lot No. FT 1312) (in corn oil)	mouse ($B_6C_3F_1$/N)	male, female	oral multiple doses (22) over 30 days t.p.: up to 90 days	3-30	no effect	variable	liver: increase (day 15) lung, heart, spleen, kidney, adrenal thyroid testis, ovary, uterus, brain: no effect	Gupta et al. (1981)
		male		30	no effect	reduced (only day 30)	thymus: decrease (only day 30)	
		female		0.3, 3, 30	no effect	increased (only day 45)	thymus: no effect	
FM BP-6 (in peanut oil)	mouse (NMRI)	female	intraperitoneal single dose t.p.: up to 192 h	150	n.r.	n.r.	liver: increase (48, 96 h), no effect (24, 192 h)	Dent et al. (1977a)
FM BP-6 (in corn oil)	mouse (C57BL/6J)	male	intraperitoneal single dose t.p.: 5 days	1.50 (mmol/kg body weight)	n.r.	no effect	liver: increase; thymus: decrease; spleen: no effect	Robertson et al. (1984c)
	mouse (DBA/2J)	male	intraperitoneal single dose t.p.: 5 days	1.50 (mmol/kg body weight)	n.r.	no effect	liver: increase; thymus, spleen: no effect	

Table 74 (contd).

PBB[a] (carrier)	Species (strain)	Sex	Exposure[b]	Dose[c]	Feed intake[d]	Weight (gain) changes Body[d]	Organ[e]	References
FM FF-1 (Lot FA 7042) (in peanut oil)	guinea-pig (Hartley, albino) (pregnant)	female	oral single dose t.p.: 2-60 days	50	n.r.	no effect	"tissues": no effect (liver, kidney, lung, perirenal fat)	Ecobichon et al. (1983)
FM BP-6 (in peanut oil)	guinea-pig Hartley	male	intraperitoneal single dose t.p.: 120 h	50	n.r.	--	liver, kidney: no effect	Smith et al. (1986)
	hamster (golden Syrian)	male	intraperitoneal single dose t.p.: 120 h	50	n.r.	--	liver, kidney: no effect	
FM (Lot 635-71)	rabbit (New Zealand, albino)	male	dermal 24 h of exposure t.p.: 14 days	100-10 000	n.r.	reduced (not significant)	liver: increase	Waritz et al. (1977)
FM BP-6 (Lot BP-158) (in milk)	calf	male	oral daily doses for 44 days	0.54 mg/day	no effect	reduced	--	Willett & Irving (1976)

Table 74 (contd).

FM BP-6 (Lot 6244 A)	cattle (pregnant)	female	oral daily doses	25 g per day	reduced (day 4)	reduced (day 20)	liver, kidney, perirenal lymph nodes: increase thymus: decrease (days 33-66)	Irving et al. (1976); Willett & Irving (1976); Durst et al. (1977); Moorhead et al. (1977)
				250 mg per day	no effect	no effect	no effect	
FM FF-1	calf	male, female	oral daily doses	100	reduced (day 36)	reduced (day 35)	--	Robl et al. (1978)
	cattle	female	oral daily doses for 158 days t.p.: 340 days (after 1 dose)	0.3	no effect	no effect	--	
FM FF-1	dog (Beagle)	male, female	oral daily doses for 7 weeks	1	n.r.	--	liver: increase	Farber et al. (1976)
	dog (Beagle)	male	oral daily doses	4	n.r.	reduced (day 30)	--	Farber et al. (1978)

Table 74 (contd).

PBB[a] (carrier)	Species (strain)	Sex	Exposure[b]	Dose[c]	Feed intake[d]	Weight (gain) changes Body[d]	Organ[e]	References
FM	Japanese quail		oral daily doses for 7 days	25-1000	n.r.	reduced	liver: increase	Strik (1973b)
FM BP-6 (in corn oil)	rainbow trout (*Oncorhynchus mykiss*)		intraperitoneal single dose t.p.: up to 15 days	150	n.r.	n.r.	liver: no effect	Elcombe & Lech (1978)
FM BP-6 (in dogfish oil)	brook trout (*Salvelinus fontinalis*)		oral multiple doses t.p.: 18 days (after 1 dose)	(200 mg/kg body weight total dose)	n.r.	reduced (not significant)	liver: no effect	Law & Addison (1981)
OcBB (in corn oil)	rat (Sprague-Dawley)	female	oral single dose t.p.: 14 days	126-2000	n.r.	no effect	n.r.	Norris et al. (1973, 1975)
OcBB (in corn oil)	rat (Sprague-Dawley)	male	oral single dose t.p.: 21 days	1000	no effect	no effect	liver: increase (days 2-11), no effect (day 21)	Lee et al. (1975b)

Table 74 (contd).

			oral daily doses (2) t.p.: 28 days (after lase dose)	3000	no effect	no effect	liver: increase (up to day 21), no effect (day 28)	Lee et al. (1975b)
OcBB (Dow Lot 102-7-72) (in 40-50% acetone: corn oil = 15:85)	rat (Sprague-Dawley)	male	oral single dose t.p.: 7 days	3400-17 000	n.r.	–	liver: increase	Waritz et al. (1977)
OcBB (in corn oil)	rat		intraperitoneal single dose t.p.: 7 days	1000	n.r.	n.r.	liver: increase	Aftosmis et al. (1972b)
	rat		inhalation 4 h exposure for 10 days	3.1 µg/litre air	n.r.	n.r.	liver: no effect	
OcBB (Dow Lot 102-7-72)	rat Sprague-Dawley)	male	inhalation 4 h exposure t.p.: 7 days	0.96 mg/litre air	n.r.	n.r.	liver: increase (not significant)	Waritz et al. (1977)
	rat (Sprague-Dawley)	not specified	inhalation 23 h/day; 7 days/week for 2-15 weeks	(25 g)	n.r.	n.r.	liver: no effect (2-15 weeks) kidney, thyroid: no effect (15 weeks)	

Table 74 (contd).

PBB[a] (carrier)	Species (strain)	Sex	Exposure[b]	Dose[c]	Feed intake[d]	Weight (gain) changes Body[d]	Organ[e]	References
OcBB (Dow Lot 102-7-72) (in corn oil)	rabbit (New Zealand; albino)	male	dermal 24 h exposure t.p.: 14 days	100-10 000	n.r.	n.r.	liver: increase (not significant)	Waritz et al. (1977)
		male	dermal 6 h/day; 5 days/week, for 2 weeks t.p.: 18 days (after last dose)	1	n.r.	no effect	liver: increase	
OcBB (Dow Lot 102-7-72) (in corn oil)	bobwhite quail	male, female	oral single dose t.p.: 14 days	12 500	n.r.	n.r.	any internal organs: no effect	
NoBB	mouse ($B_6C_3F_1$)	male, female	oral single dose t.p.: 14 days	up to 15 000	n.r.	n.r.	liver: increase	Momma (1986)
DeBB (in corn oil)	rat (Sprague-Dawley)	male, female	oral single dose t.p.: 14 days	5000	n.r.	no effect	liver: no effect	Millischer et al. (1979)

Table 74 (contd).

rat		intraperitoneal single dose t.p.: 7 days	1000	n.r.	n.r.	liver: no effect	Aftosmis et al. (1972b)
rat (Sprague-Dawley)	male, female	dermal 24 h exposure t.p.: 14 days	5000	n.r.	no effect	liver: no effect	Millischer et al. (1979)
rat (Sprague-Dawley)	male, female	inhalation 6 h/day, 5 days/week for 4 weeks	0.05-5 mg/litre air	no effect	no effect	liver: increase	

[a] Commercial PBB mixtures: FM = FireMaster®; OcBB = octabromobiphenyl; NoBB = nonabromobiphenyl; DeBB = decabromobiphenyl.
[b] t.p. = time post-exposure.
[c] In mg/kg body weight per day, unless otherwise specified.
[d] n.r. = not recorded.
[e] Absolute or relative to body weight, respectively.

Table 75. Effects on feed consumption and changes in body and organ weights caused by short-term feeding of commercial PBB mixtures

PBB[a]	Species (strain)	Sex	Dietary concentration (mg/kg feed)	Period of treatment/ observation	Feed intake[b]	Weight (gain) changes Body[b]	Organs[c]	References
FM BP-6	rat (Sprague-Dawley)	female	75, 300	2/2 weeks	no effect	no effect	liver: increase	Dent et al. (1976a)
FM	rat (Sprague-Dawley)	male	100	30/30 days	no effect	no effect	liver: increase	Sleight & Sanger (1976)
			500	30/30 days	reduced	reduced	liver: increase; kidney: no effect	
FM BP-6	rat (Sprague-Dawley)	male	50	3/3 weeks	no effect	no effect	liver: increase	Babish & Stoeswand (1977)
FM BP-6	rat (Sprague-Dawley)	female	50	day 8 of gestation through day 14 postpartum	n.r.	no effect	liver: increase	Dent et al. (1977b)
FM BP-6	rat (Holtzman)	male	5	variable	no effect	no effect (day 20)	liver: increase (weeks 2-5); kidney: decrease (week 3)	Garthoff et al. (1977)

Table 75 (contd).

	rat (Holtzman)	male	500	variable	no effect	reduced (day 20)	liver: increase (weeks 2-5); testis: no effect (week 3)	Garthoff et al. (1977)
FM BP-6	rat (Sprague-Dawley) pups	not specified	50 (in mother's or weanling's diet)	pre-, post- and perinatal exposure/age of 15-49 days	n.r.	n.r.	liver: increase	Cagen & Gibson (1978)
FM BP-6	rat (Sprague-Dawley)			day 8 of gestation to day 15 postpartum				
	mothers	female	50		n.r.	no effect	liver: increase; kidney, mammary: no effect	Dent et al. (1978b)
	pups	male, female	(50) (in mother's diet)	pre- post-, and perinatal exposure	n.r.	no effect	liver: increase	
FM BP-6	rat (Sprague-Dawley) pups	male, female	(mothers dose: 10 mg/day on gestation days 7-15)	perinatal exposure	n.r.	reduced (day 3 of age)	liver, spleen: increase (day 60 of age) (males more affected than females	Harris et al. (1978a)

Table 75 (contd).

PBB[a]	Species (strain)	Sex	Dietary concentration (mg/kg feed)	Period of treatment/ observation	Feed intake[b]	Weight (gain) changes Body[b]	Organs[c]	References
	adults	males	50-100	10/10 weeks	no effect	no effect	liver: increase	Harris et al. (1978b)
			150, 200	10/10 weeks	no effect	reduced	liver: increase; adrenal, spleen, kidney, testes, seminal vesicles: no effect	
		female	600	10/10 weeks	reduced	reduced	n.r.	
FM BP-6	rat (Holtzman)	male	50-500	5/5 weeks	n.r.	no effect	liver: increase	Kasza et al. (1978a)
FM BP-6	rat (Sprague-Dawley)	male	20	28/28 days	no effect	no effect	liver: increase	Chu et al. (1980)
FM BP-6	rat (Sprague-Dawley) pups	male,	100 (in mothers or weanlings diet)	perinatal exposure until 9 weeks of age	n.r.	reduced (more pronounced in males)	M: ventral prostate: decrease	Johnston et al. (1980)

Table 75 (contd).

FM BP-6	rat (Sprague-Dawley)	male	1-100	30/30 days	no effect	no effect	liver: increase; thymus, spleen: no effect	Akoso et al. (1982a)
		male	100	30/30 days	no effect	no effect	thyroid: increase	Akoso et al. (1982b)
FM BP-6	rat (Sprague-Dawley)	male	100	9/9 days	no effect	no effect	liver, thyroid: increase kidney: no effect	Render et al. (1982)
FM BP-6	rat (Fisher)	male	100	10/10 days	no effect	no effect	liver: increase	Raber & Carter (1986)
FM BP-6	mouse (Swiss, ICR)	female	1000	11/11 days	n.r.	--	liver: increase	Corbett et al. (1975)
		male	1000	up to 14/14 days	n.r.	reduced (day 4)	liver: increase (day 4), testis: no effect	Corbett et al. (1978a)
FM BP-6	mouse (Swiss, Webster)	female	50-200	2/2 weeks	no effect	no effect	liver: increase	Cagen et al. (1977); Cagen & Gibson (1978)
	adult pups	not specified	50 (in mothers diet)	postnatal exposure until 15 days of age	--	--	liver: increase	Cagen & Gibson (1978)

Table 75 (contd).

PBB[a]	Species (strain)	Sex	Dietary concentration (mg/kg feed)	Period of treatment/ observation	Feed intake[b]	Weight (gain) changes Body[b]	Organs[c]	References
FM	mouse (BALB/c)	not specified	100	30/30 days	n.r.	no effect	liver: increase; thymus, spleen: decrease	Fraker & Aust (1978)
		not specified	1000	14/14 days	n.r.	reduced	liver: increase; thymus: decrease (nearly athymic)	
FM BP-6	mouse (BALB/c)	female	1, 10	30/30 days	n.r.	no effect	liver, spleen: no effect; thymus: decrease	Fraker (1980)
		female	100	30/30 days	n.r.	no effect	liver: increase; thymus, spleen: decrease	
FM FF-1 (Lot No. 7042)	mouse (BALB/c ByJ)	male	5	8/8 weeks	n.r.	no effect	liver: increase	Loose et al. (1981)
			167	6/6 weeks	n.r.	no effect	liver: increase	
			167	8/8 weeks	n.r.	reduced	liver: increase	
			5	3/3 weeks	n.r.	--	thymus: no effect	
			5	6-8/6-8 weeks	n.r.	--	thymus: decrease	
			167	3-8/3-8 weeks	n.r.	--	thymus, spleen: decrease	
			5, 167	3-8/3-8 weeks	n.r.	--	lung: no effect	

Table 75 (contd).

FM FF-1 (Lot No. 1312 FT)	mouse ($B_6C_3F_1$) pups	male	mothers dose: 10 mg/kg body weight per day (22 doses)	perinatal exposure	n.r.	no effect	spleen: increase; thymus: no effect	Luster et al. (1980)
FM BP-6	guinea-pig	not specified	10	45/45 days	n.r.	no effect	liver: increase	Vos & van Genderen (1974)
FM	guinea-pig	not specified	1, 10	30/30 days	no effect	no effect	liver: no consistent effect	Sleight & Sanger (1976)
			100	up to 30 days	n.r.	reduced (week 3)	liver: increase	
			500	15/15 days	n.r.	reduced (week 1)	liver: increase	
FM BP-6	pig (growing)	not specified	20, 200	16/16 weeks	reduced	reduced	liver, kidney: increase	Ku et al. (1978)
	pig (4-week-old) (lactating)	not specified	100 (in mothers diet)	perinatal exposure	n.r.	reduced (not significant)	liver: increase (but no effect in sows)	Werner & Sleight (1981)
	pig (newborn)	not specified	100 (in mothers diet)	prenatal exposure	--	--	thyroid: increase; liver: no effect	

Table 75 (contd).

PBB[a]	Species (strain)	Sex	Dietary concentration (mg/kg feed)	Period of treatment/ observation	Feed intake[b]	Weight (gain) changes Body[b]	Organs[c]	References
FM FF-1	mink	female	1-1.54	several months	--	no effect	liver, kidney: increase (in animals that died during treatment)	Aulerich & Ringer (1979); Ringer et al. (1981)
			2.5	several months	--	no effect (within first 3 months, later reduced)		
			6-16	several months	(refused)	reduced		
FM FF-1	Rhesus monkey (adult)	female	0.3	several months	no effect	reduced	--	Allen et al. (1978)
	(infants)	not specified	0.3 (in mothers diet)	perinatal exposure; up to 12 weeks of age	--	reduced	--	
	(juvenile)	female	300	up to 137 days	no effect (until a few days prior to death)	reduced	--	

Table 75 (contd).

FM	Japanese quail	male, female	500, 1000	a few days	(refused)			Babish et al. (1975a)
			10-100	9/9 weeks	no effect	no effect	liver: increase	
FM	Bobwhite quail (*Colinus virginianus*)		100-700	5/8 days	reduced	n.r.	n.r.	Cottrell et al. (1984)
FM BP-6 (Lot No. 182 RP)	chicks (Hubbard Leghorn)	male	400	15/15 days	n.r.	reduced	bursa of Fabricius: decrease	Vos & van Genderen (1974)
			15, 30	63/63 days	n.r.	reduced	bursa of Fabricius, spleen decrease	
"PBB" (FM)	pullet		50, 200	4/4 weeks	n.r.	reduced	--	Chang & Zindel (1975)
FM	chicken (White Leghorn)	male	variable, up to 200	several weeks	--	--	liver, thyroid: increase; comb: decrease; testis: increase (low dose) decrease (higher dose)	Ringer & Polin (1977)
		female	125	several weeks	reduced	--	--	
	chicks (White Leghorn)		75	several weeks	--	reduced	--	

Table 75 (contd).

PBB[a]	Species (strain)	Sex	Dietary concentration (mg/kg feed)	Period of treatment/ observation	Feed intake[b]	Weight (gain) changes Body[b]	Organs[c]	References
FM BP-6	chicken (White Leghorn)	female	20, 64, 200 640, 2000	8/16 weeks 2/2 weeks 2/2 weeks	no effect reduced (refused)	no effect reduced reduced	-- -- --	Cecil & Bitman (1978)
FM FF-1	chicken (White Leghorn)	female	0-25 125 3125	5/5 weeks 5/5 weeks 5/5 weeks	no effect reduced refused	-- -- --	-- -- --	Polin & Ringer (1978a)
FM	chicks (White Leghorn)	male	75-250	up to 42 days	reduced	reduced	liver, thyroid: increase; comb, testes, spleen, bursa, thymus: decrease	Ringer (1978)
FM FF-1	cockerels (White Leghorn)	male	10, 100	28/28 days	no effect	no effect	liver: increase; bursa: decrease; thyroid, spleen, testicles, comb: no effect	Dharma et al. (1982)
OcBB	rat		100	28/28 days	--	--	liver: increase	Aftosmis et al. (1972a)

Table 75 (contd).

OcBB	rat (Sprague-Dawley)	male	100-1000	30/30 days	no effect	no effect	liver: increase; heart, testes, brain: no effect; kidney: increase	Norris et al. (1973, 1975)
			1000, 10 000	30/30 days				
OcBB	rat (Sprague-Dawley)	male	100, 1000	2-4/2-4 weeks	no effect	no effect	liver: increase	Lee et al. (1975a)
			1000	4/22 weeks	no effect	no effect	liver: increase	
OcBB (Dow Lot 102-7-72)	rat (Sprague-Dawley)	male	100, 1000	2-4/2-22 weeks	no effect	no effect	liver: increase	Waritz et al. (1977)
DeBB	rat (Sprague-Dawley)	male, female	2000	13/13 weeks	no effect	no effect	liver: increase	Millischer et al. (1979)

[a] Commercial PBB mixtures: FM = FireMaster®; OcBB = octabromobiphenyl; DeBB = decabromobiphenyl.
[b] n.r. = Not recorded.
[c] Absolute or relative to body weight, resp.

feed for 50 weeks (total dose: approximately 1.5 g), however, the time of onset of these symptoms was not specified (Allen et al., 1978). A decreased heart rate (bradycardia) was measured in White Leghorn cockerels fed 150 mg FireMaster® FF-1/kg feed for approximately 9 weeks (Heinemann & Ringer, 1976; Ringer, 1978). Another characteristic sign in chickens was general oedema (Ringer & Polin, 1977; see also section 8.2.1.3).

At lethal doses, the "wasting syndrome" (see section 8.1) can also be accompanied by other symptoms. Rats, which became moribund, had hunchback posture, sunken eyes, appeared dehydrated, and were lethargic (Gupta & Moore, 1979). Minks have been reported to show an unthrifty appearance (Aulerich & Ringer, 1979; Ringer et al., 1981). Cattle that died later showed many similar clinical signs, but they also had excessive lacrimation and salivation, diarrhoea and depressed heart and respiratory rates (Irving et al., 1976; Durst et al; 1977, 1978b; Moorhead et al., 1977). In two rhesus monkeys, the time to death was as long as 3-5 months. In addition to body weight loss, the dead animals exhibited alopecia and oedema, particularly on the face and eyelids (including loss of eyelashes), and dry scaly skin (Allen et al., 1978). Observations of intoxicated Bobwhite quails, prior to death, included asthenia, low carriage, an unkempt appearance, wing droop, diarrhoea, limited ataxia, and general lethargy (Cottrell et al., 1984).

8.2.1.2 Haematology and clinical chemistry

a) Haematology

At lethal doses, leukopenia and erythropenia were observed in a rhesus monkey (Allen et al., 1978), but not in cattle (Moorhead et al., 1977). Packed cell volume, white blood cell count, and red blood cell count fell gradually in the monkey (dietary concentration: 300 mg/kg of feed; total dose: 6.4 g of FireMaster® FF-1), while changes in packed cell volume, haemoglobin content, total erythrocyte and leukocyte counts, and differential leukocyte counts were minimal in the cows (dose: 25 g FireMaster® BP-6 per day).

At sublethal doses, haematological parameters of rhesus monkeys remained within normal limits (Allen et al., 1978). The same was true for cattle (Moorhead et al., 1977; Robl et al., 1978), with the exception of a calf dosed with 100 mg FireMaster®

FF-1/kg body weight per day, the total leukocyte count of which was elevated (Robl et al., 1978). Rats given 30 mg FireMaster® FF-1/kg body weight per day for 30 days (22 total doses) showed a significant decrease in the packed cell volume, haemoglobin concentrations, and platelet counts at 30 days of exposure (Gupta et al., 1981) and at 6 months after the start of dosing (Gupta & Moore, 1979), but were normal at 45, 60, or 90 days after the start of dosing (Gupta et al., 1981). White and red blood cell values were only occasionally reduced; for example, there was moderate lymphopenia in female animals at 30 days of exposure (Gupta & Moore, 1979; Gupta et al., 1981). No significant differences in values for the erythrocyte count, packed cell volume, haemoglobin, and total and differential leukocyte counts were found in male rats fed various levels of FireMaster® BP-6 (1-500 mg/kg diet) for 30-60 days (Sleight & Sanger, 1976; Garthoff et al., 1977; Sleight et al., 1978); only a possible increase in total white blood cell count was noted at the 500 mg/kg feed level (Garthoff et al., 1977). A mild but significant decrease in the packed cell volume and the number of platelets was observed in mice exposed to 30 mg FireMaster® FF-1/kg body weight per day for 30 days (22 total doses). The leukocyte values were within normal limits (Gupta et al., 1981). Growing pigs in a 16-week trial showed significant reductions in haemoglobin and haematocrit only after 6 weeks of feeding 200 mg FireMaster® BP-6/kg diet (Ku et al., 1978). There was no appreciable effect on standard haematological values of nursing pigs and their sows fed FireMaster® BP-6 (10-200 mg/kg feed) during pregnancy and lactation (Werner & Sleight, 1981). White Leghorn cockerels fed PBB (FireMaster® FF-1) at dietary concentrations of 75 and 150 mg/kg from 3 to 4 days of age until 5-9 weeks showed a significant decrease in packed cell volume and haemoglobin values (Heinemann & Ringer, 1976; Ringer, 1978).

Technical octabromobiphenyl caused a significant decrease in packed cell volume and total red blood cell count in male rats fed dietary concentrations of 10 000 mg/kg for 30 days, but had no effect at dietary concentrations of 100 and 1000 mg/kg (Norris et al., 1973, 1975).

Standard haematological determinations revealed no treatment-related changes in blood from rats exposed to technical decabromobiphenyl via diet (1-2000 mg/kg) for 4-12 weeks and via inhalation (0.005-5 mg/litre, 6 h/day, 5 days/week) for 4 weeks (Millischer et al., 1979).

b) Clinical chemistry

Clinical chemistry values examined in many studies refer to serum protein (total protein, specific fractions), serum enzymes, serum glucose, blood urea nitrogen, serum lipids, serum cholesterol, and urine.

(i) Serum protein

Decreases in total serum protein, due primarily to a reduction in the albumin fraction, occurred in severely intoxicated cattle (Durst et al., 1978a; Schanbacher et al., 1978) and monkeys (Allen et al., 1978). No consistent effect of dietary PBBs on total serum protein concentrations or electrophoretic profiles was observed in pigs fed FireMaster® BP-6 at levels of 20 or 200 mg/kg for 16 weeks (Ku et al, 1978). In rats fed 5, 50, or 500 mg FireMaster® BP-6/kg for 3 weeks, total plasma protein was slightly increased by the highest concentration (Garthoff et al., 1977). A marked increase (50%) in serum protein was found in rats given 22 oral doses of FireMaster® FF-1 (30 mg/kg body weight per day) over a 30-day period and observed for some additional weeks. These changes were primarily associated with increased β-globulin fractions (Gupta et al., 1981). Reductions in serum immunoglobulin levels (γ-globulin fractions) have been reported in mice given oral doses (30 mg/kg body weight per day) of FireMaster® FF-1 (Luster et al., 1978) or diets containing 167 mg FireMaster® FF-1/kg (Loose et al., 1981).

No treatment-related changes in total serum protein were found in rats exposed to technical decabromobiphenyl (1-2000 mg/kg feed for 4-12 weeks; inhalation: 0.005-5 mg/litre; 6 h/day; 5 days/week for 4 weeks) (Millischer et al., 1979).

(ii) Serum enzymes

Alterations in serum enzymes, most of which are indicative of liver lesions, have been found in some instances.

γ-Glutamyl transpeptidase (γ-GTP) was elevated by oral doses of FireMaster® FF-1 (30 mg/kg body weight per day) in female rats and mice of both sexes (Gupta et al., 1981).

No consistent increase in serum glutamic pyruvic transaminase (SGPT) occurred in rats after dietary (Garthoff et al, 1977; Matthews et al., 1978) or oral (Gupta et al., 1981) exposure to

FireMaster®. No changes were found in cows on diets containing up to 10 mg FireMaster® FF-1/kg (Robl et al, 1978). However, a gradual increase in SGPT activity was observed in lethally intoxicated rhesus monkeys (Allen et al., 1978). Technical decabromobiphenyl did not influence SGPT in rats (Millischer et al., 1979).

Serum glutamic-oxaloacetic transaminase (SGOT) was significantly increased in cattle at high doses of PBBs (25 g FM BP-6 per day) (Moorhead et al., 1977; Durst et al., 1978b). It was unaffected in cattle given lower doses (250 mg FM BP-6/day: Moorhead et al., 1977; 0.01-10 mg FM FF-1/kg feed: Robl et al., 1978), as well as in pigs (Ku et al., 1978) or in rats (Sleight & Sanger, 1976; Garthoff et al., 1977; Sleight et al., 1978) fed FireMaster® BP-6 (20 and 200 mg/kg diet or 1-500 mg/kg diet, respectively). A possible decrease in serum GOT has been reported in rats exposed to technical decabromobiphenyl via inhalation (Millischer et al., 1979).

Lactic dehydrogenase (LDH) was within normal ranges in PBB-contaminated cows without clinical signs of toxicosis (Moorhead et al., 1977), but it was increased in a group of apparently intoxicated animals (dose: 25 g FM BP-6/day) (Moorhead et al., 1977; Durst et al., 1978b). A significant decrease was found in growing pigs (Ku et al., 1978), but not in nursing pigs and their sows (Werner & Sleight, 1981), fed FireMaster® BP-6. Electropherograms of LDH isozymes at 60 days, from rats given FireMaster® BP-6 (100 mg/kg feed), showed appreciable changes (Sleight et al., 1978).

With the exception of calves (Robl et al., 1978) and newborn pigs (Werner & Sleight, 1981), alkaline phosphatase levels in animals were unaffected by FireMaster®, e.g., rats (Sleight et al., 1978; Gupta et al, 1981), dogs (Farber et al, 1976), and growing pigs (Ku et al., 1978). Technical decabromobiphenyl also did not have any effect on alkaline phosphatase levels in rats (Millischer et al., 1979).

Serum isocitrate dehydrogenase (sICDH) did not show any discernible rise in dairy cattle dosed with FireMaster® BP-6, until doses were sufficient to cause toxicosis (25 g/day). These cows showed moderate increases in sICDH (approximately a two-fold increase). Elevation of sICDH was coincident with fetal trauma. Non-pregnant cows, equally intoxicated, showed minimal sICDH elevation (Schanbacher et al., 1987).

Serum creatine phosphokinase levels in growing pigs were unaffected by 20 or 200 mg FireMaster® BP-6/kg feed (Ku et al. 1978).

In male Japanese quails, serum glutamate dehydrogenase levels were increased by "hexabromobiphenyl" (STRIK, 1973b).

(iii) Serum glucose

A slight decrease in serum glucose was observed in rats and mice administered 22 total doses of 30 mg FireMaster® FF-1/kg body weight (Gupta et al., 1981) and in rats fed 50 mg FireMaster® BP-6/kg diet for 3 weeks (Garthoff et al., 1977), but not in rats fed 500 mg/kg diet for the same period (Garthoff et al., 1977). FireMaster® did not produce any effects on glucose concentrations in either sublethally or lethally intoxicated cattle (Durst et al., 1978a; Robl et al., 1978), and decabromobiphenyl did not affect glucose levels in rats (Millischer et al., 1979).

(iv) Blood urea nitrogen

Values for blood urea nitrogen (BUN) remained in the normal range in mice (Gupta et al., 1981) and rats (Sleight & Sanger, 1976; Garthoff et al., 1977; Sleight et al., 1978; Gupta et al., 1981) or were elevated in rats at some concentrations (Sleight & Sanger, 1976; Garthoff et al., 1977). A significant increase in BUN occurred in cows (Moorhead et al., 1977; Durst et al., 1978a) and a calf (Robl et al., 1978) that had received doses of FireMaster® high enough to produce overt signs of toxicosis (25 g FM BP-6 per day (equivalent to 50 mg/kg body weight per day, and 100 mg FM FF-1/kg body weight per day, respectively).

(v) Serum lipids

Characteristic alterations in serum phospholipid HPLC profiles, which were maintained for at least two months after dosing, were found in rats given a single oral dose of FireMaster® BP-6 (500 mg/kg body weight) (Bernert et al., 1985).

(vi) Serum cholesterol

In rats, cholesterol levels appear to be the blood parameter most sensitive to PBBs. There were dose-related increases in cholesterol concentrations in short-term (Garthoff et al., 1977; Spear et al., 1990) and long-term (see 8.4: Bernert et al., 1983; Gupta et al., 1983a,b) studies, and these increases were significant at dietary

concentrations of FireMaster® as low as 5 mg/kg (Garthoff et al., 1977). No noticeable effects of FireMaster® on cholesterol levels have been reported in cattle (Durst et al., 1978a) and pigs (Werner & Sleight, 1981). Rhesus monkeys showed a gradual decrease in serum cholesterol when they were lethally intoxicated (Allen et al., 1978).

(vii) Urinalysis

Tests of urine for pH, protein, glucose, ketones, bilirubin, occult blood, and specific gravity showed no significant changes due to FireMaster® in mice (Gupta et al., 1981) and rats (Sleight et al., 1978; Gupta et al., 1981) or due to technical decabromobiphenyl in rats (Millischer et al., 1979). Only Sleight & Sanger (1976) reported higher readings for protein in rats fed FireMaster®. Differences in urinary protein patterns between control rats and rats given FireMaster were detected by means of two-dimensional electrophoresis (Myrick et al., 1987). The principal urine changes in cattle lethally intoxicated were decreased specific gravity and moderate proteinuria (Moorhead et al., 1977; Durst et al., 1978a).

8.2.1.3 Morphological and histopathological changes

a) Liver

The liver is the site of the most prominent gross morphological and histopathological changes due to PBBs in many species.

Enlargement of the liver was a characteristic response to exposure to FireMaster®, technical octabromobiphenyl, and technical decabromobiphenyl, and it frequently occurred at concentrations lower than required to produce body weight changes (see Tables 74 and 75). Generally, increases in absolute or relative liver weights were dose and time dependent (e.g., Garthoff et al., 1977). A notable exception was in cows, which showed decreases in body weight as well as an increase in liver weights only at lethal doses (Table 74).

Grossly, the livers of rats were often friable and had a mottled surface (Sleight & Sanger, 1976; Waritz et al., 1977; Akoso et al., 1982a; Render et al., 1982; Raber & Carter, 1986). Red fluorescence of liver (and other tissues) under UVR (366 nm) indicated excess porphyrin accumulation. In contrast to rats, which developed porphyria after long-term exposure, the liver of

female mice given 30 mg FM FF-1/kg body weight per day (22 total doses) became porphyric after 45 days (Gupta et al., 1981). FireMaster® FF-1 given orally at a dose rate of 22.5 mg/kg body weight per day for 4 days caused centrolobular accumulation of Oil-red O-staining lipids in the liver of rats (Kohli et al., 1981).

The principal histopathological alterations in rodent species consisted of extensive swelling and vacuolation of hepatocytes and proliferation of smooth-surfaced endoplasmic reticulum (SER) (seen as "foamy cytoplasm" in light microscopy). The vacuoles were filled with fat indicating excess lipid accumulation. Proliferation of SER may be a morphological reflection of enhanced enzyme activity (Sleight & Sanger, 1976; Render et al., 1982). The changes depended on dose and length of exposure. They have been reported in rats after dietary intake of FireMaster® (Sleight & Sanger, 1976; Kasza et al., 1978a; Sleight et al., 1978; Hinton et al., 1979; Akoso et al., 1982a; Render et al., 1982; Raber & Carter, 1986) and of technical octabromobiphenyl (Norris et al., 1973; Lee et al., 1975a). The dietary concentrations ranged from 0.1 to 500 mg/kg for FireMaster® and from 100 to 10 000 mg/kg for octabromobiphenyl. Effects were seen as early as the tenth day of feeding 100 mg FM BP-6/kg (Raber & Carter, 1986). In contrast, during a 90-day feeding trial, technical decabromobiphenyl (dietary concentration: 100, 500, or 2000 mg/kg) caused hepatic damage only at the highest level (Millischer et al., 1979). Liver changes, as noted above, were observed also after a single i.p. injection (200-1000 μmol/kg) of FireMaster® (Goldstein et al., 1979), after single oral dosing (1000 mg/kg body weight) of FireMaster® (Kimbrough et al., 1978) and of octabromobiphenyl (Lee et al., 1975b), and after multiple oral dosing of FireMaster® (22 doses over a 30-day period: 30 mg/kg body weight per day (Gupta & Moore, 1979; Gupta et al., 1981) and of octabromobiphenyl (two doses: 3000 mg/kg body weight; Lee et al., 1975b). As soon as 24 h (Kimbrough et al., 1978), 3 days (Lee et al., 1975b), or 4 days (Goldstein et al., 1979) after treatment, histological changes could be detected.

Light and electron microscopic changes also reported in the liver of rats included reduction or disintegration of rough-surfaced endoplasmic reticulum (RER) (Lee et al., 1975a,b; Gupta et al., 1981; Akoso et al., 1982a; Raber & Carter, 1986), presence of myelin bodies (cytoplasmic inclusions; membrane whorls) (Lee et al., 1975a,b; Sleight & Sanger, 1976; Kasza et al., 1978a; Kimbrough et al., 1978; Sleight et al., 1978; Hinton et al., 1979; Gupta et al., 1981; Akoso et al., 1982a; Raber & Carter, 1986), di-

or multinucleated cells (Kasza et al., 1978a; Kimbrough et al., 1978; Gupta & Moore, 1979; Hinton et al., 1979), diminution of glycogen (Millischer et al., 1979; Gupta et al., 1981; Raber & Carter, 1986) and mitochondria that were swollen and reduced in number or had degenerated as time passed (Sleight & Sanger, 1976; Kasza et al., 1978a; Akoso et al., 1982a). There was also necrosis of hepatocytes (Kimbrough et al., 1978; Gupta & Moore, 1979; Gupta et al., 1981), and these necrotic foci were infiltrated with polymorphonuclear cells and lymphocytes (Gupta et al., 1981). With octabromobiphenyl, myelin configurations developed 7 days after treatment and subsequently disappeared one week later (Lee et al., 1975b).

Changes in the hepatocytes were more advanced in the centrilobular and midzonal regions than in the periportal area of the liver lobule (Render et al., 1982; Raber & Carter, 1986). Fatty infiltration in the livers of male rats was much more pronounced than in those of female rats (Gupta & Moore, 1979).

Male rats given 100 mg FM FF-1/kg body weight per day (22 total doses) and dying after 90 days had subacute to chronic hepatitis with marked focal proliferation of bile ducts (Gupta & Moore, 1979).

Changes in the bile canaliculus (proliferation of microvilli) were also found in mice fed 1000 mg FM BP-6/kg for 4–14 days. Changes in the hepatocytes of these mice were increase in cell size, decrease in RER, increase in SER, degeneration of mitochondria, decrease in glycogen, and increase in size and number of nucleoli (Corbett et al., 1978a). Fatty infiltration of the cytoplasm was reported only in another two studies on mice dosed with 30 mg FM FF-1/kg body weight per day (Gupta et al., 1981) or fed 167 mg FM BP-6/kg for 6 weeks (Loose et al., 1981). However, in (moribund) mice fed 167 mg FM BP-6/kg feed for 12 weeks, lipid vacuoles were not found within the cytoplasm, but, almost exclusively, within the nucleus (Martino et al., 1981). Hepatocellular necrosis has also been observed (Loose et al., 1981).

Hepatocytes of guinea-pigs were swollen and had many more large vacuoles than those of comparably dosed rats (Sleight & Sanger, 1976), even at lower dietary concentrations (< 10 mg FM/kg). Liver damage was reported to be minimal at dietary levels of 50 mg FM/kg (Vos & van Genderen, 1974), but severe centrilobular fatty changes were found at 100 and 500 mg FM BP-6/kg (Sleight & Sanger, 1976).

Livers of rabbits, dermally treated with FireMaster® at 5 or 10 g/kg body weight, showed a mottled appearance, necrotic foci, and were friable. No gross pathological effects were seen in rabbits dermally exposed to octabromobiphenyl at 10 g/kg body weight (Waritz et al., 1977).

Pigs fed FM BP-6 (up to 200 mg/kg) showed the following liver alterations: fatty change, centrolobular necrosis, swollen hepatocytes, and homogeneous cytoplasm (Werner & Sleight, 1981).

Compared with other species, liver changes observed in cattle were less dramatic. Only an early stage of centrilobular fatty degeneration and glycogen depletion were found in the enlarged livers of lethally (25 g FM BP-6/day) dosed cows. In addition, there were changes in the gallbladder and bile duct (Mercer et al., 1978; Moorhead et al., 1978). Single calves exposed to FM FF-1 for 6-12 weeks had slightly enlarged hepatocytes (dose: 1 mg/kg body weight per day) or necrosis of individual or small foci of hepatocytes (dose: 100 mg/kg body weight per day) (Robl et al., 1978).

The only consistent histopathological lesion in mink which died (exposure: 6.25 mg FM FF-1/kg feed), was a fatty infiltration of the liver (Aulerich & Ringer, 1979).

No hepatocellular damage was found in dogs given oral doses of FM BP-6 (1 mg/kg body weight per day) for seven weeks (Farber et al., 1976).

Biopsies of the livers of two rhesus monkeys given a diet containing 25 mg FM FF-1/kg at 12 weeks revealed enlargement of hepatocytes and a marked proliferation of SER (Allen et al., 1978).

Liver changes in avian species were similar to those observed in mammals. White Leghorn cockerels fed a diet of 10 or 100 mg FM FF-1/kg showed enlargement and vacuolation of hepatocytes, increased SER, swollen mitochondria, and disruption of mitochondrial cristae. But, unlike rats, increased SER was not a significant feature (Dharma et al., 1982).

b) Thymus

The thymus is also an organ sensitive to PBB exposure. Decreases in thymus weights were observed in rats, mice, and

cattle after oral or intraperitoneal doses (Table 74) and in mice after feeding (Table 75) of FireMaster® mixtures. There were no reports on thymus weight changes due to exposure to commercial octa- or decabromobiphenyl (Tables 74 and 75). The weight of the thymus was reduced as early as 6 (Robertson et al., 1981b) or 15 days (Gupta et al., 1981; Andres et al., 1983) after rats were given high doses of FireMaster® (Table 74). Frequently, decreases in thymus weights were accompanied by increases in liver weights (see: Tables 74 and 75). But, in some cases, changes in thymus weights were seen at doses lower than those required for liver changes (Fraker, 1980), or vice versa (Akoso et al., 1982a). Rats (Akoso et al., 1982a) and mice (Fraker & Aust, 1978) both fed FireMaster® BP-6 (100 mg/kg feed) for 30 days differed in their thymic response in that rats remained unaffected and mice showed decreased thymic weight (Table 75). In contrast, rats appeared to be more sensitive than mice when given equal oral doses (30 mg/kg body weight per day for a period of 30 days) of FireMaster® FF-1 (Luster et al., 1978; Gupta et al., 1981; Table 74). Two strains of inbred mice are known to differ in their thymic sensitivity to FireMaster® (Robertson et al., 1984c: Table 74).

In some studies, the histological appearance of the thymus of rats and mice that had survived exposure to FireMaster® was only minimally, or not, affected (Gupta & Moore, 1979; Gupta et al., 1981; Loose et al., 1981; Akoso et al., 1982a), even when organ weights were altered. In other studies, a preferential atrophy of the cortex of the thymus was found in rats and mice similarly exposed (Luster et al., 1978; Fraker, 1980). At high doses (1000 mg FM BP-6/kg feed), "surviving" mice (30%) were essentially athymic by day 14 (Fraker & Aust, 1978). The thymus was markedly involuted also in moribund rats. The normal architecture of the thymus was obliterated with marked atrophy and loss of demarcation between the cortical and medullary regions and disappearance of cortical thymocytes (Gupta & Moore; 1979). Moderate to marked atrophy of the thymus was also observed in guinea-pigs (Vos & van Genderen, 1974) or cattle (Moorhead et al., 1978) that were lethally intoxicated.

The bursa of Fabricius, an analogous organ in avian species, was also affected by FireMaster® (Table 75: Vos & van Genderen, 1974; Ringer, 1978; Dharma et al., 1982). Reductions in weight occurred at exposures as low as 10 mg/kg feed in cockerels (Dharma et al., 1982). Histologically, the bursa showed depletion of the lymphoid cells especially in the medulla (Vos & van Genderen, 1974; Ringer, 1978; Dharma et al., 1982).

c) Spleen

Changes in spleen weights are given in Tables 74 and 75. Feeding of FireMaster® (100-200 mg/kg equivalent to 10-20 mg/kg body weight per day) had no effect on the spleen weights of young rats (Harris et al., 1978b; Akoso et al., 1982a), but resulted in a decrease in the spleen weights of mice (equivalent to 15-30 mg/kg body weight per day) (Fraker & Aust, 1978; Fraker, 1980; Loose et al., 1981). An increase in spleen weights was observed in pups of both rats (Harris et al., 1978a) and mice (Luster et al., 1980) perinatally exposed to FireMaster®. No effects were found in some oral dosing studies on rats (Harris et al., 1978a; Gupta et al., 1981); in another study, spleen weights were decreased (Luster et al., 1978), and in the highest-dosage study reported spleen weights increased (Gupta & Moore, 1979). On the other hand, rats that received i.p. injection of FireMaster® showed decreases in spleen weight at the higher doses (Robertson et al., 1981b; Andres et al., 1983) and increases at the lower dose (Robertson et al., 1981b). While female mice orally dosed with FireMaster® showed decreased spleen weights (Luster et al., 1978), pregnant and nursing females comparably dosed exhibited increased spleen weights (Luster et al., 1980). No effect was found in mice, 5 days after a single i.p. injection of FireMaster®, though the liver and thymus were affected (Robertson et al., 1984c). Spleen weights of chicks fed FireMaster® were reduced (Vos & van Genderen, 1974; Ringer, 1978) or remained unaffected (Dharma et al., 1982).

Significant histopathological changes in the spleen have not been reported, except in rats that were moribund from high doses of FireMaster®. In these animals, the splenic lymphatic follicles were small because of a lack of periarterial lymphoid cells (Gupta & Moore, 1979).

d) Thyroid

Exposure to FireMaster® resulted in an increase in thyroid weight, if there was any weight change (see Tables 74 and 75). Increases in thyroid weight have been observed in rats (Sleight et al., 1978; Allen-Rowlands et al., 1981; Akoso et al., 1982b; Render et al., 1982), newborn pigs (Werner & Sleight, 1981) and in chickens (Ringer & Polin, 1977; Ringer, 1978). When no weight change occurred (rats: Sleight et al., 1978; Gupta et al., 1981; mice: Gupta et al., 1981; chickens: Dharma et al., 1982), the extent of exposure was not always less than in the former studies.

Octabromobiphenyl tested in one inhalation study did not have any effect on thyroid weight in rats (Waritz et al., 1977).

Histological changes in the thyroid gland developed in rats at dietary concentrations of FireMaster® BP-6 as low as 5 mg/kg (Kasza et al., 1978b). Hyperplasia of follicular cells occurred in rats (Kasza et al., 1978b; Sleight et al., 1978) and newborn pigs (Werner & Sleight, 1981). The normal low cuboidal follicular epithelium was altered to one that had a more columnar appearance (Kasza et al., 1978b; Sleight et al., 1978). The most prominent ultrastructural lesions found in rats fed 5-500 mg FireMaster®/kg for 5 weeks were dose-dependent. They included abnormal lysosomes and colloid droplets in the cytoplasm, vacuolated mitochondria with disrupted cristae, luminal surfaces with short and abnormally branched microvilli or devoid of microvilli, and abnormal cytoplasmic processes into the lumen (Kasza et al., 1978b).

e) Kidney

In most studies using rodents (Sleight & Sanger, 1976; Waritz et al; 1977; Harris et al., 1978a,b; Gupta et al., 1981; Render et al., 1982; Ecobichon et al., 1983; Smith et al., 1986), kidney weights did not change with PBB exposure (Tables 74 and 75). Increases in kidney weights were caused by FireMaster® in minks (Aulerich & Ringer, 1979) pigs (Ku et al., 1978), and cattle (Moorhead et al., 1977), and by octabromobiphenyl in rats (Norris et al., 1973). A single study reported a decrease in kidney weight in rats fed FireMaster® BP-6 (Garthoff et al., 1977).

In cattle, kidneys were severely affected, and doubled in size in animals that were moribund from high doses of FireMaster® (Moorhead et al., 1977). The kidneys were distended with fluid, and pale tan to gray in colour. Perirenal lymph nodes were enlarged and oedematous. The principal histological lesions consisted of dilatation of collecting ducts and convoluted tubules, and tubular epithelial degenerative changes (Moorhead et al., 1977). Similar renal lesions were found in calves treated with different doses of FireMaster® (0.1-100 mg FM FF-1/kg body weight per day, for 2-12 weeks). The severity of renal damage was related to dose level and length of exposure (Robl et al., 1978). Despite the extensive morphological damage, effective renal plasma flow rates and glomerular filtration rates were not affected in cows (Mercer et al., 1978; Schanbacher et al., 1978).

Ultrastructural analysis of kidneys of rats and mice given a single i.p. injection of 150 mg "PBB" (not specified)/kg body weight revealed proliferation of SER and increased numbers of peroxisomes in the proximal tubule of the rat, 15 days after dosing. Proliferation of SER was confined to only one segment (S_3) of the proximal tubule. Mice had only marginal increases in SER and no significant increases in peroxisomes (Rush et al., 1986).

f) Stomach

Biopsies of the stomachs of two rhesus monkeys given FireMaster® FF-1 (25 mg/kg diet) were made at 12 weeks. In the gastric mucosa, there was evidence of early epithelial hyperplasia and penetration of the submucosa by glandular epithelium (Allen et al., 1978).

g) Testicle

Changes in the weights of the testes due to PBB exposure (see Tables 74 and 75) were not found in rats (Norris et al., 1973; Garthoff et al., 1977; Harris et al., 1978b; Gupta et al., 1981; Castracane et al., 1982) and mice (Corbett et al., 1978a; Gupta et al., 1981). The results of studies on chickens (Ringer & Polin, 1977; Ringer, 1978; Dharma et al., 1982) were inconsistent (see Table 75).

Histologically, treatment-associated changes (e.g., hypospermatogenesis) were observed in the testes of male calves administered FireMaster® FF-1 (0.1-100 mg/kg body weight per day) for 2-12 weeks (Robl et al., 1978). Chickens fed FireMaster® (50 mg/kg of feed) showed lipid infiltration into the testicular parenchyma (Ringer & Polin, 1977).

h) Fluid accumulation

The presence of fluid accumulation, i.e., hydropericardium and ascites, was noted in chickens (Heinemann & Ringer, 1976; Ringer, 1978). This lesion is known as "chick oedema disease" (McConnell, 1980). Oedema were observed also in the skin of rhesus monkeys (Allen et al., 1978) and in the kidney, perirenal lymph nodes, and the gastrointestinal tract of cattle (Moorhead et al., 1978) that were lethally intoxicated.

Occasionally, weight changes in organs other than those discussed above have been reported (see Tables 74 and 75, but they appear to be of minor importance.

Some special effects occurring after single or short-term exposure to PBBs are reviewed in the respective sections.

8.2.2 *Individual PBB congeners and comparative studies*

A lot of individual PBB congeners have been examined for prominent general signs of toxicity, such as changes in body and relative organ weights (see Tables 76 and 77) and for histopathological changes (see Tables 78 and 79). It is evident from these records that individual PBB congeners differ in their pattern of toxicity. The more toxic isomers and congeners cause a decrease in thymus and/or body weight and produce pronounced histological changes in the liver and thymus. Despite variations in experimental protocols, a tendency can be seen that the most severe effects are elicited by congeners listed under category I. The relative severity of damage decreases in categories II and III with the least effects in the last group. Within a category, the degree of bromination may also influence toxicity. Categorization of halogenated biphenyls has been made on a structural basis (Parkinson et al., 1983; Safe, 1984). Category I comprises isomers and congeners lacking *ortho*-substituents. They are referred to as coplanar PBBs. Mono-*ortho*-substituted derivatives constitute the second category. Other PBBs (mainly those with two or more *ortho*-bromines) have been organized into the third category. Structure-activity relationships are discussed in detail by several authors (e.g., Goldstein, 1979; Parkinson et al., 1983; Safe, 1984).

Orders of toxicity derived from comparative studies included only a limited number of congeners in any given study, but they agreed with the trends described above. Ecobichon et al. (1979) evaluated ultrastructural effects of lower and higher brominated congeners on hepatocytes of rats and showed that the highly brominated congeners (tetra-, penta-, hexa-, octabromobiphenyls) were more active than the low bromine-containing congeners (di-, tribromobiphenyls). Results of comparative studies dealing with higher brominated isomers and congeners, predominantly constituents of the FireMaster®-mixture, and the mixture itself have been summarized in Table 80.

In all combinations tested, 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) was found to be the most toxic PBB. This congener, only

Table 76. Effect of individual PBB congeners on body weight (or body weight gain) and relative organ weights of mice and rats (dosing studies)

PBB congener	Dose[a]	Species (strain) (No.)	Sex	Exposure[b] (solvent)	Weight changes[c] in:			References
					Body	Liver	Thymus	
Category[d] I PBBs ("Coplanar" congeners)								
4,4'-di	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	no effect	--	Ecobichon et al. (1979)
3,4,4',tri	250	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	increased	no effect	Parkinson et al. (1983)
3,4,4'-tri	300	rat (Wistar) (3)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	increased	reduced	Robertson et al. (1982b)
3,4,4',5-tetra	250	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	reduced	increased	reduced	Parkinson et al. (1983)
3,4,4',5-tetra	60	rat (Wistar) (4)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	increased	reduced	Robertson et al. (1982)

Table 76 (contd).

3,3',4,4'-tetra	21.3	rat (Sprague-Dawley) (3)	male	oral single dose (corn oil) t.p.: up to 14 days	no effect	no effect	(reduced)[f]	Millis et al. (1985b)
3,3',4,4'-tetra	250	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	increased	reduced	Parkinson et al. (1983)
3,3',4,4'-tetra	150	rat (Wistar) (4-5)	male	intraperitoneal single dose (corn oil) t.p.: 2 weeks	reduced	increased	reduced	Andres et al. (1983); Robertson et al. (1983b)
3,3',4,4'-tetra	4.25[g]	rat (Sprague-Dawley) (6)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 2 weeks	no effect	increased	no effect	Millis et al. (1985a)
3,3',4,4'-tetra	60	rat (Wistar) (4)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	increased	reduced	Robertson et al. (1982b)
3,3',4,4'-tetra	1500	mouse (C57BL/6J and DBA/2J) (10)	male	intraperitoneal single dose (corn oil) t.p.: 5 days	no effect	increased	reduced	Robertson et al. (1984c)

Table 76 (contd).

PBB congener	Dose[a]	Species (strain) (No.)	Sex	Exposure[b] (solvent)	Weight changes[c] in:			References
					Body	Liver	Thymus	
3,3',4,4',5-penta	100	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	reduced	increased	reduced	Parkinson et al. (1983)
3,3',4,4',5-penta	60	rat (Wistar) (4)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	increased	reduced	Robertson et al. (1982b)
3,3',4,4',5,5'-hexa	21.3	rat (Sprague-Dawley) (3)	male	oral single dose (corn oil) t.p.: up to 14 days	no effect	(increased)[f]	(reduced)[f]	Millis et al. (1985b)
3,3',4,4',5,5'-hexa	100	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	reduced	increased	reduced	Parkinson et al. (1983)
3,3',4,4',5,5'-hexa	3.19[g]	rat (Sprague-Dawley) (6)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 2 weeks	no effect	increased	no effect	Millis et al. (1985a)

Table 76 (contd)

3,3',4,4',5,5'-hexa	60	rat (Wistar) (4)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	increased	reduced	Robertson et al. (1982b)
3,3',4,4',5,5'-hexa	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) t.p.: 7 days[d]	--	increased	--	Ecobichon et al. (1979)
Category II PBBs (Mono*ortho* "coplanar" derivatives)								
2,3',4,4'-tetra	250	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	no effect	no effect	Parkinson et al. (1983)
2,3',4,4'-tetra	1500	mouse	male	intraperitoneal single dose (corn oil) t.p.: 5 days				Robertson et al. (1984c)
		(C57BL/6J) (5)			no effect	no effect	no effect	
		(DBA/2J) (5)			no effect	increased	no effect	
2,3',4,4',5-penta	250	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	increased	no effect	Parkinson et al. (1983)

Table 76 (contd).

PBB congener	Dose[a]	Species (strain) (No.)	Sex	Exposure[b] (solvent)	Weight changes[c] in: Body	Liver	Thymus	References
2,3',4,4',5-penta	164[g]	rat (Sprague-Dawley) (6)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 2 weeks	reduced no effect	increased increased	reduced no effect	Dannan et al. (1982c) Millis et al. (1985a)
2,3',4,4',5,5'-hexa	144[g]	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 7 days	reduced	increased	(reduced)[f]	Dannan et al. (1978a)
2,3,3',4,4',5-hexa	144[g]	rat (Sprague-Dawley) (4)	male	intraperitoneal 2 doses dose (polyethylene glycol) t.p.: 7 days	reduced	increased	reduced	Dannan et al. (1982a)
2,3,3',4,4',5-hexa	3.8-60	rat (Wistar) (1-4)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	no effect	--	Robertson et al. (1981a)
2,3,3',4,4',5'-hexa	100	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	no effect	no effect	Parkinson et al. (1983)

Table 76 (contd).

Category III PBBs (Others)								
4-mono	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (day 1,2,3) (peanut oil) t.p.: 7 days[e]	--	no effect	--	Ecobichon et al. (1979)
2,2'-di	289[g]	rat (Sprague-Dawley) (3)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 2-22 days	--	no effect	--	Moore et al. (1979a)
2,2'-di	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	no effect	--	Ecobichon et al. (1979)
2,5'-di	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	no effect	--	
2,2'5-tri	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	no effect	--	
2,3',5-tri	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (peanut oil) t.p.: 7 days[e]	--	no effect	--	

Table 76 (contd).

PBB congener	Dose[a]	Species (strain) (No.)	Sex	Exposure[b] (solvent)	Weight changes[c] in:			References
					Body	Liver	Thymus	
2,4,6-tri	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (peanut oil) t.p.: 7 days[e]	--	no effect	--	Ecobichon et al. (1979)
2,4',5-tri	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (peanut oil) t.p.: 7 days[e]	--	increased	--	
3,3',5,5'-tetra	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (peanut oil) t.p.: 7 days[e]	--	increased	--	
2,3',4'5-tetra	150	rat (Wistar) (4)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	no effect	--	Robertson et al. (1980)
2,2',5,5'-tetra	500	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	increased	no effect	Parkinson et al. (1983)
2,2',5,5'-tetra	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (peanut oil) t.p.: 7 days[e]	--	increased	--	Ecobichon et al. (1979)

Table 76 (contd).

2,4,4',6-tetra	500	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	no effect	no effect	Parkinson et al. (1983)
2,2',4,5',6-penta	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	increased	--	Ecobichon et al. (1979)
2,3',4,4',6-penta	500	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	no effect	no effect	Parkinson et al. (1983)
2,2',4,5,5'-penta	500	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	increased	no effect	
2,2',4,5,5'-penta	164[g]	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 7 days	no effect	no effect	no effect	Dannan et al. (1982a)
		(6)		t.p.: 14 days	no effect	increased	no effect	Millis et al. (1985a)
2,2',3,4,4',5'-hexa	144[g]	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 7 days	no effect	increased	no effect	Dannan et al. (1982a)

Table 76 (contd).

PBB congener	Dose[a]	Species (strain) (No.)	Sex	Exposure[b] (solvent)	Weight changes[c] in:			References
					Body	Liver	Thymus	
2,2',4,4',6,6'-hexa	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	increased	--	Ecobichon et al. (1979)
2,2',4,4',5,5'-hexa	590[g]	rat (Fischer 344/N) (6)	male, female	oral 22 doses (over 30 days) (corn oil) t.p.: 15, 30, 45, 60, 90 days[e]	no effect	increased	no effect	Gupta et al. (1981)
2,2',4,4',5,5'-hexa		rat (Fischer) (4)	female	intraperitoneal single dose (corn oil) t.p.: 4 days				Goldstein et al. (1979)
	40				no effect	no effect	--	
	200, 1000				no effect	(increased)[f]	--	
2,2',4,4',5,5'-hexa	500	rat (Long Evans) (3)	male	intraperitoneal single dose (corn oil) t.p.: 4 days	no effect	increased	no effect	Parkinson et al. (1983)

Table 76 (contd).

2,2',4,4',5,5'-hexa	144[g]	rat (Sprague-Dawley) (6)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 2 weeks	no effect	increased	no effect	Moore et al. (1978b); Millis et al. (1985a)
2,2',4,4',5,5'-hexa	600	rat (Wistar) (4-6)	male	intraperitoneal 3 doses (days 1,2,3) (peanut oil) t.p.: 7 days[e]	--	increased	--	Ecobichon et al. (1979)
2,2',4,4',5,5'-hexa	590[g]	mouse (B6C3F1/N) (6)	male, female	oral 22 doses (over 30 days) (corn oil) t.p.: 15, 30, 45, 69, 90 days[e]	no effect	increased	no effect	Gupta et al. (1981)
2,2',3,3',4,4'5-hepta	127[g]	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose (polyethylene glycol) t.p.: 7 days	no effect	increased	no effect	Dannan et al. (1982a)
2,2',3,4,4',5,5'-hepta	127[g]	rat (Sprague-Dawley) (3)	male	intraperitoneal single dose (polyethylene glycol) t.p.: up to 22 days	--	increased	--	Moore et al. (1979a)

Table 76 (contd).

PBB congener	Dose[a]	Species (strain) (No.)	Sex	Exposure[b] (solvent)	Weight changes[c] in: Body	Liver	Thymus	References
2,3,3',4,4',5,6-hepta	6	rat (Wistar) (2)	male	intraperitoneal 2 doses (days 1,3) (corn oil) t.p.: 5 days[e]	--	no effect	--	Robertson et al. (1981a)
2,2',3,3',4,4',5,5'-octa	115[g]	rat (not specified)	male	intraperitoneal single dose (solvent not specified) t.p.: 7 days	--	increased	--	Besaw et al. (1978)

[a] Total dose in μmol/kg body weight.
[b] t.p. = Time post-exposure; -- = data not given.
[c] Only statistically significant changes; organ weight changes relative to body weight.
[d] Categorization according to Safe (1984); see also text in section 8.2.2.
[e] After first dose.
[f] Only absolute data given.
[g] Calculated from original value given in mg/kg body weight.

Table 77. Effect of various hexabromobiphenyl isomers on feed intake, body weight (or body weight gain) and (relative) organ weights (feeding studies)

PBB congener	Species (strain) (No.)	Sex	Dietary concentration (mg/kg feed)	Feeding period (days)[c]	Food intake	Effects Weight changes[a] Body	Liver	Thymus	Other organs	References
Category[b] I PBBs										
3,3',4,4',5,5'-hexa	rat (Sprague-Dawley) (6)	male	10	30	reduced	reduced	increased	reduced	spleen: reduced brain: no effect thyroid: increased	Akoso et (1982a,b)
	rat (Sprague-Dawley) (6)	male	1	9	no effect	no effect	no effect			Render et al. (1982)
			10	9	reduced	reduced	increased	reduced		
			100	9	reduced	reduced	increased	reduced		
	(2)		100	20	refused (day 16)					
Category II PBBs										
2,3',4,4',5,5'-hexa	rat (Sprague-Dawley) (6)	male	1, 10	30	no effect	no effect	no effect	no effect	brain: increased thyroid: no effect	Akoso et al. (1982a,b)
			100	30	no effect	no effect	increased	no effect	brain: increased thyroid: no effect	

Table 77 (contd).

PBB congener	Species (strain) (No.)	Sex	Dietary concentration (mg/kg feed)	Feeding period (days)[c]	Food intake	Effects Weight changes[a] Body	Liver	Thymus	Other organs	References
	cockerel (White Leghorn) (10)	male	4, 10	28	no effect	no effect	no effect		bursa of Fabricius, thyroid, spleen, testicles, comb: no effect	Dharma et al. (1982)
Category III PBBs										
2,2',4,4',5,5'-hexa	rat (Sprague-Dawley) (6)	male	1	30	no effect	no effect	increased	no effect	brain: increased thyroid: no effect	Akoso et al. (1982a,b)
	(6)		10, 100	30	no effect	no effect	increased	increased	brain: increased thyroid: no effect	

Table 77 (contd).

rat (Sprague-Dawley) (6)	male	10	9	increased	no effect	increased	n.r.	kidney: no effect	Render et al. (1982)
		100	9	no effect	no effect	increased	n.r.	kidney: no effect	
mouse (C57 BL), pregnant (3)	female	100, 300	gd 6 through 15	no effect	no effect	increased	n.r.		Welsch & Morgan (1985)
		500, 750	sacrifice gd 17	no effect	reduced	increased	n.r.		
		1000		reduced	reduced	increased	n.r.		
cockerel (White Leghorn) (10)	male	10	28	no effect	no effect	no effect	n.r.	bursa of Fabricius, thyroid, spleen, testicles, comb, no effect (both concentrations)	Dharma et al. (1982)
		62	28	no effect	no effect	increased	n.r.		

[a] Only statistically significant changes; organ weight changes relative to body weight except for Render et al. (1982) giving absolute data.
[b] Categorization according to Safe (1984); see also text in section 8.2.2.
[c] gd = Gestation day.
[d] n.r. = Not recorded.

Table 78. Histopathology in relation to individual PBB congeners (dosing studies)

PBB congener	Species (strain) (No.)	Sex	Exposure[c]	Dose[b]	Histopathological effects[f] Liver	Thymus	Other organs	References
Category[a] I PBBs								
4,4'-di	rat (Wistar) (6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	Ecobichon et al. (1977)
3,3',4,4'-tetra	rat (Sprague-Dawley) (3)	male	oral single dose t.p.: up to 14 days	21.3	+	+ +	8 tissues: 0	Millis et al. (1985b)
	rat (Sprague-Dawley) (6)	male	intraperitoneal single dose t.p.: 2 weeks	4.25[e]	+	0	11 tissues: 0	Millis et al. (1985a)
	rat (Wistar) (4)	male	intraperitoneal single dose t.p.: 2 weeks	150	+	+ +	spleen, kidney: 0	Andres et al. (1983);Robertson et al. (1983b)
3,3',4,4',5,5'-hexa	rat (Sprague-Dawley) (3)	male	oral single dose t.p.: up to 14 days	21.3	+ +	+ +	8 tissues: 0	Millis et al. (1985b)
	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	Ecobichon et al. (1979)

Table 78 (contd).

Category[a] II PBBs								
2,3',4,4',5-penta	rat (Sprague-Dawley) (6)	male	intraperitoneal single dose t.p.: 2 weeks	164[e]	+	0	9-11 tissues: 0	Dannan et al. (1982c); Millis et al. (1985a)
2,3',4,4',5,5'-hexa	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose t.p.: 1 week	144[e]	+ +	n.r.	9 tissues: 0	Dannan et al. (1982a)
2,3,3',4,4',5-hexa	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose t.p.: 1 week	144[e]	+ +	+ +	9 tissues: 0	
Category[a] III PBBs								
4-mono	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	0	n.r.	n.r.	Ecobichon et al. (1979)
2,2'-di	rat (Sprague-Dawley) (3)	male	intraperitoneal single dose t.p.: up to 22 days	289[e]	0	0	8 tissues: 0	Moore et al. (1979a)
2,5'-di	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	0	n.r.	n.r.	Ecobichon et al. (1979)

Table 78 (contd).

PBB congener	Species (strain) (No.)	Sex	Exposure[c]	Dose[b]	Histopathological effects[f]			References
					Liver	Thymus	Other organs	
2,2',5-tri	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	0	n.r.	n.r.	Ecobichon et al. (1979)
2,3',5-tri	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	0	n.r.	n.r.	
2,4,6-tri	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	
2,4',5-tri	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	
3,3',5,5'-tetra	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	
2,2',5,5'-tetra	rat (Wistar) (not specified)	male	intraperitoneal single dose t.p.: 2 weeks	150	+	0	spleen, kidney: 0	Robertson et al. (1983b)
	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	Ecobichon et al. (1979)

Table 78 (contd).

2,2',4,5',6-penta	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	Ecobichon et al. (1979)
2,2',4,5,5'-penta	rat (Sprague-Dawley) (4-6)	male	intraperitoneal single dose t.p.: 1-2 weeks	164[e]	+	0	9-11 tissues: 0	Dannan et al. (1982a); Millis et al. (1985a)
2,2',3,4,4',5'-hexa	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose t.p.: 1 week	144[e]	+	0	9 tissues: 0	Dannan et al. (1982a)
2,2',4,4',5,5'-hexa	rat (Fischer 344/N)	male, female	oral 22 doses t.p.: up to 90 days[d]	1052[e]	+ 0	0	16 tissues: 0	Gupta et al. (1981)
2,2',4,4',5,5'-hexa	rat (Fischer) (4)	male	intraperitoneal single dose t.p.: 4 days	200-1000	+	n.r.	n.r.	Goldstein et al. (1979)
	rat (Sprague-Dawley) (3-6)	male	intraperitoneal single dose t.p.: up to 14 days	144[e]	+	0	8-11 tissues: 0	Moore et al. (1978b); Millis et al. (1985a)
	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	Ecobichon et al. (1979)
2,2',4,4',6,6'-hexa	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	600	+	n.r.	n.r.	

Table 78 (contd).

PBB congener	Species (strain) (No.)	Sex	Exposure[c]	Dose[b]	Histopathological effects[f] Liver	Thymus	Other organs	References
2,2',3,3',4,4',5-hepta	rat (Sprague-Dawley) (4)	male	intraperitoneal single dose t.p.: 1 week	127[e]	+	0	9 tissues: 0	Dannan et al. (1982a)
2,2',3,4,4',5,5'-hepta	rat (Sprague-Dawley) (3)	male	intraperitoneal single dose t.p.: up to 22 days	127[e]	+	0	8 tissues: 0	Moore et al. (1979a)
2,2',3,3',4,4',5,5'-octa	rat (not specified)	male	intraperitoneal single dose t.p.: 7 days	115[e]	+	0	several tissues: 0	Besaw et al. (1978)
	rat (Wistar) (4-6)	male	intraperitoneal 3 doses t.p.: 7 days[d]	500	+	n.r.	n.r.	Ecobichon et al. (1979)

[a] Categorization according to Safe (1984); see also text in section 8.2.2.
[b] Total dose in μmol/kg body weight.
[c] t.p. = Time post-exposure.
[d] After first dose.
[e] Calculated from original value given in mg/kg body weight.
[f] n.r. = Not recorded; 0 = Lesion not observed; + = Lesion observed (number of "+" denote severity).

Table 79. Histopathology to individual PBB congeners (feeding studies)

PBB congener	Species (strain) (No.)	Sex	Dietary concentration (mg/kg feed)	Feeding period (days)	Histopathological effects[b] Liver	Thymus	Other organs	References
Category[a] I PBBs								
3,3',4,4',5,5'-hexa	rat (Sprague-Dawley) (6)	male	1	10	+	0		Render et al. (1982)
			10	10	+ +	+ +		
			100	10	+ +	+ +	spleen, lymph nodes: +	
	rat (Sprague-Dawley) (6)	male	1	30	+	0	thyroid: +	Akoso et al. (1982a,b)
			10	30	+ +	+ +	thyroid, pituitary gland: +	
Category[a] II PBBs								
2,3',4,4',5,5'-hexa	rat (Sprague-Dawley) (6)	male	1, 10, 100	30	+	0	thyroid: +	
	cockerels (White Leghorn) (10)	male	10	28	+	n.r.	bursa of Fabricius: +	Dharma et al. (1982)

Table 79 (contd).

PBB congener	Species (strain) (No.)	Sex	Dietary concentration (mg/kg feed)	Feeding period (days)	Histopathological effects[b] Liver	Thymus	Other organs	References
Category[a] III PBBs								
2,2',4,4',5,5'-hexa	rat (Sprague-Dawley) (6)	male	10, 100	10	+	0	18 tissues: 0	Render et al. (1982)
	rat (Sprague-Dawley) (6)	male	1, 10, 100	30	+	0	thyroid: +	Akoso et al. (1982a,b)
	cockerel (White Leghorn) (10)	male	4, 10	28	0	n.r.	bursa of Fabricius: 0	Dharma et al. (1982)
			62	28	+	n.r.	bursa of Fabricius: +	

[a] Categorization according to Safe (1984); see also text in section 8.2.2.
[b] n.r. = Not recorded; 0 = Lesion not observed; + = Lesion observed (number of "+" denote severity).

a very minor constituent of FireMaster®, resembles 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the typical and the most toxic member of the class of polyhalogenated hydrocarbons (e.g., Poland & Knutson, 1982). Of the major FireMaster® constituents, 2,3,3′,4,4′,5-hexabromobiphenyl (BB 156) appeared to be the most toxic, followed by 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167) and 2,3′,4,4′,5-pentabromobiphenyl (BB 118). The main component of the FireMaster®-mixture, 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153) was relatively nontoxic as well as the second most abundant constituent, 2,2′,3,4,4′,5,5′-heptabromobiphenyl (BB 180). Compared with the mixture itself, 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) was consistently more toxic than FireMaster® and 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153) less toxic. With 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167), different results were obtained from a dosing study (Dannan et al., 1978a) and two feeding studies (Akoso et al., 1982a,b; Dharma et al., 1982). The latter attributed FireMaster® a higher toxicity than 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167); 2,2′,4,5,5′-pentabromobiphenyl (BB 101) was less effective in producing adverse effects than 2,3′,4,4′,5-pentabromobiphenyl (BB 118), which matched FireMaster® in some aspects (see Table 80).

Dannan et al. (1982b) recombined 9 purified FireMaster® constituents, namely BB 101 (2,2′,4,5,5′-penta-,) BB 118 (2,3′,4,4′,5-penta-), BB 153 (2,2′,4,4′,5,5′-hexa-), BB 138 (2,2′,3,4,4′,5′-hexa-), BB 167 (2,3′,4,4′,5,5′-hexa), BB 156 (2,3,3′,4,4′,5-hexa-), BB 180 (2,2′,3,4,4′,5,5′-hepta-), BB 170 (2,2′,3,3′,4,4′,5-hepta-), and BB 194 (2,2′,3,3′,4,4′,5,5′-octabromobiphenyl), totalling 97% of either FireMaster® mixture, to form a reconstituted FireMaster® BP-6-like mixture and compared some effects of the reconstituted mixture to those of crude FireMaster® mixtures BP-6 and FF-1. Rats were treated with a single dose (90 mg/kg body weight of either mixture) and sacrificed one week later. Evaluating changes in body and selected organ (liver, thymus, spleen) weights, the conclusion was reached that adverse effects of FireMaster® (FF-1 or BP-6) must be due to the effects of the congeners studied. Moreover, it was found that the increase in liver weights was greater with FM BP-6 and the reconstituted mixture than with FM FF-1, consistent with the higher proportion of minor components (BBs: 118, 138, 167, 156) in FM BP-6 (25% versus 15%).

Differences in toxicity between PBBs were sometimes of a qualitative kind, but mostly they were quantitative. Some striking relations will be reviewed in detail according to the parameter tested.

Table 80. Order of toxicity of higher brominated PBB congeners and the FireMaster® mixture on the basis of comparative studies

Species	Parameter tested	PBBs tested[a]										Order of toxicity	References
		FM	101	118	153	138	167	156	180	170	169		
Dosing studies													
Rat	body weight gain	x					x					167 > FM	Dannan et al. (1978a)
Rat	liver weight and histopathology	x			x							FM > 153	Moore et al. (1978b); Goldstein et al. (1979)
Rat	liver weight and histopathology	x							x			FM > 180	Moore et al. (1979a)
Rat (Mouse)	body and organ weights, histopathology	x			x							FM > 153	Gupta et al. (1981)
Rat	body and organ weights, histopathology	x		x								118 > FM	Dannan et al. (1982c)
Rat	body and organ weights, histopathology	x				x	x	x		x		156 > 167 > 138, 170 > 101	Dannan et al. (1982a)

Table 80 (contd).

Rat	body and organ weights			x	x			x	169 > 118, 153	Parkinson et al. (1983)
Rat	liver histopathology		x	x	x				118, 153 > 101	Millis et al. (1985a)
Feeding studies										
Rat	death, body and organ weights, histopathology	x			x			x	169 > FM > 153	Sleight et al. (1981)
Rat	feed intake, body and organ weights, histopathology	x			x	x		x	169 > FM > 167 > 153	Akoso et al. (1982a,b)
Rat	death, feed intake, body and organ weights, histopathology	x			x			x	169 > FM, 153	Render et al. (1982)
Cockerel	organ weights, histopathology	x			x	x			FM > 167 > 153	Dharma et al. (1982)

[a] FM = FireMaster® mixture (BP-6 or FF-1); PPB numbering according to Ballschmiter & Zell (1980):
101, 118 = pentabromobiphenyls (2,2',4,5,5'-; 2,3',4,4',5-).
153, 138, 167, 156, 169 = hexabromobiphenyls (2,2',4,4',5,5'-; 2,2',3,4,4',5'-; 2,3',4,4',5,5'-; 2,3,3',4,4',5-; 3,3', 4,4', 5,5'-).
180, 170 = heptabromobiphenyls (2,2',3,4,4',5,5'; 2,2',3,3',4,4'5-).

8.2.2.1 Food intake, overt clinical signs, body weight changes

So far, in the congeners tested, food intake of rats was reduced only by 3,3'4,4',5,5'-hexabromobiphenyl (Table 77: Akoso et al., 1982a; Render et al., 1982). The effective dietary concentrations ranged from 1 to 100 mg/kg. A much higher concentration of 2,2',4,4',5,5'-hexabromobiphenyl (1000 mg/kg of feed) was needed to evoke reduction in the food consumption of mice (Table 77: Welsch & Morgan, 1985).

Rats, moribund from 3,3',4,4',5,5'-hexabromobiphenyl treatment, had symptoms similar to those observed with FireMaster® toxicosis (see section 8.2.1.1). They became less active, had a roughened hair coat, developed sunken eyes, and were emaciated (Render et al., 1982).

3,3',4,4',5,5'-Hexabromobiphenyl significantly decreased body weight (Render et al., 1982) or body weight gain (Akoso et al., 1982a) in rats, while the same concentrations of FireMaster® BP-6, 2,2',4,4',5,5'-hexa- and 2,3',4,4',5,5'-hexabromobiphenyl in the diet had no effects. When rats were injected i.p. with identical amounts of several constituents of FireMaster® (BBs: 101, 138, 167, 156, 170), only 2,3',4,4',5,5'-hexabromobiphenyl (BB 167) and 2,3',4,4',5,5'-hexabromobiphenyl (BB 156) depressed body weight gain (Dannan et al., 1978a, 1982a). The body weight gain of rats treated with BB 167 was half that of FireMaster®-treated animals (Dannan et al., 1978a). Rats given BB 118 (2,3',4,4',5-hexabromobiphenyl) also gained less weight per day than those given FireMaster® (Dannan et al., 1982c).

Liver weights in rats were increased by all treatments with congeners of category I, except for 4,4'-dibromobiphenyl. The lowest effective dose used was 2 mg/kg body weight (Millis et al., 1985a). Significant effects were seen as early as 4 days after dosing (e.g., Parkinson et al., 1983). Many of the congeners listed under categories II and III were also capable of increasing liver weights (see Tables 76 and 77). Generally, all the changes in organ weights were dose-dependent. Gradual differences between congeners were also seen. Liver weights were significantly higher in rats given 3,3',4,4',5,5'-hexabromobiphenyl than the liver weights in 3,3',4,4'-tetrabromobiphenyl-treated rats, 6 days after a single dose (Millis et al., 1985b). In studies comparing the effects of five FireMaster® constituents (BB 101: 2,2',4,5,5'-penta; BB 138: 2,2',3,4,4',5'-hexa; BB 167: 2,3',4,4',5,5'-hexa; BB 156: 2,3,3',4,4',5-hexa; BB 170: 2,2',3,3',4,4',5-hepta), 7 days after

dosing, 2,3,3′,4,4′,5-hexabromobiphenyl (BB 156) caused the largest increase in liver weights (60% increase) while 2,2′,4,5,5′-pentabromobiphenyl (BB 101) failed to enlarge this organ. Increases caused by FireMaster® and BB 167 (2,3′,4,4′,5,5′-hexa) were similar (Dannan et al., 1978a, 1982a). The increases in liver weights due to BB 153 (2,2′,4,4′,5,5′-hexa), the main component of FireMaster®, were far less than the increase in response to FireMaster®, approximately 33% versus 60-80% (Moore et al., 1978b; Goldstein et al., 1979).

Nevertheless, the increase was rapid with a 25% increase within two days of treatment (Moore et al., 1978b). The effect of 2,2′,3,4,4′,5,5′-heptabromobiphenyl (BB 180), the second most abundant component of FireMaster®, was also less than that caused by the mixture itself (Moore et al., 1979a). When FireMaster® BP-6, 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167), 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153), and 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) were added to the diet of rats for 30 days, BB 153 and BB 169 significantly increased liver weights at 1 mg/kg, but FireMaster® and BB 167 did not. At 100 mg/kg, FireMaster® increased liver weight more than BB 153 or BB 167 (Akoso et al., 1982a).

Thymus weights in rodents were decreased by most of the treatments with congeners of category I. Among congeners in category II, 2,2′,4,4′,5-pentabromobiphenyl (BB 118), 2,3′,4,4′,5,5′-hexabromobiphenyl (BB 167), and 2,3,3′,4,4′,5-hexabromobiphenyl (BB 156) were capable of reducing thymus weights. Congeners listed under the third category failed to reduce thymus weights (see Tables 76 and 77). Both 3,3′,4,4′-tetra and 3,3′,4,4′,5,5′-hexabromobiphenyl caused a significant reduction in the thymus weights of rats, 3,3′,4,4′,5,5′-hexabromobiphenyl being more effective than 3,3′,4,4′-tetrabromobiphenyl (Millis et al., 1985b). There was a 50-60% loss in thymic weight in rats injected i.p. with BB 167 or BB 156 and sacrificed 7 days later (Dannan et al., 1978a, 1982a). However, thymus weight: body weight ratios were not significantly affected when rats were fed BB 167 or FireMaster® BP-6 for 30 days (Akoso et al., 1982a). In the same study, 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) significantly decreased the ratio, while there was an increase with 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153).

In cockerels fed FireMaster® FF-1, BB 153, or BB 167, for 28 days, only FireMaster® FF-1 reduced relative bursal weights (Dharma et al., 1982).

When young rats were fed diets containing FireMaster® BP-6, 2,2′,4,4′,5,5′-hexa-, 2,3′,4,4′,5,5′-hexa-, or 3,3′,4,4′,5,5′-hexabromobiphenyl, for 30 days, thyroid weight was increased only by 100 mg FireMaster® BP-6/kg feed and by 1 and 10 mg 3,3′4,4′,5,5′-hexabromobiphenyl/kg feed (Akoso et al., 1982b).

8.2.2.2 *Haematology and clinical chemistry*

Haematological and clinical chemistry findings were of minor importance in comparative studies. γ-Glutamyl transpeptidase (γGTP) was elevated in female rats at high doses of both FireMaster® FF-1 (30 mg/kg body weight per day) and 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153) (16.8 mg/kg body weight per day) 30 and 60 days after the last dose (Gupta et al., 1981).

8.2.2.3 *Morphological and histopathological changes*

Rats fed diets containing 100 mg FireMaster® BP-6/kg or 10 or 100 mg 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169)/kg had friable yellow livers (Render et al., 1982). The architectural structure of the lobules was abnormal after feeding 3,3′,4,4′,5,5′-hexabromobiphenyl (Akoso et al., 1982a; Millis et al., 1985b), and bile duct hyperplasia was observed (Render et al., 1982).

With the exception of the lower brominated congeners of category III, all PBB congeners caused histopathological changes in the liver (see Tables 78 and 79). The extent of the changes depended on the dose and the individual congener. The least severe effects were confined to a slight proliferation of hepatic SER (e.g., 4,4′-dibromobiphenyl: Ecobichon et al., 1977). More progressive, general changes were enlargement of hepatocytes and increased numbers of cytoplasmic lipid vacuoles. Corresponding ultrastructural lesions consisted mainly of increased SER and lipid vacuolation (see Tables 78 and 79). Additional changes seen with the more toxic congeners included myelin body formation (membrane whorls) (BBs: 118, 167, 156, 169), disorganization of RER (BB 169), an increase in number of binucleated hepatocytes (BB 169), pycnotic nuclei (BB 169), and, occasionally, multifocal areas of necrosis (BB 169) (Akoso et al., 1980, 1982a; Sleight et al., 1981; Dannan et al., 1982a,c; Render et al., 1982; Millis et al., 1985b).

The thymus was affected by 3,3′,4,4′-tetrabromobiphenyl (Andres et al., 1983; Millis et al., 1985b), possibly by BB 167

(Dannan et al., 1978a: "several" tissues: not accurately specified), by BB 156 (Dannan et al., 1982a) and by BB 169 (Sleight et al., 1981; Akoso et al., 1982a; Render et al., 1982; Millis et al., 1985b). There was a loss of thymocytes, especially in the cortex, the demarcation between cortex and medulla was indistinct, and macrophages were prominent in the remaining portion of the cortex.

One study reported histological alterations in the thyroid of rats treated with 2,2′,4,4′,5,5′-hexa- (BB 153), 2,3′,4,4′,5,5′-hexa (BB 167), or 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169), and in the pituitary gland with BB 169 (Akoso et al., 1982b). Prominent lesions of the thyroid were extensive hyperplasia and hypertrophy of follicular cells and a lack of colloid. The pituitary gland showed swollen and vacuolated chromophobe cells.

The spleen and lymph nodes of rats given 100 mg 3,3′,4,4′,5,5′-hexabromobiphenyl/kg feed for 10 and 20 days had an increased number of macrophages intermixed with mature lymphocytes. Changes were similar to those seen in the thymus, but were not as pronounced (Render et al., 1982).

The main component of FireMaster®, 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153), is the congener most frequently examined and implicated in many comparative studies.

The principal changes seen with BB 153 were vacuolation and enlargement of hepatocytes with proliferation of SER. They occurred in dosing studies (Moore et al., 1978b; Ecobichon et al., 1979; Goldstein et al., 1979; Gupta et al., 1981; Millis et al., 1985a) as well as in feeding studies (Sleight et al., 1981; Akoso et al., 1982a; Dharma et al., 1982), and were observed as early as two days after treatment (Moore et al., 1978b). Generally, the ultrastructural changes in BB 153-exposed rats were less severe than those in rats exposed to the FireMaster® mixture (e.g., Goldstein et al., 1979; Gupta et al., 1981; Akoso et al., 1982a). Myelin figures and marked disorganization of RER, as seen with the FireMaster® mixture, were not observed with BB 153 in comparative studies (Gupta et al., 1981; Akoso et al., 1982a). Moreover, changes caused by FireMaster® FF-1 in the livers of rats persisted, while the livers of rats dosed with BB 153 were comparable to those of the controls, 60 days after treatment (Gupta et al., 1981).

The histological appearance of thymuses in rats was not affected by BB 153 (Tables 78 and 79), but, in cockerels, the lymphoid cells of the bursa of Fabricius were depleted by 62 mg BB 153/kg feed, by 10 mg FireMaster® FF-1/kg feed, and by 10 mg BB 167/kg feed (Dharma et al., 1982). When BB 153, the FireMaster® mixture, BB 167, and BB 169, were fed to rats, proliferation of SER, decreased RER, and increased fat droplets were seen in hepatocytes, with all chemicals, but, with BB 169 (3,3′,4,4′,5,5′-hexabromobiphenyl), proliferation of SER was not as prominent as with the other three PBBs. In contrast, the RER was severely altered by BB 169 (Akoso et al., 1982a).

Myelin bodies were observed in rats fed 100 mg BB 169/kg for 20 days (Render et al., 1982) or FireMaster® BP-6 for 30 days (Akoso et al., 1982a), or BB 167 for 60 days (Akoso et al., 1980). A comparative experimental series testing single doses of six FireMaster® constituents, namely BB 118 (Dannan et al., 1982c; Millis et al., 1985a), BBs 101, 138, 167, 156, and 170 (Dannan et al., 1978a, 1982a) found the least severe histological changes with BB 101, and intermediate effects, which were limited to the proliferation of SER and cytoplasmic vacuolation in hepatocytes, with BB 138 and BB 170. The most pronounced changes resulted from BBs 118, 167, and 156 and consisted of proliferation of SER, increases in fat vacuoles and myelin figures in hepatocytes (BBs 118, 167, 156) and thymus damage (BB 156). Rats given a single equimolar dose of 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) or 3,3′,4,4′-tetrabromobiphenyl showed moderate to severe hepatic changes 14 days after treatment with BB 169, while the tetrabromobiphenyl-treated rats showed only mild hepatic changes (Millis et al., 1985b).

The microscopic hepatic effects of 2,2′,3,4,4′,5,5′-heptabromobiphenyl (BB 180) and of 2,2′,3,3′,4,4′,5,5′-octabromobiphenyl (BB 194) were reported to be similar to those of BB 153 (Besaw et al., 1978; Moore et al., 1979a, 1980).

8.3 Skin and eye irritation, sensitization, dermal lesions, and acne

Common skin and eye irritation tests, as well as sensitization tests, resulted in no, or only mild, reactions due to the technical PBB mixtures tested, namely octabromobiphenyl and decabromobiphenyl (Table 81).

Table 81. Skin and eye irritation or sensitization tests of commercial PBB mixtures

PBB[a]	Species	Application	Test	Observations	References
OcBB	guinea-pig (Hartley)	50% (w/v) slurry in propylene glycol (0.05 ml)	irritation (intact shaved dorsal skin)	mild irritation	Waritz et al. (1977)
OcBB	guinea-pig (Hartley)		sensitization	no sensitization	
		1) 1 x 50% (w/v) slurry in propylene glycol	intact shaved skin		
		2) 9 x 50% slurry (topical application)	abraded shaved skin		
		3) 2 weeks later: 1 x 50% slurry	abraded shaved skin		
OcBB	guinea-pig (Hartley)		sensitization	no sensitization	
		1) 1 x 50% (w/v) slurry in propylene glycol	intact shaved skin		
		2) 4 x 1% (w/v) solution in dimethyl sulfoxide (intradermal injection)			
		3) 2 weeks later: 1 x 50% slurry	abraded shaved skin		

Table 81 (contd).

PBB[a]	Species	Application	Test	Observations	References
OcBB	rabbit (New Zealand)		irritation		Norris et al. (1973)
		dry solid (single and multiple exposures)	intact shaved skin abraded shaved skin	no response slight erythematous and edematous response	
OcBB	rabbit (New Zealand)	moistened with water (single exposure) (repeated exposure)	intact shaved skin intact shaved skin	no response slight erythematous response	
OcBB	rabbit (New Zealand)	moistened with water (single and repeated exposures)	abraded shaved skin	moderate erythematous and slight oedematous response	
	rabbit (New Zealand)	dry solid	eye irritation	transient irritation of the conjunctival membranes	

Table 81 (contd).

PBB[a]	Species	Application	Test	Observations	References
OcBB	rabbit	powder (100 mg)	eye irritation	no irritating or corneal effects; mild conjunctival redness and swelling and a copious discharge (disappeared within 4 h)	Waritz et al. (1977)
DeBB	rabbit	50% in olive oil	irritation (intact shaved skin)	mild irritation	Millischer et al. (1979)
DeBB	rabbit	50% in olive oil	eye irritation	no irritating effect	
DeBB	rabbit	powder	eye irritation	mild irritating	

[a] Commercial PBB mixtures: OcBB = Octabromobiphenyl; DeBB = Decabromobiphenyl.

However, diverse lesions in the skin and skin appendages of certain animal species, e.g., rhesus monkeys and cattle, occurred after the ingestion of the FireMaster® mixture (Table 82). The main features were dry scaly skin and hair loss. Hyperkeratosis of the interfollicular epidermis and of the hair follicle, and atrophy and squamous metaplasia of the sebaceous glands were observed on microscopic examination of these lesions. As with related compounds, comparable epidermal changes have not generally been found in other laboratory animals, such as guinea-pigs or rats, but they were similar to those observed in humans following PBB exposure (section 9) and were described as chloracne (McConnell, 1980; Kimbrough, 1980b; Poland & Knutson, 1982).

The rabbit ear (inner surface), but not any other part of the rabbit skin (Crow, 1983), is particularly sensitive to acne-causing compounds, which was first recognized by Adams et al. (1941). The reaction is hyperkeratosis. Painting the rabbit ear has become a standard bioassay to detect hyperkeratotic (acnegenic) activity. Results of rabbit ear tests obtained with diverse PBBs (technical octabromobiphenyl, technical decabromobiphenyl FireMaster® mixture, fractions of this mixture, and purified PBB congeners) have been summarized in Table 83. The FireMaster® mixture itself produced hyperkeratosis, but its main components, BB 153 (2,2′,4,4′,5,5′-hexa) and BB 180 (2,2′,3,4,4′,5,5′-hepta), did not. Fractionation of FireMaster® indicated that most activity was associated with the more polar fraction containing minor components (Needham et al., 1982). Sunlight irradiation of BB 153 also yielded products that caused severe hyperkeratosis. It is not clear whether one or more of the suspected PBBs is responsible for hyperkeratotic activity (Patterson et al., 1981). The model congener 3,3′,4,4′,5,5′-hexabromobiphenyl and 3,3′4,4′-tetrabromobiphenyl were shown to be hyperkeratotic (Table 83).

8.4 Long-term toxicity

Toxic effects of PBBs, observed after long-term exposures, as well as a long time after exposure had ceased, are summarized in Tables 84 and 85. Experimental animals tested were rats, mice, cattle, minks, and rhesus monkeys. The majority of studies refer to the commercial FireMaster® mixture.

The following comments refer mainly to the general signs of long-term toxicity. Other long-term effects will be reviewed in detail in the respective sections, e.g., carcinogenicity (section 8.7), reproductive dysfunctions (section 8.5).

Table 82. Dermal lesions observed in cattle, rhesus monkeys, and rabbits after exposure to PBBs

PBB[a]	Species	Route	Dose (duration)	Dermal lesions observed	References
FM BP-6	cattle	oral	25 g/day (for 33-60 days)	subcutaneous emphysema and haemorrhage; changes in the eyelids: hyperkeratosis, with accumulations of keratin in hair follicles of the epidermis and squamous metaplasia with keratin cysts in the tarsal glands	Moorhead et al. (1977, 1978)
FM FF-1	calf	oral	100 mg/kg body weight (up to 12 weeks)	keratitis, alopecia, hyperkeratosis involving the head, cervical and dorsal thoracic region	Robl et al. (1978)
	oral		0.1, 10, 100 mg/kg body weight (up to 12 weeks)	acanthosis, hyperkeratosis and/or dermal infiltrates of mononuclear cells (dose-dependent severity)	
FM FF-1	rhesus monkey adult (male)	in diet	25 mg/kg feed (for 25 weeks) total dose: approx. 1 g	alopecia, dry scaly skin, loss of eyelashes; generalized subcutaneous oedema, marked oedema of the eyelids; keratinization of hair follicles and sebaceous glands	Allen et al. (1978)
	juvenile (female)	in diet	25 mg/kg feed (for 50 weeks) total dose: approx. 1.5 g	moderate loss of hair including eyelashes, dry scaly skin; periorbital oedema	

Table 82 (contd).

PBB[a]	Species	Route	Dose (duration)	Dermal lesions observed	References
	juvenile (female)	in diet	300 mg/kg feed (for 137 days) total dose: approx. 6.4 g	a rather generalized loss of hair, absent eyelashes; considerable periorbital congestion and oedema; keratinization of hair follicles	Allen et al. (1978)
FM FF-1	rhesus monkey	in diet	1.5 mg/kg feed (for over 5 months) total dose: approx. 75 mg	periorbital oedema	Allen & Lambrecht (1978)
OcBB	rabbit	dermal (ear)	not specified (1 month)	erythema, exfoliation in the ear	Norris et al. (1973)
Various PBBs	rabbit	dermal (ear)	variable	hyperkeratosis in the ear	see Table 83

FM = FireMaster®; OcBB = Technical octabromobiphenyl.

Table 83. Hyperkeratotic activity of commercial PBB mixtures, the fractionated[a] FireMaster® mixture and purified PBB congeners, derived from the rabbit ear test

PBB[d]	Comments	Dose[b] (solvent)	Hyperkeratosis[c] not observed	Hyperkeratosis[c] observed	References
DeBB (Adine 0102)		200, 2000 (acetone)	x		Atochem (1990)
OcBB		not specified (chloroform)	x		Norris et al. (1973)
FM FF-1 (lot FH 7042)					
mixture itself		60 (not specified)		x	Kimbrough et al. (1977)
polar fraction		not specified (not specified)		x (+ + +)	
non-polar fraction		not specified (not specified)		x (+)	
FM BP-6					
mixture itself		6.5 µg/kg body weight (benzene-decane, 1:9)		x	Hass et al. (1978)
fraction 1 (non-polar)	containing PBBs	6.5 µg/kg body weight (benzene-decane, 1:9)		x	

Table 83 (contd).

PBB[a]	Comments	Dose[b] (solvent)	Hyperkeratosis[c] not observed	Hyperkeratosis[c] observed	References
FM FF-1 (lot FH 7042)					
mixture itself		100 (toluene)		x (+ +)	Needham et al. (1982)
less polar fractions		50-210 (toluene)	x		
more polar fraction	containing minor components of the FM mixture	185 (toluene)		x (+ + +)	
Compound 4	predominantly BB 153	5 (toluene)	x		
Compound 8	predominantly BB 180	3.3 (toluene)	x		
2,2',4,4',5,5'-hexabromobiphenyl (BB 153) (96% pure)		10 (not specified)	x		Patterson et al. (1981)

Table 83 (contd).

PBB[d]	Comments	Dose[b] (solvent)	Hyperkeratosis[c] not observed	Hyperkeratosis[c] observed	References
sunlight degradation products of BB 153	mixture of BB 153 and other PBBs (probably BB 101, BB 118 and 3,3',4,4'-tetra-bromobiphenyl)	10 (not specified)		x (+ + +)	Patterson et al. (1981)
3,3',4,4',5,5'-hexa-bromobiphenyl		0.32-9.6 (toluene)		x (+ +)	Needham et al. (1982)
3,3',4,4'-tetra-bromobiphenyl		0.245 and 0.02 (not specified)		x (+ +)	

[a] The mixture was fractioned by different methods (on Florisil: Hass et al., 1978; on alumina: Kimbrough et al., 1977; by HPLC and GC: Needham et al., 1982).

[b] Total dose in mg/rabbit ear, unless otherwise specified.

[c] (+), (+ +), (+ + +) = severity of hyperkeratosis.

[d] DeBB = technical decabromobiphenyl; OcBB = technical octabromobiphenyl; FM = FireMaster®.
BB 101 = 2,2',4,5,5'-pentabromobiphenyl; BB 118 = 2,3',4,4',5-pentabromobiphenyl; BB 153 = 2,2',4,4',5,5'-hexabromobiphenyl; BB 180 = 2,2',3,4,4',5,5'-heptabromobiphenyl.

Table 84. Long-term effects observed after exposure to PBBs by gavage

PBB[a]	Species (strain) (No.)[b]	Sex	Dosage regimen[c]	Dose[d]	Observed effects[e]	References
FM FF-1 (lot FH 7042) (in peanut oil)	rat (Sherman) (5)	male, female	single dose t.p.: 6,10,14 months	1000	liver: lipid accumulation (more pronounced in males); uroporphyrin accumulation (females); histopathological changes; neoplastic nodules; increase in relative weight	Kimbrough et al. (1977, 1978)
FM FF-1 (lot No. 1312 FT) (in corn oil)	rat (Fischer 344/N) (9)	male, female	22 doses over 30 days; t.p.: 6 months after first dose	30	liver: marked hepatotoxic effects; atypical nodules	Gupta & Moore (1979)
FM FF-1 (lot. 7042) (in corn oil)	rat (Sherman) (65)	female	single dose t.p.: 23 months	1000	liver: porphyria; neoplastic nodules; foci or altered areas; carcinoma; adenofibrosis	Kimbrough et al. (1981)
	(16)	female	single dose t.p.: 22 months	200	liver: neoplastic nodules; altered areas; multinucleated cells	
	(30)	female	12 doses over 3 weeks; t.p.: 24 months	100	liver: neoplastic nodules; foci or altered areas; carcinoma; adenofibrosis	

Table 84 (contd).

FM FF-1 (lot. FF 1312 FT) (in corn oil)	rat (Fischer) (4-10)	female	122 doses over 6 months t.p.: 6 months after first dose	0.1, 1, 3, 10	increased white blood cell and lymphocyte counts (0.1-10); decrease in body weight (3,10); decrease in thymus weight (3,10); increase in relative spleen weight (3,10); decrease in adrenal weight (10); immune alterations (3,10)	Luster et al. (1980)
FM FF-1 (lot 1312 FT) (in corn oil)	rat (Fischer 344/N) (3)	male, female	22 doses over 30 days t.p.: 120 days after first dose	30	decrease in body weight; increase in relative liver weight; decrease in relative thymus weight (F); increase in serum protein (β-globulin fraction); porphyria (F); pronounced hepatocellular alterations	Gupta et al. (1981)
2,2',4,4',5,5'-hexabromo-biphenyl (99% purity (in corn oil)	rat (Fischer 344/N)	male female	22 doses over 30 days t.p.: 120 days after first dose	16.8	increase in relative liver weight (M); minimal hepatocellular changes	
FM FF-1 (lot 7042) (in corn oil)	rat (Sherman)	male	single dose t.p.: 18 months	500	no significant effects on body and liver weight; increase in serum cholesterol and total serum phospholipids; enhancement of hepatic peroxidation; reduced retinol levels in serum and liver microsomes; reduced α-tocopherol content in microsomes (but not in serum)	Bernert, Jr et al. (1983)

Table 84 (contd).

PBB[a]	Species (strain) (No.)[b]	Sex	Dosage regimen[c]	Dose[d]	Observed effects[e]	References
FM FF-1 (lot. 1312 FT) (in corn oil)	rat (Fischer 344/N) (10)	male, female	125 doses over 6 months; i.p.: 6 months after first dose	0.1, 0.3 1, 3, 10	no effect on food consumption; dose-related decrease in body weight gain; dose-related increase in the absolute and relative liver weights (Female: 0.1-10; Male: 0.3-10); decrease in thymus weight (0.3-10); increase in spleen weight (1-10); decrease in Hb and PCV values, in MCV and MCH values (10); dose-related increase in serum cholesterol; decrease in serum thyroid hormone levels; porphyrin accumulation in liver, bone, teeth (more pronounced in Female (1-10); dose-related hepatocellular alterations; increase in white blood cell count (Female: 1-10); increase in serum GGTP (Female: 10); decrease in serum glucose (Female: 10); dose-related decrease in serum protein, primarily due to albumin (Female: 0.1-10); carcinoma in urinary bladder (Female:10); histopathological changes in the thyroid glands and kidneys (Male: 10); decrease in serum triglyceride (Male: 0.3-10)	Gupta et al. (1983a)

Table 84 (contd).

FM FF-1 (lot. 1312 FT)	rat (Fischer 344) (11-40)	male, female	125 doses over 6 months; t.p.: = up to 29 months after first dose	0.1,0.3 1, 3, 10	dose-related body weight reductionso; dose-dependent porphyrogenic effects on teeth, bones, liver (1-10); enlarged, pale, or mottled livers with necrotic foci (1-10); hepatocellular alterations (1-10); dose-dependent incidence of liver tumours and cholangiocarcinoma (higher doses); dose-dependent decline in survival time (Male: 1-10); chronic progressive nephropathy (Male: 1-10); gastric ulcers and hyperplastic gastropathy (Male: 3,10)	Gupta et al. (1983b)
FM FF-1 (lot. FF 1312 FT) (in corn oil)	mouse ($B_6C_3F_1$) (4-10)	female	122 doses over 6 months; t.p.: 6 months after first dose	10	increase in body weight; increase in relative spleen weight; slight immune alterations	Luster et al. (1980)
FM FF-1 (lot 1312 FT) (in corn oil)	mouse ($B_6C_3F_1$/N) (3)	male, female	22 doses over 30 days; t.p.: 120 days after first dose	30	no effect on food consumption; increase in relative liver weight, histopathological alterations in liver	Gupta et al. (1981)
2,2',4,4',5,5'-hexabromobiphenyl (99% purity) (in corn oil)	mouse ($B_6C_3F_1$/N) (3)	male, female	22 doses over 30 days; t.p.: 120 days after first dose	16.8	no effect on food consumption and body weight gain; increase in relative liver weight; minimal hepatocellular alterations	

Table 84 (contd).

PBB[a]	Species (strain) (No.)[b]	Sex	Dosage regimen[c]	Dose[d]	Observed effects[e]	References
FM FF-1 (lot. 1312 FT) (in corn oil)	mouse ($B_6C_3F_1$) (10)	male, female	125 doses over 6 months	0.1, 0.3, 1, 3, 10	no effect on food consumption; decrease in body weight gain (only Male: 10); increase in body weight (only Female: 10); increase in absolute and relative liver weight (Female: 0.3-10; Male: 1-10); increase in spleen weight (Female: 10); decrease in uterine weight (Female: 10); haematological alterations: dose-related increase in red blood cell count; dose-related decrease in MCV; decrease in platelet counts (Female: 3,10); leukocytosis (Female: 10); clinical chemistry changes: increase in serum levels of GGTP and SGPT (10) and alkaline phosphatase (10); decrease in serum glucose (Female: 10); dose-related hepatic porphyria (more pronounced in Female) pale and mottled livers (higher doses); dose-related microscopic changes in the liver (1-10)	Gupta et al. (1983a)

Table 84 (contd).

FM FF-1 lot. 1312 FT) (in corn oil)	mouse ($B_6C_3F_1$) (8-27)		125 doses over 6 months; t.p.: up to 30 months after first dose	0.1, 0.3, 1 ,3, 10	shortened survival time (Male: 10); hepatic porphyria (Male: 3); slight reduction in body weight (Male: 10); enlarged liver; fluid accumulation in peritoneal cavity; liver carcinoma (10); metastasis to lung (Female: 10); hyperplasia and adenoma of follicular cells of thyroid	Gupta et al. (1983b)
FM BP-6 (in gelatin capsule)	cattle (6)		daily doses for 60 days t.p.: 80-190 days after first dose	250 mg/day	no adverse clinicopathological chanages	Durst et al. (1978a)
FM BP-6 (in gelatin capsule)	cattle (No. not specified)		daily doses for 60 days t.p.: 220 days after last dose	250 mg/day	no gross or histopathological signs of toxicosis	Moorhead et al. (1978)
FM FF-1 (in gelatin capsule)	cattle (6)	female	daily doses for 158 days t.p.: 182 days after last dose	0.3	no effects on milk production, body weights, amount of food consumed; no effects on haematological and clinical chemistry and urinalysis values; (1 cow: overgrowth of hooves from day 129)	Robl et al. (1978)

Table 84 (contd).

PBB[a]	Species (strain) (No.)[b]	Sex	Dosage regimen[c]	Dose[d]	Observed effects[e]	References
FM BP-6 (in gelatine capsule)	cattle	(Female) (1-4)	daily doses for 60, 180 202 days t.p.: up to 1500 days after first dose	250 mg/day	no effect on milk production, body weight, number of infections or general injuries; increased frequencies of reproductive dysfunctions	Durst et al. (1978b) Willett et al. (1980)

[a] FM = Fire Master®.
[b] No. = number of animals.
[c] t.p. = time post-exposure.
[d] In mg/kg body weight per day, unless otherwise specified.
[e] Hb = Haemoglobin; PCV = packed cell volume; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin.

Table 85. Long-term effects of feeding PBBs to young or adult animals

PBB[a]	Species (strain) (No.)[b]	Sex	Dietary concentration (mg/kg feed)	Feeding/ observation period	Observed effects[c]	References
"Hexabromobiphenyl" (Monsanto Co., St. Louis)	rat (Sprague-Dawley) (8)	female	50	7 months	increase in relative weights of liver, ovary, and thyroid	Sepkovic & Byrne (1984)
FM BP-6	rat (Sprague-Dawley) (10)	female	1, 10, 50	5-7 months	no effect on food consumption, body weight, and relative thyroid weight; slightly elevated liver weight (10, 50); primary hypothyroidism	Byrne et al. (1987)
FM BP-6	rat (Sprague-Dawley) (10)	female	1, 5, 10, 50	5 or more months	no effect on food consumption and relative liver weight; decrease in relative adrenal weight; depression of circulating levels of adrenal cortex hormones	Byrne et al. (1988)
OcBB (Dow Chemical)	rat (Sprague-Dawley) (not specified)	male, female	0.01-1	180 days	no effect on food consumption and body weight	Norris et al. (1973)

Table 85 (contd).

PBB[a]	Species (strain) (No.)[b]	Sex	Dietary concentration (mg/kg feed)	Feeding/ observation period	Observed effects[c]	References
OcBB (Dow Chemical)	rat (Sprague-Dawley) (8)	male	100	4/22 weeks	return to normal liver weights	Lee et al. (1975a); Waritz et al. (1977)
			1000	4/22 weeks	increased liver weights; hepatocellular alterations	
OcBB (Monsanto Co., St. Louis)	rat (Sprague-Dawley) (8)	female	50	7 months	increase in relative liver weight	Sepkovic & Byrne (1984)
NoBB (Bromkal 80-9D)	mouse	male, female	100, 300	18 months	decrease in body weight (Male, Female); shortened survival time (300 mg/kg; Male); enlargement of thyroid glands (300 mg/kg; Female); decrease in triglyceride and non-esterified fatty acids; reduction of pentobarbital sleeping time (13 months); liver carcinoma (Male, Female)	Momma (1986)
FM FF-1	mink (9)	male, female	6.25	210 days (mean)	deaths; decrease in body weight; increase in relative liver and kidney weights; liver histopathology	Aulerich & Ringer (1979); Ringer et al. (1981)

Table 85 (contd).

	mink (8)	female	1-2.5	9 months	10% reduction in body weight (2.5); adverse effects on reproduction	Aulerich & Ringer (1979); Ringer et al. (1981)
FM FF-1	rhesus monkey (7)	female	0.3 (total dose: > 25 mg)	7 months-> 1 year	weight loss; sterile abscesses (2/7); reproductive dysfunctions	Allen et al. (1978); Allen & Lambrecht (1978); Lambrecht et al. (1978)
	rhesus monkey (not specified)	?	1.5 (total dose: approximately 75 mg)	> 5 months	weight loss; periorbital oedema; immunological alterations	Allen & Lambrecht (1978)
FM FF-1	rhesus monkey (adult) (1)	male	25 (total dose: approximately 1 g)	25 weeks	death; weight loss; haematological and clinical chemistry changes: decrease in PCV, cholesterol, total serum protein and albumin; increase in serum GPT activity; epidermal changes: alopecia, dry scaly skin, loss of eyelashs; keratinization of hair follicles and sebaceous glands;	Allen et al. (1978)

Table 85 (contd).

PBB[a]	Species (strain) (No.)[b]	Sex	Dietary concentration (mg/kg feed)	Feeding/observation period	Observed effects[c]	References
					oedema; generalized subcutaneous oedema and marked oedema of eyelids; enlarged heart and liver; hyperplastic gastroenteritis; severe ulcerative colitis; hypoactive seminiferous tubules; hyperplasia of bile duct epithelium	
FM FF-1	rhesus monkey (juvenile) (1)	female	25 (total dose: approximately 1.5 g)	50 weeks	no weight gain; loss of hair (including eyelashes); dry scaly skin; periorbital oedema; increase in serum GPT activity	Allen et al. (1978)
FM FF-1	rhesus monkey (juvenile)	female	300 (total dose: approximately 6.4 g)	137 days	death; weight loss; haematological and clinical chemistry changes: decrease in PCV, white blood cell count, red blood cell count, serum cholesterol, serum protein; increase in serum GPT activity	

Table 85 (contd).

					epidermal changes: loss of hair (including eyelashes); atrophy and squamous metaplasia of the sebaceous glands; keratinization of hair follicles; periorbital congestion and oedema; subcutaneous oedema; enlarged hepatocytes; hyperplastic gastroenteritis; hyperplasia of the epithelium of the bladder and of the bile ducts; focal areas of haemorrhage in the adrenal glands	
FM FF-1	rhesus monkey (adult) (3)	female	1.5 (total dose: 70 mg)	36 weeks	weight loss; decrease in serum cholesterol enlarged hepatocytes with moderate fatty infiltration (as indicated by liver biopsy)	Lambrecht et al. (1978)
	rhesus monkey (adult juvenile) (2)	male, female	25 (total dose: approximately 500 mg)	14 weeks	weight loss (Male, adult) or lack of weight gain (Female, juvenile); decrease in serum cholesterol; hyperplastic gastritis	

[a] FM = FireMaster®; OcBB = technical octabromobiphenyl; NoBB = nonabromobiphenyl.
[b] No. = number of animals.
[c] PCV = packed cell volumes.

8.4.1 Rat

8.4.1.1 Overt clinical signs, body weight changes, food intake

In rats, the low-dose, long-term feeding of FireMaster® (Byrne et al., 1987, 1988) or technical octabromobiphenyl (Norris et al., 1973) had no effect on food consumption and body weight (Table 85). Nevertheless, the fur of PBB-fed animals was slightly less dense and slightly coarser than that of control animals (Byrne et al., 1987). A dose-dependent decline in survival time (Gupta et al., 1983b), and body weight reductions or depressed rates of body weight gain as a function of time and dose (Luster et al., 1980; Gupta et al., 1981, 1983a,b) have been found in rats orally dosed with FireMaster® (Table 84); also there was no significant difference in food consumption between treated and control animals (Gupta et al., 1981, 1983a).

8.4.1.2 Haematology and clinical chemistry

Several haematological and clinical chemistry parameters were altered, some in only one sex (Table 84: Kimbrough et al., 1977; Luster et al., 1980; Bernert et al., 1983; Gupta et al., 1983a). Rats of both sexes had decreased haemoglobin and packed cell volume values (Gupta et al., 1983a), a dose-related increase in serum cholesterol (Bernert et al., 1983; Gupta et al., 1983a), and a dose-related hepatic porphyria (Gupta et al., 1983a).

8.4.1.3 Morphological changes

Most of the livers of treated rats from higher dose groups were pale or slightly yellow and mottled (Gupta et al., 1983a) and contained white necrotic foci (Gupta et al., 1983b). Porphyrin accumulation in the liver, bone, and teeth, seen as red fluorescence under UVR, was more pronounced in treated females compared with treated males (Kimbrough et al., 1977; Gupta et al., 1983a,b). After withdrawal of treatment, visual fluorescence declined slightly in the lower dose groups (1 and 3 mg FM/kg body weight), but remained the same in the 10 mg FM/kg body weight dose groups (males and females) during lifetime observation (Gupta et al., 1983a,b).

In long-term studies, an increase in the relative liver weights of rats exposed to FireMaster® or a related mixture was usually found (Kimbrough et al., 1978; Gupta et al., 1981, 1983a; Sepkovic & Byrne, 1984; Byrne et al., 1987), but in some instances (Bernert

et al., 1983; Byrne et al., 1988), there was no effect on liver weight (see Tables 84 and 85). [During a six-month exposure to FireMaster®, the increases in absolute and relative liver weights were dose-related (Gupta et al., 1983a)].

Long-term feeding of commercial octabromobiphenyl (OcBB) also caused an increase in relative liver weights (Sepkovic & Byrne, 1984; Table 85). Rats fed OcBB for 4 weeks still had increased liver weights at 18 weeks of recovery or had returned to near normal limits, depending on the concentration of OcBB in the test diet (Lee et al, 1975a; Table 85).

The only individual PBB congener tested over the long-term, namely 2,2′,4,4′,5,5′-hexabromobiphenyl, caused an increase in the relative liver weight in male rats only (Gupta et al., 1981; Table 84).

Weight changes following PBB exposure, noted in organs other than the liver, included a decrease in the thymus (Luster et al., 1980; Gupta et al., 1981, 1983a), an increase in the spleen (Luster et al, 1980; Gupta et al., 1983a), a decrease in the adrenal glands (Luster et al., 1980; Byrne et al., 1988), and an increase in the thyroid and ovary (Sepkovic & Byrne, 1984) (see Tables 84 and 85).

8.4.1.4 Histopathological changes

Hepatocellular alterations (exclusive of hepatocellular carcinomas), observed in long-term studies with FireMaster® (see Table 84), consisted mainly of enlarged hepatocytes, fatty infiltration, proliferation and disorganization of RER, single cell necrosis, multinucleated cells, microabscesses, atypical foci, and bile duct proliferation (Kimbrough et al., 1977, 1978, 1981; Gupta et al., 1981, 1983a,b).

In contrast to FireMaster®-treated rats, rats given 2,2′,4,4′,5,5′-hexabromobiphenyl over 30 days tended to recover when examined during postexposure periods (Gupta et al., 1981).

Myelin figures, induced by the feeding of technical OcBB, persisted, together with fatty changes, as late as 18 weeks after withdrawal of a test diet containing 1000 mg OcBB/kg; however, the normal morphology of RER was restored independently of the occurrence of myelin figures, after treatment was discontinued (Lee et al., 1975a).

Although there was no significant difference in the weights of the thyroid gland, slight to moderate microscopic changes were observed, primarily in male rats exposed for 6 months to 10 mg FireMaster®/kg body weight. The thyroid gland had thin, sparse, or bluish colloid with basophilic stippling and some follicles were lined with columnar epithelium and contained a few epithelial papillary projections (Gupta et al., 1983a).

The kidneys of male rats equally treated consistently showed atrophy of a few glomerular tufts with marked dilatation of Bowman's capsule, which contained amorphous eosinophilic staining material. A few glomerular tufts also appeared oedematous (Gupta et al., 1983a). Male rats, exposed to FireMaster® for 6 months (dose levels: 1-10 mg/kg body weight per day) and observed for a lifetime, showed a higher incidence of chronic progressive nephropathy than the controls. Their kidneys were characterized by eosinophilic proteinaceous casts, sclerosis and thickening of glomerular tufts and Bowman's capsule, mononuclear leukocytic infiltration, and interstitial fibrosis (Gupta et al., 1983b).

Gastric ulcers and hyperplastic gastropathy of the glandular portion of the stomach were found with significantly increased incidence in male rats held under the same conditions (dose levels: 3 or 10 mg FM/kg body weight per day). Microscopic lesions consisted of hyperplasia of the mucosal epithelium, glandular metaplasia to goblet cells, hyperchromasia, and increased mitosis (Gupta et al., 1983b).

8.4.2 Mouse

As far as it has been tested (Table 84), FireMaster® has not produced any significant effects on food consumption in mice of both sexes (Gupta et al., 1981, 1983a). Interestingly, there were increases in the body weights of female mice with long-term exposure to FireMaster®, while a decrease occurred only in males at the high dose (Luster et al., 1980; Gupta et al., 1983a,b). The high dose of FireMaster® also shortened the survival time of males (Gupta et al., 1983b). There were no significant differences in food consumption and body weight gain in mice treated with 2,2′,4,4′,5,5′-hexabromobiphenyl (Gupta et al., 1982).

A number of haematological and clinical chemistry changes have been found in mice exposed for 6 months to FireMaster® (Table 84; Gupta et al., 1983a). Hepatic porphyrin levels were

increased in a dose-related manner after a six-month exposure (Gupta et al., 1983a), but (unlike levels in rats) they tended to decrease following cessation of exposure (Gupta et al., 1983b).

Organ weight changes noted in long-term studies on mice (Table 84) consisted of an increase in liver (Gupta et al., 1981, 1983a,b) and spleen (Luster et al., 1980; Gupta et al., 1983a) weights and a decrease in uterine weights (Gupta et al., 1983a). Most of the affected mice observed for a lifetime contained serosanguineous fluid in the peritoneal cavity (Gupta et al., 1983b). The livers of mice with long-term exposure were pale and contained, primarily in males, grayish white foci (Gupta et al., 1981, 1983a).

Microscopic alterations were marked swelling of hepatocytes, foamy or vacuolated cytoplasm with hyaline bodies, focal coagulative necrosis or scattered single cell necrosis of hepatocytes, and atypical hepatocellular foci (Gupta et al., 1983a). Hyperplasia was observed in the follicular cells of thyroid (Gupta et al., 1983b).

Adverse effects (besides liver carcinoma; see section 8.7), observed after an 18-month exposure of mice to technical nonabromobiphenyl (Bromkal 80-9D), included decreases in body weight, enlargement of the thyroid gland, and biochemical alterations (Momma, 1986; Table 85).

8.4.3 *Cattle*

Except for a single animal, cattle with long-term exposure to low doses of FireMaster® FF-1 or BP-6, observed for up to 220 days post-treatment (see Table 84) did not show any adverse effects with regard to food intake, clinical signs, clinicopathological changes, or performance (Durst et al., 1978a,b; Moorhead et al., 1978; Robl et al., 1978). However, reproductive dysfunction occurred more frequently (Willett et al., 1980; see also section 8.5).

8.4.4 *Mink*

Minks were found to be very susceptible to PBB toxicity (Table 85: Aulerich & Ringer, 1979). When fed with FireMaster® for several months, they responded with food rejection, loss of weight, an unthrifty appearance, and death. Upon necropsy of animals that died, increases in relative liver and kidney weights and a fatty infiltration of the liver were evident. A relatively low

daily intake of FireMaster® by female mink had an adverse effect on their reproductive performance (see also section 8.5).

8.4.5 Rhesus monkey

Rhesus monkeys are also among the species more sensitive to FireMaster® (Table 85: Allen et al., 1978; Allen & Lambrecht, 1978; Lambrecht et al., 1978). At exposures of 1.5-300 mg FM/kg feed, they developed weight loss or a lack of weight gain, haematological and clinical chemistry changes, loss of hair, skin lesions, oedema, enlargement of the heart and liver, areas of haemorrhage in the adrenal glands; reduced spermatogenesis, and immune incompetence. Microscopic changes in the liver included enlarged hepatocytes with fatty infiltration. The most severe lesion was hyperplastic gastroenteritis and the accompanying ulcerations. Exposures to 25 or 300 mg FM/kg feed also caused death. The female monkeys fed with lower doses of FireMaster® (0.3 mg/kg diet), for over one year, did not develop any of the signs of intoxication noted above, except for weight loss. However, they were affected by reproductive dysfunctions (see also section 8.5).

8.4.6 Pre- and perinatal exposure

Long-term effects following pre- or perinatal exposure to FireMaster® have been recorded in rats and cattle.

Stunted growth, increased mortality rates, and liver tumours were observed in the offspring of Sherman rats given 200 mg FireMaster® FF-1/kg body weight on days 7 and 14 of pregnancy, when a total of 50 male and 50 female offspring per group were followed until they were 2 years old (Groce & Kimbrough, 1984). Sprague-Dawley rats (No. = 10), perinatally exposed (day 8 of pregnancy-28 days post partum) to FireMaster® BP-6 (100 mg/kg of feed) and weaned on to a PBB-free diet, had increased relative liver weights at 28 and 150, but not 328 days of age. Although the liver was not enlarged 10 months after weaning, hepatic histopathological alterations, such as cellular swelling, vacuolation, some necrosis, and eccentric and pyknotic nuclei were observed throughout this residual phase. Other long-lasting alterations were stimulation of renal and hepatic microsomal enzymes, and a reduction in the duration of anaesthesia produced by pentobarbital (McCormack et al., 1980). In a multigeneration study (McCormack et al., 1981), rats perinatally exposed to FireMaster® BP-6, as described above (F1-generation), were allowed to mature sexually

and bred with littermates to produce the F2-generation. Even these F2-animals exhibited increased relative liver weights and histopathological liver changes at 28 days of age. The light microscopic changes included vacuolation, focal necrosis, pyknotic nuclei, swelling, and myelin bodies. However, the severity of lesions was much less prominent in F2-animals than in F1-animals.

PBBs given to a single generation also produced hepatic and renal microsomal enzyme stimulation, a reduction in the duration of anaesthesia elicited by pentobarbital or a large dose of progesterone, and a decrease in the concentration of vitamin A in the liver, in both subsequent generations (F1 and F2).

Cows whose dams or granddams had received daily oral doses of FireMaster® BP-6 (up to 250 mg/day) for 60–202 days showed no general health problems, but they had conception difficulties (Willett et al., 1982).

8.5 Reproduction, embryotoxicity, and teratogenicity

Effects of PBBs on reproduction (reproductive system, overall reproductive performance, embryotoxicity, teratogenicity) have been summarized in Tables 86 and 87. Most of the studies refer to the FireMaster® mixture. Few reports deal with technical octabromobiphenyl (Aftosmis et al., 1972a; Waritz et al., 1977) or technical decabromobiphenyl (Millischer et al., 1979), and, among the individual PBB congeners, only 2,2',4,4',5,5'-hexabromobiphenyl has been evaluated by a few authors.

8.5.1 PBB mixtures

8.5.1.1 Mammals

a) Reproductive system and performance.

As listed in Tables 74 and 75, administration of FireMaster® by gavage and in the diet had no effect on the weight of male (Garthoff et al., 1977; Corbett et al., 1978a; Harris et al., 1978b, Gupta et al., 1981; Castracane et al., 1982) or female (Gupta et al., 1981) sex organs in rats and/or mice. An exception was an increase in the uterine weight of mice dosed for 6 months with FireMaster® (Gupta et al., 1983a). Testes weights in rats fed commercial OcBB also remained unaffected (Norris et al., 1973). However, there was a reduction in the ventral prostate weight-to-body weight

Table 86. Summary of effects of PBBs on reproduction (reproductive system, overall reproductive performance, embryotoxicity, teratogenicity): dosing studies

PBB	Species (No.)[b]	Exposure[c]	Dose[d]	Major effects	Remarks	References
FM BP-6	rat (Wistar) (3-15)	oral single dose one of gd 6-14 s.t.: gd 20	400, 800	reductions in fetal and placental weight; fetal death (primarily 800 mg/kg body weight per day at day 7-12); malformed (cleft palate; diaphragmatic hernia) fetuses (400 mg/kg body weight per day: 0-11.8%; 800 mg/kg body weight per day: 0-60%)		Beaudoin (1977)
FM FF-1	rat (No. not specified (15)	oral multiple doses (6) gd 6-16 at 2 day intervals s.t.: gd 19	100 (total dose: 600 mg/kg body weight	none	no effects on number of fetuses, dead implants, fetal malformation	Ficsor & Wertz (1976); Wertz & Ficsor (1978)
FM BP-6	rat (Sprague-Dawley) (6-8)	oral multiple doses gd 7-15 s.t.: gd 20	0.25-10 mg/day	reduced fetal weight and crown-rump length (only 0.25 mg/day)	no effects on implantation number of live fetuses or gross malformations	Harris et al. (1978a)

Table 86 (contd).

		s.t.: 48, 60 days of age	10 mg/day	reductions in offspring weight (from 3 days of age onwards, more pronounced in male pups); increased postnatal mortality (at weaning 14.3% versus 1.5% in control); delay in vaginal opening of female offspring	no effects on litter size and birth weight	Harris et al. (1978a)
FM BP-6	rat (Wistar) (No. not specified)	oral multiple doses gd 0-14 on alternate days	8-160 mg per animal (total dose)	reduced implantation rates (80-160 mg); fetal death	no malformed fetuses	Beaudoin (1979)
FM FF-1	rat (Fischer 344/N) (9 males)	oral multiple doses (22) over 30 days s.t.: up to 6 months	100	moribund rats: degenerative and hyperplastic changes in the ducts deferens (73 days after treatment); surviving rats: sperm granuloma in the epididymis (6 months after treatment; 1/2[e])		Gupta & Moore (1979)
			30	acute prostatitis (4/9)[e]		

Table 86 (contd).

PBB	Species (No.)[b]	Exposure[c]	Dose[d]	Major effects	Remarks	References
FM FF-1	rat (Sherman) (16)	oral multiple doses (2) gd 7 and 14 o.t.: up to Weaning (21 days of age)	200	reduction in offspring survival rate-to-weaning		Groce & Kimbrough (1984)
FM BP-6	rat (Wistar) (7)	1) *in vivo*-treatment: oral single dose gd 9 s.t.: gd 10 2) whole embryo culture: 24 h	800	inhibited rate of embryo development *in vitro* (effects on axial rotation, heart rate, neural tube closure, formation of the anterior limb buds, somite development, and establishment of visceral yolk sac circulation); reduction in DNA content; pericardial oedema		Fisher (1980); Beaudoin & Fisher (1981)
DeBB	rat (Sprague-Dawley) (25)	oral multiple doses gd 6-15 s.t.: gd 21	10-1000	none	no teratogenicity or embryotoxicity	Millischer et al. (1979)

Table 86 (contd).

2,2',4,4' 5,5'-hexa-bromobi-phenyl (purity > 97%	mouse (C.D. - 1) (up to 25)	oral multiple doses gd 10-16 s.t.: gd 19 o.t.: 4, 20 days of age	0.3-32	none	no fetotoxicity or teratogenicity; no effects on fertility, gestation, viability, survival, and lactation indices	Lucier et al. (1978)
FM BP-6	cow (6)	oral multiple doses during pregnancy for 32-60 days o.t.: up to 60 days	25 g/day	abortion (3/6)[e] or fetal death (3/6)[e]		Durst et al. (1977, 1978b); Moorhead et al. (1977)
BM BP-6	cow (3)	oral multiple doses during pregnancy for 60 days	0.25 and 250 mg/day	none		Durst et al. (1978b)
	(1)	for 180 days o.t.: up to 305 days	250 mg/day	stillbirth (due to dystocia)		

Table 86 (contd).

PBB	Species (No.)[b]	Exposure[c]	Dose[d]	Major effects	Remarks	References
FM BP-6	cow (3-5) (4 dose groups)	oral multiple doses before breeding or during late pregnancy for 60-202 days o.t.; up to 5.5 years (1-5 parturition; 2 generations)	0.25-250 mg/day	high incidence of dystocia; increased birth weights of calves; stillbirths; increased number of inseminations required for conception in 1 and 2 generation offspring	a total of 75 calves were studied; no effects on growth, development, and survival of calves born alive	Willett et al. (1980, 1982)

[a] FM = FireMaster®; DeBB = technical decabromobiphenyl.
[b] No. = Number of females, unless otherwise specified.
[c] gd = Gestation day (in rodents sperm day = gd 0, of recorded); o.t. = observation time; s.t. = sacrifice time.
[d] In mg/kg body weight per day, unless otherwise specified.
[e] No. affected/no. treated.

Table 87. Summary of PBB effects on reproduction (reproductive system, overall reproductive performance, embryotoxicity, teratogenicity): feeding studies

PBB[a]	Species (No.)[b]	Treatment[c]	Dietary concentration[d]	Major effects	Remarks	References
FM BP-6	rat (Sprague-Dawley) (6-7)	gd 7-18 s.t.: gd 20	100, 1000	decreasing fetal weight with increasing dosage	suggestion of late fetal mortality (high dose); no teratogenicity	Corbett et al. (1975)
FM BP-6	rat (Sprague-Dawley) (at least 8)	gd 8-9th week of age s.t.: 9th week of age	100	reduction in ventral prostate weight of male offspring; increased length of estrous cycle of female offspring	no effect on fetal survival rate	Johnston et al. (1980)
FM BP-6	rat (Sprague-Dawley) (8)	gd 8-Weaning s.t.: Weaning (28 days of age)	100	reduction in survival rate-to-weaning (87% of control value); delay in vaginal opening in female offspring	no effects on length of gestation, litter size, incidence of gross external anomalies, pup body weight at birth	McCormack et al. (1981)
OcBB	rat (not specified)	gd 6-15 s.t.: gd 20	100, 1000, 10 000	gastroschisis (one fetus at each level); anasarca (one fetus at each of the two highest levels)	abstract only (no information on number of fetuses examined)	Aftosmis et al. (1972a)

Table 87 (contd).

PBB[a]	Species (No.)[b]	Treatment[c]	Dietary concentration[d]	Major effects	Remarks	References
OcBB	rat (ChR-CD) (23-27)	gd 6-15 s.t.: gd 20	100, 1000, 10 000	no significant embryotoxicity or teratogenicity	gastroschisis (1/259[e]: 1000 mg/kg: 1/1/283[e] 10 000 mg/kg); anasarca (1/259[e]: 1000 mg/kg; 1/283[e]: 10 000 mg/kg); no effects on growth or viability of embryos	Waritz et al. (1977)
FM BP-6	mouse: (Swiss, ICR) (9-12)	gd 7-18 s.t.: gd 18	50, 100, 1000	dose-related decrease in fetal weight with increasing dosage; exencephaly (5/295[g]: 100, 1000 mg/kg); cleft palate (5/208[g]: all levels[g]; hydronephrosis (2/87: 1000 mg/kg)	incidence of malformations statistically significant only compared with pooled historical controls	Corbett et al. (1975, 1978b)
FM	mouse (Swiss-Webster) (No. not specified)	gd 4-16 s.t.: gd 19	100, 200	increase in number of dead or resorbed fetuses (200 mg/kg)	(abstract only)	Preache et al. (1976)
		gd 8-16 s.t.: gd 19	100, 200	decrease in fetal body weight (200 mg/kg)		

Table 87 (contd).

		gd 8-16 o.t.: up to 6 weeks of age	50, 100	reduction in number of live offspring	no effects on postnatal mortality or body weight	Preache et al. (1976)
		days 1-29 pp o.t.: up to weaning	50, 100	increased mortality; decreased body weight		
2,2',4,4'-5,5'-hexa-bromobi-phenyl (purity: > 99%)	mouse (C57BL) (2-22)	gd 6-15 o.t.: gd 17	100, 300, 500, 750, 1000	at 300 mg/kg: decrease in pregnancy rates of plug-positive mice; at ≥ 300 mg/kg: reduced fetal body weight; malformed fetuses (cleft palate combined with a "cystic brain deviation": 5/166, 3/172, 5/46, 6/17[9], respectively, at 300-1000 mg/kg; minor abnormalities of brain development); at ≥ 500 mg/kg: reduced gravid uterine weight	17-182 fetuses were examined	Welsch & Morgan (1985)
FM BP-6	pig (2-4)	2nd half of gestation and lactation o.t.: up to weaning (4 weeks)	10, 100, 200	increased mortality during lactation	no effect on litter size	Werner & Sleight (1981)

Table 87 (contd).

PBB[a]	Species (No.)[b]	Treatment[c]	Dietary concentration[d]	Major effects	Remarks	References
FM FF-1	mink (8 females; 2 males)	for 9 months (start before breeding)	1	reduced litter size; reduced kit weight at birth and at 4 weeks; increased mortality (birth to 4 weeks)	both male and female on PBB diet; no effects on breeding or gestation periods; no teratogenicity	Aulerich & Ringer (1979)
FM FF-1	rhesus monkey (7)	for over 1 year (start 7 months prior to breeding)	0.3	prolonged menstrual cycles; decreased serum progesterone levels (4/7[e] after 6 months); excessive and prolonged implantation bleeding (2/7[e]); abortion (1/7); stillbirth (1/7[e]); reduced weight of infants at birth and at weaning (4 months of age)		Allen et al. (1978, 1979); Allen & Lambrecht (1978); Lambrecht et al. (1978)
FM FF-1	rhesus monkey (1 male)	for 25 weeks	25	hypoactive seminiferous tubules (at the time of death		Allen et al. (1978)
FM BP-6	chicken (White Leghorn) (35)	for 9 weeks	20	none	no effect on hatchability	Cecil et al. (1974)

Table 87 (contd).

"PBB"	chicken (White Leghorn) (20)	for 8 weeks	5, 10, 20	none	no effects on egg production, egg weight, egg shell thickness, and fertility; no effects on hatchability, embryonal development and progeny health	Lillie et al. (1975)
FM BP-6	chicken (White Leghorn) (10)	for 8 weeks	20	increased mortality of progeny	no effects on egg production, egg weight, egg shell thickness, fertility, hatchability, and embryonic death	Cecil & Bitman (1978)
		for 4-8 weeks	64, 200, 640, 2000	reduced egg production or stop in egg production at 200-2000 mg/kg; decreased hatchability of fertile eggs; increased mortality of progeny; reduced growth rate of progeny; embryonic deaths; embryonic abnormalities (subcutaneous oedema, oedematous cysts, unabsorbed yolk)		
FM FF-1	chicken (White Leghorn) (24)	for 5 weeks	0.2-3125	decline in egg production (MEL[f]: 30-45 mg/kg); loss of egg production (> 625 mg/kg, within 2 weeks);		Polin & Ringer (1978a,b)

Table 87 (contd).

PBB[a]	Species (No.)[b]	Treatment[c]	Dietary concentration[d]	Major effects	Remarks	References
				reduced hatchability (MEL[f]: 30-45 mg/kg); dose-related increase in offspring mortality (MEL[f]: 30-45 mg/kg; embryonic oedema		
FM FF-1	chicken (10)	for 21 days	80	decline in hatchability; oedema of embryos and newly hatched chicks	no effect on fertility	Polin et al. (1979)
2,2',4,4', 5,5'-hexa-bromobiphe-nyl (purity: not specified)	chicken (10)	for 21 days	52	none	no decline in hatchability; no oedema of chicks and and embryos	

Table 87 (contd).

FM	Japanese quail (No. not specified)	for 9 weeks	10, 20, 100	at 100 mg/kg: reduced egg production (17% versus 68% in controls); no hatchability; embryonal deaths	no eggshell thinning	Babish et al. (1975a)
FM FF-1	Japanese quail (*Coturnix coturnix japonica*) (36 males, 36 females)	for 5 weeks	80	reduced egg production	fertility and hatchability not significantly different from controls	Polin et al. (1982); Bursian et al. (1983)

[a] FM = FireMaster®; OcBB = technical octabromobiphenyl.
[b] No. = Number of females, unless otherwise specified.
[c] gd = Gestation day (in rodents sperm day = gd 0, if recorded, exception: Waritz et al. (1977): sperm day = gd 1); pp = postpartum; o.t. = observed time; s.t. = sacrifice time.
[d] In mg/kg of feed, unless otherwise specified.
[e] No. affected/no. treated.
[f] MEL = Minimum effective level.
[g] As reported by Corbett et al. (1978a).

ratio in pubescent male rats (Johnston et al., 1980; Table 87) and a delay in vaginal opening in female rats after perinatal exposure to FireMaster® (Harris et al., 1978a; McCormack et al., 1981; Tables 86 and 87). Both findings may suggest retarded sexual maturation.

Male rats, moribund from multiple doses of FireMaster®, exhibited degenerative and hyperplastic changes in the ductus deferens (hyperplasia and squamous metaplasia with keratinization in the epithelial lining of the ductus deferens). However, such changes were not observed in surviving male rats, examined six months after the treatment. Lesions found in surviving animals were acute prostatitis (30 mg/kg body weight per day) and the presence of sperm granuloma in the epididymis (100 mg/kg body weight per day) (Gupta & Moore, 1979; Table 86). A rhesus monkey, exposed to FireMaster® in the diet, had hypoactive seminiferous tubules at death (Allen et al., 1978; Table 87). Little work was done on the possible impairment of spermatogenesis. Young bulls may develop testicular atrophy and reduced spermatogenesis when exposed to FM (Robl et al., 1978), but more numerous controlled studies are needed.

The estrous cycle of cows (No. = 8) was not affected during administration of FireMaster® FF-1 (0.3 mg/kg body weight per day) for 158-228 days and during a recovery period of 112-182 days (Robl et al., 1978).

The estrous cycle of female rats was increased in length after perinatal and subsequent dietary exposure to FireMaster® BP-6 (Johnston et al., 1980; Table 87) at concentrations of 100 mg/kg (equivalent to 5 mg/kg body weight per day). Prolonged menstrual cycles were seen in rhesus monkeys after consuming FireMaster® FF-1 for six months at a concentration of 0.3 mg/kg (equivalent to 0.02 mg/kg body weight per day). This alteration was correlated with decreased serum progesterone levels (Allen et al., 1978; Lambrecht et al., 1978; Table 87).

The number of inseminations required for conception was increased in cows whose dams or grand dams had received oral doses of FireMaster® BP-6 (Willett et al., 1982; Table 86).

Most of the studies evaluating the effects of PBBs on reproductive performance started with treatment during pregnancy (Tables 86 and 87). In few instances, were females exposed before mating (Allen et al., 1978; Aulerich & Ringer, 1979; Willett et al.,

1980, 1982), and animals of both sexes were treated in only one study (Aulerich & Ringer, 1979). Under these conditions, FireMaster® reduced litter size in mice (Preache et al., 1976) and minks (Aulerich & Ringer, 1979), but not in rats (Harris et al., 1978a; McCormack et al., 1981) and pigs (Werner & Sleight, 1981). The adverse effect on litter size was observed in minks given PBB-contaminated poultry as well as in those fed FireMaster®, directly added to the diet (Aulerich & Ringer, 1979). Stillbirths occurred in cattle (Durst et al., 1978b; Willett et al., 1982) and rhesus monkeys (Allen et al., 1978; Lambrecht et al., 1978). Reduced birth weights were reported in rhesus monkeys (Allen et al., 1978; Lambrecht et al., 1978), minks (Aulerich & Ringer, 1979), and mice (Corbett et al., 1978b) at intakes of 0.3, 1, or 50-1000 mg FireMaster®/kg feed, respectively (see Table 87). On the other hand, increased birth weights of calves resulted in a higher incidence of dystocia in cows (Durst et al., 1978b; Willett et al., 1980, 1982). The growth of progeny during lactation (indicated by weight at weaning) was also reduced by FireMaster® in rats (Harris et al., 1978a), mice (Preache et al., 1976), minks (Aulerich & Ringer, 1979), and rhesus monkeys (Allen et al., 1978; Lambrecht et al., 1978).

In the study by Lambrecht et al. (1978), 14 female rhesus monkeys were used as an animal model (7 controls, 7 treated) to evaluate the toxicological effects of FM FF-1. The substance was added to the pelleted diet at a concentration of 0.3 mg/kg and 200 g of this diet was fed per day; after a dosing period of 7 months, the animals had ingested a total of 10.5 mg FM FF-1. Although the food consumption during this period was unaffected, there was a loss of 7.4% of the initial body weight in the treated group. The total exposure is not stated, but, on the basis of information given in the paper, it appears that the dams had been exposed for a total of 12.5 months at the time of the birth of the infants. After 6 months, menstrual cycles in 4/7 monkeys were lengthened (controls: 28 days; treated monkeys: 31 days). The treated animals showed a corresponding flattening of the progesterone peak. After mating, 5/7 treated monkeys delivered normal-appearing but small infants (455 g vs 519 g in controls) with reduced weight gain in these infants during the postnatal period. Two out of 7 treated monkeys aborted a mummified fetus and a stillborn infant, respectively. All control animals delivered normal-appearing infants.

The survival rate-to-weaning was adversely affected in the offspring of rats, mice, pigs, and minks, but not in calves (see

Tables 86 and 87). FireMaster® levels producing the effects were 200 mg/kg body weight per day (Groce & Kimbrough, 1984), or 10 mg/day (Harris et al., 1978a), or 100 mg/kg feed (McCormack et al., 1981) in rats, 100 mg/kg feed in mice (Preache et al., 1976) and pigs (Werner & Sleight, 1981), and 1 mg/kg feed in minks (Aulerich & Ringer, 1979).

For neurotoxic effects after perinatal exposure see section 8.11.2.

Ranges of maternal toxic parameters can be derived from Tables 71, 72, 74, and 75.

b) Embryotoxicity and teratogenicity

PBBs were embryotoxic in rats, mice, cattle, and rhesus monkeys. Rats and cows appeared to be less susceptible than mice and rhesus monkeys (see Tables 86 and 87).

Treatment of rats with a single high dose of FireMaster® (> 400 mg/kg body weight) on day 6 of pregnancy resulted in 100% embryo resorption. Generally, the number of fetal resorptions depended on the dose and the pregnancy stage at treatment. For example, after day 8 (400 mg/kg body weight dose) or day 12 (800 mg/kg body weight dose), the embryolethal effect of FireMaster® declined abruptly (Beaudoin, 1977). Reductions in both fetal and placental weights were observed only at high doses (> 400 mg/kg body weight), and the most susceptible period of pregnancy was days 11-13 (Beaudoin, 1977).

The long-term administration of lower doses (total dose: 8 or 40 mg FireMaster®/animal) during pregnancy (from day 0) markedly increased embryonic death over that seen following administration of an equivalent single dose (Beaudoin, 1979). However, long-term intake of relatively low doses (see Tables 86 and 87) during late gestation (start: day 7) did not influence fetal survival rate (Corbett et al., 1975; Harris et al., 1978a; Johnston et al., 1980), but decreased fetal weight (Corbett et al., 1975; Harris et al., 1978a). A total dose of 600 mg FireMaster®/kg body weight, given at two-day intervals (start: day 6) had no effects on fetal death or fetal weight (Wertz & Ficsor, 1978).

No significant effects on the growth or mortality of embryos were noted after the exposure of rats (Tables 86 and 87) to technical octabromobiphenyl (Waritz et al., 1977) or technical

decabromobiphenyl (Millischer et al., 1979). Single cases of fetal oedema have been observed in OcBB-treated rats (Aftosmis et al., 1972a; Waritz et al., 1977).

The incidence of dead or resorbed fetuses was increased in mice fed 200 mg FireMaster®/kg feed on days 4-16 of pregnancy (Preache et al., 1976). Feeding several concentrations of FM from day 7 (Corbett et al., 1975) or day 8 (Preache et al., 1976) of pregnancy reduced fetal weight (Table 87).

Cattle given 25 g FM/day had 3 abortions and 3 dead fetuses from 6 treated animals (Durst et al., 1977; Table 86). The fetuses were oedematous and haemorrhagic, concomitant uterine lesions were haemorrhage and necrosis of the cotyledons (Moorhead et al., 1977).

Two out of 7 rhesus monkeys fed FM (Table 87) had long implantation bleedings, one aborted a mummified fetus at 146 days of gestation and one gave birth to a stillborn infant at 154 days. The remaining 5 monkeys delivered small infants at 156-165 days of gestation (normal gestation: 165 days) (Allen et al., 1978; Lambrecht et al., 1978).

Terata due to PBB exposure have been reported only in rats and mice (Tables 86 and 87). A single high dose of FireMaster® produced cleft palate and diaphragmatic hernia in rats (Beaudoin, 1977). The majority of malformations were found following administration of 800 mg/kg body weight on day 11, 12, or 13 of gestation. No terata were noted in rats after multiple doses of FireMaster® (Table 86) (Harris et al., 1978a; Wertz & Ficsor, 1978; Beaudoin, 1979) and after feeding diets containing up to 1000 mg FireMaster®/kg feed (Corbett et al., 1975). In contrast to rats comparably treated (50-1000 mg FM/kg maternal diet), a higher incidence of exencephaly and cleft palate was seen in fetal mice, compared with pooled historical controls, but not compared with concurrent controls, though neither of these anomalies was seen in control fetuses (Corbett et al., 1975, 1978b).

It is unclear whether the few cases of fetal gastroschisis, observed in rats fed technical OcBB (Table 87), are PBB-related or fortuitous (Aftosmis et al., 1972a; Waritz et al., 1977). No teratogenicity was found in rats exposed to DeBB (Millischer et al., 1979; Table 86).

Embryo development was studied *in vitro*. Maternal rats received a single, oral dose of 800 mg FM/kg body weight on

gestation day 9, and the embryos were isolated on day 10 (24 h post-treatment) for cultivation over a 24- or 42-h period (Fisher, 1980; Beaudoin & Fisher, 1981). Teratogenic effects observed (see Table 86) were not correlated with types of malformations found in earlier *in vitro* experiments (Beaudoin, 1977). Some developmental disturbances tended to be corrected after 42 h of PBB-free culture. In addition to retarded development, there was a significant reduction in the DNA contents of cultured embryos (Fisher, 1980). The survival rate of embryos was not affected during the cultivation period (Beaudoin & Fisher, 1981).

8.5.1.2 *Avian species*

Avian reproduction was studied primarily in chickens. Cockerels fed FM at various levels (10-250 mg/kg feed), for several weeks, showed inconsistent weight changes in the comb and testes (see Table 75; Ringer & Polin, 1977; Ringer, 1978; Dharma et al., 1982). Histologically, lipid infiltration into testicular parenchyma was noted (Ringer & Polin, 1977). No studies on the reproductive performance of these birds were made.

Detrimental effects were seen when FireMaster® was fed to hens of both White Leghorn chickens and Japanese quails, the only two species studied (Table 87). Chickens (Cecil et al., 1974; Lillie et al., 1975; Cecil & Bitman, 1978; Polin & Ringer, 1978a,; Polin et al., 1979) appeared to be more sensitive to FireMaster® than the Japanese quails (Babish et al., 1975a; Bursian et al., 1983), on the basis of egg production and hatchability. Egg production in chickens was reduced by dietary levels of FireMaster® as low as 30-45 mg/kg (Ringer & Polin, 1977), while the lowest effective level reported for Japanese quails was 80 mg/kg (Bursian et al., 1983). Chickens stopped laying when concentrations of FireMaster® in diets exceeded 600 mg/kg (Cecil & Bitman, 1978). The hatchability of eggs was adversely affected by 30-45 mg FireMaster®/kg feed in chickens (Ringer & Polin, 1977) and by 100 mg FireMaster®/kg feed in Japanese quails (Babish et al., 1975a).

Increased mortality (Cecil & Bitman, 1978; Polin & Ringer, 1978a, 1978b) and reduced growth rates (Cecil & Bitman, 1978) were seen in the offspring of chickens fed FireMaster® at low levels (< 64 mg/kg; Table 87).

Embryonic deaths occurred in chickens (Cecil & Bitman, 1978; 50% of deaths on the last day of incubation) and in Japanese quails

(Babish et al., 1975b; 40% of deaths on the first day or two of development). The most common abnormality of embryos and newly hatched chicks after maternal feeding of FireMaster® was oedema (Cecil & Bitman, 1978; Polin & Ringer, 1978b; Polin et al., 1979).

Although there was a reduction in the feed intake of exposed chickens, the decreased hatchability, higher incidence of abnormalities, and poorer progeny survival could not be reproduced by pair-fed control birds (Cecil & Bitman, 1978). At high dietary levels (> 600 mg FM/kg of feed), the direct effects of FireMaster® on egg production could not be separated from the effects of reduced food consumption (Cecil & Bitman, 1978).

Adverse effects on the reproduction of chickens could return to normal after withdrawal of FireMaster® from the diet. Time for recovery depended on the concentration of PBB in the feed (Cecil & Bitman, 1978; Polin & Ringer, 1978a).

8.5.2 *Individual PBB congeners*

Individual PBB congeners have not been reported to cause weight changes in sex organs. Similarly, the testes of rats or cockerels, did not show any remarkable histological changes after treatment with 2,2′-dibromobiphenyl, 2,2′,3,4,4′,5,5′-heptabromobiophenyl, 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153), 2,3′,4,4′,5,5′ (BB 167), or 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) (Moore et al., 1979a; Gupta et al., 1981; Akoso et al; 1982a; Dharma et al., 1982; Render et al., 1982). An exception was a decrease in the gravid uterine weight of pregnant mice given more than 500 mg BB 153/kg body weight (Welsch & Morgan, 1985).

Embryotoxicity and other reproductive parameters have been studied only with BB 153 mice (Lucier et al., 1978; Welsch & Morgan, 1985) or chickens (Polin et al., 1979). BB 153 did not cause the deleterious effects (decline in hatchability, oedema) that were produced by equivalent dietary levels of FireMaster® in chickens (Polin et al., 1979; Table 87). However, BB 153 was capable of producing cleft palate and cystic lesions in the region of the cerebellum in mouse embryos (Welsch & Morgan, 1985; Table 87). These adverse effects were observed at exposure concentrations that also cause toxicity in dams. Another less complete study (Lucier et al., 1978; Table 86) did not find developmental toxicity of BB 153 in mice, possibly because of lower exposure levels, later onset of exposure, and strain differences.

8.6 Mutagenicity and related end-points

The potential of PBBs for mutagenicity has been tested with several *in vitro* and *in vivo* assays referring to four major test categories: microbial and mammalian cell mutagenesis; mammalian cell chromosomal damage (cytogenetic tests; *in vitro* and *in vivo*); mammalian cell transformation *in vitro*; and DNA damage and repair (UDS). Results have been summarized in Table 88. With one exception (Kohli et al., 1978), all studies failed to indicate any mutagenicity of individual PBB congeners or commercial PBB mixtures. Haworth et al. (1983) did not confirm the mutagenic effect of 4-bromobiphenyl observed by Kohli et al. (1978), but they used different *Salmonella* strains.

However, FireMaster® gave positive results in a recently developed test, the Microscreen assay using lambda prophage induction in *Escherichia coli*. This test has been found to be sensitive in detecting carcinogens which are negative in mutagenesis assays (Rossman et al., 1991).

8.7 Carcinogenicity

8.7.1 Carcinogenicity in long-term toxicity studies

The carcinogenic effects of PBB in long-term toxicity studies have been compiled in Table 89. From this table, it is evident that the principal site of tumours was the liver. The incidence of hepatocellular carcinoma was significantly increased in both sexes of mice and rats receiving relatively high oral doses of the FireMaster® mixture.

The results of one of these studies (Gupta et al., 1983b), carried out by the NCI/NTP (USA), were interpreted as FireMaster® showing carcinogenic effects (Haseman et al., 1984; Tennant et al., 1986). In this study, a statistically significant higher incidence of liver tumours was found at multiple doses of 3 mg FM/kg body weight per day (male rats: 21%) and of 10 mg FM/kg body weight per day (female/male rats: 35/23%; female/male mice: 88/95%). Atypical foci and neoplastic nodules were found at lower doses (Table 89). Dose-responses were statistically significant ($P < 0.01$) in male and female rats with regard to atypical foci, hepatocellular carcinoma, and cholangiocarcinoma, and, in female rats, also with regard to neoplastic nodules (Gupta et al., 1983b). Hepatocellular carcinoma could be produced, even after single dosing with FireMaster® (Kimbrough et al., 1981). Rats given a single dose of

Table 88. Summary of PBB genetic toxicity test results

Assay	Details[b]	Metabolic activation	PBB[a]	Result	Remarks	References
Salmonella mutagenesis						
S. typhimurium	strains: TA 98 TA 100 TA 1535 TA 1537	± Aroclor 1254 induced liver S-9 from rats and Syrian hamsters	FM FF-1	- - - -		Tennant et al. (1986)
S. typhimurium	strains: TA 98 TA 100 TA 1535 TA 1537	± Aroclor 1254 induced liver S-9 from rats and and Syrian hamsters	hexabromo-biphenyl[c]	- - -		Haworth et al. (1983)
S. typhimurium (spot test; Ames)	strains: TA 1535 TA 1537 TA 1538	± Aroclor induced rat liver S-9	DeBB	- - -		Millischer et al. (1979)
S. typhimurium (host-mediated assay)	strain: TA 1538	-	DeBB	-	mice receiving oral doses of 5, 10, and 20 g/kg body weight	

Table 88 (contd).

Assay	Details[b]	Metabolic activation	PBB[a]	Result	Remarks	References
S. typhimurium	strains: TA 98 TA 100 TA 1535 TA 1537	± Aroclor 1254 induced liver S-9 from rats and Syrian hamsters	2-bromobiphenyl	- - - -		Haworth et al. (1983)
S. typhimurium	strains: TA 98 TA 100 TA 1535 TA 1537	± Aroclor 1254 induced liver S-9 from rats and Syrian hamsters	3-bromobiphenyl	- - - -		
S. typhimurium	strain: TA 1538	+ Aroclor 1254 induced rat liver S-9	4-bromobiphenyl[d]	+		Kohli et al (1978)
		none		-		
S. typhimurium	strains: TA 98 TA 100 TA 1535 TA 1537	± Aroclor 1254 induced liver S-9 from rats and Syrian hamsters	4-bromobiphenyl[e]	-		Haworth et al. (1983)
Mammalian cell mutagenesis						
Adult rat liver (ARL) epithelial cells	HGPRT locus	none	FM FF-1 (lot No. 1312-FS)	-	at the highest non-toxic dose of 10^{-3} mol	Tong et al. (1983); Williams et al. (1984)

Table 88 (contd).

Human fibroblasts	HGPRT locus	rat hepatocytes	FM FF-1 (lot No. 1312-FS)	-	at the highest non-toxic dose of 10^{-4} mol	
Chinese hamster V 79 cells	HGPRT and Na-K ATPase loci	± Aroclor 1254 induced rat liver S 15	FM BP-6	-	cell survival unaffected (1-40 µg/ml)	Kavanagh et al. (1985)
Chinese hamster V 79 cells	HGPRT locus	± Aroclor 1254 induced rat liver S 15	3,3',4,4'-tetrabromobiphenyl	-	cell survival unaffected (1-10 µg/ml)	
Chinese hamster V 79 cells	HGPRT locus	none	2,2',4,4',5,5'-hexabromobiphenyl	-	reduced cell survival (20-50 µg/ml)	
WB rat liver cells	HGPRT locus	-	2,2',4,4',5,5'-hexabromobiphenyl	-	growth stimulation effects (5-20 µg/ml)	
Chinese hamster V 79 cells	HGPRT locus	none	3,3',4,4',5,5'-hexabromobiphenyl	-	reduced cell survival (7-12 µg/ml)	
WB rat liver cells	HGPRT locus	-	3,3',4,4',5,5'-hexabromobiphenyl	-	reduced cell survival	

Table 88 (contd).

Assay	Details[b]	Metabolic activation	PBB[a]	Result	Remarks	References
Mammalian cell chromosomal damage in vitro						
Chromosome aberrations	CHO cells	± Aroclor 1254 induced rat liver S-9	FM FF-1	-		Tennant et al. (1986)
Sister chromatid exchange	CHO cells			-		
Chromosome aberrations	CHO cells	± Aroclor 1254 induced rat liver S-9	hexabromobiphenyl	-		Galloway et al. (1987)
Sister chromatid exchange	CHO cells			?[f]		
Mammalian cell chromosomal damage in vivo (Cytogenetic effects)						
Chromosome aberrations	bone marrow cells rat (pregnant) six oral doses of 100 mg/kg body weight	-	FM	-	colchicine-mitosis synergism	Ficsor & Wertz (1976)

Table 88 (contd).

Chromosome aberrations	bone marrow cells mouse (male) single dose of 50 or 500 mg/kg body weight	-	FM	-	no colchicine-mitosis synergism; increase in no. of gaps	Wertz & Ficsor (1978)
Chromosome aberrations	bone marrow cells; spermatogonial cells	-	FM BP-6	-		Garthoff et al. (1977)
No. of cells in mitosis	rat (male) in diet for 5 weeks: 5-500 mg/kg feed					
Micronucleus	bone marrow cells mouse (male and female) total dose of 5, 10, or 20 g/kg body weight at 2 doses		DeBB	-		Millischer et al. (1979)
Mammalian cell transformation in vitro						
Transformation	mouse Balb/c 3T3 cells	± non-induced male F 344 rat hepatocytes	FM FF-1	-		Tennant et al. (1986)

Table 88 (contd).

Assay	Details[b]	Metabolic activation	PBB[a]	Result	Remarks	References
DNA damage and repair (in vitro)						
Unscheduled DNA synthesis (UDS)	hepatocyte primary cultures (HPCs) from rat, hamster, and mouse	-	FM FF-1	-	at the highest nontoxic doses of 10^{-3} mol (mice, hamsters) or 10^{-5} mol (rats)	Tong et al. (1983); Williams et al. (1984)
DNA damage and repair (in vivo - in vitro)						
UDS	hepatocyte primary cultures (HPCs) from treated male F 344 rats	-	FM FF-1	-		Tennant et al. (1986)
UDS	hepatocyte primary cultures (HPCs) from treated B6C3F1 mice (males and females)	-	FM FF-1	-	simultaneous measurement of hepatic cell proliferative ability: increased cell proliferation	Mirsalis et al. (1985)

[a] Commercial PBB mixtures: FM = FireMaster®; DeBB = decabromobiphenyl.
[b] HGPRT = hypoxanthine-guanine phosphoribosyl transferase.
[c] CAS No.: 36355-01-8; source: Pfaltz & Bauer.
[d] Source of PBB: Aldrich & Eastman Chemicals.
[e] Source of PBB: Pfaltz & Bauer.
[f] There was a very slight (16%) increase in SCEs without S-9 doses that produced severe cell cycle delay.

Table 89. Summary of carcinogenic effects of PBBs in long-term toxicity studies

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
FM FF-1 (lot no. 7042) (in peanut oil)	rat (Sherman) (5)	F, M	oral single dose	1000	10 months 14 months	liver: neoplastic nodules (preliminary study) (F: 4/5; M: 0/5); (F: 3/5; M: 2/5); (control: 0/5)	Kimbrough et al. (1977, 1978)
FM FF-1 (lot no. 7042) (in corn oil)	rat (Sherman) (65)	F	oral single dose	1000	23 months	liver: trabecular carcinoma (24/58 = 41.4% versus 0% in control) neoplastic nodules (42/58 = 72.4% versus 0% in control) foci or altered areas (57/58 = 98.3% versus 1/53 in control)	Kimbrough et al. (1981)
	(16)			200	18-22 months	liver: no carcinoma neoplastic nodules (5/16 = 31.2% versus 0% in control) altered areas (8/16 = 50% versus 1/19 in control)	
FM BP-6 (in corn oil)	rat (Sprague-Dawley)	F	oral two doses over 24 h	total dose: 13 and 130 mg/kg body weight	120 days	liver: small numbers of enzyme altered foci (EAF)	Rezabek et al. (1987)

Table 89 (contd).

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
FM FF-1 (lot no. 1312 FT) (in corn oil)	rat (Fischer 344/N) (9)	M	oral 22 doses over 4.5 weeks	30 100	6 months (after 1 dose)	liver: atypical nodules (2/9) liver: atypical nodules (1/2) epididymis: sperm granuloma (1/2)	Gupta & Moore (1979)
FM FF-1 (lot no. 7042) (in corn oil)	rat (Sherman) (30)	F	oral 12 doses over 4 months	100	24 months	liver: trabecular carcinoma (17/28 = 60.7% versus 0% in control) neoplastic nodules (24/28 = 85.7% versus 1/25 in control) foci or altered areas (23/28 = 82.1% versus 1/25 in control) adenocarcinoma (1/28 = 3.6% versus 0% in control) malignant tumour with metastases to heart (1/28 = 3.6% versus 0% in control) Total malignant liver tumours: 19/28 (67.8% versus 0/25 in controls)	Kimbrough et al. (1981)

Table 89 (contd).

FM FF-1 (lot no. 1312 FT) (in corn oil)	rat (Fischer 344/N) (51)	F, M	oral 125 doses over 6 months	0.1, 0.3, 1, 3, 10	6 months (after 1 dose)	liver: atypical foci (3/100); urinary bladder: squamous cell carcinoma (F: 1/51, high dose	Gupta et al. (1983a)
FM FF-1 (lot no. 1312 FT) (in corn oil)	rat (Fischer 344/N) (total: 320)	F, M	oral 125 doses over 6 months (sacrifice of 10% animals alive, 23 months post-treatment)		lifetime		Gupta et al. (1983b)
		F, M		0.1		liver: atypical foci (M: 3/39 = 8%; F= 0/21) neoplastic nodules (M: 0/39; F: 2/21 = 10%) carcinoma (M: 2/39 = 5%; F: 0/21)	
				0.3		liver: atypical foci (M: 12/40 = 30%, $P < 0.01$; F: 1/21 = 5%) neoplastic nodules (M: 1/40 = 2%; F: 0/21) carcinoma (M: 0/40; F: 0/21)	

Table 89 (contd).

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
FM FF-1 (lot No. 1312 FT) (in corn oil)	rat (Fischer 344/N (total: 320)	F, M		1		liver: atypical foci (M: 11/31 = 35%, $P < 0.01$; F: 2/11 = 18%) neoplastic nodules (M: 4/31 = 13%, $P < 0.05$; F: 2/11) carcinoma	Gupta et al. (1983b)
				3		liver: atypical foci (M: 13/33 = 39%, $P < 0.01$; F: 4/19 = 21%) neoplastic nodules (M: 4/33 = 12%; F: 5/19 = 26%, $P < 0.01$) carcinoma (M: 7/33 = 21%, $P < 0.01$; F: 3/19 = 16%)	
				10		liver: atypical foci (M: 12/31 = 39%, $P < 0.01$; F: 8/20 = 40%, $P < 0.01$ neoplastic nodules (M: 1/31 = 3% F: 8/20 = 40%, $P < 0.01$ carcinoma (M: 7/31 = 23%, $P < 0.01$; F: 7/20 = 35%, $P < 0.01$; control: 0/33) cholangiocarcinoma (M: 2/31 = 6 %, F: 7/20 = 35%, $P < 0.01$)	

Table 89 (contd)

FM FF-1 (lot 7042) (in corn oil)	rat (Sherman) (41-51)	F, M	perinatal exposure: two maternal oral doses on gestation days 7 and 14	total dose: 400 mg/kg body weight	2 years of age	liver: neoplastic nodules (M: 2/41 = 4.9%, F: 9/51 = 17.6%) trabecular carcinoma (M: 4/41 = 9.6%; F: 3/51 = 5.9%; controls: 0%)	Groce & Kimbrough (1984)
FM FF-1 (lot FF 1312-FT)	rat (Fischer 344/N) (50)	F, M	adult only exposure (in diet for 24 months)	0	24 months	liver: eosinophilic focus (M: 36%; F: 6%) oval cell hyperplasia (M: 0%; F: 0%) hepatocellular adenoma (M 2%: F: 0%) hepatocellular carcinoma (M: 0%; F: 0%)	NTP (1993)
				10		liver: eosinophilic focus (M: 90%, p < 0.01; F: 94%, $P < 0.01$) oval cell hyperplasia (M: 22%, $P < 0.01$; F: 24%, $P < 0.01$) hepatocellular adenoma (M: 20%; F: 20%) hepatocellular carcinoma (M: 4%; F: 4%) hepatocellular adenoma/carcinoma (M: 24%, $P < 0.001$; F: 24%, $P < 0.001$)	

Table 89 (contd).

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
				30		liver: eosinophilic focus (M: 92%, $P < 0.01$; F: 96%, $P < 0.01$) oval cell hyperplasia (M: 74%, P 0.01; F: 84%, $P < 0.01$) hepatocellular adenoma (M: 76%, $P < 0.001$; F: 76%, $P < 0.001$); hepatocellular carcinoma (M: 38%, $P < 0.001$; F: 8%) hepatocellular adenoma/carcinoma (M: 82%, $P < 0.001$; F: 78%, $P < 0.001$)	NTP (1993)
FM FF-1 (lot FF-1312-FT)	rat (Fischer 344/N) (50)	F, M	perinatal only exposure (female parents received FM-containing diet beginning 60 days prior to breeding and throughout gestation, lactation, and up to 4 weeks postweaning)	10	24 months	liver: eosinophilic focus (M: 58%, $P < 0.01$; F: 38%, $P < 0.01$) hepatocellular adenoma (M: 10%; F: 0%)	

Table 89 (contd).

FM FF-1 (lot FF1312-FT)	rat (Fischer 344/N) (50)	F, M	combined peri-natal and adult exposure	1:3[e]	24 months	liver: eosinophilic focus (M: 80%; F: 38%) oval cell hyperplasia (M: 8%; F: 0%) hepatocellular adenoma (M: 6%; F: 4%) hepatocelluar carcinoma (M: 2%; F: 0%)	NTP (1993)
				10:10[f]	24 months	liver; oval cell hyperplasia (M: 46% versus 22% in 10 mg/kg adult exposure group, $P < 0.01$ F: 68% versus 24% in 10 mg/kg adult exposure group, $P < 0.01$) hepatocellular adenoma (M: 32% versus 20% in 10 mg/kg adult exposure group; F: 70% versus 20% in 10 mg/kg adult exposure group) hepatocellular carcinoma (M: 2% versus 4% in 10 mg/kg adult exposure group; F: 16% versus 4% in 10 mg/kg adult exposure group) hepatocellular adenoma/carcinoma (M: 32% versus 24% in 10 mg/kg adult exposure group; F: 78% versus 24% in 10 mg/kg adult exposure group, $P < 0.001$)	

Table 89 (contd).

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
				10:30[g]	24 months	liver: oval cell hyperplasia (M: 82% versus 74% in 30 mg/kg adult exposure group; F: 88% versus 84% in 30 mg/kg adult exposure group) hepatocellular adenoma (M: 76% versus 76% in 30 mg/kg adult exposure group F: 90% versus 76% in 30 mg/kg adult exposure group) hepatocellular carcinoma (M: 46% versus 38% in 30 mg/kg adult exposure group F: 44% versus 8% in 30 mg/kg adult exposure group, $P < 0.01$)	NTP (1993)
FM FF-1 (lot no. 1312 FT) (in corn oil)	mouse (B6C3F1) (50)	F, M	oral 125 doses over 6 months	10	6 months	liver: atypical foci (11/100 versus 1/20 in control) (M: 9/50; F: 2/50)	Gupta et al. (1983a)

Table 89 (contd).

FM FF-1 (lot no. 1312 FT) (in corn oil)	mouse (B6C3F1) (8-27)	F, M	oral 125 doses over 6 months (sacrifice of 10% animals alive 24 months post-treatment)	0.1, 0.3, 10	lifetime	high dose: liver: carcinoma (M: 21/22 = 95% versus 12/25 in control; $P < 0.01$; F: 7/8 = 88% versus 0/13 in control; $P < 0.01$) metastasis to lung (F: 3/8 = 38% versus 0/13 in control; $P < 0.05$)	Gupta et al. (1983b)
FM FF-1 (lot FF1312-FT)	mouse (B6C3F1) (50)	F, M	adult only exposure (in diet for 24 months)	0	24 months	liver: eosinophilic focus (M: 6%; F: 2%) bile duct hyperplasia (M: 0%; F: 0%) hepatocellular ademona (M: 18%; F: 8%) hepatocellular carcinoma (M: 16%; F: 2%)	NTP (1993)
				10		liver: eosinophilic focus (M: 33%, $P < 0.01$; F: 36%, P < 0.01) bile duct hyperplasia (M: 8%, < 0.01; F: 18%, $P < 0.01$) hepatocellular adenoma (M: 98%, $P < 0.01$; F: 78%, $P < 0.01$) hepatocellular carcinoma (M: 61%, $P < 0.01$; F: 44%, $P < 0.01$ hepatocellular adenoma/carcinoma (M: 98%, $P < 0.001$; F: 84%, $P < 0.001$)	

Table 89 (contd).

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
				30		liver: eosinophilic focus (M: 12%, F: 8%); bile duct hyperplasia (M: 68%, *P* 0.01; F: 81%, *P* < 0.01) hepatocellular adenoma (M: 84%, *P* < 0.001; F: 96%, *P* < 0.001); hepatocellular carcinoma (M: 72%, *P* < 0.001; F: 73%, *P* < 0.001) hepatocellular adenoma/carcinoma (M: 96%, *P* < 0.001; F: 98%, *P* < 0.001)	NTP (1993)
FM FF-1 (lot FF-1312-FT)	mouse (B6C3F1) (50)	F, M	perinatal only exposure (female parents received FM-containing diet beginning 60 days prior to breeding and throughout gestation, lactation, and up to 4 weeks postweaning)	30	24 months	liver: eosinophilic focus (M: 40%, *P* < 0.01; F: 6%, *P* < 0.01) hepatocellular adenoma (M: 62%, *P* < 0.001; F: 38%, *P* < 0.001) hepatocellular carcinoma (M: 34%, F: 8%) hepatocellular adenoma/carcinoma (M: 80%, *P* < 0.001; F: 42%, *P* < 0.001)	NTP (1993)

Table 89 (contd).

FM FF-1 (lot FF 1312-FT)	mouse (B6C3F1) (50)	F, M	combined perinatal and adult exposure	10:10[f]	24 months	liver: eosinophilic focus (M: 8% versus 33% in 10 mg/kg adult exposure group, F: 32% versus 36% in 10 mg/kg adult exposure group) bile duct hyperplasia (M: 0% versus 0% in 10 mg/kg adult exposure group (F 18% versus 18% in 10 mg/kg) adult exposure group) hepatocellular adenoma (M: 94% versus 98% in 10 mg/kg adult exposure group; F: 76% versus 78% in 10 mg/kg adult exposure group) hepatocellular carcinoma (M: 63% versus 61% in 10 mg/kg adult exposure group; F: 52% versus 44% in 10 mg/kg adult exposure group)	NTP (1993)

Table 89 (contd)

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
FM FF-1 (lot FF 1312-FT)	mouse (B6C3F1) (50)	F, M	combined perinatal and adult exposure	30:10[h]	24 months	liver: eosinophilic focus (M: 0% versus 33% in 10 mg/kg adult exposure group, $P < 0.01$; F: 8% versus 36% in 10 mg/kg adult exposure group, $P < 0.01$) bile duct hyperplasia (M: 16% versus 0% in 10 mg/kg adult exposure group, $P < 0.01$; F: 12% versus 18% in 10 mg/kg adult exposure group) hepatocellular adenoma (M: 96% versus 98% in 10 mg/kg adult exposure group; F: 94% versus 78% in 10 mg/kg adult exposure group) hepatocellular carcinoma (M: 80% versus 61% in 10 mg/kg adult exposure group; F: 88% versus 44% in 10 mg/kg adult exposure group) hepatocellular adenoma/carcinoma (M: 96% versus 98% in 10 mg/kg	NTP (1993)

Table 89 (contd).

						adult exposure group; F: 100% versus 84% in 10 mg/kg adult exposure group)	
				30:30[f]	24 months	liver: hepatocellular adenoma (M: 96% versus 84% in 30 mg/kg adult exposure group, F: 87% versus 96% in 30 mg/kg adult exposure group, hepatocellular carcinoma (M: 70% versus 72% in 30 mg/kg adult exposure group; F: 62% versus 73% in 30 mg/kg adult exposure group)	NTP (1993)
NoBB (Bromkal 80-9D)	mouse (B6C3F1) (50)	F, M	in diet for 18 months	100 300	18 months	liver: carcinoma: 300/100 mg/kg (M: 28%/78%; F: 76%/17% versus 14% (M), 0% (F) in controls) neoplastic nodules: 300/100 mg/kg (M: 96%/98%, F: 92%/72% versus 38% (M), 0% (F) in controls) hepatoblastoma: 300 mg/kg (M: 2%/12% versus 0% in controls)	Momma (1986)
2,2',4,4',5,5' hexabromobiphenyl (BB 153)	rat (Sprague-Dawley) (3)	F	in diet for for 180 days	10	180 days	liver: no neoplastic nodules; no EAF	Jensen & Sleight (1986)

Table 89 (contd).

PBB	Species (strain) (No.[a])	Sex[b]	Treatment	Dose/concentration[c]	Observation period	Site or type of tumour[d]	References
				100	100 days	liver: neoplastic nodules (1/3) small numbers of EAF	
	(6)	F	in diet for 140 days	10	450 days	liver: no nodules, no carcinoma	Jensen & Sleight (1986)
3,3',4,4',5,5' hexambromobiphenyl (BB 169)	rat (Sprague-Dawley) (6)	F	in diet for 140 days	0.1	450 days	liver: no nodules, no carcinoma	
Mixture of BB 153 and BB 169	rat (Sprague-Dawley)	F	in diet for 140 days	10 plus 0.1 resp.	450 days	liver: no nodules, no carcinoma	

[a] Number per experimental group, unless otherwise specified.
[b] F = female; M = male.
[c] in mg/kg body weight per day or in mg/kg feed, unless otherwise specified.
[d] Including nodules and atypical foci (numbers in parentheses: number affected/number treated); EAF = enzyme altered foci.
[e] F1 animals born after the perinatal exposure at dietary level of 1 mg/kg PBBs received diets containing 3 mg/kg PBBs up to 2 years.
[f] F1 animals born after the perinatal exposure at dietary level of 10 mg/kg PBBs received diets containing 10 mg/kg PBBs up to 2 years.
[g] F1 animals born after the perinatal exposure at dietary level of 10 mg/kg PBBs received diets containing 30 mg/kg PBBs up to 2 years.
[h] F1 animals born after the perinatal exposure at dietary level of 30 mg/kg PBBs received diets containing 10 mg/kg PBBs up to 2 years.
[i] F1 animals born after the perinatal exposure at dietary level of 30 mg/kg PBBs received diets containing 10 mg/kg PBBs up to 2 years.

1000 mg FM/kg or 12 doses of 100 mg FM/kg body weight, by gavage, developed incidences of carcinomas of 41.4 and 67.8%, respectively (Kimbrough et al., 1981). Liver tumours were also observed in female and male rats two years after perinatal exposure to FireMaster® (Groce & Kimbrough, 1984; Table 89). Although concurrent controls did not show such lesions, the IARC Working Group noted the lack of statistical significance (IARC, 1986). Nevertheless, the incidences of 5.9% (females) and 9.6% (males), respectively, exceeded the spontaneous incidence of carcinomas of the liver in this particular strain of rat, which is reportedly less than 1% (Groce & Kimbrough, 1984).

Recently, NTP performed further carcinogenicity studies on FireMaster® to determine the following: (a) the effects of PBBs in F344/N rats and B6C3F1 mice receiving adult (F1) exposure only (0, 10, or 30 mg PBB/kg diet); (b) the toxic and carcinogenic effects of PBBs in rats and mice receiving perinatal (Fo) exposure only (10 mg/kg in rats and 30 mg/kg in mice); and (c) the effects of combined perinatal and adult exposure to PBBs (NTP, 1993). In an adult-only exposure study, both sexes in rats and mice receiving 10 or 30 mg/kg (0.5 or 1.5 mg/kg body weight per day) showed increased incidences of hepatocellular adenoma/carcinoma, quite similar to the results of the previous studies (Gupta et al., 1983b).

Perinatal-only exposure (through dietary administration of 10 mg PBBs/kg to the dams) had no effect on the incidence of hepatic neoplasms in female rats, but, in male rats, this exposure was associated with a marginally increased incidence of hepatocellular adenomas. Perinatal exposure to 30 mg PBBs/kg showed significantly increased incidences of hepatocellular adenoma/carcinoma in male and female mice.

Combined perinatal and adult exposure to PBBs confirmed the findings of the adult-only exposures in rats and mice. Although there were no enhancing effects of combined perinatal and adult exposure, perinatal exposure enhanced the susceptibility to the induction of liver tumours of adult female rats, exposed to 10 or 30 mg/kg diet. In male and female mice, it was not possible to assess adequately the enhancing effects on hepatocellular tumours of combined perinatal and adult exposure, because adult-only exposure to 10 or 30 mg PBBs/kg resulted in high incidences (84-98%) of hepatocellular adenoma/carcinoma. However, with increased perinatal exposure, there were increases in the numbers of mice with hepatocellular carcinomas and mice with multiple

hepatocellular adenomas, which suggests an enhancement of PBB-related hepatocellular carcinogenicity associated with perinatal exposure. A dietary dose of 3 mg/kg (0.15 mg/kg body weight per day) and pre- and perinatal exposure of the dam to 1 mg/kg (0.05 mg/kg body weight per day), the lowest dose in this combined perinatal and adult exposure, did not cause any adverse effects on rats.

Feeding of 10-100 mg FireMaster® BP-6 or 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153)/kg diet or of 0.1 mg 3,3′,4,4′,5,5′-hexabromobiphenyl/kg diet did not cause hepatocellular carcinoma in rats, but neoplastic nodules were found at 100 mg FireMaster® or BB 153/kg of feed (Jensen et al., 1982; Jensen & Sleight, 1986). However, the number of animals used was small, and the observation time less than 2 years.

The incidence of hepatocellular carcinomas was increased in male and female mice receiving diets containing commercial nonabromobiphenyl (Bromkal 80-9D) at 100 or 300 mg/kg diet, for 18 months; hepatoblastomas were also seen in males (Momma, 1986; Table 89).

The carcinogenic effects of commercial OcBB and DeBB have not been studied.

8.7.2 *Mechanisms of carcinogenicity*

Generally, the development of cancer is described as a multistage process consisting of initiation and promotion phases (e.g., Safe, 1984). The question of the mechanism of PBB-induced carcinogenicity is addressed in several studies.

8.7.2.1 *Tumour initiation*

As seen in section 8.6, there is no strong evidence for the mutagenicity or genotoxicity of PBBs, which is a property of known initiators. Additionally, PBBs (a mixture of almost exclusively BB 153 and BB 180) did not bind to DNA (Dannan et al., 1978b).

FireMaster® and BB 153 were also tested as tumour initiators (and promotors) in a two-stage mouse skin tumorogenesis assay (Haroz & Aust, 1979). A tumour promoter, 12-0-tetradecanoyl-phorbol-13-acetate (TPA), was applied to the skin of a mouse of a tumour-susceptible strain (SENCAR). After 14 weeks of

treatment, neither FM nor BB 153 exhibited tumour initiating (or promoting: see Table 90) activity. However, 3,3′,4,4′-tetrabromobiphenyl, tested in a two-stage rat bioassay (promotion by phenobarbital), showed some evidence for weak initiating activity (Dixon et al., 1985, 1988). In contrast to 3,3′,4,4′-tetrabromobiphenyl which can be metabolized, FireMaster® has not been tested for initiating activity in this bioassay, since FireMaster® would persist in the tissues of the animals beyond the initiation phase and throughout the promotion phase (Rezabek et al., 1987).

8.7.2.2 Tumour promotion

Varied results (Table 90) were obtained with tumour promotion assays, in which PBBs were tested in combination with known carcinogens (2-acetylaminofluorene in rats, Schwartz et al., 1980; partial hepatectomy plus i.p. administration of *N*-nitrosodiethylamine in rats, Jensen et al., 1982, 1983, 1984; Jensen & Sleight, 1986; Rezabek et al., 1987; Dixon et al., 1988; subcutaneous administration of *N*-nitrosodiethylamine in hamsters, Wasito & Sleight, 1989; 7,12-dimethyl-benz[*a*]-anthracene by skin application in mice, Berry et al., 1978; Haroz & Aust, 1979; *N*-methyl-*N*-nitro-*N*-nitroso-guanidine by skin application in mice, Poland et al., 1982).

On evaluating the development of tumours, hepatocellular carcinoma was found in rats (Jensen, 1983) and skin papilloma in mice (Poland et al., 1982). Other studies with FireMaster® resulted in negative findings (Berry et al., 1978; Haroz & Aust, 1979; Schwartz et al., 1980). Only few hepatocellular carcinomas were present in initiated rats given 2,2′,4,4′,5,5′-hexabromobiphenyl (BB 153) or 3,3′,4,4′,5,5′-hexabromobiphenyl (BB 169) or a mixture of both (Jensen et al., 1982). In a mouse skin test, BB 169 was effective in promoting papillomas, but BB 153 was not (Poland et al., 1982).

Another indicator of tumour-promoting ability in initiated rats was the counting and measuring of enzyme-altered foci (EAF; exhibiting γ-glutamyltranspeptidase activity) and hepatic nodules, which were presumed to be precursor lesions of hepatocellular carcinomas (e.g., Sleight, 1985). In these studies (see Table 90) devised by Pitot et al. (1978), FireMaster® (Jensen et al., 1982, 1984; Jensen & Sleight, 1986; Rezabek et al., 1987) and its non-toxic major congener BB 153 (Jensen et al., 1982; Jensen & Sleight, 1986) acted as tumour promoters, FM being more effective than Bb 153 at dietary concentrations of 10 and 100 mg/kg

Table 90. Effects of PBB in tumour promotion assays

PBB	Species (strain) (No.)[a]	Initiation of carcinogenesis	PBB treatment	Observation period after PBB treatment	Effects[b]	References
FM BP-6	rat (Sprague-Dawley) (F, 8-12)	simultaneous treatment: 2-acetylaminofluorene (2-FAA) in diet (300 mg/kg feed)	in diet 50 mg/kg for 57 weeks	0	inhibition of 2-FAA induced mammary and ear duct carcinogenesis; no significant effect on hepatic tumours (5/12 versus 3/8 in 2-FAA group)	Schwartz et al. (1980)
FM BP-6 (lot 6224 A)	rat (Sprague-Dawley) (F,6)	pretreatment: 70% partial hepatectomy plus *N*-nitrosodiethylamine (DEN) (single ip dose of 10 mg/kg body weight)	in diet 10 and 100 mg/kg for 180 days	0	liver: neoplastic nodules (6/6) increase in EAF ($P < 0.05$) (both levels)	Jensen et al. (1982)
FM	rat (4)	pretreatment 70% partial hepatectomy plus for 140 days DEN (single ip dose of 10 mg/kg body weight)	in diet 10 mg/kg	275 days	liver: carcinoma (4/4 versus 0 in control)	Jensen (1983)

Table 90 (contd).

FM BP-6 (lot 6224 A)	rat (Sprague-Dawley) (F,6)	pretreatment: 70% partial hepatectomy plus DEN (single ip dose of 10 mg/kg body weight)	in diet 100 mg/kg for for 15 days	0	liver: increase in EAF ($P < 0.05$)	Jensen et al. (1984)
			10 mg/kg for 140 days	0	liver: increase in EAF ($P < 0.05$)	
FM BP-6	rat (Sprague-Dawley) (F,6)	pretreatment: two-thirds partial hepatectomy plus DEN (single ip dose of 10 mg/kg body weight)	oral two doses over 24 h total dose: 13 mg/kg and 130 mg/kg body weights	120 days	liver: increase in EAF (not significant) liver: increas in EAF ($P < 0.05$)	Rezabek et al. (1987)
FM BP-6	mouse CD1 (F,30)	pretreatment: 7,12-dimethylbenz(a)anthracene (DMBA) (single dermal dose of 200 nmol)	dermal multiple doses (twice weekly over 30 weeks) 100 µg	0	skin: no papilloma	Berry et al. (1978)
FM BP-6	mouse (SENCAR) (sex, no.: not specified)	pretreatment. DMBA (single dermal subcarcinogenic dose)	dermal multiple doses (twice weekly over 14 weeks) dose: not specified	0	skin: no tumours	Haroz & Aust (1979)

Table 90 (contd).

PBB	Species (strain) (No.)[a]	Initiation of carcinogenesis	PBB treatment	Observation period after PBB treatment	Effects[b]	References
FM FF-1	mouse hairless HRS/J (F,20-26)	pretreatment: *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) (single dermal dose of 5 μmol)	dermal multiple doses (twice weekly over 20 weeks) 2 mg, 5 weeks, then	0	skin: papilloma (9/15 = 60%)	Poland et al. (1982)
FM BP-6	hamster (Syrian golden)	pretreatment: DEN (single sc dose of 80 mg/kg body weight	in diet 100 mg/kg for 140 days	133 days	respiratory tract: increase in number of tracheal papillomas ($P < 0.05$)	Wasito & Sleight (1989)
3,3',4,4'-tetrabromobiphenyl	rat (Sprague-Dawley) (F, 6)	pretreatment: 70% partial hepatectomy plus DEN (single ip dose of 10 mg/kg body weight)	in diet 0.1, 1, 5 mg/kg for 180 days	0	liver: increase in EAF (significant at the high dose)	Dixon et al. (1988)
3,3',4,4'-tetrabromobiphenyl	rat (Wistar) (F,6)	pretreatment: DEN (oral dose of 10 mg/kg body weight for 10 days)	intraperitoneal 15 μmol/kg body weight once weekly for 8 weeks	until 1 week and 9 weeks	liver: increase in EAF	Buchmann et al. (1991)

Table 90 (contd).

2,2',4,4',5,5'-hexabromobiphenyl (BB 153)	rat (Sprague-Dawley) (F,6)	pretreatment: 70% partial hepatectomy plus DEN (single ip dose of 10 mg/kg body weight)	in diet 10 and 100 mg/kg for 180 days	0	liver: neoplastic nodules (3/6) increase in EAF ($P < 0.05$) neoplastic nodules (5/6) increase in EAF ($P < 0.05$)	Jensen et al. (1982)
			in diet 10 mg/kg for 140 days	0 70 days 310 days	liver: increase in EAF ($P < 0.05$) increase in EAF ($P < 0.05$) increase in hepatic nodules ($P < 0.05$) carcinoma (1/10 versus 0 in controls)	Jensen & Sleight (1986)
	mouse (SENCAR) (sex, no.: not specified)	pretreatment: DMBA (single dermal subcarcinogenic dose)	dermal multiple doses (twice weekly over 14 weeks) dose: not specified	0	skin: no tumours	Haroz & Aust (1979)
2,2',4,4',5,5'-hexabromobiphenyl (BB 153)	mouse hairless HRS/J (F,20-26)	pretreatment MNNG (single dermal dose of 5 µmol)	dermal multiple doses (twice weekly over 20 weeks) 20 µg	0	skin: no papilloma (0/22)	Poland et al. (1982)
3,3',4,4',5,5'-hexabromobiphenyl (BB 169)	rat (Sprague-Dawley) (6)	pretreatement: 70% partial hepatectomy plus DEN (single ip dose of 10 mg/kg body weight)	in diet 0.1 mg/kg for 140 days	0 70 days 310 days	liver: no effect on EAF no effect on EAF no significant effect on hepatic nodules; carcinoma (1/11 versus 0 in controls)	Jensen & Sleight (1986)

Table 90 (contd).

PBB	Species (strain) (No.)[a]	Initiation of carcinogenesis	PBB treatment	Observation period after PBB treatment	Effects[b]	References
3,3',4,4',5,5'-hexabromobiphenyl	mouse, hairless HRS/J (f,20)	pretreatment: MNNG (single dermal dose of 5 µmol)	dermal multiple doses (twice weekly over 20 weeks) 20 µg	0	skin: papilloma (12/20)	Poland et al. (1982)
Mixture of BB 153 and BB 169	rat (Sprague-Dawley)	pretreatment 70% partial hepatectomy plus DEN (single ip dose of 10 mg/kg body weight)	in diet 10 mg BB 153/kg and 0.1 mg BB 169/kg feed for 140 days	0 70 days 310 days	liver: synergistic effect on development of EAF synergistic effect on development of hepatic nodules; carcinoma (1/11 versus 0 in control)	Jensen & Sleight (1986)
	rat (Sprague-Dawley) F_1 6)		in diet 100 mg BB 153/kg and 1 mg BB 169/kg feed for 140 days	0	liver: inhibitory effect on development of EAF	Jensen et al. (1983)

[a] No. = Number per experimental group; F = female.

[b] Numbers in parentheses signify No. affected/No. treated; EAF = Enzyme altered foci (exhibiting gamma glutamyl transpeptidase activity); DEN = *N*-nitrosodiethylamine; DMBA = 7,12-dimethyl-benz(a)anthracene; 2-FAA = 2-acetylaminofluorene; MNNG = *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

(Jensen et al., 1982). Short-term feeding of FM was as effective as long-term feeding in enhancing the development of enzyme-altered foci (Jensen et al., 1984). Similarly, an oral 24-h administration of FM was sufficient to enhance EAFs (Rezabek et al., 1987). An oral dose of 13 mg FM/kg body weight was found to be close to a possible no-effect threshold level for the enhancement of EAF (Rezabek et al., 1987). BB 169 (3,3′,4,4′,5,5′-hexa) was tested positive only at a dose (1 mg/kg feed) that was hepatotoxic (Jensen et al., 1983). It was concluded (e.g., Sleight, 1985) that toxicity and carcinogenicity are not necessarily related. Synergistic as well as inhibitory effects on tumour-promoting ability could be elicited by special combinations of BB 153 and BB 169 (Sleight, 1985; Jensen & Sleight, 1986).

Preliminary studies with FireMaster® BP-6 indicated that iron overload may enhance the hepatocarcinogenicity of PBBs in C57BL/10 ScSn male mice (Smith et al., 1990b).

Interestingly, FireMaster® and 2,2′,4,4′,5,5′-hexabromobiphenyl inhibited intercellular communication *in vitro* at non-toxic doses, a property of known tumour promoters (e.g., Sleight, 1985), but 3,3′,4,4′,5,5′-hexabromobiphenyl did not (Table 95; section 8.9). Probably, non-toxic congeners, such as BB 153, have a direct tumour-promoting effect by interfering in normal cell-to-cell communication, whereas toxic congeners like BB 169 promote tumours secondarily to hepatic degeneration and necrosis (e.g., Sleight, 1985).

8.7.2.3 PBBs acting as complete carcinogens

The development of tumours, hepatic nodules, or small numbers of EAF (Table 89) in PBB-exposed rodents that were not experimentally initiated has been interpreted in two ways: either PBBs (or some of them) have both initiating and promoting activity or the observed effects may have resulted from the promotion of "environmentally initiated" cells. As yet, neither of the two possibilities can be ruled out (Jensen et al., 1982; Sleight, 1985; Rezabek et al., 1987).

On the basis of the US National Toxicology Program (NTP) data, possible correlations between carcinogenicity and toxicity in laboratory rodents (Hoel et al., 1988) and between carcinogenicity and *in vitro* genetic toxicity assays (Tennant et al., 1987; Benigni, 1989; Ashby & Tennant, 1991) have been analysed for a series of chemicals including the FireMaster® mixture. Results confirm

that FireMaster® can be classified as a nongenotoxic (epigenetic) carcinogen (see also Loury et al., 1987; Williams et al., 1989).

8.8 Biochemical toxicity

8.8.1 Induction of microsomal enzymes

One of the most intensively studied effects of the PBBs is their induction of mixed function oxidase (MFO) enzymes. Generally, MFO inducers and MFO systems are classified into two main groups, typified by phenobarbital (PB) and 3-methylcholanthrene (MC). The inducing capabilities of commercial PBB mixtures and individual PBB isomers and congeners have been summarized in Tables 91 and 92, respectively. The results were obtained from enzymatic, spectral, electrophoretic, immunochemical, and metabolic studies (see also section 6.3.1).

8.8.1.1 Commercial PBB mixtures

With one exception dealing with octabromobiphenyl (Ahotupa & Aitio, 1978), all studies available referred to the FireMaster®-mixture (Table 91).

Consistently, FM was found to be a mixed-type inducer of hepatic microsomal enzymes in rats. Induction was observed at intakes as low as 1 mg FM/kg feed for 21 days (Babish & Stoeswand, 1977). The no-effect level of a single ip dose was 8 μmol FM/kg body weight, corresponding to 4.7 mg FM/kg body weight (Goldstein et al., 1979). When FM was given for 5 days a week, over 30–50 days, changes in hepatic enzymes occurred with doses as low as 0.3 mg/kg body weight per day (Goldstein et al., 1979). The dose of FM BP-6 effecting half maximal AHH (benzo[*a*]pyrene hydroxylase) induction was approximately 50 mg/kg body weight (Robertson et al., 1981c). Pre-, post-, or perinatal exposures were also effective in inducing microsomal enzymes in rats (Dent et al., 1977b,c, 1978b; Moore et al., 1978a; McCormack et al., 1978a, 1980, 1981). Nursing pups were approximately ten times more sensitive to these effects than the dams. The approximate no-effect level for microsomal enzyme induction in nursing rats was 0.1 mg FM/kg feed, in the diet of the adult (Moore et al., 1978a).

Induction could be detected as early as 24 h after an ip administration of 150 mg FM/kg body weight (Dent, 1978; Dent et al., 1978a) or after an oral dose of 90 mg/kg body weight

Table 91. Induction of microsomal enzymes (MFOs) by commercial PBB mixtures

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of Exposure	Period of Observation[c]	Tissue	MFO induction Induction yes	MFO induction Induction no	Type	References
FM FF-1 (various concentrations) (0.03-30 mg/kg body weight/day)	rat (Fischer F 344/N)	F	oral	9-22 doses over 30 days[b]	14-64 days	liver	x		PB + MC	Goldstein et al. (1979)
FM FF-1 (lot no. FF-1312-FT) (50-400 mg/kg body weight)	rat (Sprague-Dawley)	M	oral	single dose	1-18 days	liver	x		MC[d]	Manis & Kim (1980)
					1-3 days	intestine	x		MC[d]	
					4-18 days	intestine		x		
(0.1 mg/day)			oral	25 doses over 5 weeks	5 weeks	liver	x			
					5 weeks	intestine		x		
FM BP-6 (90 mg/kg body weight)	rat (Fischer 344)	M	oral	single dose	9, 24, 72 216 h	liver	x		PB + MC	Kluwe & Hook (1981)
						kidney	x		only MC	
						testes		x		
				4 doses over 6 days	7 days	liver	x		PB + MC	
						kidney	x		only MC	
						testes		x		

Table 91 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of Exposure	Period of Observation[c]	Tissue	MFO induction Induction yes	MFO induction Induction no	Type	References
FM BP-6 (25, 150 mg/kg body weight)	rat (Sprague Dawley)	F	intra-peritoneal	single dose	12, 24, 48, 192 h 336 h	liver	x		PB + MC	Dent et al. (1976b, 1978a)
FM BP-6 (150 mg/kg body weight)	rat (Sprague-Dawley) pups (7 or 11 days old)	not specified	intra-peritoneal	single dose	28 days	kidney	x		MC	McCormack et al. (1978a)
FM BP-6 (100 mg/rat)	rat (Wistar)	M	intra-peritoneal	2 doses on days 1 & 3	6 days	liver	x		MC[d]	Safe et al. (1978)
FM FF-1 (lot no. FF-1312 FT) (varied concentrations) (1.8-1000 µmol/kg body weight)	rat (Fischer)	F	intra-peritoneal	single dose	4 days	liver	x		PB + MC	Goldstein et al. (1979)
FM FF-1 (90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	2 weeks	liver	x		PB + MC	Dannan et al. (1982c)

Table 91 (contd).

FM BP-6 (1500 or 750 μmol/kg body weight)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	liver	x		PB + MC	Parkinson et al. (1983); Haake et al. (1985)
FM BP-6 (150 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	5, 10, 15 days	kidney	x (day 5,10)	x (day 15)	MC[d]	Rush et al. (1986)
FM BP-6 (6400 mg/kg body weight; total dose)	rat (Sprague-Dawley)	M	intra-peritoneal	4 doses over 4 days	4 days	liver small intestine	x x		PB[e] PB[e]	Traber et al. (1988a,b)
FM BP-6 (4.6-200 mg/kg of feed)	rat (Sprague-Dawley)	F	in diet	2 weeks	2 weeks	liver	x		PB + MC	Dent et al. (1976a)
FM BP-6 (50 mg/kg of feed)	rat (Sprague-Dawley)	M	in diet	5-20 days	5-20 days	liver	x		PB + MC	Babish & Stoeswand (1977)
FM BP-6 (50 mg/kg of feed)	rat (Sprague-Dawley) maternal	F	in diet	gd 8-day 14 postpartum	day 14 post-partum	liver kidney mammary gland	x x x		at organ specific patterns	Dent et al. (1977b,c)

Table 91 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of Exposure	Period of Observation[c]	Tissue	MFO induction Induction yes	MFO induction Induction no	Type	References
FM BP-6 (5, 50, 500 mg/kg feed)	rat (Holtzmann)	M	in diet	2, 3, 5 weeks	2, 3, 5 weeks	liver	x		PB[e]	Garthoff et al. (1977)
FM BP-6 (100 mg/kg feed)	rat (Sprague-Dawley)	F	in diet	3 months	3 months	liver kidney	x x		MC + PB MC	McCormack et al. (1978a,b)
FM FF-1 (lot 7042) (0.1-10 mg/kg feed)	rat (Sprague-Dawley) lactating	F	in diet	18 days postpartum	18 days	liver	x		PB + MC	Moore et al. (1978a)
FM BP-6 (25-200 mg/kg feed)	rat (Sprague-Dawley) lactating	F	in diet	gd 8-day 14 postpartum	day 14 post-partum	lung kidney mammary gland liver	x x x x		MC[d] MC[d] MC[d] MC[d]	McCormack et al. (1979a)
FM BP-6 (100 mg/kg feed)	rat (Sprague-Dawley)	M	in diet	30 days	30 days	liver	x		PB + MC	Akoso et al. (1982a)

Table 91 (contd).

FM BP-6 (100 mg/kg feed)	rat (Sprague-Dawley) maternal	F	in diet	gd 8-day 28 postpartum weanling (6 weeks)	W_1 litter, 14 weeks after W_1 and W_2 litters	liver mammary gland	x x	PB + MC MC	McCormack & Hook (1982)
FM BP-6 (50 mg/kg feed in maternal diet)	rat (pups)		placental, milk or both	pre-, post- or perinatal	at birth or at day 15 post-partum	liver	x	PB + MC	Dent et al. (1977c, 1978b)
FM FF-1 (lot 7042) (0.1-10 mg/kg feed in maternal diet	rat (Sprague-Dawley) (pups) F1		milk	postnatal	day 18 post-partum	liver	x	PB + MC	Moore et al. (1978a)
0.1-10 mg/kg feed in maternal diet plus 0.1-1 mg/kg feed	rat (Sprague-Dawley) (lactating: F1)	F	milk and in diet	postnatal until mating and day 18 postpartum	several weeks	liver	x	PB + MC	
0.1-10 mg/kg feed in maternal diet plus 0.1-1 mg/kg feed	rat (Sprague-Dawley) (pups: F2)		placental and milk	perinatal	day 18 post-partum	liver	x	PB + MC	

Table 91 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of Exposure	Period of Observation[c]	Tissue	MFO induction Induction yes	MFO induction Induction no	Type	References
FM BP-6 (100 mg/kg feed)	rat (Sprague-Dawley)		placental and milk	perinatal	weanling (28 days of age)	liver	x		PB + MC	McCormack et al. (1980)
						kidney	x		MC	
					150 days of age	liver	x		PB + MC	
						kidney	x		MC	
					328 days of age	liver	x		PB + MC	
						kidney	x		MC	
FM BP-6 (10, 100 mg/kg feed)	rat (Sprague-Dawley)		placental and milk	perinatal (F_0: gd 8-day 28 postpartum)	W_1	liver	x		PB + MC	McCormack et al. (1981)
						kidney	x		MC	
					W_2	liver	x		PB + MC	
						kidney	x		MC	
					W_3	liver		x		
						kidney		x		
FM BP-6 (150 mg/kg body weight)	mouse (NMRI)	F	intra-peritoneal	single dose	24-192 h	liver	x		PB + MC	Dent et al. (1977a)

Table 91 (contd).

FM BP-6 (75 mg/kg body weight)	mouse (C57)	M	intra-peritoneal	single dose	10 days	liver kidney lung	x	 x	MC[d]	Ahotupa & Aitio (1978)
FM BP-6 (500 μmol/kg body weight)	mouse (C57BL/) 6J)	M	intra-peritoneal	2 doses on days 1 & 3	6 days	liver	x		PB + MC	Robertson et al. (1984c)
	mouse (DBA/2J)	M	intra-peritoneal	2 doses on days 1 & 3	6 days	liver	x		PB + (MC)	
FM BP-6 (150 mg/kg body weight)	mouse (ICR)	M	intra-peritoneal	single dose	5, 10, 15 days	kidney		x		Rush et al. (1986)
FM BP-6 (1000 mg/kg feed)	mouse (Swiss/ICR)	F	in diet	11 days	11 days	liver	x		not specified	Corbett et al. (1975)
FM (100 mg/kg feed)	mouse (C57/6J)	M	in diet	28 days	28 days	liver kidney	x x		MC[d] MC[d]	Ahmadizadeh et al. (1984)
	mouse (DBA/2J)	M	in diet	28 days	28 days	liver kidney	x	 x	MC[d]	
FM BP-6 (50 mg/kg body weight)	guinea-pig (Hartley)	M	intra-peritoneal	single dose	4 days	liver kidney	x x		MC[d] MC[d]	Rush et al. (1982); Smith et al. (1986)

Table 91 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of Exposure	Observation[c]	Tissue	MFO induction Induction yes	no	Type	References
FM FF-1 (lot FA-7042) (maternal, single oral dose of 50 mg/kg body weight)	guinea-pig (Hartley) pups		placental	prenatal (from gd 65)	2 days	liver	x			Ecobichon et al. (1983)
			milk	postnatal (from 6-12 h after parturition)	2-60 days of age	liver	x (2,4, 7,28 days of age)	x (14,60, 90 days of age		
FM BP-6 (50 mg/kg body weight)	hamster (Golden Syrian)	M	intra-peritoneal	single dose	4 days	liver kidney	x	x	MC[d]	Rush et al. (1982); Smith et al. (1986)
FM BP-6 (lot 6244 A) (250 mg/day)	cattle	F	oral	90-180 days/daily dose)	90-180 days	liver	x			Schanbacher et al. (1978)
FM BP-6 (10-200 mg/kg feed)	pig (sow) (pups)	F	in diet	2nd half of gestation and lactation		liver kidney	x x			Werner & Sleight (1981)
			placental	prenatal	at birth	liver kidney		x x		
			placental and milk	perinatal	4 weeks of age	liver kidney	x x			

Table 91 (contd).

FM BP-6 (1 mg/kg body weight per day)	Beagle dog	M,F	oral	7 weeks	7 weeks	liver	x		Farber et al. (1976)
FM (10-1000 mg/kg feed)	Japanese quail	M,F	in diet	9 weeks	9 weeks	liver	x	PB*	Babish et al. (1975b)
FM FF-1 (40, 80 mg/kg feed)	Japanese quail (*Coturnix coturnix japonica*) (3 genetic lines)	M,F	in diet	5 weeks	5 weeks	liver	x	PB + MC	Polin et al. (1982); Bursian et al. (1983)
FM BP-6 (200 mg/kg body weight)	brook trout (Salvelinus *fontinalis*)		oral	18 days (multiple doses)	18 days	liver	x	MC	Law & Addison (1981)
FM BP-6 (150 mg/kg	rainbow trout (*Oncorhynchus mykiss*)		intra-peritoneal	single dose	up to 2 weeks	liver	x	MC	Elcombe & Lech (1978)

Table 91 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of Exposure	Period of Observation[c]	Tissue	MFO induction Induction yes	MFO induction Induction no	Type	References
FM BP-6 (150, 500 mg/kg body weight)	rainbow trout (*O. mykiss*)		parenteral	single dose	5 days	liver	x		MC	Franklin et al. (1981)
FM FF-1 (15 mg/kg body weight)	sheepshead minnow (*Archosargus probatocephalus*)		intra-peritoneal	single dose	up to 56 days	liver	x		MC[d]	James & Little (1981); James & Bend (1982)
OcBB (FR 25013 A, Dow Chemical) (75 mg/kg body weight)	mouse (C57)	M	intra-peritoneal	single dose	10 days	liver kidney lung	x	 x x	MC[d]	Ahotupa & Aitio (1978)

[a] Commercial PBB mixtures; FM = FireMaster®; OcBB = octabromobiphenyl.
[b] Dosing: 5 days per wee. for 30 days; examination points: 14 days (9 doses); 31 days (22 doses); 46 and 64 days (22 doses plus a 15-day and a 33-day recovery period, respectively.
[c] After first dose.
[d] Only MC-typical parameters recorded.
[e] Only PB-typical parameters recorded.

Abbreviations:
gd = gestation day; MFO = mixed function oxidase; MC = 3-methylcholanthrene; PB = phenobarbital.

Table 92. Induction of hepatic microsomal enzymes (MFOs) by PBB congeners

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of No. of doses	Observation[b]	MFO[c] induction Induction yes	no	Type[d]	References
4-mono- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1979)
2,2'-di- (90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	2-22 days		x		Moore et al. (1979a)
(600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days		x		Ecobichon et al. (1979)
2,5'-di- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			
4,4'-di- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1977, 1979)
(300)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		PB	Robertson et al. (1982b)
2,2',5-tri- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days		x		Ecobichon et al. (1979)

Table 92 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of No. of doses	Observation[b]	MFO[c] induction Induction yes	no	Type[d]	References
2,3',5-tri- (500)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1979)
2,4,6-tri- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			
2,4',5-tri- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			
3,4,4'-tri- (250)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		MC	Parkinson et al. (1983)
(300)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		MC	Robertson et al. (1982b)
2,2',5,5'-tetra- (150)	rat (Wistar)	M	intra-peritoneal	single dose	2 weeks	x		PB	Robertson et al. (1983b)
(500)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB	Parkinson et al. (1983)
(600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1979)

Table 92 (contd).

2,3',4,4'-tetra- (250)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB + MC	Parkinson et al. (1983)
(1500)	mouse (C57BL/6J)	M	intra-peritoneal	2 doses	6 days		x		Robertson et al. (1984c)
(1500)	mouse (DBA/2J)	M	intra-peritoneal	2 doses	6 days		x		
2,3',4',5-tetra- (150)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		PB	Robertson et al. (1980)
2,4,4',6-tetra- (500)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB + MC	Parkinson et al. (1983)
3,3',4,4'-tetra- (21.3)	rat (Sprague-Dawley)	M	oral	single dose	1-10 days	x		MC	Millis et al. (1985b)
(250)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		MC	Parkinson et al. (1983)
(2 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	2 weeks	x		MC	Millis et al. (1985a)
(10, 60)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		MC	Robertson et al. (1982b); Andres et al. (1983)

Table 92 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of No. of doses	Observation[b]	MFO[c] induction Induction yes	no	Type[d]	References
(750)	mouse (C57BL/6J)	M	intra-peritoneal	2 doses	6 days	x		MC	Robertson et al. (1984c)
(1500)	mouse (DBA/2J)	M	intra-peritoneal	2 doses	6 days	x		MC	
3,3',5,5'-tetra- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days		x		Ecobichon et al. (1979)
(not specified)	chicken embryo		via shell into the air sac	single dose	28 h		x		Poland & Glover (1977)
3,4,4',5-tetra- (250)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		MC	Parkinson et al. (1983)
(60)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		MC	Robertson et al. (1982b)

Table 92 (contd).

2,2',4,5,5'-penta- (BB 101) (500)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB	Parkinson et al. (1983)
(90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	7-14 days	x		PB	Dannan et al. (1982a); Millis et al. (1985a)
2,2',4,5',6-penta- (500)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1979)
2,3',4,4',5-penta- (BB 118) (250)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB + MC	Parkinson et al. (1983)
(90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	2 weeks	x		PB + MC	Dannan et al. (1982c); Millis et al. (1985a)
(30, 150)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		PB + MC	Robertson et al. (1980)
(500)	mouse (C57BL/6J)	M	intra-peritoneal	2 doses	6 days	x		PB + MC	Robertson et al. (1984c)
(500)	mouse (DBA/2J)	M	intra-peritoneal	2 doses	6 days		x		

Table 92 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of No. of doses	Observation[b]	MFO[c] induction Induction yes	no	Type[d]	References
2,3',4,4',6-penta- (500)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB + MC	Parkinson et al. (1983)
3,3',4,4',5-penta- (100)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		MC	
(60)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		MC	Robertson et al. (1982b)
2,2',3,4,4',5'-hexa- (BB 138) (90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	7 days	x		PB + MC	Dannan et al. (1982a)
2,2',4,4',5,5'-hexa- (BB 153) (16.8 mg/kg body weight)	rat (F 344/N)	F	gavage	multiple doses (over 30 days)	60 days	x		PB	Goldstein et al. (1979)
(40-1000)	rat (Fischer)	F	intra-peritoneal	single dose	4 days	x		PB	

Table 92 (contd).

(500)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		PB	Parkinson et al. (1983); Haake et al. (1985)
(90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	1-14 days	x		PB	Moore et al. (1978b); Millis et al. (1985a)
(30 mg/kg body weight)	rat (F 344)	M	intra-peritoneal	single dose	72 h	x		PB	Lubet et al. (1990)
(600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x		PB	Ecobichon et al. (1979)
(100 mg/kg feed)	rat (Sprague-Dawley)	M	in diet	30 days	30 days	x		PB	Akoso et al. (1982a)
(10, 100 mg/kg feed)	rat (Sprague-Dawley)	M	in diet	9 days	10 days	x		PB	Render et al. (1982)
(150 mg/kg body weight)	rainbow trout (*Oncorhynchus mykiss*)		parenteral	single dose	5 days		x		Franklin et al. (1981)

Table 92 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of No. of doses	Observation[b]	MFO[c] induction Induction yes	no	Type[d]	References
2,2',4,4',5,5'-hexa- (20 mg/kg body weight)	sheepshead minnow (*Archosargus probatocephalus*)		intra-peritoneal	single dose	17 days		x		James & Little (1981); James & Bend (1982)
(60, 100 mg/kg body weight)			intra-peritoneal	multiple doses	28-40 days		x		
2,2',4,4',6,6'-hexa- (600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1979)
2,3,3',4,4',5-hexa- (BB 156) (90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	7 days	x		(PB) + MC	Dannan et al. (1982a)
(3.75-60)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		(PB) + MC	Robertson et al. (1981a)

Table 92 (contd).

2,3,3',4,4',5'-hexa- (100)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x		Parkinson et al. (1983)
2,3',4,4',5,5'-hexa- (BB 167) (90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	7 days	x	PB + MC	Dannan et al. (1978a)
(100 mg/kg feed)	rat (Sprague-Dawley)	M	in diet	30 days	30 days	x	PB + MC	Akoso et al. (1982a)
2,3',4,4',5',6-hexa- (BB 168) (250)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x	PB + MC	Parkinson et al. (1983)
3,3',4,4',5,5',-hexa- (21.3)	rat (Sprague-Dawley)	M	oral	single dose	1-14 days	x	MC	Millis et al. (1985b)
(100)	rat (Long Evans)	M	intra-peritoneal	single dose	4 days	x	MC	Parkinson et al. (1983)
(30 mg/kg body weight)	rat (F 344)	M	intra-peritoneal	single dose	72 h	x	MC	Lubet et al. (1990)
(2, 30 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	1-2 weeks	x	MC	Dannan et al. (1982c); Millis et al. (1985a)

Table 92 (contd).

PBB[a] (Dose/ concentration)	Species (strain)	Sex	Route	Period of No. of doses	Observation[b]	MFO[c] induction Induction yes	no	Type[d]	References
30 mg/kg body weight	rat (F344)	M	intra-peritoneal	single dose	72 h	x		MC	Lubet et al. (1990)
(60)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days	x		MC	Robertson et al. (1982b)
(600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x			Ecobichon et al. (1979)
(1, 10 mg/kg feed)	rat (Sprague-Dawley)	M	in diet	30 days	30 days	x		MC	Akoso et al. (1982a)
(10, 100 mg/kg feed)	rat (Sprague-Dawley)	M	in diet	9 days	10 days	x		MC	Render et al. (1982)
(not specified)	chick embryo		via shell into the air sac	single dose	24 h	x		MC	Poland & Glover (1977)
(150 mg/kg body weight)	rainbow trout (*Oncorhynchus mykiss*)		parenteral	single dose	5 days	x		MC	Franklin et al. (1981)

Table 92 (contd).

2,2',3,3',4,4',5-hepta- (BB 170)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	7 days	x		PB (+MC?)	Dannan et al. (1982a)
2,2',3,4,4',5,5'-hepta- (BB 180) (90 mg/kg body weight)	rat (Sprague-Dawley)	M	intra-peritoneal	single dose	2-22 days	x		PB	Moore et al. (1979a)
(150 mg/kg body weight)	rainbow trout (*O. mykiss*)		parenteral	single dose	5 days		x		Franklin et al. (1981)
2,3,3',4,4',5,6-hepta- (6)	rat (Wistar)	M	intra-peritoneal	2 doses	6 days		x		Robertson et al. (1981a)
2,2',3,3',4,4',5,5'-octa- (BB 194) (90 mg/kg body weight)	rat (not speci-	M	intra-peritoneal	single dose	7 days	x		PB	Besaw et al. (1978)
(600)	rat (Wistar)	M	intra-peritoneal	3 doses	7 days	x		PB	Ecobichon et al. (1979)

[a] Total dose in μmol/kg body weight, unless otherwise specified.
[b] After first dose.
[c] MFO = Mixed function oxidase; PB = phenobarbital; MC = 3-methylcholanthrene.
[d] Only noted when categorized into PB- or MC- type by the authors themselves.

(Kluwe & Hook, 1981). Although most of the investigations were short-term, there was some evidence for persistent stimulation of hepatic microsomal enzymes. For example, maternal rats fed 100 mg FM/kg feed, during pregnancy and lactation, had elevated enzyme activity 14 weeks after weaning their first litter or even after weaning a second litter (recovery period: 12-16 weeks) (McCormack & Hook, 1982). Perinatal exposure to FM induced microsomal enzymes in rats at 28, 150, and 328 days of age (McCormack et al., 1980). Feeding of FM during pregnancy and lactation to F_0-animals stimulated microsomal enzymes, not only in the F_1-generation, but also in the F_2-generation (McCormack et al., 1981). Also, persistence of an increased activity of microsomal enzymes, 120 or 125 days after cessation of exposure, was noted in rats exposed to FireMaster® BP-6 during hepatocarcinogenesis assays (Jensen et al., 1984; Rezabek et al., 1987).

FM induced hepatic microsomal enzymes not only in the rat, but in all other animal species tested, i.e., mouse (Corbett et al., 1975; Dent et al., 1977a; Ahotupa & Aitio, 1978; Dannan et al., 1980; Ahmadizadeh et al., 1984; Robertson et al., 1984c), guinea-pig (Rush et al., 1982; Ecobichon et al., 1983; Smith et al., 1986), hamster (Rush et al., 1982; Smith et al., 1986), cattle (Schanbacher et al., 1978), pig (Werner & Sleight, 1981), dog (Farber et al., 1976), Japanese quail (Babish et al., 1975a,b; Bursian et al, 1983), and fish (Elcombe & Lech, 1978; Franklin et al., 1981; James & Little, 1981; Law & Addison, 1981). Unlike the mammalian situation, induction in several species of fresh- and saltwater fish was only of the MC-type (Table 91).

Although the activities of microsomal enzymes were highest in the liver, induction was also found in extrahepatic tissues including the kidney (Dent et al., 1977c, 1978b; Ahotupa & Aitio, 1978; McCormack et al., 1978a,b, 1979a,b, 1980, 1981; Kluwe & Hook, 1981; Werner & Sleight, 1981; Ahmadizadeh et al., 1984; Rush et al., 1986; Smith et al., 1986), intestine (Manis & Kim, 1980; Traber et al., 1988a,b), mammary gland (Dent et al., 1977b,c, 1978b; McCormack et al., 1979a; McCormack & Hook, 1982) and lung (McCormack et al., 1979a). However, patterns of induction were organ specific. No induction was noted in the testes of rats (Kluwe & Hook, 1981) (see also Table 91).

FM was also able to stimulate aryl hydrocarbon hydroxylase (AHH) activity in rat hepatoma cell culture (Garthoff et al., 1977).

Commercial OcBB has been tested in only one study on mice and was found to be an inducer of drug-metabolizing enzymes. However, OcBB was a less potent inducer than FM (Ahotupa & Aitio, 1978).

The FM mixture was fractionated and reconstituted in order to test whether PBBs or contaminants (e.g., brominated dibenzofurans or dibenzodioxins, or brominated naphthalenes) were responsible for the inductive effects. The results indicated that most effects associated with the mixture were due to the brominated biphenyls (Safe et al., 1978; Robertson et al., 1981b; Dannan et al., 1982b).

8.8.1.2 *Individual PBB congeners*

The capability of individual PBB congeners to induce hepatic microsomal enzymes *in vivo* is shown in Table 92. There was a broad range of responses, depending on the congener or species/strain tested. In addition to qualitative differences, the extent of the induction also differed between congeners (e.g., Ecobichon et al., 1979; Safe et al., 1981; Parkinson et al., 1983 and other references from Table 92). As far as they have been tested, *in vitro* enzyme induction assays using rat hepatoma H-4-II-E cells in culture, have confirmed the results of the *in vivo* studies (Andres et al., 1983; Bandiera et al., 1982, 1983).

The most abundant components of the FM mixture, BB 153 (2,2′,4,4′,5,5′-hexa-) and BB 180 (2,2′,3,4,4′,5,5′-hepta-), were strict PB-type inducers in rats. Congeners 118 (2,3′,4,4′,5-penta-), 138 (2,2′,3,4,4′,5′-hexa-), and 167 (2,3′,4,4′,5,5′-hexa-) showed a mixed PB- and MC-type induction, and 156 (2,3,3′,4,4′,5-hexa-) was described (Robertson et al., 1981a; Dannan et al., 1982a) to be a very potent MC-type inducer (see Table 8.8/2). 3,3′,4,4′-tetrabromobiphenyl and the model congener 3,3′,4,4′,5,5′-hexabromobiphenyl were pure MC-type inducers in rats (Table 92), 3,3′,4,4′-tetrabromobiphenyl being less effective than 3,3′,4,4′,5,5′-hexabromobiphenyl (Millis et al., 1985a,b). The ED_{50} value of 3,3′,4,4′,5,5′-hexabromobiphenyl determined in the chicken embryo was approximately 90 nmol/kg body weight (= 3.4 nmol per egg) (Poland & Glover, 1977). On the other hand, 3,3′,4,4′-tetrabromobiphenyl was at least 50 times more potent as an inducer of AHH activity than the commercial PBB mixture: ED_{50} values (measured in rats) were 1-2 μmol/kg body weight for 3,3′,4,4′-tetrabromobiphenyl and 75-80 μmol/kg body weight for FM BP-6 (Robertson et al., 1982).

Congeners that elicited PB-type induction in rats (e.g., BB 153 and BB 180) failed to do so in fish, whereas MC-type inducers were effective in both rats and fish (Table 92).

Correlations between the structure and microsomal enzyme-inducing activity (and toxicity) of individual PBB congeners have been demonstrated in several studies and reviews (e.g., Goldstein, 1980; Moore et al., 1980; Aust et al., 1981; McKinney & Singh, 1981; Robertson et al., 1982b; Andres et al., 1983; Dannan et al., 1983; Parkinson et al., 1983; Safe, 1984; Safe et al., 1985).

When 3,3′,4,4′,5,5′-hexabromobiphenyl was used to induce cytochrome P-450 in rats (at 10 μmol/kg body weight), it was found to be selectively associated with cytochrome P-450d (Voorman & Aust, 1987).

8.8.2 Endocrine interactions

PBBs have been demonstrated to interact with the endocrine system.

8.8.2.1 Thyroid hormones

Rats (No. = 10), given oral doses of FM FF-1 (Lot No. 1312 FT) over 6 months, showed dose-related decreases in serum thyroxine (T_4) and triiodothyronine (T_3). Significant decreases in T_4 were seen at doses as low as 0.3 mg PBB/kg body weight per day in males, and 1 mg/kg body weight per day in females. The reduction in T_3 was somewhat less and only significant at high doses (3-10 mg/kg body weight per day) in females (Gupta et al., 1983a). A time- and dose-dependent reduction in plasma T_4 levels was also found in male rats (n = 8-11) administered FM FF-1, by gavage, for 10 or 20 days at 1, 3, or 6 mg/kg body weight per day (Allen-Rowlands et al., 1981). In addition, the reduced plasma T_4 levels were correlated with an increase in thyroid stimulating hormone (TSH) at 20 days. At 6 mg/kg body weight per day, the thyroid uptake of iodine was increased, but the incorporation of iodine in monoiodotyrosine was decreased. While short-term feeding (7 months) of female rats with commercial hexabromobiphenyl at dietary concentrations of 1-50 mg/kg also resulted in an decrease in serum T_3 and T_4 levels (Sepkovic & Byrne, 1984; Byrne et al., 1987), feeding of technical octabromobiphenyl had no effect on serum T_3 levels (Sepkovic & Byrne, 1984). "PBB" (not specified) caused not only reduced serum T_4 levels and elevated thyrotropin levels in rats, but also produced goitres (Bastomsky, 1986).

Single ip injections of 3,3',4,4',5,5'-hexabromobiphenyl in juvenile male rats (20 and 40 mg/kg body weight) caused a significant decrease in serum T_4 concentrations, while serum T_3 levels did not change significantly during the 28-day observation period. The decrease in serum T_4 concentrations was dose-dependent (Spear et al., 1990).

Serum concentrations of T_3 and T_4 were decreased in swine and their newborn piglets at 200 mg FM BP-6/kg feed. After nursing for 4 weeks, piglets born to sows fed 100 mg FM BP-6/kg feed also showed significant reductions in T_3 and T_4 (Werner & Sleight, 1981).

8.8.2.2 *Sex hormones*

Hepatic microsomes, prepared from rats exposed to FM BP-6 (100 mg/kg of feed) from day 8 of gestation until they were killed at 4–21 weeks of age, showed an increased metabolism of progesterone (Arneric et al., 1980), testosterone (Newton et al., 1980, 1982a), and of the estrogens estradiol, estrone, and ethynylestradiol (Bonhaus et al., 1981). In contrast to the increased hydroxylation reaction, reduction of testosterone was inhibited by pretreatment with PBBs (Newton et al., 1982a). The metabolism of exogenously administered and labelled steroid hormones including progesterone, testosterone, and estradiol, was also enhanced *in vivo* in rats following perinatal exposure (gestation day 8–28 days postpartum) to 10 or 100 mg FM BP-6/kg feed, as shown by diminished steroid action and reduced radioactivity in serum and target organs (McCormack et al., 1979c). In contrast, endogenously produced concentrations of luteinizing hormone, prolactin, or corticosterone were not affected in rats treated with 100 mg FM BP-6/kg feed from gestation day 8 until the ninth week of age (Johnston et al., 1980). Rats dosed with 1, 3, or 6 mg FM FF-1/kg body weight per day for 20 days also did not show any alterations in plasma corticosterone or testosterone levels, but, at 6 mg/kg body weight per day, there was a significant reduction in plasma prolactin levels (Castracane et al., 1982). Long-term, low-dose treatment with FM BP-6 (1, 10, or 50 m/kg feed for 5–7 months) caused cumulative and dose-dependent decreases in the serum corticosterone levels of female rats, as well as reductions in the circulating levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate (Byrne et al., 1988). Alterations in the urinary metabolic profile in the corticosteroid region of the profile were observed after exposure (not specified) of rats to PBBs (not specified) (Vrbanac, 1984).

Plasma corticosterone concentrations in female mice (BALB/c) fed 100 mg FM BP-6 for 24 or 30 days were only modestly elevated (Fraker, 1980).

Endogenous concentrations of progesterone and estradiol determined in cows (No. = 2) administered toxic doses of FM BP-6 (25 g/day for 39 or 50 days) were in the range normally expected (Willett et al., 1983a). The clearance rate of radiolabelled progesterone and estradiol from the blood of both cows was decreased (Willett et al., 1983a); elimination of radiolabel from these hormones in the urine and faeces also declined (Sprosty et al., 1979; Willett et al., 1983b).

Ingestion of FM FF-1 by adult, female rhesus monkeys at concentrations of 0.3 mg/kg feed for 7 months (total dose: approximately 10 mg PBB) caused prolonged menstrual cycles and decreased concentrations of serum progesterone (Allen et al., 1978; Lambrecht et al., 1978; for details in study design see section 8.5).

8.8.2.3 *Prostaglandins*

The effect of PBBs on prostaglandin has been examined in an *in vitro* study using rat liver microsomes. A single ip injection of FM BP-6 (100 mg/kg body weight) in male rats resulted in an elevated metabolism of prostaglandin E1, 7 days after dosing (Theoharides & Kupfer, 1981).

8.8.3 *Interaction with drugs and toxicants*

Several studies have demonstrated that PBBs have the ability to alter the biological activity of a variety of drugs and toxicants. In part, it may depend on the capability of the PBBs to induce microsomal enzymes involved in the activation or deactivation of xenobiotics. A summary of interactions, reported after the treatment of animals with a combination of PBBs and drugs or toxicants, is listed in Table 93 according to enhanced or miscellaneous effects. The majority of reports are limited to the FireMaster® mixture. One study (Halvorson et al., 1985) included several congeners, and it was found that the results of interaction (formation of aflatoxin metabolites) varied according to congener.

The toxicities of carbon tetrachloride, bromobenzene, chloroform, trichloroethylene, and trichloroethane have been enhanced by FM in rodents (Roes et al., 1977; Kluwe et al., 1978, 1979, 1982; Ahmadizadeh et al., 1984). Mirex-type compounds

Table 93. Interactions of PBBs with drugs and toxicants

Species and sex[a]	PBB (dosage regimen)	Route of PBB administration	Drug/toxicant (dose)	Observed effects after combined treatment[d]	References
Enhancement of toxicity					
Rat (Sprague-Dawley) M	FM BP-6 (20 mg/kg feed for 28 days)	in diet	mirex and related compounds (Kepone, photomirex)	aggravation of histological changes due to PBB (additive rather than potentiative)	Chu et al. (1980)
Rat (Sprague-Dawley) M	FM BP-6 (100 mg/kg feed for 20 days)	in diet	carbon tetrachloride (CCl_4) (single ip dose of 0.03-2 ml/kg body weight)[b]	increase in CCl_4-induced lethality and 48-h growth retardation; increase in severity of liver damage and renal tubular functional impairment	Kluwe et al. (1982)
Mouse (NMRI) F	FM BP-6 (single dose of 150 mg/kg body weight)	intraperitoneal	bromobenzene (single ip dose of 3150 mg/kg body weight)[b]	decrease in bromobenzene LT_{50}[c]	Roes et al. (1977)
Mouse (ICR) M	FM BP-6 (1, 20, 25, or 100 mg/kg feed for 14-28 days)	in diet	chloroform ($CHCl_3$) (single ip dose of various concentrations)[b]	increase in $CHCl_3$-induced lethality (96-h LD_{50}; at 100 mg PBB/kg feed, $P < 0.05$); higher susceptibility to $CHCl_3$-induced renal and hepatic damage	Kluwe et al. (1978)

Table 93 (contd).

Species and sex[a]	PBB (dosage regimen)	Route of PBB administration	Drug/toxicant (dose)	Observed effects after combined treatment[d]	References
Mouse (C57 BL/6J) and (DBA/2J) M	FM (100 mg/kg feed for 28 days)	in diet	chloroform ($CHCl_3$) (single ip doses of 0.025-0.25 ml/kg body weight)	enhancement of $CHCl_3$ hepatoxicity (both strains); enhancement of nephrotoxicity (only in C57 strain)	Ahmadizadeh et al. (1984)
Mouse (ICR) M	FM BP-6 (1, 20, 25, or 100 mg/kg feed for 14-28 days)	in diet	carbon tetrachloride (CCl_4) (single ip dose of various concentrations)[b]	increase in CCl_4-induced lethality (96-h LD_{50}; at 20 and 100 mg PBB/kg feed, $P < 0.05$); higher susceptibility to CCl_4-induced renal and hepatic damage (e.g.: decrease in renal PAH accumulation after 0.125 ml CCl_4/kg body weight)	Kluwe et al. (1978, 1979)
Mouse (ICR) M	FM BP-6 (1, 20, 25, or 100 mg/kg feed for 14-28 days)	in diet	trichloroethylene (TRI) (single ip dose of 1 ml/kg body weight)[b]	potentiation of TRI-induced renal dysfunction (decrease in renal PAH accumulation)	
	FM BP-6 (1, 20, 25, or 100 mg/kg feed for 14-28 days)	in diet	1,1,2-trichloroethane (TCE) (single ip dose of 0.15 ml/kg body weight)[b]	potentiation of TRI-induced renal dysfunction (decrease in renal PAH accumulation)	

Table 93 (contd).

Japanese quail	FM BP-6 (single dose of 100 mg/kg body weight)	gavage	pentobarbital (single im dose of 50 (M) or 60 (F) mg/kg body weight)	increased mortality during anaesthesia when the pentobarbital was administered 2 h after PBB dosing; reduction in pentobarbital sleeping times 48 h after PBB dosing	Cecil et al. (1975)
	FM BP-6 (300 mg/kg feed for 3 days)	in diet	pentobarbital (single im dose of 50 (M) or 60 (F) mg/kg body weight)	reduction in pentobarbital sleeping times	
Miscellaneous effects					
Rat (Sprague-Dawley) F	FM BP-6 (single dose of 130-165 mg/kg body weight)	intraperitoneal	*N*-methylnicotinamide (NMN) (incubation of renal cortical slices with 6×10^{-6} mol/litre [^{14}C]-NMN)	no effect on uptake of NMN	Evers et al. (1977)
			p-aminohippuric acid (PAH) (incubation of renal cortical slices with 7.4×10^{-5} mol per litre PAH)	elevated uptake of PAH (significant only at 32 days after PBB dosing)	

Table 93 (contd).

Species and sex[a]	PBB (dosage regimen)	Route of PBB administration	Drug/toxicant (dose)	Observed effects after combined treatment[d]	References
Rat (Sprague-Dawley) F	FM BP-6 (direct exposure of renal cortical slices from untreated animals to animals to 1×10^{-3} mol/litre or 1×10^{-6} mol/litre)	*in vitro*	*N*-methylnicotinamide (NMN) (incubation with 6×10^{-6} mol/litre [^{14}]-NMN)	no effect on uptake of NMN	Evers et al. (1977)
		in vitro	*p*-aminohippuric acid (PAH) (incubation with 7.4×10^{-5} mol/litre PAH)	no effect on uptake of PAH	
Rat (Sprague-Dawley)	FM BP-6 (50 and 100 mg/kg feed in mother's diet)	pre- and/or postnatal	ouabain (single iv dose of 1 mg/kg body weight)[b]	enhanced hepatic uptake and transport of ouabain from plasma into bile in 15-day-old rats	Cagen & Gibson (1977a,b, 1978); Cagen et al. (1977)
		postnatal	ouabain (single ip doses)[b]	elevated 24-h LD_{50} values in 15-day-old rats	Cagen & Gibson (1977a)

Table 93 (contd).

Rat (Sprague-Dawley)	FM BP-6 (single dose of 200 mg/kg body weight; isolation of hepatocytes: 3 days after dosing)	intraperitoneal	ouabain (*in vitro* 150 µmol in cell suspension)	decrease in steady-state concentration of ouabain; tendency to increased rate of efflux	Eaton & Klaassen (1979)
			procaine amide ethobromide (PAEB)	increased rate of efflux	
Rat (Sprague-Dawley)	FM BP-6 (100 mg/kg feed for 2 weeks)	in diet	sulfobromophtalein (BSP) (single iv dose of 120 mg/kg body weight)[b]	lower plasma concentrations of BSP; increased biliary excretion of BSP and conjugated BSP	Cagen & Gibson (1978)
Rat (Fischer 344) M, F	FM BP-6 (100 mg/kg feed for 10 days)	in diet	cephaloridine (single ip dose of 1000-2000 mg/kg body weight)[b]	decrease in cephaloridine nephrotoxicity	Kuo & Hook (1982)
Rat (Fischer 344) M	FM BP-6 (doses of 90 mg/kg body weight per day for 2 days)	gavage	*p*-aminophenol (PAP) (100 or 200 mg/kg body weight)[b]	marked reduction in nephrotoxicity produced by PAP	Newton et al. (1982b)

Table 93 (contd).

Species and sex[a]	PBB (dosage regimen)	Route of PBB administration	Drug/toxicant (dose)	Observed effects after combined treatment[d]	References
Rat (Fischer 344) (isolated perfused kidney)	FM BP-6 (doses of 90 mg/kg body weight per day for 2 days)	gavage	*N*-acetyl-*p*-aminophenol (APAP) (3×10^{-8} mol/litre in the perfusate)[b]	accelerated excretion of mercapturic acid; enhanced ability of APAP to deplete glutathione	Newton et al. (1982c)
Rat (Sprague-Dawley) M (isolated liver microsomes)	FM BP-6 (single dose of 575 mg/kg body weight on day 1; isolation of microsomes on day 4)	intraperitoneal	aflatoxin B_1 (64 nmol per 5 ml incubation mixture)	increase in *in vitro* metabolism of aflatoxin B_1 (to aflatoxin M_1)	Shepherd et al. (1984)
Rat (Wistar) M (isolated liver microsomes)	several PBBs (2 doses of 150 µmol/kg body weight on days 1 and 3; isolation of microsomes on day 6):	intraperitoneal	aflatoxin B_1 (64 nmol per 5 ml incubation mixture)		Halvorson et al. (1985)

Table 93 (contd).

	FM BP-6			increase in *in vitro* metabolism of aflatoxin B_1 (to aflatoxin M_1)	
	2,2',4,5,5'-penta-bromobiphenyl			increase in *in vitro* metabolism of aflatoxin B_1 (to aflatoxin Q_1)	
	3,3',4,4'-tetra-bromobiphenyl			increase in *in vitro* metabolism of aflatoxin B_1 (to aflatoxin M_1)	
	2,3,4,4'5-penta-bromobphenyl			increase in *in vitro* metabolism of aflatoxin B_1 to aflatoxin M_1); decrease in metabolism to aflatoxin Q_1	
Mouse (Swiss-Webster) F	FM BP-6 (100, 200 mg/kg feed for 2 weeks)	in diet	ouabain (single iv dose of 0.1 mg/kg body weight)[b]	lower plasma ouabain concentrations no enhanced capacity for ouabain excretion	Cagen et al. (1977); Cagen & Gibson (1978)
			ouabain (diverse single doses)	no effect on ouabain 24-h LD_{50} values	Cagen et al. (1977)

Table 93 (contd).

Species and sex[a]	PBB (dosage regimen)	Route of PBB administration	Drug/toxicant (dose)	Observed effects after combined treatment[d]	References
Mouse (Swiss-Webster)	FM BP-6 (50 mg/kg feed in mother's diet)	pre- and/or postnatal	ouabain (single iv dose of 1 mg/kg body weight)[b]	enhanced disappearance of ouabain from the plasma; increase in ouabain excretion in 15-day-old mice	Cagen & Gibson (1977a,b, 1978)
			ouabain (ip dose)	no effect on ouabain 24-h LD_{50} values	Cagen & Gibson (1977a,b)
Mouse (Swiss-Webster)	FM BP-6 (100, 150, 200 mg/kg feed for 2 weeks)	in diet	indocyanine green (ICG) (single iv dose of 40 mg/kg body weight)[b]	enhanced initial disappearance of ICG from plasma (correlated with higher hepatic ICG content)	Cagen et al. (1977)
Mouse (ICR) M	FM BP-6 (100 mg/kg feed for 18 days)	in diet	ethylene dibromide (EDB) (single ip dose of 100 mg/kg body weight)[b]	decrease in renal and hepatic NPS (non-protein sulfhydryl)-depleting effects of EDP	Kluwe et al. (1981)

Table 93 (contd).

			(diverse single ip doses)	no significant effect on LD_{50} (220 mg/kg body weight versus 250 mg/kg in control)	Kluwe et al. (1981)
Mouse (ICR) M	FM BP-6 (100 mg/kg feed for 18 days)	in diet	1,2-dibromo-3-chloro-propane (DBCP) (single ip dose of 100 mg/kg body weight)[b]	decrease in renal and hepatic NPS (non-protein sulfhydryl)-depleting effects of DBCP	Kluwe et al. (1981)
Mouse M	FM BP-6 (single dose of 500 mg/kg body weight)	not specified	chloroform ($CHCl_3$) (single oral dose of 0.1 ml/kg body weight)[b]	no significant effect on GPT or OCT activity	Plaa & Hewitt (1982)

[a] F = female; M = male.
[b] Administration after PBB treatment.
[c] LT_{50} = median time to death.
[d] GPT = Glutamic-pyruvic transaminase; OCT = ornithine carbamyl transferase; PAH = *p*-aminohippurate.

aggravated the histological damage due to PBBs in rats (Chu et al., 1980). Pretreatment with FM increased mortality during anaesthesia elicited by pentobarbital in Japanese quails (Cecil et al., 1975). On the other hand, a reduction in the toxicity of some toxicants has also been observed, e.g., a reduction in ouabain lethality (Cagen & Gibson, 1977a). Some other interactions are also recorded in Table 93.

8.8.4 Effects on vitamin A storage

Like related compounds, PBBs cause profound alterations in vitamin A homeostasis. Significant reductions in hepatic vitamin A stores have been seen in rats after exposure to individual PBB congeners and the FireMaster® mixture (Table 94). 2,2′,4,4′,5,5′-Hexabromobiphenyl was less potent in reducing vitamin A levels in the liver than the FM mixture and two other hexa-isomers (Table 94).

Rats (Sherman, adult, male) given a single oral dose of 500 mg FM FF-1/kg body weight had lower levels of retinol in the serum and in liver microsomes compared with control animals, after an 18-month recovery period (Bernert et al., 1983).

Rats (Sprague-Dawley, female) treated with FM BP-6 (100 mg/kg diet for up to 140 days) had lower hepatic vitamin A and higher kidney vitamin A levels than controls, but showed an increase in serum retinol (Jensen & Zile, 1988).

Short-term feeding of 3,3′,4,4′,5,5′-hexabromobiphenyl (1 mg/kg diet for 140 days) to rats (Sprague-Dawley, female) caused a severe decrease (approximately 20-fold) in hepatic retinol and retinyl esters and a 6-7-fold increase in retinol and retinyl esters in the kidneys, while serum concentrations of retinol were unaffected by PBB feeding (Jensen et al., 1987). Examination of liver enzymes in these rats revealed reductions of 50% and 63% of acetyl-CoA-retinol acetyltransferase and retinyl palmitate hydrolase, respectively (Jensen et al., 1987). Consistent with the previous studies, there was an increased accumulation of retinol and retinyl esters in the kidneys of rats given a single oral dose of 3,3′,4,4′,5,5′-hexabromobiphenyl (2 mg/kg body weight) as well as a decrease in liver retinyl ester pools (Zile et al., 1989).

In studies using radioactive retinyl acetate, a two-fold increase in the elimination of vitamin A metabolites in the urine and faeces was observed in rats (Sprague-Dawley, male) 12 h-8 days after a

Table 94. Reduction of hepatic vitamin A content in the rat by various PBBs (single congeners and commercial mixtures)

Compound	Strain/sex	Dose and route of administration	Exposure period/ observation/period	Reduction in hepatic vitamin A concentration (%)	References
2,2',4,4',5,5'-hexabromobiphenyl	Sprague-Dawley (male)	100 mg/kg diet	30 days	28	Akoso et al. (1982a)
2,3',4,4',5,5'-hexabromobiphenyl	Sprague-Dawley (male)	100 mg/kg diet	30 days	57	
3,3',4,4',5,5'-hexabromobiphenyl	Sprague-Dawley (male)	10 mg/kg diet	30 days	59	
3,3',4,4',5,5'-hexabromobiphenyl	Sprague-Dawley (female)	1 mg/kg diet	140 days	95	Jensen et al. (1987)
FireMaster® BP-6	Sprague-Dawley (male)	100 mg/kg diet	30 days	72	Akoso et al. (1982a)
FireMaster® BP-6	Sprague-Dawley (female)	100 mg/kg diet	140 days	92	Jensen & Zile (1988)

Table 94 (contd).

Compound	Strain/sex	Dose and route of administration	Exposure period/ observation/period	Reduction in hepatic vitamin A concentration (%)	References
FireMaster® BP-6	Sprague-Dawley (female)	100 mg/kg in mother's diet	perinatal: day 8 of pregnancy until 4, 8, or 14 weeks of age	approximately 50	McCormack et al. (1982b)
FireMaster® BP-6	Sprague-Dawley (female)	100 mg/kg in mother's diet	F_0: perinatal: day 8 of pregnancy until 28 days post-partum/F_1 (28 days of age)	57	McCormack et al. (1981)
			F_0: perinatal: day 8 of pregnancy until 28 days post-partum/F_2 (28 days of age)	28	

[a] F_0 = parental generation; F_1 = first filial generation; F_2 = second filial generation.

single anorectic, oral dose of 3,3′,4,4′,5,5′-hexabromobiphenyl (2 mg/kg body weight). The potential effect of the PBB on the absorption of vitamin A was excluded by the experimental design in this study (Cullum & Zile, 1985). Similarly, long-term, dietary administration of 3,3′,4,4′,5,5′-hexabromobiphenyl (1 mg/kg diet for 140 days) resulted in a greatly increased faecal and urinary elimination of radioactivity, when rats (Sprague-Dawley, female) were given a physiological dose of [11-^{3}H]retinyl acetate (Jensen et al., 1987).

Changes in vitamin A metabolite patterns were found in tissues (liver, kidney, small intestinal mucosa) of rats after a single oral dose of 3,3′,4,4′,5,5′-hexabromobiphenyl (2 mg/kg body weight), which produced a shift of vitamin A metabolism towards the more polar forms of vitamin A, such as retinoic acid, its oxidation and conjugation products (retinoyl glucuronide), and polar retinoid metabolites (Zile et al., 1989).

The influence of the PBB on the vitamin A balance was long lasting. As seen in Table 94, in a multigeneration study, FM BP-6 produced a decrease in hepatic vitamin A concentration, even in the second generation of offspring (28 days of age) of rats when PBB was fed (100 mg/kg diet) only during the first pregnancy (day 8) until 28 days post partum. At this time, all offspring (F_1) were weaned onto a control diet, allowed to mature sexually, and bred with litter-mates to produce the F_2-generation (McCormack et al., 1981).

The influence of dietary levels of vitamin A on the toxicity of PBB has been studied. Vitamin A supplementation (up to 30 000 IU) provided only partial protection against decreases in body weight gain and thymic weight and against hyperplasia of the common bile duct in rats intoxicated with 100 mg FM BP-6/kg diet (Darjono et al., 1983). High dietary levels of vitamin A (200 000 IU) also had some inhibitory effect on carcinogenesis, i.e., on the promotion of hepatic-altered foci by 3,3′,4,4′,5,5′-hexabromobiphenyl in initiated rats (Rezabek et al., 1989).

The mechanism by which PBBs influence vitamin A homeostasis is not fully understood. Conflicting results may be because of analytical problems and biological variables. However, according to Zile et al. (1989), it is very likely that polyhalogenated aromatic hydrocarbons affect specific enzymes involved in the regulation of vitamin A storage and in the vitamin A metabolic pathway. Others have suggested that PCBs and related compounds may

interfere with Vitamin A transport in the serum by inhibiting the formation of the serum transport protein complex carrying retinol and thyroxin (Brouwer & van den Berg, 1986).

8.8.5 Porphyria

Hexabromobiphenyl is able to produce chemical porphyria in Japanese quail (Strik, 1973b), rats, and mice (Gupta et al., 1983a; Hill, 1985). Following studies on adult Japanese quail, which were orally dosed with gelatin capsules or fed diet containing up to 1000 mg/kg body weight FireMaster® BP-6, Strik (1978) stated that PBB porphyria was preceded by liver and kidney damage. Accumulation of porphyrins in the liver is not solely due to an increase in δ-amino-levulinic acid synthetase activity, but rather to drug enzyme induction and the formation of a reactive intermediate that causes centrilobular liver damage and ultimately porphyria. The hepatic mitochondria decrease in number and are damaged (elevated serum glutamic acid dehydrogenase); the proliferated endoplasmic reticulum, including the haemoprotein P-450, is no longer capable of normal activity; uroporphyrinogen decarboxylase activity is reduced to zero; renal porphyrins accumulate and are excreted in the liver and via the bile.

In tests with chick-embryo liver cell cultures, Debets et al. (1980) showed that pretreatment with inducers of the drug-metabolizing enzyme system markedly stimulated the accumulation of porphyrins, after exposure to FireMaster® BP-6. Inhibition of hepatic drug metabolism or the addition of compounds, known to trap electrophiles or radicals, protected against the porphyrinogenic action of FireMaster® BP-6 *in vitro*.

In the same test system, a DeBB solution of 10 μg/ml medium did not show any porphyrogenic potential with, or without, pretreatment with β-naphthoflavone (3 μg/ml medium) for 20 h (Koster et al., 1980). Gupta et al. (1983a) found dose-related, elevated hepatic prophyrin levels in Fischer 344/N rats and $B_6C_3F_1$ mice, orally dosed with 0.1-10.0 mg FireMaster® BP-6/kg body weight (5 steps), primarily in females.

Hill (1985) studied the urinary porphyrin pattern by ion-pair chromatography in female Sherman rats given 0 or 1 g PBB/kg body weight. The route of administration was not stated. Chronic hepatic porphyria became evident about 55-60 days after dosing, as indicated by the large increase in uroporphyrin and heptacarboxylporphyrin and the corresponding ratios of these

porphyrins to coproporphyrin. Between 85 and 100 days, chronic hepatic porphyria developed into its most severe form (*porphyria cutanea tarda*).

Summarizing all reported facts on porphyrin metabolism, Hill (1985) pointed out that chronic hepatic porphyria is characterized as a membrane disease in which there is damage to the membranes of the cell walls of the hepatocytes and organelles (i.e., mitochondria, endoplasmic reticulum) within the liver cell. The cause of damage is unknown. There is some evidence that PBBs produce changes in lipid metabolism, which in turn alters membrane structure (Bernert et al., 1983). This change in membrane structure may cause a change in membrane permeability (damage) so that porphyrins are excreted in the bile capillaries and the intercellular substance. In addition to these changes, PBBs, or their metabolites, cause the induction of δ-aminolevulinic acid synthetase and the inhibition of the enzyme uroporphyrinogen decarboxylase. The changes in enzyme activities produce a build-up of uroporphyrinogen and heptacarboxylporphyrinogen, and these precursors are excreted in the urine, where they are easily oxidized to uroporphyrin and heptacarboxylporphyrin.

A marked sex difference in the development of uroporphyria occurred after administration to 10-week-old F344/N rats of 0.005% FireMaster® BP-6 added to the diet. Thus, the propensity of female rats to develop uroporphyria appeared to be a general response to this class of halogenated chemicals. Liver to body weight ratio, liver porphyrins, and the activity of a uroporphyrinogen decarboxylase inhibitor were significantly greater in both sexes compared with appropriate controls. Comparing treated males and females, the liver to body weight ratio and uroporphyrinogen decarboxylase inhibitor activity were significantly greater in males whereas the liver porphyrin content was greater in females. Levels of total cytochrome P-450 and pentoxyresorufin and benzyloxyresorufin dealkylase activities (associated with cytochrome P450IIB1) were greater in microsomes from control, and PBB-treated male rats compared with females. In contrast, ethoxyresorufin deethylase activity (associated with cytochrome P450 IA1) was significantly greater in females (Smith et al., 1990a).

Iron potentiated the development of uroporphyria after oral exposure to FireMaster® BP-6 for 2 months (dose not stated) in 7 to 10-week-old, male Ah-responsive C57Bl/10ScSn mice (Smith et al., 1990b).

8.8.6 Miscellaneous effects

Alterations in liver microsomal membrane lipid composition, increased peroxidation activities, and an increase in membrane fluidity were found after a single oral dose of 500 mg FireMaster® BP-6/kg body weight during short- and long-term observations (Bernert et al., 1983; Bernert & Groce, 1984).

PBBs were found to inhibit rabbit muscle glycogen phosphorylase(1,4-α-D-glucan:orthophosphateα-D-glucosyltransferase,EC 2.4.1.1), an enzyme that catalyzes the breakdown of glycogen to glucose 1-phosphate. The enzyme exists in two metabolically significant forms, phosphorylase a and b. 2,2',4,4',5,5'-Hexabromobiphenyl and FireMaster® BP-6 were strong inhibitors of phosphorylase b (92% and 88% inhibition at 60 μmol/litre, respectively; K_i = 15 μmol/litre), while exhibiting little or no inhibition of phosphorylase a (Mead et al., 1982).

The activity of the enzyme uridine 5'-diphosphoglucuronyltransferase (UDP-GT), responsible for the conjugation of a wide variety of substrates, was significantly increased in microsomes prepared from rats ip injected with 3,3',4'4',5,5'-hexabromobiphenyl at 20 mg/kg body weight (Spear et al., 1990).

The influence of FireMaster® BP-6 on glutathione peroxidase activity, which is present in most mammalian species, was studied in the rat (liver cytosol). This enzyme is represented, on the one hand, by a selenium-containing enzyme, glutathione peroxidase (E.C. 1.11.1.9), which is able to reduce hydrogen peroxide to water and organic hydroperoxides to the corresponding hydroxy compounds, and, on the other hand, by certain isozymes of glutathione transferase (E.C. 2.5.1.18). The activity of the selenium-dependent glutathione peroxidase was decreased to about 50% of control values on day 16 following the ip administration of FireMaster® BP-6 (500 mg/kg body weight). Inversely, there was a potent induction of glutathione transferases during the 16-day period (Schramm et al., 1985).

Adenylate cyclase [ATP pyrophosphatase lyase (cyclizing), EC 4.6.1.1] catalyzes the conversion of adenosine triphosphate (ATP) to adenosine 3',5'-cyclic monophosphate (cyclic AMP), which acts as a central regulator of several diverse cell activities. In preliminary experiments, the *in vitro* effect of FireMaster® BP-6 on adenylate cyclase activity in the plasma membranes of rat lung alveoli was determined. At concentrations of 10 μg/ml, the

FireMaster® mixture stimulated the basal adenylate cyclase activity of plasma membranes 2- to 2.5-fold (Sidhu & Michelakis, 1978). The authors discuss the possible immunological relevance of this observation.

8.9 Effects on intercellular communication

PBBs show a significant epigenetic activity. The FireMaster® mixture and some of its major components were found to be capable of inhibiting intercellular communication, measured by metabolic cooperation between $HGPRT^+$ and $HGPRT^-$ cells in culture (Table 95). This inhibition occurred at non-cytotoxic concentrations. In contrast to FireMaster® and to its major constituents BB 153 and BB 180, 3,3',4,4',5,5'-hexabromobiphenyl and 3,3',4,4'-tetrabromobiphenyl did not interrupt cell-cell communication at noncytotoxic concentrations. However, both congeners were markedly cytotoxic (Table 95). Congeners with intermediate toxicity such as 2,3'4'4',5-PeBB (BB 118), 3,3',4,4',5'-PeBB (BB 127), and 2,3',4,4',5,5' HxBB (BB 167), were also shown to interfere with cell-cell communication at noncytotoxic concentrations. Both the cytotoxicity and the metabolic cooperation-inhibiting properties of PBB congeners seem to be related to their structure, i.e., presence or lack of *ortho*-substitution (Tsushimoto et al., 1982; Kavanagh et al., 1987; see also section 8.7.2.2).

Recently, the ability of FireMaster® BP-6 to inhibit gap junction-mediated intercellular communication has been confirmed by the FRAP assay, using cultured rat liver epithelial cells (Rezabek et al., 1988). This assay, which has been described by Wade et al. (1986), evaluated the inhibition of fluorescence redistribution after photobleaching (FRAP), which occurs between cells loaded with a fluorescent dye.

Results obtained by a similar new method, the scrape-loading/dye-transfer (SL/DT) technique (El-Fouly et al., 1987) confirmed the inhibitory potency of 2,2',4,4',5,5'-hexabromobiphenyl (Evans et al., 1988; Table 95).

Several different cell types (human fibroblasts, rat kidney epithelial cells, rat liver oval cells, rat Leydig cells, rat glial cells, mouse keratinocytes) differ in their response to chemicals that alter gap junctional intercellular communication. After exposure to FireMaster® BP-6 (20 μg/ml), intercellular communication was inhibited to different extents in three (WB rat liver oval cells,

Table 95. Inhibition of intercellular communication by PBBs: results of *in vitro* assays testing metabolic cooperation between 6-thioguanine-sensitive ($HGPRT^+$) and- resistant (HGPRT$^-$) cells or testing dye transfer[a]

PBB[a]	Cells in culture	Inhibition		Remark	References
		Yes	No		
FM BP-6	Chinese hamster V79 lung cells	x		non-lethal range of the chemical	Trosko et al. (1981)
FM FF-1	rat liver cells	x		no cytotoxicity mentioned	Williams et al. (1984)
FM BP-6	human teratocarcinoma cells	x		only slight effect on cell survival	Kavanagh et al. (1987)
FM BP-6	rat liver epithelial cells (WB-F 344)	x		at non-toxic FM concentration	Rezabek et al. (1988)
3,3',4,4',-tetrabromo-biphenyl (BB 77)	human teratocarcinoma cells		x	moderately cytotoxic	Kavanagh et al. (1987)
2,3',4,4',5-pentabromo-biphenyl (BB 118)	Chinese hamster V79 cells	x		inhibition before cytotoxicity occurs	Tsushimoto et al. (1982)

Table 95 (contd).

PBB[a]	Cells in culture	Inhibition		Remark	References
		Yes	No		
3,3'4,5,5'-pentabromo-biphenyl (BB 127)	Chinese hamster V79 cells	x		slight inhibition before cytotoxicity	Tsushimoto et al. (1982)
2,2',4,4',5,5'-hexa-bromobiphenyl (BB 153)	Chinese hamster V79 cells	x		relatively nontoxic	
	rat liver epithelial cells (WB-F344)	x	x	at non-cytotoxic concentrations	Evans et al. (1988)
	human teratocarcinoma cells	x		only slight effect on cell survival	Kavanagh et al. (1987)
2,3',4,4',5,5'-hexa-bromobiphenyl (BB 167)	Chinese hamster V79 cells	x		inhibition before cyto-toxicity occurs	Tsushimoto et al. (1982)

Table 95 (contd).

PBB[a]	Cells in culture	Inhibition Yes	Inhibition No	Remark	References
3,3',4,4',5,5'-hexa-bromobiphenyl (BB 169)	Chinese hamster V79 cells		x	highly cytotoxic	Tsushimoto et al. (1982)
	human teratocarcinoma cells		x	highly cytotoxic	Kavanagh et al. (1987)
2,2',3,4,4',5,5'-hepta-bromobiphenyl (BB 180)	Chinese hamster V79 cells	x		relatively non-cytotoxic	Tsushimoto et al. (1982)
2,2',3,3',4,4',5,5'-octabromobiphenyl (BB 194)	Chinese hamster V79 cells	x		relatively non-cytotoxic	

[a] HGPRT = Hypoxanthine-guanine phosphoribosyl transferase locus.
[b] Purity of PBB congeners tested: > 99%; FM = FireMaster®.

RG-1 rat glial cells, JB-6 mouse keratinocytes) out of the six cell types tested, rat liver oval cell being the most sensitive cell (Bombick, 1990).

8.10 Immunotoxicity

The effects of PBBs (commercial mixtures and individual congeners) on the weight and histology of the thymus, bursa of Fabricius, and spleen have been reviewed in sections 8.2 (single and short-term exposures: 8.2.1.3, commercial mixtures; 8.2.2, congeners) and 8.4 (long-term exposures). In summary, atrophy of thymus was a frequent observation following PBB exposure.

Other indicators of a suppressed immune function have been compiled in Table 96. These data refer only to the FireMaster®-mixture, because information on OcBB, DeBB, or individual PBB congeners (with the exception of 3,3',4,4'-tetrabromobiphenyl) is lacking.

In addition to the thymus or spleen, other lymphoid tissues were affected by PBB, e.g., bone marrow and the lymph nodes of dogs (Farber et al., 1978; Table 96).

Serum immunoglobulin levels in mice were changed following short-or long-term exposure to FireMaster® (Luster et al., 1978, 1980; Loose et al., 1981). Suppression of antibody response to sheep erythrocytes (or bovine gamma globulin) was reported after the short-term exposure of mice (Fraker & Aust, 1978; Luster et al., 1978; Fraker, 1980; Loose et al., 1981) and after a six-month exposure of rats (Luster et al., 1980). Conditions of study are summarized in Table 96.

Interestingly, mice showed no response in the 6-month study (Luster et al., 1980). A decrease in antibody titres to tetanus toxoid was observed in guinea-pigs (Vos & van Genderen, 1974; Table 96).

Although mortality rates following infection with *Listeria monocytogenes* were not affected by FireMaster® exposure in mice exposed long-term, an increased susceptibility to infection with Listeria was suggested, because a decrease in time to death occurred (Luster et al., 1980; Table 96). No effects on mean survival time were observed in mice fed 5 or 167 mg/kg feed for 3 or 6 weeks and then challenged by *Plasmodium berghei* (murine malaria) infection (Mudzinski et al., 1979; Loose et al., 1981).

Table 96. Immunotoxicity of FireMaster®[a]

PBB[b]	Species (strain/sex)[c]	Route	Dosing	Period of exposure	Observed effects[d]	Reference
FM FF-1 (lot FF 1312 FT)	rat (Fischer) (M)	gavage	22 doses of 0.03, 0.3, 3, or 30 mg/kg body weight	30 days	depression of T-cell responsiveness to mitogens (PHA: overall dose response: $P < 0.01$; 3 and 30 mg/kg per day: $P < 0.05$; Con A: overall dose response: $P < 0.1$; 30 mg/kg per day; $P < 0.05$)	Luster et al. (1978)
FM FF-1 (lot FF 1312 FT)	rat (Fischer) (F)	gavage	122 doses of 0.1, 0.3, 1, 3, or 10 mg/kg body weight	6 months	depression of both B-(10 mg/kg per day) and T-(1,3, or 10 mg/kg per day) cell mitogenic (PHA, Con A, PWM) and allogeneic responses ($P < 0.05$ or 0.01); decreased antibody responses to bovine globulin (10 mg/kg per day; $P < 0.1$); suppressed delayed hypersensitivity reactions (3 and 10 mg/kg per day; $P < 0.05$)	Luster et al. (1980)
FM FF-1 (lot FF 1312 FT)	mouse ($B_6C_3F_1$) (F)	gavage	22 doses of 0.03, 0.3, 3, or 30 mg/kg body weight	30 days	depression of T- and B-cell responsiveness to mitogens PHA, Con A, and LPS (overall dose response: $P < 0.01$; 3 mg/kg per day: PHA, Con A and 30 mg/kg per day: PHA, Con A, LPS: $P < 0.10$ or 0.01); decreased	Luster et al. (1978)

Table 96 (contd).

					antibody responses to SRBC (30 mg/kg per day; 27% reduction): decrease in serum IgM and IgG2 levels (30 mg/kg per day, $P < 0.01$ and 0.10, respectively)	
FM FF-1 (lot FF 1312 FT)	mouse ($B_6C_3F_1$) (F,M)	gavage	122 doses of 0.1, 0.3, 1, 3, or 10 mg/kg body weight per day	6 months	enhanced number of bone marrow colony forming units (only F at 1 and 10 mg/kg body weight per day; $P < 0.01$); decrease in serum IgG, IgM, and IgA levels (10 mg/kg body weight per day $P < 0.01$ or 0.05); increase in serum IgG (1 mg/kg body weight per day; $P < 0.01$) and IgA (0.3 mg/kg body weight per day; $P < 0.1$); depression of B- and T-cell responisiveness to mitogens (PHA, Con A, LPS) at 10 mg/kg body weight per day ($P < 0.05$); increased susceptibility to infection with *Listeria monocytogenes* (10 mg/kg body weight per day)	Luster et al. (1980)
FM FF-1 (lot FF-1312 FT)	mouse ($B_6C_3F_1$ (F,M)	peri-natal	maternal doses of 0.3, 1, 3, or 10 mg/kg body weight per day	gestation day 0 until weaning (on alternate day)	enhanced number of bone marrow colony forming units (F: 1 mg/kg body weight per day; $P < 0.05$); increased susceptibility to endotoxin (LPS, *E. coli*) (marginal dose response $P = 0.06$)	Luster (1980)

Table 96 (contd).

PBB[b]	Species (strain/sex)[c]	Route	Dosing	Period of exposure	Observed effects[d]	Reference
FM BP-6	mouse (BALB/c)	in diet	1, 10, 100 mg/kg feed	30 days	reduced antibody responses to SRBC (10, 100 mg/kg: $P < 0.001$)	Fraker & Aust (1978)
			1000 mg/kg feed	14 days	survivors incapable of mounting an antibody-mediated response to SRBC	Fraker (1980)
FM FF-1 (lot No. 7042)	mouse (BALB/cByJ) (M)	in diet	167 mg/kg feed	3 or 6 weeks	increase in endotoxin (LPS; *Salmonella typhosa*) sensitivity ($P < 0.05$); reduced primary antibody reaction to SRBC (only at 3 weeks)	Loose et al. (1981)
			5 mg/kg feed	3 or 6 weeks	reduced serum IgM levels (at 3 and 6 weeks; ($P < 0.05$)	
FM BP-6	guinea-pig (F)	in diet	10, 50 mg/kg feed	45 days	reduction in antibody titres to tetanus toxoid ($P < 0.025$) $P < 0.05$); reduced serum IgG levels (at 6 weeks, $P < 0.05$) reduced serum IgM levels (at 3 and 6 weeks; $P < 0.05$)	Vos & van Genderen (1974)

Table 96 (contd).

FM BP-6	pig (sows)	in diet	100, 200 mg/kg feed	last half of gestation and 4 weeks of lactation (12 weeks)	decreased responses of peripheral blood lymphocytes to mitogen (PHA, PWM) stimulation (200 mg/kg; $P < 0.05$)	Howard et al. (1980)
FM BP-6	pig (piglets)	peri-natal	100, 200 mg/kg feed	last half of gestation and 4 weeks of lactation (12 weeks)	normal mitogen (PHA, PWM) responses at birth; decreased mitogen responses at 4 weeks of age (PWM = 200 mg/kg; $P < 0.002$)	
FM BP-6	dog	gavage	0.06-4 mg/kg body weight per day	61 days	degenerating lymphocytes in blood smears (all levels); depletion of lymphocytes in the lymph nodes, (4 mg/kg); reduced erythro-poiesis in bone marrow (4 mg/kg); reduction in IgG-containing lymphocytes in popliteal lymph nodes (4 mg/kg)	Farber et al. (1978)

[a] Exclusive of effects on the weight and histology of thymus and spleen, which are noted in another section.
[b] FM = FireMaster®.
[c] M = Male; F = Female.
[d] Con A = Concanavalin A; LPS = bacterial lipolysaccharide; PHA = phytohemagglutinin; PWM = pokeweed mitogen; SRBC = sheep red blood cells.

An increased susceptibility to endotoxin was found in mice after short-term (Mudzinski et al., 1979; Loose et al., 1981) or perinatal (Luster et al., 1980) exposure to FireMaster® (Table 96). Mice with long-term exposure did not show endotoxin sensitivity (Luster et al., 1980). Of the individual PBB congeners, 3,3'4,4'-tetrabromobiphenyl was found to increase sensitivity to endotoxin (lipopolysaccharide from *Escherichia coli*) 1-2 days after administration (single intraperitoneal dose of 150 μmol/kg body weight) to rats (Shedlofsky et al., 1991).

FireMaster® depressed lymphoproliferative (B- and/or T-cell) responsiveness to mitogens in rats (Luster et al., 1978, 1980), mice (Luster et al., 1978, 1980), and pigs (Howard et al., 1980). Response to mitogens was variable among the species tested (Table 96), e.g., rats exposed long-term were more sensitive (dose required: < 10 mg/kg body weight per day) than mice (dose required = 10 mg/kg body weight per day) in the same study (Luster et al., 1980).

Delayed hypersensitivity reactions were depressed in adult rats at higher doses of PBBs (Luster et al., 1980; Table 96), but they were comparable to controls in mice, exposed perinatally and long-term (Luster et al., 1980).

Some haematological parameters of immunological interest, e.g., changes in peripheral lymphocyte and leukocyte counts are reported in sections 8.2.1.2. and 8.4.

In summary, there was a wide spectrum of immunotoxic effects of FireMaster® in different animal species, but immune dearrangement was often recorded at doses that produced other signs of toxicity.

8.11 Neurotoxicity

Behavioural and neurological parameters have been examined in rodents and rhesus monkeys treated with the commercial FireMaster® mixture or with its main component, 2,2',4,4',5,5'-hexabromobiphenyl (BB 153).

8.11.1 Exposure of adult animals

Adult rats (Fischer 344/N) and mice ($B_6C_3F_1$) of both sexes were exposed to oral doses of 0.03-30 mg FM FF-1/kg body weight per day or 0.168-16.8 mg 2,2',4,4',5,5'-hexabromobiphenyl

per kg body weight per day (5 days per week) for a total of 22 doses. Neurobehavioural toxicity was assessed at the end of the 30-day dosing regimen and also 30 days after cessation of dosing (Tilson et al., 1978; Tilson & Cabe, 1978, 1979). Additionally, rats having received 130 oral doses of 3 or 10 mg FM FF-1/kg body weight per day (5 days per week) were tested after 6 months of dosing (Tilson & Cabe, 1979). Mainly at the higher doses, FM FF-1, and, to a much lesser extent, BB 153 led to neuromuscular dysfunction, such as decreased motor activity, depressed neuromuscular reflexes, and impaired forelimb grip strength. Rats were generally more affected than mice. Visual placement responses were also decreased in male rats and mice by FM FF-1 and BB 153. Hypothermia (decreased rectal temperature) was caused by FM FF-1 in mice. In general, rats tended to remain the same or get worse during the 30 days of no dosing, while mice tended to improve. In another study (Geller et al., 1979), the influence of PBB on cognitive function was evaluated. Male rats (Sprague-Dawley) received "hexabrominated biphenyl" (not specified) at 1 mg/kg body weight per day (5 days per week) for a total of 20 doses during a one-month period and were then trained for a simple auditory discrimination task. PBB-treated animals did not significantly differ from controls with respect to accuracy on the discrimination task. However, throughout 24 weeks of discrimination training, PBB rats made many more extra responses and showed longer response times (response latencies), thereby reducing their efficiency. Upon completion of the behavioural study, a group of rats, dosed concurrently with the behavioural animals, was sacrificed immediately after the end of dosing, and the brains were used to prepare both intact synaptosomes and synaptic plasma membranes (Gause et al., 1979). Both calcium binding to synaptic plasma membranes and calcium uptake by intact synaptosomes was significantly reduced in the brains of rats administered 1 mg PBB/kg body weight per day. From these results, the authors derived that both spontaneous and evoked transmitter release could be reduced during PBB treatment.

8.11.2 Perinatal exposure

Functional impairment of offspring after perinatal exposure to PBBs has been observed at PBB concentrations not causing overt maternal toxicity. Locomotor activity was decreased in the offspring of Swiss-Webster-mice fed FireMaster® (100 mg/kg feed) during lactation (postnatal days 1-29). Increased mortality and decreased body weight were also seen in the pups (Preache et al., 1976). Prior to breeding, female rats (Sprague-Dawley) were

dosed orally for 20 days (5 days/week) with FireMaster® FF-1 (0.5 or 5 mg/kg body weight), and the male offspring were used for measurements of motor activity (Gause et al., 1984), pain threshold (Gause et al., 1984), operant behaviour, and response to central nervous system-active drugs (Gause et al., 1984; Geller et al., 1985). The first two of these four measurements started from weaning and resulted (over a 6 week period) in higher levels of activity and in changes in the pain threshold in animals exposed to PBB. Both of the last tests were conducted with the adult (> 75 days of age) offspring: There were no detectable effects of PBB on the acquisition or performance of the operant discrimination task; however, the pharmacological challenge showed that F_1 males from PBB-treated dams were less sensitive to both phenobarbital and d-amphetamine than F_1 males from control dams. In another study, pregnant rats (Sprague-Dawley) received oral doses of 0.2 or 2 mg FireMaster® BP-6/kg body weight per day from day 6 of gestation through day 24 postpartum (Henck & Rech, 1986). Several signs of neurobehavioural toxicity were found in male and female offspring of dams given 2 mg FireMaster® BP-6/kg per day, a dose that produced tissue levels within the range of those measured in highly exposed Michigan people. There were significant effects on the acquisition of foreword locomotion, cliff avoidance, cage emergence, and open field activity (Henck, 1986). At 6 months of age, the offspring were tested for a series of operant responses of increasing difficulty. It was found that the learning of various operant behavioural patterns was impaired in a relatively subtle manner, and that both sexes can differ in their responses (Henck, 1986; Henck & Rech, 1986).

8.12 Factors modifying toxicity, toxicity of metabolites

8.12.1 Contaminants affecting toxicity

8.12.1.1 Polybrominated naphthalenes (PBNs)

PBNs have been identified as contaminants of the commercial FireMaster® mixture (at concentrations of the order of 200 mg/kg: see section 2.1.2). In structure, they resemble other classes of halogenated aromatic hydrocarbons, such as polychlorinated naphthalenes, polyhalogenated biphenyls, dibenzodioxins, and dibenzofurans, and may elicit similar qualitative effects (e.g., Kimbrough, 1980a,b). A summary of biologic and toxicological responses reported on PBNs is given in Tables 97 and 98. It shows that some PBNs are potent toxicants and teratogens. PBNs were teratogenic in mice at dose levels below those capable of producing

overt maternal toxicity (Miller & Birnbaum, 1986). Compared with FireMaster® (consult also previous sections), PBN mixtures were much more potent in causing adverse effects. For example, a PBN mixture was at least 10 times more effective than FM BP-6 in producing maximal induction of aryl hydrocarbon hydroxylase (30 μmol/kg body weight versus 300 μmol/kg; Robertson et al., 1981a, 1984a). Although PBNs are present only at low levels in the FireMaster® mixture, some authors (Robertson et al., 1984a; Miller & Birnbaum, 1986) believe that they may contribute to the toxicity of FireMaster®.

Table 97. LD_{50} values of several polybrominated naphthalenes (PBN) in guinea-pig[a,b]

PBN	LD_{50} (μg/kg body weight)
2,3,6,7-tetrabromonaphthalene	242
1,2,4,6,7-pentabromonaphthalene	200
1,2,3,4,6,7-hexabromonaphthalene	361
1,2,3,5,6,7-hexabromonaphthalene	> 3610

[a] From: McKinney & McConnell (1982).
[b] Hartley strain guinea-pigs given a single oral dose (gavage) and observed for 30 days.

8.12.1.2 *Mixed polybromo-chlorobiphenyls*

At present, only a monochloropentabromobiphenyl has been identified as a trace impurity in FireMaster® FF-1 (see section 2.1.2). No information is available on its toxicological properties. However, there is one study by Andres et al. (1983) in which the biological and toxic effects are compared of a series of laterally substituted 3,3',4,4'-tetrahalobiphenyls containing the following variable molecular Cl/Br ratios: Br_4, Br_3Cl, Br_2Cl_2 (two isomers), $BrCl_3$, and Cl_4. Parameters examined included: growth rate, effects on the thymus, and hepatic microsomal enzyme induction in male Wistar rats, as well as enzyme induction in rat hepatoma cells in culture and relative binding affinities to the rat cytosolic receptor protein. Data obtained demonstrated that the activity of

Table 98. Summary of reported biological alterations and toxic effects of polybrominated naphthalenes

Species	Sex[a]	PBN[b]	Dosage regimen[c]	Observed effects	Reference
Pathological features					
Rat	M	1,2,3,4,6,7-HBN	oral doses of 5 mg/kg body weight per day for 4 days	centrilobular hepatic accumulation of lipid	Kohli et al. (1981)
Mouse (C57 BL/6N) (pregnant)	F	synthetic HBN mixture (mainly 1,2,3,4,6,7-HBN and 2,3,4,5,6,7-HBN)	oral doses of 0.5, 1.0, 2.5, 5.0, 7.5, or 10.0 mg/kg body weight per day on gd 6-15; s.t.: gd 18	decrease in body weight (at 7.5 and 10.0 mg/kg); increase in relative liver weight (at all levels); wasting, listlessness, vaginal bleeding, death (at 5-10 mg/kg)	Miller & Birnbaum (1986)
Rat (Fischer)	F	2,3,6,7-TBN (not identified in FireMaster®)	2 daily ip doses of 0.2 mmol/kg body weight per day; s.t.: 3 days after last dose	increased liver weight; histological liver changes	Goldstein et al. (1979)

Table 98 (contd).

Species	Sex[a]	PBN[b]	Dosage regimen[c]	Observed effects	Reference
Rat (Wistar)	M	3 synthetic PBN mixtures	single ip dose of 0.3 mmol/kg body weight on day 1; s.t.: day 15	decrease in body weight gain; enlarged livers; decreased thymuses; histological changes in liver and thymus;	Robertson et al. (1984a)
Hepatic microsomal enzyme induction					
Rat (Fischer)	F	2,3,6,7-TBN (not identified in FireMaster®)	2 ip doses of 0.2 mmol per kg body weight per day; s.t.: 3 days after last dose	MC-type induction: approximate ED_{50} = 40 µmol/kg (18 mg/kg) (approximately 10-fold more potent than FM FF-1)	Goldstein et al. (1979)
Rat (Wistar)	M	3 synthetic PBN mixtures (5-6 bromines per naphthalene)	ip doses of 15 or 150 µmol/kg body weight per day on days 1 and 3; s.t.: day 6	MC-type induction (ED_{100} = at most 30 µmol/kg)	Robertson et al. (1984a)

Table 98 (contd).

Species	Sex[a]	PBN[b]	Dosage regimen[c]	Observed effects	Reference
Fetal toxicity					
Mouse (C57 BL/6N)	-	synthetic HBN mixture	maternal oral doses of 0.5-10 mg/kg body weight per day on gd 6-15; s.t.: gd 18	dose-related increases in fetal mortality (at 5-10 mg/kg); dose-related increase in incidence of various teratogenic effects (all dose levels): - kidney lesions (100% of fetuses at 1 mg/kg)[d] - reduction in size of thymus and spleen - cleft palate (4.8% of fetuses at 1 mg/kg; 98.6% of fetuses at 2.5 mg/kg) - subcutaneous edema - sternebral anomalies - delayed cranial ossification	Miller & Birnbaum (1986); Miller et al. (1985)

[a] F = female; M = male.
[b] PBN = polybrominated naphthalene(s); HBN = hexabrominated naphthalene(s); TBN = tetrabrominated naphthalene(s).
[c] gd = gestation days; s.t. = sacrifice time; ip = intraperitoneal.
[d] Estimated NOEL (no-observed-effect level) = 0.1-0.25 mg/kg per day.

these (mixed) halogenated biphenyls was enhanced with increasing bromine (and decreasing chlorine) substitution.

8.12.2 Toxicity of metabolites

No experimental data are available on the toxicity of PBB metabolites.

8.12.3 Toxicity of photolysis and pyrolysis products

8.12.3.1 Photolysis products

Studies of the FireMaster® mixture and its main component, 2,2′,4,4′,5,5′-hexabromobiphenyl, showed that the photolysis products were more toxic than the original PBB. The parameters of toxicity compared were liver and thymus weight changes, liver histology, hepatic microsomal enzyme induction, and binding affinity to the cytosolic receptor in rats, as well as development of hyperkeratosis in the rabbit ear (Table 99). Probably, one or more of the lower brominated PBBs formed by photolysis (see section 4.2.1) are responsible for the increased potency. It is believed that the increased potency of irradiated 2,2′,4,4′,5,5′-hexabromobiphenyl is due mostly to 2,3′,4,4′,5-pentabromobiphenyl and, because of metabolism, to a lesser extent to 3,3′,4,4′-tetrabromobiphenyl (Millis et al., 1985a). The enhanced toxicity of the photolysed FireMaster® mixture may be explained similarly by increased concentrations of 2,3′,4,4′,5-pentabromobiphenyl and of congeners containing no *ortho* bromines (Robertson et al., 1983a).

8.12.3.2 Pyrolysis products

Recently, the toxicity of the pyrolyzed FireMaster® mixture has been determined *in vitro* by measurements of EC_{50} values for the induction of aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin *O*-deethylase (EROD) in rat hepatoma H-4-II E cells, and, *in vivo* by measurements of ED_{50} values for hepatic microsomal AHH and EROD induction, body weight loss, and thymic atrophy in immature male Wistar rats (Zacharewski et al., 1988). FireMaster® BP-6 was pyrolyzed at 800 °C, and the residue was extracted with toluene. Solvents used for the application of the test material to the cell cultures and for ip injection of the animals were DMSO and corn oil, respectively. Both the *in vitro* and *in vivo* dose-response effects were compared with the relative activity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and expressed as the concentrations of "2,3,7,8-TCDD equivalents".

Table 99. Summary of comparative toxicology data of photolysed PBBs

PBB	Irradiation (solvent during irradiation)	Parameter[a] (species)	Effects of PBB	Effects of irradiated PBB	References
FM BP-6 (lot 7062)	300 nm (cyclohexane)	thymus weight (rat, immature)	dose-related decreases significant at 75 mg/kg body weight	dose-related decreases; decreases significant at 25 mg/kg body weight	Robertson et al. (1981b,c)
		AHH-induction (rat, immature)	ED_{50} = 50 mg/kg body weight	ED_{50} = 9 mg/kg body weight	
		displacement of [^{3}H] TCDD from the Ah receptor (rat, immature)	EC_{50} = 300 μmol	EC_{50} = 2 μmol	Robertson et al. (1981b)
2,2',4,4',5,5'-hexabromobiphenyl (BB 153)	sunlight (hexane)	hyperkeratosis	no hyperkeratosis (rabbit ear)	severe hyperkeratosis	Patterson et al. (1981)

Table 99 (contd).

PBB	Irradiation (solvent during irradiation)	Parameter[a] (species)	Effects of PBB	Effects of irradiated PBB	References
	254 nm (hexane)	hepatic microsomal enzyme induction (rat, outbred)	PB-type	mixed type (PB and MC)	Millis et al. (1985a)
		liver weight (rat, outbred)	increase	increase (more than with BB 153)	
		liver histology (rat, outbred)	hepatocyte enlargement	moderate to severe hepatocyte enlargement	

[a] AHH = benzo[a]pyrene hydroxylase; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.
[b] MC = 3-methylcholanthrene; PB = phenobarbital.

The calculated *in vitro* and *in vivo* "2,3,7,8-TCDD equivalents" (μg/g sample) for the six bioassays ranged between 480 and 1680 μ/g (Table 100).

Table 100. FireMaster® BP-6 pyrolysate: *in vitro* and *in vivo* determination of "2,3,7,8-TCDD equivalents"[a]

Bioassay[b]	FireMaster® BP-6 pyrolysate[c]: Sample "2,3,7,8-TCDD equivalents"[d] (μg/g)
AHH induction (*in vitro*)	1400
EROD induction (*in vitro*)	480
AHH induction (*in vivo*)	540
EROD induction (*in vivo*)	520
Body weight loss (*in vivo*)	760
Thymic atrophy (*in vivo*)	1680

[a] From: Zacharewski et al. (1988).
[b] AHH = aryl hydrocarbon hydroxylase; EROD = ethoxyresorufin *O*-deethylase.
[c] Pyrolysis temperature: 800 °C.
[d] 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Several polybrominated dibenzofurans (PBDFs) have been identified in the highly complex combustion mixture of FireMaster® (see section 4.3.2). However, toxicity tests have been conducted for only one PBDF congener, namely 2,3,7,8-dibenzofuran (Moore et al., 1979b).

Generally, PBDFs may have a higher toxicity than the chloro analogues (Poland & Knutson, 1982).

The toxicity of pyrolyzed technical octabromobiphenyl (Dow, Lot 102-7-72) has been studied in a less sophisticated manner than that of FireMaster®. Rats were exposed, via inhalation, to OcBB, which had been heated at 290 °C (4 h/day, for up to 10 days) and examined for liver damage. Atmospheric concentrations of > 2.5 μg/litre (as Br) of brominated 290 °C pyrolysis products caused liver enlargement; microscopic abnormalities in the liver were not detected (Aftosmis et al., 1972b; Waritz et al., 1977).

8.13 Mechanism of toxicity including carcinogenicity

PBB and related halogenated compounds are known to elicit a large number of different effects in animal species. However, the underlying mechanisms of toxicity are unknown. It is likely that several molecular mechanisms may operate (e.g., Silberhorn et al., 1990).

As has been discussed in a number of comparative studies and reviews, there is good evidence relating the effects of PBB congeners that are MC inducers to a receptor-mediated model of toxicity (Poland & Glover, 1977, 1980; Poland et al., 1979; Goldstein, 1980; Moore et al., 1980; McKinney & Singh, 1981; Parkinson & Safe, 1981; Bandiera et al., 1982, 1983; McKinney & McConnell, 1982; Nebert et al., 1982; Poland & Knutson, 1982; Robertson et al., 1982b, 1984c,d; Safe et al., 1982, 1985; Aust et al., 1983; Dannan et al., 1983; Lai, 1984; Safe, 1984). The particular PBB-induced toxic syndrome of wasting, and other effects that are common to related halogenated compounds isosteromeric to TCDD, are related to an interaction with the cytosolic Ah - or TCDD - receptor protein. The Ah receptor is believed to be a member of the steroid/retinoid/thyroid hormone nuclear receptor superfamily, however, no endogenous ligands have been detected so far for the Ah receptor (Nebert et al., 1990; Poellinger et al., 1992). Activation of the Ah receptor, translocation into the nucleus, and binding to responsive elements on DNA are complex processes involving heat shock protein 90 and several other unknown, or less well described, steps (Poellinger et al., 1992). This activation of the Ah receptor leads by less well understood mechanisms to altered expression of a number of different genes (among these at least 6 drug-metabolizing enzymes) resulting in a pleiotypic response (Nebert et al., 1990). Furthermore, TCDD, apparently via activation of the Ah receptor, has an antiestrogenic effect by down-regulation of the nuclear estrogen receptor and affects the epidermal growth factor (EGF) receptor-binding (DeVito et al., 1991; Safe et al., 1991). The most active TCDD-like PBBs are those lacking *ortho* bromine substitution, being coplanar and approximate isostereomers to TCDD. It should be noted that the interaction between ligands and the Ah receptor, as well as the action on different genes and species differences, are only partly understood.

Under certain conditions, TCDD can elicit programmed cell death (apoptosis) in freshly isolated thymocytes from young rats

(McConkey et al., 1988). This has been suggested as an important mechanism for the effects of TCDD on cells in the thymus. It is not known whether this effect is mediated via the receptor or whether it can occur with coplanar PBBs. For tissues in general, apoptosis is believed to be important for differentiation, normal cell turnover, hormone-dependent atrophy, and tumour promotion (Nebert et al., 1990).

PBBs also have a number of other effects at the molecular and biochemical levels, e.g., increased cell proliferation in the B633F1 mouse liver (Mirsalis et al., 1985, Table 88; Loury et al., 1987; Mirsalis et al., 1989; Mirsalis & Steinmetz, 1990), and effects on membranes (Bernert & Groce, 1984) or membrane-mediated processes in rats (Shukla & Albro, 1987). PBBs substituted at the *ortho* positions cause PB-type microsomal induction. The mechanism of this type of enzyme induction is unknown. This group of PBBs also causes inhibition of intercellular communication (Trosko et al., 1981; Tsushimoto et al., 1982; Williams et al., 1984; Kavanagh et al., 1987; Rezabek et al., 1988), which has been suggested to be important for the promotion phase in the carcinogenic process.

PBB microsomal enzyme induction, as well as the induction of other drug metabolizing enzymes, may lead to a number of secondary events with enhanced metabolic conversions of both xenobiotica and endogenous compounds, such as steroid hormones. Furthermore, a high level of P450 enzymes could lead to the generation of oxygen radicals. A relationship between the induction of cytochrome P-450 enzymes (see section 8.8.1) and liver tumour promoting activity has been noted for a number of chemicals including PBBs (e.g., Lubet et al., 1989; Beebe et al., 1991; Buchmann et al., 1991).

Some of the toxic effects of PBBs could also be mediated via changes in the metabolism of vitamin A (retinol compounds and retinoic acid), which is important for cellular growth and differentiation. However, the mechanism of the effects of PBBs on vitamin A metabolism is still unknown.

9. EFFECTS ON HUMANS

The human health effects of PBBs have been reviewed by Safe (1984), Reggiani & Bruppacher (1985), Fries (1985b), IARC (1986), Kimbrough (1987), Anderson (1989), Silberhorn et al. (1990), and Waldron (1990).

9.1 General population exposure

9.1.1 Acute toxicity-poisoning incidents

Most information on the effects of PBBs on humans was obtained as the result of a poisoning incident in Michigan, USA, 1973, when several hundred kg PBBs were introduced into cattle feed through a labelling accident. Widespread human exposure in this area resulted from direct contact with contaminated feed and from the consumption of PBBs in meat, eggs, and dairy products. During an interval of more than 9 months between the accident, the identification of its cause, the beginning of statewide testing and the establishment of quarantines, commercially marketed products entered the Michigan food chain.

For exposure data see sections 5.2 and 5.3.

There was no instance of acute PBB toxicosis in humans with which to compare the potential effects at lower exposures (Fries, 1985b).

9.1.2 Epidemiological studies

In the epidemiological studies reviewed below, efforts have been made to evaluate the relationship between PBB exposure and a large number of adverse effects, including behavioural effects and subjective complaints. However, most studies suffer from major failures in design introducing confounders that make it difficult, or impossible, to draw conclusions regarding the relationship between PBB exposure and possible health effects.

A number of studies had no comparison groups. In other reports, small groups of patients were selected because of existing illness and not because their PBB body burdens were particularly elevated. Some of the outcomes measured, such as urinary porphyrin levels, liver function tests, and immunological tests, did not show any clinically relevant changes or were not positively

correlated with PBB body burdens. The clinical relevance of some of the tests is also not known, at present, because no reference values exist. Most of these reports dealt with cross sectional studies of heterogeneous groups of people. No detailed reports exist on long-term, follow-up studies.

9.1.2.1 *Studies conducted by the Michigan Department of Public Health (MDPH studies)*

The health status of 165 persons living on PBB-quarantined farms was compared with that of 133 persons living on unexposed farms in the same area. Although a variety of symptoms were reported by both groups, no consistent pattern of differences between the groups was observed. Physical examinations did not show any abnormalities of the heart, liver, spleen, or nervous system that could be related to PBB exposure. There were no differences between groups in urine analysis and blood counts (Humphrey & Hayner, 1975).

A cohort study of Michigan residents (4545 persons), exposed to PBBs, was conducted to examine, among other things, whether there was an increased incidence of acute or subacute illness in relation to PBB exposure, 4 years after the accident. Six groups with various levels of potential exposure were included in the cohort. The groups were quarantined farm residents, farm product recipients, chemical workers and their families, pilot study control participants, self-referred individuals who resided on farms that were contaminated with low amounts of PBBs, and self-referred individuals who had no direct connection with contaminated farm premises. Mean and median serum concentrations of PBBs were much higher in the first three groups than in the latter three. The prevalence of selected symptoms by group was examined. Symptoms generally were most prevalent in the two self-selected groups and were least prevalent in the group composed of chemical workers and their families. An evaluation of dose-response relationships was undertaken by dividing the cohort into seven segments on the basis of serum PBB levels. No positive associations were found between serum concentrations of PBB and reported symptom frequencies. Symptom-prevalence rates (excluding volunteers) were slightly higher in persons with no detectable PBBs in serum than in those with measurable quantities. Relationships between symptom-prevalence rates and serum PBB levels were also examined within each enrolment group, and no positive trends were found; in all groups, including chemical workers and quarantined farm residents, the highest

prevalence rates occurred in persons with the lowest serum PBB levels (Landrigan et al., 1979).

9.1.2.2 *Studies conducted by the Environmental Science Laboratory, Mount Sinai School of Medicine, New York (ESL studies)*

Anderson et al. (1978b, 1979) reported on a study of PBB-exposed farmers and residents in Michigan and a control group of unexposed Wisconsin dairy farmers, who were examined in November 1976 and March 1977, respectively. The results were given on the basis of the examination of 933 exposed persons and 229 controls in the 1978 report, and of 993 exposed subjects and 228 controls in the 1979 report.

The study included four groups: families chosen randomly from Michigan farms, consumers of produce bought directly from participating farms, self-selected Michigan families, and Wisconsin dairy farmers not exposed to PBBs. All subjects completed comprehensive questionnaires on medical histories and 43 symptoms, and they were subjected to physical examination and certain laboratory tests. Statistical analysis of the prevalence of symptoms at the time of examination or during the preceding year in the Michigan and Wisconsin populations studied, found the Michigan group to have a significantly higher prevalence of skin, neurological, and musculoskeletal symptoms. The increase was seen among the younger age groups of 16-35 years and 36-55 years. Michigan females had a higher prevalence of neurological symptoms than Michigan males (Anderson et al., 1978b).

No statistically significant, positive correlations were found between serum PBB values and any individual current symptom. Liver function tests showed that serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and lactate dehydrogenase (LDH) elevations were significantly more prevalent in the Michigan group (chi square test). No differences were seen for alkaline phosphatase. Within the Michigan group, males had a higher prevalence of SGPT and LDH increases than females, and comparing males in both groups, Michigan males had a significantly higher prevalence of SGPT and SGOT increases than Wisconsin males (Anderson et al., 1979).

The comparison of findings among residents on Michigan dairy farms (quarantined and non-quarantined farms) and corresponding consumers of produce purchased from these farms (cross-sectional clinical survey of 1029 persons) gave the following results:

prevalence of symptoms (dermatological, neurological, musculoskeletal, and gastrointestinal) in consumers of farm products from quarantined farms was similar to that found in farmers on quarantined farms; the prevalence was lower in consumers of products from non-quarantined farms. The prevalence of liver function abnormalities (increase in alkaline phosphatase, SGOT, SGPT, and LDH) was similar in dairy farmers and consumers. The distribution, mean and median values of serum PBB levels in consumers were found to be similar to those in dairy farmers (Lilis et al., 1978).

Although some results of the ESL studies were at times interpreted differently from the results of the MDPH studies, there was one area of consistent agreement. Neither set of studies demonstrated a positive dose-response relationship between PBB concentrations in serum or adipose tissue and the prevalence of symptoms or abnormal clinical measurements (Fries, 1985b).

9.1.3 Special studies

9.1.3.1 Examination of subjects with complaints

In the original cohort (Landrigan et al., 1979) a subset of individuals (19 males and 4 females), predominantly from the quarantined farms, was identified who had a number of disabling health complaints.

This group was systematically evaluated at a hospital together with a group of 28 PBB workers selected randomly from a pool of 100 people with previous occupational PBB exposure. The physical examination of this group of exposed farmers demonstrated a relatively high prevalence of hepatomegaly. Eight patients (35%) showed evidence of liver enlargement, defined as greater than 11 cm of vertical height in the midclavicular line. Liver scanning confirmed the presence of hepatomegaly in four of these individuals (17%), and two of them had a history of substantial alcohol intake. Ten individuals (43%) had skin lesions, but these were common dermatological problems, such as superficial mycoses and actinic keratosis, which are not uncommon in the general population and in people working outdoors. Biochemical and haematological testing revealed few abnormalities, and electromyograms, nerve conduction velocities, endocrine studies, and lymphocyte transformation studies did not provide any objective findings that correlated with subjective complaints. Psychiatric evaluation revealed a high prevalence of depression (78%) among

the farmers. Multiple tests of intelligence, memory, and functional ability did not demonstrate abnormalities. There was no relationship between fat PBB levels and physical or laboratory findings (Stross et al., 1981). The present study did not use epidemiological methods to evaluate the relationship between health effects and exposure to PBB and should, thus, be regarded as a report on cases in a group with known, but unquantified, PBB exposure.

9.1.3.2 *Cutaneous effects*

Three years after the Michigan PBB incident, the cutaneous effects were examined in a multidisciplinary study of the farming population (498 persons). Results were divided into two categories: subjective findings or symptoms of which subjects complained, and objective findings or signs, which were detected on physical examination. The results of the subjective findings were: 32% of adult residents and consumers associated with quarantined and non-quarantined farms complained of the development of unexplained cutaneous itching in a 3-year period from the PBB contamination episode to the time of the examination, compared with 22% reported by the control group. There was also a higher proportion of dryness reported; 32% of the quarantined and non-quarantined farm adults compared with 24% of the control group. Similarly, 17% of the farm study groups complained of the development of unexplained peeling and scaling during the same period compared with an incidence of 9% in the control group. The prevalence of erythema in the combined farm study groups was 12% compared with a prevalence of 5% in the controls. Increased unexplained nail growth was reported by 8% of the quarantined and non-quarantined adults compared with none in the controls. Increased abnormal sweating was a complaint of 22% of the quarantined and non-quarantined group compared with 13% in the controls. Unexplained hair loss was a complaint of 12% of the quarantined and non-quarantined group compared with 5% in the control group. All exposed groups had a significantly increased prevalence of skin symptoms compared with the comparison group. Of the symptoms elicited in a physician interview, rash was the most frequently reported. Among the farmers, rash was reported by 14% compared with 9% in the control group.

Objective findings, determined by examination, were diffuse unexplained alopecia in 4% of the combined quarantined and non-quarantined farm groups, compared with none in controls ($P < 0.005$) (Chanda et al., 1982).

Because of major flaws in the study design and biases introduced during the selection processes in the cohort and a poor response rate, no causal association with PBBs could be deduced from this study.

9.1.3.3 Effects on liver function

The serum activities of SGOT, SGPT, LDH, and alkaline phosphatase were measured in 614 Michigan adults exposed to PBB and 141 unexposed Wisconsin adults. The Michigan groups had a higher prevalence of elevated SGOT ($P < 0.005$) and SGPT ($P < 0.005$). A clear sex difference was observed. Michigan men had a higher prevalence of elevated SGPT ($P < 0.005$) and LDH ($P < 0.005$) than Michigan women, and a higher prevalence of elevated SGOT than Wisconsin men ($P < 0.005$) and SGPT ($P < 0.01$). On the basis of serum PBB analyses, no obvious relationship was observed between PBB values and liver function tests (Anderson et al., 1978d).

9.1.3.4 Porphyria

In 1977, urine samples were collected from members of farm families in Michigan, who had ingested PBB-contaminated meat and dairy products, beginning in 1973, and from members of farm families in Wisconsin with no known exposure to PBB (control group).

The total porphyrin excretion of both groups was below 200 μg/litre. Therefore, at this level, this parameter cannot be used as an indication of exposure of humans to PBB.

Out of a group of 142 persons, at least 47% were found with secondary coproporphyrinuria or with chronic hepatic porphyria Type A, demonstrating an abnormal porphyrin pattern. The incidence of this indicator of liver malfunction was higher in the PBB-exposed group than in the controls (6%). The study was limited to an assessment of liver damage as manifested by porphyrin excretion (Strik et al., 1979).

9.1.3.5 Effects on spermatogenesis

Analysis of semen from 52 PBB-exposed men compared with analysis of semen from a control group of 52 men not exposed to PBB revealed no differences in the distribution of sperm counts, motility, or morphology (Rosenman et al., 1979).

9.1.3.6 Paediatric aspects

In 1976, the paediatric aspects of PBB exposure were studied in Michigan children, using Wisconsin children as a control group (Barr, 1978, 1980).

Examination of the data from 292 Michigan farm children showed that the prevalence of symptoms was related to the quarantine status of the farm and to the method of invitation into the study. Serum PBB levels were related to the quarantine status of the farm, but not to the method of invitation into the study. No significant effects of age or sex were found on the prevalence of symptoms or serum PBB levels, except that the teenage (13–16 years of age) males had somewhat higher PBB levels. Despite the frequent reporting of symptoms of ill health, physical examination failed to reveal any objective alterations that could be attributed to PBBs. The most striking finding was a statistically significant negative correlation between the prevalence of symptoms and the serum PBB levels.

The effects of PBBs on 33 children born between September 1, 1973, and December 31, 1975, were evaluated in September, 1977. These children, born to families who lived on quarantined farms, were compared with 20 children who had not been exposed to PBBs. The birthdate interval was selected to obtain children who were exposed *in utero* or in early infancy, or both, the two time periods when damage to developing tissues and organ systems should have been maximal. The results of these studies failed to identify any effects on physical growth, physical examination, or neurological assessment, though the parents indicated by historical review that the exposed children had more illnesses, especially respiratory, than the control children. There were some indications of an inverse relationship between fat PBB levels and performance on selected developmental tests (Weil et al., 1981).

Seagull (1983) studied 19 of these children between the ages of 2 years 5 months and 3 years 11 months using five tests of the McCarthy Scales of Children's Abilities and concluded that four of the five tests had significant ($P < 0.05$) correlations with PBB exposure, i.e., the higher the PBB levels in the adipose tissue, the lower the child's developmental abilities.

Schwartz & Rae (1983) later studied these same children between the ages of 4 years 1 month and 6 years 1 month (N = 18 because one family refused to participate in the follow-up study)

with the entire battery of McCarthy Scales of Children's Abilities, plus the Wechsler Preschool and Primary Scale of Intelligence, and concluded that no significant ($P > 0,05$) differences existed.

These different conclusions from studies on the same children were summarized by Nebert et al. (1983) and commented on from statistical, clinical paediatric, and toxicological points of view.

The authors stated that different approaches to the analysis of the data were used and that, in one case, the ability tests of only five children were selected, because of time limitations in the study situation.

Comparison of fetal death rates among residents of Michigan's Lower Peninsula counties with a high percentage of quarantined farms and among residents of Upper Peninsula counties with no quarantined farms revealed no important differences in rates or trends after the contamination. Since counts of early spontaneous abortions were lacking, a complete assessment of the possible impact on reproductive outcome could not be made (Humble & Speizer, 1984).

9.1.3.7 Neurological and neuropsychiatric aspects

Neurological symptoms were the earliest and most prominent symptoms recorded in Michigan farm residents exposed to PBBs compared with an unexposed control farm population in Wisconsin. The prevalence and incidence of neurological symptoms were analysed in over 620 adults from Michigan and 153 from Wisconsin. Subsamples of both groups were examined in objective performance tests used for the assessment of neuropsychological dysfunction. In Michigan (particularly among males), those who exhibited the most marked symptoms tended to show diminished performance. Low indices of performance were also significantly correlated with intake of home-produced foodstuffs, particularly during the years 1972–74 and store-bought products during the years 1975–76. Between 1972 and 1976, the Michigan farm residents studied made significant changes in their consumption patterns of products suspected to be contaminated with PBBs compared with those of Wisconsin farm residents. Serum PBB levels were not found to be significantly higher in Michigan males and females exhibiting the most prominent neurological symptoms. Serum PBB levels were negatively correlated with performance test scores, particularly in males in older age groups (Valciukas et al., 1978, 1979).

Twenty-one persons exposed to PBBs were compared with hospital volunteers on a battery of tests measuring memory, motor strength and coordination, cortical-sensory perception, personality, and higher cognitive functioning. Patients exposed to PBBs were selected for the study only if they had persistent medical complaints. The adipose PBB levels were not correlated with performance on any test in the battery. The two groups did differ on the Minnesota Multiphasic Personality Inventory, suggesting an adjustment reaction with depressive symptoms and somatizing defences. Persons exposed to PBBs were also impaired compared with control subjects in tests of prose recall, short-term memory, concentration, and cognitive flexibility. However, these differences vanished when group differences on education and personality were statistically held constant. The selective admission criteria for the study limited the possibility of generalizing these findings (Brown & Nixon, 1979).

Forty-six persons (37 men and 9 women) with known exposure to PBBs were examined in a study designed to evaluate neurobehavioural complaints (Stross et al., 1979). These people complained of a serious deterioration in their health status and were unable to engage in their previous occupations. Comprehensive medical investigations were carried out including neurological studies and psychological evaluation. Electromyograms were abnormal in six patients (13%) with no consistent or diagnostic findings. Nerve conduction studies were abnormal in 19 patients (41%), with slowing in sensory nerve latencies the predominant finding. The abnormal values averaged 4.7 milliseconds compared with the normal value of < 3.9 milliseconds. There was an excellent correlation between patients with objective findings on neurological examination and abnormal nerve conduction studies (r value not stated). There was no relationship between the presence of these abnormalities and serum or fat PBB levels.

Despite the fact that an extensive battery of tests was administered in the psychological evaluation, few objective abnormalities were documented. The most common findings were those of somatic preoccupation, irritability, and mild depression. The tests of motor function were normal, while the tests of sensory modalities showed minor differences that were not outside normal limits. Most had IQs of between 100 and 140 with no differences between estimated and observed levels. Although most patients complained of memory difficulties, no objective deterioration in memory could be elicited.

The results of the psychiatric interviews showed that 31 patients (67%) were depressed. No evidence of endogenous depression was noted, and it was the opinion of the psychiatrists involved that the findings were characteristic of reactive depression.

9.1.3.8 Lymphocyte and immune function

The immunotoxicology of PBBs has been reviewed by Amos (1986) and Steele et al. (1989).

Bekesi et al. (1983b) summarized the findings of lymphocyte and immunological function studies, conducted in 1976 on 45 adult Michigan dairy farm residents who had consumed PBB-contaminated food products for periods ranging from three month to three years. Test comparisons were made with a group of 46 dairy farm residents in central Wisconsin who had not been exposed to PBB-contaminated food and to a group of 76 healthy subjects from the New York Metropolitan area (Bekesi et al., 1978, 1979a,b).

Marked changes in various immunological parameters were noted among the Michigan dairy farm residents compared with both the Wisconsin and New York control populations. The peripheral blood lymphocytes of only 27 of the 45 Michigan subjects exhibited a normal response to the T-cell mitogens phytohaemagglutinin and concanavalin A, to the alloantigens in the mixed leukocyte culture reaction, and to the B-cell mitogen (pokeweed mitogen). In the remaining 18 subjects, the lymphocytes showed an impaired functional response to all mitogens and alloantigens.

The lymphocytes of all 45 PBB-exposed study subjects showed a reduced proliferative T-cell response in mixed leukocyte cultures. The group of 18 individuals with decreased T-cell function had values measuring one-third to one-quarter of those obtained from the normal controls. The number of viable cells in the various subpopulations of peripheral blood lymphocytes were measured according to their ability to form stable rosettes with sheep erythrocytes in the case of the T-cells, while the B-lymphocytes were quantified by either direct immunofluorescence or by sheep erythrocytes sensitized with antibody and complement. The 27 Michigan farm residents with normal lymphocyte functions also exhibited the normal distribution of T- and B-lymphocytes. Eighteen of the 45 subjects with lymphocyte dysfunction showed

significantly reduced populations of T-cells. Despite the marked changes in the characteristic cell surface markers detected in the peripheral blood lymphocytes of the PBB-exposed Michigan farm residents, the marker for monocytes, determined by peroxidase staining or latex digestion, did not differ from that of either control group. Thus, the most significant deviation from the control samples was a marked increase in lymphocytes without detectable surface markers.

Five years later, Bekesi et al. (1983a,b) examined the same individuals and the data strongly suggested a persistent PBB-induced immune suppression. The findings were characterized by a decrease in the percentage and absolute number of T-lymphocytes, with a concomitant increase in the occurrence of lymphocytes without detectable membrane surface markers, and, in as many as 30% of the subjects retested, a reduction in the T-cell function.

Silva et al. (1979) assessed T- and B-lymphocyte numbers and lymphocyte transformation to 3 mitogens (phytohaemagglutinin, concanavalin A, and pokeweed mitogen) in 41 persons with a high exposure to PBBs (mean serum level 787 μg/litre, range 529-2560 μg/litre) and 57 persons with a low exposure (mean serum level 3 μg/litre, range 1-11 μg/litre). In contrast to the findings of Bekesi et al. (1978) there were no significant differences in the percentages of T- and B-lymphocytes among persons who experienced high or low PBB exposure or in control groups. Similarly, no significant depression of lymphocyte mitogenic responsiveness were found in those who experienced high or low PBB exposure compared with controls. No correlation was found between serum PBB levels and lymphocyte numbers or function.

In a comprehensive immunotoxicological study, 336 adult Michigan farm residents, 117 general consumers (for comparison), and 75 dairy farm residents in Wisconsin, who had not eaten PBB-contaminated food, were examined, as were 79 healthy subjects in New York City. Abnormalities in the Michigan groups included: hypergammaglobulinaemia, exaggerated hypersensitive response to streptococci, significant decreases in absolute numbers and percentages of T- and B-lymphocytes, and increased numbers of lymphocytes with no detectable surface markers ("null cells"). Significant reduction of *in vitro* immune function was noted in 20-25% of the Michigan farm residents who had eaten food containing PBBs. The decreased immune function detected among the PBB-exposed farm residents tended to affect families as a unit

and was independent of the age or sex of exposed individuals, contraindicating the possibility of genetic predisposition (Bekesi et al., 1987).

Lipson (1987) evaluated the effects of PBBs on the function and on the synthesis of immunoglobulins by peripheral blood lymphocytes. Concentrations of PBBs as low as 0.001 $\mu g/10^5$ cells decreased lymphocyte response to pokeweed mitogen: higher concentrations of PBBs stimulated the *in vitro* synthesis and release of immunoglobulins. PBBs had no effect on the quantity of E-rosette-forming cells, the total T- or B-cells, or the ratio of helper to suppressor T-cell subpopulations. Enhanced release of IgG was identified in lymphocyte cultures obtained from blood specimens of PBB-exposed Michigan farmers. The data from this study suggest that PBBs had exerted an adverse effect on cell function, but had produced a non-specific activation of B lymphocytes.

9.1.3.9 Carcinogenic embryonic antigen plasma levels

Carcinogenic embryonic antigen (CEA) titres were determined for 611 Michigan farmers exposed to PBBs and for a control unexposed population of 138 Wisconsin farmers. The overall prevalence of elevated CEA titres was slightly higher in the Michigan study group, but the difference was not statistically significant. Serum PBB concentrations appeared to be positively correlated with CEA titres. The authors discussed the possibility that the effect of PBBs may be additive to that of other factors that are known to result in an increased prevalence of elevated CEA titres (Anderson et al., 1978c).

The possibility of long-term effects of PBBs, such as cancer, cannot be ruled out. The induction of liver tumours in rodents is a matter of concern (Fries, 1985b).

9.1.3.10 Biochemical effects

Two hundred and sixty-two residents with a geometric mean serum PBB level of 19.9 μg/litre submitted at least one blood sample for clinical chemistry tests of 9 parameters during 4 different years. No consistent significant correlation with serum PBB levels was shown for any parameter (Kreiss et al., 1982). The authors suggested that tests with greater sensitivity and specificity for hepatic microsomal enzyme induction should be developed for future evaluations.

Lambert et al. (1987) were the first to study the effects of PBB exposure on the human cytochrome P-450 system, as determined by the caffeine breath test (CBT), in healthy non-smoking adults from rural Michigan with, and without, detectable serum PBB levels (concentration not stated) and in prepubescent children with known perinatal exposure to PBBs. The results were compared with the CBT results obtained from unexposed urban adult non-smokers and age-matched children. The unexposed and PBB-exposed children had similar CBT data. The adult groups were not significantly different from each other, except for the rural adults with detectable PBB levels who had significantly higher CBT values than the unexposed urban adults.

Lambert et al. (1990) conducted a field biochemical epidemiology study using the Michigan cohort consisting of 51 rural residents exposed to PBBs. The CBT and CMR (caffeine urinary metabolite ratio) were elevated in the subjects exposed to PBBs compared with the values obtained from urban non-smokers and were similar to those found in adults who smoked. A gender effect was seen in the PBB-exposed subjects, the median CBT and CMR values of the females being lower than the values of the males. There was a correlation between the CBT and the serum HxBB values ($r^2 = 0.2$, $p = 0.01$) but not between CMR and serum HxBB values.

PBBs induce hepatic cytochrome P-450IA2 enzyme activity in the human adult, but not in the child. Lambert et al. (1991) therefore investigated, in a prospective longitudinal study of 14 male and 15 female children exposed transplacentally and transmammillary to PBBs in 1973–75, whether PBB exposure altered the normal decrease in P-450IA2 activity that occurs during puberty. P-450IA2 activity was monitored via the CBT every 2 years, beginning in 1985, and compared with the P-450IA2 activity in gender- and Tanner stage-matched children not exposed to PBBs. Unlike the adult, PBBs did not alter P-450IA2 activity in the child or in the mid-pubescent adolescent (Wilcoxon rank, $P > 0.05$).

9.2 Occupational exposure

9.2.1 Epidemiological studies

Anderson et al. (1978a) investigated the health status of 55 employees (52 men and 3 women) of the Michigan Chemical Corporation, which manufactured PBBs from 1970 to 1974, in addition to a variety of other halogenated fire retardant chemicals.

Ten of those examined had formerly worked directly in the PBB production area, the other 45 persons worked in other departments in the plant. For these 55 workers, the route and quality of occupational exposure were probably different from those of farmers, since they could have been directly exposed to PBBs. The results were compared with those from a group of male farm residents and consumers from Michigan.

The prevalence of chest and skin symptoms among chemical workers as a group was significantly greater than among farmers. Significantly fewer symptoms were reported in the musculoskeletal category. The PBB department workers experienced symptoms in the skin category significantly more frequently than non-PBB workers. Blood chemistry results were similar for workers and farmers. However, both groups exhibited a significantly higher prevalence of elevated liver function tests (SGOT, SGPT) than a control population of unexposed farmers. Considering only workers with more than five years in the plant, a significantly higher prevalence of elevated CEA titres was present compared with the farmers.

9.2.2 Clinical studies

The only abnormality noted during physical examination in a group of PBB-exposed chemical workers consisting of 24 males and 4 females whose ages ranged from 23 to 62 years with a mean of 40 years, was the presence of hepatomegaly in two patients (7%), both of whom heavily indulged in alcoholic beverages, and abnormal skin examination in four patients (14%). In numerous biochemical tests, only minor elevations of serum uric acid, serum iron, and serum cholesterol were found in 20% of the chemical workers.

Elevation of triglyceride levels was noted in 50% of the chemical workers, with a mean of 185 mg % (SD ± 50 mg %), with an upper limit of normal of 150 mg %. No abnormalities in lymphocyte number or function could be determined, and there was no relationship between PBB levels and physical or laboratory abnormalities (Stross et al., 1981).

9.2.3 Special studies

9.2.3.1 Cutaneous effects

Halogen acne was observed on physical examination in 13% of 53 Michigan chemical workers exposed to PBBs compared with none in unexposed controls ($P < 0.001$) (Chanda et al., 1982).

9.2.3.2 Memory performance

Twenty-five chemical workers, who manufactured PBBs, were given objective tests of learning and memory. Although this group had high concentrations of PBBs in adipose tissue, mean scores on all memory tests were normal. The PBB concentration was not correlated with memory performance; the most contaminated workers showed no evidence of memory dysfunction (Brown et al., 1981).

9.2.3.3 Thyroid effects

Thyroid function was investigated in a cohort of 35 male workers, selected from 86 identified workers exposed for at least 6 weeks, manufacturing decabromobiphenyl, decabromobiphenyl ether, and bromine. The study revealed four cases of primary hypothyroidism (11.4%), but none in 89 control subjects. The bromine compounds were the only common exposure. A significantly higher number of the exposed workers had detectable serum levels of DeBB (0.5-1340 ng/ml), but not DeBBO (Bahn et al., 1980a,b).

Bialik (1982) investigated thyroid dysfunction in workers exposed for at least 240 h to decabromobiphenyl and decabromobiphenyl oxide over a 4-year period. The average period of employment was 3.9 years, mean age, 34.7 years. Medical questionnaires, physical examinations, and laboratory tests were conducted. For exposure data see section 5.3. Thyroid nodules were seen in 3 out of 18 workers exposed for 3 years or longer.

No detectable PBBs were found in the serum.

9.2.3.4 Reproductive effects

Bialik (1982) also studied reproductive effects in the same PBB workers.

A significant correlation was seen between length of employment and concentrations of follicle stimulating hormone (FSH). An abnormal FSH value was found in only one worker. A testicular cyst was found in one exposed worker, and epididymal nodules in two others. No testicular or epididymal nodules were seen among controls. No definite statement could be made concerning adverse effects on the prevalence of testicular and epididymal nodules, because of their prevalence in the general population.

9.2.3.5 Lymphocyte function

Decreased lymphocyte function occurred in four out of ten Michigan chemical workers. The decrease was related to higher plasma levels of PBBs (40-1200 μg/litre) (Bekesi et al., 1979b).

9.2.3.6 Mortality

A historical prospective mortality study was conducted by Wong et al. (1984) on 3579 white male workers employed between 1935 and 1976 at chemical plants with potential exposures to brominated compounds. Because of the lack of quantitative data, potential exposures of workers to PBBs were categorized as "routine" and "non-routine". None of 91 individuals of the cohort potentially exposed to PBBs on a routine basis died during the study period.

Among the 237 "non-routinely" exposed, two deaths were observed, though 6.36 were expected. One was due to cancer of the large intestine, the other was coded as arteriosclerotic heart disease.

10. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The International Agency for Research on Cancer (1986, 1987) evaluated the polybrominated biphenyls and concluded that there is sufficient evidence for the carcinogenicity to experimental animals of a commercial preparation of PBBs (FireMaster FF-1, various lots), composed primarily of hexabromobiphenyl with smaller amounts of penta- and heptabrominated isomers. There is considered to be inadequate evidence for their carcinogenicity in humans. Commercial mixtures of PBBs were thus classified into Group 28, possibly carcinogenic to humans.

The European Community added PBBs to the chemicals banned or severely restricted to certain uses owing to their effects on human health and the environment (CEC, 1988).

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ABBREVIATIONS USED IN THE MONOGRAPH

1. PBB nomenclature

PBB = polybrominated biphenyl
MoBB = monobromobiphenyl
DiBB = dibromobiphenyl
TrBB = tribromobiphenyl
TeBB = tetrabromobiphenyl
PeBB = pentabromobiphenyl
HxBB = hexabromobiphenyl
OcBB = octabromobiphenyl
NoBB = nonabromobiphenyl
DeBB = decabromobiphenyl

FM = FireMaster®

PBB congener numbering system used (Table 3).

2. Enzyme nomenclature

Designation of the cytochrome P-450-dependent mixed function monooxygenase (P-450) system, as relevant for PBBs:

Systematic nomenclature[a]	Trivial names
PB (phenobarbital)-inducible	
P-450 II	P-450
P-450 II B 1	P-450b
P-450 II B 2	P-450e
MC (3-methylcholanthrene)-inducible	
P-450 I	P-448
P-450 I A 1	P-450c
P-450 I A 2	P-450d

[a] From: Nebert et al. (1987, 1989).

3. Other compounds

AHH	aryl hydrocarbon hydroxylase
AP	alkaline phosphatase
BUN	blood urea nitrogen
DBBO	decabromobiphenyloxide
DMBA	7,12-dimethyl-benz(*a*)anthracene
GOT	glutamic-oxaloacetic transaminase
GPT	glutamic-pyruvic transaminase
GTP	glutamyl transpeptidase
LDH	lactic dehydrogenase
MFO	mixed function oxidase
MNNG	*N*-methyl-*N'*-nitro-*N*-nitroso-guanidine
PBCDD	polybrominated/chlorinated dibenzo-*p*-dioxin
PBCDF	polybrominated/chlorinated dibenzofuran
PBDD	polybrominated dibenzo-*p*-dioxin
PBDF	polybrominated dibenzofuran
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDF	polychlorinated dibenzofuran
PEG	polyethylene glycol
TPA	12-*O*-tetradecanoylphorbol-13-acetate

4. Other abbreviations

ALD	approximate lethal dose
F	female
GLC	gas liquid chromatography
HPLC	high pressure liquid chromatography
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median
M	male
NCI	National Cancer Institute (USA)
No.	number of animals
NTP	National Toxicology Program (USA)
RER	rough-surfaced endoplasmic reticulum
SER	smooth-surfaced endoplasmic reticulum
t.p.	time post-exposure
UV	ultraviolet
WHO	World Health Organization

RESUME ET EVALUATION, CONCLUSIONS ET RECOMMANDATIONS

1. Résumé et évaluation

1.1 Identité, propriétés physiques et chimiques, méthodes d'analyse

On désigne par biphényles polybromés ou polybromobiphényles (PBB) un groupe d'hydrocarbures halogénés obtenus par substitution des hydrogènes du noyau biphényle par le brome. On ne les connaît pas à l'état naturel. Leur formule brute est $C^{12}H^{(10-x-y)}Br^{(x+y)}$ dans laquelle x et y peuvent prendre toutes les valeurs de 1 à 5. Il y a théoriquement 209 homologues possibles. On n'en a synthétisé et caractérisé que quelques-uns. Les PBB produits dans un but commercial consistent essentiellement en hexa-, octa-, nona- et décabromobiphényles, mais ils contiennent également d'autres homologues. Ce sont des retardateurs de flammes de type additif et, en mélange avec les polymères ou solides secs, ils exercent une action retardatrice sur les flammes par filtrage, avec libération de bromure d'hydrogène en cas d'inflammation.

Les PBB sont préparés au moyen d'une réaction du type Friedel et Crafts, par action du brome sur le biphényle avec ou sans solvant organique et en présence de chlorure d'aluminium, de bromure d'aluminium, de fer, etc, comme catalyseur.

La plupart des recherches ont été consacrées au FireMaster® BP-6 et au FF1 qui étaient impliqués dans la catastrophe du Michigan où ce composé a été ajouté par inadvertance à de la nourriture pour animaux à la place d'oxyde de magnésium. L'intoxication des animaux qui s'en est suivie a abouti à la perte de milliers de bovins, porcs et moutons et de millions de poulets.

La composition du FireMaster® varie d'un lot à l'autre mais il est principalement composé de 2,2',4,4',5,5'-hexabromobiphényle (60 à 80%) et de 2,2',3,4,4',5,5'-heptabromobiphényle (12 à 25%) à côté d'homologues inférieurs dus à une bromation incomplète. Parmi les constituants mineurs du FireMaster® on a également observé la présence de bromochlorobiphényles et de polybromonaphtalènes. Le FireMaster FF-1 (poudre blanche) est du FireMaster BP-6 (paillettes brunes) auquel on a ajouté 2% de silicate de calcium comme antiagglomérant.

Les PBB sont des solides dont la faible volatilité décroît à mesure qu'augmente le nombre d'atomes de brome. Ils sont pratiquement insolubles dans l'eau, solubles dans les graisses et légèrement à fortement solubles dans divers solvants organiques; la solubilité diminue également à mesure qu'augmente le nombre d'atomes de brome. Ces composés sont relativement stables et chimiquement inertes, encore que des mélanges de PBB fortement substitués subissent une photodégradation avec débromation réductrice sous l'action du rayonnement ultraviolet.

Les produits de la décomposition thermique expérimentale des PBB dépendent de la température, de la quantité d'oxygène présente et d'un certain nombre d'autres facteurs. L'étude de la pyrolyse du FireMaster BP-6 en l'absence d'oxygène (600 à 900 °C) a montré qu'il se forme des bromobenzènes et des bromobiphényles inférieurs mais pas de polybromofuranes. En revanche, la pyrolyse en présence d'oxygène (700 à 900 °C) conduit à la formation de bromodibenzofuranes bi- à hepta substitués. Des quantités plus importantes ont été trouvées en présence de polystyrène et de polyéthylène. La pyrolyse du FireMaster BP-6 en présence de PVC à 800 °C a fourni un mélange de bromochlorobiphényles. On ignore qu'elle est la nature des produits d'incinération des matériaux contenant des PBB. On manque également de données sur la toxicité des dioxines et des furanes bromés et chlorobromés, mais on estime qu'elle doit être à peu près du même ordre que celle des dioxines et des furanes chlorés.

Après la catastrophe du Michigan, la principale technique d'analyse qu'on a utilisée pour la surveillance biologique des PBB dans des échantillons de tissus et de liquides biologiques ou provenant de l'environnement, était la chromatographie en phase gazeuse avec détection par capture d'électrons. Le dosage des différents homologues peut s'effectuer par chromatographie en phase gazeuse en tube capillaire avec détection par spectrométrie de masse à sélectivité ionique. En raison du nombre élevé d'homologues possibles, les recherches sont gênées par le manque d'étalons de synthèse convenables. On utilise, pour extraire les PBB des échantillons biologiques, des méthodes du type de celles qu'on applique aux pesticides. Les PBB sont extraits avec la fraction lipidique puis purifiés.

Le fait que l'on ait récemment découvert des homologues des PBB dans des échantillons biologiques prélevés dans l'environnement général n'implique pas forcément que la concentration de ces

produits y soit en augmentation. La mise au point de techniques d'analyse plus sensibles comme la spectrométrie de masse avec production d'ions négatifs par ionisation chimique, pourrait en être la cause. Il est donc urgent de procéder à des études rétrospectives. L'amélioration des méthodes de purification devrait permettre d'effectuer le dosage spécifique des homologues coplanaires toxiques car des données sont également nécessaires à leur sujet.

1.2 Sources d'exposition humaine et environnementale

La production commerciale du FireMaster® a commencé aux Etats-Unis en 1970. Elle a été arrêtée après la catastrophe du Michigan (novembre 1974). On estime qu'entre 1970 et 1976 les Etats-Unis ont produit 6000 tonnes de PBB (produits du commerce). La production de l'octabromobiphényle et du décabromobiphényle s'est poursuivie aux Etats-Unis jusqu'en 1979. En outre, l'Allemagne a produit jusqu'à la moitié de 1985 un mélange de PBB fortement bromés, le Bromkal 80-9 D. La France produit actuellement du décabromobiphényle (Adine 0102) de qualité technique. Autant qu'on sache, c'est le seul PBB qui soit actuellement produit.

Les PBB ont fait leur apparition sur le marché comme retardateurs de flamme au début des années 1970. Avant novembre 1974, l'hexabromobiphényle était le principal PBB produit dans le commerce aux Etats-Unis; il était incorporé aux résines ABS (acrylonitrile-butadiène-styrène) dans la proportion de 10% et utilisé principalement pour la fabrication de divers accessoires d'automobiles, les peintures et les vernis ainsi que dans la mousse de polyuréthanne. Les autres retardateurs de flamme à base de PBB ont des applications similaires.

Des PBB peuvent passer dans l'environnement au cours du processus normal de production à la faveur d'émissions dans l'air, dans les eaux usées, ou encore par libération dans le sol et dans les décharges, mais les concentrations correspondantes se sont révélées faibles en général.

Ces produits peuvent également passer dans l'environnement lors du transport et de la manipulation ou par suite d'accidents comme cela s'est produit dans le Michigan.

Il y a également risque de pénétration dans l'environnement lors de l'incinération de produits contenant des PBB ou lors d'incendies

au cours desquels il se forme d'autres substances toxiques comme des polybromodibenzofuranes ou des dérivés mixtes bromochlorés.

La majeure partie du volume totale de ces produits finit de toute façon par se retrouver dans l'environnement soit tels quels, soit sous forme de produits de décomposition.

1.3 Transport, distribution et transformation dans l'environnement

Il n'est pas démontré que les PBB puissent être transportés à longue distance dans l'atmosphère, mais la présence de ces composés chez les phoques de l'Arctique indique qu'ils sont largement disséminés sur la planète.

Les principales voies de pénétration des PBB dans l'environnement aquatique sont, d'une part la pollution des eaux réceptrices, les décharges de déchets industriels et, d'autre part le lessivage de dépotoirs de déchets industriels, ou encore, l'érosion de sols pollués. Les PBB sont pratiquement insolubles dans l'eau et on les retrouve principalement dans les sédiments des lacs et des rivières pollués.

La pollution du sol peut trouver son origine dans des sources polluantes ponctuelles comme par exemple des unités de production de PBB ou des dépotoirs. Une fois qu'ils ont pénétré dans le sol, les PBB ne semblent pas être facilement mobilisables. On a constaté qu'ils étaient 200 fois plus solubles dans le produit de lessivage d'une décharge que dans l'eau distillée; cela pourrait entraîner une plus large distribution dans l'environnement. Du fait de leurs propriétés hydrophobes, les PBB sont facilement adsorbés sur le sol à partir des solutions aqueuses. On a observé que les différents homologues étaient adsorbés préférentiellement en fonction des caractéristiques du sol (par exemple la teneur en matières organiques) ainsi que de la position et du nombre des atomes de brome.

Les PBB sont stables et persistants; ils sont lipophiles et ne sont en outre que légèrement solubles dans l'eau; certains homologues sont peu métabolisés et s'accumulent dans la fraction lipidique des organismes vivants. Une fois libérés dans l'environnement, ils peuvent entrer dans la chaîne alimentaire où ils subissent une concentration.

On a décelé des PBB dans les poissons de diverses régions. Les PBB peuvent pénétrer dans l'organisme des mammifères et des oiseaux par suite de l'ingestion de ces poissons.

Il est improbable que les PBB subissent une dégradation chimique purement abiotique (à l'exclusion d'une photodécomposition). On a fait état d'une persistance des PBB sur le terrain. Des échantillons de sol prélevés sur l'emplacement d'une ancienne unité de production de PBB ont été analysés plusieurs années après l'accident du Michigan; ils contenaient encore des PBB mais la proportion des divers homologues était différente, ce qui indique qu'il y avait eu décomposition partielle des résidus de PBB dans les échantillons en question.

Au laboratoire, les PBB sont facilement décomposés par le rayonnement ultraviolet. La photodécomposition d'un mélange commercial (FireMaster®) a provoqué une diminution de la concentration des homologues les plus substitués. La vitesse et le degré de photolyse des PBB dans l'environnement n'ont pas été déterminées avec précision, encore que l'observation sur le terrain montre que les PBB de départ sont très tenaces, avec dégradation partielle des homologues les moins bromés.

D'après les études en laboratoire, les mélanges de PBB semblent assez résistants à la dégradation microbienne.

On ne connaît pas d'exemple de fixation ou de décomposition des PBB par les végétaux. Par contre, les PBB sont facilement absorbés par l'organisme animal et bien qu'ils se soient révélés très persistants chez les animaux, on a tout de même retrouvé de petites quantités de métabolites. Ces métabolites consistaient principalement en dérivés hydroxylés et, dans certains cas, il y avait des traces de PBB partiellement débromés. Aucune étude sur les métabolites soufrés analogues à ceux des PCB n'a été publiée.

La bioaccumulation des PBB a été étudiée dans les poissons. En ce qui concerne les animaux terrestres, on l'a étudiée chez différentes espèces d'oiseaux et de mammifères. Les données ont été fournies par des observations sur le terrain, par l'étude des conséquences de la catastrophe du Michigan et par des études d'alimentation contrôlée. En général, on a constaté que l'accumulation des PBB dans les graisses de l'organisme était liée à la dose et à la durée d'exposition.

La bioaccumulation des différents homologues des PBB augmente avec le degré de bromation, au moins jusqu'aux dérivés tétrabromés. On peut penser que les homologues plus substitués s'accumulent dans une proportion encore plus importante. Toutefois, on ne dispose d'aucun renseignement sur le décabromobiphényle; il est possible qu'il soit peu absorbé.

On a signalé la présence de dibenzofuranes bromés et de PBB partiellement débromés comme produits de la décomposition thermique des PBB. La formation de ces composés dépend de plusieurs variables (par exemple, température, oxygène).

1.4 Concentrations dans l'environnement et exposition humaine

On ne dispose que d'un seul rapport sur la concentration des PBB dans l'atmosphère. Il s'agit d'une étude au cours de laquelle on a mesuré la concentration de ces composés au voisinage des trois unités de production et de traitement des PBB aux Etats-Unis d'Amérique.

La concentration des PBB dans les eaux de surface du même secteur ainsi que dans la décharge du Comté de Gratiot (Michigan, Etats-Unis d'Amérique) qui avait reçu entre 1971 et 1973 plus de 100 000 kg de déchets contenant 60 à 70% de PBB, a fait l'objet d'une surveillance.

Les données relatives à la surveillance des eaux souterraines au voisinage de la décharge du Comté de Gratiot ont révélé la présence de traces de PBB, même au-delà du voisinage immédiat de la décharge; toutefois aucun de ces composés n'a été décelé dans les puits d'eau potable du secteur.

On dispose de données sur la pollution tellurique par les PBB dans les secteurs où des PBB ont été ou sont produits, utilisés ou rejetés et également sur la pollution tellurique des terrains agricoles du Michigan contaminés par ces composés.

Lors de la catastrophe du Michigan, du FireMaster® a été ajouté par inadvertance à de la nourriture pour animaux. Il a fallu presque une année pour qu'on s'aperçoive de cette erreur et pour que les analyses révèlent que les PBB étaient en cause. Pendant cette période (de l'été 1973 à mai 1974), des animaux et des produits animaux contaminés ont été utilisés pour l'alimentation humaine et ont pénétré dans l'environnement de l'Etat du Michigan. Des centaines d'exploitations agricoles ont été affectées; il a fallu abattre et enterrer des milliers d'animaux et détruire des milliers de tonnes de produits agricoles.

La plupart des données concernant la contamination de la faune sauvage par les PBB concernent des poissons et des oiseaux des Etats-Unis d'Amérique et d'Europe (essentiellement la sauvagine vivant à proximité des sites industriels) ainsi que des mammifères marins.

Selon des rapports récents sur la contamination de poissons, de mammifères terrestres ou marins et d'oiseaux aux Etats-Unis d'Amérique et en Europe, ces composés seraient très disséminés. La composition en homologues dans les échantillons de poissons est très différentes de celle qu'on trouve dans des produits commerciaux. Pour les principaux, ils pourraient dans beaucoup de cas résulter d'une débromation photochimique du décabromobiphényle (BB 209), mais cela n'a pas été confirmé.

On a observé une exposition professionnelle chez des employés d'usines chimiques aux Etats-Unis d'Amérique, ainsi que chez des ouvriers agricoles, à la suite de l'accident du Michigan. Les taux médians de PBB dans le sérum et les tissus adipeux étaient plus élevés chez les employés de l'industrie chimique. On ne dispose pas de renseignements en provenance d'autres pays ou d'autres entreprises sur l'exposition professionnelle lors de la fabrication, de la formulation et de l'utilisation commerciale de ces produits.

On ne dispose pas, pour la plupart des populations humaines, d'une documentation qui fournisse des données de première main sur l'exposition aux PBB de diverses origines. Dans le Michigan, on a observé de très nombreux cas d'exposition humaine résultant d'un contact direct avec de la nourriture pour animaux contaminée et pour l'essentiel, de la consommation de viande, d'oeufs et de produits laitiers qui avaient également été contaminés par des PBB. Au moins 2000 familles (principalement des exploitants agricoles et leurs voisins) ont été fortement contaminées. En Allemagne, on a récemment décelé des PBB dans du lait de vache et du lait humain.

La composition en homologues de ces échantillons diffère de celle que l'on trouve dans le poisson. La concentration relative du BB 153 est plus élevée dans le lait humain que dans le poisson.

Les voies d'exposition de la population générale aux PBB sont mal connues. Pour autant que l'on sache, ils ne sont pas présents à fortes concentrations dans l'air ambiant ni dans l'eau. Plus importants à cet égard sont probablement les produits alimentaires riches en lipides tirés d'eaux contaminées. On ne possède aucun renseignement sur le niveau d'exposition dans l'air intérieur ni sur l'exposition par voie percutanée par suite d'un contact avec des retardateurs de flammes à base de PBB.

La composition en homologues observée dans le lait humain prélevé en Allemagne rappelait celle que l'on trouvait dans le lait

de vaches de la même région, mais à concentrations sensiblement plus élevées.

Pour évaluer l'apport journalier de PBB par l'intermédiaire de la nourriture dans la population générale, on ne dispose que de très peu de données. Si l'on suppose que le poisson contient 20 µg de PBB/kg de matières grasses et 5% de matières grasses et qu'une personne de 60 kg consomme 100 g de poisson par jour, on arrive à une ingestion journalière de 0,002 µg/kg de poids corporel. Avec une concentration de PBB de 0,05 µg/kg de matières grasses dans le lait (4% de matières grasses) et une consommation de lait de 500 ml/jour, la même personne en ingèrera quotidiennement environ 0,00002 µg/kg de poids corporel.

Un nourrisson de 6 kg consommant 800 ml de lait humain (3,5% de matières grasses) par jour ingèrera 0,01 µg de PBB/kg de poids corporel, si le lait contient de 2 µg de PBB/kg de matières grasses.

1.5 Cinétique et métabolisme

La résorption des PBB dans les voies digestives varie selon le degré de bromation, les composés les moins bromés étant les plus facilement résorbés.

Les données relatives à la résorption du DeBB et de l'OcBB/NoBB sont insuffisantes.

On retrouve des PBB dans l'ensemble du règne animal et des populations humaines, les concentrations d'équilibre les plus élevées étant observées dans les tissus adipeux. Les concentrations sont relativement élevées également dans le foie, particulièrement en ce qui concerne les homologues les plus toxiques qui semblent se concentrer dans cet organe. Le coefficient de partage des différents homologues varie d'un tissu à l'autre. En général, on note une tendance marquée à la bioaccumulation. Chez les mammifères, la transmission des PBB à la descendance se produit par la voie transplacentaire et par le lait maternel. On a constaté la présence de 2,2',4,4',5,5'-hexabromobiphényles dans du lait humain à des concentrations 100 fois plus élevées que dans le sérum maternel. Lors d'une étude portant sur plusieurs générations de rats, l'administration de PBB à une seule génération a entraîné la présence de résidus décelables dans plus de deux des générations suivantes. Chez les oiseaux, la teneur en PBB de l'organisme maternel entraîne également la présence de résidus dans les oeufs.

Des nombreux homologues des PBB persistent dans les systèmes biologiques. Ainsi, les constituants les plus abondants du FireMaster®, de même que l'octabromobiphényle et le décabromobiphényle, n'ont pas paru être métabolisés ou excrétés dans une proportion sensible. Les études métaboliques *in vitro* montrent que l'on peut établir des relations structure-activité dans le cas du métabolisme de PBB. Les PBB pourraient être métabolisés par les microsomes induits par le phénobarbital à la condition de posséder des atomes de carbone adjacents non bromés, en *méta* et en *para* du pont biphényle, sur au moins un des cycles. La métabolisation des homologues inférieurs par les microsomes induits par le 3-méthylcholanthrène nécessite la présence d'atomes de carbone non bromés en *ortho* et *méta* du pont biphényle sur au moins un des cycles; en outre, un degré important de bromation empêche la métabolisation. Chez les vertébrés, les principaux produits de métabolisation *in vitro* et *in vivo* des homologues inférieurs sont des dérivés hydroxylés. Le rendement métabolique observé est relativement faible. La réaction d'hydroxylation d'effectue probablement par l'intermédiaire d'un oxyde d'arène ou par hydroxylation directe.

L'homme, le rat, le singe rhésus, le porc, la vache et le poulet éliminent les PBB, principalement dans leurs matières fécales. Dans la plupart des cas, il semble que la vitesse d'excrétion soit faible. Les concentrations de 2,2',4,4',5,5'-hexabromobiphényles observées dans la bile et les matières fécales de sujets humains étaient égales à environ 50-70% des taux sériques et à environ 0,5% des taux dans les tissus adipeux. Les traitements administrés en vue d'améliorer l'élimination des PBB chez l'animal ou l'homme n'ont guère eu de succès. Le lait constitue une autre voie d'élimination des PBB.

Après administration de PBB à des rats et à d'autres animaux, on a constaté que les relations entre la concentration tissulaire des PBB et le temps étaient complexes et variables. Ces relations ont pu être établies en utilisant divers modèles comportementaux. On a calculé que la demi-vie d'élimination du 2,2',4,4',5,5'-hexabromobiphényles à partir des tissus adipeux du rat était d'environ 69 semaines. Dans le cas des singes rhésus, on a trouvé une demi-vie de plus de quatre ans. Chez l'homme, on estime que la demi-vie moyenne se situe dans le cas de ce composé entre 8 et 12 ans. Dans la littérature, on trouve des valeurs allant de 5 à 95 ans. On constate quelques différences dans la rétention et le "turnover" des divers homologues. Les résultats fournis par l'analyse du sérum des agriculteurs et des travailleurs de l'industrie chimique en vue

de doser le 2,3',4,4',5-pentabromobiphényle étaient incohérents. Cette incohérence est probablement due à la diversité des sources d'exposition. Les ouvriers étaient exposés à la totalité des constituants du FireMaster® alors que la population du Michigan n'avait consommé que de la viande et du lait contaminés contenant des mélanges de PBB différents par suite de la métabolisation des produits initiaux par les animaux de boucherie. Après administration d'octobromobiphényle à des rats, on n'a pas noté de diminution des taux de brome dans les tissus adipeux. On ne dispose d'aucune donnée sur la rétention du décabromobiphényle.

L'organisme humain a davantage tendance à retenir certains homologues des PBB que celui des animaux de laboratoire. C'est un facteur à prendre en considération lorsqu'on évalue le danger pour la santé humaine que représentent ces composés.

En conclusion, toutes les données disponibles indiquent que les PBB ont une forte tendance à s'accumuler et à persister dans les organismes vivants. Ils sont peu métabolisés et leur demi-vie chez l'homme est de 8 à 12 ans ou davantage.

1.6 *Effets sur les êtres vivants dans leur milieu naturel*

On ne dispose que de quelques données au sujet des effets que les PBB exercent sur les êtres vivants dans leur milieu naturel. Elles portent sur les microorganismes, les puces d'eau, les oiseaux aquatiques et les animaux d'élevage.

Les oiseaux aquatiques qui nichent sur les îles du nord-ouest du lac Michigan ont été étudiés afin de voir si les polluants du milieu étaient susceptibles d'affecter leur reproduction. On a ainsi procédé au dosage de 17 polluants et notamment de PBB, dont aucun n'a paru avoir d'effets notables sur la reproduction.

Les animaux d'élevage qui avaient ingéré une nourriture à laquelle avait été ajouté par inadvertance du FireMaster® FF-1 à la place d'oxyde de magnésium, sont tombés malades. Dans la première ferme fortement contaminée que l'on ait observée, l'exposition moyenne estimative des vaches était égale à 250 mg/kg de poids corporel. Les signes cliniques d'intoxication consistaient dans une réduction de 50% de la consommation de nourriture (anorexie) et une diminution de 40% de la production laitière, dans les semaines suivant l'ingestion des aliments contaminés. Bien qu'en l'espace de 16 jours on ait cessé de donner aux animaux la nourriture en question, la production laitière n'est pas revenue à

sa valeur normale. Certaines vaches ont présenté une pollakiurie, un larmoiement, avec en outre des hématomes, des abcès, une croissance anormale des sabots, une boiterie, une alopécie, une hyperkératose et une cachexie; plusieurs animaux sont morts dans les six mois suivant l'exposition. Au total, la mortalité dans cette exploitation a été de 24/400. Chez les veaux âgés de six à 18 mois, elle était beaucoup plus élevée. Environ 50% d'entre eux sont morts dans les six semaines avec seulement deux survivants sur 12 au bout de cinq mois. Ces animaux étaient atteints d'hyperkératose sur l'ensemble du corps. On a également noté divers problèmes affectant la reproduction.

Les résultats des autopsies sont connus pour certaines des vaches qui étaient mortes dans les six mois suivants l'exposition. L'étude histopathologique a révélé la présence d'altérations variables au niveau du foie et des reins.

Plusieurs des signes cliniques et des altérations anatomopathologiques indiqués ci-dessus ont été confirmés par la suite par des études d'alimentation contrôlée (anorexie, déshydratation, hyperlarmoiement, émaciation, hyperkératose, problèmes de reproduction, modification d'un certain nombre des paramètres biochimiques, lésions rénales).

Chez les troupeaux faiblement contaminés, on a noté une chute de la production et des cas de stérilité. Ces résultats contrastent avec ceux des études contrôlées, qui n'ont pas révélé des différences sensibles entre les troupeaux faiblement contaminés et les troupeaux témoins.

A l'origine, la substitution accidentelle concernait des aliments pour bovins, mais d'autres types de nourriture animale ont subi une contamination croisée, notamment par l'intermédiaire du matériel servant à la préparation de ces aliments. Il est probable que l'exposition qui s'en est suivie n'a pas été aussi intense que dans le cas des bovins. La contamination d'autres animaux a été signalée (volailles, porcs, chevaux, lapins, chèvres et moutons) et ces animaux ont été abattus; toutefois, les troubles dont ils auraient pu souffrir n'ont pas été précisés.

On ne dispose d'aucun renseignement au sujet des effets des PBB sur l'écosystème.

1.7 Effets sur les animaux d'expérience et les systèmes d'épreuve in vitro

Les valeurs de la DL_{50} pour les mélanges du commerce correspondent à une toxicité aiguë relativement faible (DL_{50} > 1 g/kg de poids corporel) pour le rat, le lapin et la caille, après administration par voie orale ou percutanée. Une fois la dose de PBB administrée, il y a d'ailleurs un certain délai avant l'apparition des manifestations toxiques et la mort. C'est la dose totale administrée qui détermine l'ampleur de l'intoxication, qu'elle soit donnée en une seule fois ou qu'elle soit fractionnée et administrée sur une courte période (jusqu'à 50 jours). La toxicité des PBB s'est révélée plus importante après des doses multiples qu'après une dose unique. L'exposition aux PBB n'entraine pas immédiatement la mort.

Les quelques études effectuées sur des mélanges commerciaux d'octo- et de décabromobiphényles n'ont pas provoqué de mortalité chez les rats ni les poissons. En ce qui concerne les différents homologues des PBB, on n'a étudié que trois hexaisomères, le 3,3',4,4',5,5'-HxBB et le 2,3',4,4',5,5'-HxBB étant plus toxiques pour le rat que le 2,2',4,4',5,5'-HxBB. Sur la base des données disponibles qui restent limitées, l'OcBB et le DeBB se révèlent moins toxiques et sont moins bien résorbés que les mélanges de PBB.

De nombreuses études destinées à faire ressortir les effets aigus et les effets à court terme ont montré que, parmi les signes d'intoxication par les PBB (la plupart du temps, du FireMaster), figurait une réduction de la consommation de nourriture. Aux doses mortelles, on ne peut pas attribuer la mort à des lésions anatomopathologiques affectant un organe déterminé mais plutôt à un syndrome "cachectique" qui se développe chez l'animal et constitue le premier signe d'intoxication. Au moment de la mort, la perte de poids peut atteindre 30 à 40%. Les quelques études consacrées à l'OcBB et au DeBB techniques n'ont pas révélé d'effets de ce genre.

C'est essentiellement au niveau du foie que l'on observe les altérations morphologiques et histopathologiques imputables à l'exposition aux PBB. Ainsi l'hypertrophie du foie s'observe fréquemment à des doses plus faibles que celles qui entraînent une perte de poids. Chez les rongeurs, les principales altérations histopathologiques pourraient être un gonflement et une vacuolisation généralisée des hépatocytes, la prolifération du réticulum endoplasmique agranulaire et la nécrose des cellules

individuelles. La gravité des lésions dépend de la dose et de la composition du mélange administré.

On a observé une diminution du poids du thymus chez des rats, des souris et des bovins après absorption de FireMaster®, mais non d'OcBB ou de DeBB.

On a fait état d'une augmentation du poids de la thyroïde et de modifications histologiques au niveau de cette glande chez le rat à des concentrations faibles.

Il est évident que les différents homologues des PBB ne présentent pas le même type de toxicité. Les isomères et les homologues les plus toxiques provoquent une réduction du poids du thymus ou du corps et déterminent des altérations histologiques marquées au niveau du foie et du thymus. On a classé les byphényles halogénés en fonction de leur structure. La catégorie 1 comporte les isomères et les homologues qui n'ont pas de substituants en *ortho* (PBB coplanaires). Les dérivés monosubstitués en *ortho* constituent la deuxième catégorie. Les autres PBB (principalement ceux qui comportent deux bromes ou davantage en *ortho*) sont classés dans la troisième catégorie. Les homologues de la catégorie 1 ont tendance à provoquer les effets les plus graves alors que ceux de la deuxième et de la troisième catégorie entraînent des effets toxicologiques qui vont diminuant. A l'intérieur d'une même catégorie, le degré de bromation peut également avoir une influence sur la toxicité.

Sur toutes les combinaisons étudiées, c'est le 3,3',4,4',5,5'-HxBB qui s'est révélé le plus toxique. Cet homologue est présent à faibles concentrations dans le FireMaster®. Parmi les principaux constituants du FireMaster®, c'est le 2,3,3',4,4',5-HxBB qui s'est révélé le plus toxique devant le 2,3',4,4',5,5'-HxBB et le 2,3',4,4',5-PeBB, dans cet ordre. Le principal constituant du FireMaster®, le 2,2',4,4'5,5'-HxBB s'est révélé relativement non toxique, de même que le 2,2',3,4,4',5,5'-HpBB, qui vient en seconde position par ordre de concentration.

On ne connaît pas très bien la toxicité des mélanges d'OcBB et de DeBB techniques eu égard à leur teneur en divers homologues (et autres contaminants éventuels).

Les tests habituels d'irritation cutanée et oculaire de même que les tests de sensibilisation qui ont été effectués sur des mélanges de PBB techniques (OcBB et DeBB) n'ont révélé aucune réaction ou

du moins, seulement des réactions légères. Toutefois on a relevé une hyperkératose et une alopécie chez les bovins exposés et des lésions rappelant la chloracné ont été observés chez les singes rhésus après ingestion de FireMaster®. Le FireMaster® a produit une hyperkératose de la surface interne de l'oreille chez le lapin, mais ses deux principaux constituants (le 2,2',4,4',5,5'-HxBB et le 2,2',3,4,4',5,5'-HpBB) ne produisaient pas cet effet. En fractionnant le FireMaster®, on a constaté que l'essentiel de son activité était le fait des fractions les plus polaires contenant des constituants mineurs. En traitant des lapins avec de l'HxBB exposé à la lumière solaire, on a constaté l'apparition d'une hyperkératose grave au niveau de l'oreille.

L'administration de faibles doses d'OcBB technique pendant une longue période à des rats n'a pas affecté leur consommation de nourriture ni leur poids corporel, mais on a constaté chez les rats qui avaient reçu pendant sept mois une dose de 2,5 mg/kg de poids corporel, une augmentation du poids relatif du foie. L'administration pendant une longue durée à des rats de FireMaster® mêlé à leur nourriture à la dose de 10 ng/kg de poids corporel pendant six mois, est restée sans effet sur leur consommation de nourriture. En revanche à la dose de 1 mg/kg de poids corporel administrée sur une période de six mois, on constatait une modification du poids du foie. Chez les rattes qui recevaient 0,3 mg/kg de poids corporel de FireMaster®, on constatait une réduction du poids du thymus. Des altérations histopathologiques ont également été observées. Des études d'alimentation contrôlées poursuivies pendant une longue période sur des bovins exposés à de faibles doses de FireMaster®, n'ont pas fait ressortir d'effets nocifs, à en juger par la prise de nourriture, les signes cliniques, les modifications clinicopathologiques ou le rendement du bétail. Les visons, les cobayes et les singes se sont révélés plus sensibles à l'intoxication par les PBB.

On a observé chez le rat des effets à long terme attribuables à la rétention des PBB après administration de fortes doses de FireMaster® au cours de la période prénatale ou périnatale.

Les effets délétères les plus fréquemment observés sur la reproduction consistaient en une résorption du foetus et une moindre viabilité de la progéniture. Chez les visons, on observait encore certains effets à la concentration de 1 mg/kg de nourriture. Une réduction de la viabilité de la progéniture a été observée chez des singes rhésus après 12,5 mois d'exposition au FireMaster® (dose: 0,3 mg/kg de nourriture). Les singes ont reçu une dose

quotidienne de ce mélange, égale à 0,01 mg/kg de poids corporel et la dose totale était de 3,8 mg/kg de poids corporel. Il n'a pas été possible d'évaluer les études de reproduction ni les études neurocomportementales effectuées sur des singes et des rats à faibles doses, car les publications en question n'étaient pas suffisamment explicites quant au protocole expérimental des essais. Chez les rongeurs, on a observé un faible pouvoir tératogène à des doses élevées, susceptibles d'être toxiques pour les mères.

Les PBB perturbent les fonctions endocrines. Chez des rats et des porcs on a observé une réduction des taux sériques de thyroxine et de triiodothyronine qui était liée à la dose. Les PBB perturberaient également, dans la plupart des cas, les taux d'hormones stéroïdiennes. L'ampleur des effets dépend de l'espèce ainsi que de la dose et de la durée de l'administration.

Les PBB ont également produit une porphyrie chez des rats et des souris mâles à des doses quotidiennes ne dépassant pas 0,3 mg/kg de poids corporel. La dose quotidienne maximale sans effets était de 0,1 mg/kg de poids corporel. On constatait une influence marquée des PBB sur l'accumulation de vitamine A ainsi que des effets sur la métabolisme intermédiaire.

Après exposition aux PBB, on observe fréquemment une atrophie du thymus et on a constaté que d'autres tissus lymphoïdes étaient également affectés. On a également mis en évidence d'autres indicateurs témoignant d'une dépression des fonctions immunitaires par le FireMaster®. On manque de données concernant l'OcBB, le NoBB, le DeBB ou les différents homologues des PBB.

Un des effets des PBB qui ait été le plus intensivement étudié est l'induction des oxydases à fonction mixte. De fait, on a systématiquement constaté que le FireMaster® se comportait comme un inducteur de type mixte des enzymes microsomiennes du foie chez le rat et chez toutes les autres espèces étudiées. Cette induction a été également observée dans d'autres tissus, mais dans une moindre mesure. L'aptitude à induire les enzymes microsomiennes hépatiques varie d'un homologue à l'autre. On a mis en évidence des corrélations entre la structure et l'aptitude à induire les enzymes microsomiennes.

Plusieurs études ont montré que les PBB étaient capables de modifier l'activité biologique de divers médicaments et substances toxiques. Cela s'explique peut-être en partie par le fait que les

PBB sont capables d'induire les enzymes microsomiennes qui interviennent dans l'activation ou la désactivation des substances xénobiotiques.

Le FireMaster® et certains de ces principaux constituants se sont révélés capables d'inhiber la communication intercellulaire in vitro. Cette inhibition s'est produite à des concentrations non cytotoxiques. Cette cytotoxicité, de même que la capacité d'inhiber la coopération métabolique paraît liée à la structure et plus précisément à la présence ou à l'absence de substitution en *ortho*.

Les épreuves *in vitro* et *in vivo* (mutagénèse des cellules microbiennes et mammaliennes, altération des chromosomes de cellules mammaliennes, transformation des cellules mammaliennes, lésion et réparation de l'ADN) n'ont pu mettre en évidence de mutagénicité ou de génotoxicité imputables aux divers homologues des PBB ou aux mélanges qui sont vendus dans le commerce.

Les études de toxicité à long terme ont montré que le foie était la principale cible des effets cancérogènes du PBB. Chez des souris et des rats, mâles et femelles, qui recevaient du FireMaster® par voie orale, on a noté une augmentation sensible de l'incidence des carcinomes hépatocellulaires. Des effets cancérogènes sur le foie ont également été observés chez des souris qui avaient reçu pendant 18 mois une alimentation contenant une dose totale de 100 mg/kg ou davantage de Bromkal 80-9D (nonabromobiphényle technique) en doses quotidiennes de 5 mg/kg de poids corporel. La dose quotidienne de PBB la plus faible qui ait produit des tumeurs (pour la plupart, des adénomes) chez des rongeurs, était de 0,5 mg/kg de poids corporel pendant deux ans. Les rats qui en avaient reçu quotidiennement 0,15 mg/kg de poids corporel, en plus de ce qu'il leur avait été administré pendant la période prénatale et périnatale, n'ont pas présenté le moindre effet indésirable. La pouvoir cancérogène de l'octabromobiphényle et du décabromobiphényle techniques n'a pas été étudié.

Ni le FireMaster BP-6 ni le 2,2′,4,4′,5,5′-hexabromobiphényle ne se sont comportés comme des initiateurs tumoraux (en utilisant le TPA comme promoteur) ou comme des promoteurs tumoraux (en utilisant la DMBA comme initiateur) lors d'épreuves biologiques sur l'épiderme de souris. Toutefois, en utilisant le même modèle (épiderme de souris) et avec du DMBA ou de la MNNG comme initiateur, le FM FF-1 et le 3,3′,4,4′5,5′-hexabromobiphényle mais non pas le 2,2′,4,4′5,5′-hexabromobiphényle, ont

présenté une activité tumoro-promotrice. Lors d'une épreuve biologique sur foie de rat effectuée en deux temps, et avec du phénobarbital comme promoteur, on a constaté que le 3,3',4,4'-tétrabromobiphényle se comportait comme un initiateur faible. Avec ce même modèle animal, en présence de diéthylnitrosamine et après hépatectomie partielle, on a constaté que le FM, le 3,3',4,4'-tétrabromobiphényle et le 2,2',4,4',5,5'-hexabromobiphényle, mais non pas le 3,3',4,4',5,5'-hexabromobiphényle, se comportaient comme des promoteurs tumoraux.

Les résultats des études sur la communication cellulaire, les résultats négatifs fournis par les études de génotoxicité et de mutagénicité, ainsi que ceux des épreuves de promotion tumorale, montrent que les mélanges de PBB et les divers homologues étudiés provoquent l'apparition de cancers par un mécanisme épigénétique. On ne dispose d'aucun renseignement sur l'octa-, le nona-, le décabromobiphényles techniques.

Le mode d'action qui est à la base des nombreuses manifestations de la toxicité des PBB et des composés apparentés reste inconnu. Toutefois, certains des effets observés, comme le syndrome cachectique, l'atrophie du thymus et l'hépatotoxicité, les manifestations dermatologiques et les effets délétères sur la fonction de reproduction peuvent être attribués à une interaction avec les récepteurs Ah ou TCDD, interaction qui entraîne une modification de l'expression d'un certain nombre de gènes. L'interaction avec ces récepteurs varie selon les divers homologues, les homologues coplanaires étant les plus actifs.

Nombre des effets des PBB s'observent après une exposition de longue durée. Cela s'explique peut-être par le fait que certains homologues s'accumulent fortement et que l'organisme ne les métabolise et ne les élimine que difficilement. Il s'en suit une accumulation de ces composés dans l'organisme qui finit par submerger les mécanismes de compensation et entraîne des effets délétères.

Certains contaminants connus du FireMaster®, en l'occurrence des polybromonaphtalènes (PBN) sont fortement toxiques et tératogènes. Bien qu'ils ne soient présents qu'en petites quantités dans le FireMaster®, il n'est pas exclu qu'ils contribuent à sa toxicité.

Les études portant sur le FireMaster® et son principal constituant le 2,2',4,4'5,5'-HxBB, ont montré que leurs produits de

photolyse étaient plus toxiques que les composés initiaux. Les produits du pyrolyse du FM provoquent l'induction des oxydases à fonction mixte, une perte de poids et une atrophie du thymus. On a également observé que les produits de pyrolyse de l'OcBB technique produisaient une hypertrophie du foie.

1.8 Effets sur l'homme

On ne connaît aucun exemple d'intoxication aiguë par les PBB chez l'homme auquel on puisse comparer les effets potentiels à faibles doses résultant de l'accident survenu dans le Michigan aux Etats-Unis d'Amérique en 1973. Les principales études épidémiologiques ont été menées par le Michigan Department of Public Health (MDPH) et l'Environmental Science Laboratory de la Mount Sinaï School of Medicine, New York (ESL).

On estime que les personnes les plus fortement contaminées avaient consommé 5 à 15 g de PBB sur une période de 230 jours par l'intermédiaire du lait. Il est possible que la consommation de viande ait constitué une source de contamination supplémentaire. Chez certains des agriculteurs et chez la plupart des membres de la population générale du Michigan, le niveau d'exposition était beaucoup plus faible, la dose totale étant de 9 à 10 mg. Il est possible cependant que certaines personnes aient reçu une dose totale d'environ 800 à 900 mg. (Une dose totale de 9 mg correspond à 0,15 mg/kg de poids corporel et une dose de 900 mg, à 15 mg/kg de poids corporel pour un adulte moyen de 60 kg; pour un enfant, la dose par kg/poids corporel serait plus élevée).

En 1974, la première étude du MDPH a consisté à comparer l'état de santé des personnes travaillant dans les fermes mises en quarantaine, à celui du personnel des fermes de la même région qui n'étaient pas frappées par cette mesure. Dans les deux groupes, on a constaté divers symptômes, mais sans pouvoir dégager de différences. Aucune anomalie inhabituelle n'a été constatée, qu'il s'agisse du coeur, du foie, de la rate, du système nerveux, des résultats de l'analyse d'urine et de la NFS, non plus qu'en ce qui concerne tous les autres parametres médicaux examinés. Une étude ultérieure très complète menée par le MDPH et portant sur des groupes soumis à une exposition de degré variable, n'a pas permis de mettre en évidence de corrélation positive entre les taux sériques de PBB et la fréquence des symptômes ou des affections observés. L'ESL a étudié environ 990 personnes vivant sur des exploitations agricoles, 55 travailleurs de l'industrie chimique et un groupe de producteurs de lait du

Wisconsin qui ont fait office de témoins. Les symptômes étaient plus fréquent chez les exploitants du Michigan que chez ceux du Wisconsin. C'est dans le cas des symptômes neurologiques et musculo-squelettiques, au sens large, que les différences étaient les plus importantes. De même les taux sériques de certaines enzymes hépatiques et de l'antigène carcino-embryonnaire étaient plus fréquemment élevés chez les fermiers du Michigan que chez ceux du Wisconsin. La prévalence des symptômes respiratoires et cutanés était plus forte chez les travailleurs de l'industrie chimique avec également des symptômes musculo-squelettiques moins fréquents que chez les agriculteurs. Les résultats des travaux de l'ESL n'ont pas toujours été interprétés de la même manière que ceux d'autres études comparables, mais tous sont d'accord sur un point. Aucune de ces séries d'études n'a mis en évidence de corrélation dose-réponse positive entre les taux de PBB dans le sérum ou les tissus adipeux et la prévalence des symptômes ou des anomalies cliniques. Un certain nombre d'aspects cliniques ont été étudiés de manière plus intensive par des méthodes spéciales. En particulier, l'examen des aspects neurologiques au moyen de tests objectifs de performance a révélé, dans une étude tout du moins, l'existence d'une corrélation négative entre les taux sériques de PBB et les résultats des tests, en particulier chez les hommes d'âge mûr. Quant aux autres études, elles n'ont pas mis en évidence de relation entre la concentration des PBB dans le sérum ou les tissus adipeux et les résultats d'une batterie de tests portant sur la mémoire, la force musculaire, la coordination, la perception cortico-sensorielle, la personnalité, les fonctions cognitives supérieures et d'autres fonctions. Les aspects pédiatriques de l'exposition aux PBB ont été étudiés dans les familles examinées par l'ESL. Bien que de nombreux symptômes aient été signalés, l'examen médical n'a pas révélé d'anomalie objective attribuable à l'exposition au PBB. Des opinions différentes se sont exprimées à propos des effets neurospychologiques plus subtils observés dans la descendance de ces personnes et les résultats des études portant sur la capacité de développement sont également controversés. Cela vaut aussi pour l'étude des lymphocytes et de la fonction immunitaire. C'est ainsi que selon plusieurs auteurs, il n'y avait pas de différences entre les groupes à fort et faible taux sérique de PBB pour ce qui concerne le nombre de lymphocytes et les fonctions lymphocytaires, alors que d'autres ont constaté une réduction sensible des sous-populations de lymphocytes T et de lymphocytes B chez environ 40% des personnes exposées dans le Michigan, par rapport aux groupes non exposés, avec en outre une altération de la fonction lymphocytaire, à savoir une diminution de la réponse aux mitogènes.

Dans les études épidémiologiques qui ont été passées en revue, on s'est efforcé d'évaluer la relation entre l'exposition aux PBB et un grand nombre d'effets sur le comportement et de symptômes subjectifs. Cependant, la plupart des ces études présentent de graves insuffisances au niveau de la conception et en particulier, elles laissent subsister des facteurs de confusion qui rendent difficile, voire impossible, toute conclusion sur la relation éventuelle entre l'exposition aux PBB et d'éventuels effets sur la santé. On ne dispose pas d'un recul suffisant pour pouvoir évaluer les effets cancérogènes éventuels de ces composés.

On a identifié deux petits groupes de travailleurs exposés de par leur profession à un mélange de PBB ou à du DeBB et du DBBO. Des lésions rappelant une chloracné ont été observées chez 13% des travailleurs exposés au mélange de PBB, alors que ceux qui avaient été exposés au DeBB ne présentaient pas de telles lésions. Toutefois la prévalence de l'hypothyroïdie était plus élevée dans ce groupe.

1.9 Evaluation globale de la toxicité et de la cancérogénicité

La seule étude toxicologique qui ait été effectuée à vie sur des animaux d'expérience a été menée récemment dans le cadre du Programme national de toxicologie (National Toxicology Programme, NTP) sur des rats et des souris. La dose la plus faible étudiée qui produisait encore des effets cancérogènes était égale à 0,5 mg/kg de poids corporel et par jour (formation de tumeurs hépatiques chez les rongeurs). D'autres études du même genre ont mis en évidence un effet cancérogène à la dose quotidienne de 3 mg/kg de poids corporel, sur une durée de six mois. L'étude de six mois montre qu'une exposition pendant une durée inférieure à la vie normale de l'animal à des doses voisines, entraîne également des effets délétères analogues. Il est possible qu'à plus faibles doses, les PBB exercent des effets sur la reproduction des primates sous-hominiens et des visons.

En outre, l'étude de deux ans effectuée dans le cadre du NTP a montré qu'une dose quotidienne de 0,15 mg/kg de poids corporel avec exposition prénatale et périnatale de la mère à une dose quotidienne de 0,05 mg/kg de poids corporel, ne produisait aucun effet nocif. Par conséquent, la dose totale absorbée quotidiennement à partir de la nourriture, de l'eau, de l'air et du sol devrait être inférieure à 0,15 μg/kg de poids corporel, si l'on extrapole les résultats obtenus concernant la dose sans effet nocif observable lors d'une étude de cancérogénicité positive, en appliquant à cet

effet un coefficient d'incertitude (coefficient de sécurité) de 1000, puisque ces composés induisent probablement des cancers par un mécanisme épigénétique.

On estime que la dose totale reçue par le sous groupe de population du Michigan se situait entre 0,15 et 15 mg/kg de poids corporel sur une période de 230 jours. Si on rapporte cette dose à la durée moyenne de vie normale d'un être humain, cela correspondrait, pour cette population, à une dose quotidienne de 0,6 ng à 6 μg/kg de poids corporel.

On estime que pour les adultes de la population générale, l'apport quotidien total de PBB par kg de poids corporel à partir des sources répertoriées, est de l'ordre de 2 ng; il est de 10 ng pour les nourrissons nourris au sein. Il convient de noter que ces estimations reposent sur des données régionales très limitées.

Ces calculs reposent sur l'hypothèse que la concentration des PBB n'atteindra pas un état stationnaire au cours de l'existence et que l'on peut substituer une exposition forte sur une courte durée à une exposition faible sur une longue durée, étant donné que ces composés sont très mal métabolisés et excrétés.

On ne dispose pas de données suffisantes pour l'OcBB, le NoBB et le DeBB pour calculer quel serait l'apport quotidien total maximal ne produisant pas d'effets indésirables.

2. Conclusions

La plupart des homologues des PBB qui entrent dans la composition des retardateurs de flammes vendus dans le commerce, sont lipophiles, persistants et s'accumulent dans les biotes. Ces composé subissent une bioamplification le long des réseaux trophiques et constituent une menace, en particulier pour les organismes qui se trouvent en fin de réseau. En outre, certains constituants des PBB sont les précurseurs de dibenzofuranes polybromés toxiques qui se forment lors de la combustion.

Outre les émissions qui se produisent au cours de la fabrication et de l'utilisation des PBB, ceux-ci pénètrent dans l'environnement du fait de la très large utilisation des retardateurs de flammes dont ils sont les constituants. Une part très importante des PBB produits finit par passer dans l'environnement du fait de la très grande stabilité de ces composés.

On trouve également des PBB dans des échantillons prélevés dans l'environnement et sur des sujets humains, en des lieux éloignés des endroits où l'on sait que ces composés sont produits. La composition en homologues des PBB dans les échantillons provenant de l'environnement ne correspond pas à celle que l'on trouve dans les produits techniques, ce qui indique qu'il y a transformation dans le milieu, peut-être à la suite d'une débromation photochimique.

On dispose actuellement des très peu de données sur l'ampleur de l'exposition de la population générale aux PBB. Toutefois, dans les quelques cas où on a procédé à des mesures, on a pu mettre en évidence des traces de PBB. Actuellement, cette exposition ne cause pas d'inquiétude, mais il faudrait éviter que ces composés ne continuent à s'accumuler. D'après les observations faites sur l'homme à la suite de l'accident du Michigan, il semblerait que les personnes contaminées aient été exposées à des doses de plusieurs ordres de grandeur supérieures à celles que l'on observe dans la population générale. On n'a pas observé dans la population du Michigan d'effets concluants qui puissent être attribués à l'exposition aux PBB, encore que la période de suivi ne soit pas suffisante pour permettre à d'éventuels cancers de se manifester. Etant donné que les taux de PBB dans les tissus adipeux et le sérum restent élevés dans la population du Michigan, il y a poursuite de l'exposition interne. En revanche, on a bien observé des effets toxiques chez les bovins de cette région. On explique cette discordance par le fait que les bovins avaient été davantage exposés.

L'exposition professionnelle n'a été étudiée que dans deux unités de production des Etats-Unis d'Amérique. Il semble que chez les travailleurs employés à la production des PBB, il puisse y avoir apparition de lésions rappelant une chloracné; quant aux travailleurs exposés au DeBB, ils peuvent présenter une hypothyroïdie. Aucune enquête n'a été menée chez les travailleurs qui confectionnent des produits commerciaux à base de deca-, d'octa- ou de nona-bromobiphényles.

Les PBB sont extrêmement persistants chez les organismes vivants et ils peuvent conduire à une intoxication chronique et à des cancers. Bien que la toxicité aiguë soit faible, on constate l'apparition de cancers à des doses quotidiennes de 0,5 mg/kg de poids corporel avec une dose sans effet observable de 0,15 mg/kg de poids corporel et par jour. On a observé un certain nombre d'effets toxiques chroniques chez les animaux de laboratoire à des

doses quotidiennes de l'ordre de 1 mg/kg de poids corporel, administrées pendant de longues périodes.

3. Recommandations

3.1 Généralités

Le Groupe de travail estime qu'il faut éviter à l'homme et à l'environnement d'être exposés aux PBB en raison de la forte persistance et de la forte bioaccumulation de ces composés ainsi que des effets nocifs qu'ils peuvent provoquer en cas d'exposition de longue durée à de faibles doses. Aussi convient-il de ne plus utiliser de PBB dans des produits du commerce.

Comme les données dont on dispose sur la toxicité du DeBB et de l'OcBB sont limitées, qu'ils sont extrêmement persistants et susceptibles d'être dégradés dans l'environnement et qu'en outre, leur combustion entraîne la formation de dérivés encore plus toxiques, ils ne doivent pas être utilisés dans le commerce, du moins tant qu'on aura pas démontré que cet usage est sans danger.

La cohorte du Michigan est toujours en observation et il est nécessaire que les données obtenues soient publiées.

3.2 Recherches futures

Il convient de développer la surveillance des PBB chez l'homme et dans l'environnement, et en particulier sur les lieux de travail, qu'il s'agisse de la fabrication proprement dite des PBB ou de leur utilisation; cette surveillance devra porter sur chaque homologue en particulier et englober également l'OcBB, le NoBB et le DeBB. Ces composés doivent figurer dans les programmes de surveillance des dérivés halogénés actuellement en cours. On devra notamment continuer à suivre la tendance des concentrations de PBB dans l'environnement et leur distribution géographique. On procédera également à un relevé des décharges où des PBB sont susceptibles de passer dans l'environnement.

Il faudrait procéder à des expériences de thermolyse simulant les conditions d'un incendie accidentel ou de l'incinération de déchets municipaux. Des travaux complémentaires devront également être consacrés à l'étude du mécanisme de la toxicité et de la cancérogénicité des PBB et des composés apparentés. Les PBB peuvent être utilisés comme modèles pour ces recherches. Tous ces travaux devront utiliser des homologues purifiés.

Les effets des PBB sur la reproduction restent mal connus. Aussi serait-il souhaitable d'effectuer des études de longue durée bien conçues, concernant l'effet des faibles doses sur la reproduction, en utilisant une espèce vulnérable.

Il importe également d'obtenir davantage de renseignements sur la biodisponibilité et la toxicocinétique de l'OcBB/NoBB, du DeBB et d'un certain nombre d'homologues.

RESUMEN Y EVALUACION, CONCLUSIONES Y RECOMENDACIONES

1. Resumen y evaluación

1.1 Identidad, propiedades físicas y químicas y métodos analíticos

Los bifenilos polibromados o polibromobifenilos (PBB) son un grupo de hidrocarburos halogenados formados por sustitución del hidrógeno del bifenilo por bromo. No se conoce ningún PBB de origen natural. Estas moléculas responden a la fórmula $C_{12}H_{(10-x-y)}Br_{(x-y)}$, donde x e y están comprendidos entre 1 y 5. Por consiguiente, teóricamente son posibles 209 formas moleculares, pero sólo se han sintetizado individualmente y caracterizado un reducido número. Los PBB fabricados para uso comercial consisten principalmente en hexa-, octa-, nona-, y decabromobifenilos, pero contienen también otros productos de la misma familia. Son pirorretardantes que se emplean como aditivos, y que mezclados con material polimérico líquido o sólido seco le confieren propiedades pirorretardantes de tipo filtrante; en caso de ignición se produce una liberación química de ácido bromhídrico.

La fabricación de los PBB se basa en una reacción de Friedel-Crafts entre el bifenilo y el bromo, en presencia de un disolvente orgánico en ocasiones, y de un catalizador que puede ser cloruro de aluminio, bromuro de aluminio o hierro.

La mayor parte de las investigaciones realizadas se refieren a los productos FireMaster BP-6 y FF-1, responsables de la catástrofe que se produjo en Michigan cuando, inadvertidamente, fueron agregados al pienso de los animales en lugar del óxido de magnesio que correspondía. La consiguiente contaminación acarreó la muerte de miles de cabezas de ganado vacuno, porcino y ovino, así como de millones de pollos.

La composición de la mezcla FireMaster® varía de un lote a otro, pero sus principales componentes son el 2,2′,4,4′,5,5′-hexabromobifenilo (60-80%) y el 2,2′,3,4,4′,5,5′-heptabromobifenilo (12-25%), junto con los cuales se hallan también otros compuestos menos bromados que son el resultado de una reacción de bromación incompleta. Se han detectado también bromoclorobifenilos y naftalenos polibromados como componentes minoritarios de FireMaster®. FireMaster FF-1 (polvo blanco) se obtiene a partir de FireMaster BP-6 (escamas pardas), por adición, como agente antiaglutinante, de silicato de calcio al 2%.

Los PBB son sólidos de baja volatilidad; ésta disminuye al aumentar el número de átomos de bromo. Son prácticamente insolubles en agua, solubles en grasas, y entre poco y muy solubles en diversos disolventes orgánicos; la solubilidad también disminuye al aumentar el número de átomos de bromo. Son compuestos relativamente estables y químicamente inertes, pero las mezclas de PBB muy bromados se fotodegradan y sufren una debromación reductiva al ser expuestas a la radiación ultravioleta.

Los productos de la descomposición térmica experimental de los PBB dependen de la temperatura, de la cantidad de oxígeno presente y de otros varios factores. Las investigaciones realizadas sobre la pirólisis de FireMaster BP-6 en ausencia de oxígeno (600-900 °C) han demostrado que se forman bromobencenos y bifenilos menos bromados, pero no así furanos polibromados. Por el contrario, la pirólisis en presencia de oxígeno (700-900 °C) generó una cierta cantidad de di- a heptabromodibenzofuranos. En presencia de poliestireno y polietileno se hallaron niveles más altos. La pirólisis de FireMaster BP-6 en presencia de PVC a 800 °C dio lugar a una mezcla de bromoclorobifenilos. No se dispone de información sobre la naturaleza de los productos de incineración de los materiales que contienen PBB. Poco se sabe acerca de la toxicidad de las dioxinas y furanos bromados y bromados/clorados, pero se estima que debe ser de aproximadamente la misma magnitud que la de las dioxinas y furanos clorados.

La principal técnica analítica empleada para el control biológico de los PBB en muestras del medio y en tejidos y líquidos biológicos tras la catástrofe de Michigan fue la cromatografía de gases con detector de captura de electrones. Los diversos productos de la familia pueden determinarse individualmente mediante cromatografía de gases capilar, y aún es posible conseguir una detección más específica si se emplea la espectrometría de masas de control de determinados iones. Como el número de posibles miembros de esta familia de productos es muy elevado, las investigaciones se ven dificultadas por la falta de patrones sintéticos adecuados. Los métodos empleados para extraer PBB de muestras biológicas se han venido basando en los usados con los plaguicidas. Los PBB son extraídos con la grasa, y purificados a continuación.

El hallazgo reciente de PBB en muestras biológicas de fondo no significa necesariamente que su concentración esté aumentando en el medio: ello podría deberse a la aparición de técnicas analíticas más sensibles, como la espectrometría de masas de ionización

química de iones negativos. De ahí la necesidad de realizar cuanto antes estudios retrospectivos. Los métodos mejorados de purificación exhaustiva permiten realizar análisis específicos de los PBB coplanares tóxicos, datos que son igualmente necesarios.

1.2 Fuentes de exposición humana y ambiental

La producción comercial de FireMaster® comenzó en los Estados Unidos en 1970, pero se interrumpió tras la catástrofe de Michigan (noviembre de 1974). La producción estimada de PBB en los Estados Unidos entre 1970 y 1976 fue de 6000 toneladas (cantidades comerciales); hasta 1979 se siguió produciendo en el país octabromobifenilo y decabromobifenilo. En Alemania se produjo hasta mediados de 1985 una mezcla de PBB altamente bromados conocida como Bromkal 80-9 D. Actualmente se produce en Francia decabromobifenilo (Adine 0102) de calidad técnica. Al parecer, esos son los únicos PBB que se siguen produciendo hoy en dia.

Los PBB se introdujeron a principios de los años setenta como pirorretardantes. Hasta noviembre de 1974 el PBB más importante comercialmente en los Estados Unidos era el hexabromobifenilo, producto que se incorporaba a los plásticos (10% de contenido de PBB), de acrilonitrilo-butadieno-estireno (ABS), material usado principalmente en la fabricación de pequeños utensilios y componentes de automóvil, revestimientos, barnices y espuma de poliuretano. Los otros PBB pirorretardantes tienen aplicaciones similares.

Durante el proceso normal de producción pueden tener lugar pérdidas de PBB en el medio ambiente, por emisión a la atmósfera o por su incorporación a aguas residuales, suelos o vertederos, pérdidas que sin embargo, según se ha observado, son por lo general de escasa importancia.

Estos compuestos pueden llegar también al medio durante su transporte y manipulación, así como de manera accidental, como ocurrió en Michigan.

Existe también la posibilidad de que pasen al medio de resultas de la incineración de materiales que contienen PBB, o a causa de fuegos accidentales, formándose en estos casos otros productos tóxicos, como polibromodibenzofuranos o derivados mixtos de bromo y cloro.

La mayor parte de los compuestos así formados acaban difundiéndose a la larga al medio, como tales o en forma de productos de degradación.

1.3 Transporte, distribución y transformación en el medio ambiente

No hay pruebas de que los PBB se propaguen por la atmósfera a grandes distancias, pero la presencia de estos compuestos en muestras de focas del Artico pone de manifiesto una amplia distribución geográfica.

Las principales vías conocidas de llegada de los PBB al medio acuático son los vertidos de desechos industriales y los lixiviados de lugares de vertimiento industrial que alcanzan las aguas, así como la erosión de suelos contaminados. Los PBB son casi insolubles en agua y se hallan sobre todo en los sedimentos de lagos y ríos contaminados.

Los focos de contaminación del suelo pueden ser las fábricas o los depósitos de residuos de PBB. Los PBB que llegan a penetrar en el suelo no se desplazan fácilmente. Se ha observado que los PBB son 200 veces más solubles en el lixiviado de un vertedero que en el agua destilada, lo que puede significar una mayor propagación en el medio ambiente. Debido a sus propiedades hidrofóbicas, cuando están en solución acuosa estos productos son fácilmente adsorbidos por los suelos. Se observó una adsorción preferencial de determinados PBB en función de las características del suelo (por ejemplo de su contenido orgánico) y del número y posición de los radicales de bromo.

Los PBB son estables y persistentes, lipofílicos, y sólo ligeramente solubles en agua; algunos de los compuestos de esta familia apenas son metabolizados y se acumulan en los compartimentos lipídicos de la biota. Una vez liberados en el medio ambiente, pueden alcanzar la cadena alimentaria y concentrarse en ella.

Se han detectado PBB en el pescado capturado en varias regiones. La ingestión de pescado es una vía de transmisión de PBB a los mamíferos y las aves.

Se considera improbable que los PBB se degraden mediante reacciones químicas puramente abióticas (excluidas las reacciones fotoquímicas). Se ha notificado la persistencia de PBB en el terreno. Al cabo de varios años del accidente de Michigan, el

análisis de muestras del suelo de un antiguo centro de fabricación de PBB reveló la presencia, aún, de ese tipo de productos, aunque el perfil de los PBB era distinto, debido a la degradación parcial sufrida por los residuos en la muestra de suelo.

En condiciones de laboratorio los PBB son degradados fácilmente por la radiación ultravioleta. La fotodegradación de la mezcla comercial FireMaster® se refleja en una menor concentración de los PBB que presentan más sustituyentes. No se han determinado con exactitud ni la velocidad ni la magnitud de las reacciones fotoliticas que sufren los PBB en el medio, pero las observaciones realizadas sobre el terreno muestran una elevada persistencia de los PBB originales, o bien una degradación parcial a formas menos bromadas.

En las investigaciones de laboratorio las mezclas de PBB parecen bastante resistentes a la degradación microbiana.

No se ha descrito ningún fenómeno de captación o degradación de PBB por las plantas. En cambio, los PBB son fácilmente absorbidos por los animales, en los que se ha observado que son muy persistentes, aun cuando se han detectado pequeñas cantidades de metabolitos. Los principales productos metabólicos eran hidroxiderivados, y en algunos casos se hallaron indicios de la existencia de PBB parcialmente debromados. No se ha descrito investigación alguna sobre posibles metabolitos sulfurados análogos a los de los PCB.

Se ha investigado la bioacumulación de PBB en el pescado, así como la que se produce en animales terrestres, en este caso mediante el estudio de especies de mamíferos y aves. Los datos obtenidos proceden de observaciones sobre el terreno, de la evaluación de la catástrofe de Michigan, y de estudios controlados de alimentación de los animales. Por lo general se observó que la acumulación de PBB en la grasa corporal dependía de la dosis y de la duración de la exposición.

Al analizar individualmente los PBB, se observa que su bioacumulación aumenta con el grado de bromación, al menos hasta los tetrabromobifenilos. Cabe suponer que los productos más bromados de la familia se acumulan aún en mayor medida. No obstante, no se dispone de información sobre el decabromobifenilo, cuya absorción es posiblemente escasa.

Se ha notificado la generación de dibenzofuranos bromados o PBB parcialmente debromados como productos de la descomposición térmica de los PBB. Su aparición depende de varios factores, como por ejemplo la temperatura, el oxígeno, etc.

1.4 Niveles ambientales y exposición humana

Tan sólo se dispone de los resultados de un estudio sobre los niveles de PBB en la atmósfera. En dicho estudio se determinaron las concentraciones de esos productos en las proximidades de tres plantas de fabricación o procesamiento de PBB de los Estados Unidos.

Se analizaron también los niveles alcanzados en las aguas superficiales en esas mismas inmediaciones y en el vertedero del distrito de Gratiot/Michigan (EE.UU.), al que entre 1971 y 1973 fueron a parar más de 100 000 kg de desechos, constituidos en un 60–70% por PBB.

El análisis de las aguas subterráneas del vertedero del distrito de Gratiot reveló la presencia de cantidades ínfimas de PBB incluso fuera de la zona del vertedero, pero no se detectaron PBB en los pozos de agua de bebida del entorno.

Se dispone de datos sobre la contaminación del suelo por PBB en zonas de fabricación, empleo o evacuación de PBB, así como en los suelos de los campos de las granjas de Michigan contaminadas por PBB.

La catástrofe de Michigan sobrevino porque, por inadvertencia, se añadió FireMaster® al pienso destinado a los animales. No fue sino al cabo de casi un año cuando se descubrió el error de mezcla, y los análisis efectuados mostraron que el origen del problema eran los PBB. Durante ese periodo (verano de 1973 a mayo de 1974), los animales contaminados y sus productos se difundieron entre los suministros de alimentos para el hombre y en el medio en el estado de Michigan. Centenares de granjas se vieron afectadas, y miles de animales tuvieron que ser sacrificados y enterrados, al igual que hubo que enterrar miles de toneladas de productos agrícolas.

La mayor parte de los datos disponibles sobre la contaminación de la fauna por PBB se refieren a peces y aves de los Estados Unidos y Europa, sobre todo aves acuáticas, de las inmediaciones de centros industriales, y mamíferos marinos.

Los últimos estudios sobre la contaminación por PBB de peces, mamíferos terrestres y marinos y aves de los Estados Unidos y Europa muestran una amplia distribución de esos compuestos. El perfil de los PBB hallados en las muestras de pescado es muy distinto del hallado en los productos comerciales. Muchos de los picos más importantes podrían ser el resultado de la debromación fotoquímica del decabromobifenilo (BB 209), hipótesis no confirmada.

Tras el accidente de Michigan se observaron casos de exposición profesional entre los empleados de fábricas de la industria química de los Estados Unidos, así como entre los trabajadores agrícolas. Los niveles medianos de PBB en suero y tejido adiposo eran mayores entre los trabajadores de la industria química. No se dispone de información de otros países o compañías sobre la exposición profesional asociada a la fabricación, formulación y usos comerciales de esos productos.

Respecto a la mayoría de las poblaciones humanas, no se han notificado datos directos sobre la exposición a PBB a partir de diversas fuentes. En relación con el caso de Michigan (Estados Unidos) se ha notificado la exposición humana masiva resultante del contacto directo con pienso contaminado y, sobre todo, del consumo de carne, huevos y productos lácteos que contenían PBB. Al menos 2000 familias (principalmente agricultores y sus vecinos) se vieron expuestas a muy altos niveles. Recientemente se han detectado PBB en muestras de leche de vaca y leche humana en Alemania.

El perfil de los PBB de estas muestras difiere del hallado en el pescado. Así, la concentración relativa de BB 153 es mayor en la leche humana que en el pescado.

Las vías de exposición de la población general a los PBB no se conocen con precisión. A tenor de los conocimientos actuales, el aire y el agua ambientales no contienen niveles elevados. Los alimentos ricos en lípidos, sobre todo los procedentes de aguas contaminadas, son probablemente muy importantes a ese respecto. No se dispone de información sobre los niveles de exposición en el aire de espacios interiores ni sobre la exposición cutánea a materiales con PBB pirorretardantes.

El perfil de los PBB detectados en la leche humana analizada en Alemania era parecido al hallado en la leche de vaca de la misma región, pero los niveles detectados en las muestras humanas eran considerablemente mayores.

Son muy pocos los datos disponibles para fundamentar el cálculo de la ingesta diaria de PBB a través de los alimentos por parte de la población general. Si suponemos que el pescado contiene 20 μg PBB/kg de lípido y un 5% de lípidos y que una persona de 60 kg consume 100 g de pescado al día, la ingesta resultante es de 0,002 μg/kg de peso corporal al día. Para esa misma persona, una concentración de PBB de 0,05 μg/kg de lípido en la leche (4% de lípidos) y un consumo de leche de 500 ml/día determinarían una ingesta de PBB de aproximadamente 0,00002 μg/kg de peso corporal al día.

Si suponemos que la leche materna contiene 2 μg PBB/kg de lípido, un lactante de 6 kg que consuma 800 ml de esa leche (3,5% de lípidos) al día ingerirá 0,01 μg PBB/kg de peso corporal al día.

1.5 Cinética y metabolismo

La absorción gastrointestinal de los PBB varía según el grado de bromación; así, los compuestos menos bromados se absorben más fácilmente.

La información disponible sobre la absorción de DeBB y OcBB/NoBB es insuficiente.

Los PBB están distribuidos en todas las especies animales y en el hombre y alcanzan su mayor concentración de equilibrio en el tejido adiposo. También se han hallado niveles relativamente altos en el hígado, sobre todo de los PBB más tóxicos, que al parecer tienden a concentrarse en ese órgano. Los coeficientes de reparto de los diversos PBB entre varios tejidos parecen diferir. Por lo general se observa una marcada tendencia a la bioacumulación. En los mamíferos la transferencia de PBB a la descendencia se produce a través de la placenta y de la leche. Se observó que la leche humana contenía niveles de 2,2',4,4',5,5'-hexabromobifenilo más de 100 veces superiores a los niveles séricos maternos. En un estudio realizado sobre varias generaciones de ratas, tras administrar PBB a una de las generaciones se observaron residuos detectables en más de dos generaciones sucesivas. Los huevos de especies aviares también se vieron afectados por el contenido corporal materno de PBB.

Muchos PBB tienden a persistir en los sistemas biológicos. No se obtuvieron indicios de un metabolismo o excreción importantes de los componentes más abundantes en la mezcla FireMaster® ni del octa- o decabromobifenilo. Los estudios metabólicos *in vitro*

mostraron que hay relaciones estructura-actividad que explican el metabolismo de los PBB. Los microsomas inducidos por FB (fenobarbital) sólo metabolizaban los PBB que poseían carbonos adyacentes no bromados, *meta* y *para* respecto al puente bifenilo en al menos uno de los anillos. La metabolización por microsomas inducidos por MC (3-metilcolantreno) estaba condicionada por la presencia de posiciones adyacentes *orto* y *meta* no bromadas en al menos un anillo del PBB, que debía tener pocos sustituyentes, ya que una mayor bromación parecía impedir el metabolismo. Se ha observado que, en los vertebrados, los derivados hidroxilados son unos de los principales productos del metabolismo, *in vitro* e *in vivo*, de los bifenilos menos bromados; la intensidad de la transformación metabólica fue relativamente baja. La hidroxilación se produce probablemente tanto mediante la generación previa de óxidos de hidrocarburos aromáticos como de forma directa.

El hombre, la rata, el rhesus, el cerdo, la vaca y la gallina eliminan los PBB fundamentalmente por las heces. En la mayoría de los casos la velocidad de excreción parece ser baja. Las concentraciones de 2,2',4,4',5,5'-hexabromobifenilo observadas en la bilis y las heces humanas equivalían aproximadamente a entre 1/2 y 7/10 de los niveles séricos y a aproximadamente el 0,5% de los niveles observados en el tejido adiposo. Los tratamientos aplicados para facilitar la eliminación de los PBB por los animales o el hombre fueron de escasa o nula eficacia. Otra forma de eliminación es la excreción a través de la leche.

Tras la administración de PBB a ratas y otros animales, las concentraciones tisulares del producto evolucionaron con el tiempo de forma compleja y diversa. Esa evolución se ha descrito mediante modelos de varios compartimentos. Se calculó una semivida de aproximadamente 69 semanas para la eliminación del 2,2',4,4',5,5'-hexabromobifenilo de la grasa corporal de la rata. En el rhesus se observó una semivida de más de cuatro años. En el hombre se calcula que la semivida de ese mismo compuesto oscila como promedio entre 8 y 12 años; pero, según lo publicado, ese margen podría estar comprendido entre 5 y 95 años. Hay algunas diferencias de retención y de recambio entre los distintos PBB. Los resultados de los análisis del suero de agricultores y trabajadores de la industria química por lo que se refiere al 2,3',4,4',5-pentabromobifenilo fueron incongruentes, probablemente porque las fuentes de exposición eran distintas. Los trabajadores de la industria estaban expuestos a todos los componentes de la mezcla FireMaster®, mientras que la población

de Michigan estuvo expuesta a carne y leche contaminadas por otra combinación de PBB, debido a los cambios metabólicos sufridos por los compuestos en los animales de trabajo. En un estudio realizado en ratas, los niveles de bromo del tejido adiposo no disminuyeron cuando se administró octabromobifenilo de calidad técnica. No se dispone de información sobre la retención del decabromobifenilo.

El hombre presenta quizá una mayor tendencia a retener determinados PBB que la observada en los animales de experimentación. Este factor debería tenerse en cuenta a la hora de evaluar los riesgos que entrañan esos productos químicos para la salud humana.

En resumen, todos los datos disponibles indican que los PBB presentan una marcada tendencia a la bioacumulación y la persistencia. Se metabolizan lentamente, y sus semividas en el hombre son del orden de al menos 8 a 12 años.

1.6 *Efectos en los seres vivos del medio ambiente*

Los pocos datos de que se dispone sobre los efectos de los PBB en los seres vivos del medio ambiente se refieren a microorganismos, pulgas de agua, aves acuáticas y animales de trabajo.

Se realizó un estudio sobre las aves acuáticas que anidaban en las islas del noroeste del lago Michigan para averiguar si los contaminantes del medio tenían alguna influencia en su reproducción. Se determinaron los niveles de 17 contaminantes, incluidos diversos PBB, pero al parecer ninguno tenía efectos pronunciados sobre la reproducción.

El ganado de labor que ingirió el pienso que por error contenía FireMaster® FF-1 en lugar de óxido de magnesio enfermó. El valor promedio estimado de la exposición sufrida por las vacas de la primera explotación en que se observó una alta contaminación fue de 250 mg/kg de peso corporal. Los signos clínicos de toxicidad consistieron en una reducción del 50% del consumo de pienso (anorexia) y una disminución del 40% de la producción de leche, manifestaciones observadas algunas semanas después de la ingestión del pienso contaminado. Aunque la administración del pienso suplementado se interrumpió a los 16 días, la producción de leche no se reanudó. Algunas de las vacas presentaron una mayor frecuencia miccional y lacrimación y desarrollaron hematomas, abscesos, crecimiento anormal de las pezuñas, cojera,

alopecia, hiperqueratosis y caquexia; varias murieron menos de seis meses después de la exposición. Globalmente, la tasa de mortalidad en esa explotación fue de 24/400. Sin embargo, entre los terneros de 6 a 18 meses la tasa de mortalidad fue mucho más alta: aproximadamente un 50% murieron al cabo de menos de seis semanas, y sólo dos de 12 sobrevivieron más de cinco meses. Los animales desarrollaron hiperqueratosis por todo el cuerpo. Se observaron también diversos problemas relacionados con la reproducción.

Se han notificado los resultados de las autopsias de algunas de las vacas adultas que murieron durante los primeros seis meses tras la exposición. Los estudios histopatológicos revelaron alteraciones de diverso tipo del hígado y los riñones.

Varios de los signos clínicos y cambios patológicos señalados anteriormente fueron confirmados más tarde mediante estudios controlados de administración de pienso (anorexia, deshidratación, lacrimación excesiva, emaciación, hiperqueratosis, problemas de reproducción, ciertos cambios de los parámetros químicos clínicos y lesiones renales).

Se notificó una caída de la producción y la aparición de esterilidad en las manadas afectadas por un bajo nivel de contaminación. Esto contrasta con los resultados de unos estudios controlados en los que no se halló ninguna diferencia significativa entre los rebaños sometidos a una contaminación baja y los rebaños testigo.

Aunque el error que provocó el accidente afectó originalmente al pienso del ganado vacuno, el pienso de otros animales también se vio afectado por la contaminación cruzada que se produjo, por ejemplo, en los mezcladores de las compañías productoras del pienso. Probablemente la exposición no llegó a ser tan alta como la del ganado vacuno. Se notificó también la contaminación de otros animales que fueron igualmente sacrificados (aves de corral, cerdos, caballos, conejos, cabras y ovejas), pero sin concretar las manifestaciones de la enfermedad.

No se dispone de información sobre los efectos de los PBB en el ecosistema.

1.7 *Efectos en los animales de experimentación y en los sistemas de prueba* in vitro

Las DL_{50} de las mezclas comerciales administradas por vía oral o cutánea muestran un nivel relativamente bajo de toxicidad aguda

(DL_{50} > 1 g/kg de peso corporal) en la rata, el conejo y la codorniz. En estos casos la muerte y las manifestaciones agudas de toxicidad aparecieron con mayor retraso tras la administración de PBB. La dosis total administrada determinó el grado de toxicidad, ya se tratase de una dosis única, ya de dosis repetidas durante breves periodos (hasta 50 días). La toxicidad de los PBB fue mayor cuando se administraron varias dosis que cuando se administró una sola dosis. Se observa un efecto dilatorio sobre la mortalidad tras la exposición a los PBB.

Los escasos estudios realizados con mezclas comerciales de octa- y decabromobifenilo no revelaron ninguna influencia en la mortalidad de ratas y peces. Por lo que se refiere al análisis individual de los PBB, sólo se han analizado tres hexaisómeros: 3,3',4,4',5,5'-HxBB, 2,2',4,4',5,5'-HxBB y 2,3',4,4',5,5'-HxBB, el último de los cuales es más tóxico para la rata que el anterior. A juzgar por los datos limitados de que se dispone, el OcBB y el DeBB parecen menos tóxicos que las mezclas de PBB y son peor absorbidos.

En numerosos estudios sobre los efectos agudos y a corto plazo, entre los signos de toxicidad por PBB (sobre todo por FireMaster) se ha observado una disminución del consumo de pienso. A dosis letales, la muerte no se puede atribuir a la alteración patológica de un determinado órgano sino más bien a un «sindrome de emaciación» que desarrollan los animales como primera manifestación de toxicidad. En el momento de la muerte la pérdida de peso puede ser de hasta un 30-40%. Los pocos estudios realizados con OcBB y DeBB de calidad técnica no revelaron ningún efecto de ese tipo.

Los cambios morfológicos e histopatológicos causados por la exposición a los PBB afectan sobre todo al hígado. El aumento de tamaño de este órgano se produce con frecuencia a dosis inferiores a las requeridas para inducir cambios en el peso corporal. En las especies roedoras las alteraciones histopatológicas consisten principalmente en la hinchazón y vacuolación masivas de los hepatocitos, la proliferación del retículo endoplasmático liso y una necrosis de células aisladas. La gravedad de las lesiones depende de la dosis y del tipo de PBB administrados.

Se observó una disminución del peso del timo en la rata, el ratón y el ganado vacuno tras la exposición a FireMaster®, pero no así a OcBB o DeBB.

En algunas publicaciones se menciona un aumento del peso de la glándula tiroides y cambios histológicos en el tiroides de la rata, efectos observados a bajas concentraciones.

Está demostrado que los distintos PBB difieren en cuanto al perfil de toxicidad. Los PBB más tóxicos provocan una disminución del peso del timo y/o del organismo y causan cambios histológicos pronunciados en el hígado y el timo. Se ha propuesto una clasificación de los bifenilos halogenados basada en criterios estructurales. La clase 1 abarca los productos de la familia (con sus distintos isómeros) que carecen de sustituyentes en posición orto (PBB coplanares). La segunda clase abarca los monoderivados con sustituyente en posición orto. Los otros PBB (principalmente los que poseen dos o más orto-bromos) pertenecen a la tercera clase. Los PBB de la clase 1 son los que suelen tener efectos más graves, mientras que los productos de la segunda y la tercera clases presentan una toxicidad decreciente. Dentro de cada clase la toxicidad depende también del grado de bromación.

En todas las combinaciones analizadas, el PBB más tóxico resultó ser el 3,3',4,4',5,5'-HxBB. Este compuesto está presente a baja concentración en la mezcla FireMaster®. De los principales componentes de ésta, el más tóxico fue el 2,3,3',4,4',5-HxBB, seguido del 2,3',4,4',5,5'-HxBB y el 2,3',4,4',5-PeBB. El principal componente de la mezcla FireMaster, el 2,2',4,4',5,5'-HxBB, era relativamente atóxico, al igual que el 2,2',3,4,4',5,5'-HpBB, segundo componente más abundante.

La influencia del contenido de los diversos PBB (y de otros posibles contaminantes) sobre la toxicidad de las mezclas de calidad técnica de OcBB y DeBB no se conoce con tanto detalle.

Las pruebas habituales de irritación cutánea y ocular y de sensibilización efectuadas con las mezclas PBB de calidad técnica analizadas (OcBB y DeBB) fueron negativas, o a lo sumo revelaron una reacción moderada. No obstante, se observaron hiperqueratosis y pérdida de pelaje en el ganado vacuno, y lesiones parecidas al cloracne en el rhesus, provocadas en los animales por la ingestión de FireMaster®. Esta mezcla provocó hiperqueratosis en la superficie interna de la oreja del conejo, cosa que no ocurrió con sus principales componentes (2,2',4,4',5,5'-HxBB y 2,2',3,4,4',5,5'-HpBB). El fraccionamiento de la mezcla FireMaster® mostró que la mayor parte de la actividad correspondía a las fracciones más polares, que contenían componentes minoritarios. La aplicación de HxBB irradiado con luz solar provocó una grave hiperqueratosis en la oreja del conejo.

En trabajos realizados en la rata, la administración prolongada de dosis bajas de OcBB de calidad técnica no influyó ni en el consumo de pienso ni en el peso corporal, pero se observó un aumento del peso relativo del hígado de las ratas expuestas a dosis de 2,5 mg/kg de peso corporal durante 7 meses. La administración prolongada de FireMaster® a ratas a dosis de 10 mg/kg de peso corporal durante 6 meses no influyó en el consumo de alimento. La administración durante 6 meses de dosis de 1 mg/kg de peso corporal afectó al peso del hígado. El peso del timo disminuyó en las ratas hembras a las que se administraron 0,3 mg/kg de peso corporal. Se observaron también cambios histopatológicos. Los estudios prolongados y controlados de administración de pienso a ganado vacuno expuesto a dosis bajas de FireMaster® no pusieron de manifiesto ningún efecto adverso por lo que se refiere a ingesta de alimentos, signos clínicos, cambios clinicopatológicos o desarrollo físico. El visón, el cobayo y el mono parecen más susceptibles a la toxicidad por PBB.

Se han estudiado los efectos a largo plazo provocados en la rata por los PBB retenidos tras la exposición pre- o perinatal a dosis altas de FireMaster®.

Los efectos adversos más frecuentes sobre la reproducción fueron los embarazos malogrados o perdidos y la disminución de la viabilidad de la descendencia. Se observaron aún ciertos efectos en el visón a concentraciones de 1 mg/kg de alimento. Se observó también una disminución de la viabilidad de la descendencia de rhesus expuestos durante 12,5 meses a FireMaster® (0,3 mg/kg de alimento). Los monos recibieron una dosis diaria de 0,01 mg/kg de peso corporal y una dosis total de 3,8 mg/kg de peso corporal. Los resultados de los estudios sobre reproducción y neurología del comportamiento realizados con monos y ratas expuestos a dosis bajas no pudieron ser evaluados debido a que la información aportada en los artículos publicados acerca del diseño de los experimentos era insuficiente. Se observó un débil efecto teratógeno en experimentos realizados con roedores, a dosis elevadas que podrían haber causado una cierta toxicidad en la madre.

Los PBB interaccionan con el sistema endocrino. En la rata y el cerdo se observaron disminuciones dosis-dependientes de la tiroxina y la triyodotironina séricas. También se ha notificado que los PBB alteran los niveles de las hormonas esteroides en la mayoría de los casos. La intensidad del efecto depende de la especie, así como de la dosis y la duración del tratamiento.

Los PBB provocan porfiria en la rata y en el ratón macho a dosis de sólo 0,3 mg/kg de peso corporal al día. El nivel sin efecto fue de 0,1 mg/kg de peso corporal al día. Se observó una pronunciada influencia de los PBB sobre la acumulación de vitamina A, así como efectos sobre el metabolismo intermediario.

Una observación frecuente tras la exposición a PBB fue la atrofia del timo, y se han observado también efectos en otros tejidos linfoides. Se ha demostrado asimismo la existencia de otros signos de depresión de la función inmunitaria en respuesta a la mezcla FireMaster®. No hay datos disponibles sobre los OcBB, NoBB y DeBB ni sobre PBB particulares.

Uno de los efectos más estudiados de los PBB es la inducción que provocan de las enzimas de actividad oxidasa de función mixta (MFO). Como era de esperar, se descubrió que FireMaster® era un inductor de tipo mixto de las enzimas microsómicas hepáticas tanto en la rata como en todas las demás especies animales estudiadas. Este fenómeno de inducción se observó también en menor medida en otros tejidos. La capacidad de inducción de las enzimas microsómicas hepáticas variaba de un PBB a otro; no obstante, se han descubierto correlaciones entre su estructura y la actividad de inducción de las enzimas microsómicas.

Varios estudios han puesto de manifesto que los PBB pueden modificar la actividad biológica de diversos fármacos y sustancias tóxicas. Esto se debe quizá en parte a la capacidad de los PBB para inducir las enzimas microsómicas implicadas en la activación o desactivación de los productos xenobióticos.

Se observó que FireMaster® y algunos de sus principales componentes podían inhibir la comunicación intercelular *in vitro*; esta inhibición se produce a concentraciones no citotóxicas. Tanto la citotoxicidad como las propiedades de inhibición de la cooperación metabólica parecen guardar relación con la estructura de los PBB, concretamente con la presencia o ausencia de sustituyentes en posición orto.

Los ensayos realizados *in vitro* e *in vivo* (mutagénesis de células microbianas y de mamífero, lesiones cromosómicas de células de mamífero, transformación de células de mamífero, lesión y reparación del ADN) no han revelado ningún tipo de mutagenicidad o genotoxicidad causadas por PBB particulares o por mezclas comerciales de los mismos.

Los estudios de toxicidad prolongados han revelado que el principal órgano de manifestación de los efectos carcinógenos de los PBB es el hígado. La incidencia de carcinoma hepatocelular aumentó significativamente en las ratas y los ratones machos y hembras a los que se administró la mezcla FireMaster® por vía oral. Se han notificado efectos carcinógenos en el hígado de ratones sometidos a dietas que contenían Bromkal 80-9D (nonabromobifenilo de calidad técnica) a dosis de 100 mg/kg (5 mg/kg de peso corporal al día) o más durante 18 meses. La dosis más baja de PBB que produjo tumores (fundamentalmente adenomas) en los roedores fue de 0,5 mg/kg de peso corporal al día durante 2 años. Las ratas que recibieron 0,15 mg/kg de peso corporal al día además de la exposición pre- y perinatal no sufrieron ningún efecto adverso. No se ha estudiado la carcinogenicidad del octabromobifenilo y el decabromobifenilo de calidad técnica.

En un bioensayo realizado sobre la piel del ratón no se observó ninguna actividad de iniciación tumoral (usando 12-O-tetradecanoilforbol-13-acetato (TPA) como agente activador) o activación tumoral (usando 7,12-dimetil-benz(a)antraceno (DMBA) como iniciador) por parte de FireMaster BP-6 o del 2,2',4,4',5,5'-hexabromobifenilo. Sin embargo, en otros modelos basados en la piel del ratón (en los que se empleó DMBA o DN-metil-*N*'-nitro-*N*-nitroso-guamidina (MNNG) como iniciadores), FM FF-1 y el 3,3',4,4',5,5'-hexabromobifenilo, pero no así el 2,2',4,4',5,5'-hexabromobifenilo, tuvieron efecto como activadores tumorales. En un bioensayo de dos fases realizado con hígado de rata usando fenobarbital como activador, el 3,3',4,4'-tetrabromobifenilo mostró una débil actividad iniciadora. En el modelo de dos fases utilizado con el hígado de rata, con empleo de dietilnitrosamina y hepatectomía parcial, la mezcla FM, el 3,3',4,4'-tetrabromobifenilo y el 2,2',4,4',5,5'-hexabromobifenilo, pero no así el 3,3',4,4',5,5'-hexabromobifenilo, tuvieron efecto como activadores tumorales.

Los resultados de los estudios sobre la comunicación celular, los resultados negativos de los estudios de genotoxicidad y mutagenicidad y los resultados de los ensayos de activación tumoral indican que las mezclas y los miembros de la familia estudiados provocan cáncer por mecanismos epigeneticos. No se dispone de información sobre los octa-, nona-, o decabromobifenilos de calidad técnica.

Se desconocen los mecanismos de acción subyacentes a las numerosas manifestaciones de toxicidad de los PBB y de otros compuestos relacionados. No obstante, algunos de los efectos,

como el sindrome de emaciación, la atrofia del timo, la hepatotoxicidad, los trastornos cutáneos y la toxicidad sobre el sistema reproductor podrían guardar relación con la interacción con el llamado receptor Ah- o TCDD, que alteraría la expresión de una serie de genes. Los distintos PBB difieren en lo que respecta a esa interacción con el receptor, y en ese sentido los coplanares son más activos.

Muchos de los efectos de los PBB se observan sólo después de una exposición prolongada. La razón podría ser la marcada acumulación de algunos de ellos y la escasa capacidad del organismo para metabolizarlos y eliminarlos. Ello determina la progresiva concentración del producto en el organismo; los mecanismos de compensación se ven desbordados y aparecen los efectos adversos.

Algunos naftalenos polibromados (PBN), que se sabe son contaminantes de FireMaster®, tienen potentes efectos tóxicos y teratógenos. Las concentraciones de PBN presentes en esa mezcla son bajas, pero es posible que contribuyan a su toxicidad.

Los estudios realizados sobre la mezcla FireMaster® y su principal componente, el 2,2',4,4',5,5'-HxBB, mostraron que los productos de fotólisis eran más tóxicos que el PBB original. Los productos de la pirólisis de FM causaron la inducción del sistema enzimático MFO, pérdida de peso corporal y atrofia tímica. Los productos de pirólisis del OcBB de calidad técnica provocaron un aumento del tamaño del hígado.

1.8 Efectos en el hombre

No había ningún ejemplo de toxicosis aguda por PBB en el hombre con el que poder comparar los efectos potenciales de las bajas exposiciones que siguieron a la intoxicación accidental acaecida en Michigan (Estados Unidos) en 1973. Los principales estudios epidemiológicos fueron realizados por el Departamento de Salud Pública de Michigan (MDPH) y el Laboratorio de Ciencias del Medio Ambiente (ESL) de la Facultad de Medicina Mount Sinai de Nueva York.

Se calculó que las personas más expuestas habían consumido entre 5 y 15 g de PBB durante un periodo de 230 días a través de la leche. Podría haberse producido una cierta exposición adicional a través de la carne. La exposición de algunos de los agricultores y de la mayoría de la población general de Michigan fue mucho menor: 9-10 mg de exposición total. No obstante, algunas de estas

últimas personas podrían haber recibido una dosis total de aproximadamente 800-900 mg. (Una dosis total de 9 mg corresponde a 0,15 mg/kg de peso corporal, y 900 mg, a 15 mg/kg de peso corporal, cifras referidas a un adulto de 60 kg de peso como valor promedio; la dosis/kg de peso corporal sería mayor en los niños).

En 1974, en el primer estudio llevado a cabo por el MDPH se procedió a comparar el estado de salud de las personas de las granjas sometidas a cuarentena con el de las personas de las explotaciones no sometidas a cuarentena de la misma zona. Los dos grupos declararon diversos síntomas, pero no se observó ninguna diferencia entre ambos. No se detectaron alteraciones inhabituales del corazón, hígado, bazo, sistema nervioso, orina, sangre o cualquiera de los otros parámetros médicos examinados. En un estudio completo llevado a cabo más adelante por el MDPH, que abarcaba grupos sometidos a distintos niveles de exposición, no se observó relación alguna entre las concentraciones séricas de PBB y la incidencia de los síntomas o enfermedades notificados. En los estudios del ESL se examinó aproximadamente a 990 residentes de las explotaciones agrícolas, a 55 trabajadores de la industria química y a un grupo de trabajadores de la industria láctea que fueron utilizados como testigos. La incidencia de síntomas entre los agricultores de Michigan fue mayor que la hallada entre los agricultores de Wisconsin. Las mayores diferencias fueron las observadas dentro del amplio apartado de síntomas neurológicos y musculoesqueléticos. En los agricultores de Michigan se halló una mayor prevalencia de aumentos de las concentraciones séricas de algunos antígenos carcinoembrionarios y enzimas hepáticas que en los agricultores de Wisconsin. Los trabajadores de la industria química presentaron una mayor prevalencia de síntomas torácicos y cutáneos y una menor prevalencia de síntomas musculoesqueléticos que los agricultores. Aunque la interpretación de los resultados de los estudios del ESL divergió en ocasiones de la de otros resultados de estudios comparables, hubo un aspecto en que los datos coincidieron: ninguno de los estudios puso de manifiesto una relación dosis-respuesta positiva entre los niveles de PBB en el suero o el tejido adiposo y la prevalencia de síntomas o trastornos clínicos. Se investigaron varios aspectos clínicos mediante estudios especiales más detallados. En uno de ellos, el examen del sistema neurológoco mediante pruebas funcionales objetivas reveló una correlación negativa entre los niveles séricos de PBB y los resultados de las pruebas funcionales, sobre todo entre los varones de los grupos de edad avanzada. Los otros estudios no mostraron ninguna relación

entre las concentraciones de PBB en el suero o la grasa y la actividad funcional determinada mediante una batería de pruebas en las que se analizaron la memoria, fuerza motora, coordinación, percepción corticosensorial, personalidad, funciones cognitivas superiores y otro tipo de funciones. Se examinaron los aspectos pediátricos de la exposición a PBB en algunas de las familias estudiadas por el ESL. Se notificaron numerosos síntomas, pero la exploración física no reveló ningún trastorno objetivo que pudiera atribuirse a los PBB. Hubo opiniones discrepantes acerca de los efectos neuropsicológicos en la descendencia, más sutiles, y los resultados de las investigaciones sobre los signos de desarrollo de las capacidades siguen siendo objeto de polémica. Lo mismo ocurre con la investigación sobre los linfocitos y la función inmunitaria. Algunos autores no hallaron ninguna diferencia numérica o funcional entre los linfocitos de los grupos que presentaban niveles altos y bajos de PBB en el suero, mientras que otros autores detectaron una disminución significativa de las subpoblaciones de linfocitos T y B en aproximadamente un 40% del grupo expuesto de Michigan en comparación con los grupos no expuestos, así como trastornos de la función linfocitaria, concretamente una menor respuesta a los mitógenos.

El análisis de los estudios epidemiológicos realizados muestra que se ha procurado evaluar la relación entre la exposición a PBB y un elevado número de efectos adversos, incluidos efectos sobre la conducta y trastornos subjetivos. No obstante, la mayoría de esos estudios adolecen de fallos graves de diseño pues introducen imprecisiones que hacen difícil, por no decir imposible, extraer conclusiones acerca de la relación entre la exposición a PBB y los posibles efectos sobre la salud. Además, el seguimiento no se ha prolongado lo necesario para poder evaluar los posibles efectos carcinógenos.

Se identificó a dos pequeños grupos de trabajadores que habían sufrido exposición ocupacional a una mezcla de PBB o a DeBB y decabromobifenilóxido. Se observaron lesiones parecidas al cloracne en el 13% de los trabajadores expuestos a la mezcla de PBB, lesiones ausentes en cambio en los trabajadores expuestos al DeBB. No obstante, en este último grupo se observó una prevalencia significativamente mayor de hipotiroidismo.

1.9 Evaluación global de la toxicidad y carcinogenicidad

El único estudio realizado con una mezcla de PBB y prolongado durante todo el ciclo de vida fue el bioensayo llevado a cabo hace

poco con ratas y ratones en el marco del Programa Nacional de Toxicología (NTP) de los Estados Unidos. La dosis más baja con efectos carcinógenos fue de 0,5 mg/kg de peso corporal al día (tumores hepáticos en roedores). En otros estudios realizados al efecto se observó una respuesta carcinógena con 3 mg/kg de peso corporal al día administrados durante 6 meses. El estudio prolongado durante 6 meses demuestra que una exposición a dosis análogas limitada a parte del ciclo de vida tiene también efectos adversos similares. A dosis inferiores se observan efectos sobre el sistema reproductor en los primates y el visón.

Además, en el estudio llevado a cabo durante 2 años por el NTP con ratas, una dosis diaria de 0,15 mg/kg de peso corporal al día y la exposición prenatal y perinatal de la madre a 0,05 mg/kg de peso corporal al día no provocó ningún efecto adverso. Así pues, la ingesta diaria total a partir de los alimentos, el agua, el aire y el suelo debería ser inferior a 0,15 μg/kg de peso corporal al día, cifra extrapolada del NOAEL (nivel sin efectos adversos observados) observado en un estudio de carcinogenicidad que arrojó resultados positivos, usando un factor de incertidumbre (seguridad) de 1000, dado que estos compuestos probablemente producen cáncer por un mecanismo epigenético.

Se calculó que la dosis total recibida por la subpoblación de Michigan había sido de entre 0,15 y 15 mg/kg de peso corporal durante un periodo de 230 días. Para esa población, la división de esas dosis por el valor promedio de la duración de la vida del ser humano arrojaría una cifra equivalente a una dosis diaria de entre 6 ng y 0,6 μg/kg de peso corporal al día.

Se ha calculado una ingesta total de 2 ng PBB/kg de peso corporal al día, de fuentes conocidas, para los adultos de la población general, y de 10 ng/kg de peso corporal al día para los lactantes alimentados con leche materna. No debe olvidarse que estos cálculos están basados en datos de carácter muy limitado y regional.

Estos cálculos se basan en el supuesto de que durante el ciclo de vida los PBB no alcanzan un estado estacionario, y de que una exposición alta y breve equivale a una exposición baja y prolongada, toda vez que estos compuestos son metabolizados y excretados con suma lentitud.

La información disponible sobre los OcBB, NoBB, y DeBB no es suficiente para poder calcular una ingesta diaria total carente de efectos adversos.

2. Conclusiones

La mayoría de los PBB presentes en los pirorretardantes comerciales son lipofílicos, persistentes y bioacumulables. Estos compuestos tienden a concentrarse en las tramas alimentarias del medio y suponen una amenaza, especialmente para los organismos que ocupan los niveles superiores de esas tramas. Además, en caso de combustión, algunos PBB generan dibenzofuranos polibromados tóxicos.

Aparte de las emisiones que se producen durante su fabricación y empleo, los PBB pasan al medio como consecuencia del uso generalizado de pirorretardantes. Debido a la gran estabilidad de los PBB, una parte considerable de ellos alcanza en un momento u otro el medio.

También se detectan PBB en muestras ambientales o humanas de lugares alejados de los focos conocidos. El perfil de PBB de las muestras del medio no se corresponde con el hallado en los productos de uso industrial, lo que indica que éstos sufren transformaciones en el medio ambiente, posiblemente como resultado de una debromación fotoquímica.

Se dispone actualmente de muy poca información sobre el grado de exposición de la población general a los PBB. No obstante, en los pocos casos en que se determinaron sus niveles se descubrieron cantidades ínfimas. En la actualidad, ese nivel de exposición no resulta preocupante, pero deberá evitarse que prosiga la acumulación. Los datos sobre las personas afectadas en Michigan indican que en este caso las exposiciones fueron varios órdenes de magnitud superiores a la de la población general. No se han observado efectos concluyentes sobre la salud atribuibles a la exposición a PBB en la población de Michigan, pero el periodo de seguimiento no ha sido lo suficientemente dilatado para descartar la aparición de cáncer. Los niveles de PBB en el tejido adiposo y el suero de la población de Michigan siguen siendo altos, por lo que la exposición interna continúa. Por el contrario, sí se observó la aparición de toxicidad en el ganado vacuno de Michigan. Esta discrepancia se explica por el diferente grado de exposición del ganado.

Sólo se han estudiado casos de exposición profesional en dos fábricas de los Estados Unidos. Parece que los trabajadores que producen PBB pueden desarrollar lesiones parecidas al cloracne, y los expuestos a DeBB, hipotiroidismo. No se han realizado estudios

sobre los trabajadores que incorporan deca- u octa-/nona-bromobifenilo en productos comerciales.

Los PBB persisten durante mucho tiempo en los organismos vivos, y se ha demostrado que producen toxicidad crónica y cáncer en los animales. Así, se indujo cáncer a una dosis de 0,5 mg/kg de peso corporal al día, pese a la baja toxicidad aguda asociada a esa dosis, y el nivel sin efectos observados fue de 0,15 mg/kg de peso corporal al día. Se han observado diversos efectos tóxicos crónicos en animales de experimentación tras la exposición prolongada a dosis de aproximadamente 1 mg/kg de peso corporal al día.

3. Recomendaciones

3.1 Recomendaciones generales

El Grupo Especial de Trabajo considera que el hombre y el medio ambiente no deben verse expuestos a los PBB, habida cuenta de su elevada persistencia y bioacumulación y de los efectos adversos que pueden aparecer tras la exposición prolongada a muy bajos niveles. Por consiguiente, deberá interrumpirse todo uso comercial de los PBB.

Respecto al DeBB y el OcBB, teniendo en cuenta los escasos datos sobre su toxicidad, su extrema persistencia y su posible degradación en el medio ambiente, así como la mayor toxicidad de los compuestos persistentes generados durante la combustión, no deberán ser empleados comercialmente, a menos que se demuestre su inocuidad.

Es sabido que se siguen formulando observaciones sobre la cohorte de Michigan, información que convendría fuese publicada.

3.2 Futuras investigaciones

La futura vigilancia de los PBB en el hombre y en el medio, incluida la vigilancia en el lugar de trabajo en las industrias de fabricación o uso de esos productos, deberá ampliarse, deberá centrarse en PBB específicos, y deberá incluir los OcBB/NoBB y DeBB. Es preciso incorporar también estos compuestos en los programas en curso de vigilancia de otros productos halogenados. La evolución temporal y la distribución geográfica de los niveles de PBB en el medio ambiente deberán seguir siendo objeto de vigilancia. Habrá que controlar también la liberación de PBB en el medio a partir de los lugares de evacuación de desechos.

Deberán efectuarse experimentos de termólisis mediante la simulación de fuegos accidentales y la incineración municipal. Conviene realizar nuevas investigaciones sobre los mecanismos de toxicidad y carcinogenicidad de los PBB y de otros compuestos relacionados. Los PBB podrian servir como modelo para el estudio de esos mecanismos, y en las investigaciones al efecto deberán emplearse PBB purificados.

Los efectos de los PBB sobre la reproducción no están bien dilucidados. Por consiguiente, deberán realizarse estudios bien diseñados y prolongados sobre los efectos de las dosis bajas en la reproducción, usando para ello una especie vulnerable.

Es preciso disponer también de más información sobre la biodisponibilidad y toxicocinética de los OcBB/NoBB y DeBB, así como de determinados productos de la misma familia.

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