Format for submitting pursuant to Article 8 of the Stockholm Convention the information specified in Annex E of the Convention

Introductory information

Name of the submitting Party/observer

NGO Observer: Environmental Health Fund on behalf of the International POPs Elimination Network (IPEN)

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Chemical name

Hexabromobiphenyl (HBB)
CAS=36355-01-8
Common trade names: FireMaster BP-6 and Fire Master FF-1

Date of submission

27 January 2006

(a) Sources, including as appropriate (provide summary information and relevant references)

(i) Production data:

Quantity

[1] "Approximately 13.3 million pounds of PBBs were produced in the United States from 1970 to 1976. Only three commercial PBB products were manufactured (i.e., hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl) and these three products were based on a limited number of congeners (Hardy 2002b). Hexabromobiphenyl constituted about 11.8 million pounds (ca 88%) and octa- and decabromobiphenyl constituted ≈1.5 million pounds together of this total (Neufeld et al. 1977). Over 98% of the hexabromobiphenyl was produced asFireMaster BP-6 and the residual as FireMaster FF-1 (Hesse and Powers 1978). Michigan Chemical Corporation, St. Louis, Michigan, the sole producer of hexabromobiphenyl in the United States, stopped producing this PBB in 1975. White Chemical Co., Bayonne, New Jersey, and Hexcel Corporation, Sayreville, New Jersey, manufactured octa- and decabromobiphenyl in the United States until 1979 (IARC 1986; Neufeld et al. 1977). Shortly after the 1973 1974 agriculture contamination episode in Michigan (see Section 5.2), PBB production in the United States was voluntarily discontinued (Hardy 2000); PBBs are no longer produced in the United States (SRI 2001). Re-initiation of manufacture of PBBs requires approval from the EPA. Production of decaPBB in Great Britain was discontinued in 1977 and highly brominated PBBs were produced in Germany until mid-1985. Until the

year 2000, the only PBB in commercial production was decabromobiphenyl, which was manufactured by one company (Atochem) in France (Hardy 2000)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

Location

[2] "Commercial production of PBBs began in approximately 1970 and manufacture was discontinued in the United States in 1976, subsequent to a major agricultural contamination episode that occurred in Michigan in 1973….Michigan Chemical Corporation, the major producer of PBBs from 1970 to 1976, marketed mixtures of PBBs under the trade name FireMaster (e.g., BP-6 and FF-1). However, the FireMaster trade name has also been used for other brominated flame retardants using different numerical designations. Other former producers of PBBs in the United States included White Chemical Corporation (Bayonne, New Jersey) and Hexcel Corporation (Sayreville, New Jersey), which both produced technical mixtures of octabromobiphenyl and decabromobiphenyl until 1979. The trade names of some commercial PBB mixtures formerly produced in other countries are: Berk Corporation, Great Britain (e.g., BerkFlam, Flammex); Chemische Fabrik Kalk, Germany (e.g., Bromkal); and Ugine Kuhlmann (now Atofina in France) (e.g., Adine)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

(ii) Uses

[3] "In the past, PBBs were used as additive flame retardants to suppress or delay combustion. Additive flame retardants are added to the polymer material, but are not chemically incorporated into the polymer matrix. Because PBBs are not chemically bound to the polymer matrix, they may migrate out of the matrix with time (WHO 1994b). PBB applications were almost exclusively limited to a particular thermoplastic (arylonitrile-butadienestyrene, ABS) used in electronic equipment housings (Hardy 2002b). Prior to termination of production, hexabromobiphenyl was used as a fire retardant mainly in thermoplastics for constructing business machine housings and in industrial (e.g., motor housing), and electrical (e.g., radio and TV parts) products. Smaller amounts were used as a fire retardant in coating and lacquers, and in polyurethane foam for auto upholstery (Neufeld et al. 1977)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

(iii) Releases

Discharges

[4] "In the past, an estimated 0.0046 pounds have been lost to sewers for every 1,000,000 pounds of PBBs produced at manufacturing sites (Neufeld et al. 1977). The Michigan Chemical Corporation discharged an estimated 0.25 pounds of PBBs/day to the Pine River as effluent (Di Carlo et al. 1978). The Michigan Chemical Corporation estimated that the solid waste generated during the manufacture of FireMaster BP-6 was 5% of the FireMaster BP-6 and FireMaster FF-1 produced (Di Carlo et al. 1978). Since Michigan

Chemical Corporation produced ≈11.8 million pounds of FireMaster BP-6 and FireMaster FF-1 from 1970 to 1974 (Di Carlo et al. 1978), solid wastes containing a total of 590,000 pounds of PBBs would have been sent to disposal. About one-half of this waste was deposited in the Gratiot County landfill in St. Louis, Michigan (Di Carlo et al. 1978), and the rest was possibly landfilled at other locations. Contaminated animal carcasses, poultry and eggs, animal feed, butter, cheese, and other milk products following the Michigan agriculture contamination episode were disposed of in a sanitary landfill in Cadillac, Michigan (Dunckel 1975). Approximately 11.8 million pounds of hexabromobiphenyl were used in commercial and consumer products in the United States, most in the production of plastic products with an estimated use life of 5– 10 years (Neufeld et al. 1977). Since the cessation of production, all of these products, such as TV cabinet and business machine housings, must have been disposed of by land filling or incineration (Neufeld et al. 1977). The formation of polybrominated dioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) during the incineration of plastics containing PBBs remains a distinct possibility (Luijk and Govers 1992; O'Keefe 1978)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

Losses

[5] "PBBs were excreted in cattle manure and, as such, were also environmentally distributed in Michigan [USA] via waste disposal on farms." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

[6] "In 1973, livestock on certain farms in Michigan were exposed to FireMaster FF-1 after it was mistaken as a feed supplement and mixed with feed that was distributed within the state for several months before being discovered. Health problems in dairy cattle, reported in the fall of 1973, were the first signs that this episode occurred, but the accidental addition of PBBs to animal feed was not identified as the cause of the problem until the spring of 1974." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

Emissions

[7] "In the past, PBBs were released into the air during the manufacture of these compounds in three areas: through the vents of the hydrogen bromide recovery system, from the centrifugation area for recovering PBBs from slurries produced by bromination, and from the drying, pulverizing, and bagging area of the finished product (Di Carlo et al. 1978). An estimated 0.07 pounds/million pounds of the PBBs produced were lost from the hydrogen bromide-recovery vent (Di Carlo et al. 1978). No data are available for the air pollution factor (amount released/million pounds produced) at the centrifugation site. The concentrations of FireMaster BP-6 in the Michigan Chemical Corporation bagging area were 0.016–0.032 mg/L of air during the bagging operation and 0.003 mg/L of air after the completion of bagging (Di Carlo et al. 1978). In 1977, the maximum air losses of PBBs at production sites were estimated to total 1,125 pounds of PBBs for every 1 million pounds of PBBs produced (Di Carlo et al. 1978). Another process that could release lower levels of brominated biphenyls in the air is the incineration of PBBs. Pyrolysis of hexabromobiphenyl in the absence and presence of air has produced small

amounts of lower brominated biphenyls (Thoma and Hutzinger 1987). No data are available on the importance of this source for the release of PBBs in the air during the incineration of PBBs. However, since the vast majority of products containing PBBs are expected to be out of circulation after more than 25 years since the voluntary ban, incineration will not be a significant source of PBBs to air. PBBs have been identified in 1 air sample, collected from 1,647 NPL hazardous waste sites, where they were detected in some environmental media (HazDat 2004)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

[8] "In the past, PBBs were released to water during the manufacturing process. An estimated 0.0046 pounds were lost to sewers for every 1,000,000 pounds of PBBs produced at manufacturing sites (Neufeld et al. 1977). To manufacture PBBs, water was added to the reaction mixture when the desired extent of bromination was achieved. Ultimately, this water was discharged as effluent into surface water. Samples of effluents from the Michigan Chemical Corporation contained PBB concentrations 503 ppm (Di Carlo et al. 1978). Runoff water from the manufacturing plants containing PBBs also contaminated surface water (Di Carlo et al. 1978). Landfill sites used to dispose of wastes from PBB production can also be a source of PBBs in water. Concentrations of PBBs in groundwater from one such landfill in St. Louis, Michigan were low (0.1–0.2 ppb), but those in water from a drainage ditch and catch basin were much higher (0.35–1.2 ppm) (Di Carlo et al. 1978). PBBs have been identified in 2 and 5 surface water and groundwater samples, respectively, collected from 1,647 NPL hazardous waste sites (HazDat 2004)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

[9] "The important former sources of PBBs in soil are manufacturing operations, disposal of PBB-containing finished products, and agricultural operations contaminated in the original episode in 1973–1974. The concentrations of PBBs in soils from bagging and loading areas of the Michigan Chemical Corporation were 3,500 and 2,500 mg/kg, respectively (Di Carlo et al. 1978). Similarly, soil from sites adjacent to the Hexcel Corp and the White Chemical Company, the manufacturers of octabromo- and decabromobiphenyl, contained decabromobiphenyl and other lower brominated biphenyls down to hexabromobiphenyl (Di Carlo et al. 1978). The disposal into landfills of solid wastes generated during the production of PBBs was another important source of PBBs in soil (Neufeld et al. 1977). Photodecomposition of FireMaster BP-6 in soil could also be a source of lower brominated biphenyls (Ruzo and Zabik 1975; Trotter 1977) in soil. Approximately 11.8 million pounds (5,350,000 kg) of hexabromobiphenyl was used in commercial and consumer products in the United States, mostly in the production of plastic products. Since the cessation of production of hexabromobiphenyl, all of these products, such as TV cabinet and business-machine housings, with a usable life of 5–10 years must have been disposed of by landfilling or incineration (Neufeld et al. 1977). Disposal of these plastic materials in waste-disposal sites is an important source of PBBs in soil. The migration of plastic-incorporated PBBs to soil would be very low since PBBs would be tightly bound into the plastic (Neufeld et al. 1977). The indirect source of PBBs in soil was the contaminated farms in Michigan. Approximately 650 pounds (290 kg) of

PBBs was mixed in cattle feeds that were delivered to Michigan farms during 1973–1974 (Fries 1985b). About 50% of this amount was excreted in the feces of the exposed animals and remained on the farms in places of fecal deposition and manure disposal (Fries 1985b). Soil in fields that received contaminated manure contained as high as 300 µg/kg PBBs, whereas soil in resurfaced cattle-exercise lots contained as high as 1,000 2,000 µg/kg of PBBs (Fries 1985b). PBBs have been identified in 5 soil and 3 sediment samples collected from 1,647 NPL hazardous waste sites (HazDat 2004)." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

(b) Hazard assessment for endpoints of concern, including consideration of toxicological interactions involving multiple chemicals **(provide summary information and relevant references)**

Human

[10] "This study suggests that PBB exposure may impact ovarian function as indicated by menstrual cycle length and bleed length. However, these associations were found among the small number of women with recent weight loss suggesting either a chance finding or that mobilization of PBBs from lipid stores may be important. These results should be replicated with larger numbers of women exposed to similar lipophilic compounds." (Davis SI, Blanck HM, Hertzberg VS, Tolbert PE, Rubin C, Cameron LL, Henderson AK, Marcus M. Department of Epidemiology, Rollins School of Public Health, Emory University, Georgia, USA. Menstrual function among women exposed to polybrominated biphenyls: a follow-up prevalence study. Environ Health 9:4-25, August 2005)

[11] "Although the available human data regarding developmental effects of PBBs are inconclusive, the results from animal studies strongly suggest that PBBs may cause mild to severe developmental effects in humans, including growth retardation, alteration of neuropsychological development, and structural malformations." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

[12] The study assessed pubertal development in 327 females aged 5-24 years old who were exposed to PBB in Michigan in utero and in many cases also during breast feeding. "We found that breastfed girls exposed to high levels of PBB in utero (> or =7 parts per billion) had an earlier age at menarche (mean age = 11.6 years) than breastfed girls exposed to lower levels of PBB in utero (mean age = 12.2-12.6 years) or girls who were not breastfed (mean age = 12.7 years). This association persisted after adjustment for potential confounders (menarche ratio = 3.4, 95% confidence interval = 1.3-9.0). Perinatal PBB exposure was associated with earlier pubic hair stage in breastfed girls, but little association was found with breast development. The associations observed here lend support to the hypothesis that pubertal events may be affected by pre- and postnatal exposure to organohalogens." (Blanck HM, Marcu M, Tolbert PE, Rubin C, Hnderson AK, Hertzberg VS, Zhang RH, Cameron L. Biological and Biomedical Sciences Division, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. Epidemiology 11:641-647, November 2000)

[13] "We conducted a nested case-control study with 1,925 women enrolled in a polybrominated biphenyl (PBB) registry to examine the association between breast cancer and serum PBBs. Twenty women who developed breast cancer were matched to 290 control subjects on sex, race, and age. Women with serum PBB levels of 2.0-3.0 parts per billion (ppb) [odds ratio (OR) = 3.5; 95% confidence interval (CI) = 0.9-13] or 4.0 ppb or greater (OR = 3.1; 95% CI = 0.8-12) had a higher estimated risk for breast cancer than women with less than 2.0 ppb. The odds ratios were unchanged when available breast cancer risk factors were included in the analysis." (Henderson AK, Rosen D, Miller GL, Figgs LW, Zahm SH, Sieber SM, Rothman N, Humphrey HF, Sinks T. Health Studies Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. Breast cancer among women exposed to polybrominated biphenyls. Epidemiology 6:544-546, September 1995)

[14] "To study the impact of PBBs, 336 adult Michigan farm residents, 117 general consumers for comparison, 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 hypergammaglobulinemia, exaggerated hypersensitive response to streptococci, significant decrease in absolute numbers and percentage of T and B-lymphocytes, and increased number 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 PBB. The decreased immune function detected among the PBB-exposed farm residents tended to affect families as a unit and was independent of exposed individuals' age or sex, pointing against the possibility of genetic predisposition." (Bekesi JG, Roboz JP, Fischbein A, Mason P. Department of Neoplastic Diseases, Mount Sinai School of Medicine of the City University of New York, New York, USA. Immunotoxicology: environmental contamination by polybrominated biphenyls and immune dysfunction among residents of the State of Michigan. Cancer Detect Prev Suppl 1:29-37, 1987)

[15] "Immunoprecipitation followed by mass spectrometric quantification determined that the distribution of PBB among plasma, erythrocytes, mononucleocytes and polymorphonucleocytes was 89:9:less than 1:less than 1. In plasma 80% of the PBB was bound to apolipoproteins B and A in a 3:1 ratio. No preferential absorption of PBB congeners was found in the blood compartments suggesting that changes in the relative abundances of PBB congeners observed in longitudinal studies on Michigan subjects reflect differences in excretion rates or metabolism. A repeat in 1981 of the immunodiagnostic tests conducted in 1976 revealed a virtually complete persistence of the immune dysfunctions in the Michigan farmers exposed to PBB a decade ago." (Roboz J, Greaves J, Bekesi JG. Polybrominated biphenyls in model and environmentally contaminated human blood: protein binding and immunotoxicological studies. Environ Health Perspect 60:107-113, May 1985)

[16] Nineteen PBB-exposed Michigan children were tested with five McCarthy Scales of Children's Abilities tests. Correlations of log PBB levels in fat and scores on the development tests ranged from -0.5228 to -0.3004. "Children with higher body burdens of PBB (greater than .100 ppm) scored significantly lower than exposed children with lower body burdens on the same four tests, and on a composite score representing overall performance. These results suggest the existence of an inverse relationship between body levels of PBB and some developmental abilities in young children." (Seagull EA.

Developmental abilities of children exposed to polybrominated biphenyls (PBB). Am J Public Health 73:281-285, March 1983)

[17] Forty-five adult Michigan farm residents exposed to PBBs were examined for immunological status. “Abnormalities in the Michigan group included significant decrease in absolute numbers and percentages of T and B-lymphocytes and increased number of lymphocytes with no detectable surface markers ("null cells"). Significant reduction of in vitro immune function was noted in 35--40% of the Michigan farm residents who had eaten food containing PBB. Despite the absence of any apparent numerical reduction, both T and B lymphocyte subpopulations of peripheral blood lymphocytes showed evidence of functional defect. Ten of the 45 Michigan farmers studied showed impaired PHA-induced blastogeneic response, due to the decreased number and percent of T-cells in the PBLs. The decreased immune function detected among the PBB-exposed farm residents tended to affect families as a unit and was independent of exposed individuals' age or sex, speaking against the possibility of genetic predisposition.” (Bekesi JG, Anderson HA, Roboz JP, Roboz J, Fischbein A, Selikoff IJ, Holland JF. Immunologic dysfunction among PBB-exposed Michigan dairy farmers. Ann NY Acad Sci, 320:717-728, May 1979)

[18] “In November 1976, the Environmental Sciences Laboratory conducted comprehensive examinations of 933 farmers and residents in Mighigan who were likely to have consumed farm products contaminated with PBB. A comparison group of 229 Wisconsin dairy farmers were examined in March 1977 and the same scientific and medical staffs that conducted the Michigan survey were responsible and the same procedures used. A complete history of symptomatology by organ system, including year of first onset, duration, frequency, and severity of each symptom was obtained by a physician on all adults examined. 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 16-35 and 36-55. Michigan females had a higher prevalence of neurological symptoms than the Michigan males. The existing differences could not be explained without considering an etiologic role for exposure to PBB.” (Anderson HA, Lilis R, Selikoff IJ, Rosenman KD, Valciukas JA, Freedman S. Unanticipated prevalence of symptoms among dairy farmers in Michigan and Wisconsin. Environ Health Perspect 23: 217-226, April 1978)

[19] “Clinical findings are reported for a group of 55 employees of the Michigan Chemical Corporation which manufactured FireMaster BP-6 from 1970 to 1974, in addition to a variety of other halogenated fire retardant chemicals. The results are compared with those from a group of male farm residents and consumers from Michigan examined at the same time. An increased prevalence of chest and skin symptoms was observed, compared with farmers. Skin symptoms were more prevalent among former PBB production personnel. Musculosketal symptoms were less prevalent among these workers than among farmers. Serum PBB concentrations are signicantly higher than among farmers. Blood chemistry results were similar for workers and farmers. However, both groups exhibited a significantly higher prevalence of elevated liver function tests (SGOT, SPGT) than a

control population of nonexposed farmers. Both farmers and chemical workers showed an association of elevated CEA with serum PBB greater than 10 ppb." (Anderson HA, Wolff MS, Fischbein A, Selikoff IJ. Investigation of the health status of Michigan chemical corporation employees. Environ Health Perspect 23: 187-191, April 1978)

Reproductive - developmental

[20] Pregnant C57BL/6J mice were exposed to coplanar HBB (3,3',4,4',5,5'-hexabromobiphenyl) or non-coplanar HBB (2, 2',4,4'6,6'-hexabromobiphenyl). Neonatal lethality within the first 72 h postpartum was significant in coplanar HBB-treated mice at doses as low as 2.5 mg/kg, whereas no deaths were seen in mice whose mother had received non coplanar HBB at 100 mg/kg. Further experiments revealed the association of neonatal deaths with in utero (not lactational) exposure to coplanar HBB. Using genetic strains of mice with differing amounts of aryl hydrocarbon receptor, the authors note that coplanar HBB appears to act through the high-affinity aryl hydrocarbon receptor. (Curran CP, Miller KA, Dalton TP, Vorhees CV, Miller ML, Shertzer HG, Nebert DW. Department of Environmental Health and Center for Environmental Genetics (CEG), University Cincinnati Medical Center, Cincinnati, Ohio, U.S.A. Genetic Differences in Lethality of Newborn Mice Treated in utero with Coplanar versus Non-Coplanar Hexabromobiphenyl. Toxicol Sci. November 16, 2005)

[21] "The thyroid gland is an unequivocal target of PBBs in animals, and evidence in humans is suggestive of a similar relationship. Effects in workers exposed to unspecified PBBs and/or decabromobiphenyl included increased serum thyrotropin, low or borderline low serum thyroxine (T4), and increased thyroid antimicrosomal antibody titers. A spectrum of effects has been observed in rats exposed for acute and intermediate durations, ranging from decreases in serum levels of serum T4 and serum triiodothyronine (T3) to histological and ultrastructural changes in the follicles. The preponderance of these studies tested FireMaster FF-1 or FireMaster BP-6 in rats, although chronic exposure to FireMaster FF-1 induced thyroid follicular hyperplasia in mice." Similar thyroid effects also occurred in offspring of treated rats and pigs. (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

[22] "Fetotoxic and developmental effects have been observed in studies of FireMaster FF-1 or FireMaster BP-6 in several species of laboratory animals. Embryolethal effects or increased mortality among nursing young were observed in rats after oral exposure during gestation and in monkeys after exposure before conception and during pregnancy. Because the dosage (0.012 mg/kg/day) causing these serious developmental effects in monkeys is the lowest tested in any chronic study of PBBs, it is not possible to derive an MRL for chronic-duration exposure. Structural malformations in fetuses, including cleft palate, were also observed in rats and mice after exposure to these PBBs during gestation…Studies with FireMaster FF-1 and FireMaster BP-6 found that body weight gain was reduced in the offspring of rats and mice after exposure during gestation, in rat offspring after exposure during gestation and lactation, and in mink kits after parental exposure before and during pregnancy. Liver effects, including increased liver weight and hepatic cytochrome P-450 enzymic activity, hepatocyte enlargement, vacuolization, and other degenerative changes, were observed in the offspring of rats, mice, and/or swine fed FireMaster FF-1 or FireMaster BP-6 during gestation and/or lactation. Performance deficits in tests of operant behavior were observed in offspring of rats and

mice after oral exposure to FireMaster FF-1 or FireMaster BP-6 during pregnancy and lactation." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

[23] The effect of HBB on thyroxine was examined in juvenile male Wistar rats injected with 0, 20, or 40 mg/kg 3,3',4,4',5,5'-hexabromobiphenyl. The results indicate that fractional clearance rate of thyroxine increased by 84%; the daily metabolic clearance rate increased by 128%; the daily thyroxine disposal rate increase by 41%; and the thyroxine distribution space increased by 21%. The authors note that these results greater thyroxine binding in major organs and an increase in the peripheral metabolism of thyroxine. Further experiments showed a 4.8-fold induction of uridine 5'-diphosphoglucuronyltransferase activity in liver microsomes. (Spear PA, Higueret P, Garcin H. Departement alimentation et nutrition, Universite de Bordeaux I, Talence, France. Increased thyroxine turnover after 3,3',4,4',5,5'-hexabromobiphenyl injection and lack of effect on peripheral triiodothyronine production. Can J Physiol Pharmacol. 68:1079-1084, August 1990)

[24] Low doses (0, 1, 4, 10, and 50 ppm) of FireMaster BP-6 were administered to female Sprague-Dawley rats over 5-7 months to study effects on the thyroid. "Together these data indicate that PCB-PBB-induced decreases in serum T3 and T4 result primarily from direct damage to the thyroid rather than any enhanced hepatic or other peripheral catabolism per se. Expanded T4 distribution space demonstrated that nonthyroid damage was also an important factor in reducing serum T4. Cell membrane damage associated with PCB-PBB intoxication may have expanded pools for T4 dilution. The findings are consistent with reported histological and ultrastructural damage caused by PCB and PBB. It also appears that TSH plays little role in PCB-PBB-induced hypothyroidism." (Byrne JJ, Carbone JP, Hanson EA. Hypothyroidism and abnormalities in the kinetics of thyroid hormone metabolism in rats treated chronically with polychlorinated biphenyl and polybrominated biphenyl. Endocrinology 121:520-527, August 1987)

[25] The embryotoxicity of HBB congener, 2,2',4,4',5,5' hexabromobiphenyl, was tested in B6C3F1 mice at 0, 100, 300, 500, 750, or 1000 ppm from gestation day 6 – 15. Concentrations of HBB greater 300 ppm adversely affected pregnancy rates and some mice died at the 750 ppm dose. In the offspring HBB caused cleft palate and a cystic lesion in the brain at concentrations greater than or equal to 300 ppm. (Welsch F, Morgan KT. Placental transfer and developmental toxicity of 2,2',4,4',5,5'-hexabromobiphenyl in B6C3F1 mice. Toxicol Appl Pharmacol. 81:431-442, December 1985)

[26] HBB congener, 2,4,5,2',4',5'-hexabromobiphenyl, was transferred to the placenta in the albino Hartley strain of guinea pigs. "Transplacentally-acquired residues of the order of 45 micrograms HBB/g were found in both maternal and fetal adipose tissue and in fetal liver." Levels of 4 – 7 ug/g HBB were found in maternal kidney, lung, and liver after a single oral dose of 50 mg/kg body weight. Levels of 1 – 2 ug/g HBB were found in kidneys and lungs of fetuses and pups. Two days after treatment, 22.4 +/- 7.8 micrograms/g HBB was found in breast milk. Induction of hepatic microsomal mono-oxygenases was observed concomitant with elevated levels of HBB. (Ecobichon DJ, Hidvegi S, Comeau AM, Cameron PH. Transplacental and milk transfer of polybrominated biphenyls to perinatal guinea pigs from treated dams. Toxicology. 28:51-63, September 28, 1983)

Cancer

[27] Studies in F344/N mice (3, 10, 30 ppm exposure levels)**: "**Increased incidences of the following nonneoplastic lesions were associated with the administration of polybrominated biphenyls: eosinophilic foci, cytoplasmic vacuolization, oval cell hyperplasia, and hypertrophy in the liver of males and females; acanthosis, inflammation, and ulceration of the forestomach in exposed males; and cystic endometrial hyperplasia of the uterus in 0:30 ppm females." "…perinatal exposure was associated with a marginally increased incidence of hepatocellular adenoma in male rats (0:0 ppm, 1/50; 10:0 ppm, 5/50). The incidences of nonneoplastic lesions in the liver were increased in exposed males (eosinophilic foci and cytoplasmic vacuolization) and females (eosinophilic foci)." Studies in B6C3F1 mice (3, 10, 30 ppm exposure levels)**: "**The major organ affected by toxicity of polybrominated biphenyls was the liver. Animals evaluated at 9 months had lower body weights than the controls, hepatomegaly, and histopathologic changes in the liver." Increased incidences of nonneoplastic liver lesions including cytomegaly (hypertrophy), fatty change (cytoplasmic vacuolization), bile duct hyperplasia, eosinophilic and clear cell foci, and necrosis of individual hepatocytes were related to treatment with polybrominated biphenyls. Increased incidences and severity of chronic nephropathy in the kidney and excessive hematopoiesis in the spleen of 0:30 ppm males and females were also considered to be related to exposure to polybrominated biphenyls." "For male and female F344/N rats, a combined analysis of the incidences of leukemia in the adult-only, perinatal-only, and combined perinatal and adult exposure groups revealed an apparent association between increasing incidences of mononuclear cell leukemia and exposure to polybrominated biphenyls."
(USA National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Polybrominated Biphenyls (CAS No. 67774-32-7)(Firemaster FF-1(R)) in F344/N Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 398:1-235, August 1993)

Immunotoxicity

[28] "Ortho-substituted PBBs activated respiratory burst, measured by the chemiluminescence assay, and elevated intracellular calcium. The most active polybrominated congener 2,2',5-TBB increased chemiluminescence in a concentration-dependent manner, and ED(50) was approximately 10 microM. PBBs stimulated elevation of intracellular [Ca(2+)] in human granulocytes. The [Ca(2+)]i was elevated from 50 to 250 nM." (Kristofferson A, Voie OA, Fonnum F. Norwegian Defence Research Establishment, Division for Environmental Toxicology, Kjeller, Norway. Ortho-substituted polybrominated biphenyls activate respiratory burst in granulocytes from humans. Toxicol Lett. 129:161-166, March 2002)

[29] "Concentrations of PBB as low as 0.001 microgram/10(5) cells decreased lymphocyte response to pokeweed mitogen; higher concentrations of PBB stimulated the in vitro synthesis and release of immunoglobulins. PBB 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 PBB exerted an adverse effect on cell function, but produced a nonspecific activation of B lymphocytes." (Lipson SM. Effect of polybrominated biphenyls on the growth and maturation of human peripheral blood lymphocytes. Clin Immunol Immunopathol 43:65-72, April 1987)

[30] Both the HBB congener, 3,4,5,3',4',5'-hexabromobiphenyl, and Aroclor 1254 administered at 2-6 mg/kg significantly inhibited plaque forming response to subsequent challenge with sheep erythrocytes in Ah locus positive (C57Bl/6N or B6C3F1N) mice. HBB was approximately 100 times more potent than Aroclor 1254. (Lubet RA, Lemaire BN, Avery D, Kouri RE.Induction of immunotoxicity in mice by polyhalogenated biphenyls. Arch Toxicol. 59:71-77, July 1986)

Neurotoxicity

[31] FireMaster BP-6 was administered orally to female Sprague-Dawley rats at 0, 0.2 or 2 mg/kg from gestation day 6 – 24 post partum. Offspring were evaluated. "An overall evaluation of behavior by multivariate analysis of variance revealed significant PBB-related effects for acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity of male and female offspring from dams administered 2 mg/kg. Delays in acquisition of forward locomotion and suppressed open-field activity were the most prominent effects. These indications of growth retardation and neurobehavioral toxicity occurred at concentrations of PBB in offspring body fat in the range of those which have been reported for highly exposed human subjects with neurological sequelae." (Henck JW, Mattson JL, Rezabek DH, Carlson CL, Rech RH. Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan, USA. Developmental neurotoxicity of polybrominated biphenyls. Neurotoxicol Teratol 16:391-399, July – August 1994)

[32] Rats (albino males F-344/N) and mice (B6C3F1) were dosed by gavage with FireMaster FF-1 (0.3 – 30 mg/kg) and 2,4,5,2',4',5'-hexabromobiphenyl (0.168 – 16.8 mg/kg). FireMaster decreased body weight and performance on test such as activity in the open field, forelimb grip strength, and muscular reflexes. HBB was much less potent. "Visual placement responses were also decreased in some animals, while hypothermia was observed in others." "These experiments indicate that oral dosing with levels of PBBs below those required to produce signs of acute toxicity produced behavioral or neurological toxicity when given repeatedly." (Tilson HA, Cabe PA, Mitchell CL. Behavioral and neurological toxicity of polybrominated biphenyls in rats and mice. Environ Health Perspect 23: 257-263, April 1978.)

Gap junctions

[33] Halogenated hydrocarbons including polybrominated biphenyls were tested for their ability to inhibit gap junctional intercellular communication (GJIC) in normal human breast epithelial cells. Non co-planar HBB, 2,2´,4,4´,5,5´-HBB inhibited GJIC in a dose dependent, reversible manner from 0 – 66 uM after 90 minutes of treatment as demonstrated by a reduction in the number of gap junction plaques after immunofluorescent staining. Further experiments showed alternations in the phosphorylation patterns of gap junction proteins. Concentrations of 0 – 160 uM co-planar HBB, 3,3´,4,4´,5,5´-HBB, did not inhibit GJIC. A mixture of dieldrin and 2,4,5-hexabromobiphenyl significantly inhibited GIJC even though the concentration of each component did not inhibit GIJC when tested alone. (Kang KS, Wilson MR, Hayashi T, Chang CC, Trosko JE. Department of Pediatrics/Human Development, Michigan State University, East Lansing,

MI 48824, USA. Inhibition of gap junctional intercellular communication in normal human breast epithelial cells after treatment with pesticides, PCBs, and PBBs, alone or in mixtures. Environ Health Perspect. 104:192-200, February 1996)

[34] Firemaster BP-6 and individual HBB congeners were tested for their ability to affect cell-cell communication in human teratocarcinoma cells. Both Firemaster BP-6 and 2,2',4,4',5,5'-hexabromobiphenyl inhibited cell-cell communication with only slight effects on survival. The congener, 3,3',4,4'-tetrabromobiphenyl, was moderately cytotoxic and was also ineffective at blocking cell-cell communication. The congener, 3,3',4,4',5,5'-hexabromobiphenyl, was highly cytotoxic. (Kavanagh TJ, Chang CC, Trosko JE. Effect of various polybrominated biphenyls on cell-cell communication in cultured human teratocarcinoma cells. Fundam Appl Toxicol. 8:127-131, January 1987)

Retinoids

[35] Tissue levels of retinoids were measured in male Sprague-Dawley rats after exposure to PCBs and PBBs including 3,3',4,4',5,5'-hexabromobiphenyl. HBB reduced the activity of hepatic retinyl ester hydrolase and the levels of hepatic retinyl palmitate and increased the levels of renal retinyl palmitate. (Chen LC, Berberian I, Koch B, Mercier M, Azais-Braesco V, Glauert HP, Chow CK, Robertson LW. Graduate Center for Toxicology, University of Kentucky, Lexington 40506-0054. Polychlorinated and polybrominated biphenyl congeners and retinoid levels in rat tissues: structure-activity relationships. Toxicol Appl Pharmacol. 114:47-55, May 1992)

[36] Tissue levels of retinoids were measured in female rats after exposure to 1 mg/kg HBB (3,3',4,4',5,5'-hexabromobiphenyl). In the liver, HBB decreased retinol by 20-fold and retinyl esters by 23-fold. In kidneys, HBB increased retinol by 6.4-fold and retinyl esters by 7.4-fold. The serum concentration of retinol was not affected and activities of acyl-CoA:retinol acyltransferase and retinyl palmitate hydrolase were reduced. The authors note that HBB causes major disturbances in vitamin A metabolism since feeding results in a loss of ability of liver to store vitamin A, and severely alters the uptake and metabolism of vitamin A in the kidneys. (Jensen RK, Cullum ME, Deyo J, Zile MH. Department of Pathology, Michigan State University, East Lansing 48824. Vitamin A metabolism in rats chronically treated with 3,3',4,4',5,5'-hexabromobiphenyl. Biochim Biophys Acta. 926:310-320, December 1987)

(c) Environmental fate **(provide summary information and relevant references)**

Chemical/physical properties

Please see POPRC1-INF-7

Persistence

Please see POPRC1-INF-7

How are chemical/physical properties and persistence linked to environmental transport, transfer within and between environmental compartments, degradation and transformation to other chemicals?

[37] HBB was irradiated with ultraviolet light and the resulting mixture identified and tested for effects on liver enzymes. Photoproducts of irradiation of 2,4,5,2',4',5'-hexabromobiphenyl included 2,4,5,3',4'-pentabromobiphenyl (-PBB), 2,4,5,2',5'-PBB, and 3,4,3',4'-tetrabromobiphenyl (3,4-TBB). All three products as well as the mixture increased liver weight and caused a mixed induction of liver drug metabolizing enzymes. (Millis CD, Mills R, Sleight SD, Aust SD. Photolysis products of 2,4,5,2',4',5'-hexabromobiphenyl: hepatic microsomal enzyme induction and toxicity in Sprague-Dawley rats. Fundam Appl Toxicol. 5:555-567, June 1985)

Bio-concentration or bio-accumulation factor, based on measured values (unless monitoring data are judged to meet this need)

Please see POPRC1-INF-7

(d) Monitoring data (provide summary information and relevant references)

Human

[38] Forty human serum pools collected from 1985 – 2002 in the US were examined for PBDEs, HBB, and PCB. The results indicated that levels of HBB have declined from approximately 8 ng/g lipid in 1985 to 3.5 ng/g lipid in 2002 since their phase-out in the 1970s. (Sjodin A, Jones RS, Focant JF, Lapeza C, Wang RY, McGahee EE 3rd, Zhang Y, Turner WE, Slazyk B, Needham LL, Patterson DG Jr. Organic Analytical Toxicology Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341-3717, USA. Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. Environ Health Perspect. 112:654-658, May 2004)

[39] The study examined serum HBB levels in 1772 women exposed to HBB in Michigan with an age range of 1 – 45 years. “Median serum levels at enrollment were 2.0 ppb PBB and 5.0 ppb PCB. A decline in serum PBB level over an interval that ranged from 1 to 146 months (median=31) was observed for 44.6% of the women (median=1.0 ppb), while 12.2% showed an increase (median=1.0 ppb).” “Relative to women whose contaminant levels were stable, higher initial serum level was a predictor of decline for both PBB and PCB (OR=1.66, 95% CI 1.52-1.82; OR=3.26, 95% CI 2.58-4.12, respectively)…” “…age< or =10 years at exposure (OR=1.72, 95% CI 1.03-2.86) and residence on a quarantined farm (OR=1.40, 95- CI 1.03-1.90) were predictors of a decrease in PBBs. Factors related to an increase in PBB levels were age< or =10 years at exposure (OR=0.30, 95% CI 0.10-0.96) and initial PBB level (OR=1.24, 95% CI 1.15-1.33)…” “Early age at exposure appears to be an important predictor of changes in serum PBB levels over time.” (Sweeney AM, Symanski E, Burau KD, Kim YJ, Humphrey HE, Smithci MA. University of Texas, Houston School of Public Health, Houston, Texas, USA. Changes in serum PBB and PCB levels over time among women of varying ages at exposure. Environ Res 86:128-139, June 2001)

[40] “PBB serum levels were detected in 36 of the 51 PBB-exposed subjects. The serum half-life of HBB was determined by comparing the current serum HBB values to the subject's previous serum values obtained 5 to 8 years earlier. The median HBB half-life was 12 years (range 4-97 years). The CBT (caffeine breath test) and CMR (caffeine

urinary metabolite ratio) were elevated in the subjects exposed to PBBs as compared to the values obtained from urban nonsmokers and were similar to those found in adults who smoke. 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 males. There was a correlation between the CBT and the HBB serum values (r2 = 0.2, p = 0.01) but not between CMR and HBB serum values. The CBT and CMR were easily conducted in the field and appear to be useful metabolic probes of cytochrome P-450I activity in human environmental toxicology." (Lambert GH, Schoeller DA, Humphrey HE, Kotake AN, Lietz H, Campbell M, Kalow W, Spielberg SP, Budd M. Pediatrics Department, Michael Reese Hospital, University of Chicago, IL 60628. The caffeine breath test and caffeine urinary metabolite ratios in the Michigan cohort exposed to polybrominated biphenyls: a preliminary study. Environ Health Perspect. 89:175-181, November 1990)

[41] Ten years after the PBB poisoning in Michigan, this study examined 196 tissues from 15 autopsy cases in Grand Rapids, Michigan, USA. Only 4 samples did not have HBB above the 0.5 ng/g detection limit. Perirenal fat contained the highest levels of HBB with an average of 475 ng/g. The second highest levels were found in the adrenal, atheromatus aorta and thymus with levels about half of those observed in perirenal samples. Other tissues showed levels one-tenth the concentrations of the perirenal samples. The authors estimated the half-time of HBB elimination to be at least 7.8 years and noted that HBB would persist in human tissues throughout the lifetime of the contaminated individuals. (Miceli JN, Nolan DC, Marks B, Hariharan M. Persistence of polybrominated biphenyls (PBB) in human post-mortem tissue. Environ Health Perspect. 60:399-403, May 1985)

[42] "Approximately 85% of the Michigan population received some exposure to PBB because dairy product marketing involves mixing milk from many farms. A few cases of high human exposure, which may have been as great as 10 g, occurred when residents of the more highly exposed farms consumed their own products." (Fries GF. The PBB episode in Michigan: an overall appraisal. Crit Rev Toxicol 16:105-156, 1985)

[43] "Cord serum and maternal milk levels of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) were examined in relation to maternal serum levels. Maternal serum levels were significantly higher than cord serum levels for both types of compounds. Placental passage was indicated by significant maternal to cord serum correlations for both PCBs (r = .42) and PBBs (r = .81). Correlations between maternal serum and milk levels were similar. Higher PBB correlations were probably due to greater reliability in the measurement of PBB levels in serum and milk." (Jacobson JL, Fein GG, Jacobson SW, Schwartz PM, Dowler JK. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. Am J Public Health 74:378-379, April 1984)

Animal

[44] The liver and eggs of common cormorants from Japan were analyzed for polybrominated biphenyls, PBDEs, dioxins, and furans. Concentrations of polybrominated biphenyls ranged from 3.0 – 33 ng/g lipid in liver and 3.4 – 82 ng/g lipid in eggs. The authors note the similarity between bioaccumulation of polybrominated biphenyls and PCBs in both liver and eggs. (Watanabe K, Senthilkumar K, Masunaga S, Takasuga T, Iseki N, Morita M. Shimadzu-Techno Research Inc., #1, Nishinokyo-shimoaicho, Nakagyo-ku, Kyoto

604-8436, Japan. Brominated organic contaminants in the liver and egg of the common cormorants (Phalacrocorax carbo) from Japan. Environ Sci Technol. 38:4071-4077, August 2004)

[45] Polybrominated biphenyls (PBBs) and PBDEs were measured in lake trout from the Great Lakes (USA and Canada). The lowest concentrations of PBBs were observed in lake trout from Lake Superior with levels of 1.7+/-0.89 ng/g lipid. The highest concentrations of PBBs were observed in lake trout from Lake Huron with levels of 15+/-8.5 ng/g lipid. The predominant congener in all samples was 2,2',4,4',5,5'-hexabromobiphenyl (BB-153) which is a major component of the FireMaster BP-6 commercial mixture. (Luross JM, Alaee M, Sergeant DB, Cannon CM, Whittle DM, Solomon KR, Muir DC. Department of Environmental Biology, University of Guelph, Ont., Canada. Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian Great Lakes. Chemosphere. 46:665-672, February 2002)

(e) Exposure in local areas **(provide summary information and relevant references)**

- general

[46] "Most of the information on human health effects of PBBs comes from studies of Michigan residents who accidentally ingested milk, meat, and eggs that came from farms that used animal feed contaminated with FireMaster FF-1. In 1973, livestock on certain farms in Michigan were exposed to FireMaster FF-1 after it was mistaken as a feed supplement and mixed with feed that was distributed within the state for several months before being discovered. Health problems in dairy cattle, reported in the fall of 1973, were the first signs that this episode occurred, but the accidental addition of PBBs to animal feed was not identified as the cause of the problem until the spring of 1974." (Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004)

- as a result of long-range environmental transport

[47] Sixty-two unhatched eggs from predatory bird species in Norway were analyzed for HBB, PBDEs, TBBP A and other substances. "BB 101 and 153 were found in eggs of all investigated bird species. Especially in samples of white-tailed sea eagle, peregrine falcon and goshawk additional unknown penta- and hexabrominated biphenyls were detected." (Herzke D, Berger U, Kallenborn R, Nygard T, Vetter W. Norwegian Institute for Air Research, NO-9296 Tromso and NO-2027 Kjeller, Norway. Brominated flame retardants and other organobromines in Norwegian predatory bird eggs. Chemosphere 61:441-449, October 2005)

[48] Elevated levels of polybrominated biphenyls (up to 1.1 ng/g wet weight) were measured in biota from Lake Ellasjoen, an Arctic lake. (Evenset A, Christensen GN, Kallenborn R. Akvaplan-niva, Polar Environmental Centre, N-9296 Tromso, Norway. Selected chlorobornanes, polychlorinated naphthalenes and brominated flame retardants in Bjornoya (Bear Island) freshwater biota. Environ Pollut 136:419-430, August 2005)

- information regarding bio-availability

[49] Bioavailability of HBB was determined by measuring it in the fat of livestock raised on farms with soil contamination of HBB. "Ratios of concentrations in fat to concentrations in soil were 0.37 for dairy heifers, 0.27 for primaparous dairy cows, 0.10 for multiparous dairy cows, 0.27 for beef cows, 0.39 for beef calves, 0.37 for ewes, and 1.86 for swine. 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." Absorption of HBB from soil ranged from 56% - 65%. (Fries GF. Bioavailability of soil-borne polybrominated biphenyls ingested by farm animals. J Toxicol Environ Health. 16:565-79, 1985)

(f) National and international risk evaluations, assessments or profiles and labelling information and hazard classifications, as available **(provide summary information and relevant references)**

Agency for Toxic Substances and Disease Registry, USA Department of Health and Human Services. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. September 2004

State of California, USA, Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Safe Drinking Water and Toxic Enforcement Act of 1986, Chemicals Known to the State of California to Cause Cancer or Reproductive Toxicity, December 2, 2005. Polybrominated biphenyls listed in both categories. http://www.oehha.ca.gov/prop65/prop65_list/files/P65single120205.pdf

(g) Status of the chemical under international conventions

Please see UNEP/POPs/POPRC.1/INF/10 Status of chemicals under consideration in other international forums.