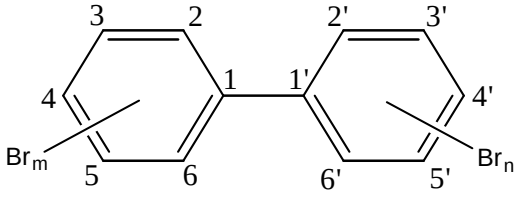
3. RELEVANCE TO PUBLIC HEALTH—PBBs

3.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PBBs IN THE UNITED STATES

Polybrominated biphenyls (PBBs) are brominated organic compounds used as flame retardant additives in plastics, textiles, and other materials. As additives, they are physically mixed into product applications, rather than chemically bound. Therefore, they have the potential to migrate from the plastic matrix into the environment when conditions are ideal. 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. Concern regarding the health effects of PBBs is mainly related to exposures that have resulted from the regionally localized Michigan episode.

PBBs are classes of structurally similar brominated hydrocarbons in which 2–10 bromine atoms are attached to the molecular structure (i.e., biphenyl). Monobrominated structures (i.e., one bromine atom attached to the molecule) are often included when describing PBBs. There are 209 different molecular combinations, or congeners, that are possible for PBBs. However, unlike polychlorinated biphenyls (PCBs), only a subset of these 209 congeners exists in commercial mixtures. Based on the number of bromine substituents, there are 10 homologous groups of PBB congeners (monobrominated through decabrominated), with each homologous group containing one or more isomers. The mono-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, nona-, and decabromo- congeners can exist in 3, 12, 24, 42, 46, 42, 24, 12, 3, and 1 isomers, respectively. The general chemical structures of PBBs are similar when viewed in one dimension, as shown below, where m+n = 1–10:



where m + n = 1–10

Due to the position and number of bromine atoms, there are important three-dimensional differences in the structures of PBBs that can influence the molecules' receptor interactions and toxicological properties (see Section 5.5, Mechanisms of Action).

People are environmentally exposed to PBBs of different congeneric composition than the source commercial mixtures due to differential partitioning and transformation of the individual congeners in the environment, including transformation in food animals (e.g., dairy cattle in the case of PBBs). Additionally, as discussed in Section 5.4, because PBBs are lipophilic and some congeners are not readily metabolized, they are likely to be retained in the body for long periods of time (years).

Three commercial PBB mixtures were manufactured: hexabromobiphenyl, octabromobiphenyl, and decabromobiphenyl. The two main commercial hexabromobiphenyl PBB mixtures had the trade names FireMaster BP-6 and FireMaster FF-1. FireMaster FF-1 was produced by grinding FireMaster BP-6 and adding 2% calcium polysilicate as an anticaking agent. The hexabromobiphenyl mixtures contained varying proportions of di- through octabrominated homologues. 2,2',4,4',5,5'-Hexabromobiphenyl is the most abundant congener in the mixtures (53.9–68.0%), followed by 7.0–27.3% of 2,2',3,4,4',5,5'-hepta-bromobiphenyl. Commercial octabromobiphenyl mixtures contained a large proportion (47.4–60.0%) of nonabromobiphenyl congeners, whereas commercial decabromobiphenyls contain predominately (96.8%) decabromobiphenyl congener.

Limited data are available on health effects of commercial decabromobiphenyl and octabromobiphenyl mixtures, although the hexabromobiphenyl mixtures FireMaster BP-6 and FireMaster FF-1 have been extensively tested. 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.

Available information on the metabolism of PBBs in livestock is insufficient to ascertain whether the people affected in Michigan ingested the original PBB mixtures or metabolic products of the PBBs. Based on limited information in dairy cattle and additional data in laboratory animals as discussed in Section 5.4.2.2, it is reasonable to assume that mainly unchanged penta-, hexa-, and heptabromobiphenyl congeners were consumed in animal products during the contamination episode. PBBs were excreted in cattle manure and, as such, were also environmentally distributed in Michigan via waste disposal on farms. The general population outside of Michigan could possibly have been exposed to PBBs by the

oral route via the food chain, and the inhalation and dermal routes represent the most likely routes of exposure to PBBs in occupational settings.

3.2 SUMMARY OF HEALTH EFFECTS

Most of the information on human health effects of PBBs comes from studies of Michigan populations where PBB-contaminated cattle feed accidentally led to entrance into the feed/food chain, and some information is available on health effects in PPB-exposed chemical workers. Although the human studies consist largely of observations on groups that are not well defined and lack accurate intake data, they do provide a picture of the health status of the affected people and an indication of potential effects for the general population who may be exposed to lower levels of PBBs. Thus far, there is little convincing evidence linking exposure to PBBs and adverse health effects in Michigan farm residents. A variety of symptoms (e.g., neurological and neuropsychiatric, gastrointestinal, hepatic, dermal, and musculoskeletal) have been reported, but the prevalence of these symptoms has not been definitively linked to the extent or types of exposure. Other reported effects in humans include neurodevelopmental effects in exposed children and immunological changes. Physical examinations and laboratory tests have shown few abnormalities that corresponded to the complaints, and prevalences of symptoms have not been correlated with serum PBB levels. However, the possibility of long-term effects cannot be ruled out.

Most toxicity studies of PBBs in animals involved oral exposure, and numerous effects have been documented including hepatic, renal, dermal/ocular, immunological, neurological, and developmental. Other effects of oral exposure to PBBs include decreased thyroid function, body weight loss, and liver cancer. Adverse hepatic effects, as well as dermal and ocular effects, also have been observed in a limited number of dermal studies in animals. No significant adverse effects were observed in animal inhalation studies of PBBs, but only two studies have been conducted, and the mixtures that were tested (octabromobiphenyl and decabromobiphenyl) are not the lower brominated products (i.e., Firemaster mixtures) expected to be the most toxic based on oral data. A number of PBB effects are dioxin-like and consistent with the Ah receptor-mediated mechanism of action, including altered vitamin A homeostasis, thymic atrophy, dermal and ocular effects (e.g., chloracne and inflammation of eyelids), and body weight changes (wasting syndrome). The main health effects of PBBs are discussed in detail below.

Thyroid Effects. 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 (T_4),

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 T_4 and serum triiodothyronine (T_3) 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.

Thyroid effects were produced in rats in acute-duration studies at doses as low as 3 mg/kg/day (reduced serum levels of T_4 hormone), but not at 1 mg/kg/day, and in rats in intermediate-duration studies at doses as low as 0.05 mg/kg/day (increased number and decreased size of follicles). No information is available on possible changes in thyroid hormones following chronic exposure. Histological examinations in chronic-duration studies found no thyroid alterations in rats at doses as high as 1.5 mg/kg/day (highest tested dose), although follicular cell hyperplasia was induced in mice at ≥1.3 mg/kg/day. The no-observed-adverse-effect level (NOAEL) of 1 mg/kg/day was used as the basis for an acute-duration minimal risk level (MRL) for oral exposure. The acute-duration lowest-observed-adverse-effect level (LOAEL) for hepatic effects is identical to the LOAEL for acute thyroid toxicity, but is a less appropriate basis for the MRL because organ functional implications are not as clear. The intermediate-duration LOAELs for thyroid and hepatic effects are also comparable to each other, but neither of these LOAELs is suitable for an intermediate MRL because reproductive and developmental toxicity occurred at a lower dosage. The thyroid LOAEL for chronic-duration exposure is unsuitable for deriving a chronic MRL because decreased survival occurred at the same dose (lower doses were not tested), and thyroid, liver, and other effects occurred at lower doses in intermediate-duration studies.

Hepatic Effects. Histologically and ultrastructurally documented liver damage is a consistent and prominent finding among animals exposed to PBBs by the oral route, but studies of Michigan residents who were likely to have ingested PBB-contaminated food are inconclusive. The human studies do not demonstrate any clear association between abnormal liver-associated serum indices (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase [LDH], bilirubin) or liver enlargement and PBB exposure. No information is available on hepatic effects of PBBs in humans exposed by the inhalation or dermal routes. Although the available studies on liver effects in humans are largely inconclusive, the animal data, as summarized below, suggest that humans may also be affected.

Hepatic effects ranging from microsomal enzyme induction and liver enlargement to fatty changes and necrosis have been observed in rodents and other laboratory animal species exposed orally to FireMaster PBBs in acute-, intermediate-, and/or chronic-duration studies. Acute- and intermediate-duration oral data for octabromobiphenyl mixtures are only available for rats and suggest that hepatic histopathologic effects are milder than for FireMaster mixtures at similar doses. Similarly, intermediate-duration oral data for decabromobiphenyl mixture suggest that this PBB mixture is a less potent hepatotoxicant than an octabromobiphenyl mixture. No pathologic effects were reported in the liver of rats exposed to an octabromobiphenyl mixture in acute- and intermediate-duration inhalation studies, or in an intermediate-duration study with a decabromobiphenyl mixture, but it is unclear if histology was evaluated following the intermediate-duration octabromobiphenyl mixture exposure. Acute dermal exposure to commercial mixtures of hexabromobiphenyl, but not octabromobiphenyl, has been reported to produce gross necrotic changes in the liver of rabbits. Hepatocyte enlargement and degenerative changes (vacuoles or necrosis) are the most sensitive adverse hepatic effects that have been observed in the acute-, intermediate-, and chronic-duration oral studies with FireMaster PBBs. The lowest hepatic LOAELs for acute and intermediate durations are identical or essentially the same as the LOAELs for thyroid effects. The acute-duration LOAEL for thyroid toxicity is used as the basis for an acute oral MRL, but neither hepatic nor thyroid LOAELs for intermediate-duration exposure are suitable for MRL derivation because reproductive and developmental toxicity occurred at a lower dosage. Hepatotoxicity occurred at the lowest dosage tested in chronic studies with rats and mice, and the hepatic LOAEL in mice also caused thyroid effects. Neither the rat nor the mouse LOAEL is a suitable basis for a chronic MRL, however, due to decreased survival at the same dosage and weight loss and developmental toxicity in monkeys at a lower chronic dosage.

Altered vitamin A homeostasis, primarily manifested as decreased hepatic storage of vitamin A, is another established effect of PBBs in animals. Vitamin A is essential for normal growth and cell differentiation, particularly differentiation of epithelial cells, and some PBB-induced epithelial lesions resemble those produced by vitamin A deficiency. Because it is the primary storage site for vitamin A, the liver has a major role in retinol metabolism. Esterification of dietary vitamin A, hydrolysis of stored vitamin A, mobilization and release into the blood of vitamin A bound to retinol-binding protein, and much of the synthesis of retinol-binding protein occurs in the liver.

Immunological and Lymphoreticular Effects. Altered lymphocyte transformation responses among populations exposed to PBB following the Michigan contamination episode have been reported by some investigators. Others have not been able to confirm these findings. However, it is clear that no

correlation can be established between altered immune parameters and PBB levels in serum. Some have suggested that PBBs associated with white blood cells is possibly the cause of the immunological dysfunction resulting from exposure to PBBs. This would imply that total PBB in plasma is not necessarily a good marker for immune dysfunction. Continuous examination of this cohort may resolve the controversy.

Studies in animals, mostly intermediate-duration studies in rodents, indicate that a variety of immunological parameters such as spleen and thymus weights, antibody production, and lympho-proliferative responses can be affected by treatment with commercial PBB mixtures. The only chronic study found increased splenic hematopoiesis in mice, but no histological changes in the spleen, thymus, or lymph nodes of rats. It is apparent, however, that some of these effects are only seen at PBB levels that cause overt toxicity. Steroids are known to influence the immune response. Corticosterone levels were elevated in plasma of mice that were exposed to FireMaster BP-6 in the diet for 30 days, although the increase was not enough to be responsible for the observed immunological effect (reduced antibody-mediated response to sheep red blood cells). Thymic atrophy and a reduction in lymphocyte markers were reported in cows treated with PBB doses of 67 mg/kg/day for ≤60 days. However, these results should be interpreted with caution since the animals approached death at this dose. Based on the data available, it is difficult to suggest any particular species as the most sensitive. This is because different studies usually examined different end points, using different exposure protocols. It is unclear whether morphological changes in the reticuloendothelial system are more sensitive indicators of altered immune status than are functional changes. Although the limited data on humans are largely inconclusive, PBBs have altered immune responses in a variety of animal species, which suggests that humans may also be affected.

Neurological Effects. Data from studies on Michigan residents exposed to PBBs as a result of the 1973 feed contamination episode and data from a limited number of animal studies both suggest that exposure to PBBs may cause subtle effects on neuropsychological performance and development in humans. Symptoms of neurological effects, including fatigue, weakness, and decrements in the capacity to perform physical or intellectual work, were reported frequently by groups of farm families and residents of Michigan who were likely to have consumed farm products (milk, meat, and eggs) contaminated with PBBs; however, associations between PBB levels in serum or fat and the frequency of subjectively reported neurological symptoms were not found in several studies. The administration of neuropsychological tests to orally-exposed Michigan residents has not revealed abnormalities or associations between test performance and PBB levels in serum or fat. Similarly, no association between

performance in neuropsychological tests and serum PBB levels was made in a study of a small number of chemical workers exposed to unspecified PBBs via inhalation and/or dermal contact.

Examinations of a small number of children (19) believed to have been exposed *in utero* or in early infancy during the peak of the Michigan PBB-feed contamination episode have not found consistent or marked effects on neuropsychological development. One study found a statistically significant association between performance in neuropsychological development tests and PBB levels in adipose tissues when the children were ≈2.5–4 years old, but a later examination when the children were ≈4–6 years old did not find such an association for the same tests.

Studies with rats have shown that oral exposure to PBBs at dose levels of ≈10 mg/kg/day for intermediate durations (1–6 months) produced decreased motor activity and weakness of the hind limb, but not operant behavior deficits or histopathological alterations of brain or spinal nerve tissue. Performance deficits in tests of learning behavior were observed in the offspring of female rats and female mice treated with oral doses of PBBs at approximate daily dose levels ranging from 0.2 to 10 mg/kg during gestation and lactation. Effects on acquisition of forward locomotion, cliff avoidance, cage emergence, and open-field activity were found in offspring of rats that were exposed to 2 mg/kg/day from day 6 of gestation through day 24 postpartum and observed until postnatal day 60.

Dermal and Ocular Effects. Dermal lesions characterized as acne have been observed in humans occupationally exposed to PBBs. Increased prevalences of skin disorder symptoms, including rashes, acne, darkening or thickening of the skin, discoloration or deformity of fingernails or toenails, peeling and scaling, erythema, and hair loss, were reported by Michigan residents who were likely to have ingested PBB contaminated food. There was no association between serum PBB levels and prevalence of symptoms in one study, but physical examinations in the other study confirmed a slightly increased incidence of alopecia. Polymer fibers containing octabromobiphenyl mixture caused no dermal effects when placed on covered human skin for 6 days.

Acute-, intermediate-, and chronic-duration oral studies have found no histological alterations in the skin, pinnae, ear canals, or salivary glands of rats or mice exposed to FireMaster FF-1 or FireMaster BP-6. Alopecia, loss of eyelashes, generalized subcutaneous edema, dry scaly skin, and periorbital edema developed in three monkeys that were exposed to low doses of FireMaster FF-1 for several months; related histological findings included sebaceous gland atrophy and metaplasia and keratinization of hair follicles. Uncharacterized dermatosis was observed in similarly treated pigs. Hyperkeratosis of the

eyelids and metaplasia of the tarsal glands with keratin cysts developed in cows that ingested FireMaster BP-6 for up to 60 days. Acute dermal application of FireMaster FF-1 induced hyperkeratosis, dilation and keratinization of hair follicles, and partial atrophy of the sebaceous glands in rabbits, but effects of octabromobiphenyl and decabromobiphenyl mixtures were generally mild (slight erythema and edema). Octabromobiphenyl mixture was not a sensitizer when applied to guinea pig skin. Although somewhat limited, the animal and human data are generally consistent and indicate that although PBBs can cause local responses such as irritation by direct dermal contact, exposure does not need to occur by the dermal route to produce cutaneous effects.

Unspecified signs of ocular irritation were observed in rats intermittently exposed to a high (5,000 mg/m^3) dust concentration of decabromobiphenyl mixture for 4 weeks, but severity was not reported, and recovery was not assessed. Octabromobiphenyl and decabromobiphenyl mixtures caused mild eye irritation in rabbits when applied as a dry solid. Histopathological changes have not been observed in the eyes of rats or mice exposed orally to FireMaster FF-1 or FireMaster BP-6 in studies of acute, intermediate, or chronic duration. Xerophthalmia (extreme dryness of the conjunctiva) was reported in rats fed FireMaster BP-6 in an intermediate-duration study. Based on effects in animals, direct exposure to PBBs is likely to be irritating to human eyes.

Body Weight Effects. Animal studies provide strong evidence that oral exposure to FireMaster PBBs causes a wasting syndrome characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally preceding death. Effects on body weight have been observed in single dose, intermediate- and chronic-duration oral studies with rats, mice, guinea pigs, mink, monkeys, and/or cows. Changes in body weight were also observed in rabbits following acute dermal exposure to commercial mixtures hexabromobiphenyl, but not octabromobiphenyl, suggesting that the syndrome is independent of exposure route and is a potential effect of PBBs in humans.

Reproductive Effects. A limited amount of data is available regarding the reproductive effects of PBBs in humans. The distribution of sperm counts, sperm motility, and sperm morphology was investigated in a small number (50) of male Michigan residents who ingested food produced on PBB-contaminated farms or who worked in a PBB manufacturing company. The study found no evidence for PBB-related effects compared with a putatively unexposed control group. No relationship was found between serum PBB levels and frequency and duration of breast-feeding in a retrospective study of women exposed to PBBs during the Michigan episode. A study of fetal mortality rates in Michigan counties did not include data for fetal mortalities occurring during the first trimester of pregnancy.

Animal studies provide limited evidence that FireMaster FF-1 and FireMaster BP-6 PBBs cause adverse reproductive effects in a variety of species. Increased menstrual cycle duration and prolonged implantation bleeding were observed in female monkeys fed approximate daily dose levels of 0.012 mg/kg for 7 months before breeding and during pregnancy. A corresponding decrease in serum levels of progesterone suggests that the reproductive effects in the monkeys are related to PBB-induced endocrine imbalance. This dosage (0.012 mg/kg/day) is the lowest tested in any intermediate-duration study and also caused fetal deaths in the monkeys after ≈1 year of exposure. Although the reproductive effects are less serious, concern for serious developmental toxicity following exposures of <1 year precludes deriving an MRL for intermediate-duration exposure. Implantation was completely blocked in 40–67% of female rats treated with gavage dose levels ≥28.6 mg/kg on alternate days between gestation days 0 and 14. Alterations in male reproductive organs were observed at doses that caused death in male rats (necrosis of the epithelial lining of the ductus deferens after 100 mg/kg for 4–5 weeks) and in a monkey (hypoactive seminiferous tubules after ≈0.73 mg/kg/day for 25 weeks). No alterations in litter size or fertility were observed in a study of male and female minks fed ≤0.39 mg/kg/day for 6–7 months prior to breeding and during pregnancy or in the F_1 or F_2 generations of female parental rats fed as much as 5 mg/kg/day during the postimplantation phase of gestation and through weaning.

Based on the observations of adverse effects on reproduction in animals exposed to PBBs, the possibility that PBBs may cause reproductive harm in humans cannot be refuted and suggests that exposure of women to PBBs prior to and during the early phases of pregnancy may be of particular concern.

Developmental Effects. Consistent or marked abnormalities have not been found in examinations of the physical and neuropsychological development of children exposed *in utero* or in early infancy during the peak of the Michigan PBB episode. Likewise, a comparison of fetal mortality rates for Michigan counties with a high percentage of quarantined farms and those for Michigan counties with no quarantined farms did not clearly establish or refute the possibility that the Michigan PBB episode caused developmental problems in exposed people.

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. Increased incidences of fetuses with extra ribs were reported in a study of rats orally exposed to commercial octabromobiphenyl mixture during gestation, but oral exposure to commercial decabromobiphenyl mixture was not embryotoxic, fetotoxic, or teratogenic in rats. 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.

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.

Cancer. There is no epidemiological evidence of an association between exposure to PBBs and increased prevalence of cancer (all sites) in Michigan residents who were likely to have ingested PBB-contaminated food. These data are inconclusive due to a short latency period of 4 years. Suggestive relationships between increasing serum levels of PBBs and risks of breast cancer, digestive system cancer, and lymphoma (not otherwise specified) were found in case-control studies of Michigan PBB registry enrollees who were followed for approximately 20 years.

Oral studies with rats and mice demonstrate that FireMaster FF-1 is an unequivocal hepatocarcinogen. Hepatocellular adenomas, carcinomas, and/or liver neoplastic nodules were induced in these species following single or repeated (intermediate- and chronic-duration) exposures. These types of liver neoplasms even developed in the offspring of rats administered a single gavage dose during gestation or offspring of mice treated by diet during the perinatal period (throughout gestation and lactation). Liver neoplasm incidences were much higher in rats and mice exposed for up to 2 years in the only chronic bioassay than in the other studies that involved shorter-duration exposures of up to 6 months followed by an observation period of up to 2 years. Based on findings in male rats and mice of both sexes in this

study, there is some evidence that combined perinatal and adult dietary exposure to FireMaster FF-1 enhanced the susceptibility of hepatocellular neoplasms in animals receiving adult exposure.

Tumors were not clearly or consistently observed in nonhepatic tissues of animals exposed to FireMaster FF-1. Induction of thyroid follicular cell adenoma was inconclusive in mice in both National Toxicology Program bioassays. Equivocal increases in incidences of mononuclear cell leukemia were observed in adult-only exposed rats in the NTP chronic study, and combined perinatal and adult exposure showed no significant increase. Combined analysis of the incidences of this leukemia in the adult-only, perinatal only, and combined perinatal and adult exposure groups, however, showed an apparent association between increasing incidences and dose, and incidences in some of the groups exceeded historical control ranges. Evidence is available that oral administration of FireMaster BP-6 promotes development of initiated tumors in rats (liver enzyme-altered foci assays) and hamsters (tracheal papilloma assay).

Based on the results of the oral studies of FireMaster FF-1 in rats, there is sufficient evidence to conclude that PBBs are carcinogenic in animals and potentially carcinogenic in humans. PBBs, as a group, have been classified as possibly carcinogenic to humans by IARC (Group 2B). This classification is based on sufficient evidence for carcinogenicity to animals and inadequate evidence of carcinogenesis in humans. NTP concluded that PBBs are reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity in animals. The EPA has not classified the carcinogenicity of PBBs. Because there is insufficient information about which constituents of the PBB mixtures are carcinogenic and the congener profile to which people may be exposed environmentally is likely to be different from the original PBB source, it is assumed that PBB mixtures of any composition are potentially carcinogenic. This assumption has uncertainty since it cannot be verified with current knowledge, and because the mechanism of PBB carcinogenesis in rodents has not been definitively elucidated.

3.3 MINIMAL RISK LEVELS

A number of the toxic effects of PBBs, including immunotoxicity, inhibition of body weight gain, and hepatic changes, appear to be mediated by a common mechanism of toxic action that involves a specific cytosolic molecular receptor (Ah receptor) (see Chapter 5, Section 5.5.2, Mechanisms of Toxicity). Although numerous factors can influence the toxicity of PBBs; including differences in absorption, distribution, and retention among animal species, at the tissue level, the potency of some individual congeners is determined by the magnitude of the response that is initiated by its binding with the Ah receptor. The binding affinity, in turn, is determined by the substitution pattern of the congener, and

many of the most toxic congeners resemble the structural configuration of 2,3,7,8-TCDD, and therefore are dioxin-like in toxicity. However, congeners that exhibit Ah receptor-mediated responses constitute a fraction of the components in commercial PBB mixtures. Therefore, it is presumed that congeners that act by other mechanisms also contribute to the toxicity of PBB mixtures, and the toxicity of PBBs is commonly classified as either "dioxin-like" or "nondioxin-like." The mechanism(s) of toxicity for nondioxin-like PBB congeners is less clearly elucidated, but also may involve receptors (e.g., the estrogen receptor), or the involvement of reactive intermediates (e.g., arene oxides) that can form potentially toxic covalently bound substrate-macromolecular adducts.

People are environmentally exposed to PBB mixtures of different congeneric composition than the original commercial PBB products. Although the toxicity or potency of environmental PBB mixtures consequently may be greater or less than that of commercial mixtures, there are insufficient mixture toxicity data on which to directly base MRLs for environmental PBBs. Due to the likelihoods that (1) multiple mechanisms (Ah-receptor-dependent mechanisms, Ah-receptor independent mechanisms, or both) may be involved in health effects induced by PBBs, (2) different PBB congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PBBs with differing biological activities, as well as to the lack of a suitable approach for quantitatively evaluating joint toxic action from concurrent exposures to PBBs and other structurally similarly compounds (e.g., PCBs, CDDs, CDFs, and PBDEs) in the environment, data from commercial PBB mixtures are used to develop MRLs for assessing health risks from environmental exposures to PBBs.

Inhalation MRLs

No MRLs have been derived for inhalation exposure to PBBs because human and animal data for all durations are either insufficient or lacking. Insufficiencies in the human inhalation data include mixed-chemical and unquantified exposures. The animal inhalation database is limited by inadequately reported studies and lack of any information on the mixtures likely to be most toxic (i.e., FireMaster PBBs).

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute oral exposure (14 days or less) to PBBs.

The acute oral MRL was based on a NOAEL for decreased serum levels of thyroid T_4 hormone identified in groups of 8–11 male rats that were treated with 0, 1, 3, or 6 mg/kg/day doses of an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days (Allen-Rowlands et al. 1981). The MRL was

estimated by dividing the NOAEL by an uncertainty factor of 100 (component factors of 10 for animal to human extrapolation and 10 for human variability). Levels of serum T_4 were significantly ($p<0.05$) reduced at ≥3 mg/kg/day, indicating that the lowest dose (1 mg/kg/day) is the NOAEL. Despite the fact that an appropriate statistical test (t-test rather than an ANOVA with multiple comparison tests) was used to analyze the data, ATSDR is confident with the designation of the NOAEL and LOAEL values. The data in the manuscript are presented graphically, with the animal numbers presented as a range (8–11 animals/group); thus, an ANOVA could not be performed from published report. However, using the graphical data, the change in plasma T_4 levels in the 3 mg/kg/day groups is clearly on the order of 20–30%, which represents a biologically significant change. As such, the identification of 3 mg/kg/day as a LOAEL, and 1 mg/kg/day as a NOAEL, is not contraindicated by the lack of appropriate statistical analysis.

Decreased serum T_4 is considered adverse due to unequivocal evidence from numerous studies that the thyroid is a target of PBBs with a spectrum of effects, including decreases in serum T_3 and T_4 hormone, thyroid enlargement, effects in the follicular cells (e.g., reduced size, hyperplasia with columnar appearance and papillary projections), and accumulation of colloid droplets (Akoso et al. 1982b; Byrne et al. 1987; NTP 1983; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975b; Sepkovic and Byrne 1984; Sleight et al. 1978). Additional information on the derivation of the acute-duration oral MRL for PBBs is provided in Appendix A.

Intermediate- and chronic-duration oral MRLs were not derived because serious developmental and reproductive effects were observed in monkeys that had been exposed to PBBs for durations that spanned the intermediate and chronic categories at the lowest dose tested in the database. This dose (0.012 mg/kg/day) caused increased menstrual cycle duration and implantation bleeding after 6–7 months of exposure and fetal deaths (fetal abortion and stillbirth) after ≈1 year of exposure in monkeys, with surviving infants having decreased birth weight and decreased postnatal weight gain (Allen et al. 1978, 1979; Lambrecht et al. 1978). Additionally, weight loss occurred in the maternal monkeys. The 0.012 mg/kg/day serious LOAEL for developmental and reproductive effects is lower than the lowest less serious LOAELs for thyroid effects in rats (0.05 mg/kg/day) (Akoso et al. 1982b) and hepatic effects in guinea pigs (0.04 mg/kg/day) (Sleight and Sanger 1976). As the most sensitive effect seen following intermediate-duration oral exposure was a serious LOAEL, without an accompanying NOAEL, concern for serious developmental and reproductive toxicity following exposures of <1 year therefore precludes deriving an MRL for intermediate-duration exposure. Derivation of an MRL for chronic oral exposure is similarly precluded by the serious developmental effect (stillbirth) that occurred following exposures

exceeding 1 year in duration. The serious LOAEL in monkeys is lower than the lowest chronic dosages tested in other species (0.5 and 1.3 mg/kg/day in rats and mice, respectively) that caused decreased survival (NTP 1992). ATSDR's classification of LOAELs into less serious and serious effects is discussed in the introduction to Section 5.2.