2. RELEVANCE TO PUBLIC HEALTH

2.1 Background and Environmental Exposures to PCBs in the United States

PCBs are a category of chemicals that were manufactured in the United States between about 1930 and 1977, predominantly for use as coolants and lubricants in electrical equipment such as capacitors and transformers due to their general chemical inertness and heat stability. PCBs are complex mixtures of chlorinated biphenyls that vary in the degree of chlorination. For example, the commercial product Aroclor 1254 is a mixture of mono- through heptachlorinated biphenyl congeners with an average chlorine content of approximately 54%. However, significant lot-to-lot differences in congeneric composition occurred among similar mixtures. The manufacture of PCBs in the United States was stopped due to evidence that they accumulate and persist in the environment and can cause toxic effects.

No known consumer product currently manufactured in the United States contains PCBs, but PCBs are still released during some industrial processes. Once released into the environment, the compositions of commercial PCB mixtures are altered through processes such as volatilization and other kinds of partitioning, chemical or biological transformation, and preferential bioaccumulation. These processes are dependent upon the degree of chlorination of the biphenyl molecule. PCBs, particularly the higher chlorinated congeners, adsorb strongly to sediment and soil, where they tend to persist with half-lives of months to years. PCBs bioaccumulate in food chains and are stored in fatty tissues due to their stability and lipophilicity. Bioaccumulated PCBs are of particular relevance to human health because of their persistence in the body.

The general population may be exposed to PCBs by ingesting contaminated food and by inhaling contaminated air (see Chapter 6). Food consumption has been and continues to be the major source of body burden of PCBs in the general population. The estimated dietary intake of PCBs for an average adult was about 0.03 µg/kg/day in 1978, but this had declined to <0.001 µg/kg/day by 1991. There is evidence that diets high in fish from PCB-contaminated waters, such as in the Great Lakes-St. Lawrence River basins, can significantly increase a person's dietary intake of PCBs. Breast-fed infants of mothers who have diets high in contaminated fish may have a particularly increased risk for PCB exposure due to its presence in the milk. Human PCB exposure has also been attributed to inhalation of indoor air, especially at locations that still use electrical equipment containing PCBs.

An important issue related to evaluating health effects of PCBs in humans is exposure assessment. Exposure to PCBs has been assessed by measuring PCBs in blood, breast milk, and adipose tissue. Umbilical cord blood also has been used to estimate exposure *in utero*. In addition, fish consumption has been utilized as surrogate of PCB exposure in some studies, but this measure of exposure has not always been reliable. Mean serum PCB levels range from 0.9–1.5 ppb (µg/L), in recent years, in individuals who do not have diets high in fish from waters contaminated with PCBs. In the absence of human data, environmental sampling (soil, sediment, air, food, water) has also been used to estimate exposure.

2.2 Summary of Health Effects

The preponderance of the biomedical data from human and laboratory mammal studies provide strong evidence of the toxic potential of exposure to PCBs. Information on health effects of PCBs is available from studies of people exposed in the workplace, by consumption of contaminated rice oil in Japan (the *Yusho* incident) and Taiwan (the *Yu-Cheng* incident), by consumption of contaminated fish, and via general environmental exposures, as well as food products of animal origin. As summarized below and detailed in Chapter 3, health effects that have been associated with exposure to PCBs in humans and/or animals include liver, thyroid, dermal and ocular changes, immunological alterations, neurodevelopmental changes, reduced birth weight, reproductive toxicity, and cancer. The human studies of the *Yusho* and *Yu-Cheng* poisoning incidents, contaminated fish consumption, and general populations are complicated by the mixture nature of PCB exposure and possible interactions between the congeneric components and other chemicals (see Chapter 3 for additional information). Therefore, although PCBs may have contributed to adverse health effects in these human populations, it cannot be determined with certainty which congeners may have caused the effects. Animal studies have shown that PCBs induce effects in monkeys at lower doses than in other species, and that immunological, dermal/ocular, and neurobehavioral changes are particularly sensitive indicators of toxicity in monkeys exposed either as adults, or during pre- or postnatal periods.

Hepatic Effects. The hepatotoxic potential of PCB mixtures is well-documented in animals by oral and other routes of exposure. The spectrum of possible hepatic effects in animals is broad and includes microsomal enzyme induction, liver enlargement, increased serum levels of liver enzymes and lipids, and histopathologic alterations that progress to fatty and necrotic lesions and tumors. The findings of human studies, however, are not as obvious. Many of the human studies involving worker and other populations with high body burdens of PCBs report associations between PCBs and hepatic indices such as liver enzymes, lipids, and cholesterol. Studies of people exposed to PCBs by ingestion of contaminated fish or

contaminated rice oil in the *Yusho* or *Yu-Cheng* incidents have reported increases in serum levels of some liver enzymes (e.g., γ-glutamyltranspeptidase [GGT], aspartate aminotransferase [AST], and/or alanine aminotransferase [ALT]) that are suggestive of microsomal enzyme induction or possible liver damage. Tests for some nonroutinely-studied liver indices (e.g., accelerated erythrocyte sedimentation rate, high titer in thymol turbidity, increased M fraction of lactate dehydrogenase, and increased alkaline phosphatase and ribonuclease levels) also indicate possible liver damage in some *Yusho* patients.

Definitive conclusions regarding human hepatotoxiciy are hampered by limitations in study design of available studies, such as exposure misclassification, lack of controls, lack of correction for common confounding variables (e.g., age and alcohol consumption), and natural partitioning of PCBs to serum lipids. The lack of unequivocal evidence in humans that is seen in laboratory animals may result from many factors, including species differences in susceptibility or sensitivity to PCBs, and dissimilarities in exposure levels, durations, and mixture compositions.

Hepatotoxic effects commonly induced in laboratory animals exposed to commercial PCB mixtures include increased serum levels of liver enzymes indicative of hepatocellular damage (e.g., AST and ALT), serum and tissue biochemical changes indicative of liver dysfunction (e.g., altered levels of lipids, cholesterol, porphyrins, and vitamin A), and histopathologic changes (particularly fat deposition), fibrosis, and necrosis. Intermediate- and chronic-duration oral studies have shown hepatotoxic effects in monkeys that include fatty degeneration, hepatocellular necrosis, and hypertrophic and hyperplastic changes in the bile duct at oral doses of PCBs as low as 0.1–0.2 mg/kg/day (Aroclor 1254 or 1248).

Induction of microsomal enzymes appears to be the most sensitive hepatic alteration produced by Aroclors and other PCB mixtures in laboratory animals. While microsomal enzyme induction is not necessarily adverse, it may have indirect implications for human health through protective or toxic effects that are secondary to enhanced metabolic detoxification or bioactivation of exogenous or endogenous substances. Examples of this include possible interference with medical therapy due to increased metabolism of administered drugs, the possibility of disease secondary to the altered metabolism of endogenous substances such as hormones, and increased activation of promutagens and procarcinogens as shown, for example, for the secondary carcinogen dimethylnitrosamine.

Hepatic porphyria is an indicator of liver dysfunction that has been induced in animals following intermediate-duration oral or dermal exposure to Aroclors and other PCB mixtures. Increased urinary excretion of porphyrins has been reported in two studies of PCB workers, and Type B hepatic porphyria

(a uroporphyrin/coproporphyrin ratio >1) was a consistent finding in *Yu-Cheng* patients, including children born to exposed mothers. However, clinically evident porphyrias have not been reported in people with occupational or *Yusho/Yu-Cheng* PCB exposures.

The liver, which is the site of approximately 90% of the vitamin A in the body, has a major role in vitamin A metabolism. Altered vitamin A homeostasis, primarily manifested as decreased hepatic storage of vitamin A, is another demonstrated effect of PCB mixtures and single congeners in orally-exposed rats and rabbits. Vitamin A is essential for normal growth and cell differentiation, particularly differentiation of epithelial cells, and PCB-induced epithelial lesions in monkeys have been observed to resemble those produced by vitamin A deficiency. Whether the PCB-related disturbances in vitamin A homeostasis are due to a direct effect on hepatic regulation or to effects on extrahepatic feedback processes has not been established.

Endocrine Effects. Concern about potential effects of PCBs on thyroid hormones is based on two main considerations: (1) extensively corroborated findings in experimental animals that exposure to PCBs *in utero* and/or during early development (e.g., through breast milk) can deplete levels of circulating thyroid hormones in the fetus or neonate, which may give rise to a hypothyroid state during development; and (2) the recognition of the importance of thyroid hormones in normal development of the brain, as is evident from neurodevelopmental disorders and deficits associated with hypothyroidism. The latter are typified by iodine deficiency (e.g., endemic cretinism), which can produce a wide range of neurodevelopmental deficits, including auditory, motor, and intellectual deficits. These outcomes underscore the importance of thyroid hormones in the normal development of the fetal cochlea, basal ganglia, and cerebral cortex, which begin to develop in humans during the second trimester of gestation. This is also the time period during which the fetal thyroid gland becomes functional.

Direct evidence linking PCB exposures to thyroid morbidity in humans is limited. The risk for goiter was significantly increased among the *Yu-Cheng* cohort, indicating the possibility of excess thyroid disease in an adult population that experienced relatively high exposures to mixtures of PCBs and polychlorinated dibenzofurans (PCDFs). Other more limited observations in adults include reports of increased thyroid gland volume among workers and nearby residents of a PCB production facility. Studies that examined relationships between PCB exposure and thyroid hormone status in children or adults reported a variety of different results, with findings of both positive and negative correlations between PCB exposure and circulating levels of thyroid stimulating hormone (TSH) or thyroxine (T_4) or triiodothyronine (T_3) hormones.

The most compelling evidence for a potential thyroid hormone involvement in PCB toxicity in humans is based on observations made in experimental animals, including rodents and nonhuman primates. Major findings include (1) histological changes in the thyroid gland indicative of both stimulation of the gland (similar to that induced by TSH or a hypothyroid state) and a disruption of the processing of follicular colloid needed for normal production and secretion thyroid hormone; (2) depression of T_4 and T_3 hormone levels, which may effectively create a hypothyroid state; (3) increased rates of elimination of T_4 and T_3 from serum; (4) increased activities of T_4-UDP-glucuronyl transferase (UDP-GT) in liver, which is an important metabolic elimination pathway for T_4 and T_3; (5) decreased activity of iodothyronine sulfotransferases in liver, which are also important in the metabolic elimination of iodothyronines; (6) decreased activity of iodothyronine deiodinases including brain Type-2 deiodinase, which provide the major pathways for the production of the active thyroid hormone, T_3; and (7) decreased binding of T_4 to transthyretin, which is an important transport protein for both T_4 and T_3. These observations indicate that PCBs can disrupt the production of thyroid hormones, both in the thyroid and in peripheral tissues, can interfere with their transport to peripheral tissues, and can accelerate the metabolic clearance of thyroid hormones.

The most convincing evidence that PCBs can exert toxicity by disrupting thyroid hormone system derives from two studies in rats. In one study, neurobehavioral deficits in pups exposed to Aroclor 1254 *in utero* and during nursing, were significantly attenuated by subcutaneous injections of T_4 that increased serum T_4 and T_3 concentrations that were otherwise depressed in the PCB-exposed animals. While this study examined relatively high doses of Aroclor 1254, it nevertheless demonstrated neurodevelopmental effects that are directly relevant to observations made in epidemiological studies and to neurological sequelae of fetal hypothyrodism, including disturbances of motor function and hearing. In the second study, increased testes weight and sperm production in rats that were administered Aroclor 1254 on postnatal days 1–25 were attenuated by injections of T_4 on postnatal days 1–25, which also prevented the depression in serum T_4 concentrations. These observed effects may reflect a disruption of the normal sexual maturation process, which is known to be associated with neonatal hypothyroidism in humans. Other effects of PCBs on endocrine function that have been observed in experimental animals include effects on the adrenal glands and serum adrenal steroid levels.

There is suggestive evidence that PCBs can produce both agonistic and antagonistic estrogenic responses. A wide variability of responses observed across PCB type and assays indicates the involvement of multiple mechanisms. The specific mechanism of action appears to vary, with competitive binding to estrogen receptors being congener/metabolite specific. Anti-estrogenic activities appear to be more

strongly associated with PCBs that are Ah receptor agonists, whereas hydroxylated metabolites of PCBs seem to be at least partly responsible for responses to PCBs that may involve changes in estrogen receptor-dependent physiological processes. In general, results from both *in vitro* and *in vivo* studies indicate that PCBs have much lower estrogenic potency than the endogenous hormone, 17β-estradiol. PCB mixtures have been shown to produce comparatively weak estrogenic responses, and mixtures having multiple *ortho* chlorines (or their hydroxylated metabolites) have been suggested to be to partly responsible for some observed estrogenic responses. For example, immature female offspring of laboratory animals exposed to a PCB congener mixture simulating the congener content of human milk from 50 days prior to mating until birth showed significantly increased uterine weights, a parameter known to be under estrogenic influence. In the case of anti-estrogenic responses to PCBs, effects appear to be concentration dependent. Anti-estrogenic responses have been observed in studies using tissues from both humans and rodents.

Dermal and Ocular Effects. Dermal lesions including skin irritation, chloracne, and pigmentation of nails and skin have been observed in humans following occupational exposure to PCBs, and from the accidental ingestion of rice oil contaminated with high concentrations of PCBs, chlorinated dibenzofurans (CDFs) and other halogenated chemicals during the *Yusho* and *Yu-Cheng* poisoning incidents. Of the dermal effects observed in workers, chloracne (a dermatologic condition that starts with formation of comedones [keratin plugs in the pilosebaceous orifices] and inflammatory folliculitis) is the most likely to have been associated with exposure to PCBs.

Ocular effects including hypersecretion of the Meibomian glands, abnormal pigmentation of the conjunctiva, and swollen eyelids have also been observed in humans occupationally exposed to PCBs. These ocular alterations almost always accompany chloracne. Ocular effects may continue to appear after exposure has ceased, possibly as a result of accumulation of the causative agent in skin adipose. Chronic-duration oral exposure studies in monkeys showed that adverse dermal and ocular effects can occur at dose levels as low as 0.005 mg/kg/day.

Immunological Effects. There are indications of altered immune status in adult and infant human populations that were orally exposed to mixtures of PCBs and other chemicals. The most conclusive findings were in the *Yusho* and *Yu-Cheng* populations that experienced the highest levels of PCB exposure and least complex exposure mixture. Interpretation of the data from the other human studies is complicated by responses that were generally subtle and exposures that included a number of persistent toxic substances in addition to PCBs that are also potentially immunotoxic. As detailed in Chapter 3

(Section 3.2.3.2), there appears to be an overall consistency of effects among the human studies supporting sensitivity of the immune system to PCBs and these other chemicals, particularly in infants exposed *in utero* and/or via breast feeding. For example, susceptibility to respiratory tract infections was increased in *Yusho/Yu-Cheng* adults and their children, and there was an association between infectious illnesses and PCBs in the children of the mothers who consumed Lake Michigan or Sheboygan River fish. Children born to *Yu-Cheng* mothers also had an increased prevalence of middle ear infections, and the incidence of acute otitis media was increased in Inuit infants of mothers whose diets were based on marine mammal fat. Serum IgA and/or IgM antibody levels were decreased in the *Yusho* and *Yu-Cheng* populations as well as in the Inuit children. Monocyte counts were reduced in *Yu-Cheng* patients and in the infants of a Dutch mother-child study, and changes in T lymphocyte subsets were found in the *Yu-Cheng*, Inuit child, and Dutch child populations.

Substantial evidence of the immunotoxicity of PCBs in research animals lends strong support to the human data. Particularly relevant findings in animals include reduced antibody responses and levels of T-lymphocytes and their subsets, which are similar to changes observed in some of the human populations. The antibody response to sheep red blood cell (SRBC) antigens is the immune parameter most commonly and consistently shown to be affected by PCBs in animals; reduced responses have been demonstrated in most tested species, including adult and infant monkeys, which are sensitive to this effect at chronic PCB doses as low as 0.005 mg/kg/day (Aroclor 1254). A no observed adverse effect level for immunological effects was not identified.

Studies of rats, mice, guinea pigs, and rabbits showed that intermediate-duration exposures to relatively high doses of commercial PCB mixtures caused morphological and functional alterations in the immune system. Effects observed in these species included thymic and splenic atrophy, reduced antibody responses to SRBC and other foreign antigens, increased susceptibility to infection by viruses and other microbes, reduced skin reactivity to tuberculin, and increased proliferation of splenic lymphocytes in response to mitogenic stimulation.

Oral studies of Aroclor mixtures in monkeys confirm that the immune system is sensitive to PCBs. Immunological effects of PCBs in monkeys include decreased antibody responses to SRBC, increased susceptibility to bacterial infections, altered lymphocyte T-cell subsets, decreased lymphoproliferative response to mitogens, and histopathologic changes in the thymus, spleen, and lymph nodes. Results of studies in gestationally- and lactationally-exposed infant monkeys are consistent with the data in adult animals showing immunosuppressive effects of PCBs at doses as low as 0.005 mg/kg/day (Aroclor 1254),

with reductions in IgM and IgG antibody levels to SRBC and mitogen-induced lymphocyte transformation that generally paralleled the findings in maternal animals. Immunological alterations were induced in infant monkeys that were orally exposed to a PCB congener mixture simulating the congener content of human milk at a dose level of 0.0075 mg/kg/day for the first 20 weeks of life.

Neurological Effects. The neurological effects of PCBs have been extensively investigated in humans and animals. Substantial data suggest that PCBs play a role in neurobehavioral alterations observed in newborns and young children of women with PCB burdens near background levels. In general, the observed alterations are subtle. In some studies, those alterations were found to disappear as the children grow older (2–4 years old), while other studies have reported neurobehavioral deficits still present in 11-year-old children mostly due to *in utero* exposure to PCBs. Laboratory animal studies provide strong substantiating evidence that PCBs can induce adverse neurological effects in developing animals as well as in adults.

Epidemiological findings in infants and children include abnormal reflexes and deficits in memory, learning, and IQ. Prospective studies of children born to mothers exposed to PCBs by consumption of contaminated fish from the Great Lakes and of children from women in North Carolina, the Netherlands, and Germany strongly suggest that PCBs play a significant role in neurodevelopmental toxicity observed in some of these children at birth and continuing during early life. In the various cohorts studied, some common findings of neurodevelopmental effects have been reported, although affected end points have not been the same in all studies. For example, newborns from women who ate high amounts of contaminated Lake Michigan fish (high PCB exposure) had a greater number of abnormal reflexes and more motor immaturity than newborns of mothers who consumed less fish (low PCB exposure). Similar observations were made in a North Carolina study of children born to women with low PCB levels, and in an Oswego, New York study of children from women with high consumption of PCB-contaminated fish from Lake Ontario. There was a significant association between poorer habituation and autonomic scores for the newborns and highly chlorinated (7–9 chlorines) PCB congeners in umbilical cord blood of Lake Ontario fisheaters, but not with abnormal reflexes. No significant association was found between any neurological scores in newborns of the Lake Ontario fisheaters and lightly (1–3 chlorines) or moderately (4–6 chlorines) chlorinated PCBs, DDE, lead, mercury, or hexachlorobenzene. A study of Dutch children found that neither reflex nor postural cluster scores of a neurological examination were associated with prenatal exposure to four predominant nonplanar PCB congeners (measured in maternal or umbilical cord plasma). However, hypotonia, although not with abnormal reflexes, was related to levels of coplanar (dioxin-like) PCBs in breast milk.

Assessment of infants from the various cohorts with the Bayley Scales of Infant Development has revealed additional consistency across studies. This group of tests yields a mental development index (MDI) and a psychomotor development index (PDI) score, both of which are scaled like a standard IQ test. In the North Carolina cohort, a significant decrease in PDI scores at the ages of 6 and 12 months was associated with prenatal exposure to PCBs (assessed as PCBs in maternal milk at birth), but the association lost statistical significance at the ages of 18 and 24 months. No significant association was observed between PDI scores between 6 and 24 months of age and postnatal exposure to PCBs (in milk during breast feeding). There was no significant association between MDI scores and either prenatal or postnatal exposure to PCBs.

Alterations in memory functions were reported in children from the Michigan cohort at 7 months, 4 years, and 11 years of age. Memory and IQ score deficits were associated with prenatal exposure to PCBs, as measured by PCBs in umbilical cord blood. The most highly exposed children were 3 times as likely to have low average IQ scores and twice as likely to be at least 2 years behind in reading comprehension.

Central nervous system effects of PCBs have been confirmed in laboratory animals. For example, decreased performance on a memory task was reported in 60-day-old rats exposed *in utero* to *ortho*-substituted PCB congeners. In monkeys, effects included neurobehavioral changes in juvenile animals that were treated postnatally for 20 weeks with a low-dose (7.5 µg/kg/day) of a mixture of PCB congeners representing 80% of the congeners found in human milk. At age 20 weeks PCB levels were 1.7–3.5 ppm in fat and 1.84–2.84 ppb in blood, which are very similar to levels found in the general population. These monkeys showed deficits in several tasks, including spatial delayed alternation, acquisition of fixed interval, and differential reinforcement of low rate performance, which were indicative of impaired learning, perseveration, and ability to inhibit inappropriate responding. Numerous studies have investigated neurotransmitter levels in the prefrontal cortex (important in the regulation of short-term memory or representational memory for spatial information) and other brain areas following exposure of laboratory mammals to PCBs. The most consistent finding in such studies has been a decrease in the concentration of dopamine in different areas of the brain; however, more information is necessary to associate specific behavioral alterations with specific neurochemical changes.

It is unknown which specific PCB congeners may be neurodevelopmental toxicants in humans. Data from the Oswego fisheater study showed that behavioral alterations in newborn children were associated with the presence of highly chlorinated (7–9 chlorines) PCB congeners in umbilical cord blood. This is

consistent with findings that the distribution of PCB congeners in Great Lakes contaminated fish is shifted toward more highly chlorinated congeners. Studies with single PCB congeners suggest that both dioxin-like (coplanar) and non-dioxin-like PCB congeners are capable of inducing neurobehavioral alterations in animals, but it appears that ortho-substituted PCB congeners are more active than coplanar PCBs in modifying cognitive processes.

A relatively small amount of information is available on neurological effects of PCBs in adult humans. In a study of aging adults exposed to PCBs through consumption of contaminated sportfish from Lake Michigan, no adverse neurological effects were found attributable to exposure to PCBs. Other studies of adult populations with occupational exposure to PCBs have not been as conclusive for adverse neurological effects attributable solely to PCB exposure.

Reproductive Effects. Limited data indicate that menstrual disturbances in women and effects on sperm morphology and production, which are effects that can result in difficulty in a couple conceiving, may be associated with exposure to PCBs . Overall, the studies of reproductive end points in humans are limited; however, the weight of the existing human and animal data suggests that PCBs present a potential reproductive hazard to humans.

In a small number of occupationally-exposed women, there was no apparent effect of Aroclors 1254, 1242, and/or 1016 on mean number of pregnancies. A study of the general population found that blood PCB levels were higher in women who had repeated miscarriages, but levels of other organochlorine compounds were also elevated. Studies that examined reproductive end points in women whose diets contained Great Lakes fish found suggestive evidence that consumption of the fish may be associated with a slightly shorter length of menstrual cycle and reduced fecundability among couples attempting pregnancy, but not with increased risk of conception delay. The slight decreases in menstrual length seen in this population were considered of unknown clinical relevance. Menstrual cycle changes (altered intervals, duration, and flow) have also been observed in women exposed to higher doses of PCBs during the *Yusho* poisoning incident. However, another general population study did not find an association between endometriosis or increased risk for spontaneous fetal death and concentrations of PCBs in the blood.

These reproductive effects are supported by a number of studies in laboratory animals. Menstrual alterations in monkeys and estrus changes in rats have been observed following oral exposure to Aroclor PCB mixtures. For example, high doses of Aroclor 1254 causes prolonged estrus cycle in adult rats

exposed for several weeks, delayed first estrus in offspring of rats following gestational and lactational or lactational-only exposure, and altered estrus cycle patterns in young and mature offspring of rats following lactational exposure. In monkeys, menstrual cycle durations became erratic or longer following exposure to $0.1 mg/kg/day Aroclor 1248 for 7–9 months, although no clear changes in menstrual cyclicity resulted from chronic exposure to lower dose levels (0.005–0.08 mg/kg/day) of Aroclor 1254. In addition, delayed onset of estrus was also observed in adult mink and their offspring in a 2-generation reproduction study involving exposure to Great Lakes fish.

The reproductive toxicity of commercial PCB mixtures in female animals is well-established. In addition to estrus and menstrual changes, effects that have been observed in various species include reduced implantation rate in adult rats and/or their offspring exposed during gestation and lactation, decreased conception in mice, partial or total reproductive inhibition in minks, and decreased fertility in monkeys. Minks and monkeys are particularly sensitive, with effects occurring in these species at oral doses of Aroclor 1254 and 1248 in the range of 0.1–1 mg/kg/day in intermediate-duration studies, and as low as 0.02 mg/kg/day in monkeys following chronic exposure to Aroclor 1254. Reproductive failure in minks associated with fetal death was attributed to degenerative changes in the placental vasculature. Impaired ability to conceive and decreased fetal survival are well-documented in female monkeys following repeated oral exposure to Aroclors 1254 and 1248. Reduced conception rates, as well as increased incidences of abortions, resorptions, or stillbirths, were observed in monkeys fed Aroclor 1254 at dose levels as low as 0.02 mg/kg/day for 37 months before breeding and subsequently throughout mating and gestation.

The ability of PCBs to cause reproductive effects in males is less clear-cut than in females. Sperm counts, fertility history, and testicular examinations were normal in workers who were exposed to Aroclor PCBs for several years. However, analysis of semen showed that increasing concentrations of some individual congeners, but not total PCBs, were associated with decreasing sperm motility in infertile men.

A limited amount of information is available on reproductive effects of PCBs in male laboratory animals. Four monkeys chronically exposed to 0.1 mg/kg/day Aroclor 1248 developed effects that included clinical signs of toxicity, decreased libido, and marked hypoactivity of the seminiferous tubules, including an absence of mature spermatozoa, after the first year of exposure. Fertility was markedly reduced in male offspring of rats that were lactationally exposed to relatively high doses of Aroclor 1254. The reduction in male fertility appears to be due to impaired ability of sperm to fertilize eggs because sperm production, morphology, and motility were not affected and plasma follicle-stimulating hormone (FSH)

and testosterone concentrations were not reduced. Oral and subcutaneous studies with single congeners have also shown that gestational and neonatal exposures can adversely affect morphology and production of sperm and fertility in male rats and mice.

Developmental Effects. This section summarizes effects of PCBs on anthropometric measures at birth as well as physical growth during infancy. Effects of perinatal exposure to PCBs on other end points in the offspring, such as the thyroid gland and thyroid hormone status, end points known to be very important for structural and functional aspects of normal development of the brain and sexual organs, are discussed in the Endocrine Effects and Reproductive Effects sections, respectively. Neurodevelopmental effects of PCBs are summarized in the Neurological Effects section.

Studies of the children of environmentally-exposed women have produced mixed results. While some studies have shown significant, negative associations between anthropometric measures at birth (and at early ages) and exposure to PCBs, other studies have reported either significant positive associations or no associations at all. The wide range of results may reflect the different degree of controlling for confounders and/or the different exposure measures. For example, of the studies of women who consumed contaminated fish from the Great Lakes, the study of Lake Michigan fisheaters found that reduced birth weight, head circumference, and gestational age in newborns, as well as body weight at 4 years, were associated with prenatal exposure to PCBs (measured in umbilical cord blood). In the Oswego cohort (Lake Ontario fish consumption), there was no significant association between birth weight, head circumference, or gestational age and prenatal exposure to PCBs, as assessed by the same fish consumption measures used in the Michigan study, which had higher levels of PCB exposure. In two additional studies of Lake Michigan women, fish consumption had a positive effect on birth weight. It has been postulated that this may be related to the beneficial effects of certain fatty acids in fish. A study of Swedish wives of Baltic Sea fishermen found an increased risk of low birth weight with increasing maternal blood concentrations of a PCB congener used as surrogate of PCB exposure during the year of childbirth. In a Dutch general population cohort, a reduced birth weight, but not head circumference or body length at 10 days of age, was associated with prenatal exposure to PCBs (measured in umbilical cord blood). Reduced growth between birth and 3 months was associated with prenatal exposure in formula-fed children, but no such association was seen in breast-fed children, suggesting that any detrimental effect observed in newborns due to prenatal exposure to PCBs may have been counteracted by the benefits of breast feeding. In the Dutch children, no significant association was seen between growth between the ages of 3–7 months, 7–18 months, or 18–42 months and any measure of exposure to

PCBs. In addition, a study of the general population in Finland found no significant association between birth weight and the concentration of PCBs in breast milk.

Studies of rodents exposed to relatively high doses of PCBs have commonly found decreased birth weight, and reduced weight gain after birth following exposure *in utero* and through suckling. The latter finding suggests that significant transfer of PCBs may occur through breast feeding. Long-term studies with much lower doses of Aroclors 1016 and 1248 in monkeys also reported decreased birth weight. Studies with low doses of Aroclor 1254 (0.0005–0.08 mg/kg/day) in monkeys found no significant effects on anthropometric measures at birth or on growth thereafter, although dermal and ocular signs of PCB intoxication were noted.

Cancer. Carcinogenicity of PCBs in humans has been investigated in retrospective occupational studies that evaluated cancer mortality in workers exposed during capacitor manufacturing and repairing, and in case-control studies of the general population that examined associations between cancer and serum or adipose tissue levels of PCBs resulting from environmental exposures. Based on indications of PCB-related cancer at several sites, particularly the liver, biliary tract, intestines, and skin (melanoma), the human studies provide suggestive evidence that PCBs are carcinogenic. There is unequivocal evidence that PCBs are hepatocarcinogenic in animals.

The suggestive evidence for the carcinogencity of PCBs in humans is supported by extensive conclusive evidence in animals. PCBs have been classified as probable human carcinogens by both IARC and EPA, based mainly on the sufficient evidence of carcinogenicity in animals. The human evidence of carcinogenicity is regarded as limited by IARC and inadequate but suggestive by EPA, although neither assessment is based on all currently available studies. NTP similarly concluded that PCBs are reasonably anticipated to be carcinogenic in humans based on sufficient evidence of carcinogenicity in animals. (See Chapter 3 [Section 3.2.8] for a detailed discussion of the bases for these determinations.)

2.3 Minimal Risk Levels

As indicated above in the beginning of Section 2.1, people are environmentally exposed to PCB mixtures of different congeneric composition than commercial PCB mixtures. Although the toxicity or potency of environmental PCB mixtures consequently may be greater or less than that of commercial mixtures, there are insufficient mixture toxicity data on which to directly base minimal risk levels (MRLs) for

environmental PCBs. One approach that has been widely considered for estimating the risk from environmental exposure to PCBs is the toxic equivalency factor (TEF) method. As discussed in Chapter 3 (Section 3.5.2), the TEF approach can be used to estimate the potency of PCB mixtures by comparing the relative toxicity of individual PCB congeners to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), which is the most toxic and extensively studied of these structurally-related halogenated aromatic hydrocarbons. Although TEFs are used to some extent to guide public health decisions because of the limited toxicological data for complex environmental mixtures and many of their components, the approach has received limited validation and has a number of limitations related to assumptions that the components jointly act in an additive manner through a common Ah-receptor mechanism of toxicity. In particular, the TEF approach does not account for evidence that non-Ah-receptor-binding congeners are major components in PCB-containing environmental mixtures that may contribute to induction of health effects (Hansen 1998; Safe 1998a, 1998b). Although there is certainly a large body of data to support the TEF approach to assessing PCB toxicity, this is by no means without question, primarily because of evidence of non-additive interactions between specific PCB congeners and between some PCB congeners and 2,3,7,8-TCDD (see Chapter 3, Section 3.9), as well as increasing evidence that PCB-induced effects may involve Ah-receptor-dependent mechanisms, Ah-receptor-independent mechanisms, or both. Because of the likelihoods that (1) multiple mechanisms may be involved in PCB-induced health effects, (2) different PCB congeners may produce effects by different mechanisms, and (3) humans are exposed to complex mixtures of interacting PCBs with differing biological activities, commercial PCB mixtures (e.g., Aroclor 1254) and experimental PCB mixtures (e.g., formulations representing the congeners found in human breast milk) are used to develop health guidance values, such as MRLs, for environmental mixtures in assessing health risks from exposure.

Inhalation MRLs

No inhalation MRLs were derived for PCB mixtures due to lack of adequate human and animal data.

Oral MRLs

- An MRL of 0.03 µg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to PCBs.

The intermediate oral MRL is based on a LOAEL of 0.0075 mg/kg/day for neurobehavioral alterations in infant monkeys that were exposed to a PCB congener mixture representing 80% of the congeners

typically found in human breast milk (Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a). The MRL was estimated by dividing this LOAEL by an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from monkeys to humans, and 10 for human variability). Groups of five and eight male monkeys were orally administered doses of 0 or 0.0075 mg/kg/day, respectively, from birth to 20 weeks of age. The dose level represents the approximate daily intake of a nursing human infant whose mother's milk contains 50 ppb PCBs. Beginning at 3 years of age, the monkeys were tested for behavioral effects using a series of nonspatial discrimination reversal problems followed by a spatial delayed alternation task. Additional testing was done at 4.5 and 5 years of age. Treated monkeys showed decreases and variable increases in response latencies across three tasks of nonspatial discrimination reversal, as well as retarded acquisition of a delayed alternation task and increased errors at short delay task responses (Rice 1997). These findings were interpreted as a learning/performance decrement rather than an effect on memory *per se.* Treated monkeys also displayed alterations in fixed-interval and fixed-ratio performance tasks that were interpreted as impaired learning, perseverative behavior, and/or inability to inhibit inappropriate responding as a result of postnatal PCB exposure (Rice 1997). Testing of the monkeys at 4.5–5 years of age showed that treated animals performed in a less efficient manner than controls under a differential reinforcement of low rate (DRL) schedule of reinforcement (Rice 1998). There were no differences between groups on the accuracy of performance on a series of spatial discrimination reversal tasks, although some treated monkeys made more errors than others on certain parts of the experiment. Further tests conducted at about 5 years of age did not find treatment-related effects on a series of concurrent RI-RI (random interval) schedules of reinforcement (Rice and Hayward 1999a). This schedule was designed to study behavior in transition (learning) as well as at steady state. However, there was a difference between treated and control monkeys on performance on a progressive ratio (PR) schedule, which may be indicative of retarded acquisition of the steady-state PR performance.

The 0.0075 mg/kg/day LOAEL is a particularly relevant basis for MRL derivation due to the composition of the PCBs (a congener mixture analogous to that in human breast milk), dose level (approximate daily intake of a nursing human infant whose mother's milk contains 50 ppb PCBs), and resulting PCB adipose tissue and blood levels (near background concentrations found in the general human population). Support for the 0.0075 mg/kg/day LOAEL is provided by occurrence of minimal immunological alterations in the same monkeys (Arnold et al. 1999), as well as clinical signs of toxicity (ocular and dermal changes) and decreased antibody responses in offspring of other monkeys that were exposed to a similarly low dose level of a commercial PCB mixture (0.005 mg/kg/day Aroclor 1254) for approximately 46 weeks during gestation and nursing (Arnold et al. 1995). The next highest intermediate-duration dose level (i.e., above

0.0075 mg/kg/day) tested in any species is 0.02 mg/kg/day, which is a serious LOAEL for fetal toxicity in monkeys (Arnold et al. 1995). Additional information on the critical and supporting studies used to derive the intermediate-duration MRL is provided in Appendix A.

- An MRL of 0.02 µg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to PCBs.

The chronic oral MRL was is based on a LOAEL of 0.005 mg/kg/day for immunological effects in adult monkeys that were evaluated after 23 and 55 months of exposure to Aroclor 1254 (Tryphonas et al. 1989, 1991a). The MRL was estimated by dividing this LOAEL by an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from monkeys to humans, and 10 for human variability). This study included groups of 16 female Rhesus monkeys that self-ingested capsules containing 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day doses of the PCBs. Comprehensive immunological evaluations showed that IgM (all doses except 0.02 mg/kg/day) and IgG (all doses) antibody levels to SRBC were significantly reduced compared to controls after 23 months (Tryphonas et al. 1989). Secondary challenge with SRBC after 55 months showed decreasing dose-related trends in the IgM and IgG anamnestic responses, although only IgM was significantly lower than controls at all dose levels (Tryphonas et al. 1991a). Other immunologic changes included changes in numbers of lymphocyte T-cell subsets (significantly decreased ratio of T-inducer/helper cells to T-cytotoxic/suppressor cells) at 0.08 mg/kg/day (only dose level tested) after 23 months, and dose-related trends for several endpoints (e.g., decreasing lymphocyte proliferation in response to mitogenic stimulation, decreasing phagocytic activity of peripheral blood monocytes) after 55 months. Support for the critical LOAEL is provided by mild dermal and ocular manifestations of PCB toxicity, including eyelid swelling and various finger and toe nail changes, in the same monkeys at 0.005 mg/kg/day and higher doses (Arnold et al. 1993a). Additionally, a number of other studies using higher dose levels of PCB have demonstrated immunological and dermal/ocular effects in monkeys following intermediate or chronic exposures. The LOAEL resulted in PCB tissue and blood levels that are near background concentrations found in the general human population (Kimbrough 1995). The next highest dose level, 0.02 mg/kg/day, is a serious LOAEL for reproductive toxicity (reduced conception) and fetal toxicity when monkeys from the same study were bred after 37 months of exposure (Arnold et al. 1995). Additional information on the critical and supporting studies used to derive the chronic-duration MRL is provided in Appendix A.

As affirmed by a panel of international experts (see Appendix E), human data provide support for this chronic oral MRL. Using data from the North Carolina cohort (Gladen et al. 1988; Rogan et al. 1986a,

1986b), Tilson et al. (1990) estimated a NOAEL of 0.093 µg/kg/day for developmental effects in humans. This NOAEL was calculated by first estimating the concentration of PCBs in breast milk that resulted in no significant neurodevelopmental alterations in neonates as assessed with the Brazelton Scale; this concentration was 3.4 ppm (Gladen et al. 1988; Rogan et al. 1986a). The assumption was then made that the concentration of PCBs in women's breast milk is equal to the concentration of PCBs in the fat throughout the rest of the body. It can then be calculated that for 25-year-old women who weigh 60 kg and have 25% body fat, 3.4 ppm would result from a lifetime daily PCB dose of 0.093 µg/kg/day (Tilson et al. 1990). Since the analytical method might have caused the researchers to overestimate the concentration of PCBs in breast milk by a factor of 2 (Tilson et al. 1990), this NOAEL may be appropriately estimated to be 0.05 µg/kg/day, rather than 0.093 µg/kg/day. If an uncertainty factor of 3 were applied to the NOAEL of 0.05 µg/kg/day to account for intraspecies variation, this would result in a rounded dose of 0.02 µg/kg/day, which is exactly equivalent to the chronic-duration oral MRL derived above from data in monkeys. It should be pointed out that because losses of PCBs through excretion, lactation, and metabolism were not factored in the dose calculations, the actual dose that results in 3.4 ppm in breast milk fat would be higher than the reported NOAEL. Also, if dose calculations were based on women older than 25 years, the estimated daily dose would be lower than the reported NOAEL. Finally, it is possible that exposure to other bioaccumulative toxic substances could, in part, have contributed to other effects seen in this study. Nonetheless, it is both meaningful and relevant that the chronic oral MRL for PCBs is lower than the estimated NOAEL for the most sensitive human population in the Tilson et al. (1991) cohort.