

Appendix C
PCB Toxicological Profile

C.1 Overview of PCB Toxicity and Carcinogenicity

Polychlorinated Biphenyls (PCBs) represent a group of synthetic organic chemicals that consists of 209 individual chlorinated biphenyls (called congeners) (reviewed in ATSDR, 1997). PCBs are either colorless or light yellow in color and can be oily liquids or solids depending on the composition of the mixture. Because of their insulating capacity, stability, and low burning capacity, PCBs were used in capacitors, transformers, and other electrical equipment prior to 1977. Commercially available PCB mixtures are known in the U.S. by their industrial trade name, Aroclor. The name, Aroclor 1254, for example, means that the molecule contains 12 carbon atoms (the first 2 digits) and approximately 54% chlorine by weight (second 2 digits). Use of PCBs was generally banned in 1977 after they were found to build up in the environment and to have harmful effects.

Although PCB use was generally stopped over 20 years ago, they still exist in old electrical equipment and environmental media to which humans can be exposed (reviewed in ATSDR, 1997). Because of the ubiquitous presence of PCBs in the environment, general routes of human exposures can include contaminated outdoor or indoor air, drinking water, direct dermal contact, and food. Fish can have levels of PCBs much higher than the water in which they swim from exposure to contaminated sediments and/or eating prey that contain PCBs. Beef and dairy cattle can contain PCBs from grazing on PCB-containing plants. People can be exposed to PCBs in the workplace primarily through inhalation and dermal contact due to repair, maintenance and disposal of PCB-containing electrical equipment. Specific routes of exposures applicable for the Hudson River are discussed in *Section 2.1.3 Potential Exposure Routes*.

C.2 Summary of PCB Carcinogenicity

C.2.1 Carcinogenic Potential in Animals

The USEPA has determined that sufficient evidence exists to show that PCB mixtures are carcinogenic in animals. The available PCB animal carcinogenicity studies are summarized in USEPA's 1996 reassessment of the toxicity data on the potential carcinogenic potency of PCBs (USEPA, 1996b), as well as in the USEPA's Integrated Risk Information System (IRIS), an electronic database which

provides the Agency's consensus review of chemical-specific toxicity data (USEPA, 1999c). Of the studies presented which support observations of animal carcinogenicity, the most thorough is a study by Mayes *et al.*, (1999). In this study, female and male Sprague Dawley rats were used to examine the carcinogenic potential of a number of different Aroclors (1260, 1254, 1242, and 1016) at a number of different dose levels (25, 50, or 100 ppm) with an exposure duration of 104 weeks. These mixtures contain overlapping groups of congeners that span the range of congeners most often found in environmental mixtures. In female rats, a statistically significant increase in liver adenomas and carcinomas were observed with exposure to all Aroclors tested. In male rats, a significant increase in liver cancers was observed for Aroclor 1260. Additionally, thyroid follicular cell adenomas or carcinomas were increased for all Aroclors in male rats only. Interestingly, these investigators observed a decrease in mammary tumors in female rats exposed to Aroclor 1260, 1254, and 1242.

A number of other animal studies also demonstrated an increase in cancer incidence with exposure to PCB mixtures (USEPA, 1999c; USEPA, 1996b). Kimbrough (1975) observed liver carcinomas in female Sherman rats fed diets of 100 ppm Aroclor 1260 for 21 months. The National Cancer Institute (NCI) observed hepatocellular adenomas and carcinomas in female and male Fischer 344 rats fed 100 ppm Aroclor 1254 for 24 months (NCI, 1978). Similarly, Norback and Weltman (1985) observed a statistically significant increase in hepatocellular carcinomas in female and male Sprague-Dawley rats exposed to 100 ppm Aroclor 1260 in the diet for 16 months, 50 ppm for 8 months, followed by 5 months on a control diet when compared to the control rats. Gastric lesions in rats from this NCI study were further examined and found to have a statistically increased level of adenocarcinomas (Morgan *et al.*, 1981; Ward, 1985).

C.2.2 Carcinogenic Potential in Humans

The USEPA has classified PCBs as a probable human carcinogen (B2), based on a number of studies in animals showing liver tumors with a number of different PCB mixtures which are believed to span the range of congeners found in environmental mixtures (see Section C.2.1) (USEPA, 1996). Human carcinogenicity data for PCB mixtures is currently "inadequate, but suggestive" (USEPA, 1999c). USEPA (1996) describes three cohort studies that analyzed deaths from cancer in PCB capacitor manufacturing plant workers. In the first study, 2100 capacitor manufacturing plant workers in Italy were

followed and deaths attributed to cancer were determined (Bertazzi *et al.*, 1987). The study included 1,556 females and 544 males that had worked for at least one week at the capacitor plant. Both Aroclor 1242 and 1254 had been used at the facility. For females, an excess risk of death from hematologic cancer was reported. This excess was statistically significant compared to local rates, but not to national rates. In males, an increase in death from gastrointestinal tract cancer was observed. This increase was statistically significant when compared to both local and national rates.

In the second study, Sinks *et al.* (1992) conducted a retrospective cohort study of 3,588 electrical capacitor workers with known exposures to PCBs in air. There were more deaths observed than expected for malignant melanoma and cancer of the brain and nervous system. The risk of malignant melanoma was not related to cumulative PCB exposure (*i.e.*, no dose-response, but the exposure information was poor). The authors concluded that the possibility that the results are due to chance, bias, or confounding cannot be excluded.

In the third study, Brown (1987) determined the cancer mortality rate for capacitor manufacturing workers in New York and Massachusetts. In this study, 2,588 workers (1,318 females and 1,270 males) that had worked for at least 3 months in areas thought to have potential high exposure to PCB mixtures were followed. Aroclors 1254, 1242 and 1016 were used at different times in both plants. The investigators observed a statistically significant increase in death from cancer of the liver, gall bladder, and biliary tract compared to national rates.

Recently, Dr. Kimbrough and others (1999) published a paper describing a study of workers from two General Electric Company capacitor manufacturing plants in New York State. In this study, mortality (deaths) from all cancers was determined for the study group, which comprises 7,075 female and male workers who worked at the General Electric Company facilities for at least 90 days between 1946 and 1977.

USEPA's review of the Kimbrough *et al.* (1999) paper identified a number of limitations that suggest the study may not change USEPA's conclusions regarding the health effects of PCBs, including the following:

- More than 75% of the workers in the study never worked with PCBs.
- The actual level of PCB exposure in the remaining workers could not be confirmed.
- Less than 25% of the workers who were exposed to PCBs at the General Electric Company facilities were employed in these jobs for more than a year. Such short-term occupational exposure is generally not comparable to the long-term exposure that may occur in the environment.
- At the end of the study period in December 1993, most of the workers were still quite young (average age, 57). Because cancer deaths usually occur in older individuals, the workers in the General Electric Company study may have been too young to die from cancer.
- The study did not investigate vulnerable populations such as children, the elderly or people with existing health problems.

Due to the limitations identified by USEPA in its review of the Kimbrough *et al.* (1999) study, USEPA expects that the study will not lead to any change in its cancer slope factors for PCBs, which were last reassessed in 1996. Nevertheless, USEPA will complete its ongoing external peer consultation regarding the Kimbrough *et al.* (1999) study prior to making a final determination on this matter.

C.2.3 PCB Cancer Slope Factors

The Cancer Slope Factor, or CSF, is an upper bound estimate of carcinogenic potency used to calculate risk from exposure to carcinogens, by relating estimates of lifetime average chemical intake to the incremental risk of an individual developing cancer over their lifetime. The USEPA's Integrated Risk Information System (IRIS), which provides the Agency's consensus review of toxicity data (USEPA, 1999a-c), provides both upper-bound and central-estimate CSFs for three different tiers of PCB mixtures. These CSFs are based on the USEPA's 1996 reassessment of the toxicity data on the potential carcinogenic potency of PCBs (USEPA, 1996b). They were derived following the proposed revisions to the USEPA Carcinogen Risk Assessment Guidelines (USEPA, 1996a), including changes in the method of extrapolating from animals to humans, and changes in the categories for classifying the carcinogenic potential of chemicals.

In order to develop CSFs for use in human health risk assessments for exposure to environmental PCBs, USEPA (1999c) reviewed all of the relevant animal and human data, and focused on two studies: Brunner *et al.* (1996) and Norback and Weltman (1985). Human equivalent doses were determined from dose-response data from these two studies. A tiered approach for cancer potencies of PCB mixtures was then developed based on both exposure route and congener type.

The first tier, "High Risk and Persistence," applicable to food chain exposures, sediment or soil ingestion, dust or aerosol inhalation, dermal exposure, early-life exposure, and mixtures with dioxin-like, tumor promoting, or persistent congeners, has an upper-bound and central-estimate CSF of 2.0 and 1.0 (mg/kg-day)⁻¹, respectively. The second tier, "Low Risk and Persistence," applicable to ingestion of water-soluble congeners, inhalation of evaporated congeners, and dermal exposure (if no absorption factor has been applied), has an upper-bound and central-estimate CSF of 0.4 and 0.3 (mg/kg-day)⁻¹, respectively. The third tier, "Lowest Risk and Persistence," applicable only to mixtures where congeners with more than four chlorines comprise less than one-half percent of the total PCBs, has an upper-bound and central-estimate CSF of 0.07 and 0.04 (mg/kg-day)⁻¹, respectively.

Cancer risk is estimated by multiplying the appropriate CSF by a lifetime daily dose. Using this method, EPA has calculated an upper-bound unit risk for ingestion of PCB congeners in water to be 1 x 10⁻⁵ per µg/L. Drinking water concentrations associated with a risk of 1 in 10,000, 100,000, and 1,000,000 are 10, 1, and 0.1 µg/L, respectively.

C.3 Summary of PCB Non-cancer Toxicity

C.3.1 Potential for Non-cancer Effects in Humans and Animals

A number of non-cancer health effects have been associated with PCB exposure (reviewed in ATSDR, 1997; ATSDR, 1996; USEPA, 1996). The prominent observed effect in workers exposed to large quantities of PCBs was a skin condition known as chloracne. Other effects such as depression, fatigue, nose irritation, and gastrointestinal discomfort were suggested to be associated with workplace PCB exposure. Studies in rats that have been exposed to high doses of PCBs have shown mild liver damage, stomach effects, thyroid gland injuries, acne, and with high enough doses, death. Studies in

rabbits exposed to high PCB doses have also shown kidney effects. In low-dose, long-term exposure studies, reproductive, eye, and nail effects have also been observed.

Coplanar PCB congeners are thought to cause adverse health effects by binding to the aryl hydrocarbon receptor, similar to dioxin. Non-coplanar PCB congeners (ortho-substituted congeners) are believed to cause adverse health effects, such as neurotoxicity and behavioral changes, although the mechanism of action is less certain (reviewed in Fischer *et al.*, 1998).

There are several on-going studies assessing the non-cancer health effects in children consuming PCBs in fish. Two of the more recent investigations by Patandin (1999) and Lanting (1999) involved a prospective follow-up study of Dutch breast-fed and formula-fed infants from birth until 42 months of age, to evaluate the effect of perinatal background exposure to PCBs and dioxins on growth and development in young children. Significant associations between perinatal exposure to PCBs and dioxins and adverse effects on growth, immunologic parameters, and neurodevelopmental and behavioral effects were reported. Some effects were apparent during infancy (adverse effects on growth and neurological effects), while others were not apparent until preschool age (cognitive and behavioral effects).

PCBs have also been investigated as potential endocrine disruptors. An environmental endocrine disruptor is defined as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, development, and/or behavior" (USEPA, 1997, pg. 1). For example, some studies have suggested that PCBs increase the risk of breast cancer, while other studies have failed to show an association between PCB exposure and breast cancer (reviewed in USEPA, 1997). Overall, the USEPA Risk Assessment Forum concluded that it is not possible to attribute a cause and effect association between PCB exposure and breast cancer given the sparse data currently available. Similarly, an association between endometriosis and high levels of PCBs in blood has been reported, but the evidence for a causal relationship is considered very weak (reviewed in USEPA, 1997). Due to the similar structural properties of PCBs and normal thyroid hormones, PCBs may also cause thyroid effects such as hypothyroidism *via* competition for receptor binding sites (reviewed in USEPA, 1997).

There is currently considerable scientific debate about whether environmental chemicals acting *via* endocrine disruptor mechanisms are responsible for adverse health effects in humans (reviewed in USEPA, 1997). Because the human body has negative feedback mechanisms to control the fluctuations of hormone levels, exposures to chemicals at the levels found in the environment may be insufficient to disrupt endocrine homeostasis. Current screening assays that measure hormone receptor binding thus may or may not be associated with a corresponding adverse health effect.

Overall, the USEPA is aware and concerned about the potential effects of environmental endocrine disruptors on human health, and is currently supporting significant research in this area along with other federal agencies. However, "there is little knowledge of or agreement on the extent of the problem," and "further research and testing are needed" (USEPA, 1997b, pg. vii). The USEPA Science Policy Council's Interim Position is that "based on the current state of the science, the Agency does not consider endocrine disruption to be an adverse endpoint *per se*, but rather to be a mode or mechanism of action potentially leading to other outcomes, for example, carcinogenic, reproductive, or developmental effects, routinely considered in reaching regulatory decisions" (USEPA, 1997b, pg. viii).

C.3.2 PCB Reference Doses

The chronic RfD represents an estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specifically developed to be protective for long-term exposure to a compound, with chronic duration ranging from seven years to a lifetime as a Superfund guideline (USEPA, 1989b). The USEPA's Integrated Risk Information System (IRIS), which provides the Agency's consensus review of toxicity data (USEPA, 1999a-b), provides RfDs for two Aroclor mixtures, Aroclor 1016 and Aroclor 1254; there is no RfD available for Total PCBs. Although there is an IRIS file for Aroclor 1248, the USEPA determined the available health effects data to be inadequate for derivation of an oral RfD (USEPA, 1999d). There are no Reference Concentrations (RfCs) currently available for either total PCBs or any of the Aroclor mixtures (USEPA, 1999a-c).

C.3.2.1 Aroclor 1016 RfD

The USEPA derived an oral RfD of 7×10^{-5} mg/kg-day for Aroclor 1016 based on a series of reports of a single study conducted in monkeys (Barsotti and van Miller, 1984; Levin *et al.*, 1988; Schantz *et al.*, 1989, 1991; as summarized in USEPA, 1999a). In this study, female rhesus monkeys were administered Aroclor 1016 in the diet for 22 months at doses of 0, 7, and 28 $\mu\text{g}/\text{kg}\text{-day}$. Animals were exposed 7 months prior to breeding and continued until offspring were 4 months of age. Although there was no evidence of overt toxicity observed, hairline hyperpigmentation, decreased birth weight, and possible neurologic impairment were observed in the offspring. The observed hyperpigmentation occurred at the lowest dose tested (7 $\mu\text{g}/\text{kg}\text{-day}$), but was not considered by the USEPA to be a critical adverse effect. Both reduced birth weight and possible neurologic impairment were observed at 28 $\mu\text{g}/\text{kg}\text{-day}$. EPA chose a NOAEL of 7 $\mu\text{g}/\text{kg}\text{-day}$ and a LOAEL of 28 $\mu\text{g}/\text{kg}\text{-day}$ based on reduced birth weight.

The USEPA used an uncertainty factor (UF) of 100 based on the following: intraspecies variability and protection of sensitive individuals (UF=3), interspecies variability (UF=3), database limitations (UF=3), and the use of a subchronic study (UF=3). Application of the total UF of 100 to the NOAEL of 7 $\mu\text{g}/\text{kg}\text{-day}$ results in an oral RfD for Aroclor 1016 of 7×10^{-5} mg/kg-day.

C.3.2.2 Aroclor 1254 RfD

The USEPA has derived an RfD for chronic oral exposure to Aroclor 1254 based on effects observed in rhesus monkeys fed Aroclor 1254 (USEPA, 1999b). Female rhesus monkeys were fed daily dosages of 0, 5, 20, 40 or 80 $\mu\text{g}/\text{kg}\text{-day}$ of Aroclor 1254 in gelatin capsules for more than five years. A number of investigators evaluated health effects over the five-year period. General health and clinical pathology evaluations were conducted during the first 37 months and reported by Arnold *et al.* (1994a; 1994b, as summarized in USEPA, 1999b). Immunologic evaluations were conducted after 23 and 66 months by Tryphonas *et al.* (1989; 1991a; 1991b, as summarized in USEPA, 1999b). Truelove *et al.* (1990, as summarized in USEPA, 1999b) and Arnold *et al.* (1993a, as summarized in USEPA, 1999b) evaluated the monkeys for reproductive endocrinology changes after 24 or 29 months. Hydrocortisone levels were evaluated after 22 months and reported by Loo *et al.* (1989, as summarized in USEPA, 1999b) and Arnold (1993b, as summarized in USEPA, 1999b). Although a number of other toxicological

parameters were evaluated, the five studies by Arnold *et al.* (1993a, 1993b, as summarized in USEPA, 1999b) and Tryphonas *et al.* (1989, 1991a, 1991b, as summarized in USEPA, 1999b) were the studies used by the USEPA to derive the oral RfD.

Arnold *et al.* (1994a) identified eye toxicity and finger and toe nail changes as part of their general health and clinical pathology evaluations. These investigators observed a significant increase in the frequency of inflamed Meibomian glands and incidence of eye exudate in treated monkeys as compared to controls. Additionally, a statistically significant increase in the incidence of certain nail changes (nail folding, elevated nails, nail separation, prominent beds) was observed in treated animals. Both the eye and nail effects were observed at the lowest dose of 5 µg/kg-day.

Tryphonas *et al.* (1989; 1991a,b) examined changes in IgG, IgM, helper T-cells, and suppressor T-cells following a challenge with sheep red blood cells in Rhesus monkeys exposed to Aroclor 1254 for 23 months. These researchers noted significant reductions in IgG and IgM at the lowest dose tested (5 µg/kg-day) and T-cell changes at the 80 µg/kg-day dose level.

EPA derived the oral RfD based on a lowest-observed-adverse-effect-level (LOAEL) of 5 µg/kg-day and the observance of the following critical effects: ocular exudate, inflamed and prominent Meibomian glands, distorted growth of finger and toe nails and decreased antibody (IgG and IgM) response to sheep erythrocytes. An UF of 300 was applied by EPA to derive an oral RfD of 2×10^{-5} mg/kg-day to account for: intraspecies variability (UF=10), interspecies variability (UF=3), the use of a LOAEL value (UF=3), and the use of a subchronic study (UF=3).

C.4 Summary of Other PCB Guidelines and Regulations

The following is a discussion of selected PCB-related guidelines and regulations.

C.4.1 FDA Tolerance for PCBs in Fish

The U.S. Food and Drug Administration (FDA) promulgated a regulation lowering the tolerance level for PCBs in the edible portion of fish and shellfish destined for interstate commerce from 5 mg/kg to

2 mg/kg in 1979 (FDA, 1979) which became effective in 1984. This tolerance level of 2 mg/kg remains in effect today (FDA, 1996). The tolerance level was based on weighing the results of a risk assessment against the magnitude of potential food loss resulting from a lowered tolerance level. It is important to point out that the methodology of the FDA risk assessment precludes application of its results to the Upper Hudson River Human Health Risk Assessment risk assessment for fish ingestion. The FDA limit was developed under different legislation and regulatory responsibilities in 1979 using FDA guidance. Additionally, the FDA specifically states that this tolerance is intended to apply to fish entering interstate commerce, and that this level may not be protective for locally caught fish from contaminated areas.

To arrive at a tolerance of 2 mg/kg, the FDA considered national per capita fish consumption, looking at the general distribution of PCB levels in fish for sale across the U.S. The FDA risk assessment was performed by assuming that the tolerance level of 2 mg/kg would be the maximum concentration in fish encountered by a heavy fish consumer, and that PCB concentrations in fish consumed would be distributed below 2 ppm in a manner reflecting a mix of fish from diverse sources (Cordle, 1982). The tolerance is not based on the assumption that all fish consumed contain 2 mg/kg PCBs. Because the distribution of PCB concentrations in fish caught in the Upper Hudson River by local anglers is likely to be different from the distributions of PCB concentrations in fish for sale across the U.S., the risk associated with regularly eating Upper Hudson River fish will differ from the risks associated with the FDA assessment for a 2 ppm tolerance, even if Hudson River fish do not exceed 2 mg/kg.

C.4.2 USEPA Maximum Contaminant Level in Drinking Water

The USEPA has promulgated a maximum contaminant level (MCL) for PCBs in drinking water of 0.5 µg/L (USEPA, 1998a), which corresponds to a lifetime cancer risk of 10^{-4} assuming lifetime ingestion of 2 liters of water per day, and the old CSF of $7.7 \text{ (mg/kg-day)}^{-1}$. A lifetime cancer risk of 10^{-5} is calculated assuming lifetime ingestion of 2 liters of water per day, and the new CSF of $0.4 \text{ (mg/kg-day)}^{-1}$ for water ingestion.

C.4.3 USEPA Ambient Water Quality Criteria

USEPA has issued ambient water quality criteria for PCBs of 4.4×10^{-5} µg/L and 4.5×10^{-5} µg/L, corresponding to a lifetime cancer risk of 10^{-6} , based on the ingestion of both water and organisms (fish and shellfish) and ingestion of organisms only (USEPA, 1998b). These ambient water quality criteria are applicable to seven Aroclor mixtures (*i.e.*, Aroclor 1016, 1221, 1232, 1242, 1248, 1254, and 1260). The risks are primarily attributable to ingestion of fish and remain similar whether ingestion of drinking water is considered or not. USEPA is proposing a new ambient water quality criteria of 1.7×10^{-4} µg/L for ingestion of water and organisms or ingestion of water for total PCBs (USEPA, 1998c).

C.4.4 New York State Ambient Water Quality Criteria

The New York State Department of Environmental Conservation has issued ambient water criteria for PCBs in surface waters. The aquatic-based criteria is 0.001 µg/L, and the health-based criteria (assuming ingestion of water) is 0.01 µg/L (NYSDEC, 1993). These values are higher than the USEPA-derived ambient water quality criteria.

C.5 References

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