PUBLIC HEALTH IMPLICATIONS OF EXPOSURE TO POLYCHLORINATED BIPHENYLS (PCBs)

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ABSTRACT

This paper summarizes the health implications associated with exposure to polychlorinated biphenyls (PCBs), primarily through fish consumption. Recent studies complement and add to the scientific data gathered over the last two decades that document health consequences associated with exposures to PCBs. Although much of the research has been undertaken in the Great Lakes basin, the health implications are international. The findings of elevated PCB levels in human populations, together with findings of developmental deficits and neurologic problems in children whose mothers ate PCB-contaminated fish, have compelling implications. The weight of evidence clearly indicates that populations continue to eat fish containing PCBs and that significant health consequences are associated with consumption of large amounts of some fish. Although PCBs are declining in the environment, health concerns are still warranted.

Recent findings indicate that susceptible populations (e.g., certain ethnic groups, sport anglers, the elderly, pregnant women, children, fetuses, and nursing infants) continue to be exposed to PCBs via fish and wildlife consumption. Human health studies discussed in this summary indicate that: 1) reproductive function may be disrupted by exposure to PCBs; 2) neurobehavioral and developmental deficits occur in newborns and continue through school-aged children who had in utero exposure to PCBs; 3) other systemic effects (e.g., self-reported liver disease and diabetes, and effects on the thyroid and immune systems) are associated with elevated serum levels of PCBs; and 4) increased cancer risks, e.g., non-Hodgkin's lymphoma, are associated with PCB exposures.

I. INTRODUCTION

Polychlorinated biphenyls (PCBs) are synthetic organic chemicals comprising 209 individual chlorinated biphenyl compounds (known as congeners). Exposure to each of these compounds is associated with different levels of risk for harmful effects. There are no known natural sources of PCBs. Although PCBs are no longer manufactured in the United States, people can still be exposed to them. The two main sources of exposure to PCBs are the environment and the workplace. Due to resistance to degradation, PCBs persist in the environment for decades.

Recent studies conducted in the Great Lakes basin indicate that a) fish consumption remains the major route of exposure to PCBs and b) health consequences are associated with these exposures. The following summary identifies those groups at risk because of exposure to PCBs and summarizes recently published information on exposure, sociodemographics, and health findings for these groups.

II. FINDINGS ASSOCIATED WITH PCB EXPOSURE IN HUMAN POPULATIONS

Some of the initial findings of PCBs in human populations were reported by Harold Humphrey of the Michigan Department of Public Health and his colleagues. Their work in the 1970s and 1980s demonstrated a correlation between levels of PCBs in breast milk and maternal consumption of contaminated fish (Humphrey 1983).

The Michigan Maternal Infant Cohort Study (Fein et al. 1984; Jacobson et al. 1985, 1990a, b) was designed to assess the effects of eating contaminated fish on pregnant women and their newborn infants. There were 242 infants born to women who consumed moderate to high amounts of Lake Michigan fish, and 71 infants whose mothers did not eat Lake Michigan fish. The investigators reported both developmental disorders and cognitive deficits in the children of mothers who had eaten contaminated fish during the six years preceding the pregnancy and who continued to do so during the pregnancy. Developmental effects included statistically significant decreases in gestational age (4.9 days), birth weight (160–190 g), and head circumference (0.6 cm). These developmental effects were still evident 5 to 7 months after the infants' births. Neurobehavioral deficits observed included depressed responsiveness, impaired visual recognition, and poor short-term memory at 7 months of age. At 4 years of age, these children still had deficits in weight gain, depressed responsiveness, and reduced performance on the visual recognition-memory test (i.e., one of the best validated tests for the assessment of human cognitive function).

Although these data indicate transgenerational effects, some questions remain regarding causality because of recognized limitations in the studies. These limitations included a nonrandom sampling technique for the selection of the study population and limited statistical power because of the small size of the control group. In addition, only total PCBs were analyzed. Some of the analytical methods used in the studies (e.g., the pooling of blood samples) are no longer recognized as the most appropriate analytic protocols. Although this study controlled for maternal alcohol and cigarette use, several potential confounders have been identified, including exposure to other chemical contaminants and the mothers' health status at the time of the study. Nevertheless, a more recent retrospective analysis by Swain (1991) –who used the epidemiologic criteria of Susser (1986)– found that the relationship between PCB exposure and

transplacental passage was "strongly affirmed," and the relationship between PCB exposure and developmental effects and cognitive deficits "were affirmed with reasonable certainty."

Other studies of human populations contribute to the overall weight of evidence for adverse health effects associated with exposure to PCBs. In the North Carolina Breast Milk and Formula Project, mothers had background levels of PCB exposure (Rogan and Gladen 1985). Deficiencies in psychomotor development were noted in children of women who had greater exposures to PCBs. They did not exceed test-retest differences; however, these children continued to exhibit a statistically significant delay in psychomotor development up to 2 years of age. At subsequent examinations at ages 3, 4, and 5 years, these effects were not observed (Gladen and Rogan 1991). It has been proposed that neurobehavioral effects (e.g., spatial learning/memory and motor deficits) are caused by complex interactions between neuroendocrine and neurophysiologic systems (Lindström et al. 1995).

Studies in Japan (1968) and Taiwan (1979) of PCB exposure (Harada et al. 1976; Wong and Huang 1981; Hsu et al. 1985) from consumption of contaminated rice oil also contributed to the weight of evidence that xenobiotic agents disrupt normal endocrine function and are associated with neurobehavioral deficits. The illnesses in these two countries were referred to as Yusho disease (Japan) and Yu-Cheng disease (Taiwan). Infants born to women who had been exposed to PCBs exhibited numerous effects, including neurobehavioral deficits. Cognitive testing (Bayley mental and psychomotor developmental indices, Stanford-Binet test, and the Wechsler Intelligence Scale for Children [WISC-R]) indicated significantly lower overall age-adjusted developmental scores among the exposed children. Developmental delays were seen at all ages and were greater in children who were smaller in size, had neonatal signs of intoxication, and/or had a history of nail deformities. Results of follow-up testing (Stanford-Binet test and WISC-R) when the children were 4–7 years of age, indicated that effects on cognitive development persisted for several years after exposure (Chen et al. 1992). Although these neurobehavioral deficits were similar to the findings of the Jacobsons (1985), they were much more pronounced and could have resulted primarily from the presence of dibenzofurans as co-contaminants in the rice oil. The PCBs were heated in thermal heat exchangers before contamination of the rice oil occurred and also during cooking, resulting in the production of relatively high concentrations of chlorinated dibenzofurans (CDFs) and polychlorinated quaterphenyl (PCQ) impurities by thermal degradation. For this reason, and based predominantly on comparisons with Japanese workers who had higher PCB blood levels and few or none of the symptoms present in the rice oil poisonings, CDFs were generally considered to be the primary causal agent (Bandiera et al. 1984; Kunita et al. 1984; Masuda and Yoshimura 1984; Ryan et al. 1990; Safe 1990; Takayama et al. 1991; Tanabe et al. 1989; ATSDR 1993).

More recent work involving a re-examination of previous findings and newer results from a study of 73 Yu-Cheng children demonstrated that relative to neighborhood, matched controls, they have a) a persistent delay in growth (specifically, height, total lean mass and soft tissue mass), b) increased behavioral problems at 3–9 years of age, and c) reduced penile length in boys aged 11–14 years (Guo et al. 1995). In addition, children born during 1985–1991 to Yu-Cheng mothers had developmental delays that were associated with maternal exposure to PCBs and CDFs. Chao et al. (1997) also demonstrated that the prevalence of middle ear disease was higher in children exposed to PCBs and CDFs than in their matched controls.

Adverse health effects also have been reported in persons exposed to PCBs who had evidence of other contaminants in body fluids. A study of Inuit women from Hudson Bay indicated very high levels of PCBs and dichlorodiphenylethene (DDE) in breast milk (Dewailly et al. 1989); these results prompted an examination of the health status of Inuit newborns (Dewailly et al. 1993a). Correlation analysis revealed a statistically significant negative association between male birth length and levels of hexachlorobenzene, mirex, PCBs, and chlorinated dibenzodioxins (CDDs)/CDFs in the fat of mothers' milk. No significant differences were observed between male and female newborns for birth weight, head circumference, or thyroid-stimulating hormone.

The Dutch PCB/Dioxin Study also investigated multiple chemical exposures (Huisman et al. 1995a). The researchers examined the effects of low-level exposure to certain PCBs, furans, and dioxins on neurologic development in the developing fetus and newborn. The neurologic examinations were conducted 10– 21 days after delivery for 418 newborns in two cities. Mothers were matched for planned breast feeding status. Analysis revealed that high levels of PCBs, CDDs, and CDFs in breast milk were associated with reduced neonatal neurologic optimality. Increased hypotonia was associated with high levels of coplanar PCBs in breast milk. These same neurologic effects were also observed at 18 months of age (Huisman et al. 1995b). The researchers evaluated 394 of the children at 42 months of age using the Touwen/Hempel method, at which time no adverse neurologic effects were associated with either prenatal or postnatal PCBs, or dioxin exposure (Lanting et al. 1998).

These same researchers in the Netherlands investigated the effects of PCBs and dioxin exposure (as measured in maternal breast milk) on infants' mental and psychomotor development (Koopman-Esseboom et al. 1996). The results indicated that high in utero exposure to PCBs (also measured in maternal serum) was associated with lower psychomotor scores at age 3 months. After adjustment for confounders, the mean psychomotor score of the 66% highest PCB-exposed breastfed infants (i.e., those exposed to greater than 756 mg total PCB-dioxin toxicity equivalents in breast milk) was comparable to the psychomotor score of formula-fed infants at age 7 months. There was no significant influence of the perinatal exposure to PCBs and dioxin on mental outcome at ages 3 and 7 months. The mental and psychomotor scores of these children at age 18 months were not associated with perinatal exposure to PCBs or dioxin or to duration of breast feeding.

Korrick and Altshul (1998a) have been studying a cohort of mother-infant pairs who live adjacent to a PCB-contaminated waste site, the New Bedford Harbor and estuary in southeastern Massachusetts. Out of 122 mothers, the investigators identified four women who had high breast milk levels of PCBs. The estimated total PCBs ranged from 1,100 to 2,400 ng/g milk fat in these four women, compared with an overall mean of 320 ng/g milk fat for the total cohort. The congener profile and history of one of the four women was consistent with past occupational PCB exposures, but the sources of PCB exposure for the other three women were not as easy to identify. Environmental exposures such as those of fish consumption were likely, whereas residence adjacent to a PCB-contaminated site was considered an unlikely exposure source.

An occupational health study conducted in New York also involved exposure to PCBs (Taylor et al. 1984). This study investigated the relationship of PCB exposure to birth weight and gestational age in 338 infants of mothers occupationally exposed to PCBs during the manufacture of capacitors in upstate New York..

Two groups of women were investigated a) the direct exposure group (worked in job areas with direct exposure to PCBs during the manufacturing process) and b) indirect or low exposure. The results included a decrease in gestational age (6.6 days) and a reduction of weight (153 grams) at birth in infants of mothers directly exposed to PCBs.

Taylor et al. (1989) conducted a follow-up study of 405 women in this occupationally exposed population . Estimated serum total PCB levels in women with direct-exposure jobs were more than four-fold higher than for women in indirect-exposure jobs. After adjustment for confounding variables a significant decrease was found in birth weight and gestational age. These results were similar to the earlier findings reported by the Jacobsons.

Several occupational or epidemiologic studies have indicated or demonstrated other adverse health effects from exposure to PCBs, including cancer and effects on the cardiovascular, hepatic, immune, musculoskeletal, endocrine, gastrointestinal, and dermal systems. Kreiss et al. (1981) have reported a 30% increase over the national average incidence of borderline and definite hypertension observed in a population from Triana, Alabama. Increased serum PCB levels were significantly associated with increased systolic and diastolic blood pressure. The relationship between serum PCB levels and systolic blood pressure disappeared when serum cholesterol and triglyceride levels were considered, but the association between PCB and diastolic blood pressure remained significant. Consumption of contaminated fish was considered the primary source of PCB exposure.

Stehr-Green et al. (1986a, 1986b) also observed increased serum cholesterol and triglyceride levels in a population who resided near a waste site for 5 years. These significantly increased levels were associated with elevated serum PCB levels in this population. In addition, hepatic effects were significantly associated with serum PCB levels. There was a significant positive correlation of total bilirubin with serum PCB levels, and a significant negative correlation of serum albumin with serum PCB levels.

The following investigators have observed effects on the immune system of persons exposed to PCBs. Svensson et al. (1994) assessed various parameters of immunocompetence in a group of men who regularly ate fish obtained from the Baltic Sea. Of the various parameters assessed (e.g., white cell count, lymphocyte levels, and serum immunoglobulin levels), there was a significant negative correlation between the percentage of natural killer cells and weekly consumption of fatty fish (e.g., salmon). Effects on the immune system have also been observed in the Yu-Cheng and Yusho populations (Tryphonas 1995). These have been in the form of a) persistent respiratory distress (e.g., bronchitis and upper respiratory infections) in half of the persons with Yu-Cheng disease, b) significant decreases in IgA and IgM antibody levels 2 years after exposure but normal after 3 years, c) significant decline in the percentage of total T-lymphocytes in persons with Yu-Cheng disease and a slight increase in T-helper cells and a slight decrease in T-suppressor cells in persons with Yusho disease 14 years after exposure, and d) enhanced responses to mitogens (i.e., pokeweed and concavalin) (Guo et al. 1995). Immune system effects have also been observed in Inuit infants who were believed to receive elevated levels of PCBs and dioxins from their mother's breast milk; they demonstrated a decline in the ratio of the $CD4^+$ (helper) to $CD8^+$ (cytotoxic) T-cells at ages 6 and 12 months (but not at 3 months) (Dewailly et al. 1993b). In the Netherlands, infants exposed prenatally and postnatally to PCBs/dioxins who were examined from birth through 18 months of age, revealed that higher prenatal and postnatal levels of PCBs and dioxins were associated with a) lower monocyte and granulocyte counts at age 3 months and b) increases in the total number of T-cells and the number of cytotoxic T-cells at age 18 months (Weisglass-Kuperus et al. 1995). In Sweden, a decrease in natural killer (NK) cells was significantly correlated with

increased serum PCB levels (Hagamar et al. 1995). Significant associations with NK cells were also found for p,p'-DDT and two PCB congeners (mono-ortho and non-ortho). No changes were found in other lymphocyte cells.

Fischbein et al. (1979) reported joint pain in workers who were exposed to a variety of PCB Aroclors. Humphrey et al. (1983) found a 10% prevalence of unspecified joint problems among families who lived on farms and who consumed dairy products and beef contaminated with PCBs.

Koopman-Esseboom et al. (1994) also investigated the effect of dioxins and PCBs on thyroid hormone status among the Dutch population. Higher CDD, CDF, and PCB levels in human milk correlated significantly with a) lower plasma levels of maternal total triiodothyronine and total thyroxine and b) higher plasma levels of thyroid-stimulating hormone in infants during the second week and third month after birth. Infants exposed to higher levels also had lower plasma-free thyroxine and total thyroxine levels in the second week after birth.

A review by Hauser (1998) examined the relationship between thyroid hormone function and PCB exposure. Thyroid hormones are essential for normal behavioral, intellectual, and neurological development. For example, untreated congenital hypothyroidism can result in irreversible mental retardation, whereas thyroid diseases with more moderate impairment of thyroid function (e.g., resistance to thyroid hormone) cause less severe intellectual and behavioral abnormalities, including attention deficit hyperactivity disorder. There is increasing evidence in animal and human studies that exposure to certain environmental pollutants, including PCBs and dioxins, during the perinatal period can impair learning, memory, and attentional processes in offspring. The precise mechanisms of action of the adverse effects these toxicants exert on neurodevelopment have not yet been elucidated, although it is possible that they are partially or predominantly mediated by alterations in hormone binding to the thyroid hormone receptor.

Additionally, a gastrointestinal effect, appetite loss, was reported in a cross-sectional study of PCB-exposed transformer workers (Emmett et al. 1988) and electrical equipment manufacturing workers exposed to various Aroclors (Smith et al. 1982). A characteristic health outcome common in the occupational setting is chloracne (acneform eruption caused by some chlorinated organic chemicals), and skin rashes are also associated with exposure to Aroclors (Baker et al. 1980; Bertazzi et al. 1987; Emmett et al. 1988; Fischbein et al. 1979, 1982, 1985; Maroni et al. 1981; Meigs et al. 1954; Ouw et al. 1976; Smith et al. 1982).

Epidemiologic studies raise concerns about the potential carcinogenicity of PCBs, although the specific results differ by study. Capacitor manufacturing workers exposed to a variety of commercial PCB mixtures containing 41–54% chlorine had increased mortality from liver, gall bladder, and biliary tract cancer (Brown 1987), gastrointestinal tract cancer (Bertazzi et al. 1987), or malignant melanoma (Sinks et al. 1992). An analysis of these and a smaller study (Gustavsson et al. 1986) found the combined results significant for liver, gall bladder, and biliary tract cancers, and for malignant melanoma (Nicholson et al. 1994). Earlier, petrochemical refinery workers exposed to Aroclor 1254 and other chemicals had shown significantly increased mortality from malignant melanoma (Bahn et al. 1976). More recently, electric utility workers exposed to PCBs had significantly increased mortality from malignant melanoma and brain cancer (Loomis et al. 1997).
Recent case-control studies have found associations between non-Hodgkin's lymphoma and PCB concentrations in adipose tissue (Hardell et al. 1996) and serum (Rothman et al. 1997). In the Rothman

study of persons without known occupational exposure to PCBs, mean PCB blood levels of 13.3 ppb yield highly significant (p=0.0008) increased odds of non-Hodgkin's lymphoma. Case-control studies have not found significant associations between serum PCBs and breast cancer (Krieger et al. 1994; Wolff et al. 1993) or between concentration of PCBs in bone marrow and leukemia in children (Scheele et al. 1992); these results have not been fully studied for their implications. Hoyer and colleagues (1998) found a dose response relationship between serum concentrations of dieldrin and breast cancer but not with PCBs and DDT. In the previously described Yusho and Yu-Cheng episodes in Japan and Taiwan, respectively, where humans consumed rice oil contaminated with PCBs, the incidence of liver cancer was increased (Masuda 1994); however, this incidence has been attributed, at least in part, to heating of the PCBs and rice oil, which causes formation of chlorinated dibenzofurans (Morita et al. 1978).

Yu et al. (1997) recently evaluated the mortality rate of 1,837 persons in Taiwan who were exposed to PCBs and CDFs The analysis pertained to deaths in this cohort through December 31, 1991. The incidence of chronic liver disease and cirrhosis was significantly increased for the cohort in comparison with the general population of Taiwan; these researchers used a standardized mortality ratio (SMR) as a gauge.

More recently, 154 women with postmenopausal breast cancer (primary and histologically confirmed) were compared with 192 postmenopausal community controls to examine the effect of exposure to DDE, hexachlorobenzene, mirex, and PCBs (Moysich et al. 1998). Information on diet, reproductive and medical history, and lifestyle was collected by interviewing the study participants. Serum samples were obtained from the women and were analyzed by gas chromatography for DDE, hexachlorobenzene, mirex, and 73 PCB congeners. The findings suggested that a specific subset of the women with environmental exposure to PCBs (i.e., parous women who had never breastfed) may be at increased risk for breast cancer after menopause.

III. STUDIES IN ANIMALS

Neurotoxicity has been observed in several animal species exposed in laboratory studies to PCBs. Decreased performance in discriminating learning tasks at 6 and 12 months of age has been observed among offspring of female monkeys exposed to Aroclor 1248 (Bowman et al. 1978; Bowman and Heironimus 1981; Mele et al. 1986). The same monkeys tested at 44 months of age were hypoactive in comparison with controls. Levin et al. (1988) reported neurobehavioral deficits in offspring of monkeys fed Aroclor 1248. Schantz et al. (1989) reported deficits in spatial discrimination of infant monkeys whose mothers were exposed to Aroclor 1016. Signs of neurotoxicity were observed in rats exposed to Aroclor 1242, including diminished exploratory behavior, decreased responses to pain stimuli, and unusual gait (Bruckner et al. 1973). Some of these studies were conducted using the types of PCBs most often found in human breast milk.

Rice (1999) also observed neurobehavioral deficits in monkeys exposed to PCBs. In this study monkeys were dosed from birth to 20 weeks of age with a PCB congener mixture representative of the PCBs found in breast milk of Canadian women. Neurobehavioral assessment on a series of tasks was performed when the monkeys were between 2.5 and 5 years old.
Significant deficits were observed which included retarded learning and difficulty in learning complex tasks. Additionally, the researcher indicated that treated animals demonstrated less efficient behavior because they made many more responses per reinforcement than did controls. No group differences were

observed for the number of errors on a series of spatial discrimination reversal tasks. The researcher suggests that these results have implications for the potential contribution of exposure to PCBs through breast milk to behavioral impairment.

Thyroid hormone levels are critical for normal growth and development, and alterations in thyroid hormone levels may have significant implications. The available data indicate that numerous environmental substances modulate the endocrine system. Rats exposed to PCBs had reduced serum levels of T_4 and T_3. Histologic findings included thyroid gland enlargement, reduced follicular size, follicular cell hyperplasia, and accumulation of colloidal droplets and large, abnormally shaped lysosomes in the follicular cells (Byrne et al. 1987; Collins et al. 1977). Serum levels of the adrenal cortex hormones, dehydroepiandrosterone and dehydroepiandrosterone sulfate, were decreased after dietary exposure to either Aroclor 1242 or 1221. The decrease in serum hormonal levels was dose-related and increased with increasing degree of mixture chlorination (Byrne et al. 1988).

PCB-induced effects on the immune system that were demonstrated in several species of animals represented the basis for the EPA reference dose (RfD) for Aroclor 1254. Rats treated with Aroclor 1254 had reduced thymus weights and reduced natural killer cell activities (Smialowicz et al. 1989). Mice exposed to either Aroclor 1242 or 1248 had decreased resistance to infection leading to death (Loose et al. 1978; Thomas and Hinsdill 1978). Monkeys exposed to very small doses of Aroclor 1254 had a significant decrease in IgM and IgG levels in primary response to challenge with sheep red cells (Tryphonas et al. 1989). Therefore, the immune system in monkeys is considered one of the most sensitive systems to the effects of PCBs in animals.

Reproductive function may be disrupted by exposure to PCBs. Studied species include rhesus monkeys, rats, mice, and mink. Female rhesus monkeys exposed to PCBs had alterations in menstrual cycles (e.g., duration and bleeding), decreases in fertility, increased number of abortions, and reduced number of conceptions). Effects were observed long after the dosing with PCBs occurred (Barsotti et al. 1976; Arnold et al. 1990). Reproductive disturbance (evidenced by reduced birth weight) represents the basis for the EPA RfD for Aroclor 1016.

Cancer Studies in Animals

Four commercial PCB mixtures - Aroclors 1016, 1242, 1254, and 1260 - have been tested in rats for their potential to cause cancer. All mixtures induced liver tumors when fed to female rats; Aroclor 1260 also induced liver tumors in male rats (Mayes et al. 1998). Several of these tumors were hepatocholangiomas, a rare biliary tract tumor seldom seen in control rats. In the same study, thyroid gland follicular cell tumors were increased in males but not females. These mixtures contained overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures. Previously, lifetime dietary exposure to commercial mixtures with 60% chlorine induced liver tumors in three rat strains (Kimbrough et al. 1975; Schaeffer et al. 1984; Norback and Weltman 1985; Moore et al. 1994). Although many of these tumors were benign, sequential morphologic analyses demonstrated the eventual progression of the benign liver lesions to malignant carcinomas (Norback and Weltman 1985).
Commercial mixtures with 54% chlorine induced gastrointestinal tumors (National Cancer Institute 1978; Morgan et al. 1981; Ward 1985). Less-than-lifetime dietary exposure to commercial mixtures with 42 - 60% chlorine induced precancerous liver lesions in rats and mice (Kimbrough et al. 1972, 1974; Kimura and Baba 1973; Ito et al. 1973, 1974; Rao and Banerji 1988).

Before the comprehensive study conducted by Mayes et al. (1998), only commercial mixtures with 60% chlorine had been adequately tested, and there was controversy about whether mixtures with lower chlorine content were carcinogenic. The Mayes et al. study strongly supported the stance that all PCB mixtures can cause cancer, thus resolving the key question about the cancer hazard. Both the EPA and the International Agency for Research on Cancer (IARC) have concluded that PCBs are probably carcinogenic to humans (U.S. EPA 1996a; IARC 1978, 1987).

When the rat study conducted by Mayes et al. was published, EPA reassessed the cancer risk associated with environmental exposure to PCBs (U.S. EPA 1996b; Cogliano 1998). The reassessment considered how health risks could be increased or decreased by the environmental processes of partitioning, chemical transformation, and preferential bioaccumulation. (Partitioning refers to different fractions of a mixture separating into air, water, sediment, and soil. Chemical transformation occurs through biodegradation in the environment. Preferential bioaccumulation through the food chain tends to concentrate some highly chlorinated congeners, which can be among the most toxic and persistent.)

EPA's reassessment concluded that bioaccumulation of PCBs in fish is especially hazardous to humans who eat them. Many PCBs persist in the human body and retain biologic activity after the exposure stops. In a 46-month study of capacitor workers following elimination of PCB usage, Wolff and colleagues (1992) reported that with the exception of PCB 2,4,4',5 (Congener 74) and PCB 2,3',4,4' (Congener 66), PCBs elimination half-lives of the lower chlorinated congeners ranged from 1 to 6 years. Total higher chlorinated PCBs did not decrease significantly, with elimination half-lives ranging from 8-24 years. Research by Safe and colleagues (1985; Safe 1989) determined that the congeneric composition of PCBs in human milk, while not resembling a commercial mixture, was dominated by congeners which were minor components of Aroclors, such as 1260. The research indicates that it is the more highly chlorinated PCB congeners and those that lack unsubstituted meta-para positions that are resistant to metabolism and tend to accumulate in tissues. Bioaccumulated PCBs appear to be a) more toxic than commercial PCBs and b) more persistent in the body. The risks associated with exposure through the food chain can be higher than other types of exposure.

EPA's reassessment provided a range of cancer slope factors. The highest slope factor is appropriate for exposure pathways where environmental processes tend to increase risk: food chain exposure; contaminated sediment or soil ingestion; dust or aerosol inhalation; exposure to dioxin-like, tumor-promoting, or persistent congeners; and early-life exposure (all pathways and mixtures). A lower slope factor is appropriate for exposure pathways where environmental processes tend to decrease risk: ingestion of water-soluble congeners and inhalation of evaporated congeners. In addition to providing slope factors for different exposure pathways, upper-bound cancer slope factors were compared with the corresponding central estimates. The use of usual upper-bound values was found to increase cancer slope factor estimates by only twofold.

IV. RECENT RESEARCH FINDINGS FROM HUMAN HEALTH STUDIES IN THE GREAT LAKES BASIN

In 1990, Congress amended the Great Lakes Critical Programs Act, stipulating that the EPA, in consultation with ATSDR and the Great Lakes states, submit a research report to Congress assessing the potential health effects of water pollutants in the Great Lakes basin (U.S. EPA 1995). This report

identified significant gaps in scientific research bearing on human health effects of Great Lakes toxicants, leading to a program of research, the ATSDR Great Lakes Human Health Effects Research Program (GLHHERP).

ATSDR's GLHHERP is designed to investigate and characterize the association between the consumption of contaminated Great Lakes fish and short- and long-term harmful human health effects. Several human populations have been identified who have a potentially higher risk for short- and long-term health effects because of their elevated exposure to and or physiologic sensitivity to PCBs and other contaminants in Great Lakes fish. These susceptible populations include sport anglers, Native Americans, Asian Americans, child-bearing aged women, pregnant women, children, the elderly, the urban poor, and fetuses and nursing infants of mothers who eat contaminated Great Lakes fish. ATSDR's GLHHERP has focused its research efforts on these populations in the Great Lakes basin.

The GLHHERP is in its seventh year of a comprehensive research program administered through the award of grants to state health departments and academic institutions in the Great Lakes basin. Through November 1998, Congress has appropriated approximately $19 million to support human health effects studies. The following sections summarize findings to date from this program.

Exposure

The early human effects observed from exposure to PCBs within the Great Lakes and St. Lawrence River basins were reported by Humphrey (1983, 1988). More recent research findings support these earlier reports of an association between consumption of contaminated Great Lakes sport fish and body burdens of PCBs. The PCB body burdens of fish-consuming populations in the Great Lakes basin who eat this fish are two-fold to four-fold higher than those in the overall U.S. population. Findings also include the following:

- at-risk populations (i.e., Native Americans, sport anglers, the elderly, pregnant women, and fetuses and nursing infants of mothers who consume contaminated Great Lakes fish) continue to be exposed to PCBs and other persistent substances such as dioxins, chlorinated pesticides, and mercury (Anderson et al. 1998; Dellinger et al. 1996; Fitzgerald et al. 1996; Hanrahan et al. 1997; He et al. 1998; Lonky et al. 1996; Schantz et al. 1996); the amount of fish consumed determines the level of exposure;

- fish consumption appears to be the major pathway of exposure (Birmingham et al. 1989; Newhook 1988; Fitzgerald et al. 1996);

- a significant trend of increasing body burden is associated with increased fish consumption (Fitzgerald et al. 1996);

- persons who eat sport-caught fish consumed 2-3 times more fish than the overall U.S. population (Courval et al. 1996; Fitzgerald et al. 1996; Schantz et al. 1996);

- persons who ate Great Lakes sport fish for more than 15 years have two to four times more pollutants in their serum than nonfisheaters (Schantz et al. 1996);

- men annually consumed more fish than women (Courval et al. 1996; Fitzgerald et al. 1996);

- women ate fish obtained from the Great Lakes during most of their reproductive years (Courval et al. 1996; Lonky et al. 1996; Waller et al. 1996).

Fitzgerald et al. (1998) recently conducted a study to determine the relationship between the consumption of contaminated Great Lakes fish and levels of PCBs and congeners in breast milk of women in the Mohawk Indian tribe. From 1986 through 1992, 97 of these women provided samples of their breast milk for this study; the comparison or control group comprised 154 white women. After the authors adjusted for potential confounding variables, tribal women who gave birth in 1986-1989 (the earliest time studied) had a significantly higher milk total PCB concentration of 0.602 ppm (fat adjusted) compared with 0.375 ppm for the control group ($p=0.009$). In addition, tribal women had significantly higher geometric mean concentrations for nine PCB congeners. These differences were not apparent for later births and samplings.

The investigators indicated that the reduction in breast milk PCB concentrations over time paralleled a corresponding decrease in local fish consumption by the tribal women, and they concluded that this reduction in fish consumption might have resulted from the fish advisories that were issued recommending against the consumption of local fish by pregnant and nursing women. Their recent data indicated that 95% of both men and women in the tribe are aware of these advisories and that 66% of men and 40% of women have changed fish consumption patterns as a result (Fitzgerald et al. 1998).

Hanrahan et al. (1997) investigated serum PCB levels and Great Lakes sport fish (GLSF) consumption in five Great Lakes states. Frequent fish consumers were identified as Wisconsin anglers, charter boat captains, and their spouses. Infrequent consumers were persons determined by the self-reported estimated number of GLSF meals eaten per year. Subsets of these two groups were asked to donate serum for PCB analysis. The authors controlled for age, body mass, lake (Michigan, Huron, or Erie), and sex. The results indicated frequent fish consumers ate an average of 46 GLSF meals per year and had a geometric mean PCB level of 7.78 ppb. Infrequent consumers ate less than 6 GLSF meals per year and had a geometric mean PCB level of 1.0 ppb. PCB levels differed considerably according to the lake in which the fish were obtained; consumers of Lake Michigan fish had significantly higher geometric mean PCB levels than consumers of fish obtained from Lakes Huron and Erie. In addition, the data indicated that the total number of years of eating GLSF was the best predictor of PCB body burden. Previously, Hovinga (1993) reported a geometric mean PCB blood level of 6.8 ppb in 95 persons who had eaten less than 6 pounds of Lake Michigan fish per year, compared with 19 ppb in 112 persons who ate greater than 24 pounds of fish from Lake Michigan per year. Testing of these participants was conducted in 1991. The PCB blood levels of the frequent fish consumers were in the same range as those levels (10.3 ppb) found to be significantly associated with non-Hodgkin's lymphoma (Rothman et al. 1997).

Anderson et al. (1998) also determined the profile of contaminants in frequent consumers of GLSF obtained from Lakes Erie, Huron, and Michigan. Participants in this study ate an average of 49 GLSF meals per year (mean duration: 33 years). In comparison, the U.S. population in the Great Lakes basin reported eating an average of 6 GLSF per year. The investigators analyzed whole blood, serum, or urine samples for organochlorine compounds, 11 persistent and 10 nonpersistent pesticides, and 7 metals, including mercury and lead. The mean tissue levels of most persistent bioaccumulative compounds in the Great Lakes sport anglers ranged from less than a twofold increase to eight times greater (PCB congener 126) than what is found in the general U.S. population. The overall mean totals for toxic equivalent for dioxins, furans, and coplanar PCBs were greater than background levels of the general U.S. population, that is, dioxin levels were 1.8 times; furans, 2.4 times greater; and coplanar PCBs, 9.6 times greater. The

investigators concluded that consumption of GLSF was the most likely explanation for the observed contaminant levels in these anglers.

Lonky et al. also compared the pattern and concentration of PCBs in umbilical cord blood of 145 women who reported never eating GLSF with 143 women who reported eating at least 40 PCB-equivalent fish pounds (Stewart et al. 1999). The investigators found that, although the average level of total PCBs in cord blood was low (approximately 1.0 ppb), both the proportion (mole%) and absolute concentration (ppb) of the most heavily chlorinated and persistent PCB homologues (C17–C19) were markedly elevated in the cord blood of neonates born to women who ate fish. Moreover, the concentration of the most heavily chlorinated PCB homologues significantly depended upon how recently the fish were eaten relative to the time of pregnancy. The investigators concluded that maternal consumption of GLSF increases the risk for prenatal exposure to the most heavily chlorinated PCB homologues.

West (1993) surveyed 2,451 licensed anglers in Michigan who were fish consumers out of a total population of 368,557. Analysis of the data base indicated that a projected 11,900 anglers eat one meal per week or more of coho, chinook, or unidentified noncommercial salmon (Jacobs 1995).

He et al. (1998) evaluated changes in sport-caught fish consumption and serum levels of PCBs among individuals in Michigan during three time periods, i.e., from 1973–1974, 1979–1982, and 1989–1991 (n=156, 1255, and 728, respectively). The researchers found that over time, there was a decline both in the number of sport fish meals consumed (median = 66, 54, and 31 per year, respectively), and the total amount of sport fish consumed (median = 40, 38, and 16 pounds per year, respectively). Median serum PCB levels were two to three times higher in fisheaters during each time period (14.0 versus 6.0 ppb, 19.4 versus 7.0 ppb, and 17.3 versus 5.8 ppb, respectively). The researchers also indicated that men reported eating more sport fish than women during each time period. After adjustment for age, gender, education, and region, PCB levels were associated with current annual sport fish consumption. The researchers concluded that even though individuals decreased their fish consumption over time, this decline did not cause a similar decline in serum PCB levels.

In a 1992–1993 study assessing the exposure to persistent environmental contaminants of adults consuming sport-caught fish in Cornwall and Mississauga, Ontario, the estimated average daily consumption of these fish was 21.3 g/day (Kearney et al. 1995). Health Canada (1998) has determined the PCB levels of 10 of the most frequently caught and consumed GLSF species in Canada. Mean values for 9 of the 10 sport fish species ranged from 10 ng/g in largemouth bass to 1,151 ng/g in lake trout; the overall average was 379 ng/g. Health Canada has estimated (considering PCBs from all media) that the total daily intake of PCBs among adults, who eat an average of 21.3 grams of sport-caught fish per day, is six times greater (137.2 ng/kg/bw/day) than the intake of 21.8 ng/kg/bw/day estimated for the general Canadian population.

Researchers have also investigated the role of various environmental pathways of exposure to Great Lakes contaminants. Earlier multimedia studies by Birmingham et al. (1989) and Newhook (1988) indicated that most (80 - 90%) cases of human exposure to chlorinated organic compounds occur through the food pathway. A more recent multimedia study supports these findings and indicates that the primary pathway of exposure to persistent toxic substances (e.g., PCBs) is from fish consumption (Fitzgerald et al. 1996.)

PCBs are considered the dominant organochlorine residue in Great Lakes fish (Michigan Department of Environmental Quality, 1996). Using risk assessment values then available and several consumption assumptions, Dourson and Clark (1990) deduced that PCBs would contribute the majority of the noncancer risks from Great Lakes fish consumption, although organochlorine pesticides could contribute some to the overall risk.

Other key exposure studies are summarized in Table 1 (Johnson et al. 1998).

Table 1. Findings in Human Populations–Exposure Studies

Population	***Findings***	***Reference***
Lake Michigan Fisheaters cohort	PCB levels in breast milk and maternal serum were correlated with consumption of contaminated fish.	Humphrey 1983
Elderly cohort of Lake Michigan sport anglers	PCBs, DDE, and mercury levels were significantly higher in high fisheaters. High fisheaters presented disproportionately higher body burden levels of PCBs and DDE than low fisheaters in each age group, that is, 50–59, 60–69.	Schantz et al. 1996
Pregnant African-American women who consumed Lake Michigan fish	Women were exposed to PTSs via fish consumption during most of their reproductive years; 75% of these women were <26 years of age and had been eating lake fish for >15 years.	Waller et al. 1996
Reproductive-aged (i.e., 18–34 years) Lake Michigan sport anglers	Approximately 50% had eaten 1–12 sport-caught fish meals in the preceding year, and 20% had eaten 13–24 meals. Men reported having eaten more fish meals than females, with some males eating ≥49 fish meals per year.	Courval et al. 1996
Charter boat captains, their spouses, and Great Lakes anglers	Serum levels of dioxin, furans, and coplanar PCBs differed by sex of participants. The fish species predicted coplanar PCBs and furan body burden levels but not dioxin.	Falk et al. 1997
Population	***Findings***	***Reference***
Charter boat captains, their spouses, and Great Lakes anglers	Frequent fish consumers ate an average of 46 GLSF meals per year and had a mean PCB level of 7.78 ppb. Infrequent consumers ate < 6 GLSF meals per year and had a mean PCB level of 1.0 ppb.	Hanrahan et al. 1997

Table 1. Findings in Human Populations–Exposure Studies		
Pregnant women who consumed Lake Ontario fish	Women in the high-fish-consumption group had eaten an average of 2.3 salmon or trout meals per month for an average of 16 years.	Lonky et al. 1996
Native Americans (Mohawk) in New York state	Mean serum PCB levels in men were 5.4 ppb (maximum: 31.7 ppb), versus 5.0–7.7 ppb in the general U.S. population (Jensen 1989). Serum PCB levels were associated with the number of fish meals eaten per year and with increasing age.	Fitzgerald et al. 1996
Sport anglers of Asian origin on the St. Lawrence River	Bangladeshi fisheaters ate an annual average of 46.8 sport fish meals, and Vietnamese fisheaters ate an average of 40.7 meals — considerably less than the average of 57 meals eaten by native residents of Quebec.	Shatenstein et al. 1997
3,751 persons from five Canadian Great Lakes Areas of Concern (AOC)	These persons were eating fish species for which local guidelines do not exist, preparing fish in different ways, and eating fish more frequently than recommended by current guidelines.	Cole et al. 1997
Canadian sport anglers from the St. Lawrence River basin	Mercury intake from the most contaminated fish species exceeded the recommended acceptable daily doses. The estimated intake of PCBs was 10 to 100 times lower than the daily acceptable dose.	Gauvin et al. 1997

Health Effects

Recent studies indicate that exposure to Great Lakes contaminants might cause disturbances in reproductive parameters and cause neurobehavioral and developmental deficits in newborns and older children.

Courval et al. (1997) have reported early findings of their study investigating exposure to PTSs and conception failure among Michigan anglers. Six hundred and twenty-six married couples were identified through surveys and questionnaires sent to anglers and their partners. Conception failure was defined as the inability to conceive after 12 months. On the basis of answers to questionnaires, 15% of couples reported conception failure. Among men, the unadjusted odds ratios (ORs) for conception failure were 1.2, 1.3, and 2.0 across the three increasing levels of sport-caught fish consumption in comparison with no consumption (trend test $p=0.06$). After adjustment for variables (i.e., age, region of residence in Michigan, smoking status, and alcohol consumption), the ORs were 1.4, 1.8, and 2.8, respectively. For women, the unadjusted ORs for conception were 0.9, 1.0, and 1.4 with increasing fish consumption (trend test $p=0.35$). When the same covariates and the male partners' sport-caught fish consumption

were included in the model for conception failure in women, the ORs were 0.8, 0.8, and 1.0, respectively. These data suggest a modest association, in men only, of sport-caught fish consumption with the risk for conception failure.

Mendola et al. (1995) conducted a study of 1,820 multigravida women from the cohort of New York State anglers to determine the risk for clinically recognized spontaneous fetal death associated with exposure to PTSs, such as PCBs from fish consumption. Fish consumption data were obtained from food frequency questionnaires, and history of spontaneous fetal death was assessed from computerized birth certificates. Analyses were stratified by number of previous pregnancies and were controlled for smoking and maternal age. No significant increases in risk for fetal death were noted across four measures of exposure: a lifetime estimate of PCB exposure based on species-specific PCB levels, the number of years of fish consumption, kilograms of sport-caught fish consumed in 1990–1991, and a lifetime of fish consumption. The authors concluded that there was no significant relationship between low-to-moderate PCB intake ($\leq$7 mg in a life time) and risk for clinically recognized spontaneous fetal death.

Mendola et al. (1997) also assessed the relationship between menstrual cycle length and consumption of PCB-contaminated Lake Ontario sport-caught fish in 2,223 females planning to become pregnant who were in the cohort of New York State anglers. Species-specific fish consumption, medical and reproductive histories, sociodemographic characteristics, and other lifestyle behaviors were assessed by questionnaires and telephone interviews. Exposure measures corresponded to those of Mendola et al. (1995). Multiple-regression analyses were used to establish models of cycle length adjusted for age and other factors, but not for all important factors. Cycle length was significantly reduced (by about 1 day) for the whole group and by about one-half day for the women with regular cycles who ate more than one fish meal per month. Women who had regularly eaten contaminated fish during the preceding 7 years also had shorter cycles. The frequency of fish consumption and an index of a lifetime of PCB exposure appear to have a stronger relationship with menstrual cycle length than the number of years of fish consumption. The authors concluded that these preliminary findings underscore the need for further study of environmental factors in association with reproductive end points that are hormonally mediated.

This same team of investigators also assessed the relationship between consumption of contaminated fish and time-to-pregnancy (TTP) and found no adverse association between the duration of consumption and TTP (Buck et al. 1997). This study population comprised 874 female cohort members with known TTP during the 3-year study period. Multiple-regression analyses were adjusted for known factors affecting TTP; however, the authors cautioned that this was a small population of women who were fertile and intended to become pregnant. Of the 1,234 women in the New York State anglers cohort who reported being pregnant, 874 (71%) had a known TTP; these women were chosen as the study population. After various statistical models (which included duration of fish consumption , TTP, and other covariates) were utilized, there was no adverse association between the duration of consumption of contaminated fish from Lake Ontario and time-to-pregnancy.

Lonky et al. (1996) investigated pregnant women and the effects of maternal exposure to contaminants in Lake Ontario fish on their newborns and found that in utero exposure was associated with neurobehavioral deficits that can be assessed soon after birth. Five hundred and thirty-six newborns of women who consumed a PCB-indexed amount of fish in a lifetime either

- of ≥40 pounds (high exposure), or
- of ≺40 pounds (low exposure), or
- who had consumed no Lake Ontario fish (controls)

were examined using the Neonatal Behavioral Assessment Scale (NBAS) at 12–24 hours and 25–48 hours after birth. Newborns of mothers in the high-exposure category exhibited

- a greater number of abnormal reflexes,
- less mature autonomic responses, and
- less attention to visual and auditory stimuli

in comparison with newborns of low- or no-fish–consuming mothers, after adjustment for a variety of potentially confounding factors. These results indicated that, despite moderate consumption of salmon or lake trout fish (about 30 g/day), newborns of mothers in the high-exposure group scored more poorly on the NBAS than those newborns from the low-exposure or control group.

These results replicate and extend the neonatal results of the Lake Michigan Maternal Infant Cohort study by Jacobson et al. (1984). The Lake Michigan Maternal Infant Cohort study was the first epidemiologic investigation to demonstrate an association between the self-reported amounts of Lake Michigan fish eaten by pregnant women and behavioral deficits in their newborns (as assessed by the NBAS). The Michigan investigators found that 242 infants born to mothers who had eaten the greatest amount of contaminated fish during pregnancy had (a) more abnormally weak reflexes, (b) greater motor immaturity and more startle responses, and (c) less responsiveness to stimulation.

The same research team (Lonky et al. 1996) studied the effect of recency on neonatal coping behavior and infant temperament at 24 months of age (Darvill et al. 1997). NBAS and Infant Behavior Questionnaire (IBQ) data were used to assess the effect of recency of maternal fish consumption on neonatal coping behavior (NBAS) and infant temperament (IBQ). Four groups were formed: Group 1-infants, whose mothers reported eating fish throughout their pregnancy; Group 2- infants, whose mothers reported eating fish up until learning of their pregnancy; Group 3-infants, whose mothers reported having eaten fish before 1985; and Group 4-infants, whose mothers had not eaten fish (i.e. the control group). All of the women in groups 1, 2, and 3 reported having eaten at least 2.3 salmon or trout meals per month during their lifetimes. Six of seven NBAS cluster scores were analyzed by multivariate analysis of covariance (MANCOVA); habituation was analyzed by analysis of covariance (ANCOVA) because of small sample size.

Preliminary analysis of the initial MANCOVA of 24-month IBQ scores revealed an effect of recency of fish consumption for four of six measured dimensions of temperament: activity level $F(3,171) = 2.81$, $p=0.041$; fear $F(3,171)=3.55$, $p=0.016$; smiling and laughter $F(3,171)=2.83$, $p=0.040$; and soothability $F(3,171)=2.71$, $p=0.047$. After controlling for demographics, parity, use of illicit drugs, and home environment , MANCOVA analysis found there was an overall significant effect for group membership; however, no individual IBQ scales were significant. To further explore the relationship of recency of fish consumption and individual IBQ scales, data were evaluated in a stepwise discriminant function analysis. After the entry of all control variables, the following IBQ scales were significant contributors to these functions: duration of orienting, distress to limitations, smiling and laughter, and fear. These findings, paralleling some of the neurobehavioral effects observed by Jacobson and colleagues, were the first to

suggest an association between prenatal exposure to toxic substances and a wide range of effects on infant temperament.

A follow-up examination of 212 children from the Lake Michigan Maternal Infant Cohort Study indicated that the neurodevelopmental deficits found during infancy and early childhood still persisted at age 11 years (Jacobson and Jacobson 1996). These children had been exposed in utero through the consumption of contaminated fish by their mothers during the six years before and during pregnancy. After adjustment for many confounding factors, including maternal alcohol consumption, cigarette use, socioeconomic status, maternal age, parity of the mother, and exposure to lead and mercury, the results indicated that the most highly exposed children (based on maternal milk PCB concentration)

- were three times more likely than controls to have low full-scale verbal IQ scores,
- were twice as likely to lag behind at least two years in reading comprehension, and
- have difficulty paying attention.

These intellectual impairments were attributed to in utero exposure to PCBs and to related contaminants at concentrations slightly higher than those found in the overall population. How the presence of lead and mercury relate to levels of PCBs in the same children was unclear, but impairment was also associated with higher concentrations of these other substances.

Korrick (1998b) is also investigating the associations between low-level in utero PCB exposures and health outcomes in newborns and infants. Mothers of these children reside in one of four communities adjacent to the New Bedford Harbor Superfund site, which is known to be significantly contaminated with PCBs. Results of the preliminary data analyses indicate that infant visual memory (assessed by the Fagan Test of Infant Intelligence), which is predictive of cognitive performance in later childhood, may be impaired by in utero PCB exposures. The authors reported that evidence is emerging in both this study and studies by other researchers that suggests low-level in utero pollutant exposure is associated with altered developmental achievement and growth in infancy and later childhood.

Schantz et al. (1997) have investigated fine motor function in older Great Lakes fisheaters. The 180 participants included persons aged 50–90 years who were categorized in two groups: Lake Michigan fisheaters (i.e., persons who ate $\geq$24 pounds of sport-caught fish per year) and nonfisheaters (those who ate $\leq$6 pounds per year). The outcome measures were the participants' raw scores on the Static Motor Steadiness Test (SMST) and Grooved Pegboard Test (GPT). The median serum total PCB concentration was 12 ppb for high-consumption fisheaters and 5 ppb for low-consumption fisheaters (maximum values: 75 ppb and 26 ppb, respectively). The median serum DDE concentration was 10 ppb for high-consumption fisheaters and 5 ppb for low-consumption fisheaters (maximum values: 145 ppb and 33 ppb, respectively). The median mercury level in high-consumption fisheaters was above that of low-consumption fisheaters, 2 ppb versus 0 ppb (maximum values: 21 ppb and 5 ppb, respectively).

Because of the high correlation between serum PCB and DDE levels in this sample population, the effects of these substances were assessed jointly using a single derived exposure variable: low = both PCB and DDE at or below the median of their respective distributions; intermediate = PCB and/or DDE in the third quartile; and high = PCB and/or DDE in the upper quartile of their distributions. Regression analyses and analysis of variance (ANOVA) were used to assess the effects of PCB and DDE exposure on motor function, controlling for all significant correlates from each of four classes of variables

(demographic characteristics, lifestyle, medications and medical condition, and psychological status). Unadjusted analyses indicated that high exposure to PCBs and DDE was associated with decreased performance on the GPT. A regression model was developed that included all variables; age was the most significant factor in this model, and exposure to PCB and DDE was not significant. Similar analyses were performed for the SMST, and exposure to PCBs and DDE was not significant in the final, covariate-adjusted model ($p=0.21$). The authors concluded that in this cross-sectional analysis of their data, PCB and DDE exposure from consumption of Great Lakes fish does not impair fine motor function. However, their study also includes a longitudinal component. Analysis of "change scores" reflecting the degree of decline in motor function by individual participants over time may prove to be a more sensitive indicator of exposure-related effects.

Mergler et al. (1997, 1998) have reported findings of early nervous system dysfunction among adults exposed to PCBs and other persistent toxic substances. A study on early neurotoxic effects of environmental exposure via fish consumption was conducted in Southwest Quebec. Persons who ate fish caught in the St. Lawrence Lakes (SLL) were identified through questionnaires. Three hundred men and women aged 20–69 years participated in this study; 121 reported eating SLL fish, and 179 reported never eating SLL fish. Comparisons of neurologic outcomes adjusted for age, education, and alcohol intake by participants indicated that SLL fisheaters had significantly ($p<0.05$) greater motor slowing, poorer results on certain tests of memory and attention, and higher scores on the Confusion Scale of the Profile of Mood States Test. Multiple regression analyses, performed by using an index of fish consumption, showed that motor slowing and attention difficulties were directly related to the frequency of SLL fish consumption ($p<0.01$). In addition, those who ate fish during both summer and winter had poorer results than those who ate fish during only one season. Persons who did not eat SLL fish had test results than participants in the other groups. These findings suggest that nervous system alterations are associated with eating SSL fish and that the deficit increases with consumption.

An ongoing epidemiologic study is investigating the potential for health effects among Native Americans exposed to persistent toxic substances (Dellinger et al. 1997; Tarvis et al. 1997; Gerstenberger et al. 1997). Fish consumption, species consumed, and medical histories were obtained from 541 Native Americans on eight tribal lands in Minnesota, Wisconsin, and Michigan. Preliminary results indicated elevated serum PCB levels (mean: 3.7 ppb; maximum: 9.6 ppb) were correlated with self-reported diabetes and liver disease in both the Red Cliff cohort and in the ongoing Ojibwa cohort. Concentrations of hair mercury were <10 ppm (range: 0.321 ppm–9.06 ppm) and serum PCBs were <12 ppb. The average annual fish consumption rate was 23 grams per day. To date, no neurobehavioral effects have been confirmed in the Ojibwa cohort. The investigators have concluded that the Native Americans in their study tended to be higher consumers of fish, have elevated levels of mercury and PCBs in comparison with the overall population, and may be at higher risk for health effects. The results of these studies are presently being evaluated and interpreted.

Sociodemographics

Studies of susceptible populations in the Great Lakes basin indicate wide variation in social behaviors. For example, fish is an essential component of the diets of certain local minority populations and Native Americans, and these persons also eat fish that have higher levels of contaminants. However, knowledge of and adherence to health advisories for sport-caught fish differs by population. An epidemiologic study

of Native American men found that 97% were aware of the advisories regarding eating local fish (Fitzgerald et al. 1996). Waller et al. (1996) indicated that knowledge of fish advisories may be low among minority populations, and that these populations tend to consume fish that have higher levels of contaminants (e.g., catfish and buffalo).

A survey conducted by West (1993) found that licensed anglers had considerable knowledge of fish advisories. Seventy-one percent of these respondents reported they heeded the fish advisories and changed the species of GLSF in their diets. Sixty-five percent of respondents reported not eating the skin of fish, with similar response rates for Native American, African American, and white persons. Although 49% of licensed anglers followed recommendations to trim off the fat on the fish, only 26% of African Americans reported this behavior. Only 33% of the general population broiled, grilled, or baked fish as recommended by fish advisories, with lower percentages reported for Native Americans and African Americans.

In comparison, Tilden et al. (1997) conducted a population-based telephone survey of adult residents in the eight Great Lakes states to estimate the prevalence of GLSF consumption during the preceding year and awareness of a fish consumption health advisory. An estimated 4.7 million adults had eaten GLSF during that time period; 43.9% of those respondents were women. Although 49.9% of respondents who had eaten GLSF were aware of a health advisory, this reported awareness differed significantly by sex: 58.2% of men and 39.1% of women were aware. The researchers used logistic regression to determine that awareness was associated with male sex (odds ratio [OR]=2.3; 95% CI=1.5–3.5), white race (OR=4.2; 95% CI=1.9–9.1, college degree (OR=3.1; 95% CI=1.3–7.6, and consuming >24 GLSF meals during the year (OR=2.4; 95% CI=1.4–4.3). Only half of respondents who had eaten GLSF reported awareness of a health advisory concerning eating such fish. In addition, the researchers indicated 80% of minorities who had eaten GLSF were unaware of the fish advisories. Awareness was especially low among women, suggesting the need for targeted risk communication programs.

V. EXPOSURE INTERPRETATION

Exposure to PCBs as derived or measured for use in epidemiologic analyses does not always correspond with the units in which humans eat fish or other foods. Some calculations have been undertaken to provide a perspective on the quantities identified in two studies discussed in this summary.

A sample of 2,451 licensed anglers in Michigan (representing 0.7% of all licensed anglers in the state) participated in the 1991–1992 Michigan Sport Anglers Fish Consumption Survey, which was administered to determine the estimated number of anglers who eat GLSF. Persons who reported eating noncommercial or sport fish kept records of the amount of fish they had eaten. The mean amount (and upper 95th percentile) of salmon eaten by weekly salmon consumers was 35.6 (40.0) g/day for chinook, 41.6 (74.8) g/day for coho, and 42.6 (86.5) g/day for unidentified noncommercial salmon species.

Lake Michigan coho salmon (average length: 23 inches) contain an average of 0.75 ppm total PCBs, and chinook salmon (average length: 28 inches) contain an average of 1.1 ppm total PCBs (Michigan Department of Environmental Quality, 1996). If cleaning and cooking the fish reduce PCB levels by 50%, daily PCB intakes for persons who eat fish obtained from Lake Michigan would range from an average of 15 µg PCB/day (i.e., weekly coho salmon consumption) to 40 µg PCB/day at the upper 95th percentile of persons who eat unidentified noncommercial salmon species. For a woman who weighs 60

kg, the corresponding daily intake would range from 0.25 to 0.67 µg PCBs/kg/day. West et al. (1993) reported that 50–60% of this angler population follow recommendations about trimming the skin and belly fat off of the fish they eat, and about 30% broil, grill, or bake their fish.

In comparison, the State of Minnesota (Shubat 1990) estimated a PCB intake of 30.5 µg PCBs per day for those women in the Jacobson et al. study (1984, 1985, 1990) (i.e., in the Jacobson study, children had neurologic effects associated with maternal exposure). For the women (average weight 62 kg) who were evaluated, the estimated average daily PCB dosage associated with adverse effects (i.e., when fish were assumed to be the only PCB source) was 0.49 µg PCBs/kg/day. The estimated PCB intake in Jacobson's et al. studies was about 24 times greater than the recommended ATSDR Minimum Risk Levels (MRL) or the EPA RfD (ATSDR 1997). In the Jacobson et al. study, participants whose consumption amounts and species of fish eaten were based on recall of an average of 16.1 years (range: 1-40 years) before the study reported consuming the equivalent of an average 6.7 PCB-kg/year (standard deviation [SD]: 5.8; range:1.2–41.7 PCB-kg). These estimates were based on the highest annual rate of consumption, a cumulative rate during pregnancy, and the assumption that 0.2 kg of fish were eaten at each meal. PCB concentrations for Jacobson's derivations in 1984 were based on data reported by Humphrey (1976). During the year before pregnancy, these women ate an estimated 4.4 PCB-kg (SD: 4.4; range: 0.0– 26.5 PCB-kg).

Studies on skin removal and fish trimming practices indicated that PCBs and DDT can be reduced about 50% (Reinert et al. 1972; Skea et al. 1979; Voiland et al. 1991). PCB reductions attributed to cooking were more variable (Zabik 1979, 1993). A Great Lakes States Task Force has recommended considering an overall 50% single lipophilic contaminant reduction from preparation and cooking to be a realistic expectation for salmon and lake trout (Anderson et al. 1993).

In the Lonky et al. (1996) study, amounts were assessed just before or at the onset of pregnancy. High-exposure women ate an estimated average of about 30 g/day of Lake Ontario fish. PCB-equivalents were calculated on the basis of the fish species eaten and reported trimming and cooking behaviors. In 1991, Lake Ontario coho and chinook salmon contained an average of 1.6 ppm total PCBs. In 1989, lake trout averaged 2.5 ppm (Forti 1996). If the same 50% reduction in PCB levels is applied to the results of the West et al. (1993) study, women in the high-exposure group would have had an estimated daily exposure of 32 µg PCB/day (or an average daily intake of 0.45 µg PCB/kg–day for the women weighing 60 kg in the high-exposure group) if equal amounts of salmon and trout were eaten.

Thus, despite sources of uncertainty in the Jacobson et al. (1996) and the Lonky et al. (1996) studies and in estimations of PCB exposures, the derived maternal PCB intakes associated with developmental effects were notably similar. Moreover, the PCB intakes resulting from consumption for some Great Lakes fish (e.g., salmon) reported by West et al. (1993) were similar to those estimates by Jacobson and Lonky. In addition, PCB doses associated with adverse neurobehavioral effects in monkeys were similar to those associated with adverse neurobehavioral findings in humans.

VI. SUMMARY

The following findings summarize the information in this report.

- Susceptible human populations are being exposed to PCBs via fish consumption.

- Many residents in the Great Lakes basin ate more fish than the 6.5 g/day often estimated for the general U.S. population.
- High consumption of PCB-contaminated GLSF is associated with increased body burden levels of PCBs.
- These body burden levels are higher than in the general U.S. population.
- Men eat more fish than women eat, and both men and women eat Great Lakes fish during most of their reproductive years.
- Neurobehavioral and developmental deficits occur in newborns exposed in utero to PCBs; and continue in school-aged children. Some observed results have also been associated with prenatal exposure to heavy metals (e.g., mercury and lead).
- Current fish intake rates and derived PCB exposures for some persons are similar to those associated with adverse health effects among children included in epidemiologic studies.
- Reproductive function might be disrupted by exposure to PCBs, although more research is required to resolve this possibility.
- Exposure to PCBs in fish places adult men, women beyond their reproductive years, and the elderly at increased risk for cancer; they might also be at increased risk for immune and endocrine system effects.
- Exposure to PCBs might increase the risk for clinical effects such as non-Hodgkin's lymphoma, diabetes, and liver disease.
- Although PCBs are the primary contaminants associated with increased risk resulting from consumption of GLSF, other compounds that also contribute to the overall increased risk include organochlorine pesticides, mercury, dioxin, and dibenzofurans.

The research findings discussed in this summary have strong public health implications when viewed together with earlier findings. Data for more than 10,000 at-risk persons are being collected, analyzed, and interpreted. Initial research findings on body burdens and adverse health effects support earlier reports of an association between eating contaminated GLSF and body burdens of persistent toxic substances. These body burdens, reflecting exposures to a variety of persistent substances such as PCBs and organochlorine pesticides, are three- to four-fold higher in some groups than in the general U.S. population. Research is ongoing to assess other potential effects of these contaminants on human health.

As research progresses, more will become known about the human health implications of PCBs and other contaminants found in the environment. However, enough scientific information is now available to warrant actions by health care providers, public health officials, and environmental organizations.

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