# HEALTH CONSULTATION

## TECHNICAL SUPPORT DOCUMENT FOR A POLYCHLORINATED BIPHENYL REFERENCE DOSE (RfD) AS A BASIS FOR FISH CONSUMPTION SCREENING VALUES (FCSVs)

**November 1, 2012**

Prepared by:

Michigan Department of Community Health
Under A Cooperative Agreement with the
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

# Table of Contents



# List of Tables

## List of Figures



## List of Equations



## List of Appendices

# Acronyms and Abbreviations

| | |
|---|---|
| / | per |
| ° | degree |
| A | Arctic beluga blubber |
| AC | Asian-Canadians |
| AhR | arylhydrocarbon receptor |
| AhRR | AhR repressor |
| ALT | alanine aminotransferase |
| AOM | acute otitis media |
| ARNT | Aryl Hydrocarbon Receptor Nuclear Translocator |
| AST | aspartate aminotransferase |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMD | Benchmark dose |
| BMDL | lower limit of a Benchmark dose |
| BMI | body mass index |
| BMMC | bone marrow-derived mast cells |
| BROD | benzyloxyresorufin O-dearylase |
| BUN | blood urea nitrogen |
| BW | body weight |
| CA EPA | California Environmental Protection Agency |
| CALUX | chemical-activated luciferase gene expression |
| CASA | computer-aided sperm motility analyzer |
| CD | clusters of differentiation |
| CEPA | Canadian Environmental Protection Act |
| CHAMACOS | Center for the Health Assessment of Mothers and Children of Salinas |
| CHDS | Child Health and Development Study |
| CI | confidence interval |
| COX-2 | cyclooxygenase-2 |
| CRISMAS | Copenhagen Rigshospitalet Image house Sperm Motility Analysis System |
| CSF | cancer slope factor |
| CYP | cytochrome P450 |
| DDE | dichlorodiphenyl dichloroethylene |
| DDT | dichlorodiphenyl trichloroethane |
| dl | dioxin-like |
| DNA | deoxyribonucleic acid |
| EC | Euro-Canadians |
| $ED_{10}$ | 10% increased incidence in liver tumors |
| EPA | United States Environmental Protection Agency |

| | |
|---|---|
| EPIC | European Prospective Investigation into Cancer and Nutrition |
| EROD | ethoxyresorufin O-deethylase |
| F0 | parental |
| F1 | first filial (offspring of F0) |
| F2 | second filial (offspring of F1) |
| FAWCAC | Fish and Wildlife Contaminant Advisory Committee |
| FCSV | Fish Consumption Screening Value |
| FFS | female factor subfertility |
| FT4 | free thyroxine |
| g | grams |
| GGT | γ-glutamyl transferase |
| GLSFATF | Great Lakes Sport Fish Advisory Task Force |
| GST | glutathione S-transferase |
| Hb | hemoglobin concentration |
| Hct | hematocrit |
| HDL | high-density lipoprotein |
| IARC | International Agency for Research on Cancer |
| Ig | immunoglobulin |
| IQ | Intelligence Quotient |
| IUPAC | International Union of Pure and Applied Chemistry |
| KC500 | Kannechlor 500 |
| kg | kilogram |
| kg-day | kilogram-day |
| L | liter |
| $LED_{10}$ | 95% lower confidence bound on the $ED_{10}$ |
| LH | Lake Huron |
| LO | Lake Ontario |
| LOAEL | lowest observed adverse effect level |
| LRTI | lower respiratory tract infections |
| MCH | mean cell hemoglobin |
| MCHC | mean cell hemoglobin concentration |
| MCV | mean cell volume |
| MDCH | Michigan Department of Community Health |
| MDNRE | Michigan Department of Natural Resources and Environment |
| MFCAP | Michigan Fish Consumption Advisory Program |
| MFCMP | Michigan Fish Contaminant Monitoring Program |
| MFS | male factor subfertility |
| mg | milligram |
| ml | milliliter |
| MoE | Ministry of Environment (Ontario, Canada) |
| MRL | Minimal Risk Level |
| mRNA | messenger ribonucleic acid |

| | |
|---|---|
| MROD | methoxyresorufin O-deethylase |
| NAG | neutral α-glucosidase |
| NEC | Northeast Cape |
| ng | nanograms |
| NHANES | National Health and Nutrition Examination Survey |
| NHL | Non-Hodgkin's lymphoma |
| NHNP | normal human neural progenitor |
| nmol | nanomole |
| NOAEL | no observed adverse effect level |
| NYSACS | New York State Angler Cohort Study |
| OH-PCBs | hydroxylated polychlorinated biphenyls |
| PBB | polybrominated biphenyls |
| PBDE | polybrominated diphenyl ethers |
| PCB | polychlorinated biphenyl |
| PCDD | polychlorinated dibenzo-p-dioxin |
| PCDF | polychlorinated dibenzofurans |
| PCQ | polychlorinated quaterphenyls |
| pg | picograms |
| PHAH- | PCB congener mixture without PCB 153 |
| PHAH+ | PCB congener mixture with PCB 153 |
| pmol | picomole |
| PND | post-natal day |
| POPs | persistant organic pollutants |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| PROD | pentoxyresorufin O-deethylase |
| PTDI | provisional tolerable daily intake |
| RBC | red blood cell count |
| RfD | reference dose |
| SD | standard deviation |
| SE | standard error |
| SHBG | sexual hormone-binding globulin |
| SL | St Lawrence beluga blubber |
| T2DM | type 2 diabetes mellitus |
| T3 | triiodothyronine |
| T4 | thyroxine |
| T4-UDP-GT | UDP-glucuronosyltransferase |
| TBG | thyroxine-binding globulin |
| TCDD | 2,3,7,8-tetrachlorodibenzo-p-dioxin |
| TDI | tolerable daily intake |
| TEFs | toxic equivalency factors |

| | |
|---|---|
| TEQ | toxic equivalent value |
| TRβ | recombinant human thyroid receptor |
| TSH | thyroid stimulating hormone |
| TTP | time to pregnancy |
| TTR | trandthyretin |
| U.S. | United States |
| U.S.S.R. | Union of Soviet Socialist Republics (country no longer exists) |
| UDPGT | UDP glucuronosyltransferase |
| UF | uncertainty factors |
| UGT | UDP-glucuronosyl-transferase |
| URTI | upper respiratory tract infections |
| UV | ultraviolet |
| WHO | World Health Organization |
| XRE | xenobiotic response element |
| $ZnSO_4$ | zinc sulfate |
| µg | microgram |

## Disclaimer

The technical support document includes and relies on scientific information that was not available to Agency for Toxic Substances and Disease Registry (ATSDR) when the Toxicological Profile for Polychlorinated Biphenyls was finalized, and this document is not intended to replace ATSDR Minimal Risk Levels (MRLs) or recommendations.

## Summary

The Michigan Department of Community Health (MDCH) issues fish advisories for Great Lakes sport-caught fish. One of the contaminants present in the fish is polychlorinated biphenyls (PCBs), which are persistent organic pollutants. Exposure to PCBs has been linked to numerous human health effects, including impaired immune function, cancer, altered thyroid hormones, and reproductive effects. The purpose of this document is to review the recent literature on PCBs and recommend changes in the Michigan Fish Consumption Advisory Program (MFCAP), if necessary, to ensure that the consumption advice remains protective of public health and the basis of the screening levels can be evaluated and updated as needed.

MDCH's conclusion about the presence of PCBs in Michigan fish:
*MDCH concludes that eating unlimited amounts of certain fish from lakes in Michigan throughout the year could harm people's health. This is a public health hazard.* Fish consumption advisories may be required for certain fish species at specific locations. People with higher fish consumption have been shown to have higher levels of PCBs than the general population. Other studies have associated health effects with increased PCB levels found in fish eaters.

Next steps:
Use the proposed reference dose (RfD), protective of immunological effects and other non-carcinogenic effects, to develop updated PCB fish contaminant screening values (FCSVs) and utilize these values to provide fish consumption advice in Michigan. MDCH will issue advisories in the Michigan Fish Advisory using new PCB FCSVs.

Continue monitoring of fish in Michigan for PCBs. The MDCH Analytical Chemistry Laboratory will continue to screen fish, collected for the Michigan Fish Contaminant Monitoring Program (MFCMP; administered by the Michigan Department of Environmental Quality [MDEQ]).

Provide the Fish and Wildlife Contaminant Advisory Committee (FAWCAC) and other relevant groups (Great Lakes Sport Fish Advisory Task Force and Great Lakes Human Health Network) with a copy of this document. MDCH will share a copy of this document so that FAWCAC and other relevant groups will have this information.

## Purpose and Health Issues

MDCH is in the process of updating the FCSVs used in the MFCAP. PCBs are persistent organic pollutants that are present in Great Lakes fish. Exposure to PCBs has been linked to numerous

human health effects, including impaired immune function, cancer, altered thyroid hormones, neurodevelopmental and reproductive effects. The purpose of this document is to review the recent literature on PCBs and recommend changes in the MFCAP, if necessary, to ensure that the consumption advice remains protective of public health and the basis of the screening levels can be evaluated and updated as needed.

# Background

Introduction

PCBs were first synthesized in 1888 (Feeley 1995) and were later produced for commercial purposes. Commercial mixtures of PCBs are a complex mix of isomers and congeners (Safe et al. 1985). Individual PCB isomers or congeners are described according to the position of the chlorine atom(s) on the molecule (Abramowicz 1995). Isomers of PCBs are those with the same number of chlorines, no matter the location of the chlorines. An example of isomers are 2,2',5-trichlorobiphenyl and 2,4,4'-trichlorobiphenyl,which both contain three chlorines. Congeners of PCBs are those with different numbers of chlorines (Giesy and Kannan 1998), for example 2,4,4'-trichlorobiphenyl (three chlorines) and 3,3',4,4'-tetrachlorobiphenyl (four chlorines). Only a total of 130 congeners are expected to occur in commercial mixtures, although 209 congeners are theoretically possible (Feeley 1995). Along with the chemical name, such as 3,3',4,4'-tetrachlorobiphenyl (PCB 77), PCB congeners have identification numbers, ranging from 1 to 209, used by the International Union of Pure and Applied Chemistry (IUPAC).

Individual commercial mixtures have 60 to 90 congeners and were produced under the trade name Aroclor in the United States (Bedard et al. 2006). The last two digits of the four-digit number following "Aroclor" represent the percent of chlorine present in the mixture by weight. For example, Aroclor 1254 is 54% chlorine, by weight. Aroclor 1016, which does not follow the naming conventions, has 41% chlorine by weight (EPA 2008). Aroclor 1016 was developed later and had a different proportion of congeners, but a similar percentage of chlorine, than Aroclor 1242. The Aroclor tradename was also used for mixtures of other polyhalogenated aromatic mixtures (Giesy and Kannan 1998).

Approximately 700,000 tons of PCBs were produced in the U.S. between 1929 and 1977 with about 75,000 tons exported. Global production was estimated to be 1.1 to 1.5 million tons from 1930 to 1993 with approximately one-third of that amount circulating in the global environment. Around 97% of the historical consumption was in the northern hemisphere (Erdal et al. 2008). PCB mixtures were produced and sold under different names in different countries, such as Clophens (Germany), Phenoclors and Pyralenes (France), Fenclors (Italy), Fenochlors (Spain), Kanechlors (Japan), Sovol (U.S.S.R.), Delor (Czechoslovakia), and Chlorofen (Poland) (Giesy and Kannan 1998).

PCBs are heat and fire resistant, have low electrical conductivity, and high thermal conductivity. Commercial use started in 1929, as dielectric and heat exchange fluids and lubricating oils (Skerfving et al. 1994). PCBs were used in transformers and electrical capacitors, hydraulic fluids, oil additives to paints, window caulking, ceiling and floor tiles (Carpenter 2006), solvent extenders, plasticizers, flame retardants, and organic diluents (Abramowicz 1995).

Western European and North American countries banned PCB production in the 1970s (Giesy and Kannan 1998). In the U.S., PCBs were only used in closed systems after 1977 with an U.S. Environmental Protection Agency (EPA) ban on use of mixtures with greater than 50 parts per million (ppm) in 1979 (Erdal et al. 2008). Eastern Europe and Russia did not ban PCB production until the early 1990s (Giesy and Kannan 1998). However, up to 200 chemical processes may generate PCBs as byproducts (Erdal et al. 2008).

Several hundred million pounds of PCBs were historically released to the environment (Abramowicz 1995). PCB congeners partition, chemically transform, and bioaccumulate over time and based on the position and number of chlorines (EPA 1996A). PCBs persist in sediment, accumulate in biota, and biomagnify through the food chain (Bedard et al. 2006). They accumulate in adipose tissue (fat) and their ability to be in adipose tissue (lipophilicity) increases with increasing chlorination (Skerfving et al. 1994).

The PCB mixtures currently found in the environment do not match congener profiles of commercial mixtures. Congener selective environmental processes, such as reductive dechlorination, alter the amount of specific congeners present (Ganey and Boyd 2005). The Great Lakes are a source of PCBs to the atmosphere, but the air-water exchange may be at equilibrium. PCBs remain in sediments, with the amount of time they remain there (mean residence times) varying by congener. For example, PCB 153 has a mean residence time of 110 years while PCB 180 has a mean residence time of 70 years (Erdal et al. 2008).

People with the most significant exposure to PCBs are industrial workers (occupational exposure) and people consuming freshwater fish from contaminated waterbodies (Cordle et al. 1982). An estimated total yearly intake for humans is 300 micrograms (µg)/person, with 70 to 72% of that amount due to fish consumption (Feeley 1995). Judd et al. (2004) estimated mean fish and other seafood consumption rates of 45 grams (g)/person/day for Michigan anglers and 18 g/person/day for Ontario anglers. Based on that estimated consumption, populations that eat contaminated fish, such as recreational anglers, Native American Tribes, and subsistence fishers may have a significant exposure to PCBs (Judd et al. 2004).

Physical and Chemical Parameters

There are theoretically 209 PCB congeners; all with their own metabolism and toxicity characteristics, but only about 130 of the congeners are likely to be part of the commercial mixtures (Skerfving et al. 1994; Feeley 1995). PCBs have good solubility in non-polar solvents, oils, and fats; a low vapor pressure; low electrical conductivity; high thermal conductivity; high ignition temperatures; and a high resistance to chemical factors (Beyer et al. 2008). Although all congeners are lipophilic (will dissolve in fats), there is increasing lipophilicity with increasing chlorination (Carpenter 2006).

Each biphenyl ring can have between one to 10 chlorines (EPA 2008). See Figure 1 for the basic structure of a PCB molecule. The two benzene rings that make up the biphenyl can rotate. When the two rings are in the same plane, the molecules are referred to as coplanar (planar). If the rings are at a 90 degree (°) angle to each other, the molecule is referred to as non-coplanar (non-planar) (Faroon et al. 2000). A coplanar conformation makes the PCB congener similar to the conformation of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (flat structure) (Safe et al. 1985).

The degree of planarity that a PCB congener has depends on the number of chlorine substitutions in the ortho positions (Faroon et al. 2000). Non- and mono-ortho PCBs have a coplanar conformation, which provides them with dioxin-like activity (Skerfving et al. 1994). Mono-ortho PCBs (chlorine substitution at one ortho position) partially reduces the ability of that congener to have dioxin-like activity. Di-ortho PCBs (chlorine substitutions at two ortho positions) have very little dioxin-like activity (Safe et al. 1985).

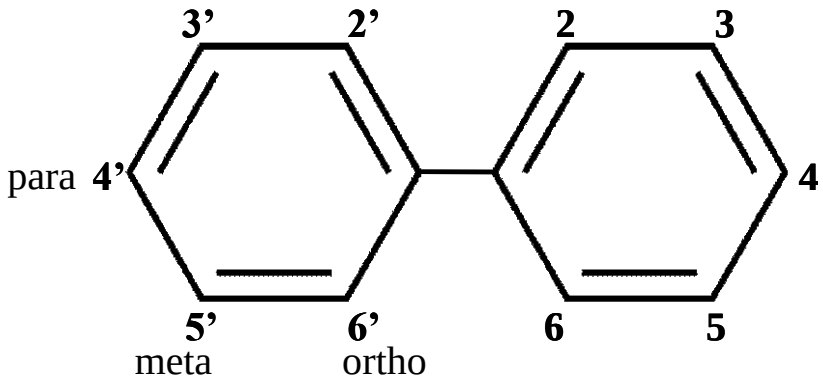


Figure 1: Basic structure of a PCB molecule. Chlorine can replace hydrogen on any of the four ortho (2', 6', 2, and 6), four meta (3', 5', 3, and 5) or two para (4' and 4) positions.

The number and position of chlorines on the molecule determine the physical and biological properties. The less chlorines present, the more water soluble, more volatile, and more easily metabolized. If there are a larger number of chlorines, the molecule is resistant to biodegradation and can bioaccumulate in the environment. Congeners with chlorines at the meta and para positions have a planar configuration and show dioxin-like activity, however, if there is more than one chlorine in an ortho position the molecule would not show significant dioxin-like activity (Carpenter 2006). Toxic equivalency factors (TEFs) for Aroclor 1248 and 1254 are similar (Burkhard and Lukasewycz 2008), indicating that they have a similar amount of dioxin-like activity. TEFs are established for dioxin-like compounds and represent the amount of dioxin-like activity a PCB congeners will have relative to TCDD, which has a TEF of 1.0. TEFs are multiplied by the amount of each PCB congener present in a sample and added together resulting in a toxic equivalent value (TEQ). Table 1 presents the TEFs for the coplanar PCB congeners.

PCB can biotransform or be modified in the environment to a hydroxylated form. Hydroxylated PCBs can be found in fish species from the Great Lakes. The oxygen and hydrogen (hydroxyl group) attached to the PCB increases the water solubility of the chemical, while leaving it hydrophobic enough to accumulate in aquatic organisms. The biotransformation of PCBs depends on chlorine substitution patterns (Buckman et al. 2006).

Along with biotransforming, PCBs can degrade under various conditions. Biological systems can degrade PCBs through an aerobic oxidative process or an anaerobic reductive process. Aerobic degradation occurs mainly to congeners with fewer chlorines, while anaerobic degradation affects more highly chlorinated PCB congeners. Anaerobic degradation preferentially removes

chlorines at meta and para positions, increasing the amount of lower chlorinated congeners with chlorine substitutions at ortho positions. Anaerobic degradation results in reduced levels of coplanar dioxin-like PCBs (Abramowicz 1995).

Table 1: Coplanar Polychlorinated biphenyls (PCBs) and International Union of Pure and Applied Chemistry (IUPAC) identification numbers along with toxic equivalency factors (TEFs) from the World Health Organization (WHO) (Van den Berg et al. 2006).

| Type | IUPAC identification number | Name | TEF |
|---|---|---|---|
| Non-ortho | 77 | 3,3',4,4'-tetrachlorobiphenyl | 0.0001 |
| | 81 | 3,4,4',5-tetrachlorobiphenyl | 0.0003 |
| | 126 | 3,3',4,4',5-pentachlorobiphenyl | 0.1 |
| | 169 | 3,3',4,4',5,5'-hexachlorobiphenyl | 0.03 |
| Mono-ortho | 105 | 2,3,3',4,4'-pentachlorobiphenyl | 0.00003 |
| | 114 | 2,3,4,4',5-pentachlorobiphenyl | 0.00003 |
| | 118 | 2,3',4,4',5-pentachlorobiphenyl | 0.00003 |
| | 123 | 2',3,4,4',5-pentachlorobiphenyl | 0.00003 |
| | 156 | 2,3,3',4,4',5-hexachlorobiphenyl | 0.00003 |
| | 157 | 2,3,3',4,4',5'-hexachlorobiphenyl | 0.00003 |
| | 167 | 2,3',4,4',5,5'-hexachlorobiphenyl | 0.00003 |
| | 189 | 2,3,3',4,4',5,5'-heptachlorobiphenyl | 0.00003 |

Analytical Methods

Total PCB amounts can be reported from either the Aroclor analysis (peak matching) or congener analysis (peak summing). The peak matching technique uses commercial mixtures, Aroclors, as a standard and peaks in the samples are matched to a certain number of peaks from that standard. Weathering of PCBs may change the pattern and make peak matching difficult (Giesy and Kannan 1998). The Aroclor analysis does not adequately represent the bioconcentrated PCB mixtures found in fish tissues (EPA 2000A).

The peak summing method for measuring total PCBs uses individual congeners as standards and adds all the peaks from the samples (Giesy and Kannan 1998). Muir and Sverko (2006) reported that a minimum of seven PCBs (28/31, 52, 101/90, 118, 138, 153, and 180) are essential for monitoring PCB levels in fish and food products globally.

The MDCH Analytical Laboratory measures PCB levels based on individual congeners (MDEQ 2010) using gas chromatography with electron capture detection, similar to EPA method 8082 (M. Geiger, personal communication 2010). The amount of each individual congener is added together for the total PCBs present in the fish tissue sample (MDEQ 2010). The World Health Organization (WHO) lists the dioxin-like (dl) PCB congeners as 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189 (Van den Berg et al. 2006). Michigan tests for nine of the dl-PCB congeners (77, 126, 105, 118, 156, 157, 167, and 180). Certain fish are analyzed for all of the coplanar congeners (M. Geiger, personal communication 2010). Along with inclusion in the total PCB value, coplanar PCB congeners are included in the TEQ value. The TEQ is an estimate total

2,3,7,8-TCDD–like activity of the mixture (Van den Berg et al. 2006**)**. The TEFs for the coplanar PCBs are multiplied by the amount present, and will give a TEQ that can then be added to the TEQ of other dioxin-like chemicals.

Fish Advisories

As of 1998, 37 states had issued 679 fish advisories due to PCB levels. PCB levels in fish may be 2,000 to 1,000,000 times higher than concentrations found in surrounding waters (EPA 1998). In 2008, 1,025 fish advisories were issued due to the presence of PCBs, slightly up from the 1,023 fish advisories issued in 2006 (EPA 2009).

The California EPA (CA EPA) considered both a non-cancer and a cancer risk value as possibilities for a fish advisory tissue level. The CA EPA chose a non-cancer risk reference dose (RfD) of $2 \times 10^{-5}$ milligrams per kilogram per day (mg/kg-day), which was calculated from the EPA's RfD for Aroclor 1254. Using that value, three fish consumption recommendations are set based on fish tissue PCB concentrations. These consumption recommendations are for three meals per week (PCB levels less than or equal to 21 parts per billion [ppb] [0.021 ppm]), two meals per week (PCB levels greater than 21 to 41 ppb [0.021 to 0.041 ppm]), and one meal per week (PCB levels are greater than 42 to 120 ppb (0.042 to 0.12 ppm). The CA EPA recommends no consumption for fish with PCB levels greater than 120 ppb (0.12 ppm) (CA EPA 2008).

Recommendations for bluefish consumption, based on PCB concentrations, were set by an interstate workgroup composed of states along the Atlantic Ocean. Recommendations were calculated for an excess carcinogenic risk of not more than one additional cancer in 100,000 people or a non-cancer risk with or without PCB reduction during cooking. Consumption of one meal per week was recommended for fish ranging from 11 to 87 ppb PCBs and one meal per month was recommended for fish ranging from 43 to 346 ppb, depending on the parameters. Authors of the report highlighted the possibility of a neuropsychological endpoint being the most sensitive for humans; however, no points of departure could be identified from currently existing studies for use in development of a reference dose (ACIW 2008).

The Ministry of the Environment in Ontario, Canada uses the consumption restriction values derived from Health Canada's two guidelines for PCBs. Consumption restrictions are issued when the PCB fish tissue levels are higher than 0.105 ppm. The Ministry of the Environment recommends no consumption when PCB fish tissue levels are above 0.844 ppm, for the general population, and 0.211 ppm, for the sensitive population, which is women of childbearing age and children under 15 years of age (MoE 2009).

Currently, MDCH issues fish advisories for PCBs based on the total concentration of all congeners found in a fish tissue sample. In addition, MDCH includes the measured concentrations of dioxin-like PCBs in the calculation of a total dioxin TEQ for that sample. In this way, MDCH accounts for both the dioxin-like and non-dioxin-like mechanisms of toxicity when issuing fish advisories in Michigan. MDCH currently has two different protocols for PCB trigger levels, one for the general population (men over age 15 and women over age 45) and one for the sensitive population (children under 15 years of age and women ages 15 to 45). MDCH advises the general population to restrict consumption of fish when 10% of the fish of that species and length have PCB tissue levels above 2.0 ppm. If 50% of the fish tissue levels are

above 2.0 ppm, MDCH recommends that the general population not eat those fish. For the sensitive population, MDCH uses the health protective value of 0.05 µg/kg-day set by the Great Lakes Sport Fish Advisory Task Force (GLSPATF 1993). That value was selected using a weight-of-evidence approach and is protective of immune system alterations (GLSPATF 1993). Five advisory categories were developed from the health protective value of 0.05 µg/kg-day, and fish are placed in categories, typically due to median total PCB concentration. The advisory levels include an assumption of a 50% reduction of PCB levels for trimming and cooking. Table 2 presents the current MDCH consumption recommendations for the general and sensitive populations.

Table 2: Michigan Department of Community Health current polychlorinated biphenyl (PCB) fish tissue trigger level (in parts per million [ppm]), advisory levels, and consumption advice (MDNRE 2008).

| Consumption category | PCB fish tissue levels (median values for the sensitive population) |
|---|---|
| General Population | |
| One meal a week | 10% of the fish tissue levels for a particular species and length are above 2.0 ppm |
| Do not eat | 50% of the fish tissue levels for a particular species and length are above 2.0 ppm |
| Sensitive Population | |
| Unlimited | less than 0.05 ppm |
| One meal a week | 0.05 ppm to less than 0.2 ppm |
| One meal a month | 0.2 ppm to less than 1.0 ppm |
| Six meals a year | 1.0 ppm to less than 1.9 ppm |
| Do not eat | 1.9 ppm and above |

## Discussion

Environmental Contamination

*Atmospheric transport and deposition*

Although the U.S. banned production and sales of PCBs in 1976, PCBs are still in the atmosphere, and industrial and urban centers are still PCBs sources (Sun et al. 2006). PCBs are present in the atmosphere due to vaporization from products containing PCBs (primary source) and from the Great Lakes (secondary source) (Sun et al. 2007). Persistent toxic substances, such as PCBs, can be carried by air currents and can condense out of the vapor phase in cold polar air and be deposited in the snow (Carpenter et al. 2005).

Based on sampling stations along the shoreline of Lake Michigan, atmospheric PCBs from Chicago, IL, Milwaukee, WI, Toronto, Canada have been identified as potential sources of PCBs to Lake Michigan (Sun et al. 2006, Sun et al. 2007). PCBs in Chicago air have a half-life of three

to seven years, although the congener profile has remained similar over the years. Atmospheric PCB levels in Chicago are similar to other cities and sources are transformers, capacitors, municipal sludge drying beds, and landfills (Sun et al. 2006).

### *Great Lakes Fish Tissue Concentrations*

Great Lakes fish have been measured for PCB levels since the early 1980s. PCB levels were first measured using Aroclor standards and, more recently, using PCB congener standards. Tables 3, 4, 5, and 6 present mean levels of PCBs in fish from Lakes Superior, Erie, Huron, and Michigan. PCB levels calculated from Aroclor and congener standards were averaged for each species. Although some data may no longer be used in the MFCAP, all data were included in these tables. Some differences and variability of PCB levels in different fish species could be due to the number of samples. Some species were tested in all of the lakes, while other species, such as Siscowet, are unique to certain lakes. The species that were tested in all of the lakes were Chinook, Coho, Lake Whitefish, Rainbow Trout, Walleye, and Yellow Perch.

Table 3 presents the PCB levels in Lake Superior fish collected between 1984 and 2008. PCB levels ranged from 0.001 to 6.86 ppm. Siscowet, only caught from Lake Superior, had the highest mean PCB concentration of all the fish tested from Lake Superior, while Burbot had the lowest PCB levels.

Table 3: PCB levels (in parts per million [ppm]) in Lake Superior fish[a].

| Fish species | Year(s) collected | Sample number[b] | Mean[c] (ppm) ± SE[d] | Range (ppm) |
|---|---|---|---|---|
| Brown Trout | 1999 | 10 | 0.137 ± 0.025 | 0.025-0.336 |
| Burbot | 2006 | 10 | 0.021 ± 0.003 | 0.006-0.031 |
| Chinook | 1988-2000 | 27 | 0.426 ± 0.05 | 0.096-1.30 |
| Coho | 1994-1997 | 41 | 0.083 ± 0.01 | 0.026-0.29 |
| Lake Herring | 1994-2007 | 31 | 0.046 ± 0.007 | 0.001-0.136 |
| Lake Trout | 1984-2008 | 255 | 0.434 ± 0.043 | 0.002-6.096 |
| Lake Whitefish | 1984-2007 | 95 | 0.078 ± 0.004 | 0.013-0.208 |
| Longnose Sucker | 1998 | 10 | 0.078 ± 0.015 | 0.036-0.196 |
| Rainbow Trout | 2006 | 9 | 0.039 ± 0.01 | 0.014-0.10 |
| Siscowet | 1987-2007 | 148 | 0.82 ± 0.068 | 0.054-6.86 |
| Walleye | 2006 | 16 | 0.029 ± 0.006 | 0.005-0.105 |
| Yellow Perch | 1993 | 10 | 0.025 ± 0 | 0.025 |

a = Data is from the MFCMP database and was obtained from Joe Bohr, MDNRE.
b = Samples may be whole fish, skin-on fillets, or skin-off fillets.
c = PCB levels based on Aroclor and congener standards were averaged together.
d = SE is standard error.

PCB levels from Lake Erie fish are shown in Table 4. Fish were collected between 1985 and 2008, and PCB levels ranged from 0.015 to 33.929 ppm. Carp had the highest PCB levels, with a mean of 3.657 ppm. Yellow Perch had the lowest mean, at 0.122 ppm.

Table 4: PCB levels (in parts per million [ppm]) in Lake Erie fish[a].

| Fish species | Year(s) collected | Sample number[b] | Mean[c] (ppm) ± SE[d] | Range |
|---|---|---|---|---|
| Carp | 1985-2008 | 271 | 3.657 ± 0.250 | 0.034-33.929 |
| Channel Catfish | 1986-2008 | 40 | 2.666 ± 0.381 | 0.126-10.760 |
| Chinook | 1997 | 7 | 0.680 ±0.129 | 0.285-1.353 |
| Coho | 1984 | 15 | 0.387 ± 0.016 | 0.310-0.460 |
| Freshwater Drum | 1991-2006 | 32 | 0.598 ± 0.122 | 0.023-2.277 |
| Gizzard Shad | 1993-2006 | 15 | 0.9 ± 0.075 | 0.619-1.663 |
| Lake Whitefish | 1997 | 9 | 1.36 ± 0.191 | 0.412-2.301 |
| Largemouth Bass | 2006 | 20 | 0.477 ± 0.135 | 0.024-2.624 |
| Northern Pike | 1993 | 2 | 0.440 ± 0.090 | 0.35-0.530 |
| Rainbow Trout | 1997 | 10 | 0.493 ± 0.064 | 0.265-0.922 |
| Redhorse Sucker | 1993 | 10 | 1.118 ± 0.272 | 0.26-3.160 |
| Smallmouth Bass | 1997-2006 | 18 | 0.675 ± 0.071 | 0.317-1.552 |
| Walleye | 1986-2008 | 302 | 1.159 ± 0.071 | 0.020-6.382 |
| White Bass | 1993-2006 | 34 | 0.679 ± 0.050 | 0.299-1.425 |
| White Perch | 1995-2004 | 20 | 0.643 ± 0.071 | 0.172-1.380 |
| Yellow Perch | 1993-2006 | 57 | 0.122 ± 0.015 | 0.015-0.500 |

a = Data is from the MFCMP and was obtained from Joe Bohr, MDNRE.
b = Samples may be whole fish, skin-on fillets, or skin-off fillets.
c = PCB levels based on Aroclor and congener standards were averaged together.
d = SE is standard error.

PCB levels presented in Table 5 ranged from 0.001 to 31.8 ppm for the fish collected from Lake Huron. Fish from Lake Huron were collected from 1983 to 2008. Similar to fish tested from Lake Erie, Carp had the highest mean PCB levels, with 2.301 ppm. Round goby, an invasive species, had the lowest PCB levels, at 0.013 ppm. Yellow Perch had the next lowest PCB level, with 0.054 ppm.

PCB levels from fish collected, between 1983 and 2008, in Lake Michigan are presented in Table 6. The PCB levels ranged from 0.001 to 35.78 ppm. As with fish from Lakes Erie and Huron, the highest mean PCB level was in Carp (2.743 ppm). Rock Bass had the lowest mean PCB level, at 0.002 ppm.

Table 5: PCB levels (in parts per million [ppm]) in Lake Huron fish[a].

| Fish species | Year(s) collected | Sample number[b] | Mean[c] (ppm) ± SE[d] | Range |
|---|---|---|---|---|
| 9-spine stickleback | 2005 | 12 | 0.069 ± 0.001 | 0.062-0.071 |
| Alewife | 1993-2007 | 159 | 0.26 ± 0.002 | 0.102-0.27 |
| Brown Trout | 1986-1993 | 57 | 0.972 ± 0.082 | 0.351-2.943 |
| Burbot | 1990 | 4 | 0.161 ± 0.07 | 0.079-0.37 |
| Carp | 1984-2008 | 409 | 2.301 ± 0.111 | 0.026-13.540 |
| Channel Catfish | 1984-2005 | 170 | 1.641 ± 0.203 | 0.07-31.8 |
| Chinook | 1983-1998 | 296 | 0.871 ± 0.024 | 0.13-2.38 |
| Chub | 1993 | 4 | 0.2 ± 0.046 | 0.084-0.301 |
| Coho | 1983-1998 | 83 | 0.58 ± 0.043 | 0.062-3.060 |
| Freshwater Drum | 1986-2007 | 11 | 0.059 ± 0.016 | 0.001-0.190 |
| Lake Trout | 1983-2007 | 256 | 1.042 ± 0.050 | 0.110-6.307 |
| Lake Whitefish | 1983-2007 | 81 | 0.295 ± 0.022 | 0.025-0.965 |
| Northern Pike | 1986-2004 | 21 | 0.067 ± 0.016 | 0.002-0.325 |
| Rainbow Trout | 1991-1993 | 20 | 0.517 ± 0.048 | 0.138-1.110 |
| Round goby | 2007 | 60 | 0.013 ± 0.001 | 0.003-0.026 |
| Smelt | 2005 | 40 | 0.019 ± 0.001 | 0.012-0.022 |
| Spottail Shiner | 1995-2003 | 153 | 0.176 ± 0.003 | 0.080-0.215 |
| Walleye | 1984-2008 | 410 | 0.773 ± 0.047 | 0.005-7.740 |
| White Bass | 1993-2008 | 31 | 0.754 ± 0.119 | 0.069-2.290 |
| White Perch | 1994 | 8 | 0.506 ± 0.067 | 0.358-0.953 |
| White Sucker | 1987-2004 | 49 | 0.185 ± 0.029 | 0.011-1.080 |
| Yellow Perch | 1987-2004 | 187 | 0.054 ± 0.005 | 0.001-0.534 |

a = Data is from the MFCMP and was obtained from Joe Bohr, MDNRE.
b = Samples may be whole fish, skin-on fillets, or skin-off fillets.
c = PCB levels based on Aroclor and congener standards were averaged together.
d = SE is standard error.

Chinook, Coho, Lake Whitefish, Rainbow Trout, Walleye, and Yellow Perch were collected and tested from all four lakes. Differences are present between PCB levels from fish collected from different lakes. These differences might be due to different numbers of fish that were collected from each lake and differences in the sizes or ages of the fish.

Table 6: PCB levels (in parts per million [ppm]) in Lake Michigan fish[a].

| Fish species | Year(s) collected | Sample number[b] | Mean[c] (ppm) ± SE[d] | Range |
|---|---|---|---|---|
| Brown Trout | 1986-2003 | 95 | 1.333 ± 0.085 | 0.311-5.960 |
| Burbot | 1991-2001 | 19 | 0.128 ± 0.035 | 0.005-0.600 |
| Carp | 1988-2008 | 146 | 2.743 ± 0.298 | 0.019-34.906 |
| Chinook | 1983-1997 | 463 | 1.234 ± 0.026 | 0.010-3.950 |
| Coho | 1983-1998 | 563 | 0.644 ± 0.015 | 0.050-2.410 |
| Lake Trout | 1983-2006 | 279 | 1.809 ± 0.161 | 0.046-35.780 |
| Lake Whitefish | 1983-1999 | 119 | 0.569 ± 0.035 | 0.010-2.530 |
| Longnose Sucker | 1988-2005 | 31 | 1.322 ± 0.180 | 0.110-3.900 |
| Northern Pike | 1987 | 10 | 0.235 ± 0.084 | 0.036-0.960 |
| Rainbow Trout | 1985-2004 | 104 | 0.580 ± 0.032 | 0.055-1.321 |
| Redhorse Sucker | 2004-2008 | 20 | 0.110 ± 0.024 | 0.009-0.369 |
| Rock Bass | 2004-2008 | 18 | 0.002 ± 0.0005 | 0.001-0.009 |
| Smallmouth Bass | 1992-2008 | 53 | 0.078 ± 0.015 | 0.001-0.537 |
| Splake | 1992-1993 | 7 | 1.950 ± 0.261 | 1.040-2.940 |
| Walleye | 1987-2007 | 130 | 0.903 ± 0.068 | 0.010-4.678 |
| White Sucker | 1988-2005 | 29 | 0.272 ± 0.052 | 0.017-1.120 |
| Yellow Perch | 1986-1997 | 180 | 0.086 ± 0.005 | 0.025-0.650 |

a = Data is from the MFCMP and was obtained from Joe Bohr, MDNRE.
b = Samples may be whole fish, skin-on fillets, or skin-off fillets.
c = PCB levels based on Aroclor and congener standards were averaged together.
d = SE is standard error.

Exposure Pathways Analysis

An exposure pathway contains five elements: (1) the contaminant source, (2) contamination of environmental media, (3) an exposure point, (4) a human exposure route, and (5) potentially exposed populations. An exposure pathway is complete if there is a high probability or evidence that all five elements are present. Table 7 describes human exposure to PCBs from ingestion of fish.

Table 7: Exposure pathway for human exposure to polychlorinated biphenyls (PCBs).

| Source | Environmental Medium | Exposure Point | Exposure Route | Exposed Population | Time Frame | Status |
|---|---|---|---|---|---|---|
| Historical use and atmospheric deposition in the Great Lakes | Fish (contamination from the water and sediments magnifying in the food web) | Great Lakes, inland lakes, or river fish | Ingestion | Anyone who eats Great Lakes, inland lakes, or river fish (residents and tourists) | Past, Present, and Future | Complete |

People who reported Great Lakes fish consumption have had blood PCB levels higher than populations who ate little to no fish (Anderson et al. 1998, Hanrahan et al. 1999). It should be noted that not all studies have identified a statistical association between PCB levels and fish consumption.

## Toxicological Evaluation

### *Toxicokinetics*

PCBs are efficiently absorbed from the gastrointestinal tract and respiratory system of mammals and then rapidly distributed throughout the body. It is estimated that greater than 90% of the PCBs are absorbed from the gastrointestinal tract (Feeley 1995). PCBs can also be absorbed through the skin (Skerfving et al. 1994).

After absorption, high PCB concentrations initially occur in muscle and liver, followed by redistributed to adipose (fat) and other lipid-containing tissues such as skin (Kimbrough and Krouskas 2003). Redistribution occurs mostly with higher chlorinated congeners that are less easily metabolized, which then build up in adipose tissues and can alter lipid metabolism (Kimbrough and Krouskas 2003; Carpenter 2006).

PCBs reach a developing fetus by crossing the placenta. However, cord blood PCB levels can often be lower than levels in maternal blood due to lower fat content in cord blood. PCBs are readily excreted in human milk (Skerfving et al. 1994).

PCBs are metabolized in the liver by the cytochrome P450 dependent monooxygenase system with the lower chlorinated congeners being more rapidly metabolized and eliminated (Carpenter 2006). PCBs show a biphasic elimination, with an initial elimination phase that is consistent for all the congeners, then a later longer elimination phase that is congener dependent. High doses of PCBs are eliminated more quickly than lower doses. Main excretory routes for PCBs are bile and breast milk, with smaller amounts eliminated in feces, hair, and urine (Feeley 1995).

PCBs are only slowly eliminated from human bodies. The rate at which a PCB is eliminated is called a “half-life” and is defined as the amount of time it takes for half of a dose of PCBs to be eliminated from the body. Different PCB congeners have different half-lives, depending on the degree of chlorination (Skerfving et al. 1994). Because PCBs are eliminated so slowly, they can build up in the body if people continue to take in PCBs over time. The level of PCBs in body tissues is called the *body burden* and may affect metabolism and elimination.

In humans, PCB half-lives are long and can vary from three to five years with a high body burden and 13 to 17 years with a low body burden (Carpenter 2006). Because they are less easily metabolized and eliminated, highly chlorinated PCB congeners tend to remain in the body longer (Hsu et al. 2005).

Additional discussion of Toxicokinetics is provided in Appendix B.

*Biomonitoring in Great Lakes sport fish consumers*

PCBs bioaccumulate (build up) in body fluids and tissues with higher fat content including adipose tissue, blood lipids, and breast milk.[1] PCB levels in breast milk are typically higher than in blood because the lipid content of breast milk (45 g lipids/liter [L]) is higher than that of blood serum (6.36 g lipids/L [Bernert et al. 2007]). Body burdens of PCBs typically increase with increasing age (Schantz et al. 2001; Nichols et al. 2007).

An estimated 4.2 million adults consume Great Lakes sport fish annually. Beginning in the 1980's, several investigations have been conducted to evaluate intake and body burden of PCBs, as well as health effects among Great Lakes sport fish consumers (Anderson et al. 2008).

Ojibwa tribal members, 48 female and 41 male, were assessed for PCB levels. The participants ranged in age from 18 to 71 with a mean age of 37.9 years. Blood samples were available for 75 individuals, and 66 samples were analyzed for PCB levels. For 11 participants, PCB levels ranged from below the level of quantitation to 1.6 ppb. For the other 55 participants, PCB levels had a mean of 3.7 ppb and maximum value of 9.6 ppb. The three most frequently eaten species were lake trout, walleye, and whitefish. No association was identified between fish consumption and PCB serum levels. However, there was a significant association between fish consumption and age (Gerstenberger et al. 1997).

Consumers of sport fish from three of the Great Lakes (Lake Michigan [n = 9], Lake Huron [n = 11], and Lake Erie [n = 11]) participated in a study to measure PCBs (four coplanar and 32 non-coplanar congeners) and other contaminants in their blood. Participants (21 men, ages 41 to 76 [mean age 52], and 10 women, ages 36 to 71 [mean age 49]) were surveyed for consumption habits and demographics (Anderson et al. 1998).

Male participants ate 78 fish meals in the previous year and 55 of those were Great Lakes fish. They had been eating sport fish for 15 to 58 years (mean 37 year) and Great Lakes sport fish for 15 to 58 years (mean 34 years). Female participants ate 77 fish meals in the previous year and 34 of those meals were Great Lakes sport fish. Women had been eating sport fish for 20 to 58 years (mean 32 years) and Great Lakes sport fish for 11 to 58 years (mean 29 years). PCB levels are presented in Table 8. Coplanar PCBs were reported in TEQ concentrations (Anderson et al. 1998) and are not listed here. The same congeners were prevalent in all groups.

[1] Human PCB levels are reported in a variety of formats. Some of them include amount of PCBs, usually in nanograms (ng) per milliliter (ml) of blood, parts per billion (ppb), or ng per gram (g) lipid.

Table 8: Blood PCB levels (in parts per billion [ppb]) in sport fish consumers from three of the Great Lakes (Anderson et al. 1998).

| Total PCBs[a] | Great Lakes sport fish consumers | | | | Comparison group (n = 41); non-Great Lakes sport fish consumers (from Jacksonville, Arkansas) |
|---|---|---|---|---|---|
| | All (n = 31) | Lake Michigan sport fish (n = 9) | Lake Huron sport fish (n = 11) | Lake Erie sport fish (n = 11) | |
| Mean (ppb) | 5.2 | 8.6 | 5.7 | 2.2 | 1.2 |
| Range (ppb) | 1.2 to 15.2 | 3.6 to 15.2 | 1.3 to 12.9 | 1.2 to 3.2 | 0.46 to 2.9 |

a = Total PCBs consist of 32 non-coplanar congeners.

PCB levels were again measured in Great Lake fish consumers. The frequent fish consumers were Great Lakes charter boat captains and the reference population was composed of infrequent Great Lake fish consumers. Blood samples were collected from 538 participants (439 frequent consumers and 99 infrequent consumers). The frequent fish consumer ate more fish meals (men 52.7 meals/year and women 45.6 meals/year) compared to the reference population (men 39.6 meals/year and women 33.5 meals/year). Frequent fish consumers had significantly higher levels of PCBs compared to the reference population. There were significant differences between PCB levels from participants who consumed Great Lakes fish, from primarily Lake Michigan and Lake Erie, and the appropriate reference population for both men and women (Hanrahan et al. 1999). Table 9 presents the PCB levels in Lakes Michigan, Erie, and Huron sport fish consumers.

Table 9: PCB levels (in parts per billion [ppb]) in frequent consumers of Great Lakes fish and reference population (Hanrahan et al. 1999).

| Great Lake fish source | PCBs (geometric mean in ppb) | | | |
|---|---|---|---|---|
| | Frequent consumers | | Reference population | |
| | Male (n) | Female (n) | Male (n) | Female (n) |
| Michigan | 7.2 (98) | 2.5 (83) | 1.5 (23) | 0.9 (22) |
| Huron | 3.8 (65) | 2.3 (37) | 1.3 (3) | 0.7 (3) |
| Erie | 3.7 (89) | 1.6 (67) | 1.4 (31) | 1.0 (17) |

He et al. (2001) investigated PCB levels in Michigan anglers, using three surveys that together span twenty years. The first survey was with a cohort recruited between 1973 and 1974. Fisheaters (n = 73) were defined as those with a consumption of greater than or equal to 24 pounds. Non-fisheaters were defined as consuming less than six pounds. The second survey included 1,255 participants (115 from the first survey and 1,140 new participants) and was from 1979 to 1982. The second survey included 608 fisheaters. The third survey, from 1989 to 1993, enrolled 717 participants from the second survey and 11 new participants. The third survey included 358 fisheaters. Both the number of fish meals (men and women) consumed in a year and the number of pounds of fish consumed was similar for the first and second surveys and decreased from survey two to survey three (He et al. 2001).

PCB serum levels were measured using an Aroclor 1260 standard. The range ($25^{th}$ quartile to $75^{th}$ quartile) was 10 to 38.6 ppb for male fisheaters and 7.5 to 22.8 ppb for female fisheaters. Non-fisheaters' PCB serum levels ranged ($25^{th}$ quartile to $75^{th}$ quartile) from 4.3 to 15.0 ppb for men and from 3.9 to 10.1 ppb for women. Age, total fish consumption, and gender were all predictors of Aroclor 1260 serum levels (He et al. 2001).

PCB blood levels were measured in participants from the New York State Angler Cohort Study (NYSACS). Fish consumers (n = 110) serum was analyzed for PCB congeners and the most prevalent congeners totaled 346.8 ppb (nanograms (ng)/g) serum lipids, which represented 44% of the sum of all PCBs measured (median 780.6 ppb serum lipids). The serum of non-consumers (n = 93) was also analyzed for total PCBs and the most prevalent congeners totaled 252.0 ppb serum lipids, which was 37% of the total PCBs (median 668.8 ppb serum lipids). From this study, the authors concluded that Lake Ontario sport fish contribute to the body burden of ortho-PCBs in western New York anglers and sportsmen (Bloom et al. 2005).

Frequent and infrequent (n = 508) Great Lakes sport fish consuming residents from the Great Lakes Basin were selected from a population recruited in 1993. The participants had, on average, 34 years of sport fish consumption and ate 1.9 sport fish meals/month. The participants (350 men and 158 women) had 101 PCB congeners measured in blood. The sum of all 101 PCB congeners ranged from less than 0.1 to 4,309 ppb (geometric mean = 310 ppb) in men and less than 0.1 to 1,422 ppb (geometric mean = 136 ppb) in women. The geometric mean for men was higher than PCB levels in a reference group composed of National Health and Nutrition Examination Survey (NHANES) participants. The NHANES participants had 21 PCB congeners measured in blood. The sum of those 21 PCB congeners ranged from 21.0 to 3,240 ppb (geometric mean = 156 ppb) in men (n = 299) and 17.0 to 2,093 ppb (geometric mean = 154 ppb) in women (n = 301) (Anderson et al. 2008).

Another population assessed for PCB levels is the Akwesasne Mohawk Nation on the St Lawrence River in the state of New York and the Canadian provinces of Ontario and Quebec. Samples were collected between 1998 and 2000 from 753 adult Akwesasne Mohawks (489 women and 264 men) between the ages of 18 and 95 years. The range of the total PCB was from 0.29 to 48.32 ppb and the mean was 4.39 ± 4.18 ppb serum (median = 3.18 ppb). Men had a higher median total serum PCB level than women (men's median was 3.81 ppb and women's median was 2.94 ppb). Age and total serum PCB levels significantly correlated with each other. The exposure identified was consistent with the general U.S. population. PCB 153, 138, and 180, and other persistent congeners, dominated the PCB profile (DeCaprio et al. 2005).

Additional discussion of human biomonitoring studies is in Appendix C.

*Observational Epidemiology Studies with Great Lakes fish consumers*

Children, born in western Michigan hospitals in 1980-1981, were enrolled in a study when their mothers were surveyed for Lake Michigan fish consumption. The women included in the study either ate no Lake Michigan fish or ate more than 11.8 kg over a six year period. Fish consumption, for the group that ate Lake Michigan fish, averaged 6.7 kg per year (about two or three salmon or lake trout meals per month). PCB in cord serum was measured based on Aroclor

1016 and 1260 standards. PCB cord serum levels averaged 2.5 ng/milliliter (ml) (standard deviation 1.9 ppb) (Jacobson et al. 1984).The Michigan cohort children were examined within three days after birth (Jacobson et al. 1984), at seven months (Jacobson et al. 1985), at age four (Jacobson et al. 1990), and at age 11 (Jacobson and Jacobson 1996).

Michigan cohort infants, all but four, were tested with the Brazelton Neonatal Behavioral Assessment Scale 48 to 72 hours after birth. Although PCB cord serum levels were measured, maternal fish consumption was the measure of PCB exposure due to non-detectable PCB cord serum values. Individual tests were groups into seven clusters. Results from three of the test clusters, autonomic maturity (includes a greater propensity to startle), reflexes, and range of state (includes irritability), were associated with PCB exposure. The non-exposed control infants (no maternal Lake Michigan fish consumption) were compared to the highest exposed infants (highest maternal Lake Michigan fish consumption). The highest exposed infants had a significantly greater likelihood of poorer scores on the reflex and range of state clusters (Jacobson et al. 1984).

The Michigan cohort children were tested again at seven months of age. One hundred and twenty-three infants were given Fagan's recognition memory test, which uses pictures of women's and babies' faces to determine the time an infant looks at a novel picture after being shown two identical pictures for a set amount of time. A higher level of PCB exposure, with either PCB cord serum levels or maternal fish consumption, was significantly predictive of reduced recognition memory in the infants. Infants with a higher prenatal exposure to PCB had a poorer performance on the visual recognition test (Jacobson et al. 1985).

Seventy-five percent of the initial Michigan cohort enrollees (n = 236) were assessed for effects of PCB and other contaminant exposure on cognitive functioning at four years of age. Children were assessed on five domains of functioning and intelligence quotient. PCB levels measured in cord serum (n = 146) were the measure of prenatal exposure. Postnatal exposure was estimated from maternal milk PCB levels (n = 120) and duration of lactation. Children's PCB body burden was measured at age four in serum (127 at four years old and 27 at five years of age). Cord PCB levels averaged 2.5 ± 2.0 ppb (mean ± standard deviation [SD]), maternal serum averaged 5.9 ± 3.6 ppb, and maternal milk averaged 835.9 ± 388.4 ppb. Maternal milk was the main source of the children's serum PCB levels at four years. Serum PCB levels were higher for the children breast fed at least six months (5.1 ± 3.9 ppb) than the children who were breast fed less than six months (1.2 ±1.6 ppb) or those who were not breast fed (0.3 ± 0.7 ppb) (Jacobson et al. 1990).

Higher PCB cord levels were significantly associated with lower scores on three tests that measured the child's ability to recall strings of words, sentences, or a story and the child's ability to repeat progressively longer strings of numbers, both as given and backward. Higher maternal milk PCB levels were significantly associated with lower scores on these tests. A longer duration in nursing tended to result in higher scores on two of the three tests, attributed to increased intellectual stimulation. The children's PCB body burden, at age four, and post-natal PCB exposure was not related to scores on any of the tests. Overall, the authors concluded that the prenatal PCB exposure resulted in a poorer short-term memory functioning in early childhood (Jacobson et al. 1990).

The Michigan cohort children were assessed again at age 11 (Jacobson and Jacobson 1996).Two hundred and twelve children (68% of the original number) were given tests measuring various aspects of cognitive functioning. PCB levels were measured in cord serum, maternal serum, maternal milk, children's serum at age four, and children's serum at age 11. Children's PCB serum levels averaged 1.0 ± 1.0 ppb (mean ± standard deviation) at age 11 (Jacobson and Jacobson 1996).

Scores from five different tests, given to the Michigan cohort children at age 11, were significantly lower with a higher prenatal PCB exposure. The authors note that no child included in the study had gross intellectual impairment, but there was an increase in the lower end of the normal Intelligence Quotient (IQ) range, which may result in reduced school performance. As found in this population at age four, only prenatal PCB exposure was significantly associated with lower scores and not postnatal PCB exposure. The authors cautioned that children in this cohort might have had exposure to additional contaminants that are responsible for these effects and PCB from food sources other than Lake Michigan fish may produce similar effects (Jacobson and Jacobson 1996).

Children in the Michigan cohort were tested for sustained attention, focused attention, executive functioning, and working memory at age eleven (n = 148). Prenatal PCB exposure was significantly associated with several test scores, indicating poorer concentration and a requirement for increased processing time. Based on the test results, the children have focused attention and executive functioning deficits. The authors note that the adverse effects, related to prenatal PCB exposure, seem to be stronger in children who were not breastfed (defined as less than six weeks breastfed) (Jacobson and Jacobson 2003).

Adults, in a cohort of fisheaters and non-fisheaters established by MDCH[2] in the early 1980s (Michigan angler cohort), were screened for fine-motor impairment. All participants, 104 fish eaters (49 men and 55 women) and 84 non-fish eaters (34 men and 50 women), were over 50 years of age in 1992. Fisheaters had an annual consumption of 24 to 270 pounds of Lake Michigan fish per year (median = 38.5 pounds/year) during the initial enrollment. At the time of this study participants reported a median fish consumption of seven pounds per year. Non-fish eaters had an annual consumption of less than six pounds. Serum PCB and dichlorodiphenyl dichloroethylene (DDE) levels were highly correlated and were assessed jointly (Schantz et al. 1999). Table 10 presents the number of people in each exposure group.

Table 10: Number of people in each polychlorinated biphenyl (PCB) and dichlorodiphenyl dichloroethylene (DDE) exposure group (in parts per billion [ppb]) (Schantz et al. 1999).

| Groups | Low (PCB <7.9 ppb and DDE <8.1 ppb) | Intermediate (PCB 7.9 to 13.8 ppb and/or DDE 8.1 to 15.0 ppb) | High (PCB ≥ 13.9 ppb and/or DDE ≥ 15.1 ppb) | Total number of participants |
|---|---|---|---|---|
| Fish eaters | 15 (15%) | 38 (38%) | 48 (48%) | 101 |
| Non-fish eaters | 50 (64%) | 16 (21%) | 12 (15%) | 78 |

[2] Formerly the Michigan Department of Public Health

The authors did not observe a relationship between exposure to PCBs or DDE from Lake Michigan fish and the effects measured in this study. However, the authors noted that participants might have other effects not measured in this study. The Michigan angler cohort were tested in memory and learning, executive functions, and visual-spatial function and results were reported in a later study (Schantz et al. 1999).

Higher PCB exposure resulted in lower scores on memory and learning tests (statistically significant on the verbal delayed recall on the logical memory portion of the Wechsler Memory Scale and not statistically significant on the verbal delayed recall measured by the California Verbal Learning Test). However, visual memory, executive, and visual-spatial function scores were not affected by PCB levels (Schantz et al. 2001).

Daughters of women (n = 151) involved in Michigan angler cohort, from 1973 to 1991, participated in a study to determine if prenatal PCBs or DDE exposure resulted in an early age at menarche (first menstruation). Serum organochlorine levels during pregnancy were extrapolated from PCB levels measured in 1973-1974 and 1989-1991. Age at menarche ranged from nine to 11 years old and extrapolated maternal PCB and DDE levels were higher for women with a younger age of menarche. DDE levels, but not PCB levels were statistically related to lower age of menarche (Vasiliu et al. 2004).

MDCH set up a cohort, the Great Lakes Fish Eaters Study, to assess if PCB levels altered birth weight. This cohort was involved in three different surveys, with PCB levels, measured based on an Aroclor 1260 standard, in 1973 to 1974, 1979 to 1982, and 1989 to 1991. Births, from 310 female cohort members (maximum age 45), after 1968 were assessed. Maternal PCB levels were higher for children born earlier (from 1969 to 1972). Children's birth weights were significantly reduced, by 500 g, in the mothers with the highest PCB serum levels (>25 µg/L). However, only seven infants (one girl and six boys) were in the highest maternal PCB group and this conclusion may have been affected by the small number of infants (Karmus and Zhu 2004).

The health departments of Wisconsin, Illinois, Indiana, Ohio, and Michigan formed a consortium under the Congressional Great Lakes Critical Programs Act of 1990 to examine health risks from consumption of PCB and DDE contaminated fish. Participants consisted of frequent and infrequent fish consumers and were interviewed by telephone between 1993 and 1995. The frequent fish consuming cohort (Captains) were licensed sport fishing charter boat captains and their spouses (n = 1,863 households). Infrequent fish consumers were randomly selected members of the general population (n = 1,274 households). Data was complete for 143 mother-infant pairs. Mothers in the Captains cohort had a geometric mean of 1.76 ppb (nanograms/milliliter) for serum PCBs (median = 1.76 ppb, range = 0.46 to 12.08 ppb). This was significantly higher than the serum PCB geometric mean (0.85 ppb) for mothers in the infrequent consumers cohort (median = 0.81 ppb, range = 0.53 to 1.66 ppb). Serum PCB concentrations were not significantly associated with lower birth weight (Weisskopf et al. 2005).

The Mohawk Nation at Akwesasne consists of approximately 10,000 people living at the intersection of New York State and the Canadian provinces of Ontario and Quebec on the St Lawrence River. It is close to three Superfund sites, which have contaminated the river with

PCBs (originally Aroclor 1248). Fish were an important historical source of protein for the Mohawk Nation, until fish advisories were set in the 1980s. After fish advisories were issued, breast milk and serum PCB levels decreased (DeCaprio et al. 2005).

Study participants (n = 352) were Mohawk adults 30 years or older that have lived at or near Akwesasne for at least 5 years. Blood samples were obtained after fasting and 101 PCB congeners were measured. Total PCB levels ranged from 84.8 to 7,110.0 ppb lipid weight with a mean ± SD of 748.8 ± 635.6 ppb lipid weight. There was a significant association between serum PCB and pesticide levels and diabetes after adjustments. Diabetes, in this population, was defined as having a fasting glucose value greater than 125 mg/deciliter. The authors concluded that organochlorine compounds increased the risk of developing diabetes (Codru et al. 2007).

Along with examining the link between PCBs and diabetes, Mohawk at Akwesasne have participated in studies to examine the link between PCBs and cardiovascular disease (self-reported). Fasting blood samples were collected from 335 adult Mohawks living on or near the reservation from 1995 to 2000. The range of total serum PCBs was 1.2 to 25.8 ppb with an average of 4.2 ppb. Information from this study lead the authors to conclude that a relationship exists among serum PCB and pesticide levels, serum lipids, and cardiovascular disease (Goncharov et al. 2008).

Mohawk people previously identified as having PCB levels higher than the general population, participated in a study of the relationship between testosterone concentrations and serum levels of total PCBs, 12 PCB congeners, five PCB groups, and pesticides. Over 700 people (257 men and 446 women) were included in the study and ranged from 18 to 95 years of age. There was no significant relationship between PCB and testosterone levels for women. Men had a significant relationship between testosterone and total PCB blood levels. Significant negative associations were also identified between specific PCB congeners (74, 99, 153, and 206) and testosterone levels (Goncharov et al. 2009).

The relationship between PCBs and neuropsychological functioning was assessed in Mohawk men and women from Akwesasne. Participants (n = 353, 113 men and 240 women) ranged in age from 17 to 79 years, with a mean of 38 ± 13.3 years. Some measures of neuropsychological functioning (executive functioning, motor functioning, and memory) were significantly related to PCB exposure. The authors noted that the decline in test scores was not at levels of clinical concern. Scores on tests for executive functioning began to decrease at PCB body burden levels of 2.0 to 25 ppb. Motor functioning test scores, for fine motor behavior and finger dexterity, decreased at PCB body burden levels above approximately 2.0 ppb. Test scores for memory also indicated that memory deterioration occurred at PCB body burden levels greater than 2.0 ppb (Haase et al. 2009).

School-age children were evaluated for a lower IQ associated with environmental PCB exposure. The purpose of this study was to determine if the relationship between IQ and prenatal PCB exposure observed in a cohort of Lake Michigan fisheaters could be replicated in children exposed to PCBs around Lake Ontario. PCB levels from participants in the Oswego cohort (from the Lake Ontario basin) were lower than levels from participants in the Collaborative Perinatal Project (from 12 national clinics). Children participating in the Oswego study, born between

1991 and 1994, were tested at nine years of age (those with cord blood samples, n = 187; those with cord and placental tissue samples, n = 156). The authors found significant negative associations between placental PCB levels and IQ scores. Estimations, assuming scores would drop linearly, were that scores dropped 2.9 IQ points; 4.1 Verbal IQ points; 3.3 Verbal Comprehension Index points; or 4.4 Freedom from Distractibility points per increase of 1.0 ppb PCB in placental tissue. Cord blood PCB levels were not related to IQ (Stewart et al. 2008).

The New York State Angler Cohort Study (NYSACS) was composed of 10,518 male anglers, 913 female anglers, and 6,651 spouses or partners of male anglers (Buck et al. 1997). Associations between reproductive endpoints or thyroid hormones and PCB levels were assessed in this population.

Members of the NYSACS were assessed for time to pregnancy (TTP). TTP is a measure of the ability to become pregnant. Residents, between the ages 18 to 40, of one of the 16 counties surrounding Lake Ontario were asked for TTP information in 1993. Known TTP was reported by 874 participants, however 30 were excluded for a lack of fish consumption data. Forty-five percent of those reporting a known TTP reported smoking once or more than once (ever or never question) and 42% ate contaminated fish from Lake Ontario (those with no consumption advisories). The authors found no significant adverse association between consumption of contaminated sport fish from Lake Ontario and TTP. No information was collected on other factors that would alter TTP, such as caffeine or alcohol (Buck et al. 1997).

A later study carried out with the NYSACS population examined whether conception delay occurred in this population. Selected women had one or more pregnancies between 1991 and 1993 and known TTP. Conception delay was defined as 12 or more menstrual cycles with unprotected intercourse before a pregnancy occurred. Seventy-eight percent of the women (total of 785 women) had a TTP less than or equal to six months and 11% had a TTP 13 or more months. Over half of the fathers (66%) ate Lake Ontario fish between 1955 and 1991, but only 38% reported eating Lake Ontario fish (one or more meals) in 1991. The mean estimated PCB exposure from fish consumption for the fathers was 6.6 ± 12.3 mg. The authors concluded that fish consumption did not increase the risk of conception delay, based on known TTPs. The authors noted two factors that may have altered the conclusion of the study: a selection bias was present (participants had to know the TTP) and inclusion of women with unplanned pregnancies (40 to 50% of all pregnancies in the U.S. are unplanned) or women who never became pregnant may have altered the outcome and fish consumption was unknown between 1991 and 1993 (Buck et al. 1999).

An additional study measuring reproductive ability was conducted using participants of the NYSACS. Nearly 600 women (n = 584) were eligible as their partners' fish consumption data was available. Fish consumption was higher for men as compared to women and men reported more recent fish meals and had higher mean estimated PCB indices. The probability of conceiving was lower for women who consume Lake Ontario fish in comparison with non-fish eaters. The authors noted that populations of women that may have been more heavily exposed and may not have become pregnant were excluded (Buck et al. 2000).

The NYSACS followed 99 women attempting to get pregnant for 12 menstrual cycles. At the end of the study, women were grouped into three categories: those with live births, those with pregnancy losses, and those that were infertile. No statistical differences were identified in the PCB levels among the three groups (Bloom et al. 2007).

Thirty-eight participants (six women and 32 men) in the NYSACS had PCB (77 congeners) and thyroid hormones measured in their blood. There was no significant association between thyroid stimulating hormone (TSH) or free thyroxine (FT4) and the sum of the PCBs (Bloom et al. 2009).

Additional discussion of these studies is in Appendix E.

*Selection of a Toxicological Endpoint for the PCB FCSV*

When evaluating the potential adverse human health effects of chemicals, greater weight is given to effects that have been observed in human populations. However, human studies are often difficult to interpret because every person lives differently, people may be exposed to multiple chemicals at the same time, individuals may be more or less sensitive to specific chemicals, and difficulty determining exposure in real life situation. It takes many exposed people in a well-designed study to see increases in common conditions, for example organ disease or cancer. Since it is unethical to conduct experiments that could potentially hurt people, toxicologists often rely on the results of animal studies where experimental conditions such as the chemical dose and number of subjects can be carefully controlled, and where adverse health effects can be more easily observed.

The toxicity of PCBs does not always depend on the total amount, but rather the congeners present (Giesy and Kannan 1998), since the toxicity of PCBs depends on their structure. Congeners without chlorines in the ortho positions, otherwise known as coplanar PCBs, have dioxin-like activity. Dioxin-like activity occurs when the congeners bind to the cytosolic aryl hydrocarbon receptor (AhR) (Bezdecny et al. 2005). Ultimately, a similar pattern of gene expression, and downstream effects, will occur from treatment with coplanar PCBs, dioxins, and other dioxin-like chemicals.

Non dioxin-like activity is due to a different mechanism of action, with each congener having its own profile of actions in biological systems. These mechanisms include reduction of dopamine synthesis in neurons, activation of neutrophils, and interference of estrogen and thyroid hormone function. Non dioxin-like activity can result in generation of reactive oxygen species, and can lead to cancer promotion (Carpenter 2006). Additional discussion of mechanisms of toxicity is in Appendix D.

*Carcinogenicity*

The WHO International Agency for Research on Cancer (IARC) classifies PCBs as *Group 2A carcinogens, with limited evidence for human carcinogenicity* (IARC 1987). The National Toxicology Program 11$^{th}$ Report on Carcinogens describes PCBs as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity in experimental animals (NTP 2009). The EPA considers mixtures of PCBs to be *probable human carcinogens* based on sufficient evidence of carcinogenicity in animals (EPA 1997A).

MDCH reviewed the available studies reporting human health effects of exposure to PCBs. While these studies qualitatively suggest that PCBs may cause cancer in humans, the existing studies are inadequate as the basis of a quantitative calculation of the carcinogenic risks posed to people. See Appendix D for a detailed discussion of these studies.

In the absence of adequate evidence from human studies, the EPA used animal studies to derive oral cancer slope factors (CSF) for PCBs ranging from 0.04 to 2.0 per mg/kg-day. The CSFs for food chain exposure to PCBs are 1.0 (central-estimate slope factor) and 2.0 (upper-bound slope factor) per mg/kg-day (EPA 1997A). The CSFs were developed from a Sprague-Dawley rat carcinogenicity study by Brunner et al. (1996).

Cogliano (1998) summarizes the Brunner et al. (1996) carcinogenicity study data and an EPA report discussing use of that data as a basis for the PCB CSFs. The study included 50 male and 50 female Sprague-Dawley rats fed Aroclor mixtures in rodent chow. The treatment groups were 50, 100, or 200 ppm Aroclor 1016; 50 or 100 ppm Aroclor 1242; 25, 50, or 100 ppm Aroclor 1254; or 25, 50, or 100 ppm Aroclor 1260. One hundred male and 100 female rats were in the untreated control group. These rats were fed for 24 months and then tumor incidence and other parameters were assessed. The liver tumor incidence was analyzed and statistically increased liver tumor incidences, both malignant and non-malignant, were identified for male rats fed Aroclor 1260 and female rats fed Aroclor 1260, 1254, 1242 and 1016. The number of tumors identified as malignant increased with dose (Cogliano 1998). Additional details of the study can be found in Appendix D.

Based on these data an estimated dose for a 10% increased incidence in liver tumors ($ED_{10}$) was calculated as was a 95% lower confidence bound on that value ($LED_{10}$) (Cogliano 1998). These values (0.086 and 0.067 mg/kg-day for $ED_{10}$ and $LED_{10}$, respectively) were used to calculate the central and upper-bound slopes.

Additional discussion of carcinogenicity is in Appendix D.

*Developmental Effects*

A range of adverse developmental effects have been observed in humans exposed to PCBs before birth including neonatal deficits in behavior, such as propensity to startle and neuromuscular functioning; infant visual recognition, short-term memory functioning in early childhood, and deficits in childhood executive functioning and focused attention (Jacobson et al. 1984, et al. 1985, Jacobson et al. 1990, Jacobson and Jacobson 1996). PCB levels, for the general population, are associated with measurable developmental effects. This indicates that the developing fetus may be sensitive to widely encountered levels of PCB exposure.

MDCH reviewed the available studies of developmental effects in humans associated with exposure to PCBs. (See the Observational Epidemiology Studies with Great Lakes fish consumers section or Appendix E for a discussion of the studies.) While these studies qualitatively suggest that PCBs may cause developmental effects in humans, the existing studies are inadequate as the basis of a quantitative calculation of the effective dose of PCBs. While the neuropsychological developmental effects observed in Michigan children may be a critical effect

in people, exact knowledge of the PCB dose that may have caused these effects is not certain. Although the PCB exposure dose is uncertain, Jacobson et al. (2002) calculated a lower limit of a Benchmark dose (BMDL) from studies on a Michigan cohort of children. The authors noted that the Michigan cohort used in the BMDL development might not be the most sensitive population. The BMDL can be used to calculate, for reference purposes only, an estimated RfD of 0.02 µg/kg-day for human neuropsychological developmental effects, described in Appendix G. The available information concerning PCB exposures that may cause neurological effects in humans should be reevaluated periodically and if better knowledge of PCB exposure levels is determined, the FCSV updated if needed.

In the absence of adequate evidence from human studies, the EPA used a no observed adverse effect level (NOAEL) for reduced birth weights in non-human primates (rhesus monkeys) to calculate an RfD for Aroclor 1016 of 0.07 µg/kg-day, (EPA 1996B).

In calculating the RfD, the EPA applied a total uncertainty factor of 100:

- A 3-fold factor was applied to account for sensitive individuals. This study confirms the findings of human studies that indicate that infants exposed to PCBs before birth through the placenta represent a sensitive subpopulation.
- A 3-fold factor was applied applied for extrapolation from rhesus monkeys to human. A full 10-fold factor is not needed because of the general physiological similarity between these species.
- An additional factor of 3 is applied because of limitations in the database. While there is a wealth of animal laboratory data and human epidemiologic information regarding PCBs, additional studies are still needed.
- Because the study was less than chronic, a partial factor of 3 is used to account for extrapolation from a subchronic exposure to a chronic RfD.

*Immunological Effects*

A variety of immunological effects have been associated with PCB exposure, including allergies, reduced antibody production, rheumatoid arthritis, and increased incidence of respiratory infections (Van Den Heuvel et al. 2002, Heilmann et al. 2006, Lee et al. 2007C, Glynn et al. 2008, Arnold et al. 1999). The groups involved in these studies included infants, children, young adults, adult women, and non-human primates. While the dose humans were exposed to in these studies was unknown, effects on the immune system were measured. The variety of effects and groups that were impacted indicate that many populations may be at risk for PCB associated immune effects.

Van Den Heuvel et al. (2002) investigated whether lifetime exposure to PCBs and dioxin-like compounds are associated with alterations in the immune system. Two hundred adolescents (120 girls and 80 boys), who lived in the suburbs of Hoboken and Peer, participated in the study. The suburbs of Hoboken and Peer are adjacent to the city of Antwerp, Belgium and are near chemical and petroleum industries in Antwerp's seaport. The study participants had a mean age ± standard deviation of 17.4 ± 0.8 years (Van Den Heuvel et al. 2002).

Girls and boys had several significantly different hematological parameters and had statistically significant differences in levels of PCBs (sum of PCB 138, 153, and 180) in their serum. Along

with measuring the amount of PCBs in the serum, the authors measured dioxin-like activity in the study participants. The dioxin-like activity was measured with the chemical-activated luciferase gene expression (CALUX) bioassay. Eosinophil, CD16 and CD56 double positive cell levels, and immunoglobulin E (IgE) levels had a significantly negative correlation to dioxin-like activity calculated with the CALUX assay. IgA levels significantly correlated positively to the total marker PCB levels. Dioxin-like activity, measured by CALUX, was also negatively associated with the odds of having a positive allergy test to house dust mite, cat dander, and grass pollen; upper airway allergic disease; and using medication for asthma. The total marker PCBs are positively associated with having hay fever or asthma (Van Den Heuvel et al. 2002).

Two cohorts children from the Faroe Islands were enrolled in a study to examine the effects of PCB levels on antibody production against the tetanus and diphtheria vaccines. PCB levels were assessed in maternal serum, maternal milk, and children's serum. A simplified total PCB concentration was calculated as sum, of PCB 138, 153, and 180, multiplied by 2.0. The first cohort was enrolled in 1994-1995 and PCB analysis was done on 124 children's blood samples, at age 7.5 years. The second cohort was enrolled in 1999-2001, and PCB serum levels were obtained for 116 children at 18 months of age. A significant relationship between increased maternal serum PCB levels and reduced antibodies against tetanus was identified in the first cohort, which was associated with increased prenatal PCB exposure. The authors concluded that increased PCB levels might interfere with maintenance of antibody levels. In the second cohort, a significant negative correlation between current serum PCB levels and reduced antibodies against diphtheria was identified (Heilmann et al. 2006).

NHANES data from 1999 to 2002 included self-reporting of clinical diagnosis or history of arthritis and subtypes of arthritis. Four dl-PCBs and five non-dl-PCBs were measured in the NHANES participants (n = 1,721). Only women with increased dl- and non-dl-PCB levels had a significant trend toward increased risk for prevalence of arthritis. Of the congeners tested, two dl- (PCBs 74 and 118) and three non-dl-PCBs (PCBs 170, 180, and 187) significantly increased the risk of prevalence of arthritis. Rheumatoid arthritis, but not osteoarthritis was significantly associated with increased PCB levels. Arthritis that was not classified as rheumatoid or osteoarthritis was significantly associated with non-dl-PCBs, but not dl-PCBs (Lee et al. 2007C).

Women seeking prenatal care in Uppsala County, Sweden were enrolled in a study to examine immunological effects in infants and the relationship to maternal PCB levels. Ninety infants from the cohort had blood samples drawn and white blood cells measured, with 52 samples analyzed for lymphocyte subsets. The percent of CD4-CD8+ T cells had a significant negative association with PCB 153, di-ortho PCBs, and mono-ortho PCB TEQ. There was also a significant increase in the odds ratio for respiratory infections for infants with PCBs exposure compared to unexposed infants at three months of age or less. The authors concluded that high prenatal exposure to PCBs might increase the risk of respiratory infections (Glynn et al. 2008).

Non-human primates, rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) monkeys, were treated with a PCB mixture created to simulate the congener mix present in human breast milk from Canadian women. Nine rhesus monkeys (five male, four females) and 16 male cynomolgus monkeys were divided into control or treatment groups (control: six cynomolgus and one female and two male rhesus monkeys; treatment: 10 cynomolgus and three female and

three male rhesus monkeys). The monkeys were orally given 7.5 µg PCB congeners/kg daily, in corn oil or PRIMA-LAC, from two to four days old until 20 weeks of age. A variety of effects were examined throughout the study, including general health status, formula intake and feed and water consumption, body weight, tooth eruption, somatic measurements, weekly clinical evaluation, blood and adipose PCB levels, serum biochemistry, and immunology testing (Arnold et al. 1999).

No differences in body weight, tooth eruption, or size differences were identified between the control and treated groups. When measured throughout the 20 weeks of dosing, certain PCB congeners represented a greater amount in the blood than other PCB congeners. PCB 105 was a large proportion of the total PCB amount in the four monkeys treated with PCBs in corn oil. PCBs 74, 118, 138, 153, and 180 increased in amount over the treatment time. The monkeys fed PCBs in PRIMA-LAC only had minimal increases to blood PCB levels and individual congeners could not be determined. In adipose tissue, PCB 105 levels did not increase over time, but levels of PCBs 74, 118, 138, 153, and 180 did increase during the treatment. Half-lives for the PCBs in both rhesus and cynomolgus monkeys ranged from 9.75 (~2.4 months) to 102.13 (~1.9 years) weeks. A significant increase in platelet number was observed in treated rhesus monkeys. There were no significant differences in antibody production (IgG and IgM) in control versus treated rhesus or cynomolgus monkeys. While there was no significant difference in lymphocyte proliferation between control and treated monkeys, there was a significant difference an absolute mean B cell levels between control and treated cynomolgus monkeys (Arnold et al. 1999).

See Appendices E and F for a detailed discussion of the above studies.

While these studies qualitatively suggest that PCBs may cause immunological effects in humans, the existing studies are inadequate as the basis of a quantitative calculation of the effective dose of PCBs. In the absence of adequate evidence from human studies, the EPA calculated an RfD for Aroclor 1254 of 0.02 µg/kg-day based on a lowest observed adverse effect level (LOAEL) in monkeys for endpoints that include inflamed Meibomian glands (glands around the eyes) and decreased antibody (IgG and IgM) response to sheep erythrocytes (red blood cells) (EPA 1996C).

In calculating the RfD, the EPA applied a total uncertainty factor of 300.

- A 10-fold factor was applied to account for sensitive individuals.
- A 3-fold factor was applied to extrapolate from rhesus monkeys to humans. A full 10-fold factor is not needed because the species are physiological similar.
- A 3-fold factor was applied for the use of a minimal LOAEL. A full 10-fold factor is not needed since the clinical (for example, inflamed Meibomien glands) observed at the LOAEL are not severe.
- A 3-fold factor was applied because the study was conducted over less than the lifetime of the monkeys. A full 10 fold factor was not needed because the changes observed did not appear to be dependent upon duration of exposure.

*Selection of the MDCH PCB Reference Dose (RfD)*

After a thorough review of the available literature and RfDs developed by the EPA, MDCH selected the RfD of 0.02 µg/kg-day for Aroclor 1254 as the basis for the FCSV. This value was selected for several reasons. First, there is a variety of PCB associated immune effects that have been reported in humans, both children and adults. Second, an estimated RfD for neuropsychological effects (See Appendix G) is also 0.02 µg/kg-day, which indicates that the Aroclor 1254 RfD would, even considering exposure uncertainties discussed above, be protective against those types of developmental effects. Third, in a study using Aroclor 1254, prenatal exposure to 80 µg/kg-day did not alter infant monkey birth weights (Arnold et al. 1997). The 80 µg/kg-day is higher than the the point-of-departure used as a basis for the Aroclor 1254 RfD, and so this RfD will be protective of additional developmental effects. Fourth, fish tend to retain higher chlorinated congeners, more similar to the congeners present in Aroclor 1254 than Aroclor 1016 (Gerstenberger and Dellinger 2002; Jordan et al. 1999).

This RfD provides screening values that might not account for health effects that result from dioxin-like activity that specific PCB congeners may have. Michigan issues fish advisories both for PCBs and dioxins (including dioxin-like chemicals). Along with the total amount of PCBs in fish, the certain PCB congeners, those with TEFs, can be included in the total TEQ. MDCH recommends continuing, for the dl-PCB congeners, addition of the dl-PCB TEQ into the total TEQ. Issuance of fish advisories will then cover all dioxin-like and non-dioxin like activity of contaminants in the fish. (See the Toxicity in Humans section and Appendix D for discussion of the different mechanisms of toxicity.)

Appendix G also includes sample screening levels based on cancer risk (one excess case in 100,000). They were developed using the 2.0 per mg/kg-day upper bound cancer slope factor (CSF) for PCBs from the EPA (EPA 1997A). This slope factor is used for food chain exposure; when dioxin-like, tumor-promoting, or persistent congeners are present; and for early-life exposure (for all pathways and mixtures). The EPA has not developed CSFs for specific mixtures of PCBs, such as Aroclor 1254 or Aroclor 1248.

The FCSVs based on cancer risk (See Appendix G.) are lower than those developed from the RfD, although FCSVs based on an RfD may also be protective against cancer as well.[3] PCBs, as discussed in other sections are tumor promoters, and do not appear to be tumor initiators or mutagenic. Per EPA guidelines (EPA 2006), an RfD may be used for carcinogens that have a mode of action that is not mutagenic. (Additional discussion of this issue is in Appendix G.) If this were the case, an RfD could be calculated using a point-of-departure based on carcinogenic effects. A possible point-of-departure is the $LED_{10}$,[4] from a rat carcinogenesis study (Brunner et al. 1996), that was used by the EPA for calculation of the upper bound CSF of 2.0 per mg/kg-day (EPA 1996A). The human equivalent dose for the $LED_{10}$, 67 µg/kg-day, was converted from the the estimated dose that would cause 10% of the rats to develop cancer. That dose, 67 µg/kg-day, is over 10 times higher than both the BMDL used for calculation of a sample RfD based on

[3] Currently (March 2012), the EPA uses a cancer slope factor to assess carcinogenic risk for PCBs.

[4] The lower 95% limit on a dose associated with 10% tumor incidence ($LED_{10}$) was used to provide a frame of reference for the value. Use of the $LED_1$ would result in a dose (6.7 µg/kg-day) similar to the LOAEL used for the Aroclor 1254 RfD. In both cases, these values may indicate that the Aroclor 1254 RfD would be protective of carcinogenic effects, given that PCBs have not been identified as mutagenic.

neurological effects in humans (1.7 µg/kg-day) and the LOAEL (5.0 µg/kg-day) used for calculation of the RfD based on immunologic effects in monkeys. Applying a total uncertainty factor of 100 (10-fold for use of a point-of-departure with health effects, 10-fold for sensitive individuals) or even 1000 (10-fold for LOAEL to NOAEL, 10-fold for sensitive individuals, 10-fold for database limitations for carcinogenic effects in humans) would result in an RfD that ranges from about three to about thirty times higher than the RfD based on immunological effects. Further consideration may need to be given to the use of cancer risk point-of-departure in calculations of an RfD or for development of FCSVs.

Children's Health Considerations

Children can be at greater risk than adults from certain kinds of exposure to hazardous substances. A child's lower body weight and higher intake rate results in a greater dose of hazardous substance per unit of body weight. Fetuses are exposed during development to PCBs in contaminated fish that the mother eats. If toxic exposure levels are high enough during critical growth stages, the developing body systems of children can sustain permanent damage. Infants may have a reduced capacity to metabolize and eliminate PCBs, due to still developing organ systems. Further exposure to newborn and older babies could occur through the mother's breast milk.

Breast milk may contain higher levels of PCBs than certain species of fish due to the high levels of lipids (fat) present in breast milk. Nursing infants are believed to be potentially highly exposed to PCBs, along with people whose diet is high in game fish, game animals, and domestic animals (EPA 1996A). Estimated intake for nursing infants is 1.5 to 27 µg/kg, an amount approximately 50 fold higher than adult intake (EPA 1996A).

## Conclusions

MDCH concludes that eating unlimited amounts of certain fish from lakes in Michigan throughout the year could harm people's health. This is a public health hazard. Fish consumption advisories may be needed for certain fish species at specific locations. People with higher fish consumption have been shown to have higher levels of PCBs that the general population. Other studies have associated health effects with increased PCB levels found in fish eaters.

## Recommendations

Use the proposed RfD, protective of immunological effects and other effects, to develop updated PCB FCSVs and utilize these values to provide fish consumption advice in Michigan.

Continue monitoring of fish in Michigan for PCBs.

Provide the Fish and Wildlife Contaminant Advisory Committee (FAWCAC) and other relevant groups (Great Lakes Sport Fish Advisory Task Force and Great Lakes Human Health Network) with a copy of this document.

## Public Health Action Plan

1. MDCH will issue advisories in the Michigan Family Fish Consumption Guide using new PCB FCSVs (see Appendix G for sample FCSVs).

2. The MDCH Analytical Chemistry Laboratory will continue to screen fish, collected for the Michigan Fish Contaminant Monitoring Program (MFCMP) (administered by the Department of Natural Resources and Environment).

3. MDCH will share a copy of this document so that FAWCAC and other relevant groups will have this information.

# Preparers of Report


**Michigan Department of Community Health**
**Division of Environmental Health**

Jennifer Gray, Ph.D.
Toxicologist
Toxicology and Response Section

Linda D Dykema, Ph.D.
Toxicologist, Principal Investigator
Toxicology and Response Section

Kory Groetsch, M.S.
Toxicologist
Toxicology and Response Section

**ATSDR Region 5 Office**

Mark Johnson
Office of Regional Operations

**ATSDR Division of Health Assessment and Consultation**

Trent LeCoultre, Technical Project Officer
Cooperative Agreement Program Evaluation Branch

# References


Abramowicz DA. 1995. Aerobic and anaerobic PCB biodegradation in the environment. Environ Health Perspect Suppl 103(5):97-99.

Agudo A, Goni F, Etxeandia A et al. 2009. Polychlorinated biphenyls in Spanish adults: determinants of serum concentrations. Environ Res 109 (5):620-628.

Alvarez-Pedrerol M, Ribas-Fito N, Torrent M et al. 2008. Effects of PCBs, p,p'-DDT, p,p'-DDE, HCB and beta-HCH on thyroid function in preschool children. Occup Environ Med 65 (7):452-457.

Anderson HA, Falk C, Hanrahan L, et al. 1998. Profiles of Great Lakes critical pollutants: A sentinel analysis of human blood and urine. Environ Health Perspect 106(5):279-289.

Anderson HA, Imm P, Knobeloch L et al. 2008. Polybrominated diphenyl ethers (PBDE) in serum: findings from a US cohort of consumers of sport-caught fish. Chemosphere 73 (2):187-194.

Aozasa O, Ohta S, Nakao T et al. 2008. PCB contamination assessment of yusho patients by using preserved human umbilical cord. Bull Environ Contam Toxicol 81 (6):578-582.

Arnold DL, Bryce F, McGuire PF, et al. 1995. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (*Macaca mulatta*) monkeys. Part 2. Reproduction and infant findings. Food Chem Toxicol 33:457-474.

Arnold et al. 1997 Arnold DL, Nera EA, Stapley R, et al. 1997. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (*Macaca mulatta*) monkeys and their nursing infants. Part 3: Post-reproduction and pathological findings. Food Chem Toxicol 35(12):1191-1207.

Arnold DL, Stapley R, Bryce F, et al. 1998A. A multigeneration study to ascertain the toxicological effects of Great Lakes salmon fed to rats: Study overview and design. Regul Toxicol Pharmacol 27:S1-S7.

Arnold DL, Bryce F, Miller D et al. 1998B. The toxicological effects following the ingestion of chinook salmon from the Great Lakes by Sprague-Dawley rats during a two-generation feeding-reproduction study. Regul Toxicol Pharmacol 27 (1 Pt 2):S18-27.

Arnold DL, Bryce F, Mes J, et al. 1999. Toxicological consequences of feeding PCB congeners to infant Rhesus (*Macaca mulatta*) and Cynomolgus (*Macaca fascicularis*) monkeys. Food Chem Toxicol 37:153-167.

Atlantic Coast Interstate Workgroup (ACIW). 2008. Report of the Interstate Workgroup on Evaluating Atlantic Coastal Advisories for Recreationally Caught Striped Bass and Bluefish based on PCBs. http://www.maine.gov/dhhs/eohp/fish/9_08Final.pdf.

Axelrad DA, Goodman S, Woodruff TJ. 2009. PCB body burdens in US women of childbearing age 2001-2002: An evaluation of alternate summary metrics of NHANES data. Environ Res 109 (4):368-78.

Bedard DL, Bailey JJ, Reiss BL et al. 2006. Development and characterization of stable sediment-free anaerobic bacterial enrichment cultures that dechlorinate aroclor 1260. Appl Environ Microbiol 72 (4):2460-2470.

Bernert JT, Turner WE, Patterson DG, Jr. et al. 2007. Calculation of serum "total lipid" concentrations for the adjustment of persistent organohalogen toxicant measurements in human samples. Chemosphere 68 (5):824-831.

Beyer A, Biziuk M. 2008. Methods for determining pesticides and polychlorinated biphenyls in food samples-problems and challenges. Crit Rev Food Sci Nutr 48 (10):888-904.

Bezdecny SA, Roth RA, Ganey PE. 2005. Effects of 2,2',4,4'-tetrachlorobiphenyl on granulocytic HL-60 cell function and expression of cyclooxygenase-2. Toxicol Sci 84 (2):328-34.

Bloom MS, Vena JE, Swanson MK et al. 2005. Profiles of ortho-polychlorinated biphenyl congeners, dichlorodiphenyldichloroethylene, hexachlorobenzene, and Mirex among male Lake Ontario sportfish consumers: the New York State Angler cohort study. Environ Res 97 (2):178-194.

Bloom MS, Buck Louis GM, Schisterman EF et al. 2007. Maternal serum polychlorinated biphenyl concentrations across critical windows of human development. Environ Health Perspect 115 (9):1320-1324.

Bloom MS, Vena JE, Olson JR et al. 2009. Assessment of polychlorinated biphenyl congeners, thyroid stimulating hormone, and free thyroxine among New York state anglers. Int J Hyg Environ Health 212 (6):599-611.

Boix J, Cauli O, Felipo V. 2010. Developmental exposure to polychlorinated biphenyls 52, 138 or 180 affects differentially learning or motor coordination in adult rats. Mechanisms involved. Neuroscience 167 (4):994-1003.

Borlak J, Jenke HS. 2008. Cross-talk between aryl hydrocarbon receptor and mitogen-activated protein kinase signaling pathway in liver cancer through c-raf transcriptional regulation. Mol Cancer Res 6 (8):1326-1336.

Brody JG, Moysich KB, Humblet O et al. 2007. Environmental pollutants and breast cancer: epidemiologic studies. Cancer 109 (12 Suppl):2667-2711.

Brown JF, Jr., Mayes BA, Silkworth JB et al. 2007. Polychlorinated biphenyls modulated tumorigenesis in Sprague Dawley rats: correlation with mixed function oxidase activities and superoxide (O2*) formation potentials and implied mode of action. Toxicol Sci 98 (2):375-394.

Brunner MJ, Sullivan TM, Singer AW et al. 1996. An assessment of the chronic toxicity and oncogenicity of Aroclor 1016, Aroclor 1242, Aroclor 1254, and Aroclor 1260 administered in diet to rats. Battelle study no. SC920192, Columbus, OH.

Bryce F, Hayward S, Stapley R et al. 2000. Consequences of Aroclor 1254 ingestion on the menstrual cycle of rhesus (*Macaca mulatta*) monkeys. Food Chem Toxicol 38 (11):1053-1064.

Buck GM, Sever LE, Mendola P, et al. 1997. Consumption of contaminated sport fish from Lake Ontario and time-to-pregnancy. Am J Epidemiol 146:949-954.

Buck GM, Mendola P, Vena JE, et al. 1999. Paternal Lake Ontario fish consumption and risk of conception delay, New York State angler cohort. Environ Res 80:S13-S18.

Buck GM, Vena JE, Schisterman EF, et al. 2000. Parental consumption of contaminated sport fish from Lake Ontario and predicted fecundability. Epidemiology 11:388-393.

Buck Louis GM, Dmochowski J, Lynch C et al. 2009. Polychlorinated biphenyl serum concentrations, lifestyle and time-to-pregnancy. Hum Reprod 24 (2):451-458.

Buckman AH, Wong CS, Chow EA et al. 2006. Biotransformation of polychlorinated biphenyls (PCBs) and bioformation of hydroxylated PCBs in fish. Aquat Toxicol 78 (2):176-185.

Burgin et al. 2001 Burgin DE, Diliberto JJ, Derr-Yellin EC et al. Differential effects of two lots of aroclor 1254 on enzyme induction, thyroid hormones, and oxidative stress. Environ Health Perspect 2001; 109 (11):1163-1168.

Burkhard LP, Lukasewycz MT. 2008. Toxicity equivalency values for polychlorinated biphenyl mixtures. Environ Toxicol Chem 27 (3):529-534.

California Environmental Protection Agency (CA EPA). 2008. Development of Fish Contaminant Goals and Advisory Tissue Levels for Common Contaminants in California Sport Fish: Chlordane, DDTs, Dieldrin, Methylmercury, PCBs, Selenium, and Toxaphene. http://oehha.ca.gov/fish/gtlsv/pdf/FCGsATLs27June2008.pdf

Campbell AS, Yu Y, Granick S et al. 2008. PCB association with model phospholipid bilayers. Environ Sci Technol 42 (19):7496-7501.

Cao Y, Winneke G, Wilhelm M et al. 2008. Environmental exposure to dioxins and polychlorinated biphenyls reduce levels of gonadal hormones in newborns: results from the Duisburg cohort study. Int J Hyg Environ Health 211 (1-2):30-39.

Carpenter DO. 2006. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. Rev Environ Health 21 (1):1-23.

Carpenter DO, DeCaprio AP, O'Hehir D et al. 2005. Polychlorinated biphenyls in serum of the Siberian Yupik people from St. Lawrence Island, Alaska. Int J Circumpolar Health 64 (4):322-335.

Casey AC, Berger DF, Lombardo JP, et al. 1999. Aroclor 1242 inhalation and ingestion by Sprague-Dawley rats. J Toxicol Environ Health 56:311-342.

Cheek AO, Kow K, Chen J, et al. 1999. Potential mechanisms of thyroid disruption in humans: Interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. Environ Health Perspect 107(4):273-278.

Chevrier J, Eskenazi B, Bradman A et al. 2007. Associations between prenatal exposure to polychlorinated biphenyls and neonatal thyroid-stimulating hormone levels in a Mexican-American population, Salinas Valley, California. Environ Health Perspect 115 (10):1490-1496.

Chevrier J, Eskenazi B, Holland N et al. 2008. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. Am J Epidemiol 168 (3):298-310.

Chu I, Poon R, Yagminas A et al. 1998. Subchronic toxicity of PCB 105 (2,3,3',4,4'-pentachlorobiphenyl) in rats. J Appl Toxicol 18 (4):285-292.

Chu I, Lecavalier P, Hakansson H et al. 2001. Mixture effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and polychlorinated biphenyl congeners in rats. Chemosphere 43 (4-7):807-814.

Codru N, Schymura MJ, Negoita S et al. 2007. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans. Environ Health Perspect 115 (10):1442-1447.

Cogliano VJ. 1998. Assessing the cancer risk from environmental PCBs. Environ Health Perspect 106(6):317-323.

Cole et al. 2002 Cole DC, Sheeshka J, Murkin EJ et al. 2002. Dietary intakes and plasma organochlorine contaminant levels among Great Lakes fish eaters. Arch Environ Health 57 (5):496-509.

Cooper GS, Savitz DA, Millikan R et al. 2002. Organochlorine exposure and age at natural menopause. Epidemiology 13 (6):729-733.

Cordle F, Locke R, Springer J. 1982. Risk assessment in a federal regulatory agency: An assessment of risk associated with the human consumption of some species of fish contaminated with polychlorinated biphenyls (PCBs). Environ Health Perspect 45:171-182.

Covaci A, Voorspoels S, Roosens L et al. 2008. Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in human liver and adipose tissue samples from Belgium. Chemosphere 73 (2):170-175.

Craft ES, DeVito MJ, Crofton KM. 2002. Comparative responsiveness of hypothyroxinemia and hepatic enzyme induction in Long-Evans rats versus C57BL/6J mice exposed to TCDD-like and phenobarbital-like polychlorinated biphenyl congeners. Toxicol Sci 68 (2):372-380.

Dallaire F, Dewailly E, Vezina C et al. 2006. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. Environ Health Perspect 114 (8):1301-1305.

Dallaire R, Dewailly E, Ayotte P et al. 2008. Effects of prenatal exposure to organochlorines on thyroid hormone status in newborns from two remote coastal regions in Quebec, Canada. Environ Res 108 (3):387-392.

Dallaire R, Muckle G, Dewailly E et al. 2009.Thyroid hormone levels of pregnant inuit women and their infants exposed to environmental contaminants. Environ Health Perspect 117 (6):1014-1020.

Dallinga JW, Moonen EJ, Dumoulin JC et al. 2002. Decreased human semen quality and organochlorine compounds in blood. Hum Reprod 17 (8):1973-1979.

Dean CE, Jr., Benjamin SA, Chubb LS et al. 2002. Nonadditive hepatic tumor promoting effects by a mixture of two structurally different polychlorinated biphenyls in female rat livers. Toxicol Sci 66 (1):54-61.

DeCaprio AP, Johnson GW, Tarbell AM et al. 2005. Polychlorinated biphenyl (PCB) exposure assessment by multivariate statistical analysis of serum congener profiles in an adult Native American population. Environ Res 98 (3):284-302.

Elzanaty S, Rignell-Hydbom A, Jonsson BA et al. 2006. Association between exposure to persistent organohalogen pollutants and epididymal and accessory sex gland function: multicentre study in Inuit and European populations. Reprod Toxicol 22 (4):765-773.

Engel LS, Lan Q, Rothman N. 2007. Polychlorinated biphenyls and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 16 (3):373-376.

Ennaceur S, Gandoura N, Driss MR. 2008. Distribution of polychlorinated biphenyls and organochlorine pesticides in human breast milk from various locations in Tunisia: levels of contamination, influencing factors, and infant risk assessment. Environ Res 108 (1):86-93.

Erdal S, Berman L, Hryhorczuk DO. 2008. Multimedia emissions inventory of polychlorinated biphenyls for the U.S. Great Lakes states. J Air Waste Manag Assoc 58 (8):1022-1032.

Everett CJ, Frithsen IL, Diaz VA et al. 2007. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999-2002 National Health and Nutrition Examination Survey. Environ Res 103 (3):413-418.

Faroon O, Jones D, de Rosa C. 2000. Effects of polychlorinated biphenyls on the nervous system. Toxicol Ind Health 16 (7-8):305-333.

Feeley MM. 1995. Biomarkers for Great Lakes priority contaminants: halogenated aromatic hydrocarbons. Environ Health Perspect 103 Suppl 9:7-16.

Feeley MM, Jordan SA. 1998. Dietary and tissue residue analysis and contaminant intake estimations in rats consuming diet composed of Great Lakes salmon: A multigeneration study. Regul Toxicol Pharmacol 27(1 Part 2):S8-S17.

Feeley MM, Jordan SA, Gilman AP. 1998. The Health Canada Great Lakes multigeneration study – summary and regulatory considerations. Regul Toxicol Pharmacol 27:S90-S98.

Fierens S, Mairesse H, Heilier JF et al. 2003. Dioxin/polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium. Biomarkers 8 (6):529-534.

Fonnum F, Mariussen E, Reistad T. 2006. Molecular mechanisms involved in the toxic effects of polychlorinated biphenyls (PCBs) and brominated flame retardants (BFRs). J Toxicol Environ Health A 69 (1-2):21-35.

Fournier M, Degas V, Colborn T et al. 2000. Immunosuppression in mice fed on diets containing beluga whale blubber from the St Lawrence estuary and the Arctic populations. Toxicol Lett 112-113:311-17.

Fritsche E, Cline JE, Nguyen NH et al. 2005. Polychlorinated biphenyls disturb differentiation of normal human neural progenitor cells: clue for involvement of thyroid hormone receptors. Environ Health Perspect 113 (7):871-876.

Ganey PE, Boyd SA. 2005. An approach to evaluation of the effect of bioremediation on biological activity of environmental contaminants: dechlorination of polychlorinated biphenyls. Environ Health Perspect 113 (2):180-185.

Gerstenberger SL, Tavris DR, Hansen LK et al. 1997. Concentrations of blood and hair mercury and serum PCBs in an Ojibwa population that consumes Great Lakes region fish. J Toxicol Clin Toxicol 35 (4):377-386.

Gerstenberger SL, Dellinger JA, Hansen LG. 2000. Concentrations and frequencies of polychlorinated biphenyl congeners in a Native American population that consumes Great Lakes fish. J Toxicol Clin Toxicol 38 (7):729-746.

Giesy JP, Kannan K. 1998. Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): Implications for risk assessment. Crit Rev Toxicol 28 (6):511-569.

Givens ML, Small CM, Terrell ML et al. 2007. Maternal exposure to polybrominated and polychlorinated biphenyls: infant birth weight and gestational age. Chemosphere 69 (8):1295-1304.

Glynn A, Thuvander A, Aune M et al. 2008. Immune cell counts and risks of respiratory infections among infants exposed pre- and postnatally to organochlorine compounds: a prospective study. Environ Health 7:62.

Goncharov A, Haase RF, Santiago-Rivera A et al. 2008. High serum PCBs are associated with elevation of serum lipids and cardiovascular disease in a Native American population. Environ Res 106 (2):226-39.

Goncharov A, Rej R, Negoita S et al. 2009. Lower serum testosterone associated with elevated polychlorinated biphenyl concentrations in Native American men. Environ Health Perspect 117 (9):1454-1460.

Grandjean P, Budtz-Jorgensen E, Barr DB et al. 2008. Elimination half-lives of polychlorinated biphenyl congeners in children. Environ Sci Technol 42 (18):6991-6.

Great Lakes Sport Fish Advisory Task Force (GLSPATF) 1993. Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory. http://www.fish.state.pa.us/images/fisheries/fcs/pcb_fishtech.pdf.

Guo YL, Yu M-L, Hsu C-C, et al. 1999. Chloracne, goiter, arthritis, and anemia after polychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. Environ Health Perspect 107(9):715-719.

Guo YL, Hsu PC, Hsu CC et al. 2000. Semen quality after prenatal exposure to polychlorinated biphenyls and dibenzofurans. Lancet 356 (9237):1240-1241.

Ha MH, Lee DH, Jacobs DR. 2007. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999-2002. Environ Health Perspect 115 (8):1204-1209.

Haag-Gronlund M, Kato Y, Fransson-Steen R et al. 1997. Promotion of enzyme altered foci in female rat 2,3,3',4,4',5-hexachlorobiphenyl. Toxicol Appl Pharmacol 147 (1):46-55.

Haase RF, McCaffrey RJ, Santiago-Rivera AL et al. 2009. Evidence of an age-related threshold effect of polychlorinated biphenyls (PCBs) on neuropsychological functioning in a Native American population. Environ Res 109 (1):73-85.

Halldorsson TI, Thorsdottir I, Meltzer HM et al. 2008. Linking exposure to polychlorinated biphenyls with fatty fish consumption and reduced fetal growth among Danish pregnant women: a cause for concern? Am J Epidemiol; 168 (8):958-965.

Hanrahan LP, Falk C, Anderson HA, et al. 1999. Serum PCB and DDE levels of frequent Great Lakes sport fish consumers – A first look. Environ Res 80:S26-S37.

Hauser R, Chen Z, Pothier L et al. 2003. The relationship between human semen parameters and environmental exposure to polychlorinated biphenyls and p,p'-DDE. Environ Health Perspect 111 (12):1505-1511.

He JP, Stein AD, Humphrey HE et al. 2001. Time trends in sport-caught Great Lakes fish consumption and serum polychlorinated biphenyl levels among Michigan Anglers, 1973-1993. Environ Sci Technol 35 (3):435-440.

Heilier JF, Nackers F, Verougstraete V et al. 2005. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. Fertil Steril 84 (2):305-312.

Heilmann C, Grandjean P, Weihe P et al. 2006. Reduced antibody responses to vaccinations in children exposed to polychlorinated biphenyls. PLoS Med 3 (8):e311.

Herbstman JB, Sjodin A, Apelberg BJ et al. 2008. Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polybrominated diphenyl ether (PBDE) and neonatal thyroid hormone levels. Environ Health Perspect 116 (10):1376-1382.

Hertz-Picciotto I, Charles MJ, James RA et al. 2005. In utero polychlorinated biphenyl exposures in relation to fetal and early childhood growth. Epidemiology 16 (5):648-656.

Hsu JF, Guo YL, Yang SY et al. 2005. Congener profiles of PCBs and PCDD/Fs in Yucheng victims fifteen years after exposure to toxic rice-bran oils and their implications for epidemiologic studies. Chemosphere 61 (9):1231-1243.

National Toxicology Program (NTP) Report on Carcinogens, Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. (updated: February 2009; accessed: June 2010) Available from: http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932

Ikeda M. 1996. Comparison of clinical picture between Yusho/Yucheng cases and occupational PCB poisoning cases. Chemosphere 32 (3):559-566.

Imamura T, Matsumoto S, Akahane M et al. 2009. Cutaneous symptoms such as acneform eruption and pigmentation are closely associated with blood levels of 2,3,4,7,8-penta-chlorodibenzofurans in Yusho patients, using data mining analysis. BMC Res Notes 2:27.

International Agency for Research on Cancer (IARC). 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 7: Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1 to 42. World Health Organization, Lyon, France.

Iverson F, Mehta R, Hierlihy L et al. 1998. Microsomal enzyme activity, glutathione S-transferase-placental form expression, cell proliferation, and vitamin A stores in livers of rats consuming Great Lakes salmon. Regul Toxicol Pharmacol 27 (1 Pt 2):S76-89.

Jacobson JL, Jacobson SW, Schwartz PM, et al. 1984. Prenatal exposure to an environmental toxin: A test of the multiple effects model. Dev Psychol 20:523-532.

Jacobson SW, Fein GG, Jacobson JL, et al. 1985. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 56:853-860.

Jacobson JL, Jacobson SW, Humphrey HE. 1990. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 116 (1):38-45.

Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335 (11):783-789.

Jacobson JL, Janisse J, Banerjee M et al. 2002. A benchmark dose analysis of prenatal exposure to polychlorinated biphenyls. Environ Health Perspect 110 (4):393-398.

Jacobson JL, Jacobson SW. 2003. Prenatal exposure to polychlorinated biphenyls and attention at school age. J Pediatr 143 (6):780-788.

Johnson-Restrepo B, Kannan K, Rapaport DP et al. 2005. Polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissue from New York. Environ Sci Technol 39 (14):5177-5182.

Jordan SA, Feeley MM. 1999. PCB congener patterns in rats consuming diets containing Great Lakes salmon: analysis of fish, diets, and adipose tissue. Environ Res 80 (2 Pt 2):S207-S12.

Judd N, Griffith WC, Faustman EM. 2004. Contribution of PCB exposure from fish consumption to total dioxin-like dietary exposure. Regul Toxicol Pharmacol 40 (2):125-135.

Kania-Korwel I, Hornbuckle KC, Peck A et al. 2005.Congener-specific tissue distribution of aroclor 1254 and a highly chlorinated environmental PCB mixture in rats. Environ Sci Technol 39 (10):3513-3520.

Karmaus W, Zhu X. 2004. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: a cohort study. Environ Health 3 (1):1.

Kato Y, Haraguchi K, Yamazaki T et al. 2003. Effects of polychlorinated biphenyls, kanechlor-500, on serum thyroid hormone levels in rats and mice. Toxicol Sci 72 (2):235-241.

Kato Y, Ikushiro S, Haraguchi K et al. 2004. A possible mechanism for decrease in serum thyroxine level by polychlorinated biphenyls in Wistar and Gunn rats. Toxicol Sci 81 (2):309-315.

Khan MA, Lichtensteiger CA, Faroon O et al. 2002. The hypothalamo-pituitary-thyroid (HPT) axis: a target of nonpersistent ortho-substituted PCB congeners. Toxicol Sci 65 (1):52-61.

Kimbrough RD, Krouskas CA. 2003. Human exposure to polychlorinated biphenyls and health effects: a critical synopsis. Toxicol Rev 22 (4):217-233.

Kunz S, Schwarz M, Schilling B et al. 2006. Tumor promoting potency of PCBs 28 and 101 in rat liver. Toxicol Lett 164 (2):133-143.

Kuriyama S, Fidalgo-Neto A, Mathar W et al. 2003. Effect of low dose mono-ortho 2,3',4,4',5 pentachlorobiphenyl on thyroid hormone status and EROD activity in rat offspring: consequences for risk assessment. Toxicology 186 (1-2):11-20.

Lee DH, Lee IK, Song K et al. 2006. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. Diabetes Care 29 (7):1638-1644.

Lee DH, Lee IK, Jin SH et al. 2007A. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care. 30(3):622-8.

Lee DH, Lee IK, Porta M et al. 2007B. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetologia 50 (9):1841-1851.

Lee DH, Steffes M, Jacobs DR. 2007C. Positive associations of serum concentration of polychlorinated biphenyls or organochlorine pesticides with self-reported arthritis, especially rheumatoid type, in women. Environ Health Perspect 115 (6):883-888.

Levin M, Morsey B, Mori C et al. 2005. Non-coplanar PCB-mediated modulation of human leukocyte phagocytosis: a new mechanism for immunotoxicity. J Toxicol Environ Health A 68 (22):1977-1993.

Longnecker MP, Klebanoff MA, Brock JW et al. 2001. Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. Diabetes Care 24 (6):1099-1101.

Longnecker MP, Klebanoff MA, Brock JW et al. 2005. Maternal levels of polychlorinated biphenyls in relation to preterm and small-for-gestational-age birth. Epidemiology 16 (5):641-7.

Masuda Y, Schecter A, Papke O. 1998. Concentrations of PCBs, PCDFs and PCDDs in the blood of Yusho patients and their toxic equivalent contribution. Chemosphere 37 (9-12):1773-1780.

Mayes BA, McConnell EE, Neal BH, et al. 1998. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixtures Aroclors 1016, 1242, 1254, and 1260. Toxicol Sci 41(1):62-76.

Michigan Department of Environmental Quality (MDEQ) 2010. Michigan Fish Contaminant Monitoring Program 2010 Annual Edible Portion Report. MI/DEQ/WRD-11/028. http://www.michigan.gov/documents/deq/wrd-swas-fcmp-2010report_361228_7.pdf.

Ministry of the Environment (MoE). 2009. Guide to Eating Ontario Sport Fish 2009 – 2010 Edition. Twenty-fourth Edition, Revised. Ontario, Canada. Queen's Printer for Ontario. http://www.ene.gov.on.ca/publications/590b14.pdf.

Muir D, Sverko E. 2006. Analytical methods for PCBs and organochlorine pesticides in environmental monitoring and surveillance: a critical appraisal. Anal Bioanal Chem 386 (4):769-789.

Narita S, Goldblum RM, Watson CS et al. 2007. Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators. Environ Health Perspect 115 (1):48-52.

Nichols, B. R., Hentz, K. L., Aylward, L., et al. 2007. Age-specific reference ranges for polychlorinated biphenyls (PCB) based on the NHANES 2001-2002 survey. J Toxicol Environ Health A 70 (21): 1873-1877.

Nomiyama K, Tanizaki T, Arizono K et al. 2007. Endocrine effects generated by photooxidation of coplanar biphenyls in water using titanium dioxide. Chemosphere 66 (6):1138-45.

Onozuka D, Yoshimura T, Kaneko S et al. 2009. Mortality after exposure to polychlorinated biphenyls and polychlorinated dibenzofurans: a 40-year follow-up study of Yusho patients. Am J Epidemiol 169 (1):86-95.

Pappas BA, Murtha SJE, Park GAS, et al. 1998. Neurobehavioral effects of chronic ingestion of Great Lakes chinook salmon. Regul Toxicol Pharmacol 27:S55-S67.

Rhainds M, Levallois P, Dewailly E et al. 1999. Lead, mercury, and organochlorine compound levels in cord blood in Quebec, Canada. Arch Environ Health 54 (1):40-7.

Richthoff J, Rylander L, Jonsson BA et al. 2003. Serum levels of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) in relation to markers of reproductive function in young males from the general Swedish population. Environ Health Perspect 111 (4):409-13.

Rignell-Hydbom A, Rylander L, Hagmar L. 2007. Exposure to persistent organochlorine pollutants and type 2 diabetes mellitus. Hum Exp Toxicol 26 (5):447-52.

Ruiz P, Faroon O, Moudgal CJ et al. 2008. Prediction of the health effects of polychlorinated biphenyls (PCBs) and their metabolites using quantitative structure-activity relationship (QSAR). Toxicol Lett 181 (1):53-65.

Rylander L, Stromberg U, Dyremark E, et al. 1998. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. Am J Epidemiol 147:493-502.

Rylander L, Rignell-Hydbom A, Hagmar L. 2005. A cross-sectional study of the association between persistent organochlorine pollutants and diabetes. Environ Health 4:28.

Safe S, Bandiera S, Sawyer T, et al. 1985. PCBs: Structure-function relationships and mechanism of action. Environ Health Perspect 60: 47-56.

Schantz SL, Gardiner JC, Gasior DM et al. 1999. Motor function in aging Great Lakes fisheaters. Environ Res 80 (2 Pt 2):S46-S56.

Schantz SL, Gasior DM, Polverejan E et al. 2001. Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of Great Lakes fish. Environ Health Perspect 109 (6):605-11.

Schecter A, Kassis I, Papke O. 1998. Partitioning of dioxins, dibenzofurans, and coplanar PCBs in blood, milk, adipose tissue, placenta and cord blood from five American women. Chemosphere 37: 1817-1823.

Schilderman PA, Maas LM, Pachen DM, de Kok TM, Kleinjans JC, van Schooten FJ. 2000. Induction of DNA adducts by several polychlorinated biphenyls. Environ Mol Mutagen. 36(2):79-86.

Seegal RF, Pappas BA, Park GAS. 1998. Neurochemical effects of consumption of Great Lakes salmon by rats. Regul Toxicol Pharmacol 27:S68-S75.

Skerfving S, Svensson BG, Asplund L et al. 1994. Exposure to mixtures and congeners of polychlorinated biphenyls. Clin Chem 40 (7 Pt 2):1409-15.

Smithwick LA, Smith A, Quensen JF, 3rd et al. 2003. Inhibition of LPS-induced splenocyte proliferation by ortho-substituted polychlorinated biphenyl congeners. Toxicology 188 (2-3):319-33.

Stewart PW, Lonky E, Reihman J et al. 2008. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. Environ Health Perspect 116 (10):1416-22.

Sun P, Basu I, Blanchard P et al. 2007. Temporal and spatial trends of atmospheric polychlorinated biphenyl concentrations near the Great Lakes. Environ Sci Technol 41 (4):1131-6.

Sun P, Basu I, Hites RA. 2006. Temporal trends of polychlorinated biphenyls in precipitation and air at Chicago. Environ Sci Technol 40 (4):1178-83.

Todaka T, Hirakawa H, Hori T et al. 2007. Concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and non-ortho and mono-ortho polychlorinated biphenyls in blood of Yusho patients. Chemosphere 66 (10):1983-9.

Todaka T, Hori T, Hirakawa H et al. 2009. Concentrations of polychlorinated biphenyls in blood of Yusho patients over 35 years after the incident. Chemosphere 74 (7):902-9.

Tryphonas L, Truelove J, Zawidzka Z, et al. 1984. Polychlorinated biphenyl (PCB) toxicity in adult Cynomolgus monkeys (*M. fascicularis*): A pilot study. Toxicol Pathol 12(1):10-25.

Tryphonas L, Arnold DL, Zawidzka Z, et al. 1986. A pilot study in adult Rhesus monkeys (*M. mulatta*) treated with Aroclor 1254 for two years. Toxicol Pathol 14:1-10.

Tryphonas H, McGuire P, Fernie S, et al. 1998A. Effects of Great Lakes fish consumption on the immune system of Sprague-Dawley rats investigated during a two-generation reproductive study: I. Body and organ weights, food consumption, and hematological parameters. Regul Toxicol Pharmacol 27:S28-S39.

Tryphonas H, Fournier M, Lacroix F, et al. 1998B. Effects of Great Lakes fish consumption on the immune system of Sprague-Dawley rats investigated during a two-generation reproductive study: II. Quantitative and functional aspects. Regul Toxicol Pharmacol 27:S40-S54.

Tsukimori K, Tokunaga S, Shibata S et al. 2008. Long-term effects of polychlorinated biphenyls and dioxins on pregnancy outcomes in women affected by the Yusho incident. Environ Health Perspect 116 (5):626-30.

U.S. Environmental Protection Agency (EPA). 1996A. PCBs: Cancer dose-response assessment and application to environmental mixtures. Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development. EPA/600/P-96/001F.

U.S. Environmental Protection Agency (EPA) Integrated Risk Information System Aroclor 1016 (CASRN 12674-11-2). (updated 1996B; accessed 2010) Available from: http://www.epa.gov/ncea/iris/subst/0462.htm.

U.S. Environmental Protection Agency (EPA) Integrated Risk Information System Aroclor 1254 (CASRN 11097-69-1). (updated 1996C; accessed 2010). Available from: http://www.epa.gov/ncea/iris/subst/0389.htm.

U.S. Environmental Protection Agency (EPA). Integrated Risk Information System Polychlorinated biphenyls (PCBs) (CASRN 1336-36-3). (updated 1997A; accessed 2010). Available from: http://www.epa.gov/ncea/iris/subst/0294.htm.

U.S. Environmental Protection Agency (EPA). 1997B. Exposure Factors Handbook. Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. Office of Research and Development. EPA/600/P-95/002Fa.

U.S. Environmental Protection Agency (EPA) 1998. Update: Listing of fish and wildlife advisories. Fact Sheet. U.S. Environmental Protection Agency, Office of Water. EPA-823-F-98-009.

U.S. Environmental Protection Agency (EPA). 2000A. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories Volume 1 Fish Sampling and Analysis, Third Edition Washington DC: U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. EPA 823-B-00-007.

U.S. Environmental Protection Agency (EPA). 2000B. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories Volume 2 Risk Assessment and Fish Consumption Limits, Third Edition. Washington DC: U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. EPA 823-B-00-008.

U.S. Environmental Protection Agency (EPA) 2008. Framework for Application of the Toxicity Equivalence Methodology for Polychlorinated Dioxins, Furans, and Biphenyls in Ecological Risk Assessment Washington, DC: U.S. Environmental Protection Agency, Office of the Science Advisor, Risk Assessment Forum. EPA 100/R-08/004.

U.S. Environmental Protection Agency (EPA). 2009. National Maps and Graphics (PDF) for 2008 Data. http://www.epa.gov/waterscience/fish/advisories/nlfaslides.pdf.

Van den Berg M, Birnbaum LS, Denison M et al. 2006. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 93 (2):223-41.

Van Den Heuvel RL, Koppen G, Staessen JA et al. 2002. Immunologic biomarkers in relation to exposure markers of PCBs and dioxins in Flemish adolescents (Belgium). Environ Health Perspect 110 (6):595-600.

van der Plas SA, Haag-Gronlund M, Scheu G, et al. 1999. Induction of altered hepatic foci by a mixture of dioxin-like compounds with and without 2,2',4,4',5,5'-hexachlorobiphenyl in female Sprague-Dawley rats. Toxicol Appl Pharmacol 156:30-39.

van der Plas SA, Lutkeschipholt I, Spenkelink B et al. 2001; Effects of subchronic exposure to complex mixtures of dioxin-like and non-dioxin-like polyhalogenated aromatic compounds on

thyroid hormone and vitamin A levels in female Sprague-Dawley rats. Toxicol Sci 59 (1):92-100.

Vasiliu O, Muttineni J, Karmaus W. 2004. *In utero* exposure to organochlorines and age at menarche. Hum Reprod 19 (7):1506-12.

Vasiliu O, Cameron L, Gardiner J et al. 2006. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. Epidemiology 17 (4):352-9.

Venkataraman P, Sridhar M, Dhanammal S et al. 2004. Antioxidant role of zinc in PCB (Aroclor 1254) exposed ventral prostate of albino rats. J Nutr Biochem 15 (10):608-13.

Wade MG, Foster WG, Younglai EV et al. 2002. Effects of subchronic exposure to a complex mixture of persistent contaminants in male rats: systemic, immune, and reproductive effects. Toxicol Sci 67 (1):131-43.

Wang SL, Chen TT, Hsu JF et al. 2003. Neonatal and childhood teeth in relation to perinatal exposure to polychlorinated biphenyls and dibenzofurans: observations of the Yucheng children in Taiwan. Environ Res 93 (2):131-7.

Wang SL, Tsai PC, Yang CY et al. 2008. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care 31 (8):1574-9.

Weisskopf MG, Anderson HA, Hanrahan LP et al. 2005. Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. Environ Res 97 (2):149-62.

Whysner J, Wang CX. 2001. Hepatocellular iron accumulation and increased cell proliferation in polychlorinated biphenyl-exposed Sprague-Dawley rats and the development of hepatocarcinogenesis. Toxicol Sci 62 (1):36-45.

Windham GC, Lee D, Mitchell P et al. 2005. Exposure to organochlorine compounds and effects on ovarian function. Epidemiology 16 (2):182-90.

Wolff MS, Deych E, Ojo F et al. 2005. Predictors of organochlorines in New York City pregnant women, 1998-2001. Environ Res 97 (2):170-7.

Yu ML, Guo YL, Hsu CC et al. 1997. Increased mortality from chronic liver disease and cirrhosis 13 years after the Taiwan "Yucheng" ("oil disease") incident. Am J Ind Med 31 (2):172-5.

Yu M-L, Hsin J-W, Hsu C-C, et al. 1998. The immunologic evaluation of the Yucheng children. Chemosphere 37(9-12):1855-1865.

Yu ML, Guo YL, Hsu CC et al. 2000. Menstruation and reproduction in women with polychlorinated biphenyl (PCB) poisoning: long-term follow-up interviews of the women from the Taiwan Yucheng cohort. Int J Epidemiol 29 (4):672-7.

## Certification

This Health Consultation was prepared by the Michigan Department of Community Health under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR). It is in accordance with approved methodology and procedures. Editorial review was completed by the cooperative agreement partner.

_____

Technical Project Officer, Cooperative Agreement Program Evaluation Branch (CAPEB), Division of Health Assessment and Consultation (DHAC), ATSDR

The Division of Health Assessment and Consultation, ATSDR, has reviewed this public health consultation and concurs with the findings.

_____

Team Leader, CAPEB, DHAC, ATSDR

Appendix A: Synonyms for Polychlorinated Biphenyls (CAS #1336-36-3)

1,1'-Biphenyl, chloro derives
Apirolio (Italy)
Aroclor
Aroclor 1221
Aroclor 1232
Aroclor 1242
Aroclor 1248
Aroclor 1254
Aroclor 1260
Aroclor 1262
Aroclor 1268
Aroclor 2565
Aroclor 4465
Aroclor 5442
Aroclors
Biphenyl, chlorinated
Biphenyl, polychloro-
Caswell No. 672A
CCRIS 526
Chlophen
Chloretol
Chlorextol
Chlorinated biphenyl
Chlorinated diphenyl
Chlorinated diphenylene
Chloro 1,1-biphenyl
Chloro biphenyl
Clophen (West Germany)
Delor (Czechoslovakia)
Dykanol
Dyknol
EINECS 215-648-1
EPA Pesticide Chemical Code 017801
Fenclor (Italy)
Fenclor 42
HSDB 3945
Inerteen
Kanechlor (Japan)
Kanechlor 300
Kanechlor 400
Montar
Monter
Noflamol
PCB
PCBs
Phenochlor
Phenoclor (France)
Polychlorinated Biphenyls
Polychlorobiphenyl
Pyralene (France)
Pyranol
Santotherm
Soval (USSR)
Sovol
Therminol
Therminol 1336-36-3
Therminol fr-1
UN 2315

## Appendix B: Additional Discussion of Toxicokinetics

Half-lives for PCB congeners were calculated in two different populations. One population consisted of people poisoned, called either Yusho or Yucheng poisoning, from ingesting rice oil contaminated with PCBs. The other population are children from the Faroe Islands, who ingest PCBs from eating marine fish and mammals, including pilot whale.

Half-lives of PCB congeners were calculated from people affected by two different poisonings, Yusho and Yucheng. Blood samples were collected eight to eleven times between 1982 and 1998 from five Yusho women, ages 31 to 51 at the time of exposure. The blood samples were collected between 14 to 29.1 years after the Yusho exposure began. PCB congener half-lives from the Yusho patients were calculated to average 9.4 to 118.3 years, with a median of 14.6 years. Blood was collected seven to eight times between 1980 to 1995 from two male and 1 female Yucheng patients that were ages 17 to 33 at the time of exposure. Half-lives of PCB congeners from the Yucheng patients averaged 3.7 to 4.7 years, with a median of 4.6 years (Masuda et al. 2001).

The second population, children from the Faroe Islands, had half-lives of PCB congeners in blood assessed. The daily PCB intake for a Faroese infant was estimated as 8.0 micrograms per kilogram per day (µg/kg-day). PCB levels were reported as the sum of PCB 138, 153, and 180 multiplied by two. Two cohorts of pregnant women and their offspring were followed for several years. PCB congener half-life was examined in blood samples from Faroese children. Based on the estimated intake and the serum levels of PCBs elimination half-lives for eight major PCB congeners (105, 118, 138, 153, 16, 170, 180, and 187), the half-life range was 3.1 to 17.9 years. For those with a PCB level in the highest quartile, the half-life range was 2.7 to 9.4 years. PCBs can be excreted with fecal lipids and metabolic elimination occurs, converting PCBs into polar hydroxylated metabolites. Highly chlorinated PCBs, such as 153 and 180, can persist in the body. PCBs 138, 105, and 118 had shorter half-lives (Grandjean et al. 2008). Table B-1 presents the PCB levels in Faroese children.

Table B-1: PCB levels in two cohorts of Faroese children (Grandjean et al. 2008).

| | First cohort | | Second cohort | |
|---|---|---|---|---|
| | Age (years) | Serum PCB levels (geometric mean [50% range]) in µg/g | Age (years) | Serum PCB levels (geometric mean [50% range]) in µg/g |
| Maternal serum | NA | ND | NA | 1.22 (0.71 – 1.87) |
| First exam | 6.7 ± 0.2 | 1.71 (1.06 – 2.66) | 4.6 ± 0.1 | 0.95 (0.50 – 1.79) |
| Second exam | 13.8 ± 0.3 | 0.86 (0.47 – 1.62) | 7.6 ± 0.1 | 0.79 (0.46 – 1.43) |

NA = not applicable
ND = not determined

Appendix C: Extended Discussion of Human Biomonitoring

Great Lakes populations

Great Lakes populations include Native American tribal members and other Great Lakes sport fish consumers living in locations around the Great Lakes. Locations around the Great Lakes include Canada and various states in the U.S.

Ojibwa tribal members, 48 female and 41 male, were assessed for PCB levels. The participants ranged in age from 18 to 71 with a mean age of 37.9 years. Blood samples were available for 75 individuals, and 66 samples were analyzed for PCB levels. For 11 participants, PCB levels ranged from below the level of quantitation to 1.6 ppb. For the other 55 participants, PCB levels had a mean of 3.7 ppb and maximum value of 9.6 ppb. The three most frequently eaten species were lake trout, walleye, and whitefish. No association was identified between fish consumption and PCB serum levels. However, there was a significant association between fish consumption and age (Gerstenberger et al. 1997).

Consumers of sport fish from three of the Great Lakes participated in a study to measure PCDDs (eight congeners), PCDFs (10 congeners), PCBs (four coplanar and 32 non-coplanar congeners), chlorinated pesticides (11), lead and mercury in their blood. Urine was analyzed for 10 non-persistent pesticides or metabolites and five metals. Participants were consumers of Lake Michigan (n = 9), Lake Huron (n = 11), and Lake Erie (n = 11) sport fish. Twenty-one men, ages 41 to 76 (mean age 52), and 10 women, ages 36 to 71 (mean age 49) were surveyed for consumption habits and demographics. Male participants ate 78 fish meals in the previous year and 55 meals consisted of Great Lakes fish. They had been eating sport fish for 15 to 58 years (mean 37 year) and Great Lakes sport fish for 15 to 58 years (mean 34 years). Female participants ate 77 fish meals in the previous years and 34 of those meals were Great Lakes sport fish. Women had been eating sport fish for 20 to 58 years (mean 32 years) and Great Lakes sport fish for 11 to 58 years (mean 29 years). Mean PCB levels in the range are reported in Table C-1. Coplanar PCBs were reported in TEQ (Anderson et al. 1998) and are not listed here. The same congeners were prevalent in all groups.

Table C-1: Blood PCB levels (in parts per billion [ppb]) in sport fish consumers (Anderson et al. 1998)

| Total PCBs | All lakes sport fish consumers (n = 30) | Lake Michigan sport fish consumers (n = 9) | Lake Huron sport fish consumers (n = 11) | Lake Erie sport fish consumers (n = 11) | Comparison group (n = 41); not published non-Great Lake fish consumers |
|---|---|---|---|---|---|
| Mean (ppb) | 5.2 | 8.6 | 5.7 | 2.2 | 1.2 |
| Range (ppb) | 1.2 to 15.2 | 3.6 to 15.2 | 1.3 to 12.9 | 1.2 to 3.2 | 0.46 to 2.9 |

PCB levels were measured in an additional population of Great Lakes fish consumers. The frequent fish consumers were Great Lakes charter boat captains and the reference population was infrequent Great Lakes fish consumers. Although 4,206 participants were in the study, only 538 were blood donors (439 frequent consumers and 99 infrequent consumers). The frequent fish

consumer ate more fish meals (men 52.7 meals/year and women 45.6 meals/year) compared to the reference population (men 39.6 meals/year and women 33.5 meals/year). The frequent fish consumers had significantly increased PCB levels as compared to the reference population. See Table C-2 for the geometric mean PCB levels. There were significant differences between PCB levels from participants who consumed Great Lakes fish from primarily Lake Michigan and Lake Erie and the appropriate reference population for both men and women (Hanrahan et al. 1999).

Table C-2: PCB levels in frequent consumers of Great Lakes fish and reference population (Hanrahan et al. 1999).

| Great Lake fish source | PCBs (geometric mean in ppb) | | | |
|---|---|---|---|---|
| | Frequent consumers | | Reference population | |
| | Male (number of participants) | Female (number of participants) | Male (number of participants) | Female (number of participants) |
| Michigan | 7.2 (98) | 2.5 (83) | 1.5 (23) | 0.9 (22) |
| Huron | 3.8 (65) | 2.3 (37) | 1.3 (3) | 0.7 (3) |
| Erie | 3.7 (89) | 1.6 (67) | 1.4 (31) | 1.0 (17) |

Blood was collected from Native Americans living on an Ojibwa reservation, who eat fish from the Great Lakes, to determine if fish consumption alters serum PCB levels. Previously, this population has been reported to eat, on average, 29 fish meals per year. Participants were questioned on preferred fish species along with the total number of fish meals consumed per year. Average total PCB levels were higher in the participant group with a higher number of fish meals per year. The authors also separated the participants into those with or without diabetes. The diabetic participants, totaling nine, had a higher average serum total PCB level (Gerstenberger et al. 2000). Table C-3 presents the information discussed above.

Table C-3: Serum PCB levels (in parts per billion [ppb]) in and average fish meals consumed per year by Ojibwa volunteers (Gerstenberger et al. 2000).

| Fish species preferred (not only one eaten) | Participants (total = 61) | Average fish meals per year | Range (in ppb) | Average total PCBs (in ppb) |
|---|---|---|---|---|
| lake trout | 24 | 37 | 2.0 to 150 | 3.42 |
| walleye | 17 | 26 | 1.0 to 72 | 3.14 |
| whitefish | 13 | 24 | 1.0 to 72 | 2.85 |
| other fish (including salmon) | 7 | 26 | 1.0 to 52 | 3.08 |
| Separated by diabetic status | | | | |
| diabetic | 9 | 22 | 3.0 to 52 | 5.62 |
| non-diabetic | 52 | 31 | 0 to 150 | 2.80 |

He et al. (2001) investigated PCB levels in Michigan anglers, using three surveys that spanned twenty years. The first survey was with a cohort recruited between 1973 and 1974. Fisheaters (n = 73) were defined as those with a consumption of greater than or equal to 24 pounds. Non-fisheaters were defined as eating less than six pounds. The second survey included 1,255 participants (115 from the first survey and 1,140 new participants, with 608 fisheaters), recruited from 1979 to 1982. The third survey, from 1989 to 1993, enrolled 717 participants from the second survey and 11 new participants. The third survey included 358 fisheaters (He et al. 2001).

The number of fish meals (men and women) consumed in a year was similar for the first and second surveys, ranging from 40 to 104 meals ($25^{th}$ quartile to $75^{th}$ quartile). The number of fish meals per year for the third survey participants were lower, ranging from 12 to 52 meals per year ($25^{th}$ quartile to $75^{th}$ quartile). The number of pounds consumed shared the trend with fish meals per year, where surveys one and two had a similar number of pounds consumed (26 to 60 pounds for the $25^{th}$ quartile to the $75^{th}$ quartile), and for the third survey, number of pounds consumed was lower, from 4.5 to 31.4 pounds ($25^{th}$ quartile to the $75^{th}$ quartile) (He et al. 2001).

Although the range was similar, fish consumption significantly declined, by 8.77 pounds from survey one to survey two and significantly declined again, by 25.85 pounds, between survey two and survey three. PCB levels were measured using an Aroclor 1260 standard. The range ($25^{th}$ quartile to $75^{th}$ quartile) was 10 to 38.6 ppb for male fisheaters and 7.5 to 22.8 ppb for female fisheaters. Non-fisheaters ranged ($25^{th}$ quartile to $75^{th}$ quartile) from 4.3 to 15.0 ppb for men and 3.9 to 10.1 ppb for women. Age, total fish consumption, and gender were all predictors of PCB serum levels. PCB levels significantly increased from survey one to survey two, but PCB levels significantly decreased from survey two to survey three, similar to the decline in fish consumption (He et al. 2001).

Cole et al. (2002) measured PCB levels in three groups of participants. One group composed of Chinese and Vietnamese community members of Metro Toronto and Hamilton, another was family members, friends, or acquaintances of potential recruits, and the third group was referrals from the Sport Fish and Wildlife Consumption Study ("the Shore Survey"). There were a total of 91 participants, 40 from the first two groups and 51 from the Shore Survey (Cole et al. 2002).

The participants were classified as Asian-Canadians (AC) or Euro-Canadians (EC). The EC group had 47 participants total, 15 female and 32 male. The AC group had 44 participants total, 29 female and 15 male. There were significant differences in the time living in Canada, if the individuals were immigrants, and the body mass index for these two groups. Combined, these two groups ate an average of 108 meals of Great Lake fish per year. EC participants primarily ate yellow perch (91% of EC participants) and walleye. AC participants ate an average of approximately 18 meals a year of rock bass (80% of AC participants). The sum of all measured congeners (64 total individual or grouped congeners) from 89 of the participants had a range of 141.1–2,049.4 µg/kg. The mean, for all participants, was 531.0 µg/kg with a standard deviation of 342.0 µg/kg. Women and men in the AC group had a range of 200.0 to 2,049.4 µg/kg, while women and men in the EC group had a rage of 141.1 to 1,238.6 µg/kg (Cole et al. 2002).

PCB blood levels were measured in participants from the New York State Angler Cohort Study (NYSACS). Consumers (n = 110) were measured for PCB congeners and the most prevalent

congeners totaled 346.8 ppb serum lipids, which was 44% of the sum of all PCBs (median 780.6 ppb serum lipids). Consumers had a mean of 3.2 meals/year (median of 1.7 meals/year) of at least one of the six most highly contaminated fish species. Fish consumption, for the consumers, had a mean of 5.6 years (median 5.0) of at least one meal/year of sport fish. Non-consumers (n = 93) were also measured for total PCBs and the most prevalent congeners totaled 252.0 ppb serum lipids, which was 37% of the total PCBs (median 668.8 ppb serum lipids). Non-consumers did not eat any of the six highly contaminated species. From this study, the authors concluded that Lake Ontario sport fish contribute to the body burden of ortho-PCBs in western New York anglers and sportsmen (Bloom et al. 2005).

Serum PCBs were measured from women in the NYSACS. Participants (n = 83), who were planning to try to become pregnant within the next six months, were surveyed for factors such as smoking and alcohol consumption. Women were followed for up to 21 menstrual cycles. There were significant differences with alcohol consumption and smoking; women who were not pregnant were more likely to smoke or drink alcohol. A majority of the women were pregnant by cycle three (49.4%), and by cycle 12 73.5% were pregnant. PCB serum levels were broken down into three tertiles, and women in the upper two tertiles (highest serum PCB levels) became pregnant by menstrual cycle 13, while those in the lowest tertiles (lowest serum PCB levels) were pregnant by cycle 9. There was no information on the partner's exposures, including alcohol consumption. Although there was a difference in the number of cycles to pregnancy, no statistically significant effect of PCB exposure was identified (Buck Louis et al. 2009). Table C-4 presents the PCB tertiles and the number of women pregnant and not pregnant in each tertile.

Table C-4: Number of women pregnant in three serum PCB tertiles (Buck Louis et al. 2009).

| Total PCBs (ppb serum) | Pregnant (n = 62) | Not pregnant[a] (n = 21) |
|---|---|---|
| 10.65 to 14.53 | 17 | 10 |
| 14.53 to 16.16 | 21 | 6 |
| 16.16 to 32.76 | 24 | 5 |

a = Includes 10 women who did not become pregnant and 11 who withdrew from the study before an observed pregnancy

Frequent and infrequent (n = 508) Great Lakes sport fish consuming residents from the Great Lakes Basin were selected from a population recruited in 1993. The participants had, on average 34 years of sport fish consumption and ate 1.9 sport fish meals/month. The participants (350 men and 158 women) had 101 PCB congeners measured in blood. The sum of all 101 PCB congeners ranged from <0.1 to 4,309 ppb (geometric mean = 310 ppb) in men and <0.1 to 1,422 ppb (geometric mean = 136 ppb) in women. NHANES participants had 21 congeners measured in blood. The sum of those 21 PCB congeners ranged from 21.0 to 3,240 ppb (geometric mean = 156 ppb) in men (n = 299) and 17.0 to 2,093 ppb (geometric mean = 154 ppb) in women (n = 301) (Anderson et al. 2008). The geometric means were lower in NHANES participants, but the PCB ranges overlapped for the two groups.

Yusho and Yucheng populations

Yusho patients' blood was collected in 1990 and 1991 (n = 4), about 20 years after the incident, with additional samples collected in 1995 (n = 11) and 1996 (n = 22). The purpose was to

compare the PCB profile present with a PCB profile obtained from a control group, those with no exposure to the contaminated rice oil. The control samples consisted of pooled sera collected in 1991 and 1992, collected three times from 10 individuals in 1995, and an identical collection in 1996. Both the control pooled sera and the samples from Yusho patients collected earlier had a different PCB congener profile than the samples collected in 1995 and 1996 (Masuda et al. 1998). The range of PCB levels in control and Yusho populations is in Table C-5.

Table C-5: Range of PCB levels (in parts per billion [ppb]) in blood, lipid adjusted, in Yusho patients and a non-exposed control population (Masuda et al. 1998)

| PCB categories | Control | Yusho |
|---|---|---|
| Total PCBs (ppb) | 237.280 – 462.607 | 371.397 – 1,331.691 |
| Total coplanar PCBs (ppb) | 0.0796 – 0.258 | 0.193 – 0.39055 |
| Total mono-ortho-PCBs (ppb) | 44.2 – 88.990 | 71.034 – 272.900 |
| Total di-ortho PCBs (ppb) | 193.000 – 371.853 | 299.253 – 1,085.000 |

PCB levels were measured from preserved umbilical cord from Yusho patients that ingested the contaminated rice oil during their pregnancy. Preserved umbilical cords, from multiple children if available, were collected from six women either designated or suspected to have Yusho (two designated, four suspected) and nine healthy women. Twelve dioxin-like PCB congeners were measured in the preserved cord. Total levels ranged from 130 to 11,000 parts per trillion (ppt) (picograms/g). Umbilical cords from the designated patients ranged from 2,100 to 11,000 ppt with a mean of 6,500 ppt. Umbilical cords from the suspected Yusho patients ranged from 130 to 1,400 ppt with a mean of 580 ppt. Umbilical cords from the healthy women ranged were from 250 to 12,000 ppt, similar to Yusho patients, with a mean of 2,700 ppt, which was lower than designated Yusho patients. PCB concentration were high in the umbilical cord samples that were from births between 1968 and 1970 (Aozasa et al. 2008).

Todaka et al. (2009) conducted a congener specific analysis of PCBs present in blood from 242 Yusho patients, 74 Yusho suspected patients, and 127 normal controls in 2004 (35 years after the poisoning). Polychlorinated dibenzofurans (PCDF) levels were higher in the blood of Yusho patients than in normal controls. Of the 209 total PCB congeners, the authors tested for eight mono-ortho and 56 non-dioxin-like PCB congeners. The major PCB congeners that were identified were PCB 118, 153, and 156. The total PCB congeners present in Yusho patients ranged from 40 to 3,032 ppb with a mean of 645 ppb and a median of 536 ppb. The Yusho suspected people had slightly lower levels, with a range of 20 to 1,418 ppb and a mean of 355 ppb and a median of 317 ppb. The Yusho patients had PCB levels that were 50% higher than the normal controls and the Yusho suspected PCB levels were 20% lower than the normal controls. The normal controls may encounter PCBs in seafood consumption. Congeners that were higher in Yusho patients compared to normal controls were PCB 156, 157, 181, and 189 (Todaka et al. 2009).

<u>Other populations</u>

Five New York women had six tissue samples taken during cesarean deliveries from September 1995 to January 1996. The women had an age range of 19 to 34 years with a mean age of 27. Coplanar PCB levels were measured in six tissue samples. The tissue samples were maternal whole blood, placenta, maternal adipose tissue and cord blood (all taken during the delivery) and maternal milk and blood (taken 13 to 63 days after delivery) (Schecter et al. 1998). PCB tissue levels are in Table C-6. Maternal adipose tissue had the highest mean PCB level and cord blood had the lowest mean PCB level.

Table C-6: PCB tissue levels before, at, and after delivery (Schecter et al. 1998)

| | Total coplanar PCBs in ppt lipid weight | |
|---|---|---|
| Tissue | Range | Mean |
| Collected prior to delivery | | |
| Maternal blood | 18 to 50 | 35.4 |
| Collected at delivery | | |
| Maternal adipose | 22 to 65 | 41.0 |
| Placenta | 14 to 23 | 18.2 |
| Cord blood | <10 to 26 | 13.4 |
| Collected 13 to 63 days after delivery | | |
| Maternal blood | 13 to 35 | 27.6 |
| Milk | 18 to 42 | 30.9 |

PCB 118, 153, 138, and 180 were measured in blood from 194 pregnant women participating in the Children's Environmental Health Study at Mount Sinai Hospital in New York City. The authors cited several reasons for selecting those congeners: these were the most abundant congeners and largest proportion of total PCBs in most people, they strongly correlate to total PCB level, and many other researchers measure these congeners. The women's mean age was 25 and approximately equal numbers of women were Black, Hispanic, and White. Approximately 94% of the women had PCB levels greater than the level of detection (0.3 µg/L) (Wolff et al. 2005). The median and interquartile ranges are presented in Table C-7.

Table C-7: PCB levels (PCB 118, 153, 138, and 180) in pregnant women (n = 194) from New York City (Wolff et al. 2005)

| | PCBs in µg/L | PCBs in ppb lipid weight |
|---|---|---|
| Median | 0.79 | 151 |
| Interquartile range | 0.548 to 1.28 | 92 to 254 |

PCBs levels were measured in adipose tissue, collected from liposuction procedures. Fifty-one samples were collected (40 from women and 12 from men) from people ages 18 to 51 (mean age 31.7 ± 8). Lipid content of the samples ranged from 37 to 89% (mean 58%) and most samples had less than 200 ppb PCBs. PCB levels were three-fold lower than polybrominated diphenylethers (PBDEs). The major PCB congeners in the adipose tissue were 153 (18% of total), 138 (12% of total), 180 (11% of total), 118 (8.6% of total), 187 (4.3% of total), and 170

(3.2% of total) (Johnson-Restrepo et al. 2005). Table C-8 presents total PCB levels arranged by age, gender, and ethnicity.

Table C-8: Total PCBs in adipose tissue (in parts per billion [ppb] lipid weight) presented by age, gender, and ethnicity (Johnson-Restrepo et al. 2005).

| Age (years) | Mean ± SD (in ppb lipid weight) | Median (range) (in ppb lipid weight) |
|---|---|---|
| Mean 31.7 (n = 52) | 144 ±138 | 110 (18.9 to 816) |
| <30 (n = 22) | 128 ± 82 | 110 (47 to 356) |
| 30 to 40 (n = 22) | 189 ±182 | 135 (36.2 to 816) |
| >40 (n = 8) | 62 ± 43 | 40 (18.9 to 149) |

| Gender | Mean ± SD (in ppb lipid weight) | Median (range) (in ppb lipid weight) |
|---|---|---|
| Female (n = 40) | 157 ± 152 | 127 (18.9 to 816) |
| Male (n = 12) | 98 ± 50 | 95 (40 to 230) |

| Ethnicity | Mean ± SD (in ppb lipid weight) | Median (range) (in ppb lipid weight) |
|---|---|---|
| African American (n = 9) | 144 ± 85 | 134 (25.6 to 356) |
| Asian (n = 1) | 816 | 816 |
| Caucasian (n = 35) | 132 ± 104 | 117 (26 to 567) |
| Hispanic (n = 7) | 61 ± 19 | 72 (18.9 to 356) |

Carpenter et al. (2005) surveyed the Siberian Yupik people for PCB blood levels. Siberian Yupik people (1,400) live on St Lawrence Island, Alaska. The Yupik people maintain a traditional lifestyle and have a significant consumption of marine mammals, fish, bird eggs, local greens and berries, and polar bear, which eats seal. St Lawrence Island is 104 miles long and 20 to 30 miles across. There are two villages on the island, Gambell and Savoonga, near two U.S. military bases. One of the military bases, near Gambell is likely to be contaminated with PCBs, although the activities at this base were still classified at the time this paper was written. The other military base is at the Northeast Cape (NEC) where the Yupik people maintain hunting and fishing camps during spring and summer (Carpenter et al. 2005).

There were a total of 101 study participants, ages 19 to 75; 40 from Gambell, 44 from Savoonga who spent little or no time at NEC, and 46 from Savoonga who had camps at NEC. Blood was collected in August 2001 and between August and October 2003 and was tested for 101 PCB congeners. Serum PCB levels ranged from 0.6 to 17.8 ppb wet weight (ppb) and after lipid adjustment, the mean was 933 ppb. The mean lipid adjusted PCB levels in the three population were 785 ppb for people from Gambell, 847 ppb for the people from Savoonga (little or no time at NEC), and 1,143 ppb for people from Savoonga with camps at NEC. PCB levels for men were significantly increased compared to women's PCB levels in all groups. The authors noted that the PCB levels of the Yupik people are in the range of other Arctic people, but the Yupik people have significantly larger body burdens of PCBs than the background U.S. and Canadian populations (Carpenter et al. 2005).

Two hundred and thirty-seven samples of breast milk was collected from mother in 12 different regions of Tunisia, a country in Northern Africa along the Mediterranean Sea, between February 2003 and January 2005. The mothers were non-smokers and were self-reported to have no occupational exposure to organochlorines. The sum of seven marker PCBs (congeners 28, 52, 101, 118, 138, 153, and 180) ranged from 107 to 750 ppb lipid weight with a mean of 196 ppb lipid weight. Based on these values, the estimated daily intake of PCBs from breast milk was calculated as 0.83 µg/kg-day with a range of 0.54 to 1.76 µg/kg-day. PCB congeners 118, 153, and 180 were the main contributors to the levels of organochlorines in the milk (Ennaceur et al. 2008).

Samples of human liver and mesenteric fat was collected at autopsies (n = 25; eight males and seven females) between 2003 and 2005 in Belgium. The mean age was 37 years with a range of 9 to 70 years. Twenty-three PCB congeners were measured and values were reported as total PCBs and sum of seven marker PCB congeners. PCB levels statistically significantly correlated with age (Covaci et al. 2008). PCB levels in liver and fat are in Table C-9.

Table C-9: Levels of PCBs (in parts per billion [ppb] lipid weight) in fat and liver (Covaci et al. 2008).

| | Adipose tissue (ppb lipid weight) | | Liver (ppb lipid weight) | |
|---|---|---|---|---|
| | Mean ± SD | Range | Mean ± SD | Range |
| Sum of 7 marker PCB congeners | 334 ± 234 | 47 to 798 | 259 ± 205 | 57 to 756 |
| Total PCB (sum of all 23 congeners) | 490 ± 341 | 68 to 1,128 | 377 ± 299 | 89 to 1,138 |

Axelrad et al. (2009) examined NHANES data from 1999 to 2000, when 26 PCB congeners were measured, and 2001 to 2002, when 36 PCB congeners were measured. Of 496 women, only 9% (45 women) had measurable levels of nine specific PCB congeners in their blood. Five to eight PCB congeners were detected in 32% (166 women) of the women and one to four congeners were detected in 41% (206 women) of the women. In 17% (79 women) of the women, PCBs could not be detected or the samples were not analyzed. The median body burden of PCBs was calculated as 53 ppb lipid weight and the $95^{th}$ percentile was 133 ppb lipid weight. The authors found a relationship between body burden and age due to the fact that environmental levels have declined over time and PCB congeners are persistent, meaning older people would have a larger accumulation. PCB congeners 118, 138, 153, and 180 were the congeners most frequently detected (Axelrad et al. 2009).

Spanish participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) were assessed for PCB levels. Participants, between the ages of 35 and 64 years of age, from five regions in Spain (approximately 200 from each region) were randomly selected from the larger EPIC cohort. A total of 47 were excluded due to technical problems (n = 33) or no biological material (n = 14), so data was analyzed for 953 participants (479 men and 474 women). The participants provided an estimated food intake for the previous year. Men had PCB levels that were statistically significantly higher (30% higher) than women's. For both genders,

PCB concentrations increased by age. Serum PCBs were strongly associated with fish intake (Agudo et al. 2009). Serum PCB levels are shown in Table C-10.

Table C-10: Serum PCB levels (in parts per billion [ppb] lipid weight) in 953 Spanish participants in the European Prospective investigation into Cancer and Nutrition (Agudo et al. 2009).

| | Mean ± SD (ppb lipid weight) |
|---|---|
| PCB 118 | 39.6 ± 21.5 |
| PCB 138 | 117.5 ± 56.4 |
| PCB 153 | 205.2 ± 101.4 |
| PCB 180 | 136.4 ± 68.2 |
| Sum of the total PCBs | 498.8 ± 223.9 |

Appendix D: Additional Discussion of Toxicity in Humans and animals and Toxicity in Cell Culture Models

Molecular mechanisms of toxicity

*Coplanar (dioxin-like) PCBs*

Congeners without chlorines in the ortho positions, otherwise known as coplanar PCBs, have high affinity for and can bind to the cytosolic aryl hydrocarbon receptor (AhR) (Bezdecny et al. 2005). After a ligand binds to the AhR, the receptor-ligand complex translocates to the nucleus. Once in the nucleus, it dimerizes with the Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) and then binds to the xenobiotic response element (XRE; dioxin response element) and interacts with the basal transcription machinery (Borlak and Jenke 2008). Activation of AhR can ultimately alter expression of cytochrome P450 genes (Smithwick et al. 2003; Carpenter 2006).

Coplanar PCB congeners do not have neurotoxic effects (Fonnum et al. 2006); they are toxic due to activation of the AhR. Even though dioxins and furans more strongly activate the AhR, if coplanar PCBs are present in larger amounts, it may result in those PCBs being responsible for the AhR activity (Carpenter 2006).

*Non-dioxin-like (non-coplanar) PCBs*

Non dioxin-like activity is due to a different mechanism of action, with each congener having its own profile of actions in biological systems (Carpenter 2006). Non dioxin-like activity can result in generation of reactive oxygen species, and can lead to cancer promotion (Carpenter 2006).

Neurotoxic effects appear to be solely due to the non-coplanar PCB congeners (Fonnum et al. 2006). PCB congeners without AhR activity may cause effects that are not related to expression or activity of P450 enzymes (Carpenter 2006). Ortho-substituted PCB congeners have been linked to reduced dopamine levels in different regions of the brain in non-human primates and rats (Fonnum et al. 2006). Ortho-substituted PCBs have been shown to cause an elevation of intracellular calcium in granulocytes, which leads to a respiratory burst in neutrophils (Fonnum et al. 2006) and are reported to cause cell death due to disruption of the cell membrane (Campbell et al. 2008).

Non-coplanar PCBs are able to alter phagocytosis of human leukocytes (neutrophils and monocytes) through an AhR independent mechanism. PCB non-coplanar congener mixtures (PCB 138, 153, and 180) significantly reduced phagocytosis while PCB 169, a coplanar congener, and TCDD did not alter either neutrophil or monocyte phagocytosis (Levin et al. 2005).

*Hydroxylated PCBs (OH-PCBs)*

Hydroxylated PCBs (OH-PCBs) are formed by metabolism of coplanar PCBs by the cytochrome P450 enzymes. OH-PCBs may be estrogenic and may also have thyroid hormone activity (Nomiyama et al. 2007). PCB metabolites with hydroxyl groups in meta or para positions are structurally similar to thyroxine (T4) and can bind to trandthyretin (TTR), a thyroid hormone plasma transport protein. T4 can be displaced by PCB metabolites (Khan et al. 2002).

In one study, authors identified intermediates and the degradation pathways of three coplanar PCBs: PCB 77, 81, and 169. The three coplanar PCBs tested were degraded with ultraviolet (UV) light alone for 240 minutes (5-7% of starting amount degraded) or with UV light for 240 minutes and titanium dioxide as a photocatalyst (~90 of starting amount degraded). The affinity of the intermediates for the estrogen and thyroid receptors was then examined. Degradation intermediates from PCB 77 and 81 had estrogenic activity that was weak and strong, respectively, after 60 to 120 minutes of incubation. None of the intermediates tested had thyroid hormone activity (Nomiyama et al. 2007).

In another study, OH-PCBs bound to serum transport proteins (transthyretin and thyroid-binding globulin [TBG]) in protein extracts of Sf9 insect cells expressing recombinant human thyroid receptor (TRβ). While OH-PCBs had similar affinity to transthyretin as thyroxine (T4, thyroid hormone), only two of the seven OH-PCBs bound to TGB in vitro (cell free) (Cheek et al. 1999).

Carcinogenicity

Although PCBs have been shown to be toxic, evidence of the carcinogenicity of PCBs is less clear. One obscuring factor may be co-exposure with other contaminants along with PCBs. In a study examining the relationship between PCBs and non-Hodgkin's lymphoma (NHL) risk, the authors concluded that risk of developing NHL may be due to co-exposure with other contaminants (Engel et al. 2007).

In a review of PCBs and the relationship to breast cancer, epidemiologic research was reviewed from 1999 to 2006. Twenty-seven articles discussed PCBs and breast cancer. The authors noted that there was inconsistent evidence for an association between total PCBs and breast cancer risk. Two variants in genes were linked to an increased risk of breast cancer and PCB exposure. Three studies found that a higher breast cancer risk was associated with higher PCB exposure among post menopausal women with a variant of CYP1A1. One study identified an increased risk of breast cancer in women with a variant of the p53 tumor suppressor gene. Three additional studies related PCB exposure to breast cancer recurrence or survival (Brody et al. 2007).

The carcinogenic activity of different commercial PCB mixtures has been studied in Sprague-Dawley rats. Tumors formed in the PCB-treated rats, but the tumor formation was not expected to be through a genotoxic mechanism of action, as *in vitro* testing has not identified mutagenic activity. Two-stage bioassays, using PCB compounds of interest have identified PCBs as tumor promoters. Brown et al. (2007) used frozen tissue from rats treated with Aroclor 1016, 1242, 1254, and 1260. The tissue samples were measured for PCB levels and a variety of proteins. Correlations were identified between hepatic tumor and total PCB levels along with mixed function oxidase activity, and production of reactive oxygen species. Formation of PCB metabolites and indicators of cytotoxicity were not correlated to hepatic tumor formation. Hepatic tumor formation was correlated to specific levels of PCBs accumulated in the tissue. PCB tissue levels associated with hepatic tumor formation was 50 ppm lipid normalized in females and 500 ppm lipid normalized in males (Brown et al. 2007).

Haag-Gronlund et al. (1997) identified increased hepatic foci in female Sprague–Dawley rats after conclusion of a medium-term two-stage initiation/promotion protocol using PCB 156 (300,

1,500, 7,500 µg/kg/week) or 126 (5 µg/kg/week). When rats were treated with PCB 156 (7,500 µg/kg/week) without an initiator, foci number was not increased.

Altered hepatic foci were measure in female Sprague–Dawley rats treated with a mix of dioxin-like chemicals, including dl-PCBs (Van der Plas et al. 1999). Increased altered hepatic foci were measured, indicating that these chemicals function as tumor promoters (Van der Plas et al. 1999).

In a later study treating Sprague-Dawley rats with Aroclor 1254, increased foci were identified after 52 weeks of treatment. Increased cell proliferation was identified in the 100 ppm treatment group at 52 weeks and no DNA reactivity was identified (Whysner and Wang 2001). When Dean et al. (2002) treated female Fischer 344 rats with PCB 126, 153, or 126 + 153, no GST positive foci were found, indicating that these congeners had no initiator activity.

PCBs are not bacterial mutagens (Safe 1993). Overall, Safe (1993) concluded that PCBs were not genotoxic and that the metabolic activation process does not play a significant role in the toxicity of PCBs. Using a two-stage carcinogenesis model, Kunz et al. (2006) observed that PCB 28 and 101 were not tumor promoters. Based on a model, some PCB congeners, the lower chlorinated ones, might act as initiators. There is evidence that some metabolites of the lower chlorinated PCB congeners might be genotoxic in some in vitro and in vivo studies (Ruiz et al. 2008).

PCB mixtures did not appear to interact with DNA in male Lewis rats treated in vivo with Aroclor 1242 (Schilderman et al. 2000). There is no evidence of DNA adduct formation from individual non-persistent PCB congeners in vitro or protein adducts in vivo. Aroclor mixtures and individual PCB congeners have promotional activity. Since rat livers can have spontaneous initiation, chemicals with promotional activity alone can lead to cancer (Brown et al. 2007).

Toxicity in Cell Culture Models

HL-60 cells, a human monocyte line, can be differentiated into neutrophils (Bezdecny et al. 2005). PCB 47, a non-coplanar PCB, significantly increased degranulation and superoxide anion production in the HL-60 neutrophils, while treatment with PCB 77, a coplanar PCB, did not. Similarly, PCB 47 significantly increased the levels of cyclooxygenase-2 (COX-2) mRNA, a gene expressed during inflammation, in the cells while PCB 77 did not (Bezdecny et al. 2005).

As epidemiologic studies do not have consensus on whether there is an association between PCBs and thyroid homeostasis, the authors studied the possibility that PCBs also affected brain development by interfering with thyroid hormone signaling in primary normal human neural progenitor (NHNP) cells. Two PCB congeners were used in this study, PCB 118, a mono-ortho congener with weak dl activity, and PCB 126, a coplanar congener with strong dl activity. The cells used in this study expressed the AhR, the AhR repressor (AhRR), certain cytochrome P450 (CYP) enzymes (CYP1A1, CYP1B1, and CYP2D6), glutathione S-transferase (GST) proteins (GSTM1 and GSTT1), and UDP-glucuronosyl-transferase (UGT) 1A6. After treating the NHNP cells with PCB 118 or PCB 126, only PCB 118 appeared to have a thyroid hormone like effect. Based on results obtained, the authors concluded that PCB 118 interferes with the thyroid receptor complex. However, the authors could not determine whether the effects in the cells was due to the actual congener or metabolites of the congener (Fritsche et al. 2005).

In a human mast cell line, HMC-1 cells, Aroclor 1242 significantly increased release of β-hex, a marker of degranulation. In both HMC-1 cells and bone marrow-derived mast cells (BMMC), from C57B6 mice, Aroclor 1254 induced cell degranulation, as measured by β-hex levels, when co-treated with house dust mite extract. Aroclor 1242 also increased the β-hex levels when co-treated with house dust mite extract in BMMC. The authors speculate that, based on these results, environmental estrogens may help to explain the rising prevalence of asthma and other allergic diseases (Narita et al. 2007).

Appendix E: Extended Discussion of Observational Epidemiology Studies

Great Lakes fish associated effects

Children, born in western Michigan hospitals in 1980-1981, were enrolled in a study when the mothers were surveyed for Lake Michigan fish consumption. The women included in the study either ate no Lake Michigan fish or ate more than 11.8 kilograms over a six year period. Fish consumption averaged 6.7 kg per year (about two or three salmon or lake trout meals per month). PCB in cord serum was measured based on Aroclor 1016 and 1260 standards. PCB cord serum levels averaged 2.5 ppb (standard deviation 1.9 ppb) (Jacobson et al. 1984).The children were examined within three days after birth (Jacobson et al. 1984), at seven months (Jacobson et al. 1985), at age four (Jacobson et al. 1990), and at age 11 (Jacobson and Jacobson 1996).

Infants, all but four, were tested with the Brazelton Neonatal Behavioral Assessment Scale 48 to 72 hours after birth. Although PCB cord serum levels were measured, maternal fish consumption was the measure of PCB exposure due to unavailable PCB cord serum values. Individual tests were groups into seven clusters (response decrement, orientation, tonicity, range of state, regulation of state, autonomic maturity, and reflexes). Response decrement cluster tests were not analyzed due to missing data. Infants classified as worrisome in three of the cluster associated with PCB exposure, autonomic maturity (includes a greater propensity to startle), reflexes, and range of state (includes irritability), have the highest maternal Lake Michigan fish consumption, and poorer reflex and neuromuscular functioning (Jacobson et al. 1984).

The non-exposed control infants (no maternal Lake Michigan fish consumption) were compared to the highest exposed infants (highest maternal Lake Michigan fish consumption). The highest exposed infants had a significantly greater likelihood of worrisome scores on the reflexes and range of state clusters. There was a trend of increased likelihood for worrisome scores for the autonomic maturity cluster, but it was not significant. The authors cautioned that neonatal deficits are often transitory; any long-term implications of these worrisome scores are unclear (Jacobson et al. 1984).

A second study tested the children at seven months of age. One hundred and twenty-three infants were given Fagan's recognition memory test, which uses pictures of women's and babies' faces to determine the time an infant looks at a novel picture after being shown two identical pictures for a set amount of time. Either PCB cord serum levels or maternal Lake Michigan fish consumption were used as a measure of exposure. A higher level of PCB exposure, with either PCB cord serum levels or maternal fish consumption, was significantly predictive of reduced recognition memory in the infants. Postnatal nursing was not related to the scores on the visual recognition test. Although infants with a higher prenatal exposure to PCB had a poorer performance on the visual recognition test, the authors were again careful to caution that any long-term deficits are unknown (Jacobson et al. 1985).

Seventy-five percent of the initial enrollees (n = 236) were assessed for effects of PCB and other contaminant exposure on cognitive functioning at four years of age. As a measure of prenatal exposure, PCB levels were measured in cord serum (n = 146). Postnatal exposure was estimated from maternal milk PCB levels (n = 120) and duration of lactation. Children's PCB body burden was measured at age four in serum (127 at four years old and 27 at five years of age). PCB

amounts were based on Aroclor 1016 and 1260 standards. Additional contaminants, such as polybrominated biphenyls and chlorinated pesticides, were also measured in the children's serum (at age four), but only dichlorodiphenyl trichloroethane (DDT), of the chlorinated pesticides, was detected. Children were tested using McCarthy Scales, General Cognitive Index, Beery Test of Visual-Motor Integration, and the Peabody Picture Vocabulary Test-Revised. These tests assessed five domains of functioning and intelligence quotient. Seventeen children did not cooperate with the testing and were not included in the analysis. The excluded children did not differ from the other children in cord PCB levels, but had significantly higher maternal milk PCB levels than the children included in the analysis (Jacobson et al. 1990).

Cord PCB levels averaged 2.5 ± 2.0 ppb (mean ± SD), maternal serum averaged 5.9 ± 3.6 ppb, and maternal milk averaged 835.9 ± 388.4 ppb. Maternal milk was the main source of the children's serum PCB levels at four years. Serum PCB levels were higher for the children breast fed at least six months (5.1 ± 3.9 ppb) than the children who were breast fed less than six months (1.2 ±1.6 ppb) or those who were not breast fed (0.3 ± 0.7 ppb) (Jacobson et al. 1990).

Higher PCB cord levels were significantly associated with lower scores on the McCarthy Memory scale and on two subtests for Verbal and Numerical memory. The Verbal memory test measures the child's ability to recall strings of words, sentences, and a story, while the Numerical memory test assesses the child's ability to repeat progressively longer strings of numbers, both as given and backward. Higher maternal milk PCB levels were significantly associated with lower scores on the McCarthy Memory scale and the Verbal and Numerical memory tests. A longer duration in nursing tended to result in higher scores on the McCarthy Memory and Verbal scale, attributed to increased intellectual stimulation. The children's PCB body burden, at age four, was not related to scores on any of the tests. Overall, the authors concluded that the prenatal PCB exposure resulted in a poorer short-term memory functioning in early childhood (Jacobson et al. 1990).

The children were assessed again at age 11 (Jacobson and Jacobson 1996).Two hundred and twelve children (68% of the original number) were given the Wechsler Intelligence Scales for Children – Revised, Wide Range Achievement Test – Revised, and the Woodcock Reading Memory Tests – Revised. These tests measured cognitive functioning, reporting full scale IQ, Verbal IQ, Performance IQ, Verbal comprehension, perceptual organization, freedom from distractibility, spelling, arithmetic, word comprehension, passage comprehension, and reading comprehension. PCB levels were measured in cord serum, maternal serum, maternal milk, children's serum at age four, and children's serum at age 11. Sample numbers ranged from 113 to 179 for all media measured. PCB levels, for all but children's serum at age 11, are reported in the above study. Children's PCB serum levels averaged 1.0 ± 1.0 ppb (mean ± standard deviation) at age 11 (Jacobson and Jacobson 1996).

Full scale IQ, Verbal IQ, Verbal comprehension, freedom from distractibility, and word comprehension scores were significantly lower with a higher prenatal PCB exposure. The children with the higher prenatal PCB exposure (n = 30), defined as a concentration equivalent to PCB levels greater than or equal to 1.25 µg/g fat in maternal milk, had a significantly poorer performance in the Full scale IQ, Verbal comprehension and freedom from distractibility tests compared to the children with a lower prenatal PCB exposure (n = 148), defined as a

concentration equivalent to PCB levels less than 1.25 µg/g fat in maternal milk. The authors note that no child included in the study had gross intellectual impairment, there was an increased in the lower end of the normal IQ range, which may result in reduced school performance. As found in this population at age four, only prenatal PCB exposure was associated with lower scores and not postnatal PCB exposure. Children in this study might have had exposure to additional contaminants that are responsible for these effects and PCB from food sources other than Lake Michigan fish may produce similar effects (Jacobson and Jacobson 1996).

Children in the Michigan cohort were tested for sustained attention (Continuous performance test), focused attention (Digit Cancellation), executive functioning (Wisconsin Card Sorting Test and Stroop Color-Word Test), and working memory (Sternberg Memory paradigm, Mental Rotation, and Arithmetic and Digit Span tests from the Wechsler Intelligence Scale for Children – Revised) at age eleven (n = 148). Results from testing (a continuous performance test and a Sternberg Memory paradigm) at age four (n = 154) were included for comparison (Jacobson and Jacobson 2003).

At age 11, prenatal PCB exposure was significantly associated a greater number of errors on the Digit Cancellation test (indicating poorer concentration), reduced performance on the Sternberg Memory task, and a slower mean reaction time on the Mental Rotation test (required more processing time). Based on the test results, the authors concluded that deficits in motor speed were unlikely to be a problem, but rather the children have focused attention and executive functioning issues. The authors note that the adverse effects, related to prenatal PCB exposure, seem to be stronger in children who were not breastfed (defined as less than 6 weeks breastfed). Breastfeeding may provide nutrients necessary to attenuate effects related to prenatal PCB exposure or may provide intellectual stimulation that is missing when a child is not breastfed (Jacobson and Jacobson 2003).

Members of the New York State Angler Cohort Study (NYSACS) were assessed for time to pregnancy (TTP). TTP is a measure of the ability to become pregnant (fecundability). The NYSACS was composed of 10,518 male anglers, 913 female anglers, and 6,651 spouses or partners of male anglers. A survey was mailed in 1991 to participants between the ages 18 to 40 that were residents of one of the 16 counties surrounding Lake Ontario. In 1993, TTP was asked of the participants and 874 reported a known TTP (30 were excluded for a lack of fish consumption data). Forty-five percent of those reported a known TTP, reported smoking once or more than once (ever or never question) and 42% ate contaminated fish from Lake Ontario (those with no consumption advisories). The authors found no significant adverse association between consumption of contaminated sport fish from Lake Ontario and TTP. No information was collected on factors that would alter TTP, such as caffeine or alcohol (Buck et al. 1997).

A later study was carried out with the NYSACS population examining whether conception delay occurred with this population. Female anglers were excluded as there was no information on their husband or partner. Women were selected with one pregnancy or more between 1991 and 1993 and known TTP. Conception delay was defined as 12 or more menstrual cycles with unprotected intercourse before the pregnancy. Seventy-eight percent of the women (total of 785 women) had a TTP less than or equal to six months and 11% had a TTP of 13 or more months. Over half of the fathers (66%) ate Lake Ontario fish between 1955 and 1991, but only 38%

reported eating Lake Ontario fish (one or more meals) in 1991. The mean estimated PCB exposure from fish consumption for the fathers was 6.6 ± 12.3 mg. The authors concluded that fish consumption did not increase the risk of conception delay, based on known TTPs. The authors noted two factors that may have altered the conclusion of the study: a selection bias was present (participants had to know the TTP) and women whose pregnancy was unplanned or those who never became pregnant were not included in the study. Inclusion of these women may have altered the outcome as 40 to 50% of all pregnancies in the U.S. are unplanned. An additional unknown was fish consumption; fish consumption was not known for 1991 to 1993 (Buck et al. 1999).

An additional study measuring fecundity (biological capacity for reproduction) and fertility (demonstrated fecundity or livebirths) was conducted using participants of the NYSACS. Close to 600 women (n = 584) were eligible as their partners' fish consumption data was available. Fish consumption was higher for men as compared to women, and men reported more recent fish meals and had higher mean estimated PCB indices. Fecundability, in women, was lower for those who consume Lake Ontario fish in comparison with non-fish eaters. The authors noted that populations of women that may have been more heavily exposed and may not have become pregnant were excluded (Buck et al. 2000).

Older adults were tested for fine-motor function impairments due to exposure of PCBs and other contaminants from consumption of Great Lakes fish. Close to 1,000 individuals (n = 991; 572 fish eaters and 419 non-fish eater) from a cohort established by the Michigan Department of Public Health, currently MDCH, between 1980 and 1982 were screened for eligibility in the study. Fisheaters were those who ate sport-caught Lake Michigan fish for one or more meals per week. Those enrolled in the study ate 24 to 270 pounds of Lake Michigan fish per year (median = 38.5 pounds/year). Non-fish eaters had an annual consumption of less than six pounds. Those over 50 years of age in 1992 were eligible for the study. From the eligible pool of participants, 158 fish eaters and 188 non-fish eaters were randomly selected for participation in the study. Of those selected, 104 fish eaters (49 mean and 55 women) and 84 non-fish eaters (34 men and 50 women) agreed to participate in the study. The fish eaters, at the time of the study, had a median fish consumption of seven pounds per year. Fish eaters and non-fish eaters had similar demographic characteristics and only differed in arthritis, which was reported more frequently in male fish eaters. Serum PCB and DDE levels were highly correlated and so were assessed jointly (Schantz et al. 1999). Table E-1 presents the number of people in each exposure group.

Table E-1: Number of people in each exposure group (Schantz et al. 1999).

| Groups | Low (PCB <7.9 ppb and DDE <8.1 ppb) | Intermediate (PCB 7.9 to 13.8 ppb and/or DDE 8.1 to 15.0 ppb) | High (PCB ≥ 13.9 ppb and/or DDE ≥ 15.1 ppb) | Total number of participants |
|---|---|---|---|---|
| Fish eaters | 15 (15%) | 38 (38%) | 48 (48%) | 101 |
| Non-fish eaters | 50 (64%) | 16 (21%) | 12 (15%) | 78 |

Due to data gaps, three fish eaters and five non-fish eaters were removed from the study population. An additional two non-fish eaters were excluded due to medical complications preventing testing, resulting in 101 fish eaters and 76 non-fish eaters. The PCB and/or DDE exposure from Lake Michigan fish did not significantly impair visual-motor coordination or hand steadiness in participants of this study. The fish eater population in this study have, historically, had the highest body burdens of PCBs and DDE resulting from a non-occupational exposure. The authors noted that the lack of effects observed with this study did not mean that the exposure to PCBs or DDE from Lake Michigan fish could not cause other effects. These study participants also were tested on memory and learning, executive functions, and visual-spatial functions (Schantz et al. 1999).

After the neuropsychological testing, blood was collected from almost all of the participants (179 people, 96% of the original study population). Overall, the level of serum PCBs ranged from below the detection limit (non-detect) to 75 ppb and a median of 7.5 ppb (Schantz et al. 2001). Table E-2 presents the PCB levels in the study participants.

Table E-2: Serum PCB levels (in parts per billion [ppb]) in study participants (Schantz et al. 2001).

| | | Fish eaters | | | | Non-fish eaters | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sex | Age | sample size | Mean ± SD | median | Range | sample size | Mean ± SD | median | Range |
| male | < 60 | 16 | 15.88 ± 14.8 | 10.60 | ND – 65.20 | 11 | 6.11 ± 4.2 | 5.00 | ND – 15.30 |
| | 60 to 69 | 16 | 23.03 ± 19.1 | 17.25 | ND – 65.20 | 12 | 6.82 ± 3.5 | 5.95 | 3.40 – 15.50 |
| | ≥ 70 | 14 | 24.69 ± 19.3 | 19.95 | ND – 75.00 | 7 | 5.66 ± 2.0 | 4.90 | 4.00 – 10.00 |
| female | < 60 | 21 | 8.67 ± 4.6 | 7.60 | ND – 23.00 | 19 | 4.64 ± 2.2 | ND | ND – 9.20 |
| | 60 to 69 | 17 | 14.04 ± 6.8 | 12.40 | 4.00 – 26.30 | 16 | 8.71 ± 8.5 | 6.10 | ND – 25.90 |
| | ≥ 70 | 17 | 13.52 ± 10.8 | 12.10 | ND – 49.00 | 13 | 5.05 ± 3.8 | 4.70 | ND – 11.00 |

Higher PCB exposure resulted in lower scores on memory and learning tests (statistically significant on the verbal delayed recall on the logical memory portion of the Wechsler Memory Scale and not statistically significant on the verbal delayed recall measured by the California Verbal Learning Test). However, visual memory, executive, and visual-spatial function were not affected by PCB levels (Schantz et al. 2001).

Daughters of women (n = 151) involved in Michigan angler studies from 1973 to 1991 participated in a study to determine if prenatal PCBs or DDE exposure related to age at menarche (first menstruation). Serum organochlorine levels during pregnancy were extrapolated from PCB levels measured in 1973-1974 and 1989-1991. Age at menarche ranged from nine to 11 years old

and extrapolated maternal PCB and DDE levels for women with a younger age of menarche were higher. However, DDE levels, but not PCB levels were statistically related to lower age of menarche (Vasiliu et al. 2004).

MDCH set up a cohort, the Great Lakes Fish Eaters Study with participants from three different surveys and had PCB levels quantitated in 1973 to 1974, 1979 to 1982, and 1989 to 1991. PCB levels were quantitated based on the Aroclor 1260 standard. In 2000, 226 women were surveyed over the telephone, and 195 offspring (from 99 mothers) were born between 1969 and 1995. After excluding those with missing data or from multiple births, 168 offspring from 89 mothers were evaluated. Birth were classified by birth year and 28.6% of the births were between 1968 and 1972, 58.3% of the births were between 1973 and 1983 and 13.1% of the births were after 1983. Maternal PCB levels were higher in children born earlier (from 1969 to 1972). Children's birth weights were significantly reduced, by 500 g, in the mothers who had the highest PCB levels (>25 µg/L). However, only seven infants (one girl and six boys) were in the highest maternal PCB group (Karmus and Zhu 2004).

The health departments of Wisconsin, Illinois, Indiana, Ohio, and Michigan formed a consortium under the Congressional Great Lakes Critical Programs Act of 1990 to examine health risks from consumption of PCB and DDE contaminated fish. Participants from two different populations were interviewed by telephone between 1993 and 1995. The Captains cohort were presumed frequent fish consumers and consisted of licensed sport fishing charter boat captains and their spouses (n = 1,863 households). The infrequent consumers cohort consisted of randomly selected members of the general population (n = 1,274 households). The infrequent consumers cohort were matched to the Captains cohort by age and region (Weisskopf et al. 2005). Table E-3 presents the number of Great Lakes sport fish meals consumed by each population.

Table E-3: Fish consumption information for the Captains and infrequent consumers cohorts before pregnancy (Weisskopf et al. 2005)

| | No Great Lakes sport fish meals | 1-116 Great Lakes sport fish meals (low) | 117+ Great Lakes sport fish meals (high) |
|---|---|---|---|
| Total cohort members | 318 | 98 | 95 |
| Captains cohort sample size (% of total) | 110 (34.6%) | 98 (100%) | 95 (100%) |
| Infrequent consumers cohort | 208 (65.4%) | 0 (0) | 0 (0) |

Data was complete for 143 mother-infant pairs from both cohorts. The criterion for low birth weight children was weighing less than 2,500 grams at birth. Captains cohort mothers had a geometric mean of 1.76 ppb for serum PCBs (median = 1.76 ppb, range = 0.46 to 12.08 ppb). This was significantly higher than the serum PCB geometric mean (0.85 ppb) for mothers in the infrequent consumers cohort (median = 0.81 ppb, range = 0.53 to 1.66 ppb). However, serum PCB concentrations were not significantly associated with lower birth weight (Weisskopf et al. 2005).

The Mohawk Nation at Akwesasne consists of 10,000 people living at the intersection of New York State and the Canadian provinces of Ontario and Quebec on the St Lawrence River. It is close to three Superfund sites, which have contaminated the river with PCBs (originally Aroclor 1248). Fish was an important historical source of protein for the Mohawk Nation, until fish advisories were set in the 1980s. The Mohawk people had elevated PCB body burdens, but since fish advisories were set, breast milk and serum PCB levels have decreased (DeCaprio et al. 2005).

Samples were collected between 1998 and 2000 from 753 adult Akwesasne Mohawks (489 women and 264 men) between the ages of 18 and 95 years. The range of the total PCB was from 0.29 to 48.32 ppb and the mean was 4.39 ± 4.18 ppb serum (median = 3.18 ppb). Men had a higher median total serum PCB level than women (men's median was 3.81 ppb and women's median was 2.94 ppb). A significant correlation was identified between age and total serum PCB levels. Three percent of the men had highly elevated serum PCB levels (>20 ppb). The exposure identified in this study was consistent with the general U.S. population. The PCB profile present in the serum did not closely correspond with the profile of unaltered Aroclor 1248 profile. Toxicokinetics processes preferentially altered PCB patterns in biota and the profile was dominated by persistent congeners, such as PCB 153, 138, and 180 (DeCaprio et al. 2005).

Another investigation was carried out with participants from the Mohawk Nation. Study participants (n = 352) were Mohawk adults 30 years or older that have lived at or near Akwesasne for at least 5 years. Blood samples were obtained after fasting and 101 PCB congeners were measured. Total PCB levels ranged from 84.8 to 7,110.0 ppb lipid weight with a mean ± SD of 748.8 ± 635.6 ppb lipid weight (Codru et al. 2007). There was a significant association between serum PCB and pesticide levels and diabetes in this population, after adjustments. Organochlorine compounds increased the risk of developing diabetes (Codru et al. 2007).

Along with examining the link between PCBs and diabetes, Mohawk at Akwesanse have participated in studies to examine the link between PCBs and cardiovascular disease. Fasting blood samples were collected from 335 adult Mohawks living on or near the reservation from 1995 to 2000. The range of total serum PCBs was 1.2 to 25.8 ppb with an average of 4.2 ppb. Information from this study lead the authors to conclude that a relationship exists among serum PCB and pesticide levels, serum lipids, and cardiovascular disease (self-reported) (Goncharov et al. 2008).

School-age children were evaluated for a lower IQ associated with environmental PCB exposure. The purpose of this study was to determine if the relationship between IQ and prenatal PCB exposure observed in a cohort from Lake Michigan could be replicated in children exposed to PCBs around Lake Ontario. PCB levels from these participants were lower than levels from participants in the Collaborative Perinatal Project (from 12 national clinics). Children participating in the Oswego study, born between 1991 and 1994, had testing at nine years of age (those with cord blood samples, n = 187; those with cord and placental tissue samples, n = 156). The authors found significant associations between placental PCB levels and IQ scores. The authors estimated, with the assumption of a linear relationship, that IQ scores dropped several

points (2.9 IQ points, 4.1 Verbal IQ points, 3.3 Verbal Comprehension Index points, 4.4 Freedom from Distractibility points) per 1.0 ppb PCB. Cord blood PCB levels were not related to IQ (Stewart et al. 2008).

The relationship between PCBs and neuropsychological functioning was assessed in Mohawk men and women from Akwesasne. Participants (n = 353, 113 men and 240 women) ranged in age from 17 to 79 years, with a mean of 38 ± 13.3 years. As data was not collected for all parameters, the sample size range from 274 to 283. Some aspects (executive functioning, motor functioning, and memory) of neuropsychological functioning were significantly related to PCB exposure. The authors noted that the decline in test scores was not at levels of clinical concern. Scores on tests for executive functioning began to decrease at PCB body burden levels of 2.0 to 25 ppb. Motor functioning test scores, for fine motor behavior and finger dexterity, decreased at PCB body burden levels above approximately 2.0 ppb. Test scores for memory also indicated that memory deterioration occurred at PCB body burden levels greater than 2.0 ppb (Haase et al. 2009).

The relationship between testosterone concentrations and serum levels of total PCBs, 12 PCB congeners, five PCB groups, and pesticides was investigated in Mohawk adults at Akwesasne. The participants, men and women, were recruited from 1995 to 2000. Over 700 people (257 men and 446 women) were included in the study and ranged from 18 to 95 years of age. Mohawk people were previously identified as having PCB levels higher than the general population, with a range of 3.97 to 5.29 ppb compared to a range of 0.9 to 1.5 ppb for the general population. There was no significant relationship between PCB and testosterone levels for women. Men had a significant relationship between testosterone and total PCB blood levels. Significant negative associations were also identified between specific PCB congeners (74, 99, 153, and 206) and testosterone levels (Goncharov et al. 2009).

Thirty-eight participants (six women and 32 men) in the NYSACS had PCB (77 congeners) and thyroid hormones measured in the blood. There was no significant association between TSH or FT4 and the total PCB levels (Bloom et al. 2009).

Thyroid effects

Umbilical cord blood was collected from Maryland births between November 2004 and March 2005. Two hundred and eighty-nine samples were analyzed for four PCB congeners (118, 138/158, 153, and 180), mono-ortho PCBs (74 and 118), di-ortho PCBs (99, 138/158, 153, 180), and cytochrome P450 inducing PCBs (99, 118, 153, 180). No significant association was identified between PCB levels and high TSH or low TT4 or FT4 in cord blood or blood from blood spots. There was a trend that increasing levels of PCBs occurred in blood with lower TT4 levels (Herbstman et al. 2008).

Two hundred and eight-five women were selected to participate in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS). Women in the study had spent less time in the U.S. than women who were excluded from the study. TSH was measured in all infants at birth (blood was collected by heel stick). PCBs in maternal serum were measured with maternal blood collected at the end of the second trimester, with 34 PCB congeners measured. TSH levels were within the normal range for all children. The total PCBs level statistically

significantly increased with increasing maternal age. Some congener (PCB 99, 138, 153, 180, 183, 187, 194, and 199) levels were related to TSH levels. Overall, the levels of PCBs in the study participants were lower that those from the NHANES background data (Chevrier et al. 2007).

The CHAMACOS enrolled 601 women from October 1999 to October 2000. Of the women enrolled, 538 were followed to delivery and had a livebirth. Some of the women were excluded due to a lack of sample or information. In the final study population, there were 334 participants, with a mean age of 25.5 years. Maternal thyroid hormone and PCB levels were measured from blood collected during the second interview (n = 320) or before delivery (n = 14). Thirty-four PCB congeners were measured and 19 of the congeners were detected in more than 75% of the participants. The range of PCBs measured was 18.8 to 323.7 ppb with a geometric mean of 65.3 ppb. Fourteen of the 19 congeners most commonly measured were negatively associated with thyroid hormones (free thyroxine) and four were negatively associated with total thyroxine. No positive associations were identified (Chevrier et al. 2008).

Two study populations were examined to determine if PCB exposure altered thyroid hormone levels. Thyroid hormones are essential for proper brain development during the fetal and neonatal periods. The first study population was Inuit from Nunavik, Canada, with enrollment between 1993 and 1996. Four hundred and thirty-seven umbilical cord blood samples were collected from 491 participating newborns. The second population was from the St Lawrence River study and half were Innu. Two hundred and sixty newborns were enrolled between 1993 and 1997. Premature and low birth weight newborns were excluded from the study. The 14 most frequently measured PCB congeners were congeners 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187. PCB 153 was detected in almost every sample (99.8% of the Nunavik participants and 99.2% of the St Lawrence River participants). PCB levels measured in the Nunavik participants ranged from below the level of detection to 1,072.5 µg/kg lipid adjusted with a geometric mean of 95.0 µg/kg lipid adjusted. The PCB range for the St Lawrence River participants was below the level of detection to 677.5 µg/kg lipid adjusted with a geometric mean of 63.6 µg/kg lipid adjusted. Based on the results from this study, organochlorines (including PCBs) do not seem to alter thyroid hormone levels (Dallaire et al. 2008).

Children (n = 482) born between July 1997 and December 1998 were enrolled in a study in Menorca, Spain to determine the association between PCB levels and thyroid hormones. Although there was information for 468 children to the age four, only 259 provided blood samples for thyroid hormone measurement. The PCB congeners present in the highest proportion were PCB 153, 138, 180, and 118 with PCB 153 contributing 30% of the sum of the seven congeners analyzed. PCB levels in the blood (the sum of the seven marker congeners) ranged between 0.15 ppb and 41.17 ppb. There was a negative association between total triiodothyronine (T3) levels and the individual PCB congeners 138, 153, and 118. There was also a negative association between free T4 and PCB congener 118 (Alvarez-Pedrerol et al. 2008).

Pregnant Inuit women were measured for PCB 153, HO-PCBs and serum thyroid hormone levels. From maternal blood collected at delivery, there was a significant positive association of total HO-PCB levels and T3 plasma levels. For both cord and maternal blood, there was a

significant negative association between thyroxine-binding globulin (TBG) and PCB153 levels (Dallaire et al. 2009).

Diabetes and cardiovascular effects

Serum PCB levels were measured in pregnant women participating in the Collaborative Perinatal Project. PCB levels were compared between diabetic women (n = 44) and non-diabetic women (n = 2,201). The adjusted mean serum PCB level was statistically different between the diabetic women (3.71 µg/L) and the non-diabetic women (2.86 µg/L). This indicates an association between diabetes and PCB levels, but again, as other authors have noted, it is unclear whether elevated PCB levels caused diabetes or whether women with diabetes are likely to have elevated PCB levels (Longnecker et al. 2001).

Men and women (n = 257) with and without diabetes from five areas of Belgium participated in a study to associate PCB levels with diabetes. Nine men and women had diabetes and 248 did not. Twelve PCB congeners (PCB 3, 8, 28, 52, 101, 118, 138, 153, 180, 194, 206, and 209) were measured in the participants blood. Those with diabetes had PCB levels averaging 652 (512-831) ppb lipid weight and those without diabetes had PCB levels averaging 402 (383-423) ppb lipid weight. There was a statistically significant difference between those with and without diabetes. Additional differences were observed in total TEQ, polychlorinated dibenzo-p-dioxin (PCDD)+PCDF TEQ, and PCB TEQ values (Fierens et al. 2003).

Serum levels of POPs and the association with diabetes was assessed in Swedish fishermen and their wives. People from Sweden are exposed to POPs in fatty fish from the Baltic Sea. PCB 153 and p,p'-DDE were selected as biomarkers for POP exposure. Participants were selected from an established cohort of professional anglers and their wives and the final study group had 196 men and 184 women. PCB 153 and p,p'-DDE levels in men were associated with diabetes. Women had an association of p,p'-DDE levels, but not to PCB 153 levels, to diabetes. The authors concluded that POPs might contribute to type 2 diabetes (Rylander et al. 2005).

Levels of PCBs and polybrominated biphenyl (PBB) were measured in members of the Michigan PBB cohort and the association with diabetes was assessed. Serum PCB levels were measured for 1,384 members of the cohort using the Aroclor 1016, 1254, and 1260 standards. The number of female, but not male, cohort members with diabetes increased with higher serum PCB levels, but not serum PBB levels. Although serum PCB and PBB levels were measured at enrollment, before the development of diabetes, it is possible that those with diabetes had increased lipids in the serum before development of diabetes. The authors investigated that possibility by removing those that developed diabetes earlier (after 1976 and up to the second survey in 1991 to 1993). Women's risk of diabetes increased with increased serum PCB levels, as measured at enrollment (Vasiliu et al. 2006).

Type 2 diabetes is one of the presumptive diseases associated with exposure to dioxin-containing Agent Orange. NHANES data (1999 to 2000 and 2001 to 2002 datasets) was used to investigate whether PCB 153 and five other POPs were associated with the prevalence of diabetes. The dataset was not able to differentiate type 1 from type 2 diabetes. PCB 153 levels were correlated with age, economic standing (poverty income ratio), BMI, and waist circumference. Diabetes was strongly associated with PCB 153 and four other POPs. It is not clear, from this study,

whether PCBs or other POPs cause diabetes, or diabetes causes greater accumulation of PCBs and other POPs (Lee et al. 2006).

NHANES data (1999 to 2002) was again used to determine if POP, including PCBs, levels were associated with insulin resistance in non-diabetic subjects. POP levels were from 749 participants (46.3% male and 49.7% white) with an age range of 20 to 85 (mean 48.2 ± 18.9). Age most strongly correlated to POP levels. PCBs were not strongly associated with insulin resistance. However, two non-dioxin-like PCBs, PCB 170 and PCB 187, were significantly associated with the increased insulin resistance and may increase the risk of type 2 diabetes (Lee et al. 2007A).

Lee et al. (2007B) expanded on their previous study objectives and used information from 721 non-diabetic participants age 20 or older from the NHANES 1999 to 2002 datasets to examine the association between POPs and metabolic syndrome (a group of condition that puts people at risk for developing heart disease and diabetes). Of the total participants, 175 (24.3%) had metabolic syndrome. Dl-PCBs, non-dl-PCBs, and organochlorine pesticides were associated with metabolic syndrome. Dl-PCB associated with metabolic syndrome and individual components were PCB 126, PCB 74, PCB 118, and PCB 169. PCB 126 had an association with metabolic syndrome and individual components (waist circumference, triacylglycerol, and blood pressure). PCB 74 and PCB 118 were also associated with metabolic syndrome, but only PCB 118 was associated with individual components (waist circumference and tracylglycerol). PCB 169 was not associated with metabolic syndrome itself, but was associated with one individual component, waist circumference. Non-dl-PCBs associated with metabolic syndrome or individual components were PCB 138, PCB 153, PCB 170, PCB 180, and PCB 187. All of the non-dl-PCBs were associated with metabolic syndrome and the triacylglycerol component. Three of congeners (PCB 153, PCB 170, and PCB 180) were associated with the individual component of waist circumference and two (PCB 170 and PCB 187) were associated with fasting glucose (Lee et al. 2007B).

NHANES data (1999 to 2002) was used to examine the association of PCB 126 with diabetes. Associations were investigated for undiagnosed, diagnosed, and total (undiagnosed plus diagnosed) diabetes. Undiagnosed diabetes was determined by measuring glycohemoglobin (glucose attached to hemoglobin) levels. Levels of PCB 126 (and p,p'-DDT) were significantly associated with undiagnosed and total diabetes. From the NHANES data, 5.48% of the people had PCB 126 levels greater than 83.8 pg/g (ppt). Of those people, 29.24% had either diagnosed or undiagnosed diabetes (Everett et al. 2007).

NHANES data (1999 to 2000 and 2001 to 2002) was examined to determine if an association was present with self-reported cardiovascular disease. Data for five dioxin-like PCB congeners and six non-dioxin-like PCB congeners for 889 people (48% male and 52% female) age 12 or older was available. Dioxin-like PCB levels were significantly correlated with age and poverty income ratio for both male and female participants. For males only, dl-PCBs were significantly associated with BMI, if they were a current smoker, and alcohol consumption. Dioxin-like PCB levels in females only significantly correlated with high density lipoprotein (HDL) cholesterol and total cholesterol. For both males and females, non-dioxin-like PCB levels significantly correlated with age and HDL cholesterol. Female participants also had significant correlations

between non-dioxin-like PCB levels and poverty income ratio, BMI, triglyceride levels, and C-reactive protein levels. For male participants, there was no significant association between PCB levels and self-reported cardiovascular disease. For females, cardiovascular disease was significantly associated with both dioxin-like and non-dioxin-like PCB levels, as well as organochlorine pesticide levels. The authors did caution that the association could be a marker of another condition. They also noted that this study provides no causal relationship; there is no information on whether PCB levels caused cardiovascular disease or whether cardiovascular disease causes an increase in PCB levels (Ha et al. 2007).

Swedish anglers' wives, from a previously established cohort, were assessed for the relationship between organochlorine pollutants and type 2 diabetes mellitus (T2DM). Blood samples were collected and diabetes status was assessed for 543 women (15 women with T2DM and 528 non-diabetic women). Women participating in the study had a median age of 50 years, with a range of 29 to 59. PCB 153 was measured in the blood as a marker for POP levels. Women without diabetes had a mean PCB 153 level of 98 ppb lipid weight (median = 82 ppb lipid weight; $5^{th}$ percentile = 30 ppb lipid weight; $95^{th}$ percentile = 220 ppb lipid weight). Women with T2DM had a mean PCB 153 level of 130 ppb lipid weight (median = 110 ppb lipid weight; $5^{th}$ percentile = 56 ppb lipid weight; $95^{th}$ percentile = 250 ppb lipid weight). Increased PCB 153 levels were significantly associated with increased number of women with T2DM. Increased p,p'-DDE levels were also significantly associated with increased T2DM. Although associations between T2DM and PCB 153 were identified, the authors were careful to note that this study is not able to determine if increased blood PCB 153, or other POP, levels were causing an increase in the number of people with T2DM or if having T2DM causes an increased in blood PCB 153, or other POP, levels (Rignell-Hydborn et al. 2007).

Reproductive effects

Wives and ex-wives of anglers from the west and east coasts of Sweden reportedly consume more than twice as much fish as other women in Sweden. Fish from the east coast of Sweden (from the Baltic Sea) have been reported to have more persistent organochlorine compounds than fish from the west coast of Sweden. Previous studies have reported that infants born to angler couples on the east coast, from 1972 to 1991, had a higher frequency of low birth weight as compared to infants born to angler couples on the west coast. This study investigated the association between PCB body burden (measured using a marker PCB, PCB 153) and risk of low birth weight. Two or more control mothers, those having infants with weights between 3,250 and 4,500 g, were matched to one low birth weight infant mother, those having an infant with a birth weight between 1,500 and 2,750 g. All women were members of a cohort of women who were formerly or currently married to a Swedish east coast angler. In total, 192 women participated, with 135 control women and 57 women birthing low birth weight infants. The median plasma PCB 153 level for the control women was 920 ppt, with a range of 80 to 4,300 ppt. For the women with low birth weight infants, the median plasma PCB 153 level was 1,000 ppt (range 290 to 3,960 ppt), which was slightly higher than the control women. Higher PCB 153 levels were associated with an increased risk for low birth weight (Rylander et al. 1998).

Newborns from the province of Quebec, Canada (n = 1,109) were screened for lead, mercury, 14 PCB congeners, and 11 chlorinated pesticides. The infants were selected from June 1993 to January 1995 and were from 10 different hospitals. PCBs were measured in cord blood from 656

infants. The range from individual congeners (PCB 99, 118, 138, 153, and 180) was 0.01 to 0.45 µg/L with a geometric average of 0.514 µg/L for total PCBs, based on an Aroclor 1260 standard. Individual congeners were detected in 63.4 to 99.2% of the samples. No correlation was identified between PCB levels and birth weight (Rhainds et al 1999).

Age of natural menopause and plasma organochlorine levels were measured in participants of the Carolina Breast Cancer Study. Median PCB levels were 1.82 ppb (range 0.26 to 26.08 ppb) and the median lipid-adjusted value was 0.36 µg/g for total PCBs (n = 1,348). Based on the information from this study, the authors concluded that there was no association between PCB exposure and menopause (Cooper et al. 2002).

Men (n = 65) who assessed for fertility issues at Maastricht University Hospital in The Netherlands, were involved in a study to examine associations between semen parameters and PCB levels. Men were dived into two groups based on semen quality, men with poor semen quality were placed in the male factor subfertility (MFS) group and men with normal semen quality were placed in the female factor subfertility (FFS) group. Along with semen quality and PCB levels, genes for glutathione S-transferase (GST; genes GSTM1 and GSTT1) were assessed. No metabolism differences were identified as the correlation between the PCB level and metabolite levels did not change with different GSTM1 or GSTT1 polymorphisms. The PCB levels were positively related to the ages of the study participants. There were no relationships between PCB levels and semen parameters, sperm count, and progressive and overall motility. However, a significant relationship was identified between individual congener and total PCB concentrations and sperm morphology. PCB levels in the blood and in the seminal plasma were significantly related (Dallinga et al. 2002).

Male partners (n = 212) of sub-fertile couples were enrolled in a study, at Massachusetts General Hospital, between January 2000 and October 2001 to determine if PCBs and/or p, p'-DDE alter semen parameters. Fifty-seven PCB congeners were measured. Increased concentrations of PCB 138 significantly altered sperm motility and sperm morphology. Sperm motility and morphology were also significantly altered by the levels of enzyme-inducing PCBs (Hauser et al. 2003).

Swedish males (n = 305) ages 18 to 21 enrolled in a study to determine the association between PCB 153 and reproductive function parameters. Levels of PCB 153 in the semen ranged from 23 to 250 ppb lipid weight with a median of 65 ppb lipid weight and a mean ± SD of 68 ± 29 ppb lipid weight. Sperm motility (% D category [immotile], % CRISMAS computer-aided sperm motility analyzer [CASA] motile), sexual hormone-binding globulin (SHBG), and testosterone: SHBG ratio were significantly associated with PCB 153 levels. The testosterone: SHBG ratio is a measure of the biologically active free testosterone fraction. An increase of PCB 153 levels by 10 ppb lipid weight resulted in a 1.0% decrease in CASA motile spermatozoa. The authors concluded that this study provides tentative support for negative effects pf PCB 153 on sperm motility and free testosterone levels in men (Richthoff et al. 2003).

Fierens et al. (2003) examined the association between endometriosis and PCB levels in 142 women from five areas of Belgium. Twelve PCB congeners (PCB 3, 8, 28, 52, 101, 118, 138, 153, 180, 194, 206, and 209) were measured. Levels of the 12 marker PCBs were 294 (215-401) ppb fat in the 10 women with endometriosis and 372 (351-403) ppb lipid weight in women

without endometriosis (n = 132). There was no statistical differences between those with or without endometriosis (Fierens et al. 2003).

Windham et al. (2005) obtained similar results in a study with Laotian-born women, who were regular consumers of fish, in the San Francisco Bay area. The study examined the association of organochlorine levels and ovarian function. The women (n = 49) had a mean total fish consumption of the prior four weeks of 22 grams/day (± 33, median = 12.6 g/d). Ten PCB congeners (74, 99, 118, 138, 153, 170, 180, 187, 194, and 203) were measured in serum. The PCB levels were higher in women with older age and a longer time in the U.S., but did not correlate with the reported fish consumption. PCB levels did not seem to be associated with ovarian function (Windham et al. 2005).

Twelve PCB congeners are dioxin-like (PCBs 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189), able to act through the AhR. Healthy women, without endometriosis, infertility, pelvic pain, or dysmenorrheal, were the control group (n = 21). They were compared to women with either peritoneal endometriosis (n = 25) or deep endometriotic (adenomyotic) nodules (n = 25). All women were enrolled between January 2001 and June 2003. Dioxin-like PCB levels were significantly higher in women with deep endometriotic nodules as compared to the control women, but not the women with peritoneal endometriosis. The most abundant PCB congeners in all three groups were PCBs 126, 118, and 156. PCDD/PCDF and dioxin-like PCB levels were associated with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules in this study population (Heilier et al. 2005).

Pregnant women from the Collaborative Perinatal Project participated, from 1959 to 1965, at 12 different U.S. study centers. Associations between gestational length and birth weight and PCB levels were evaluated in 1,034 participants. The participants (n = 1,034) had, overall, 132 preterm births and 101 small-for-gestational-age births. The median serum level of PCBs was 2.8 µg/L. The authors found little evidence that low-level PCB exposure was associated with preterm birth, birth weight, or length of gestation in their study population (Longnecker et al. 2005).

Eleven PCB congeners were measured in archived serum samples from the Child Health and Development Study (CHDS). Participants in the CHDS were enrolled in the 1960s in the San Francisco Bay Area through prenatal clinics or by giving birth at specific medical centers. Close to 400 (n = 399) woman/child pairs were included in this study. Children from the CHDS were born between April 1964 and April 1967 and were examined at five years of age. PCB congeners (PCB 101, 105, 110, 118, 137, 138, 153, 156, 170, 180, and 187) and lipid levels were measured in the serum. Total PCB levels were the sum of PCBs 105, 110, 118, 137, 138, 153, 170, 180, and 187). Male infants, on average, had a lower birth weight with increasing amounts of maternal PCBs. Female infants birth weight was not associated with PCB levels. Individual PCB congeners (PCB 118, 138, 153, 170, 180) were also associated with male birth weight, but not with female birth weights. Overall, total PCB levels were positively associated with sitting height, standardized weight, and bi-iliac distance (distance between the hipbones) at five years of age (Hertz-Picciotto et al. 2005).

A study on environmental exposures and epididymal and accessory sex gland function included participants that were Swedish fishermen (n = 134) and spouses to currently pregnant women from Greenland (n = 157), Warsaw (Poland; n = 164), and Kharkiv (Ukraine; n = 153). The epididymal gland is a tightly coiled tube that stores sperm. Neutral α-glucosidase (NAG) is used as a marker of epididymal gland function. The accessory glands include the seminal vesicles and prostate gland. Significant negative associations were identified between PCB 153 levels and NAG levels in men from Greenland and Warsaw. A significant positive association was identified between PCB 153 levels and NAG in men from Kharkiv. PCB 153 levels in men from Kharkiv also significantly associated with PSA level, zinc, and fructose (Elzanaty et al. 2006).

A study of 899 infants and 444 mothers was conducted to determine of maternal PCB levels were associated with adverse health outcomes. PCB levels in maternal serum at the time of enrollment ranged from the limit of detection (5.0 ppb) to 78.0 ppb. PBB levels were also measured. Forty percent of the infants were born to mother whose PCB levels were below 5.0 ppb. Fifty-five percent of the infants were male. Gestational ages ranged between 29 to 46 weeks, with a mean of 39.8 weeks. Four percent of the infants were born pre-term, but PCB or PBB levels did not change the mean gestational age. The birth weight ranged from 508 to 5,868 grams with a mean of 3,551 ± 533 grams. Only 3.3% of the infants had low birth weight. PCB, but not PBB, levels were associated with birth weight (Givens et al. 2007).

The New York State Angler Cohort Study (NYSACS) followed 99 women attempting to get pregnant for 12 menstrual cycles  Women grouped into three categories: live births, pregnancy losses, and infertility. No statistical differences were identified in the PCB levels among the three groups (Bloom et al. 2007).

Between 1996 and 2002, PCBs (101, 105, 118, 138, 153, 156, and 180) were analyzed in 100 pregnant women's plasma. The participants had low (n = 34), medium (n = 33), and high (n = 33) intakes of commercial fish. Factors associated with plasma PCB levels were median age at recruitment, median pre-pregnancy BMI, and median total plasma lipid concentration. PCB 101 levels were below the detection limits, so total PCBs is the sum of the six remaining congeners. Total plasma PCB levels were 1.15 µg/L (median), 0.64 µg/L ($5^{th}$ percentile), 0.91 µg/L ($25^{th}$ percentile), 1.45 µg/L ($75^{th}$ percentile), and 1.88 µg/L ($95^{th}$ percentile). A significant association was identified between fatty fish intake and plasma PCB levels. Significant associations were also identified between placental weight and plasma PCBs and between birth weight and plasma PCBs. For both placental and birth weight, as PCB levels increased the weights decreased. The relationship identified between the birth weight and plasma PCBs was only identified after adjusting for gestational age, infant's sex, maternal smoking, prepregnancy body mass index, and plasma lipid concentration (Halldorsson et al. 2008).

Influence of PCBs on sex birth ratio was assessed in San Francisco, California, using records from 1964 to 1967 from participants (n = 399) in the Child Health and Development Study. PCB congeners 101, 105, 110, 118, 137, 138, 153, 156, 170, 180, and 187 (total PCB) were measured in maternal serum. Maternal total PCBs levels had a mean of 5.4 µg/L (ppb), a median of 4.7 µg/L, and a $90^{th}$ percentile of 8.7 µg/L. Using relative ratio, the male births were reduced with increasing amounts of total PCBs. The odds ratio for a male birth reduction was associated with total PCBs, PCB 105 and 170. Overall, as the maternal total PCBs increased, there was a

reduction in male children. The authors did not investigate why male births decreased with increasing concentrations of maternal total PCBs, but speculated that there may be a decrease in fertilized male embryos or an increase in male embryo or male fetal loss (Hertz-Picciotto et al. 2008).

Between September 2000 and October 2002, 196 mother-infant pairs were recruited for a study to assess PCB levels in maternal blood and milk and determine the association with hormones (estradiol and testosterone) in cord serum. Six PCB congers (28, 52, 101, 138, 153, and 180) were measured in maternal blood and milk. PCB levels in maternal blood (n = 104) ranged from 0.008 to 0.512 ppt fat and had a geometric mean of 0.140 ppt fat. In maternal milk (n = 83), PCB levels ranged from 0.01 to 0.43 ppt fat and had a geometric mean of 0.156 ppt fat. PCB congeners 138, 153, and 180 accounted for 99% of the total PCBs in both maternal blood and milk. Overall, the hormone levels measured in cord serum decreased as the organochlorines levels increased (Cao et al. 2008).

Immunological effects

Van Den Heuvel et al. (2002) investigated whether lifetime exposure to PCBs and dioxin-like compounds are associated with alterations in the immune system. Study participants were adolescents, born between 1980 and 1983, recruited in 1999, were in the last two years of secondary school (equivalent to age of U.S. children in the last two years of high school), and lived in the suburbs of Hoboken and Peer. The suburbs of Hoboken and Peer are adjacent to the city of Antwerp, Belgium and are near chemical and petroleum industries in Antwerp's seaport. Two hundred adolescents participated in the study (120 girls and 80 boys) (Van Den Heuvel et al. 2002).

The study participants had a mean age ± SD of 17.4 ± 0.8. Girls and boys had several significantly different hematological parameters (red blood cells, white blood cells, % monocytes, trombocytes [platelets], % eosinophils, % CD3 cells, % CD4 cells, % CD19 cells, % CD16+CD56 cells, IgE, and IgM). Girls and boys also had statistically significant differences in levels of PCBs (sum of PCB 138, 153, and 180) in their serum. Girls had a geometric mean of 0.99 nmol/L (189.67 pmol/g fat) and a 95% confidence interval (CI) of 0.90 to 1.09 nmol/L (172.19 to 208.45 pmol/g fat). Boys had a geometric mean of 1.67 nmol/L (359.75 pmol/g fat) and a 95% CI of 1.51 to 1.83 nmol/L (326.59 to 397.19 pmol/g fat). In this study population, the three lower chlorinated PCB congeners (PCB 28, 53, and 101) were at levels below their limits of detection. PCB 153 accounted for 46% of the total marker PCBs (PCBs 138, 153, and 180) with PCB 138 and 180 each accounting for 27% of the total (Van Den Heuvel et al. 2002).

Along with measuring the amount of PCBs, the authors measured dioxin-like activity in the serum of the study participants. The dioxin-like activity was measured with the chemical-activated luciferase gene expression (CALUX) bioassay. Briefly, the CALUX assay involves extracting the chemicals from the serum and adding it to H4IIE rat hepatoma cells. These cells have luciferase gene expression under control of the AhR, so whenever the AhR activates transcription luciferase will be expressed. Luciferase can be measured and the amount of luciferase produced by the cells indicates the amount of dioxin-like activity present in the extracted chemicals. Eosinophil and CD16 and CD56 double positive cell levels along with IgE levels significantly correlated negatively to dl activity calculated with the CALUX assay. IgA

levels significantly correlated positively to the total marker PCB levels. Dl activity, measured by CALUX, is also negatively associated with the odds of having a positive allergy test to house dust mite, cat dander, and grass pollen; upper airway allergic disease; and using medication for asthma. The total marker PCBs are positively associated with having hay fever or asthma (Van Den Heuvel et al. 2002).

Two cohorts of Faroese children were enrolled in a study to examine the effects of PCB levels on antibody production against the tetanus and diphtheria vaccines. Tetanus and diphtheria were selected as they are thymus dependant neoantigens, which means an immune response depends on antigen presentation and T and B cell function. PCB levels were assessed in maternal serum, maternal milk, and children's serum. A simplified total PCB concentration was calculated as sum of PCB 138, 153, and 180 times 2.0. The first cohort was enrolled in 1994-1995 and PCB analysis was done on 124 children's blood samples, at age 7.5 years. The second cohort was enrolled in 1999-2001, and PCB serum levels were obtained for 116 children at 18 months of age (Heilmann et al. 2006).

A significant relationship between increased maternal serum PCB levels and reduced antibodies against tetanus was identified in the first cohort. The significant reduction of antibodies against tetanus in the first cohort was associated with increased prenatal PCB exposure. In the second cohort, a significant negative correlation between current serum PCB levels and reduced antibodies against diphtheria was identified. Additionally, for the second cohort, a relationship between time since the last vaccination and reduced antibodies against tetanus or diphtheria was identified. Difference between the two cohorts may possibly be due to differences in the vaccines themselves. The tetanus toxoid, the antigen in the vaccine, may be a stronger antigen than the diphtheria toxoid and by age 7.5, children will have been exposed to the tetanus toxoid multiple times, through booster shots and as a component of the *Hemophilus influenzea* vaccine. As the older children (first cohort) have a higher amount of the antibodies against tetantus, difference may be more apparent. The second cohort, the 18 month olds, may not have had enough exposure to the tetanus toxoid to have observable differences in antibody production. The authors speculated that increased PCB levels might interfere with maintenance of antibody levels (Heilmann et al. 2006).
Differences were apparent in levels of antibodies against diphtheria though, although no differences were observed for the first cohort. The authors noted that the second cohort had higher levels of the antibodies against diphtheria as compared to the first cohort. The diphtheria toxoid could be a weaker antigen, which would explain why older children had lower antibody levels. The authors stated that if a lower PCB exposure group was included, differences in antibody levels against diphtheria may have been identified (Heilmann et al. 2006).

Organochlorine compounds, including 14 PCB congeners, and heavy metals were measured in Inuit newborns from Nunavik, Canada. PCB 153 was also measured as an indicator of the total PCB levels. Children were followed for five years and the incidences of ear infections (acute otitis media [AOM]), upper (URTI) and lower (LRTI) respiratory tract infections were recorded. The geometric mean of the total PCBs was 323.5 µg/kg lipid and of PCB 153 was 93.6 µg/kg lipid. Prenatal exposure to PCB 153 was associated with ear AOM incidence rates, with exposure to increasing amounts of PCB 153 causing increases in incidence of AOM. No association between URTI and PCB 153 was identified, but PCB 153 levels were associated with LRTI

incidence rates. DDE levels were also associated with infection incidence rates (Dallaire et al. 2006).

NHANES data from 1999 to 2002 included self-reporting of clinical diagnosis of history or arthritis and subtypes of arthritis. Four dioxin-like PCBs and five non-dioxin-like PCBs were measured in the NHANES participants (n = 1,721). Dl-PCBs correlated with age, poverty income ratio, BMI, and being a current smoker in men and age, race, and poverty income ratio in women. Non-dl-PCBs significantly correlated with age and poverty income ratio in men and age, race, poverty income ratio, BMI, and being a current smoker in women. Only women with increased dl and non-dl-PCBs had a significant trend toward increased risk for prevalence of arthritis. Of the congeners tested, two dl (PCBs 74 and 118) and three non-dl-PCBs (PCBs 170, 180, and 187) significantly increased the risk of prevalence of arthritis. Rheumatoid arthritis, but not osteoarthritis was significantly associated with increased PCB levels. Arthritis that was not classified as rheumatoid or osteoarthritis was significantly associated with non-dl-PCBs, but not dl-PCBs (Lee et al. 2007C).

Women seeking prenatal care in Uppsala County, Sweden were enrolled in a study to examine immunological effects in infants and the relationship between maternal PCB levels. PCB levels were reported as four different groups for maternal serum and milk. Ninety infants from the cohort had blood samples drawn and white blood cells measured, with 52 samples analyzed for lymphocyte subsets. The percent of CD4-CD8+ had a significant negative association with PCB153, di-ortho PCBs, and mono-ortho PCB TEQ. There was also a significant increase in the odds ratio for respiratory infections when infants were less than three months old for infants with PCBs exposure compared to unexposed infants. The authors concluded that high prenatal exposure to PCBs might increase the risk of respiratory infections (Glynn et al. 2008).

Human poisonings

Two populations ingested rice bran oil that had been accidentally contaminated with a commercial PCB mixture used during production of the oil. The oil that the people ingested was contaminated with PCBs and heat-degraded products, such as PCDFs and PCDDs. The earlier poisoning was in western Japan in 1968 and symptoms resulting from this exposure are collectively called Yusho disease. The second poisoning is referred to as Yucheng disease. It occurred in central Taiwan in 1979. Symptoms included chloracne, liver damage, immunosuppression, and neuropathy (Skerfving et al. 1994).

*Yusho*

Yusho occurred in the northern part of Kyushu Island in southern Japan in 1968. Approximately 2,000 people (1,866) were affected by ingesting rice bran cooking oil contaminated with heat exchanger PCBs during production (Ikeda 1996). Rice oil was contaminated with Kanechlor-400 (KC400), which was used as a heat transfer medium in the deodorization process of rice oil production (Yao et al. 2002). Kanechlor-400 was a commercial mixture of PCBs and PCDFs. Yusho mainly occurred in the Fukuoka and Nagasaki prefectures (Masuda et al. 2001).

Typical Yusho symptoms included acneform eruption, dermal pigmentation, and increased eye discharge. Some of the symptoms (pigmentation) corrected themselves over several years. Additional symptoms have persisted for 30 years (enzyme and hormone mediated), such as

elevated triglyceride, serum thyroxin, and serum Ig levels (Masuda et al. 2001). Originally, Yusho was thought to have been caused by PCBs alone, but is probably a result of exposure to a complex mixture of PCBs, PCQs, and PCDFs (Kanagawa et al. 2008). Women with more adipose tissue tended to have higher levels of PCBs, PCQs, and PCDFs (Kanagawa et al. 2008). Non-specific subjective symptoms that have been identified in Yusho patients includes general fatigue, weight loss, and anorexia. Characteristics symptoms of Yusho disease can be dermatological, ophthalmological, and oral (Imamura et al. 2009).

In the time since the poisoning, (34 years when this study was conducted) the typical symptoms of Yusho disease have passed and some patients have subjective symptoms. The typical symptoms were acneform eruptions, dark-brownish nail pigmentation, increased discharge from the eyes with swelling of the eyelids, pigmentation of oral mucosa, peripheral neuropathy, irregular menstruation in women, and growth retardation in children and infants. The subjective symptoms that persist in some Yusho patients include general malaise, loss of appetite, and headache. The primary cause of the symptoms may be PCDFs (Todaka et al. 2007).

Onozuka et al. (2009) followed 1,596 Yusho patients until death or the end of the study (December 31, 2007) to assess mortality. The Yusho poisoning victims were exposed to at least 74 PCB congeners and 47 PCDF congeners. Most of the Yusho patients, 37% of the women and 40% of the men, were less than 20 years old at the time of the poisoning (total 1,596 patients). Almost 500 deaths (269 males and 172 females, 441 deaths total) occurred in the 40 year follow-up period after the poisoning. The author found no increase in standardized mortality ratios for the Yusho patients as compared to the general population. However, significant elevations were identified for the Yusho males and cancer. In the Yusho women, stomach cancer was decreased, while liver cancer was elevated for both males and females. Non-cancer related mortality was not different from the general population. Differences in mortalities for the Yusho patients (male versus female) could be due to the endocrine disrupting effects of the contaminants (Onozuka et al. 2009).

As animal studies reported stillbirth and spontaneous abortions resulting from dietary PCB exposure, Tsukimori et al. (2008) evaluated pregnancies of Yusho patients. Ingested amounts of contaminants in the rice oil were estimated to be 633 mg of PCBs, 3.4 mg of PCDFs, and 0.62 mg of PCQs. The Yusho patients involved in this study (n = 214) had 512 pregnancies between 1958 and 2003. Adverse pregnancy outcome were similar in Yusho patients to unexposed women with pregnancies between 1978 to 1987 and 1988 to 2003. However, spontaneous abortions were more frequent, but not significant, in 1968 to 1977 as compared to pregnancies between 1958 to 1967. Yusho women had a two-fold increase in the proportion of spontaneous abortion, a five-fold increase in pregnancy loss, and a five-fold increase in induced abortion. Differences that were present in the 10 years immediately after the incident (1968 to 1978) were not present by 10 years after the poisoning (1978 to 1988) (Tsukimori et al. 2008).

*Yucheng*

Yucheng disease occurred in Taichung in central Taiwan in 1979 from eating rice bran cooking oil contaminated with heat exchanger PCBs during production. Approximately 2,000 people ingested the contaminated oil (2,061 people total) (Ikeda 1996). Wang et al. (2008) identified a range of ingestion for the contaminating PCBs and PCDFs in the Yucheng cohort. The estimated

consumption of PCBs was one gram, with a range of 0.77 to 1.84 g, and 3.8 mg of PCDFs. The Yucheng cohort was exposed for an average of nine months (Wang et al. 2008).

Survey results indicated that the Yucheng group were reporting more skin and oral problems compared to controls. Other symptoms that were reported more often in the Yucheng group were goiter, anemia, headaches, and arthritis. No excess cancer mortality was identified in the Yucheng group compared to the control group (Guo et al. 1999).

Diabetes is twice as prevalent in Yucheng women, but not men, as in the general population. The authors speculate that certain PCB congeners may be associated with an increased risk of diabetes occurrence (Wang et al. 2008). Yucheng women with chloracne had a statistically significant increased risk in developing hypertension and cardiovascular disease (Wang et al. 2008).

Three characteristic patterns of PCB congeners were identified in people from the Yucheng cohort. These congener patterns are composed of 33 PCB congeners with high levels of PCB 99, 138, 153, 156 ,170, 179, and 180. Total PCB levels in people of the Yucheng cohort are nine time higher than the general population, as measured 15 years after the exposure (Hsu et al. 2005).

In a mortality study, 13 years after the Yucheng incident, the Yucheng cohort had approximately 2.7 fold excess mortality rate due to chronic liver disease and cirrhosis compared with the Taiwan general population. The authors were unable to identify any increased mortality from specific neoplasms, but they did note that the cohort might to too young to observe those diseases with any frequency (Yu et al. 1997).

One hundred and five Yucheng and 101 control children, born between July 1978 and June 1987, were assessed for humoral and cell-mediated immunity differences. PCBs and PCDFs are know to be lipophillic, have long half-lives in the body, and are able to cross the placenta. The Yucheng children had statistically significant higher frequencies of influenza as compared to the control children, while other infectious disease had similar frequencies. The authors did not identify suppressed immunity in the Yucheng children and the humoral and cell-mediated immunity measures tested were similar between the Yucheng and control children (Yu et al. 1998).

In 1998, prenatally exposed men (mothers were Yucheng women) ages 16 and over were compared to 48 control volunteers (without any unusual chemical exposures) to determine if exposure to PCBs/PCDFs altered reproductive function. The proportion of sperm with a normal morphology, percentage of motile sperm, and rapidly motile sperm were reduced in prenatally exposed men (Guo et al. 2000).

Between 1979 and 1983, the Taiwan Provincial Department of Health performed health exams and registered 2,061 people. Registrants were included based on sign and symptoms or history of consumption of the contaminated rice oil. Blood PCB levels were measured from this Yucheng cohort between 1979 and 1981. Women were divided into high and low exposure groups. Children prenatally exposed (mothers were Yucheng women) had ectodermal defects,

developmental delay, and disordered behavior. The Yucheng cohort had excess mortality from non-malignant liver disease after 13 years of follow-up. Participants (n = 356) were older than those who declined to participate (n = 244). The Yucheng women (n = 356) were compared to control women (n = 312) who were similar in age that had lived in household near the Yucheng women in 1979. Yucheng women (8.8%) reported having light menstrual periods regularly in higher number compared to the control group (3.4%). Yucheng women reported having both abnormally heavy and light periods (6 women, 1.8%) while no control women reported the same. A statistically significant higher number of Yucheng women (16.6%) reported having menstrual abnormalities compared to the control women (7.5%). Yucheng women more frequently (2.5 times the control women) reported stillbirths, but had no differences in the number of spontaneous abortions. PCB levels were not linked to these effects and control women did not have PCB levels measured (Yu et al. 2000).

Female children in the Yucheng cohort were examined for alterations in sexual maturation, endocrine, and reproductive function. Children in the Yucheng cohort were matched to control children, based on age, gender, area of residence, maternal age, and combined parental educational level and occupation. This study included 48 girls, ages 13 to 19 in 1997. Mean maternal PCB levels for the Yucheng girls (n = 27) was 47.5 ppb (with a standard error of 8.9 ppb). Mean maternal PCB levels for the unexposed girls (n = 21) were lower, at 1.7 ppb (measured from pooled samples). Yucheng and unexposed girls had similar average ages at menarche, duration of menstrual bleeding per cycle, menstrual cycle length, dysmenorrheal, missed menstruation within six months, and doctors visits due to menstrual problems. Yucheng girls had a statistically significant shorter mean duration of bleeding per cycle (5.5 days) compared to the control (6.5 days). A statistically significant larger number of Yucheng girls had a mean cycle length shorter or equal to 25 days (35.5%) compared to the unexposed girls (6.3%). Yucheng girls had statistically significant higher levels of estradiol compared to the unexposed girls (Yu et al. 2000).

In 1992, when the children were seven to 11 years old, tooth development was examined in 73 children born to exposed mothers (Yucheng children) and 75 matched control children. The number of children with missing teeth and rotated teeth was statistically significantly increased in the Yucheng group as compared to the matched controls. There was also in statistically significant greater number of teeth with developmental defects in the Yucheng group as compared to the matched controls. The Yucheng children had a statistically significant smaller number of deciduous teeth (baby teeth) and more permanent teeth as compared to the matched controls at ages nine and 10. Dental effects are typically an effect of PCB exposure and not PCDF exposure (Wang et al. 2003).

# Appendix F: Discussion of Animal Toxicity Studies

## Non-human primates

Tryphonas et al. (1984) carried out a pilot study with 16 female cynomolgus monkeys to compare effects from exposure to Aroclor 1248 and 1254. Monkeys were fed 11.7 mg/kg Aroclor 1254 (equivalent to 5.0 mg/kg-day) or 4.7 mg/kg Aroclor 1248 (equivalent to 2.0 mg/kg-day) three days a week for up to 164 days. Two monkeys in the Aroclor 1248 treatment group died during exposure. The deaths were attributed to a failure of the immune system to protect against bacteria. The onset of signs of toxicity was not as rapid or uniform as those that occurred after humans or rhesus monkeys were exposed to Aroclor mixtures (Tryphonas et al. 1984).

Tryphonas et al. (1986) carried out another pilot, this time treating rhesus monkeys with Aroclor 1254. Eight adult female rhesus monkeys were treated with 280 µg/kg Aroclor 1254 five days a week (equivalent to 200 µg/kg-day) for 27 to 28 months. Signs of toxicity were apparent, but the authors noted that further testing was necessary (Tryphonas et al. 1986).

Eighty adult female rhesus monkeys were divided into five treatment groups, with 14 to 16 monkeys per group. Monkeys were orally given, by capsule, 0, 5.0, 20, 40, or 80 µg/kg-day Aroclor 1254. Pregnant females were treated after the birth, until infants were seven weeks of age. The number of females impregnated ranged from four to 11, with the number of live births ranging from one to nine in the treatment groups. The group not treated with Aroclor 1254 (0 µg/kg-day) had nine live births. Conception rates were statistically lower for groups treated with 20, 40, or 80 µg/kg-day compared to the untreated group (0 µg/kg-day). Only infants from groups treated with 0 (nine live births), 5.0 (five live births), or 40 (four live births) µg/kg-day survived more than two weeks after birth. Treatments were discontinued at that time, but began again when the infant was 22 weeks old. The treatments ceased due to the presence of the infant and the possibility that the infant may directly ingest the capsule (Arnold et al. 1995).

The infant's blood was tested at 44, 56, 64, and every 4 weeks after that until the age of 120 weeks. Statistically significant immunological effects were identified in infants whose mothers were treated with 5.0 or 40 µg/kg-day Aroclor 1254. Infants were sacrificed at 122 weeks of age (~2.3 years old) (Arnold et al. 1995). Arnold et al. (1997) further evaluated the study and found the overall effects were on the immune system and reproduction. Aroclor 1254 treatment reduced impregnation and increased fetal mortality.

The same group of eighty female rhesus monkeys were assessed by Bryce et al. (2000) for alteration in menstruation. Gynecological abnormalities were identified that resulted in significant differences in menses duration.

Non-human primates, rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) monkeys, were treated with a PCB mixture created to simulate the congener mix present in human breast milk from Canadian women. Nine rhesus monkeys (five male, four females) and 16 male cynomolgus monkeys were divided into control or treatment groups (control: six cynomolgus and one female and two male rhesus monkeys; treatment: 10 cynomolgus and three female and three male rhesus monkeys). The non-human primates were orally given 7.5 µg PCB congeners/kg daily from two to four days until 20 weeks of age (Arnold et al. 1999).

A variety of effects were examined throughout the study, including general health status, formula intake and feed and water consumption, body weight, tooth eruption, somatic measurements, weekly clinical evaluation, blood and adipose levels of PCBs, serum biochemistry, and immunology testing. No body weight differences were identified for either the rhesus or the cynomolgus monkeys. No differences were identified for tooth eruption between the control and treated groups. A slight swelling was noted under the eye of half of the treated cynomolgus monkeys, but was no longer apparent after weaning. No size differences were found between control and treated cynomolgus monkeys, but the treated rhesus monkeys grew faster as compared to the control rhesus monkeys (Arnold et al. 1999).

When measured throughout the 20 weeks of dosing, certain PCB congeners represented a greater amount in the blood than other PCB congeners. PCB 105 was a large proportion of the total PCB amount in the four monkeys treated with PCBs in corn oil. PCBs 74, 118, 138, 153, and 180 increased in amount over the treatment time. The monkeys fed PCBs in PRIMA-LAC only had minimal increases to blood PCB levels and individual congeners could not be determined. In adipose tissue, levels PCB 105 did not increase over time, but levels of PCBs 74, 118, 138, 153, and 180 did increase during the treatment (Arnold et al. 1999). PCB levels in the blood and adipose tissue are presented in Table F-1.

Half-lives for the PCBs in both rhesus and cynomolgus monkeys ranged from 9.75 (~ 2 months) to 102.13 (~2 years) weeks. These values indicate that the monkeys have a greater ability to metabolize PCB congeners as compared to humans. A significant increase in platelet number was observed in treated rhesus monkeys. There were no significant differences in antibody production (IgG and IgM) in control versus treated rhesus or cynomolgus monkeys. While there was no significant difference in lymphocyte proliferation between control and treated monkeys, there was a significant difference an absolute mean B cell levels between control and treated cynomolgus monkeys. The authors note that there were few differences between control and PCB congener treated monkeys. Overall, there were few effects on growth and development, while statistically significant changes were identified in immunological parameters (Arnold et al. 1999).

Table F-1: Blood and adipose levels in PCB-treated monkeys (Arnold et al. 1999).

| Fat levels of PCBs (ppb ± SD) | | Blood levels of PCBs (ppb ± SD) | |
|---|---|---|---|
| Rhesus – dosed in PRIMA-Lac (number of monkeys) | | | |
| Control (1) | 118.7 | Control (1) | 0.25 |
| Treated (2) | 1695.6 ± 539.9 | Treated (1) | 1.33 |
| Rhesus – dosed in corn oil | | | |
| Control | Not Determined | | Not Determined |
| Treated (3) | 5008.9 ± 2065.0 | Treated (4) | 14.41 ± 3.81 |
| Cynomolgus – dosed in PRIMA-Lac | | | |
| Control (5) | 129.4 ± 106.7 | Control (4) | 0.34 ± 0.04 |
| Treated (10) | 2470.6 ± 510.0 | Treated (7) | 2.37 ± 0.41 |

Rats: Carcinogenicity

The General Electric Company commissioned a study, carried out by Battelle to assess the chronic toxicity and oncogenicity of Aroclor 1016, 1242, 1254, and 1260 (Brunner et al. 1996). The results of the study are the basis for the EPA's CSFs for PCBs. Six hundred and fifty Sprague-Dawley rats per sex were divided into 11 treatment groups (50 rats per group) and one control group (100 rats). The rats were given Aroclor 1016 (50, 100, and 200 ppm), Aroclor 1242 (50 and 100 ppm), Aroclor 1254 (25, 50, and 100 ppm), or Aroclor 1260 (25, 50, and 100 ppm) in feed for 24 months. All rats that survived until the end of the experiment were necropsied as planned, and those animals that were found dead or were terminated in a moribund condition (while dying) were given a gross necropsy (Brunner et al. 1996).

Of the control rats, 43 male (103 total) and 31 female (103 total) survived to the planned termination. Forty-three male control rats were found dead and 17 were terminated in a moribund condition. Thirty female control rats were found dead and 42 had to be terminated in a moribund condition. Between 27 and 42 male rats and between 19 and 33 female rats in each Aroclor treatment group were either found dead or were terminated early due to a moribund condition. Tumor incidence was reported for the total number of rats in each group along with the tumor incidence for the rats terminated at the end of the experiment (Brunner et al. 1996).

Mayes et al. (1998) discussed significant results of the Brunner et al. (1996) study. The authors noted that the lot of Aroclor 1254 used in the rodent feed had twice the TEQ of most lots of Aroclor 1254. At the end of the study, hematological parameters, organ weight, incidence of liver lesions, thyroid lesions (male only), and mammary gland lesions (female only) were assessed. Hematological parameters were measured in a subset of the rats (nine to ten per group). The parameters measured were aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), total bilifubin, cholesterol, hemoglobin concentration (Hb), hematocrit (Hct), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), reticulocytes and red blood cell count (RBC). Additional parameters were assessed, but not reported (Mayes et al. 1998).

For males, significantly increased mortality occurred in the 100 ppm Aroclor 1016 and 50 ppm Aroclor 1254 ppm. PCB treated female rats had increased survival compared to the female control rats. Significantly increased survival, compared to the control female rats, occurred in all Aroclor 1016 groups, all Aroclor 1242 groups, the 25 ppm Aroclor 1254, and the 100 ppm Aroclor 1260 groups (Mayes et al. 1998).

Males treated with 25 or 100 ppm Aroclor 1254 had significantly increased serum cholesterol and those fed 100 ppm Aroclor 1260 had significantly increased GGT levels. Female rats had significant increases in serum cholesterol (100 ppm Aroclor 1242, all Aroclor 1254 groups, and 50 and 100 ppm Aroclor 1260 groups), AST (50 and 100 ppm Aroclor 1254), and GGT (50 and 100 ppm Aroclor 1254 and 50 ppm Aroclor 1260). Males had a small significant increase in MCHC (all Aroclor 1254 groups). Females had significant reductions in several hematological parameters for all Aroclor 1254 groups and some Aroclor 1016, 1242, and 1260 groups (Mayes et al. 1998).

Significant body weight differences were identified for males in the 50 and 100 ppm Aroclor 1254 groups and for females in the 100 ppm Aroclor 1242 and 25, 50, and 100 ppm Aroclor 1254 groups. Aroclor treatment increased liver to brain weight ratios, for both males and females. A significant increase in liver lesions were present in male rats fed 100 ppm Aroclor 1260 and female rats fed Aroclor 1016 (100 and 200 ppm), 1242 (all groups), 1254 (all groups), and 1260 (all groups). Male rats also had a significantly increased incidence of thyroid gland lesions in all Aroclor 1242 and 1254 groups and the 25 and 50 ppm Aroclor 1260 groups. (Mayes et al. 1998).

The EPA released a study in 1996 discussing the cancer slope factor development, based on Brunner et al. (1996) data, and application to environmental mixtures (EPA 1996A). The Brunner et al. (1996) data was reanalyzed and statistically significant increases in liver adenomas or carcinomas were found in female rats for all Aroclor treatment groups and for male rats in the Aroclor 1260 treatment groups.[5] The EPA noted that PCBs have been identified as tumor promoters, although data has indicated that some congeners may be weak tumor initiators. Central and upper bound slopes were calculated from $ED_{10}$ and $LED_{10}$ values scaled to human doses based on data from the Brunner et al. (1996) study. The upper bound CSF of 2.0 per mg/kg-day corresponds to a dose of 0.067 mg/kg-day (EPA 1996A).

Rats: Health Canada Great Lakes Multigenerational Study

Three generations of Sprague-Dawley rats were fed salmon from two of the Great Lakes, Lakes Huron and Ontario, to determine if contaminants in the fish were responsible for alterations to reproductive, immunological, or behavioral endpoints. One hundred and fifty male and 150 female rats (F0 generation, 30 per sex per group) were the parent generation (Arnold et al. 1998A). Two additional generations (F1 and F2) also participated in this experiment.

Fish in the diet were salmon from the 1991 spawning run. Lake Ontario salmon were collected from the Credit River in Streetsville, Ontario and salmon from Lake Huron were collected from the Sydenham River in Owen Sound. The groups consisted of control (rat chow), LH5% (Lake Huron Owen Sound salmon, 5.9% of the diet), LH20% (Lake Huron Owen Sound salmon, 23.8% of the diet), LO5% (Lake Ontario Credit River salmon, 5.6% of the diet), and LO20% (Lake Ontario Credit River salmon, 22.35% of the diet). Rats in the experimental groups consumed about 3.0-4.0 g fish/day (9-12 g fish/kg-day) for the 5% groups and 12.0-16.0 g fish/day (36-46 g fish/kg-day) for the 20% groups (Arnold et al. 1998A).

Rats were fed the salmon-containing diets a minimum of 70 days before breeding. Breeding males were euthanized one week after the breeding period. The offspring (F1 generation) were weaned at 21 days of age and placed on the mother (dam)'s diet. Dams were euthanized and examined. Offspring were assigned to reproductive, immunological, or behavioral test components. The reproductive testing included 120 males and 120 females (24 per sex per group) with one male and one female from each litter assigned to the control, LH20% and LO-20% groups. Two males and two females were assigned to the LH-5%, from three litters, and

[5] In the EPA analysis (EPA 1996A) of Brunner et al. (1996), the total numbers of female control rats (85 total), male control rats (98 total) and the numbers in each treatment group (ranging from 45 to 50 rats per group) were different from those reported in Brunner et al. (1996). Criteria used for inclusion of rats for determination of the total number per control or Aroclor treated group are unclear.

LO-5%, from two litters. Seventy days after weaning the F1 generation rats were bred and the F2 generation was assigned to either the behavioral or immunological testing. Forty-four male and 44 female rats were in each group, except the LH-5% group (32 males and 32 females), for the immunology testing. For the behavioral testing, 31 males and 16 females were in the control, LO-20%, and LH-20% groups, while 16 males and 16 females were in the LO-5% and LH-5% groups (Arnold et al. 1998A).

Samples of the salmon, the salmon-containing diets, and the rat tissue were analyzed for contaminant levels. Diet was analyzed at three times, spread throughout the experiments, but contaminant values were averages as there were no significant differences among the sample times. Contaminants measured include PCBs (all congeners), and select PCDDs, PCDFs, organochlorine chemicals, PAHs, metals, volatile organics, and other organic compounds. PCBs had the highest levels of the organic contaminants in salmon, with levels from LO having higher levels than LH (Feeley and Jordan 1998).

PCB 85, 99, 101, 105, 110, 118, 128, 129, 138, 149, 153, 170, 180, 187, and 199 represented 57 to 68% of the total PCB amount in the salmon. The same 15 congeners represented 56% of the total PCB amount in salmon-containing diet. The mean daily intake of rats (F0 and F1 generations) in the study ranged from 0.17 to 0.22 µg/kg-day for chow fed groups, 11.54 to 15.27 µg/kg-day for LH-5% groups, 35.91 to 49.89 µg/kg-day LH-20% groups, 18.56 to 23.20 µg/kg-day LO-5% groups, and 58.40 to 82.37 µg/kg-day LO-20% groups. Rat adipose tissue (fat) and liver samples from those eating LO had higher levels of PCB than samples from rats fed LH. Adipose samples had higher PCB levels than liver samples for all rats. The 15 congeners that represented a majority of the total PCBs in salmon and the salmon-containing diet accounted for approximately 67% of the total PCBs in the rat adipose and liver samples (Feeley and Jordan 1998).

A second study examined the PCB congener patterns in the salmon, salmon-containing diets, and rat adipose tissue. The congener profiles were similar in terms of homolog groups and in predominant congeners. A similar PCB congener pattern was identified for all salmon-containing diet groups and in both generations of rats (F0 and F1). Although the congener pattern was similar, certain congeners did not accumulate in the adipose tissue. The authors noted that the reduced accumulation may be due to less bioavailability or to increased metabolism. Similar predominant congeners were identified in the congener profile in the rat tissue samples and in profiles obtained from human samples, including human milk fat samples. A difference was identified in the decreased accumulation of a group of lower chlorinated congeners in rats as compared to human samples (Jordan and Feeley 1999).

Along with reproductive, immunological, and behavioral endpoints, general toxicology endpoints were also assessed. Statistically significant differences were observed across both generations (F0 and F1). These included: increases in adjusted liver and kidney weights in both sexes on the salmon diets, reduced blood urea nitrogen (BUN) levels in males on the 20% salmon diets, control females had lower serum potassium, the LH-20% females had heavier terminal body weights, the LH-20% females had lower levels of red blood cells, hemoglobin, hemocrit, and mean platelet volume (Arnold et al. 1998B).

Other significant differences were identified for a certain endpoints tested, although not consistently for both generations. Weight of the F0 males and F1 females was significantly increased compared to the appropriate control group rats. Significant weight difference were also identified during gestation, for both the F0 and F1 generations, between the salmon-containing diet groups. Certain organ weights were significantly different for the F0 and F1 diet groups as compared to the control groups. Significant differences were identified with liver and kidney weights for both F0 and F1 generations. The LH-20% and LO-20% groups had adjusted liver and kidney weights that were significantly greater than the control (for the F0 and F1 generations). The F0 generation had significant feed consumption differences between the diet groups and control groups (Arnold et al. 1998B).

The F1 generation had a statistically significant effect on the mating index. Control matings were significantly lower than the fish-fed rats. There were no differences in fertility indices. There was no significant difference in the number of live offspring, although the number of implants in the F0 generation were higher. No major concerns about health were identified from the data collected (Arnold et al. 1998B).

Tryphonas et al. (1998A) identified several salmon diet related effects on several parameters of the immune system and on organ weights. The F1 generation was weaned at 21 days and placed on the maternal assigned diet to 13 weeks of age. At that point, immunological endpoints were measured in some rats while others were bred or removed from the diet and placed on the control diet for 13 weeks (identified with an "R"). The same immunological endpoints were then evaluated. The F2 generation rats, offspring of the F1 rats, were weaned at 21 days old and placed on the maternal assigned diets for 13 weeks before immunological testing (Tryphonas et al. 1998A).

Although there was no food consumption differences between the male and female F1 and F2 rats, the rats removed from the salmon diets had differences in consumption before diet change. F1-R male rats had a significant increase in food consumption on the LO compared to the LH diets. F1-R females fed the LO-5% diet consumed less food than those fed the LO-20% diet. The rate of growth was higher for those on the LH diet compared to the LO diet. The rate of growth was higher for F1-R male rats fed the LO-5% diet than those fed the LO-20% diet. F2 female rats rate of growth was lower in those fed the LH-20% diet compared to those fed LH-5% or LO-20%. A lower rate of growth was associated with a larger final body weight and a larger food intake (Tryphonas et al. 1998A).

Although the F1 females had no differences in adjusted organ weights, differences were identified for other groups. Adjusted organ weights are organ weights adjusted for the body weight differences. No significant effects were identified with the F1 and F2 females. The F1 male LO-5% group had a significant reduction in adjusted mean liver weight compared to those on the LO-20% diet. The F1-R females had a significant reduction in the adjusted mean thymus weight on the LO-20% diet compared to the LO-5% and the LH-20% diets. The F2 male rats had significant effects in adjusted mean kidney, liver, and thymus weight. For the kidney weights, those on the LH-20% diet were larger than those on the LH-5% or LO-20% diets. The F2 male adjusted liver weights were larger on the 20% salmon diets compared to the 5% salmon diets,

within the LO and LH groups, and compared to those on the control diets. For the thymus, the F2 males on the LO diets had lower weights than those on the LH diets (Tryphonas et al. 1998A).

Hematology parameters were measured with peripheral blood. F1 females on the salmon diets had significantly lower red blood cells, hemoglobin, hemocrit, and mean platelet volume as compared to those on the control diet. F1 females on the salmon diets also had significantly lower means for white blood cell, neutrophils, lymphocytes, and monocytes compared to rats on the control diet. One significant difference within the diets (LO-5% versus LO-20%) was noted for neutrophil levels (Tryphonas et al. 1998A).

For F1 males, those on the salmon diets had significantly higher mean corpuscular volumes and mean corpuscular hemoglobin compared to the means of those on the control diets. The F1 males also had significantly smaller means for mean corpuscular volumes and mean corpuscular hemoglobin levels in rats fed the LH diets compared to rats fed the LO diet. Salmon fed F1 males had significantly lower mean levels of WBCs and neutrophils compared to those on the control diets. F1-R males had significantly higher monocyte levels in the LO groups compared to the LH groups. F2 females and males had several differences between the two salmon diets, but no differences between the salmon diets and the control diet (Tryphonas et al. 1998A).

Additional investigation into effects of the salmon diet on the immune system was reported in Tryphonas et al. (1998B). Spleen lymphocytes were measured in male and female F1, F1-R, and F2 rats. No significant differences between control diet rates and salmon diet rats in either generation. Significant differences for the F2 rats was identified between the LH and LO groups and within the two salmon sources. Additional significant differences in the mean number of certain types of spleen lymphocytes were identified in females (F1 F1-R, and F2 generations) and F2 males. No significant differences were identified for the plaque-forming cell assay, a measure of immune system function, between control diet rats and salmon diet rats. Significant differences were identified between the LH and LO diets and within the LH and LO diets. Significant differences were identified between the rats on the control diet and the salmon diets for another phagocytic activity assay, measuring another function of the immune system. Significant differences were identified between the cells from F1 male control diet and salmon diet rats. Cells from salmon fed rats had higher phagocytic activity than cells from control diet rats. Control diet and salmon diet rats were not significantly different after infection with a non-lethal dose of *Listeria monocytogenes*. The authors noted that while the data point to a weak effect of the salmon diet on functional aspects of the immune system, it was clear there were effects on the levels of T lymphocytes and the subsets present in F2 males fed the LO diets versus the LH diets. The authors state that this may indicate an increased susceptibility for immunologic alterations in male rats as compared to female rats (Tryphonas et al. 1998B).

Two studies investigated neurological problems in the rats from this study. One examined neurobehavioral effects. From the F1 generation, 16 rats per sex per diet were tested with an additional 15 male rats from the control LH-20% and LO-20% included. Only male rats from the F2 generation control, LH-20% and LO-20% groups were tested. A variety of tests were conducted, including elevated plus apparatus, hole board, observational tests, Morris water maze, radial arm maze, and reward reduction procedure. No significant differences were present for performance on tests measuring activity, exploration, stereotypy, and sensory and motor function

of male or female F1 rats that the authors could attribute to the diet. However, results from the radial arm maze (reference/working memory version) for male rats (both F1 and F2) that ate the 20% diets may indicate a diet-related effects. The authors point out that it does not clearly relate to clear effects of the salmon diets, but that it would be "imprudent to dismiss it until further research is done" (Pappas et al. 1998).

The second study was on neurochemical effects. The F1 and F2 generation rats were tested for various neurotransmitters, dopamine, norepinephrine, and serotonin, and choline acetyl transferase, which have all been implicated in deficits in performance of behavioral tests in rats and have been implicated in behaviors that have been reported to be altered in children exposed to contaminants in fish. Significant reductions in neurotransmitter levels were identified in F1 rats fed the salmon diet. However, it is not know whether this differences are due to the salmon diet or contaminants present in the salmon. The control group was fed with rat chow and not contaminant-free salmon. Although F2 rats were tested, results were not included due to differences between the control groups of the F1 and F2 generations attributable to sample processing differences (Seegal et al. 1998).

In the final study analyzing data from the salmon-fed rats, microsomal enzyme activity, glutathione S-transferase placental form expression, cell proliferation, and vitamin A stores were assessed. Significant differences were identified for male and female F0 and F1 rats. Rats on the salmon diets had an increase in microsomal (P450) enzyme activity. Significant differences in the amount of vitamin A stores were also identified for F0 and F1 rats on the diet as compared to the control groups. Although there was an increase in cell proliferation, there was no increase in glutathione S-transferase placental form expression. No differences were found in the health, lung, and kidney tissue of the diet and control rats; however, rats fed salmon had more lipid droplets varying sizes in the liver (Iverson et al. 1998).

In summary, no significant effects were identified for the measured reproductive parameters, significant increases in the relative liver and kidneys weights were observed in the salmon-fed F1 and F2 rat pups compared to the control rat pups, and nonspecific clinical differences were identified between the control and salmon-fed rats. Immunological differences were present in the salmon-fed rats, but most were reversible after being placed on the control diet for 13 weeks. However, significant reduction in thymus weight was measure in the F1-R female rats in the LO-20% group compared to F1-R female rats in the LO-5% and LH-5% groups. In the neurobehavioral testing, no effects were observed for spatial reference memory, activity, exploration, timidity, sensorimotor function, and behavioral stereotypy. F1 male rats, in the LO-20% group, and F2 male rats, in the LH-20% group had more working memory error, as measured by more baited arm reentries. F1 rats on the salmon diet, in particular the 20% diets, had significantly reduced dopamine levels (Feeley et al. 1998).

Additional differences were observed in activity of hepatic enzymes (i.e. cytochrome P450 enzymes) and in stored vitamin A. The authors state that although statistically significant effects were identified through out the studies, they were inconsistent among sex and generation. It is unclear as to what extent these effects are relevant to human populations. The authors note that the estimated salmon intake is higher than that of human sport fish consumers. This means the

contaminant intake, from the salmon, would be higher than the typical human sport fish consumer would ingest (Feeley et al. 1998).

Other Rodent Studies

Male and female Sprague-Dawley rats were fed PCB105 (0, 0.05, 0.5, 5, or 50 ppm; 20 animals [10 male, 10 female]/ treatment) for 13 weeks. No clinical signs of toxicity or changes in body weight were observed during the course of the experiment. Instances of fatty liver appeared to increase dose-dependently in the male rats and both female and male rats in the highest treatment groups had a significant increase in liver weight as compared to the untreated controls. For both male and female rats in the highest treatment group, significant alterations to thymus weight, serum albumin, serum cholesterol, hepatic EROD and PROD activity, uroporphyrin, UDPGT, and urinary ascorbic acid were also observed as compared to the control. Liver vitamin A levels were significantly lower than controls in male and female rats treated with 0.5, 5, and ppm PCB 105. Based on the results obtained, the authors concluded that the NOAEL level for PCB 105 was 0.05 ppm, which is equivalent to 3.9 µg/kg-day in male rats and 4.2 µg/kg-day in female rats (Chu et al. 1998).

Male Sprague-Dawley rats were used to investigate the uptake and distribution of PCBs throughout the body, if PCB alter behavior or thyroid function, and if there are differences between inhalation and ingestion of PCBs. The rats were given Aroclor 1242 in food (0.436 µg/g) or were in atmospheres with vapor-phase PCBs. Coplanar congeners identified in the mixture were PCB 81, 77, 123, 118, 114, 105, 126, 167, 156, and 157. Rats were exposed for 30 days to 32.8 µg Aroclor 1242/kg-day in food and 0.46 µg Aroclor 1242/kg-day. There were no obvious signs of toxicity. Rats accumulated significantly more total PCBs in adipose and lung tissue from exposure through the food as compared to the amount accumulated from inhalation. Total T3 and T4 levels were significantly different for both the inhalation and ingestion treatment groups as compared to the control (Casey et al. 1999).

C57Bl/6 mice were fed beef tallow (control), corn oil (control), blubber from Arctic beluga (A), blubber from St Lawrence beluga (SL), or combinations of the two blubbers (25% A + 75% SL, 50% A + 50% SL, 75% A + 25% SL) in rodent chow for three months. Blubber from the Arctic beluga was identified as slightly contaminated while the blubber from the St Lawrence beluga was identified as heavily contaminated. After three months, blood, peritoneal macrophages, and spleen were collected to assess immunological differences (Fournier et al. 2000).

No differences in body weight; spleen and thymus weights; natural killer cell activity; and CD4 or CD3 positive cells were observed in the treatment groups compared to the control beef tallow group. A significant but small decreased in the percent of cells that were CD8 positive (T cells) was found in the corn and almost all of the blubber groups, except for the 75% A + 25% SL group. A small, but significant, increase in the CD45 positive cells (natural killer, granulocytes, dendritic cells, T cells, B cells, monocytes, and macrophages) in the corn, 100% A, and 75% A + 25% SL groups. Peritoneal macrophage phagocytosis was significantly reduced by approximately half in all beluga blubber treatment groups as compared to the beef tallow groups. Specific humoral immune response was significantly decreased, by approximately 70%, in the beluga blubber treated groups as compared to the beef tallow groups. The authors note that there were no differences in effects between the slightly and heavily contaminated blubber treatment

groups. The immunosuppression identified in this study could be due to the lipid ingestion, but the contaminants could also have an immunosuppressive effect even at low concentrations (Fournier et al. 2000).

Female Sprague-Dawley rats were treated with a polyhalogenated aromatic hydrocarbon mixture, assembled to be similar to the contaminants found in Baltic herring (represents 90% of the TEQ). The mixture consisted of PCB 126, 118, 156, and 153 along with 2,3,7,8-TCDD. 1,2,3,7,8-PeCDD, and 2,3,4,7,8-PeCDF. Rats were treated with TCDD alone, Aroclor 1254, the mixture without PCB153 (PHAH-) or the mixture with PCB153 (PHAH+) (van der Plas et al. 2001). Plasma retinol (vitamin A) levels were significantly increased in the TCDD treated group while the PHAH-, PHAH+ and Aroclor 1254 groups had significantly decreased plasma retinol levels as compared to the corn oil control group. Hepatic retinyl palmitate levels were decreased in all groups except the Aroclor 1254 treated group as compared to the control. Plasma total and free T4 levels were decreased in most of the PHAH groups. In a second experiment, rats were treated with TCDD alone, Aroclor 1260, 0-1 ortho fraction, 2-4 ortho fraction, or 0-4 ortho fraction. Plasma retinol levels were significantly increased in the TCDD group but not different in any of the other groups (Aroclor 1260, PCB fractions, or PCB 153) as compared to the control group. No changes in thyroid hormone levels were identified in any treatment group. Overall, the non-dl PCB did not significantly alter either retinoid or thyroid hormone status in these experiments (van der Plas et al. 2001).

Fifteen groups (n = 5) of female Sprague-Dawley rats were orally given 0, 2.5, 25, 250, or 1000 ng TCDD/kg-day with (2 or 20 µg/kg-day) or without a PCB congener mixture. The PCB congener mixture consisted of PCB180, 118, 105, 170, 156, 114, 167, 157, 189, 123, 169, 126, and 77. Eight (PCB 105, 156, 114, 167, 157, 189, 123, and 77) of the 13 congeners are dioxin-like (coplanar) PCBs. The PCB mixture alone, either at 2.0 or 20 µg/kg-day, did not significantly change any endpoint measured as compared to the control. Liver weight, weight gain, and thymus weight in any group treated with 1000 ng TCDD/kg-day were significantly different from the untreated group. Thymus weight was also significantly different as compared to the control in the groups treated with 25 ng TCDD/kg-day along with 20 µg/kg-day. PCB treatment alone did not change any of the endpoints tested, but when treated in combination with TCDD was able to modify the toxic effects of TCDD (Chu et al. 2001).

Male Long-Evans rats were treated with Aroclor 1254 (lots 124-191 and 6024) to determine if the differences in TEQ in the two lots were responsible for differences in toxic effects. Although both lots had approximately the same weight percentage of chlorines, the TEQ values were 10-fold larger in lot 6024 as compared to lot 124-191. (See Table F-2.) Lot 6024 had significantly higher levels of ethoxyresorufin O-deethylase (EROD) and methoxyresorufin O-deethylase (MROD) enzyme activity as compared to lot 124-191 as measured on a weight basis. However, when measured on a TEQ basis, levels of EROD and MROD activity were similar. The difference in the TEQ values for the lots accounted for the differences in EROD and MROD levels. Although differences in TEQ values were able to account for some differences, TEQ levels could not predict decrease in T4 levels. As not all of the PCB congeners in the mixture are coplanar non-ortho congeners, the TEF approach may not account for non-AhR mediated toxic effects (Burgin et al. 2001).

Table F-2: Doses and TEQ values in the two lots of Aroclor 1254 (Burgin et al. 2001)

| | Dose (µg TEQ/kg) | |
|---|---|---|
| Dose (mg/kg) | Lot 124-191 | Lot 6024 |
| 0 | 0 | 0 |
| 1 | - | 0.4 |
| 3 | - | 1.2 |
| 10 | 0.4 | 4 |
| 30 | 1.2 | 12 |
| 100 | 4 | 40 |
| 300 | 12 | 120 |
| 1,000 | 40 | 400 |

Craft et al. (2002) examined species difference of hypothyroxemia induced by PCBs in rats and mice. Male and female Long-Evans rats and C57BL/6J mice were orally gavaged with PCB153 (0.3 to 300 mg/kg-day for rats and 0.9 to 90 mg/kg-day for mice), PCB 126 (coplanar; 0.03 to 100 µg/kg-day for rats and 0.003 to 300 µg/kg-day for mice), or TCDD (0.003 to 10 µg/kg-day for rats and 0.03 to 30 µg/kg-day for mice) for four days. Male and female rats, treated with PCB 126, had a significant reduction in serum T4 as compared to the controls, while no change was identified for the mice. Rats treated with PCB 126 also had a significant induction of uridine diphosphate glucuronosyltransferase (UGT). Male and female rats and mice treated with PCB 126 had significantly different EROD activity as compared to the control animals. TCDD treatment, at 0.1 µg/kg-day or higher, also significantly reduce serum T4 levels in female rats (Craft et al. 2002). PCB 153 significantly altered serum T4 levels in male and female rats and mice as compared to the control animals (Craft et al. 2002).

Pentoxyresorufin O-deethylase (PROD) activity levels were significantly higher in male and female rats and mice treated with PCB 153 as compared to control animals. A significant increase in T4 glucuronidation activity was also identified in the highest dose groups of male and female rats and mice treated with PCB153 as compared to control animals. PCB 153 decreased serum T4 levels in both rats and mice. PCB 126 also increased serum T4 levels in rats, but not in mice, which was also observed with TCDD treatment. The two species studied here had different responses to PCB126, which acts through the AhR, and PCB 153, which is AhR independent (Craft et al. 2002).

Male Sprague-Dawley rats were orally gavaged for 70 days, then blood and tissue was collected. The control group (n = 9) was gavaged with corn oil. Rats were treated with a mixture of 18 different contaminants (aldrin, p,p'-DDT, p,p'-DDE, dieldrin, endosulfan, heptachlor, hexachlorobenzene, hexachlorocyclohexane, mirex, methoxychlor, 1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, pentachlorobenzene, TCDD, Aroclor 1254, cadmium chloride, and lead chloride. Four groups (n = 10) of rats were treated with these chemicals, at levels equal (1x group) to the MRL (ATSDR), RfD (EPA), TDI (CEPA), PTDI (Health Canada), or NOAEL (for TCDD only; Feeley and Grant, 1993) or 10, 100, or 1000 fold higher doses. The 1x mixture of chemicals was considered a "safe" level for humans (Wade et al. 2002).

Blood and tissue was collected from the rats at the end of the experiment. Body weight of the rats was not altered in any of the treatment groups as compared to the control group. While many relative organ weights were not altered in the treated rats, relative weights of the liver, kidney, epididymis, and caput epididymis from rats in the 1000x group were significantly different than the relative weights in control rats. Levels of EROD and benzyloxyresorufin O-dearylase (BROD) activity significantly increased in the 100x and 1000x treatment groups as compared to levels in the control rats. Serum biochemistry results show significant alterations in cholesterol, lactate dehydrogenase, uric acid, phosphorus, urea N, and albumin in the 1000x treated rats as compared to levels from control rats. Proliferation of splenocytes was reduced in the 1000x treatment group when treated with concavalin A as compared to the control group. Natural killer cell activity was significantly lower in the rats 1000x treated group as compared to the control group. There was no difference in sperm production or chromosomal breakages in any of the groups. Overall, for most of the endpoints tested, exposure to the mixture produced little effect at the lower dose groups (Wade et al. 2002).

Female Sprague-Dawley pups were treated (n = 6 to 9/group, interperitoneal injection) with PCB 95, PCB 101, estradiol, or corn oil (control) for two days and blood and tissue was collected one or two days after the last injection. In blood and tissue collected from rats one day after the last treatment (PCB 95 doses: 4, 8, 16, and 32 mg/kg-day), there was no differences in organ weights as compared to the control. In the estradiol (100 ng/rat/day) treated rats, uterine weight was significantly increased. Serum levels of T4 decreased significantly in a dose-dependent manner in rats treated with PCB 95 as compared to the control, while serum T4 levels significantly increased in the estradiol treated rats as compared to the control. In the second group of rats (treated with PCB 95, PCB 101, estradiol, or corn oil [control]), blood and tissues were collected two days after the last treatment (PCB 95 and PCB 101 doses: 16 and 32 mg/kg-day, estradiol dose: 1.0 µg/rat). As observed with the previous group of rats, the PCB treatments did not alter relative organ weights and the estradiol increased the uterine weight as compared to the control group. PCB treatment significantly decreased serum total T4 levels (Khan et al. 2002).

Sprague-Dawley rats were used to investigate whether EROD, an enzyme that mediates the activity of CYP1A1, induction can predict toxicity of mono-ortho PCB congeners. The second goal of this study was to determine of PCB 118 interferes with thyroid hormone homeostasis after a perinatal exposure. Pregnant Sprague-Dawley rats were orally gavaged with PCB 118 (375 µg/kg) on day six of gestation. No gross toxicity was apparent in offspring or dams. PCB 118 was detected in offspring's liver and adipose tissue on post-natal day (PND) 70. Levels in liver were 69 ppb and 210 in adipose tissue. EROD activity did not change in treated offspring or in dams (after weaning). Significant increases in free and total T4 were measured in male treated offspring on PND 70 as compared to male control offspring. Treated female offspring only had a significant increase in total T4 levels. Levels of free T4 and TSH were significantly reduced after weaning in the PCB treated group as compared to control dams. The authors concluded, from these results, that PCB 118 acts via an AhR-independent mechanism causing thyroid disruption as no changes in hepatic EROD activity was observed (Kuriyama et al. 2003).

Male Wistar rats and ddy mice (an outbred strain) were injected interperitoneally (100 mg/kg) with Kannechlor-500 (KC500). KC500 treatment caused a significant increase in liver weight and hepatic microsomal enzymes (CYP450) in both rats and mice. KC500 treatment caused a

significant decrease in serum T4 levels in both rats and mice. Levels of UGT1A1 and UGT1A6 (two UDP-glucuronosyltransferase [T4-UDP-GT] enzymes) increased in rats, for up to three days after the treatment, while no increase was observed in mice (Kato et al. 2003).

Treatment with KC500 significantly decreased serum T4 levels in rats and mice, but only significantly increased the T4-UDP-GT activity in rats. The current study follows up on those results and examines the relationship between the observed decrease in serum T4 and increase in T4-UDP-GT enzymes. Two different population of male rats were used for this study, Wistar and Gunn (UGT1A-deficient Wistar rats) rats. Wistar rats have background levels of T4-UDP-GT activity that is 2.1-fold higher than levels of activity in the Gunn rats. The rats were interperitoneally injected with KC500 (100 mg/kg) or PCB 101 (112 mg/kg). Livers and blood were collected four days after the injection (Kato et al. 2004).

In both Wistar and Gunn rats, serum total T4 and free T4 were significantly decreased after treatment with KC500 or PCB 101. Treatment with either KC500 or PCB 101 increased T4-UDP-GT activity (UGT1A1 and UGT1A6) in Wistar rats. In Wistar rats, hepatic type I T4-deiodinase activity was significantly decreased by KC500, but not PCB 101, while the activity was significantly decreased by PCB101 and KC500 in Gunn rats (Kato et al. 2004).

Hydroxylated PCB metabolites were measured in serum, four days after injection of KC500 or PCB 101 (Kato et al. 2004). Three mono-hydroxylated (3-OH-PCB99, OH-PCB107, and OH-PCB138) and three dihydroxylated ([OH]2-PCB 70, [OH]2-PCB 101, and [OH]2-2,3',4',5,6-pentachlorobiphenyl) metabolites were identified in KC500 treated Wistar and Gunn rats. OH-PCB 107 was the dominant hydroxylated metabolite present, representing 89% and 56% of the total hydroxylated metabolites present in the Wistar and Gunn rats, respectively (Kato et al. 2004).

Male albino rats of the Wistar stain, 90 days of age, were injected interperitonally with 2.0 mg/kg-day for 30 days. Ten of the rats were treated as PCB control and the other 10 were orally gavaged with zinc ($ZnSO_4$; 200 mg/kg-day) for 10 days. PCB treatment significantly altered body weight; ventral prostatic weight; serum total T3, T4, TSH, testosterone, estradiol; and amount of ventral prostatic androgen and estrogen receptors in PCB treated rats compared to control rats and zinc + PCB treated rats. The authors conclude that the alterations are due to PCBs ability to trigger oxidative stress and zinc, as an antioxidant, is able to reverse these effects (Venkataraman et al. 2004).

Tissue distribution of two PCB mixtures (Aroclor 1254 and soil contaminated with Chlorofen) was examined in male Sprague-Dawley rats. Chlorofen was an Eastern European PCB mixture, manufactured between 1966 and 1970 in Poland. The mixture of PCB congeners in Chlorofen is primarily octa- and monachlorinated congeners with a chlorine content of 64% (placing it between Aroclor 1262 and 1268). The rats were injected interperitonally with soil extract mixture (PCBs extracted from Chlorofen contaminated soil, 20 mg/kg, n = 3), Aroclor 1254 (16 mg/kg, n = 4), or corn oil (control, n = 4). Blood and tissues were collected after seven days (Kania-Korwel et al. 2005).

In both the Aroclor 1254 and soil extract treated groups, the highest PCB levels were in the adipose tissue. In the group treated with the soil extract, total PCB levels were significantly higher in the spleen, but significantly lower in the skin as compared to the Aroclor 1254 treated group. The soil extract group had significantly higher PROD levels as compared to both the control and Aroclor 1254 treated rats. EROD levels in the Aroclor 1254 treated rats was significantly different than the levels in the control treated rats. Congener profiles from the liver and spleen appear different from each other and resemble the PCB mixture in the treatments (either Aroclor 1254 or soil extract mixture) (Kania-Korwel et al. 2005).

Pregnant Wistar rats were treated orally with PCB 52, 138, or 180. Offspring were treated from PND seven to PND 21. The Y maze test was used to assess the rat's ability to learn. In the test, the rats learn to locate food based on the wall color (black or white) of the maze. The number of trials necessary to learn the location of the food is recorded. Male and female rats treated with PCB 138 or 180 required significantly more trials to learn the location of the food compared to the control rats. Rats treated with PCB 52 were not different from the control rats. Rats were also tested with the rotarod test, for motor coordination. Male and female rats treated with PCB 52 had significantly less time on the rotarod compared to the control rats, but those treated with PCB 138 or 180 were not significantly different from the control rats. Based on these results, perinatal exposure to PCB 138 or 180 impaired ability to learn, but not motor coordination. Perinatal exposure to PCB 53 impaired motor coordination, but not the rat's ability to learn (Boix et al. 2010).

Appendix G: Development of Fish Consumption Screening Values (FCSVs)

Table 2 presents sample FCSVs calculated using an RfD of 0.02 µg/kg-day. The FCSVs in the table do not include any reduction of PCB concentrations due to trimming and cooking. Inclusion of any correction to account for a reduction in the concentration of PCBs is a risk management decision that is beyond the scope of this document.

Table G-1: Example Fish Contaminant Screening Values (FCSVs) for the general and sensitive populations using an RfD protective of immune system alteration.

| Population | Fish PCB Concentration (ppm) | Fish Meals |
|---|---|---|
| General Population | ≤ 0.02 | Unrestricted |
| | > 0.02 to ≤ 0.05 | One meal/week |
| | > 0.05 to ≤ 0.21 | One meal/month |
| | > 0.21 to ≤ 0.42 | Six meals/year |
| | > 0.42 | Do not eat |
| Sensitive Population (women of childbearing age and children under 15) | < 0.01 | Unrestricted |
| | > 0.01 to ≤ 0.04 | One meal/week |
| | > 0.04 to ≤ 0.18 | One meal/month |
| | > 0.18 to ≤ 0.35 | Six meals/year |
| | > 0.35 | Do not eat |

- All calculated values rounded to 2 decimal place
- RfD = 0.02 µg/kg-day
- Adapting EPA's equation for consumption limit of fish (contaminant amount [mg/kg] = (RfD*BW)/Fish consumption [kg-day] [mg/kg = ppm]) (EPA 2000B)
    - Body weight (EPA 1997B)
        - General population body weight (BW) = 78.1 kg
        - Sensitive population BW = 65.4 kg
    - Fish kg/meal = 0.227 (EPA 2000B)
    - Fish Consumption:
        - Unrestricted = 156 meals/year (97 g fish/day)
        - One meal/week = 52 meals/year (32 g fish/day)
        - One meal/month = 12 meals/year (7.4 g fish/day)
        - Six meals/year = 3.7 g fish/day

The above RfD is identical to a sample RfD of 0.02 µg/kg-day for neurological effects, measured by a test for indications of intellectual impairment. The point-of-departure (1.68714 µg/kg-day) is a value calculated from a lower limit on a benchmark dose (BMDLs) taken from Jacobson et al. (2002). Mothers, Lake Michigan sport-caught fish consumers, were enrolled in a Michigan cohort in 1980 to 1981. A prenatal PCB exposure measurement was calculated from cord and maternal serum PCB levels merged with maternal milk PCB levels. Children were tested for intelligence, measured by IQ, at age 11. Lower levels on the BMDLs ranged from 0.42 to 1.63 µg/g lipids. The authors note that the Michigan cohort is possibly less sensitive than other populations studied. For calculation of an RfD, a BMDL for a subtle, non-clinical reduction in intelligence (0.42 µg/g lipids) was selected. See Equation G-1 for the conversion of the 0.42 µg/g lipids BMDL to an RfD.

Equation G-1: Calculations for a sample Reference Dose (RfD) for neurological effects from a lower limit of a Benchmark dose (BMDL).

1. Calculate an estimated BMDL for the mean intake of PCBs (in µg/kg-day):

Estimated BMDL for the mean intake of PCBs (in µg/kg-day) = BMDL for PCBs in grams lipid of maternal milk (in µg/g) x Mean intake of grams lipid from maternal milk (in g/kg-day)

Where:

- BMDL for PCBs in grams lipid of maternal milk (in µg/g) = 0.42 µg/g (Jacobson et al. 2002)
- Mean intake of grams lipid from maternal milk (in g/kg-day) = 4.017 g/kg-day
    - Calculate the mean maternal milk intake on a gram lipids (in g/kg-day) basis:

      Mean intake of grams lipid from maternal milk (in g/kg-day) = Mean lipid intake from maternal milk (in ml/kg-day) x density of maternal milk (in g/ml)

      Where:
        - Mean lipid intake from maternal milk (in ml/kg-day) = 3.9 ml/kg-day (EPA child 2008)
        - Density of maternal milk (in g/ml) = 1.03 g/ml (EPA child 2008)

      And:
        - Mean intake of grams lipid from maternal milk (in g/kg-day) = 4.017 g/kg-day

And:

- Estimated BMDL for the mean intake of PCBs (in µg/kg-day) = 1.68714 µg/kg-day

3. Calculate an estimated RfD (in µg/kg-day) for PCBs based on neurological effects:

Estimated RfD (in µg/kg-day) = Estimated BMDL for the mean intake of PCBs (in µg/kg-day)/Uncertainty factors

Where:

- Estimated BMDL for the mean intake of PCBs (in µg/kg-day) = 1.68714 µg/kg-day
- Uncertainty factors = 100 (uncertainty factors for human variability [10] and database uncertainty [10])
    - The database uncertainty was added due to the uncertainty in the actual exposure levels of people in the study. The Jacobson et al. (1990, 1996) studies used Arochlor 1016 and 1260 as reference standards for measuring total PCBs. Whether Arochlors were mixed before using them as a standard, which peaks were used to quantify the PCBs, or other factors may alter the amount reported as total PCBs. This may mean that the PCB amounts are higher or lower that those obtained from other human epidemiological studies.

And:

- Estimated RfD (in µg/kg-day) = 0.02 µg/kg-day

Screening levels based on the EPA's oral cancer slope factor (CSF) for PCBs (2.0 per [mg/kg-day]) are in Table G-2. This CSF is the upper bound slope factor and is used for food chain exposure; when dioxin-like, tumor-promoting, or persistent congeners are present; and for early-life exposure (for all pathways and mixtures). The EPA has not developed CSFs for specific mixtures of PCBs, such as Aroclor 1254 or Aroclor 1248, as is the case for the RfDs. As stated above, reductions of PCB levels to account for trimming and cooking are not included in these screening levels. If a point-of-departure is considered for development of an RfD based on cancer risk, as PCBs are tumor promoters rather than initiators, a possible source is the $LED_{10}$, which is used to calculated the upper bound CSF (EPA 1996A). This value, 67 µg/kg-day, is a potential LOAEL, in human equivalent dose, which is higher than the BMDL used for calculation of a sample RfD based on neurological effects (1.68714 µg/kg-day) and the LOAEL (5.0 µg/kg-day) used for calculation of the RfD based on immunologic effects.

Table G-2: Example Fish Contaminant Screening Values (FCSVs) for the general and sensitive populations using an oral cancer slope factor (CSF) of 2.0 $(mg/kg\text{-}day)^{-1}$.

| Population | Fish PCB Concentration (ppm) | Fish Meals |
|---|---|---|
| General Population | < 0.004 | Unrestricted |
| | > 0.004 to ≤ 0.012 | One meal/week |
| | > 0.012 to ≤ 0.052 | One meal/month |
| | > 0.052 to ≤ 0.105 | Six meals/year |
| | > 0.105 | Do not eat |
| Sensitive Population (women of childbearing age and children under 15) | < 0.003 | Unrestricted |
| | > 0.003 to ≤ 0.010 | One meal/week |
| | > 0.010 to ≤ 0.044 | One meal/month |
| | > 0.044 to ≤ 0.088 | Six meals/year |
| | > 0.088 | Do not eat |

- All calculated values rounded to 3 decimal place
- CSF = 2.0 $(mg/kg\text{-}day)^{-1}$
- Adapting EPA's equation for consumption limit of fish (contaminant amount [mg/kg] = ([RL/CSF]*BW)/Fish consumption [kg-day] [mg/kg = ppm]) (EPA 2000B)
    - Risk Level (RL) = one excess case of cancer in 100,000
    - Body weight (EPA 1997B)
        - General population body weight (BW) = 78.1 kg
        - Sensitive population BW = 65.4 kg
    - Fish kg/meal = 0.227 (EPA 2000B)
    - Fish Consumption:
        - Unrestricted = 156 meals/year (97 g fish/day)
        - One meal/week = 52 meals/year (32 g fish/day)
        - One meal/month = 12 meals/year (7.4 g fish/day)
        - Six meals/year = 3.7 g fish/day