Reproductive, Developmental and Immunotoxic Effects of PCBs in Fish: a Summary of Laboratory and Field Studies

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LIST OF ABBREVIATIONS

A1254	Aroclor 1254
AhR	Arylhydrocarbon receptor
CYP1A	Cytochrome P450 1A
DNA	Deoxyribonucleic acid
GnRH	Gonadotropin releasing hormone
GSI	Gonadal somatic index
GtH	Gonadotropin
HPGL	Hypothalamic-pituitary-gonadal-liver axis
LD50	Lethal dose; 50%
LOAEL	Lowest observable adverse effect level
mRNA	messenger ribonucleic acid
ng/g	Nanograms per gram
ng/L	Nanograms per liter
NOAEL	No observable adverse effect level
PAH	Polycyclic aromatic hydrocarbon
PCB	Polychlorinated biphenyl
pg/g	Picograms per gram
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
REP	Relative potency
TEF	Toxic equivalency factor
TEQ	Dioxin Equivalent
ug/g	Micrograms per gram

1. Introduction and Summary of Findings

Purpose

The purposes of this report are:

- to evaluate the existing research literature addressing reproductive, developmental, and immunotoxic effects of polychlorinated biphenyls (PCBs) to fish, and
- if possible, to estimate fish tissue PCB concentrations above which these effects are likely in fish exposed to PCBs in the field (referred to in this report as "effective concentrations").

I developed this report by reviewing both laboratory and field studies on health effects of PCBs in fish and by contacting researchers currently working in this area of study.

I focus on reproductive and developmental effects and on immunotoxicity to consider biological endpoints that are both sensitive to anthropogenic contaminants and ecologically relevant. Reproductive effects are defined as any change in the hypothalamic-pituitary-gonadal-liver axis and include alterations in sex steroid hormones, gonadotropins, gonad growth, and vitellogenin production. Developmental effects refer primarily to embryo and larval growth and survival. Most studies do not continue beyond the larval stage and therefore do not evaluate potential behavioral effects or long-term effects on survival to exposed offspring. Effects on immune function include suppressed humoral response, reduced phagocytosis and reduced white pulp in the spleen.

Summary of Findings

The majority of laboratory studies I reviewed and that are conducted in the United States and Canada examine the effects of Aroclor 1254 (A1254). A smaller number of studies evaluate the effects of individual PCB congeners, mixtures of a few select PCB congeners, or other Aroclor mixtures such as 1242 or 1248. European researchers tend to use Clophen A50, a mixture that is similar to A1254. Through my research for this report, I found sufficient information to determine effective concentration values for A1254 and for PCB congener 77 (PCB 77).

I estimate that concentrations of A1254 ranging from approximately 5 ppm to 70 ppm (wet weight) in the liver, or in whole bodies of larvae, affect reproduction and development in fish. I derive this range based on a synthesis of the laboratory studies I reviewed. A1254 concentrations as low as 5 ppm in the bodies of larvae can reduce larval survival. At concentrations ranging from 25 ppm to 70 ppm in the liver of adult fish, A1254 interferes with proper functioning of the reproductive system. This includes reduced gonad growth in both male and female fish. These effects are important to individual fish, and endpoints such as reduced gonad size and reduced larval survival may result in population level effects as well.

These concentration estimates are within the range of total PCB concentrations associated with similar adverse effects found in field studies, although in most field studies other contaminants are also present. The concentration estimates representing adverse effects also fall within the range of A1254 concentrations estimated for some of the most contaminated fish in the Hudson River.

I also found that PCB 77 concentrations ranging from 0.3 ppm to 5 ppm (wet weight) in adult fish livers reduce egg deposition, pituitary gonadotropin, and the gonadosomatic index (GSI); alter retinoid concentrations (vitamin A); and reduce larval survival. In addition, concentrations of 1.3 ppm in eggs reduce larval survival. These concentrations are within the range of congener 77 concentrations estimated for some of the most contaminated fish in the Hudson River.

Finally, I use the dioxin equivalent (TEQ) approach to assess the potential harm to larval fish from exposure to some PCB congeners. This approach provides a combined measure of toxicity for all dioxin-like PCBs based on the same 'unit' -- toxicity relative to 2,3,7,8-tetrachloro-p-dioxin (dioxin) -- and considers both the potency and the tissue concentration of the congener. Potential injury was assessed for larval fish because the current TEQ methodology in fish is based on larval fish data. The TEQs calculated for Hudson River fish (in muscle tissue lipid) fall below the NOAELs and LD50s for dioxin (in egg lipid) calculated for several different fish species, but are within range of the LOAEL for lake trout, the most sensitive species tested to date. However, my calculations are based on data for only two of the three or four dioxin-like PCBs that may contaminant Hudson River fish. These results may therefore understate the TEQ for Hudson River fish and are inconclusive without more data.

Overall, the effective concentrations for reproductive and developmental toxicity set forth in this report fall within the range of the PCB concentrations found in some of the most contaminated Hudson River fish. As a result, Hudson River fish exposed to these concentrations of PCBs are likely to experience some of the adverse effects reported in laboratory studies. There are currently an insufficient number of studies to estimate the immunotoxicity of PCBs in fish.

Limitations and Uncertainties

I review and synthesize different types of information from a variety of studies to develop effective concentration values for PCBs in fish. As a result there are a number of limitations and uncertainties associated with these values. The accuracy of the effective concentrations I set forth is limited by:

- the degree to which I could accurately estimate PCB concentrations in tissues for laboratory studies that did not report concentrations;
- interspecies differences in response to PCBs, as the studies reviewed considered a variety of fish species;
- differences in response to PCBs resulting from timing of exposure in relation to the maturation cycle, as the studies reviewed varied exposure timing; and
- differences in the route of exposure (i.e., water, injection, or diet) used in each laboratory study.

It is unclear whether these limitations result in underestimation or overestimation of the concentrations I establish for toxic effects of PCBs in fish.

There are additional limitations to consider when using these effective concentrations to assess potential harm in field animals. Common problems associated with relating laboratory studies to field situations include: differences in the species and routes of exposure; differences in length of exposure (laboratory exposures are usually shorter than the typically lifetime exposure of a field animal); uncertainties associated with comparing toxic effects following exposure of naive laboratory animals with field animals that may be exposed throughout their lifetime; and comparing exposures to single chemicals with the complex mixtures of contaminants often encountered in the field.

Organization of This Report

The remainder of this report includes six sections and two appendices.

- Section 2 provides background information about the toxicity of PCBs.
- Section 3 describes the methods used to obtain and review the research literature on effects of PCBs in fish.
- Section 4 reviews the effects of PCBs on reproduction and development in fish.

- Section 5 considers interspecies differences in response to toxic chemicals.
- Section 6 reviews the effects of PCBs on immune function in fish.
- Section 7 provides a bibliography.
- Appendix 1 provides a table of TEQs calculated for Hudson River fish.
- Appendix 2 provides a list of research papers that were reviewed but determined not to be directly relevant to reproductive, developmental or immunotoxic endpoints in fish.

2. Background Information About the Toxicity of PCBs

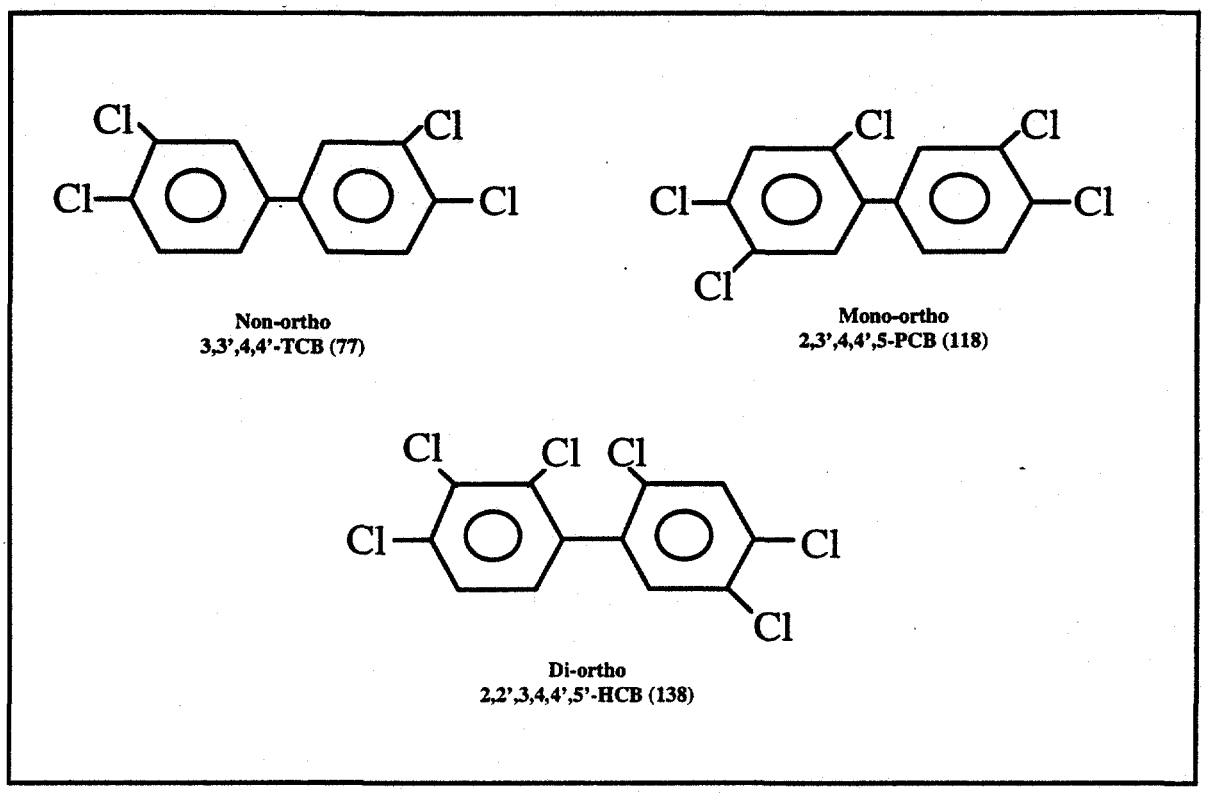
PCB Structure and Toxicity

PCBs are mixtures of chlorinated biphenyl congeners. There are three categories of PCBs: PCBs that are chlorinated in two or more ortho positions, those that are chlorinated in only one ortho position (mono-ortho), and PCBs lacking any ortho chlorination, known as non-ortho or co-planar PCBs (Figure 1). Early work on PCBs focused on PCB mixtures such as A1254, 1260 or 1248. Later work focused on individual PCB congeners, with the greatest emphasis on the co-planar PCBs. Most recently the focus is shifting back to PCB mixtures and to congeners other than the co-planars because, although the co-planar PCBs may be the most potent congeners, other congeners may have important toxic effects as well (Moore and Peterson, 1996).

PCBs cause a wide range of toxic effects across species from mammals to fish. There is a large amount of information on toxicity of PCBs and several reviews on this topic are available (Parkinson and Safe, 1987; Gray et al., 1996; Eisler and Belisle, 1996; Eisler 1986). The toxicity of PCBs varies depending on the PCB mixture and the species, sex and age of the exposed animal. In mammals, PCB exposure causes wasting syndrome, reproductive failure, teratogenicity, infertility in males, immunotoxicity (including thymic and splenic atrophy), hypothyroidism, chloracne, neurobehavioral effects, liver damage and induction of cytochrome P450; additionally PCBs may act as promoters of liver cancer (Moore and Peterson, 1996; Gray et al., 1996; Parkinson and Safe, 1987). Many of these effects also occur in fish including reproductive and developmental toxicity, immunotoxicity, liver damage, neurobehavioral effects, effects on thyroid hormones and induction of cytochrome P450 (Eisler 1986; Walker and Peterson 1994; Eisler and Belisle, 1996; Fisher et al., 1994; Fingerman and Russell, 1980). Recent studies have indicated that PCBs may alter retinoid concentrations as well (Ndayibagira et al., 1995; Palace and Brown, 1994).

Figure 1

PCB CONGENERS



Effects Selected for Review

I focus this investigation first on the effects of PCBs on reproduction and development in fish. One of the primary concerns for both wildlife and fisheries toxicologists is the effects of chemical contaminants in both individual animals and on whole populations. When monitoring the effects of chemical contaminants, there are a broad range of endpoints ranging from cellular level effects that are very sensitive to chemical exposure, to changes in population size or structure that are generally less sensitive to chemical exposure (Figure 2). There is often a trade-off between early detection of exposure and ecological relevance when assessing the effects of contaminants in the field. Cytochrome P450 induction, for example, is a very sensitive indicator of contaminant exposure, but its relationship to health effects is unclear. A change in population size or structure, however, is clearly relevant, although populations often are severely impacted by the time these changes can be observed.

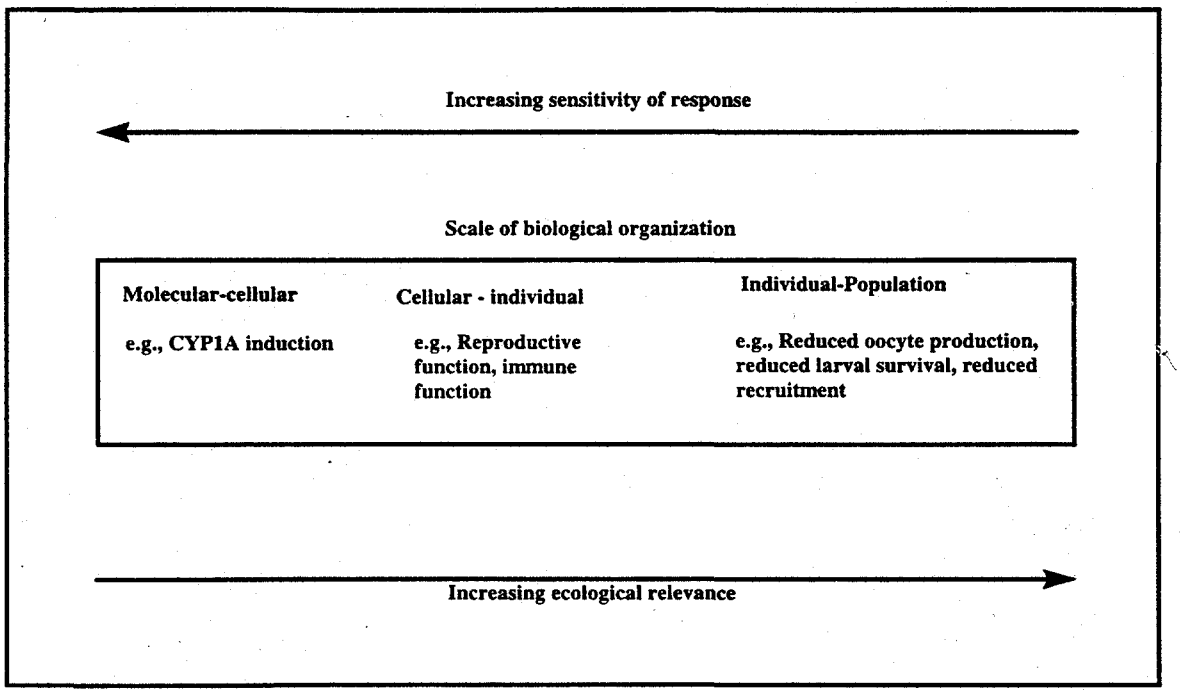
One approach to the tradeoff between early detection of exposure and ecological relevance is to select endpoints that are fairly sensitive, but that can be linked to health effects on individuals, or to population size or recruitment. In general, reproductive and developmental endpoints satisfy these criteria. Although the relationship between some endpoints such as

altered steroid hormone concentrations and individual health or population size is currently unclear, other changes such as reduced gonad size (particularly in female fish), egg production, and embryo and larval survival could impact population size.

This investigation also addresses immunotoxicity. Interest in the effects of environmental contaminants on immune function in fish has recently increased as some research has indicated that immunosupression may lead to increased disease susceptability in fish (Dunier and Siwicki, 1993). Although the consequences of immunotoxicity may not affect recruitment directly, increased disease susceptibility can affect the health of individual fish within a population. If immunotoxic effects are significant, population levels of fish could be affected.

Figure 2

RESPONSES TO ENVIRONMENTAL CONTAMINANTS BY LEVELS OF BIOLOGICAL SENSITIVITY VERSUS ECOLOGICAL RELEVANCE



Toxicity of Co-planar PCBs

The toxicity of PCBs follows a structure activity relationship (Parkinson and Safe, 1987; Safe, 1990), with the greatest potency associated with the co-planar PCBs (Safe, 1990; Walker and Peterson, 1994). The toxicity of the co-planar PCBs is believed to be mediated via the arylhydrocarbon receptor (AhR), similar to dioxin. The AhR is a highly evolutionarily conserved receptor found in most vertebrate species (Hahn et al., 1994; Hahn and Karchner, 1995). This means that it is fairly similar across species from fish to mammals, and that it may respond to specific ligands (e.g., some PCBs, polyaromatic hydrocarbons (PAH), dioxin) in a similar

The first search focused on reproductive and developmental effects of PCBs on fish. The keywords used for this search were PCB or polychlorinated biphenyl or organochlorine or endocrine disrupter, and reproduction or development, and fish. The first search resulted in 193 titles. The second search was less focused and covered any effects of PCBs in fish (excluding reproductive and developmental effects). The keywords for this search were PCB or polychlorinated biphenyls and health effects and fish. This resulted in 645 titles. This search missed several relevant papers (apparently the term 'health effects' was too limiting) so a third search was conducted using keywords PCBs or polychlorinated biphenyls and fish. This search was conducted in both 1997 and 1998. The 1997 search resulted in 4814 titles. To reduce the number of titles, papers on effects in humans (e.g., consumption of contaminated fish) were eliminated as were those found in the previous searches and any non-English papers, reducing the number to 1944 titles. The 1998 search (which also eliminated non-English papers and human effects) produced 466 titles. Finally, in 1998 one more search was added to address the question of PCB concentrations in specific fish tissues following dosing. The keywords for this search were PCBs or polychlorinated biphenyl and fish and (inject or diet or oral or laboratory or pharmacokinetic or uptake). This search resulted in 381 titles. The total of all four searches resulted in approximately 3629 titles, although there was overlap among searches (e.g., many of the papers from the first search also were found in the third search).

Step Two: Selection of Relevant Titles and Abstracts

Relevant papers were identified first by the title and then by the abstract. Abstracts were requested for any title that appeared remotely relevant. I requested abstracts for titles that suggested reproductive, developmental or immunological endpoints were observed in fish. Abstracts also were requested for some titles which indicated such topics as bioaccumulation and distribution of PCBs in fish, methods of PCB analysis or interspecies differences in response to toxicants. I did not request abstracts for papers that clearly focused on mammalian health effects from consumption of PCB contaminated fish. I reviewed approximately 905 abstracts from all four searches combined. Papers were selected for full review if either the title or the abstract indicated that fish exposed to PCBs (either in the laboratory or in the field) were examined for effects on reproduction, development or on the immune system. In addition, papers were requested for all abstracts describing interspecies differences in response to toxicants, and papers which indicated reports of tissue concentrations following injected or oral dosing. If the abstract was unclear or not available, or if there was a chance that any of these effects were reported in a paper (i.e., endpoints were not explicitly reported in the abstract), the paper was selected for review.

Abstracts were rejected if: 1) the paper focused on a species other than fish (e.g., some papers examined effects of PCBs in birds or mammals feeding on contaminated fish); 2) laboratory studies used mixtures of chemicals including PCBs (e.g., PCBs and heavy metals); 3) field studies indicated a mixture of chemicals and indicated that PCBs were not the primary

contaminant; and 4) studies related effects to toxic equivalency factors[2] rather than to actual measurements of PCBs. Step Two resulted in a total of approximately 305 papers selected for further review.

Step Three: Preliminary Review and Sorting of Selected Papers

Once I received the papers, I reviewed the abstract and introduction. At this point, any papers that were clearly off the topic of interest were excluded from further analysis. The remaining papers were read and sorted into two groups 1) papers reviewed in the report, and 2) papers listed in Appendix 2. A total of 149 papers are reviewed in the body of the report and are listed in the reference section. Papers reviewed in the report are directly relevant to the development of estimated PCB effective concentrations for reproductive, developmental or immunotoxic effects.

The papers listed in Appendix 2 provide general information for the development of this report, but were not directly useful. Some of these papers appear relevant but are not included for several reasons including: 1) the use of chemical mixtures in laboratory studies; 2) inadequate study designs (e.g., too few replicates, faulty exposure systems, inadequate controls, high doses used for determination of acute toxicity); 3) studies reported biochemical effects not directly relevant to reproduction or development; and 4) fish collected in the field were exposed to chemical mixtures in which PCBs were not the major component. A total of 147 papers are listed in Appendix 2.

Step Four: Detailed Review of Papers

The papers included in the report were reviewed in detail. Approximately 85 papers are summarized and presented in a series of tables included in Sections 4 - 6 of this report. The majority of these papers are used to develop the estimated effective concentration values. Papers that are used for this purpose provide information on PCB dose, concentration (or enough information that concentration could be estimated), and effects as described earlier. The remaining papers are used for general background information on the reproductive or immune system or for background on PCB toxicity. The majority of papers included in this report are published in peer-reviewed journals.

[2] Toxic Equivalency Factors reflect the toxicity of specific congeners relative to dioxin. TEFs were not a focus of this report in 1997. I did focus on TEFs in 1998 using a recent review of the TEF approach and methodology. This review summarizes the results from a workshop conducted by the European Center of Environmental Health of the World Health Organization and the International Program on Chemical Safety and represents the work of 24 authors active in this field.

4. Effects of PCBs on Reproduction and Development

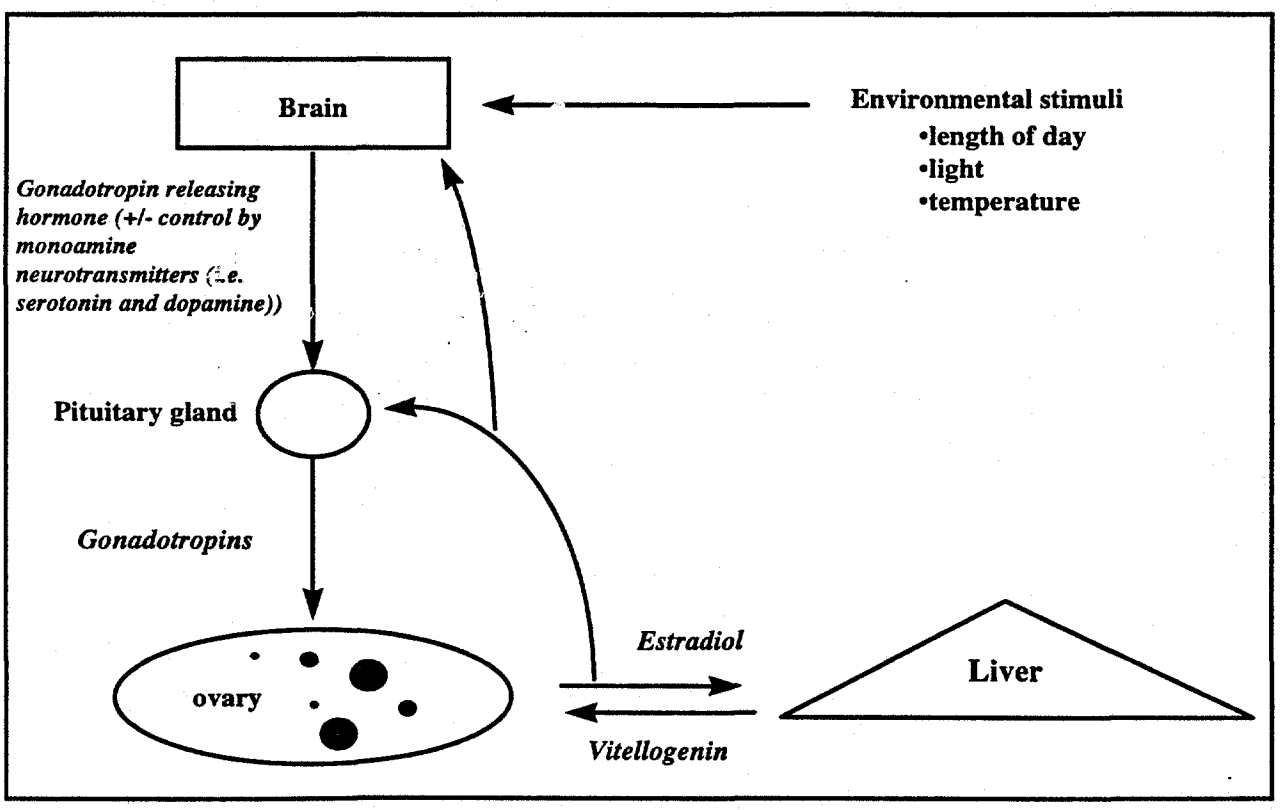
Background: Regulation of Maturation in Fish

Maturation in fish is under neuroendocrine control (Nagahama 1987; Thomas 1990). This process is illustrated in Figure 5. Basically, in maturation the brain produces gonadotropin releasing hormone (GnRH) in response to environmental and endogenous signals. The pituitary then responds to GnRH by producing gonadotropins (GtH), which then act on the gonads (ovary or testes). Gonadotropin secretion is also modulated by other neurotransmitters, including serotonin and by positive and negative feedback of steroid hormones (Nagahama 1987; Kah 1993).

The gonads respond by producing steroid hormones (estradiol or testosterone) that are transported via the blood to act on various target tissues. In the female, one important target tissue is the liver. The liver contains estrogen receptors. One consequence of estrogen receptor activation in the liver is the production of vitellogenin. Vitellogenin is a phospholipoprotein, which is then transported via the blood back to the ovary, where it is broken down and incorporated into the growing oocytes as components of the egg yolk.

Figure 5

REGULATION OF MATURATION IN FEMALE FISH
(Adapted From Nagahama, 1987)



PCBs are known to affect this hypothalamic-pituitary-gonadal-liver (HPGL) axis at almost every point (Thomas 1990). Because of its role as a storage organ (and therefore high fat content) the liver serves as a reservoir for many lipophilic chemicals including PCBs, and it is also a target for many toxic chemicals. Many of these lipophilic contaminants are incorporated into the vitellogenin and, as a result, are taken up by the developing oocyte (Ungerer and Thomas 1996). This transport of toxic chemicals into the developing oocyte is an important route of exposure for developing embryos and larvae.

Results: PCB Mixtures

The results of the literature search are presented in several tables. I begin this section with a brief discussion of how I estimate liver concentrations, including a table summarizing some of the studies used to make these estimations (Table 1). Laboratory studies demonstrating the toxic effects of PCB mixtures are presented in Table 2 (effects of A1254) and Table 3 (effects of other PCBs). These tables include reproductive effects in adults and effects of PCBs on survival and development in offspring following either maternal or water exposure. The data from Table 2 are then summarized in Tables 4 and 5. Table 4 summarizes effects of A1254 on adults, and Table 5 summarizes effects of A1254 on embryo and larval survival. These two tables are used to produce estimated effective concentrations for A1254 toxicity in fish. Table 6 summarizes PCB concentration data for fish tissues (muscle, liver, and gonad or egg) reported in several different field studies. Table 7 summarizes field studies examining PCB exposure. The studies selected for inclusion in Table 7 examine sites where PCBs are one of the main contaminants (although others may be present e.g., New Bedford Harbor), or sites where PCBs are associated with reproductive or developmental effects and many other contaminants are present.

Estimation of PCB Concentrations in Fish Liver

Doses and routes of exposure are highly variable among laboratory studies, and can be quite different from routes of exposure in the field. One method to assess potential health effects in field animals based on laboratory studies is to convert data to similar 'units,' for example the toxicity associated with PCB concentrations in a specific tissue. I chose to relate PCB toxicity to concentrations in the adult liver, since the liver is a highly perfused organ, rich in lipids (resulting in accumulation of lipophilic substances), and it plays an important role during oocyte development in fish (among its many other essential functions). In addition, for the reasons cited above, PCB concentrations are often reported for liver tissue.

In some studies concentrations are reported in several tissues, including liver and flesh or muscle. Where liver concentrations are not reported, the liver is estimated to have similar concentrations as the whole body or eggs (where those concentrations are reported). When PCB tissue concentrations are not reported at all, I estimate concentrations in the liver using one of two methods. First, if the study in question used injection as the route of exposure, I calculate total dosage injected into the fish (as ppm), and use that number for liver concentration. For

example, if fish were dosed four times in four weeks with 25 ppm, I estimate liver concentrations to be 100 ppm. If the study in question used diet as the route of exposure, I estimate liver concentrations to be 70 percent of the total dosage received. The rational used to develop these estimates is explained in further detail below.

Table 1. Concentration of PCBs in Tissues Following Laboratory Exposures by Injection

Species	Exposure Route[a]	Dose (ppm)	Liver (ppm)	Liver to dose ratio	Reference
PCB mixtures					
Mummichog (*Fundulus heteroclitus*)	PCB congener mix, 40 days after i.p. injection	0.76 3.8 19	0.75 3.1 8.2[b]	0.98 0.81 0.43	Black 1995
Mummichog	PCB mixture, 2.5 weeks after i.p. injection	1 10 100	2 16 80	2 1.6 0.8	McElroy et al., 1996
Rainbow trout	A1254 31 days after i.p. injection	3 30	0.5[c] 4.0[c]	0.16 0.13	Melancon et al., 1989
PCB congeners					
White perch (*Morone americana*)	3,3'4,4'-TCB i.p 3X over 3 months 3-6 weeks after final injection	0.025 0.25 2.5	0.03 0.05 0.5	1.2 0.2 0.2	Monosson et al., 1994
White perch	3,3'4,4'-TCB i.p. 3X over 3 months, 3-6 week after final injection	0.6 3 15	0.5 0.5 4.3	0.83 0.17 0.29	Monosson et al., 1994
Scup (*Stenotomus chrysops*)	3,3',4,4'-TCB (77) 12 days after i.p. injection	0.1 5.0	0.00125[c] 0.55[c]	0.0125 0.11	White et al., 1997
Rainbow trout (*Oncorhynchus mykiss*)	3,3',4,4'-TCB (77) 6 days after injection	0.1 1 5	0.022 0.28 0.61	0.22 0.28 0.122	Huuskonen et al., 1995
Rainbow trout	3,3',4,4',5-PCB (126) 6 days after injection	0.1 1 5	0.007 0.08 0.22	0.07 0.08 0.04	Huuskonen et al., 1995
European flounder (*Platichthys flesus*)	PCB 2,3,3',4,4',5-HCB (156) 8 days after s.c. injection	2.5	4.3	1.7	Sandvik et al., 1997
European flounder (*Platichthys flesus*)	PCB 2,3,3',4,4',5-HCB (156) 8 days after i.m.	2.5 0.5	18.6 13.0	7.4 26	Beyer et al., 1997

[a] i.p.=intraperitoneal, s.c.=subcutaneous, i.m.=intramuscular injections.
[b] Values given in dry wt, liver, converted to wet weight by dividing by 4 (Black, 1995).
[c] Concentrations estimated from figures.

Table 1 summarizes several studies used to estimate PCB concentrations in the liver after injection of A1254 or individual PCB congeners. In general, concentrations in the liver will depend on uptake, distribution, metabolism and prior exposure to individual PCB congeners. I was unable to find many studies in which A1254 was injected into fully depurated fish[3] and then measured in liver tissue as A1254, because measuring disposition of PCB in the liver was not the primary goal of these studies. Table 1 includes columns for species, route of exposure, dose, ppm in liver and the liver to dose ratio. This table also contains two sections, the first section for PCB mixtures, the second for PCB congeners. A ratio greater than one indicates accumulation in the liver to concentrations greater than the injected dosage. A ratio less than one indicates liver concentrations less than the injected dosage. Since there is very little consistency among the studies included in this table (e.g., the route and duration of exposure and type of PCB used for each study is different), it is not possible to produce a mean liver/dose ratio. The ratios reported in this table range from a low of 0.01 to a high of 26. The ratio reflects the culmination of several different processes including distribution, metabolism and depuration. The degree to which these processes occur depend on many factors including the PCB mix or congener, when the analysis occurred (days to weeks or months after injection), route of exposure, initial dose, species and sex.

The most useful studies in this table for determining liver concentrations following injection of A1254 are those that injected PCB mixtures. Three PCB mixture studies are listed in Table 1. The ratios in this section are calculated for studies by Black (1995), McElroy et al. (1996), and Melancon et al. (1989), and range from 0.13 to 2. Black (1995) injected (i.p.) a mixture of mono-*ortho* and co-planar PCBs into *Fundulus heteroclitus* and measured liver concentrations after 40 days. The calculated liver/dose ratios from this study decrease with increasing PCB dose (ratios are 0.98 to 0.43 following initial doses ranging from 0.76 to 19 ppm, respectively). McElroy et al., (1996) injected (i.p.) a PCB mixture (1:1.5 A1262:A1248) into *Fundulus heteroclitus* and measured liver concentrations after 18 days. Similar to Black (1995) the calculated ratios decrease with increasing dose (ratios are from 2 to 0.8 following doses ranging from 1 to 100 ppm). In this case, the lower doses of 1 and 10 ppm produce liver concentrations that are higher than the injected dose (i.e., liver/dose ratios greater than one). Finally the study by Melancon et al., (1989) (who injected A1254) showed the same trend (a smaller ratio with higher PCB dose) but both ratios were very low (0.16 and 0.13), indicating much lower concentrations of A1254 in the liver than the injected dose, 31 days after injection.

I estimate liver concentrations for two studies in which fish were injected with 25 ppm of A1254 (i.p) once a week for four weeks (a total of 100 ppm) (Sivarajah, et al., 1978a,b). I chose to use a ratio of 1 to estimate A1254 concentration in liver tissue for these studies. This value was selected based on a consideration of the dose used (100 ppm, similar to McElroy et al., 1996), and the length of exposure (total exposure was four weeks, but injections were given

[3] Fish with prior exposure to high concentrations of PCBs may take longer to eliminate PCBs from their system. Wirgen et al. (1992) reported liver concentrations in Atlantic Tomcod following injection with A1254, however, liver concentrations of the exposed fish were relatively high (control fish had 16 ppm in the liver) prior to exposure. For this reason, this study was not included in Table 1.

weekly, so that fish were killed within one week of the last injection, and four weeks after the first injection). The one study with A1254 by Melancon et al., (1989) resulted in liver/dose ratios much lower than 1, however these authors used lower PCB concentrations and measured A1254 in tissues after a much longer time period (31 days). This factor is most likely to overestimate the concentration of A1254 in the liver. As is clear from the data in Table 1, however, the uncertainty associated with this estimate could vary within an order of magnitude.

Several other studies in Table 1 report liver concentrations following injections of PCB congeners. These studies are relevant to the PCB congener section of this report. It is not surprising that the liver concentrations (and therefore liver/dose ratios) vary significantly with PCB congener because there can be large differences in half-life due to distribution, metabolism and excretion (Nimmi and Oliver, 1983; Opperhuizen and Schrap, 1988). Table 1 reflects these differences, as liver/dose ratios of congeners range from 0.01 to 26. Almost all ratios greater than one were calculated using data from Beyer et al. (1997) and Sandvik et al. (1997). Both of these studies used mono-ortho hexachloro-PCB 156, but employed different injection techniques. These data suggest that this compound is accumulated in the liver, is not well metabolized, and that final concentrations can vary depending on the route of exposure. In contrast, liver ratios of PCB 77 ranged from 0.013 to 1.2 of the total injected dose. It is notable that the only ratio above one was for the smallest total dose of 0.025 ppm (which is a very low dose for this congener). Ratios of less than one correspond to total doses ranging from 0.25 to 15 ppm. The low ratios for this congener are explained by the relatively rapid elimination of both metabolized and unmetabolized PCB 77 in fish (White et al., 1997).

In the congener section of this report I estimate liver concentrations of PCB 77 for several studies. The doses used in these studies range from 0.2 to 5 ppm. Based on these concentrations and the liver/dose ratios in Table 1, I use a liver/dose ratio of 0.3 to estimate liver concentrations. This will most likely result in an overestimate of concentrations of PCB 77 in liver tissue. As with the A1254 estimate, liver concentration estimates for a given dosage can vary within an order of magnitude.

When fish are exposed via the diet, several groups report that approximately 30% to 70% uptake occurs for PCB mixtures (Lieb et al., 1974; Holm et al., 1993), although assimilation can vary from less than 20 percent to more than 80 percent for individual PCB congeners (Niimi and Oliver, 1983; Opperhuizen and Schrap, 1988: De Boer and Pieters, 1991; Da Costa and Curtis, 1995; Bureau et al., 1997; Fisk et al., 1998). I estimate liver PCB concentrations for two feeding studies conducted by Thomas (1988, 1989) using A1254. Based on the studies cited above, I estimate that the fish in Thomas' studies received 70 percent of the total dose. As with the injection estimate, this estimate is more likely to overestimate PCB concentrations because it assumes efficient assimilation for almost all PCB congeners.

It is notable that PCB accumulation and distribution in fish tissues is highly influenced by the lipid content and lipid type (polar, neutral, nonpolar). Thus, accumulation and deposition of PCBs into tissues including developing oocytes can be influenced by the percent and type of

lipids in the adult fish and in the oocytes (Nimmi 1982; Kammann et al., 1990). This will likely contribute some uncertainty to the PCB concentrations estimated in this analysis, since all species are treated similarly.

Laboratory Studies: PCB Mixtures

The reproductive and developmental effects of PCBs in fish following laboratory exposure are listed in Tables 2 and 3. The categories in Tables 2 and 3 include species, dose in parts per million (ppm), tissue concentration (in ppm), effects and references. Effects of A1254 in adult animals are presented in the top portion of Table 2, followed by effects in embryos and larvae. The common names for each species are listed under species. Dose is summarized as amount (in ppm), route, frequency and total exposure period. For example "25x4(i.p) over 4 week period" indicates that fish were exposed to four 25 ppm injections over a four week period. "Tissue concentrations" refers to either the reported or estimated tissue concentrations. If concentrations are not reported in any tissue (NR), then I estimate liver concentrations as described above. Wherever possible, I summarize effects as a percent change from control using arrows to indicate a reduction or increase. If values are not reported as percent change from control, I calculate this change using the mean values provided in the reports. The last column of Tables 2 and 3 provides the references for each summarized study.

Table 3 summarizes other studies evaluating the effects of various PCB mixtures on reproduction and development. Because the toxicity of PCB mixtures varies with the degree of chlorination, there is a broad range of concentrations associated with effects, and in some cases the mixtures did not affect the endpoints used in these studies (e.g., PCB 1016, Hansen et al., 1975). In general, exposure to PCBs other than A1254 resulted in altered reproduction and reduced embryo and larval survival.

Tables 4 and 5 are constructed to aid the development of effective concentrations for A1254 toxicity. Table 4 is a summary of the data on adult fish presented in Table 2, and Table 5 is a summary of the data on embryo and larval fish presented in Table 2. Included in the tables are: concentration of A1254 in liver (reported or estimated) for Table 4, and whole body for Table 5, effects of exposure, confidence in each study, and references. Confidence in each study is determined by 1) concentrations used in the study (e.g., tissue concentrations that are orders of magnitude above environmental concentrations resulted in lower confidence); 2) consistency of effects among studies that evaluated similar endpoints (i.e., reproducibility); 3) validity of controls (e.g., tissue PCB concentrations that were similar for controls and dosed fish resulted in lower confidence); and 4) amount of information provided (statistics, chemical analysis, number of fish used, amount of data presented).[4]

[4] I had some concern about the currency of the studies, since analytical techniques have changed since the early 1970s. One main concern was differences in measured concentrations of A1254. However, in a comparison of field studies from the 1970s to more recent studies in which A1254 was measured in Hudson River fish tissue, the earlier techniques to measure A1254 were found accurate, and no correction was necessary when comparing concentrations measured using the earlier techniques (Butcher et al., 1997).

Several studies conducted in the laboratory of Peter Thomas are rated with high confidence (Table 4). The results of these studies are not only consistent with each other, but are consistent with results reported by other researchers (e.g., Sivarajah et al., 1978; Freeman and Idler, 1975). In addition, the concentrations used in these studies are environmentally relevant for sites such as the Hudson River. The studies by Sivarajah et al. (1978a,b) and Sangalang et al. (1981) are given high ratings, although the estimated tissue concentrations in Sivarajah et al. (1978a,b) may not be environmentally relevant. The study by Freeman and Idler (1975) is rated moderate because of the small amount of data presented. Mayer et al. (1977) is given a low rating because the reported tissue concentrations are vastly different (and much lower) than would be expected from feeding studies. The information previously cited suggests that concentrations in Mayer et al. (1977) would have been expected to be at least an order of magnitude higher even if potential excretion or metabolism of some PCB congeners is considered. Given this information, it is possible that either the uptake in this experiment was poor, or the tissue chemistry was inaccurate. Chen et al. (1986) is also given a low rating because it is unclear if the doses (3 to 300 ppm) were ppm in the diet or in the fish, and the authors did not report PCB concentrations in any tissues. In addition, the authors suggest that it is possible the reduced vitellogenin production may be a result of hepatic toxicity, but they did not investigate this further. This study is not included in Table 4 because I was unable to estimate tissue concentrations.

Most of the studies included in Table 5 are given high confidence ratings. Two of these studies use a water exposure (Mauck et al., 1978 and Halter and Johnson, 1974) and two use maternal exposures (Hansen et al., 1973 and Schimmel et al., 1974). Concentrations in the larvae are either provided or could be estimated, except for the studies by Halter and Johnson (1974) and Foster and Berlin (1997) (there is insufficient data available for estimating concentrations in larvae following water exposures to the eggs). In the study by Sharp and Thomas, concentrations in larvae are estimated as less than 30 ppm since the total dose in the adults is 30 ppm. This study was given a moderate rating since the data are from a meeting abstract.

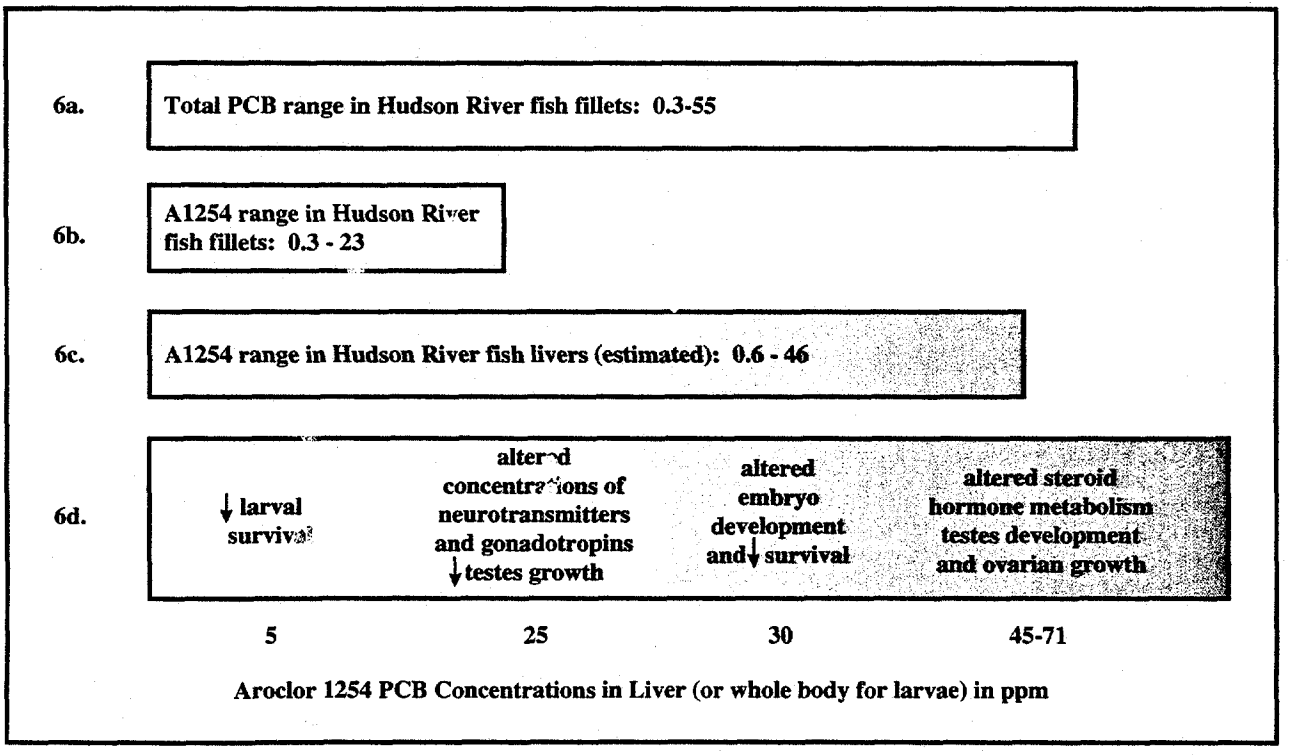
Estimation of Effective Concentrations for Adults and Larvae: A1254

The studies summarized in Table 4 demonstrate that PCB exposure resulting in approximately 25 to 100 ppm PCB in the liver of adult fish consistently causes reduced gonadal growth and altered blood plasma steroid hormone concentrations. Fry survival, as demonstrated by the studies summarized in Table 5, is decreased by PCB concentrations ranging from 5 to 125 ppm. It is possible that the wide range is a result of either different route of exposure (water exposure to eggs versus maternal exposure), assay temperature differences (12 to 14° C for the brook trout versus 25 to 30° C for the sheepshead minnows), or interspecies differences in egg and larval development or sensitivity to PCBs.

The effective concentrations for reproductive and developmental effects of PCBs in fish, and their comparison to PCB concentrations recently measured in Hudson River fish, are summarized in Figure 6 (in the figure, darker shading represents higher estimated PCB concentrations in fish livers). A recent study by McGroddy et al. (1997) measured PCB levels in 120 fish collected from various locations in the Hudson River in 1995. The total PCB levels measured in Hudson River fish fillets (with skin on one side) range from 0.3 to 55 ppm (Figure 6a). PCB measurements in McGroddy et al. were based on 107 target congeners. In general, the proportion of PCBs quantified as A1254 decreases with increasing river mile, such that PCBs quantified as A1254 range from approximately 90% at RM 40 to 42% at RM 190, which is the point where fish were most highly contaminated (S. McGroddy, pers comm) (see Figure 7).

Figure 6

COMPARISON BETWEEN PCB CONCENTRATIONS IN HUDSON RIVER FISH AND TISSUE CONCENTRATIONS OF A1254 SHOWN TO CAUSE REPRODUCTIVE AND DEVELOPMENTAL EFFECTS IN LABORATORY STUDIES.



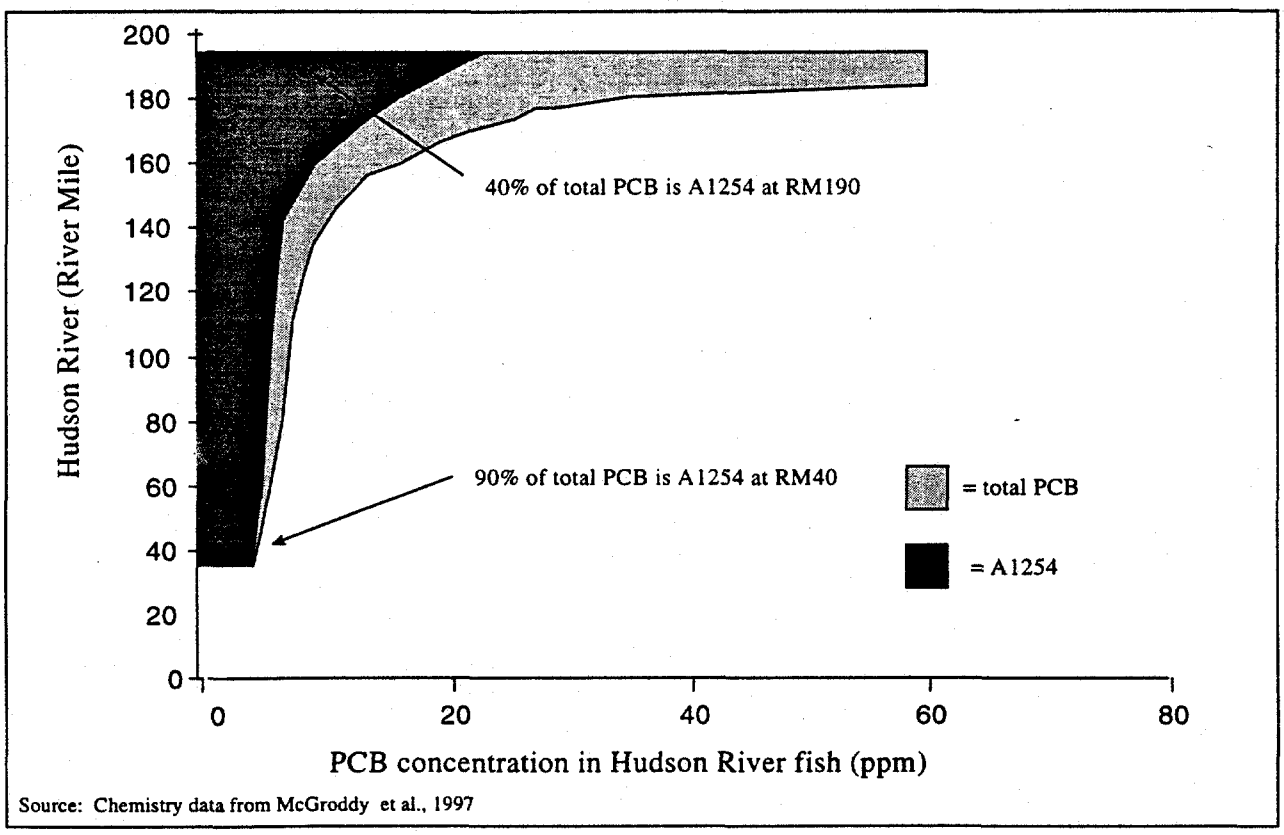
To compare laboratory toxicity results with Hudson River contamination levels, the PCBs quantified as A1254 in fish reported to have total PCBs of 55 ppm (collected at RM 190) would be approximately 23 ppm (Figure 6b).[5] To convert to concentrations likely to be measured in the liver of Hudson River fish, these values are doubled (Figure 6c). This estimation

[5] McGroddy et al. (1997) report PCB concentrations only for fish within a 95% confidence interval. Thus, some fish outside the interval have higher (and lower) PCB concentrations in their tissues.

of liver PCB values (twice the concentration found in the flesh) is based on previous studies in which PCB concentrations are reported for various tissues for wild-caught fish (Table 6). Field studies were selected for this table because I am extrapolating PCB concentrations from muscle to liver in wild-caught fish and tissue distribution may vary depending on the type of exposure (i.e., a relatively "acute" laboratory exposure vs. a chronic field exposure). The first two columns in Table 6 list the site, species and PCB mixture reported in each study. The next three columns include tissue concentrations (in ppm) for muscle, liver and ovary. The next column lists the liver/muscle ratio. The liver/muscle ratios range from <1 to 77, with the majority of studies ranging from 1 to 8. Variations in ratios are the result of several factors including sex, reproductive status, interspecies differences in lipid content, metabolism, excretion, life history, and even analytical techniques (e.g., 'pure' fillet vs. skin-on fillet). However, as reflected in the table, concentrations of PCBs in liver are often more than double that of muscle tissue (only 2 out of 10 ratios are below 2). This two-fold liver concentration estimate was selected since fillets or muscle tissue samples for the Hudson River fish were analyzed as 'skin-on' fillet, which may result in higher concentrations of PCBs compared to 'pure' fillets.

Figure 7

AROCLOR 1254 CONCENTRATIONS VS. TOTAL PCB CONCENTRATIONS IN HUDSON RIVER FISH (NOT TO SCALE)



Source: Chemistry data from McGroddy et al., 1997

Adverse effects on reproduction or development are summarized in Figure 6d. As shown in Figure 6, A1254 concentrations in Hudson River fish overlap A1254 concentrations shown to adversely affect reproduction in adult fish in laboratory studies. There is little information

relating A1254 concentrations in adult fish to A1254 concentrations in their offspring, thus it is difficult to estimate A1254 concentrations in eggs or larvae from Hudson River fish. However, several studies have reported similar or higher PCB concentrations in eggs compared to adult muscle tissue (Table 6). The egg or gonad to muscle ratios range from 0.1 to 545. The majority of the calculated ratios, however indicate five times greater concentrations of PCBs in the eggs compared to muscle tissue. It is possible, therefore, that A1254 concentrations in eggs from Hudson River fish may also be within range of A1254 concentrations (from 5-125 ppm) found to be toxic to embryos or larvae in laboratory studies.

Table 2. Reproductive and Developmental Effects of Laboratory Exposure to A1254

Species	Dose (ppm)	Tissue Concentration[a]	Effects	References
Effects in adults				
Carp	25x4 (i.p.) over 4 week period	NR (est 100 in liver)	↓Androgen by 61%[b], ↓estrogen by 35% , ↓corticosteroids by 35%, abnormal spermatozoa	Sivarajah, et al., 1978a,b
Trout	25x4 (i.p.) over 4 week period	NR (est 100 in liver)	↓Androgen by 45%, ↓estrogen by 33%, ↓corticosteroids by 44%, abnormal spermatozoa	Sivarajah, et al., 1978a,b
Atlantic croaker	3.4 in diet for 30 days.	NR (est 71 in liver)	↓Ovarian growth by 75%, ↓Testosterone, no effect on estradiol.	Thomas 1988
Atlantic croaker	5 in diet for 17 days.	NR (est 60 in liver[c])	↓Ovarian growth (GSI) by 50%, ↓estradiol by 49%, ↓GtH secretion by 54%, ↓Plasma vitellogenin, ↓hepatic estrogen receptor concentration.	Thomas 1989
Atlantic croaker	1 in diet for 30 days	13 brain 2 testes 25 liver	↓ serotonin in preoptic-anterior hypothalamic area (POAH) by 38%, ↓ dopamine in POAH by 35%, ↓ serotonin in medial and posterior hypothalamus (MPH) by 38%, ↓ dopamine in MPH by 29% ↓Testicular growth Inhibition of GtH secretion, ↓Testiscular GSI by ~79%, ↓Testosterone by ~60%, ↓11-ketotestosterone by ~73%.	Khan and Thomas 1996 Khan and Thomas 1997
Brook trout	0.2 in water for 21 days	77.9 in eggs 32.8 in skeletal muscle (est 78 in liver)	↓Testes size, ↓Spermatic fluid, ↓hatch by 22%.	Freeman and Idler, 1975
Atlantic cod	1,5,10,25,50 in diet for 5 months	45-374 (in liver)	Altered steroid production, Abnormal testes with all doses, ↓Spermatogenic elements.	Freeman et al., 1982; Sangalang et al., 1981
Rainbow trout (juvenile)	3,30,300 in diet for 6 months	NE[d]	↓ E2 induced VTG production by 60-72%.	Chen et al., 1986
Channel catfish	2.4 and 24 in diet for 193 days	4.8-21.0 in whole body, (est 5-21 in liver)	↑Thyroid activity (as measured by uptake of I^{125})	Mayer et al., 1977
Coho salmon	0.048 –480 in diet for 260 days	0.6-645 in whole body, (est 1-645 in liver)	↑Thyroid activity by 52-119%(as measured by uptake of I^{125})	Mayer et al., 1977

Table 2. Reproductive and Developmental Effects of Laboratory Exposure to A1254 (continued)

Species	Dose (ppm)	Tissue Concentration[a]	Effects	References
Effects in embryos and larvae				
Lake trout	269 ng/L in water	NE[d]	No effect on fertilization[d]	Foster and Berlin, 1997
Atlantic croaker	Adults exposed to 1 in diet for 30 days	NR (est 30 in whole body)	↑% Abnormal embryos by 33%, ↓Hatch by 14%, ↓Viable hatch by 32%, ↓Larval length.	Sharp and Thomas, 1991
Brook trout	Adults exposed to 0.2 in water for 21 days	77.9 in eggs	↓Percent hatch by 22%.	Freeman and Idler, 1975
Brook trout	Eggs exposed to 0.43-13 ug/L in water from 10 days before hatch to 118 days post hatch	17 71 125- 284 (fry, whole body)	↓Backbone phosphorus by 38%, ↓↓ hydroxyproline by 20%, ↑Backbone calcium by 100%. ↓Fry survival by 21-50% (no effect on egg hatch).	Mauck et al., 1978
Coho salmon	Eggs exposed to 5-80 ug/L in water from 2 weeks before hatch to 4 weeks post hatch	NR 10 ug/L and higher	Premature hatch by 2-5 days, ↓Hatch rate by 18 - 34%, ↓Fry survival by 30 - 93%.	Halter and Johnson 1974
Sheepshead minnow	Adults exposed for four weeks to 0.1-10.0 ug/L A1254 in water	0.88 5.1-170 (in eggs)	No effect ↓Percent fry survival 1 week post-hatch by 20-100%	Hansen et al., 1973
Sheepshead minnow	Adults and offspring exposed for 3 weeks 0.1-10.0 ug/L A1254 in water	0.88 5.1-170 (est in eggs)	no effect ↓Percent fry survival 2 weeks post-hatch by 30-90%	Schimmel et al., 1974

[a] Where reported, tissue concentrations are in parts per million (ppm) wet weight. Where no concentrations are reported, they are estimated in the liver (est. liver) by calculating total exposure to the fish for injection (i.p.) or 70% of dose for oral exposure.

[b] Percent change from controls are calculated using reported mean values (e.g., percent hatch or percent survival, or plasma concentrations of steroid hormones)

[c] Ungerer and Thomas (1996) report concentrations of 99 ppm and 55 ppm in female and male livers respectively after 30 days of feeding 5 ppm A1254.

[d] I could not estimate liver concentrations for these species because there was insufficient information (i.e., no other tissue concentration reported, no information on daily intake of PCB contaminated food).

Table 3. Reproductive and Developmental Effects of PCBs other than A1254

Species	Dose (ppm)	Tissue Concentration	Effects	References
Stickleback (adult)	Clophen A50 in diet for 3.5 months	102-289 (whole body, wet weight)	Trend toward ↓percent successful spawn (from 80% in control to 20-55% in PCB exposed fish).	Holm et al., 1993
Minnow	Clophen A50, 20,200,2000 in diet 40 days	1.6 15 170 (whole body wet wt)	No effect. Spawn delayed 7 days. Spawn delayed 21 days, ↓ Percent hatch by 82%, ↑Mortality.	Bengtsson et al., 1980
Dab	Clophen A40 14 and 26 in diet, three times over four months	0.2-0.6 in eggs	No effect in egg production, quality, fertilization, hatch or survival	Fonds et al., 1995
Atlantic salmon	A1016, 1221, 1254, 1260 mixture in water for 48 hour, health assessed over 6 months	0.85-1.53 [a] 5.59 14.16	No effect. Reduced wet weight and length after 6 months. Reduced weight and length, altered behavior, reduced predator avoidance.	Fisher et al., 1994
Rainbow trout	1,5 and 20 A1260 in the water (mg/L) for 2 hours at 25d post-hatch	2.1 2.5	Increased proportion of female offspring Increased percent females with incomplete or inconsistent oocyte development	Matta et al., 1993
Goldfish	A1248 250 i.p. injection	250 (estimated)	Stimulated metabolism of progesterone, estradiol, testosterone and cortisol, decreased plasma concentrations of estradiol, testosterone and progesterone	Matsuyama and Yano 1987[d]
Coho salmon	A1254 and A1242 in 4:1 ratio. 50 and 500 in feed for 2 or 3 months	Low dose High dose	No effect Reduced serum T3 levels, no effect on T4, increased T4/T3 ratio, reduced body weight	Leatherland and Sonstegard, 1978
Sheepshead minnow	0.1-10 ug/L A1016 in water for 28 days	4.2-66 (in eggs)	No effect on fertilization, No effect on hatching, No effect on fry survival.	Hansen et al., 1975
Fathead minnow	0.1-3.0 ug/L A1248 from embryo to spawning adult (250 days)	190 in whole body of adult males	No effect on reproduction, including hatch of offspring.	Defoe et al., 1978

Table 3. Reproductive and Developmental Effects of PCBs other than A1254 (continued)

Species	Dose (ppm)	Tissue Concentration	Effects	References
Fathead minnow	0.1-2.1 ug/L A1260 from embryo to spawning adult (250 days)	360 in whole body of adult males	No effect on reproduction, including hatching of offspring.	Defoe et al., 1978
Fathead minnow	1.3-9 ug/L A1260 for 30 days post-hatch	≥4ug/L[b]	↓ Survival by 69%, weight by 30% and length by 11%.	Defoe et al., 1978
Fathead minnow	1.1-8.5 ug/L A1248 for 30 dayspost-hatch	≥4.4 ug/L[b]	↓ Survival by 44%, weight by 66% and length by 30%.	Defoe et al., 1978
Mixtures of individual congeners				
Zebrafish	41,51,60,68,91,99,104,112,115,126,143,153,169,184,1930.008, 0.08, 0.4 ppm of each congener in food, sampled at 4 and 13 weeks	Sum PCB concentrations at 13 weeks: 0.14 1.1 2.7	 no effect on mortality, ↓ body weight[c] ↓liver somatic index (LSI) ↑mortality by 7%,↓ body weight[c]↓GSI, ↓ mature oocytes,↓LSI ↑mortality by 17%,↓ body weight[c] ↓mature oocytes, ↓LSI, ↓larval survival	Orn et al., 1998
Fundulus heteroclitus	118,105,167,156,157,189,77,126 (mixed together) 0.76, 3.8, 19 of PCB mixture (i.p.)	2.9 12.2 32.8 liver dry wt after 40 d.	none ↓egg deposition by 63%, ↓ food consumption,↑ female mortality ↓egg deposition 60%, ↓ pituitary gonadotropin, 58% adult mortality, ↓ food consumption	Black et al., 1998

[a] These concentrations are measured in embryos; health effects are measured in older fry with lower PCB concentrations (as a result of dilution during growth).

[b] Tissue concentrations not reported, unable to estimate concentrations in larvae from data provided.

[c] Weight loss due mainly to reduced gonad growth.

[d] Abstract only, published in Japanese.

Table 4. Estimation of A1254 Effective Concentrations in Fish from Laboratory Studies[a]

Concentration of A1254 in liver (ppm)	Effects	Confidence in study	References
1 (estimated)	↑Thyroid activity	L	Mayer et al., 1977
25	↓Serotonin, ↓ dopamine, ↓ testicular growth by 79%, ↓T and 11-KT, inhibition of GtH secretion *in vitro*	H	Khan and Thomas 1996; Khan and Thomas 1997
60 (estimated)	↓Ovarian growth by 50%	H	Thomas 1989
71 (estimated)	↓Ovarian growth by 75%, ↓testosterone	H	Thomas 1988
45-100	Abnormal testes, altered steroid hormone metabolism, ↓spermatogenic elements	H	Sangalang et al., 1981; Freeman et al., 1982
90 (estimated)	↓Decrease sperm fluid, ↓testicular growth	M	Freeman and Idler 1975
100 (estimated)	↓Androgens, estrogens, corticosteroids, abnormal spermatozoa	H	Sivarajah et al., 1978a,b

[a] Chen et al. 1986 is not used since concentrations could not be reliably estimated.

Table 5. Estimation of A1254 Effective Concentrations in Fish from Laboratory Studies: Effects in Embryos and Larvae[a]

Concentration of A1254 in whole body (ppm)	Effects	Confidence	References
5 (estimated)	↓Fry survival at 1 week post-hatch	H	Hansen et al., 1973
5 (estimated)	↓Fry survival at 2 week post-hatch	H	Schimmel et al., 1974
17	↓Backbone collagen	H	Mauck et al., 1978
<30 (estimated)	↓Percent hatch, larval length ↑abnormal embryos	M	Sharp and Thomas 1991
<71	↓Fry weight,	H	Mauck et al., 1978
125	↓Fry survival	H	Mauck et al., 1978

[a] Halter and Johnson (1974) and Foster and Berlin (1997) are not used in this table since concentrations in eggs or fry could not be reliably estimated.

Table 6. Concentrations of PCBs in Various Tissues Reported in Field Studies

Species	PCB	Muscle (ppm)	Liver (ppm)	Ovary (o) or gonad (g) (ppm)	Liver/ muscle	Ovary or egg /muscle	References
Baltic herring	PCB mix	0.15-1.8	0.02-0.38	0.02-0.24 (o)	<1	0.13	Hansen, 1985
Fundulus heteroclitus, Hudson River (Piermont)	PCB mix	0.24	1.25	3.33 (o)	5	14	Monosson, Elskus, McElroy pers comm.
Fundulus heteroclitus, Hudson River (Newark)	PCB mix	0.20	1.65	2.01 (o)	8	10	Monosson, Elskus, McElroy pers comm.
Atlantic cod	A1254	<0.000002-0.002	0.154	0.005 (o)	77	2	Hellou et al., 1993
Red mullet, Western Med	PCB mix	0.307	1.093	1.413 (g)	4	5	Albaiges et al., 1987
Horse mackerel, Western Med	PCB mix	0.127	0.357	4.575 (g)	3	38	Albaiges et al., 1987
Blue whiting, Western Med	PCB mix	0.034	0.040	0.32 (g)	1	9	Albaiges et al., 1987
Striped bass Shubenacadie River	PCB mix	0.01	NA	0.04	NA	4	Ray et al., 1982
Striped bass Annapolis River	PCB mix	0.02	NA	1.4	NA	70	Ray et al., 1982
Pike, southern Scandinavia	PCB mix	0.0065-0.014	NA	0.49-7.63	NA	75-545	Larsson et al., 1993
Dab, Eastern Channel, France	PCB 138 PCB 153	0.23 0.21	0.40 0.44	0.13 0.97	2 2	0.6 5	Loizeau and Abarnou, 1994

Field Studies: PCB Mixtures

Table 7 summarizes studies demonstrating an association of PCB mixtures in the field with reproductive and developmental effects. The categories in Table 7 are site, species, contaminants at the site, concentration range, observations associated with PCBs, and references. In most cases, sites are contaminated with chemical mixtures. To date, there is only one site for which data are available (Hartwell Lake, SC/GA) and that is contaminated almost exclusively by PCBs. Concentrations reported in Table 7 are either the mean concentration associated with a particular effect or the concentration ranges reported at sites where effects are associated with PCB exposure.

Table 7. Reproductive and Developmental Effects Associated with PCB Exposure in the Field

Site	Species	Contaminants at site	Concentration Range[a] ppm wet wt	Observation Associated with PCB	References
Effects in adults					
Hartwell Lake, SC/GA	Large mouth bass	PCBs	4-20 in flesh	↓Liver estrogen receptor binding, ↑ nonspecific binding ↓Testosterone, ↓White blood cell counts, ↑DNA repair, ↓Ovary size.	Garcia et al., 1997; Adams et al., 1992; USACOE, 1994
New Bedford Harbor, MA	Winter flounder	PCB Others	2-47 in liver	↓Ovary size in 1 out of 3 years[b]	Elskus 1992, Elskus, pers comm.
Puget Sound (Duwamish Waterway)	English sole	PCB PAH Others	~10 in liver ~1 in ovary	↑Fecundity ↓Egg size ↓Vitellogenin[c]	Johnson et al., 1997
Oak Ridge, TN	Redbreast sunfish	PCB, PAH, metals, Others	NR	↓Fecundity (egg clutch size)	Adams et al., 1992, Adams et al., 1989
Rotterdam Harbor (dredge material)	Flounder	28,52,101,118, 153,180 Other PCBs and chemicals	Sum: 11.9 (in liver) ppm lipid	Induced premature vitellogenesis	Janssen et al., 1997
Effects in embryos and larvae					
Baltic Sea	Baltic herring	PCB DDE PAH Others	0.24 0.02 in ovary	↓Viable hatch ↓ Larval survival	Hansen, 1985
Lake Geneva	Arctic char	PCB DDT Others	0.10-0.31 0.04-0.17 in eggs	↓Embryo survival ↓ Fertility	Monod, 1985
San Francisco Bay	Starry flounder	PCB Others	5-30 lipid (~50-200 in eggs)	↓Embryo survival	Spies and Rice 1988
Lake Michigan	Lake Trout	PCB Others	0.25-7.76 in eggs 4.19-13.88 in testes	↓Embryo survival	Mac et al., 1993
Lake Michigan	Chinook salmon	PCB Toxaphene Others	2.83-9.09 2.37-5.93 in eggs	Negative correlation with survival to "swim up"	Giesy et al., 1986
Baltic Sea	Baltic flounder	PCB Others	0.12 in ovary	↓Embryo survival, ↓Larval survival	von Western-hagen et al., 1981
New Bedford Harbor, MA	Winter flounder	PCB Others	39.6 in eggs	↓Larval length at hatch, ↓Larval weight at hatch	Black et al., 1988
New York	Striped bass	PCB DDT HCB chlordanes Others	7-32 in eggs	slightly reduced larval survival	Westin et al., 1985
Puget Sound (Urban areas)	English sole	PCB PAH Others	2.6, 3.5 in adult livers from urban areas	↓Larval survival	Casillas et al., 1991
New Bedford Harbor	mummichog	PCB (mono-and non-ortho) Other chemicals	0.4-29 liver, dry wt.	↑ embryo mortality ↑ terata ↑ adult mortality	Black et al., 1998
River Skalice, Czech Republic	Carp	28, 52, 101,153, 138, 180, 118	Sum: 0.206 wet wt. (in eggs) 0.262 wet wt. (in liver)	↑length growth rate ↓weight condition	Svobodova et al., 1996

[a] Concentrations associated with observation, concentration ranges or means are provided when no attempt was made to calculate an effect level.

[b] Reduced ovary size was observed in the first year of the study. Sample size decreased after first year.

[c] Reduced plasma VTG concentrations were associated with PCBs but were not reduced in Duwamish fish.

Three studies in Table 7 report an association between PCB exposure in the field and adverse effects in adult fish, although concentrations of PCBs associated with effects are published in only two of the studies. In Lake Hartwell, reduced estrogen receptor binding (Garcia et al., 1997), reduced testosterone concentration, reduced ovary size and a trend toward greater damage in oocytes are associated with tissue concentrations as high as 20 ppm in the flesh (which could be estimated at 40 ppm in the liver) (Adams et al., 1992; USACOE, 1994). This site is known to be contaminated primarily with PCBs, and other chemicals are reported to be too low in concentration to be of concern. The authors of one of the Lake Hartwell investigations conclude that there is a "direct relationship between the health of fish in Lake Hartwell and PCB contamination" (USACOE, 1994).

Reduced ovary size (Elskus 1989) is associated with similar concentrations of PCBs in fish from New Bedford Harbor (as high as 47 ppm in the liver). The authors report this finding in the first year of a three year study. However, they also report much smaller sample sizes after the first year (Adria Elskus, pers comm). Although PCBs are the main contaminant of concern in New Bedford Harbor, other important contaminants are known to be present as well. In general, the PCB concentrations associated with effects on steroid hormone concentration, estrogen receptor binding, and ovary size (approximately 40 ppm in the liver) are within the range of those concentrations found to have similar effects in laboratory studies (Table 2; Figure 6).

The remaining studies in Table 7 focus on the association of PCBs with embryo and larval survival. There are nine studies included in this section of the table. These studies are from sites around the world and across the United States. Although effects are associated with PCB contamination, other contaminants are acknowledged to be present at all of these sites. Reduced embryo survival is associated with PCB concentrations ranging from 0.1 to 200 ppm in the eggs. Three different studies indicate that PCB concentrations as low as 0.1 to 8 ppm could reduce embryo survival (Monod, 1985; von Westernhagen, 1981; Mac et al., 1993), and one reports reduced survival with concentrations of approximately 50 to 200 ppm in the eggs (measured as 5 to 30 ppm in the lipid) (Spies and Rice, 1988). Reduced larval survival or viable hatch (the production of apparently healthy larvae) is reported in four field studies in association with PCB concentrations ranging from 0.1 to 32 ppm in eggs or ovaries (Hansen, 1985; von Westernhagen et al., 1981; Westin et al., 1985). None of these studies reported any pathology associated with the larval mortality, precluding a comparison to pathological effects caused by PCBs in laboratory studies. A more sublethal response, reduced size (weight and length) is reported in larvae hatched from eggs with PCB concentrations of 39 ppm (Black et al., 1988). PCB concentrations from 5 to 125 ppm (eggs or larvae) reduce larval survival in laboratory studies (Table 2; Figure 6). These values are within range of the PCB concentrations associated with reduced survival in the field.

A few field studies report an association with very low (0.1 ppm) concentrations of PCBs. It is important to consider the presence of other contaminants at most of these field sites. For example, the two sites reporting an association between larval survival and low concentrations of PCBs (von Westernhagen et al., 1985, 1985; Monod, 1985) also report that other contaminants that are toxic to embryos and larvae, including DDT (or DDE), are present at these sites. Some sites contain chemicals such as dioxins and polyaromatic compounds in

addition to PCBs that can all act via the same mechanism. The effects of these chemicals may be additive, synergistic or antagonistic (as discussed in the section on TEQs). One consequence of such mixtures may be that the concentration of any single class of chemicals (e.g., PCBs) associated with toxic endpoints in the field may be lower than the concentration required to cause toxicity in the laboratory, if laboratory exposure is limited to a single compound. In addition, there are many 'natural' variables (e.g., temperature fluctuation) which may interact with chemical contaminants and influence embryo and larval mortality (von Westernhagen and Dethlefson, 1997).

Discussion and Conclusion: PCB Mixtures

The data summarized in Figure 6 indicate that adult concentrations of A1254 as low as 25 ppm in the liver may affect the functioning of the hypothalamic-pituitary-gonadal-liver axis (HPGL). Altered function of the HPGL may affect reproductive success by altering gonad growth, including oocyte development and maturation, and spawning (e.g., number of eggs spawned, delayed spawning, inhibited spawning). Any one of these results may eventually affect recruitment. In addition, several studies have shown that embryos and larvae are even more sensitive to A1254 than adult fish. It should be noted that the endpoint used in embryo and larval studies is often reduced survival. This suggests that there may be sublethal effects at even lower concentrations than those found to cause embryo or larval toxicity (such as growth or behavior). Laboratory studies have shown embryo or larval survival to be affected by concentrations as low as 5 ppm. The concentrations of A1254 shown to be toxic in the laboratory are within range of the A1254 concentrations estimated in some of the most contaminated Hudson River fish.

I was unable to locate any studies specifically evaluating the reproductive or developmental success of highly contaminated Hudson River fish (except for Westin et al., (1985): this study is unclear as to where the fish were collected). There are a number of field studies at other sites around the world that demonstrate an association between PCB contamination and altered reproductive success. In the majority of these sites there are other contaminants present that may co-occur with PCBs, including metals, DDT (and metabolites), and polycyclic aromatic hydrocarbons. All of these contaminants are known to affect reproduction in fish (Thomas, 1990; Kime, 1995), making comparisons between PCB concentrations found to be toxic in the laboratory (a single chemical exposure) and those associated with altered reproductive success in the field (most often a mixed chemical exposure) difficult. However, there is a fair amount of agreement between the concentrations and effects from laboratory studies and field studies, suggesting that A1254 exposure at concentrations from approximately 25 ppm and higher in adults livers, and 5 ppm and higher in embryos and larvae, can affect reproduction and development in fish.

Several recent studies have demonstrated acquired resistance to AhR-active chemicals in two species, *Fundulus heteroclitus* (mummichog) (Elskus et al., in press; Prince and Cooper, 1995a,b; Van Veld and Westbrook, 1995; Bello et al., 1996,) and the Atlantic tomcod (Wirgin 1992). Resistance has been demonstrated at the biochemical level (e.g., resistance to CYP1A induction: Elskus et al., in press; Van Veld and Westbrook, 1995; Wirgin et al., 1992) or as

reduced mortality (Nacci et al., in press; Prince and Cooper, 1995a,b; Horton et al., 1993). Currently the only species for which acquired resistance is known to affect embryo and larval survival following exposure to AhR-active chemicals is *Fundulus heteroclitus* (reviewed in Hahn, 1998). It is not surprising that species such as *Fundulus heteroclitus* can adapt to chemical stresses, considering its short generation time and nonmigratory behavior. Except for studies with the tomcod and *Fundulus heteroclitus*, there are no other known reports of adaptation to AhR-active chemicals in other fish species. This is, however, a relatively new focus for toxicology, and it is likely that other 'resistant' species will be identified in the future. To date, the only species that is known to become resistant to the toxic effects of PCBs is *Fundulus heteroclitus*.

Results: PCB Congeners

Since the discovery of the structure activity relationship that exists between specific PCB congeners and toxicity (for those congeners that act via the AhR), there has been a great emphasis on determining the toxicity of specific PCB congeners. Until recently this emphasis has been on AhR-active PCB congeners, which include primarily the non-ortho substituted PCBs and the mono-ortho substituted PCBs.

Laboratory Studies: PCB Congeners

The reproductive and developmental effects of specific PCB congeners in the laboratory are summarized in Table 8. The categories in this table are: species, congener, dose, tissue concentration (where concentrations are not reported, liver concentrations are estimated as described previously), effects, and references. Research on specific congeners is fairly recent in fish, and the majority of studies focus on the AhR-active congeners 77 and 126. Both congeners have a relatively high toxic equivalency factor (although PCB 126 is more toxic than 77) and are frequently present in environmental samples.

There were a sufficient number of studies on PCB 77 to construct a summary table and estimate effects resulting from various concentrations of PCB 77. Table 9 summarizes the data on PCB 77 presented in Table 8. The table presents: concentration of PCB 77 in liver, eggs or embryos (either measured or estimated); effects; confidence; and references. All but one of these studies were given a moderate confidence rating; they were assigned a moderate confidence rating because there is not a sufficient body of literature that reproduces the results of these studies. Walker and Peterson (1991) was given a high confidence rating because LD50 for Ah-active chemicals values generated by this study are expected to be reproducible. This study employed egg injection as the route of exposure. A subsequent study by Walker et al. (1994) found that the LD50s (for dioxin) were similar for both the egg injection and maternal routes of exposure, indicating that the egg injection technique is comparable to the more environmentally relevant maternal route of exposure. Concentrations of PCB 77 ranging from 0.3 to 4.5 ppm in adult livers were found to: reduce egg deposition, pituitary gonadotropin, and GSI; alter retinoid concentrations (vitamin A); and reduce larval survival. Three studies in Table 8 report reduced

embryo and larval survival following exposure to concentrations of congener 126 ranging from 0.029 to 0.074 ppm (in the embryos or eggs), demonstrating the much greater potency of this congener compared to PCB 77.

Figure 8 summarizes the effective concentrations for the toxic effects of PCB 77 to fish compared to PCB 77 concentrations recently measured in Hudson River fish (darker shading in Figure 8 represents higher estimated PCB concentrations in fish livers). The PCB 77 range for Hudson River fish fillets is from 0.03 to 0.2 ppm in fish fillets (McGroddy et al., 1997) (Figure 8a). PCB 77 concentrations estimated in Hudson River fish livers (again estimated to be twice the fillet concentration), range from 0.06 to 0.40 ppm (Figure 8b). Adverse effects on reproduction or development are summarized in Figure 8c. Concentrations of PCB 77 in Hudson River fish are within range of PCB 77 concentrations shown to adversely affect reproduction in adult fish in laboratory studies. It is notable therefore that exposure to other PCB congeners that act similarly to PCB 77 (i.e., PCB 81, 126, 169) would increase the risk of these effects if the effects are AhR mediated and if toxicity is additive or synergistic.

Figure 8

COMPARISON BETWEEN PCB CONGENER 77 CONCENTRATIONS IN HUDSON RIVER FISH AND TISSUE CONCENTRATIONS OF PCB CONGENER 77 SHOWN TO CAUSE REPRODUCTIVE AND DEVELOPMENTAL EFFECTS IN LABORATORY STUDIES

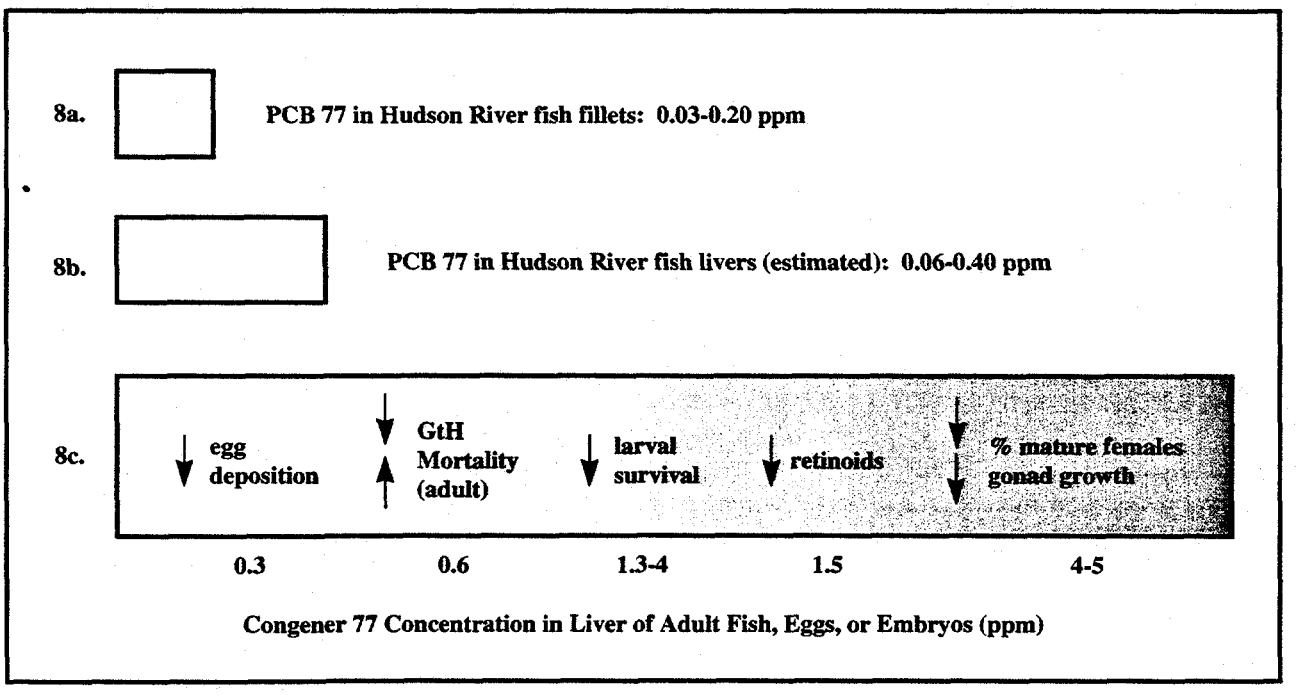


Table 8. Reproductive and Developmental Effects of Laboratory Exposure to PCB Congeners

Species	PCB Congener	Dose (ppm)	Tissue Concentration (ppm)[a]	Effects	References
White perch	77	0.1,1,5.0 (i.p.) Three times over three months	0.4-0.8 2.4-4.0 3.7-4.5 (maternal liver)	none ↓% larval survival 33-58%↓mature females, ↓GSI (male and female), ~50%↓ larval survival.	Monosson et al., 1994
Fundulus heteroclitus	77	1,10,100 (i.p.)	0.3 3 30 (estimated in liver)	48%↓Egg deposition, 77%↓Egg deposition ↓ pituitary GT 25% mortality 95%↓Egg deposition, ↓ pituitary gonadotropin, 50% mortality	Black 1995
Fundulus heteroclitus	77	0.2,0.6,2.0 (i.p.)	0.06 0.18 0.6 (estimated in liver)	none 28%↓Egg deposition 37%↓Egg deposition ↓ HSI, ↓ pituitary gonadotropin, 46% mortality	Black 1995
Striped bass	77	1 (i.p.) Three times over nine weeks	0.69-1.41 (in eggs)	No effect on estradiol No effect on testosterone No effect on vitellogenin	Monosson et al., 1996
Brook trout (adult)	77	5 ppm (i.p.)	1.5 (estimated in liver)	↓Growth rate, ↓Plasma retinal, ↓Intestinal retinoids, No effect on condition factor	Nsayibagira et al., 1995
Rainbow trout (juvenile)	77	5 (i.p.) assayed after 56 days	1.5 (estimated in liver)	↑ retinoic acid metabolism	Gilbert et al., 1995

Table 8. Reproductive and Developmental Effects of Laboratory Exposure to PCB Congeners (continued)

Species	PCB Congener	Dose (ppm)	Tissue Concentration (ppm)[a]	Effects	References
Lake trout	126	0.6, 6.3, 25 i..p. ,sampled from 1 to 30 weeks post-dosing	No tissue estimate	↓T_4 and T_3 after 3 weeks ↑T_4 and T_3 at 6 and 13 weeks	Brown et al., 1993
Lake trout	126	0,0.003, 0.01 or 0.03 as single oral dose, sampled 12 weeks post-dosing	0.002 0.007 and 0.02 (estimated in liver)	↓dihydroretinol in liver and kidney, ↓retinol palmitate and retinol in kidney ↓dihydroretinol, retinol and retinol palmitate in liver and kidney	Palace et al., 1997
Lake trout	126	Newly fertilized eggs exposed to 0.51 - 141 ng/L for 48 hr.	0.029 ug/g in eggs	LD50 (early life stage mortality)	Zabel et al., 1995
Carp	126	Newly fertilized eggs exposed to 10^{-11}-10^{-9} mole/L for 48 hours, sampled 2-9 days after single exposure	No tissue estimate 10^{-11} 10^{-10} and 10^{-9}	 no effects on embryo or larval survival, ACTH or cortisol , ↑α-MSH (pigment dispersing hormone) ↓ larval survival, ↑ ACTH, ↑Cortisol, ↑ α-MSH	Stouthart et al, 1998
Medaka	126	embryos exposed via water	0.046 ug/g 0.093 ug/g in embryos, estimated from reported bioabsorption of approximately 31%	34% embryo mortality 61.6% embryo mortality	Kim and Cooper, 1998
Lake trout	153	5ppb via water (3X a day for 15 days, static) for 17 days	7.6 in sac fry	↓% larval survival by ~89%	Broyles and Novick, 1979
Chinook salmon	153	5ppb via water (3X a day for 15 days, static) for 17 days	3.6 in sac fry	↓% larval survival by ~98%	Broyles and Novick, 1979

Table 8. Reproductive and Developmental Effects of Laboratory Exposure to PCB Congeners (continued)

Species	PCB Congener	Dose (ppm)	Tissue Concentration (ppm)[a]	Effects	References
Medaka	126, 81, 77 individually	embryos exposed via water, doses ranging from 0.3-715 pmol/ml in water	126: 0.18 81: 2.34 77: >250 ng/ml in water, embryo concentrations are unavailable	LC50 for embryo mortality	Harris et al., 1994
Rainbow trout	126, 77, 105, 118, 153 individually	embryos exposed via egg injection	126: 0.074 77: 1.3 105: >6.97 118: >6.97 153: >6.20	LD50 for early life stage mortality	Walker and Peterson, 1991
Rainbow trout	81, 169, 28, 118, 105, 156, 52, 170, 4, 128, 138 individually	embryos exposed via egg injection	81: 0.55 169: 7.11 28: >24.3 118: >57.4 105: >101.0 156: >115.0 52: >30.4 170: >41 4: >24.2 128: >119.0 138: >130.0	LD50 for early life stage mortality	Zabel et al., 1995

[a] Tissue concentrations, where reported, are in parts per million (ppm) wet weight. Where no concentrations are reported, they were estimated in the liver as described in the text. LD50 concentrations for egg injection studies are based on injected dose.

Table 9. Estimation of Effective Concentrations of PCB 77 in Fish from Laboratory Studies

Estimated or measured concentration of PCB 77 in liver (of adults), eggs or embryos (ppm)	Effects	Confidence	References
0.3 – 0.5 (estimated adult liver)	↓ egg deposition	M	Black 1995
1.0 (estimated adult liver)	↓ reduced pituitary gonadotropin, ↑ mortality in adults	M	Black 1995
1.3 (estimated eggs)	↓ larval survival	H	Walker and Peterson, 1991
2.4 - 4.0 (adult liver)	↓ larval survival	M	Monosson et al., 1994
2.5 (estimated adult liver)	↑ retinoic acid metabolism, ↓Growth rate, ↓Plasma retinol,↓Intestinal retinoids, ↔condition factor	M	Nsayibagira et al., 1995, Gilbert et al., 1995
3.7-4.5 (adult liver)	↓% mature females, ↓GSI (male and female)	M	Monosson et al., 1994

Field Studies: PCB Congeners

Reproductive and developmental effects associated with PCB congener exposure in the field are presented in Table 10. Similar to laboratory studies, there are few field studies relating effects to specific congeners. Information presented in this table include: site, observation, contaminant concentration range associated with effects, species, and references. As with the PCB mixture studies, all of these sites are contaminated with other compounds.

Table 10. Reproductive and Developmental Effects Associated with Exposure to Co-planar PCB Congeners in the Field

Site	Observation	Contaminants present at site	Concentration Range[a] ppm wet wt	Species	References
Riviere des Praries, Montreal	↑Embryonic malformations	Co-planar PCBs Other chemicals	0.03 (E)	White sucker	Branchaud, et al., 1995
Gulf of Bothnia	Yolk sac mortality (M74 syndrome)	77 126 169 and PCDFs Other chemicals	1-77 0.27-17 0-2.4 These values are in ppm lipid weight	Baltic salmon	Vourinen et al., 1997
Saint Lawrence River	↓Intestinal retinoids	77 and Co-planar PCBs Other chemicals	1.1 (E) 2.2 (E)	Lake sturgeon	Ndayibagira et al., 1995

[a] Concentrations associated with observation, concentration ranges or means are provided when no attempt was made to calculate an effect level. O=ovaries, L=liver, E=eggs.

To date, there are four studies that associate health effects to specific PCB congener exposure in the field. These studies report reduced embryo survival, reduced yolk sac survival and increased teratogenicity, as well as reduced intestinal retinoids (vitamin A, which may cause teratogenicity) in adult fish. All of these studies measure several different PCB congeners and acknowledge the presence of other contaminants at the field sites. It is therefore difficult to compare the findings from these field studies to the health effects caused by PCB 77 in the laboratory. There is some consistency between the finding of reduced retinoid concentrations following laboratory exposure to congener 77 and reduced retinoids measured in fish contaminated with co-planar PCBs. In addition, as reflected in Table 9, the observation of reduced survival in offspring associated with exposure to co-planar PCB congeners is consistent with reduced survival of larvae exposed to these congeners in the laboratory (Walker and Peterson, 1991), although the symptoms, when reported, are not the same. Walker and Peterson report the occurrence of blue-sac syndrome (yolk-sac edema and hemorrhaging) following laboratory exposure to PCBs, while Vourinen et al., (1997) reported an association between the occurrence of M74 (sac fry mortality characterized by initial hyperactivity, exopthalmia, and brain lesions) and PCBs. It is notable that M74 and other early life-stage mortality syndromes were recently associated with thiamine deficiency, although the cause of this deficiency is currently unknown (reviewed in Marcquenski and Brown, 1997).

Toxic Equivalency Quotients: PCB Congeners

In order to provide a direct comparison of exposure to AhR-active PCBs and toxicity in Hudson River fish, I calculate TEQs for fish analyzed by McGroddy et al. (1997). The key to an accurate assessment using this approach relies on the toxic equivalency factors (TEFs) developed for each congener. Unfortunately, several different TEFs exist for each individual congener based on an array of *in vitro* and *in vivo* studies in fish. Partially in response to the problem of multiple TEFs, the European Center of Environmental Health of the World Health Organization and the International Program on Chemical Safety (ECEH-WHO and IPCS) met to assess and validate a single set of consensus TEFs for mammals, birds and fish. The results of this meeting are summarized in Van den Berg et al. (1998).

The main objective of the ECEH-WHO/IPCS meeting was to develop consensus TEFs. TEFs were defined as "an *order of magnitude* estimate of the toxicity of a compound relative to [dioxin]," developed by consensus after considering all relevant *in vivo* and *in vitro* data. The relative potency (REP) value is defined as the potency of a compound relative to dioxin as determined by a single *in vitro* or *in vivo* study. Clearly the methods used to derive the TEFs and REPs are critically important for the development and use of the TEF approach as a whole. Based on the ECEH-WHO/IPCS report, *in vivo* methods were given the most weight, followed by *in vitro* techniques, with derivations based solely on structure activity relationships given the least weight. In fish, there are two studies that derive REPs using early life stage mortality in rainbow trout (Walker and Peterson, 1991; Zabel et al., 1995). The TEFs for fish recommended by the ECEH-WHO/IPCS are based mainly on these studies.

There are two main uncertainties associated with this approach. The first is the assumption that TEQs of individual congeners are additive (rather than antagonistic or synergistic). Several studies have addressed the issue of additivity and antagonism in fish (Walker et al., 1996; Newsted et al., 1995; Zabel et al., 1995a,b; Janz and Metcalf, 1991). A review of these studies and others concluded that "[i]t is unlikely that use of additivity in the TEF concept will result in a great deal of error in predicting the concentrations of TEQs due to synergism or antagonism" (Van den Berg et al., 1998). Another uncertainty is the question of interspecies differences in the relative potencies or sensitivity to AhR-active compounds or the effects caused by AhR-active compounds. This issue has also been addressed with regard to fish (Walker and Peterson, 1994; Elenon et al., 1997), and is discussed in detail in the section on interspecies differences (Section 5). Finally, it is important to note that this approach is useful for the assessment of AhR-active PCB congeners (and other AhR-active chemicals) only.

I use the TEFs suggested by the ECEH-WHO/ IPCS and chemistry data from McGroddy et al. (1997) to calculate TEQs for Hudson River fish. Based on occurrence and toxicity, the PCB congeners often considered of greatest importance in wild-caught fish are PCB 77, 81, 126, and 169 (Clarke et al., 1989; Harris et al., 1994). In a limited study of Hudson River fish, Hong and Bush (1990) reported detectable tissue concentrations of PCB 126, 77, and 81, but not 169. Thus, using the above criteria, the most important congeners in the Hudson are PCBs 77, 81 and

126. Of these three congeners, McGroddy et al. measured concentrations for PCB 77 and 126.[6] As a result, the TEQs for these fish are based on the concentrations of congeners 77 and 126 only. The TEFs (for early life stage mortality in rainbow trout) for congener 77 and 126 are 0.0001 and 0.005 respectively (Van den Berg, 1998).

TEQs for PCBs are calculated as follows: $TEQ = \sum([PCB_i] \times TEF_i)$. For example, the McGroddy et al. muscle tissue concentrations of PCBs 77 and 126 in a yellow perch caught at river mile 152 are 11.0 and 0.64 ng/g respectively. Thus the TEQ = (0.64*0.005) + (11*0.0001) = 0.0043 ng/g. This TEQ of 0.0043 ng/g, or 4.3 pg/g (parts per trillion) means that this fish was exposed to the toxic equivalent of 4.3 pg/g of dioxin. The TEQs for four different species of fish measured at five different sites along the Hudson (using data provided by McGroddy et al.) are listed in Appendix 1.

To provide some perspective on the TEQs for Hudson River fish, I compare these levels to dioxin LD50s (for early life stage mortality), lowest observed adverse effect levels (LOAEL) and no observed adverse effect levels (NOAEL) for different fish species published in Walker et al. (1991 and 1994) and Elenon et al. (1997). The LD50s and LOAELs/NOAELs from these studies are based on PCB concentrations in either eggs (wet weight) or in egg lipid (not adult muscle tissue). Since PCB distribution is highly influenced by lipids, I convert the TEQs from wet weight muscle tissue concentrations to TEQs based on lipids in the muscle (the information necessary to convert muscle concentrations to egg lipid concentrations is not available for the McGroddy et al. dataset) (Appendix 1 presents TEQ calculations for Hudson River fish). While this provides some degree of 'normalization,' there is still uncertainty with regard to comparisons across tissue type. The PCB distribution in the lipids of fish can vary with type of tissue, the type of lipid (Stow et al., 1997, Larrson et al., 1993) and the relative lipid concentration between tissues (Nimmi 1983).

The TEQs (muscle lipid) for Hudson River fish are shown in Figure 9. In the figure, these TEQs are compared to the dioxin NOAELs for two other fish species, the channel catfish and the lake trout, and the LOAEL and LD50 (or $LC_{egg}50$) for lake trout. The data used for these comparisons are published in Elenon et al. (1997) Walker et al. (1994) and Guiney et al. (1996). These species were selected for comparison because lake trout are one of the most sensitive species to dioxin toxicity[7] (at this life stage) and channel catfish are moderately sensitive. The values for the channel catfish and the lake trout were converted from pg TCDD /g egg to pg TCDD/g lipid, using the percent of lipid reported in the eggs for each species (4.8 percent and 8

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[6] Concentrations of PCB 126 were below detection limits for several fish. I estimated the PCB 126 concentration for these fish using one half the detection limit.

[7] A recent study indicates that the bull trout (*Salvelinus confluentus*), a species closely related to lake trout, is twice as sensitive to TCDD as lake trout (Lawonn et al., 1998). However, the study did not include the NOAEL or LC50.

percent for channel catfish and lake trout, respectively).[8] Figure 9 depicts TEQs in Hudson River fish (bars) compared to lake trout LD50 (dashed line at 725 pg/g egg lipid), the lake trout LOAEL (dashed line at 625 pg/g egg lipid) and the NOAEL for lake trout and channel catfish (dashed lines at 469 and 8020 pg/g egg lipid, respectively) (Walker et al., 1991 and 1994; Guiney et al., 1996; Elenon et al., 1997). This figure indicates that the majority of muscle-lipid TEQs for Hudson River fish (which range from 3 to 2250 pg/g) are within an order of magnitude of the NOAEL, LOAEL and LD50 for lake trout, a sensitive species, but are one to two orders of magnitude below the NOAEL for channel catfish, a moderately sensitive species. This suggests that the cumulative toxicity values for PCB congeners 77 and 126 in Hudson River fish are likely below concentrations associated with early life stage mortality.

As discussed earlier in this report, PCB distribution is influenced by tissue type in addition to lipid concentration. It would be most useful to compare TEQs based on egg-lipid concentrations. However, egg-lipid data were unavailable. Therefore, I estimate gonad-lipid concentrations from the muscle-lipid concentrations for striped bass using data from Ray et al. (1984). Ray et al. (1984) reported that the percent lipid in the gonads of striped bass from Annapolis Bay was 52 percent compared to 11 percent in muscle. I therefore use a factor of five to convert the TEQs based on muscle-lipid to TEQs based on gonad-lipid in striped bass.[9] The resulting estimated TEQs are shown in Figure 9 as open bars. Compared to the very low muscle-lipid TEQs, the gonad-lipid TEQs for striped bass from river mile 152 to river mile 27 exceed the lake trout NOAEL and LOAEL. These estimated TEQs, however, are still far below the NOAEL for channel catfish. These results raise the question of interspecies sensitivity to dioxin, which will be discussed further in Section 5 of this report.

Discussion and Conclusion: PCB Congeners

There are few studies on the health effects of PCB congeners in fish aside from studies used to develop toxic equivalency factors. However, there is some consistency among the laboratory studies, in that larval survival is reduced by non-ortho (or AhR-active) PCB congeners. There are also data suggesting that a negative correlation exists between non-ortho PCB congeners and larval survival in the field. The concentrations of congener 77 shown to affect egg deposition in laboratory studies are within the range of congener 77 concentrations that may occur in some of the most highly contaminated Hudson River fish (Figure 7). In addition there are other non-ortho PCB congeners (e.g., 126 and 81) present in Hudson River fish that are also AhR-active, and are even more potent than congener 77 in causing embryo mortality (Walker and Peterson, 1991; Van den Berg, in press). As discussed in the introduction to this report, the TEQ approach was designed to account for exposure to mixtures of PCB congeners such as PCB 126 and 77.

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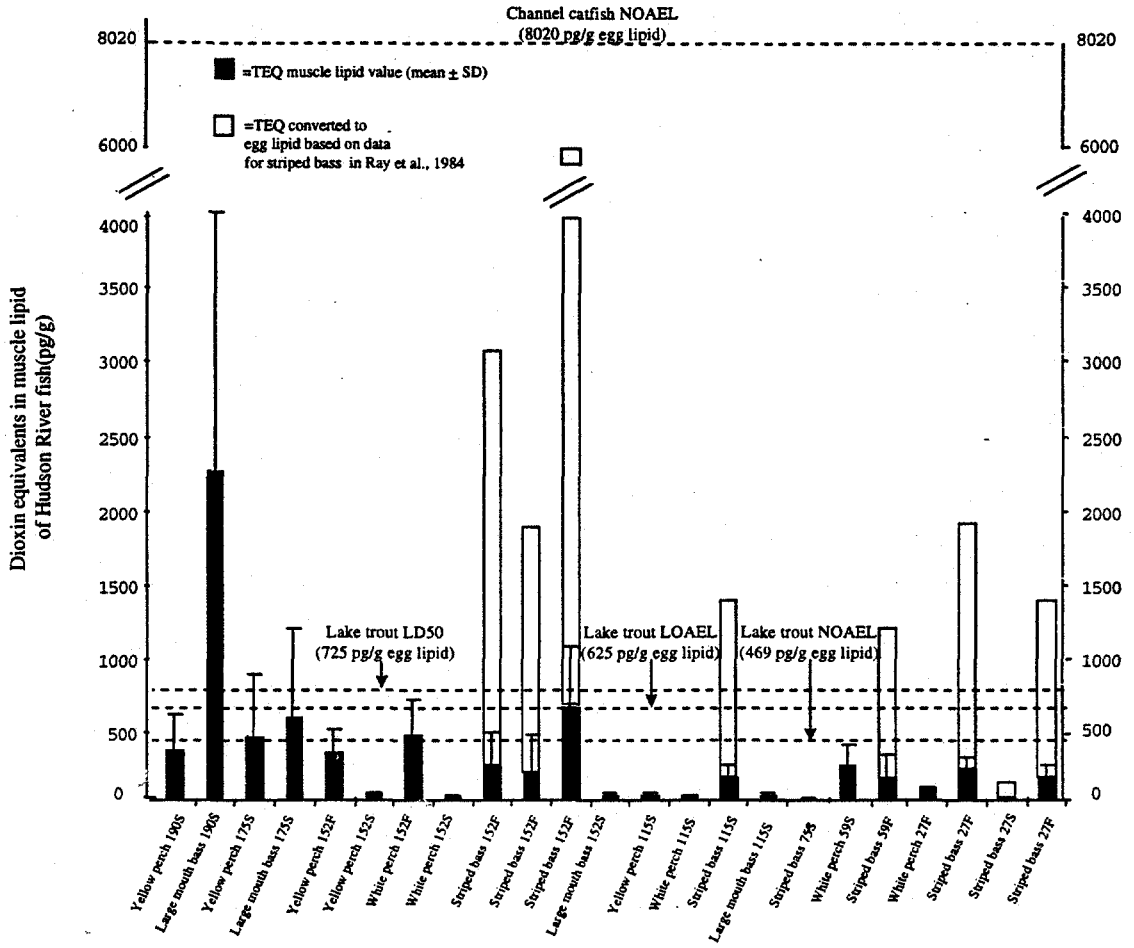
[8] The data used to make these conversions are provided in Tables 2 and 5 in the Elonen et al. (1998) study and in the text and Table 4 of Walker et al. (1994).

[9] The authors reported that PCB concentrations were ten-fold higher in the gonad compared to the muscle although lipid concentrations were only five-fold higher in the gonad.

Figure 9

DIOXIN TOXIC EQUIVALENTS (TEQs) CALCULATED FOR HUDSON RIVER FISH



Species, site, season (e.g., yellow perch 190S was sampled in spring from river mile 190)

Source: Data are from McGroddy et al. 1997, Elenon et al. 1997, Walker and Peterson, 1994 and Ray et al. 1984

The TEQs for four species of Hudson River fish, as calculated in this report, are within an order of magnitude of the NOAEL, LOAEL and LD50 for dioxin in the most sensitive species known to date, the lake trout. These TEQs are more than an order-of-magnitude below the NOAEL for channel catfish, a moderately sensitive species. However, the TEQs were based on concentrations of congener 77 and 126 only and did not include PCB 81, which may also be present in Hudson River fish.

In general the conclusions drawn from the TEQ approach and estimation of effective concentrations of congener 77 are in agreement. In both cases the PCB tissue concentrations for the most contaminated Hudson River fish are within range of potentially toxic concentrations of PCBs. The calculated TEQs may not include all toxic PCB congeners present in Hudson River fish, however, and are therefore incomplete.

5. Interspecies Differences: Comparison of Hudson River Fish Species with Laboratory and Field Test Species.

Background

One of the major uncertainties in this work is the potential for interspecies differences in response to PCBs. Differences in sensitivity to toxicants can be the result of subtle variations in different biochemical and physiological systems, or the result of a single mutation affecting an organism's ability to detoxify certain chemicals (e.g., some differences in mammalian AhR may be the result of a mutation in a single gene or amino acid). Without a basic understanding of the relationship between these processes and environmental contaminants, it is not possible to accurately assess or predict the relative sensitivity across species. This is the case for the majority of contaminants and fish species. Differences in sensitivity may also be influenced by prior exposure to certain classes of environmental contaminants. While this is not very relevant to understanding interspecies differences in fish used for bioassays (e.g., acute and chronic toxicity tests), it is relevant to laboratory and field studies of native species as discussed earlier in this report (e.g., acquired resistance). Interspecies differences are also influenced by the specific chemical of concern. One chemical, for example, may cause different effects at different concentrations across species, another may cause similar effects at similar concentrations, depending on its mechanism of action, or as demonstrated by dioxin (Elonen et al., 1998), cause similar effects across species but at very different concentrations.

Ecotoxicological risk assessment often requires extrapolation across species. As a result, several different techniques have been developed to address this issue: uncertainty factors (based on NOAELs and LOAELs of acute toxicity data), allometric scaling (based on the premise that there is a linear relationship between size and acute toxicity), no extrapolation (with the assumption that similar species will behave similarly to different chemicals), and physiologically based pharmacokinetic modeling (PBPK), a data intensive process that utilizes metabolic and toxicity data that is directly relevant to the species of concern (Hoff and Hennigson, 1998; Sample and Arenal, 1998; Calabrese and Baldwin, 1996; Sloof et al., 1986). In general, there is no agreement on the most appropriate methodology for extrapolation, aside from the PBPK, for which the required data are usually not available. Of these methods, the use of uncertainty factors or the assumption of similar responses in similar species have been applied to fish (Dwyer et al., 1995).

Calabrese and Baldwin (1996) suggest applying uncertainty factors that range from 10 to 65 for extrapolation across genus species to extrapolation across orders. These factors are based on binary comparisons of acute toxicity data across species for as many as 500 different chemicals and represent the mean uncertainty. It must be stressed that these factors are based on acute toxicity data, rather than chronic toxicity data. Although it is suggested that these uncertainty factors can be applied to chronic exposures (Calabrese and Baldwin, 1996), given the often more complex nature of chronic toxicity (e.g., absorption, distribution, and metabolism may all be more important in chronic events than in acute events) the appropriateness of using acute toxicity data for predicting chronic toxicity is currently unknown for the majority of chemicals in fish. It is also notable that in some cases the binary comparisons across orders such

as Salmoniformes (used for many laboratory and field studies) vs Perciformes (which include four Hudson River species) can result in a response interval (used to calculate the uncertainty factor) that is more similar to the response interval associated with more closely related species (i.e., species belonging to the same family or genus). Thus, application of an uncertainty factor of 65 may result in overestimation of "effective concentrations" if extrapolating across these two orders.

The assumption that similar species will behave similarly to chemicals may be valid in general for very closely related species. This premise was tested by the EPA when evaluating the use of surrogate species to assess contaminant risk to endangered species (Dwyer et al., 1995). The results of that study suggest that, in general, the species responded similarly to acute chemical exposures, although for 30 percent of the comparisons, the surrogate or test species was less sensitive to toxicity compared to the endangered or listed species.

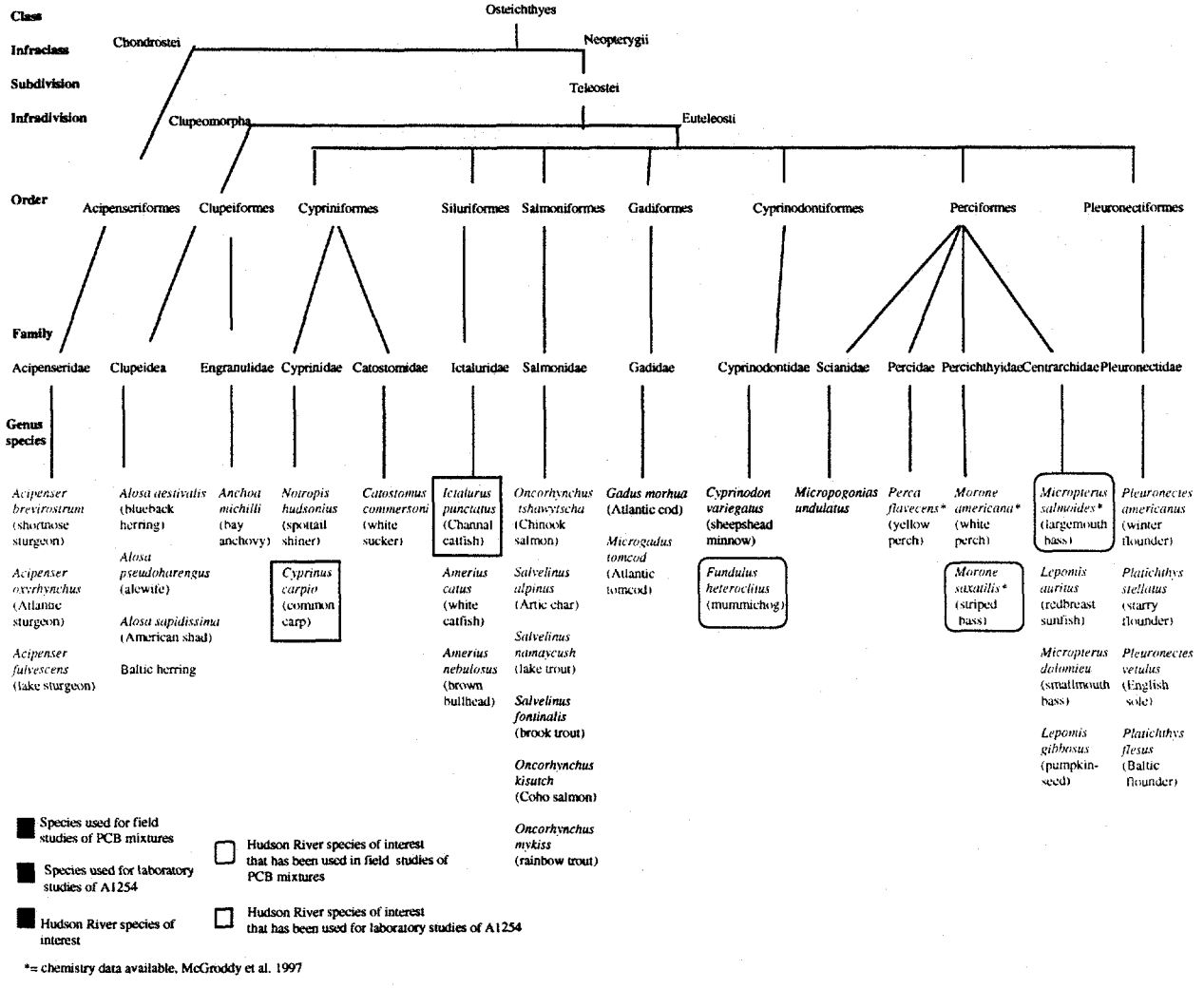
A1254, PCB Mixtures and Hudson River Fish

Since both of the methods discussed above involve consideration of genetic relatedness among species, Figures 10 and 11 were developed to compare fish species used for either laboratory studies with A1254 and PCB mixtures in the field (Figure 10), or species used for dioxin studies (Figure 11) and "important" Hudson River species. Important is defined here as ecologically or commercially important, or endangered.

All of the fish species used for the laboratory studies cited in Table 2 (black typeface), field studies cited in Tables 7 and 10 (red typeface), and the "important" Hudson River species (in green typeface) are summarized in Figure 10. The selection of Hudson River species was based on those used for chemical analysis by McGroddy et al. (1997), and information provided by John Waldman of the Hudson River Foundation (personal communication). Where there was an overlap (i.e., a Hudson River species was used for either a laboratory or field study), the green typeface is surrounded by either a black box (for laboratory study) or a red box (for a field study). An asterisk indicates that there is current chemistry data for this species (McGroddy et al., 1997). For example largemouth bass are important to the Hudson, they were used in a field study of PCBs (Garcia et al., 1997), and there is chemistry data available for large mouth bass from the Hudson River. In general, Figure 10 shows there is little overlap between Hudson River species and those species used for laboratory or field studies.

Figure 10

GENETIC HIERARCHY OF SPECIES USED FOR STUDIES OF REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF A1254 IN THE LABORATORY, PCB MIXTURES IN THE FIELD, AND HUDSON RIVER SPECIES OF INTEREST



The relationships among all the species in Figure 10 are shown using a hierarchical classification. This system is based on evolutionary relatedness, however, unlike a true phylogenetic tree, this figure does not include geologic time. This system of classification provides a general overview of interspecies relatedness. As shown in Figure 10, most species belong to the subdivision Teleostei, except for the sturgeons. The majority of species also belong to the infradivision Euteleosti, except for herring, shad, anchovy and alewife. Within Euteleosti, there are seven different orders, leading to 11 different families. I did not separate fish by genus (e.g., Salvelinus and Oncorhynchus are both listed directly under Salmonidae). Only two Hudson River species were used for laboratory studies of A1254 (common carp and channel catfish), and three have been used for field studies of PCBs (mummichog, striped bass and largemouth bass). However, several Hudson River species are closely related (within the same genus) to species used for either laboratory or field studies.

Based on the above discussion and the data presented in this report, it is not currently possible to estimate effective concentrations of PCBs for individual species residing in the Hudson River. However, the array of species shown in Figure 10, many of which demonstrated reproductive or developmental toxicity following laboratory exposure to PCB concentrations that are (or are estimated to be) within an order of magnitude, include species belonging to six different orders of fish. In addition, species for which reproductive and developmental effects have been associated with PCB exposure in the field span two classes and six orders. These data suggest that PCBs cause reproductive and developmental effects to many different and distantly related species of fish, and that effective concentrations that begin at 25 ppm in adult liver and 5 ppm in larvae may apply to at least some species of Hudson River fish.

TEQs and Hudson River Fish

Figures 11 and 12 provide some perspective on the range of sensitivity to dioxin, species relatedness, and species in the Hudson River. Similar to Figure 10, relatedness among species is shown using a hierarchical classification Species important to the Hudson River are shown in green typeface, and species with known LC50s (based on early life stage mortality) for dioxin that are not Hudson River species are shown in black typeface. In Figure 11, sensitivity to dioxin is demonstrated by boxes around the species, with red, purple and blue indicating high (LC50< 500 pg/g egg), moderate (LC50 500-1100 pg/g egg) and low sensitivity (LC50 > 1100 pg/g egg). In Figure 12, the LD50s for juvenile fish are listed below each species.

Figure 11 indicates little overlap between the species with known LC50s for dioxin and Hudson River species. The three most sensitive species all belong to the Salmonidae family. The remaining species for which there are LC50s are distributed among four orders and six families. These include two Hudson River species, white sucker (a least sensitive species) and channel catfish (a moderately sensitive species). There is no information on the Perciformes, which include several Hudson River species, and the four species for which I calculate TEQs.

Figure 11

GENETIC HIERARCHY OF SPECIES USED FOR EARLY LIFE STAGE TOXICITY TESTS WITH DIOXIN AND HUDSON RIVER SPECIES OF INTEREST

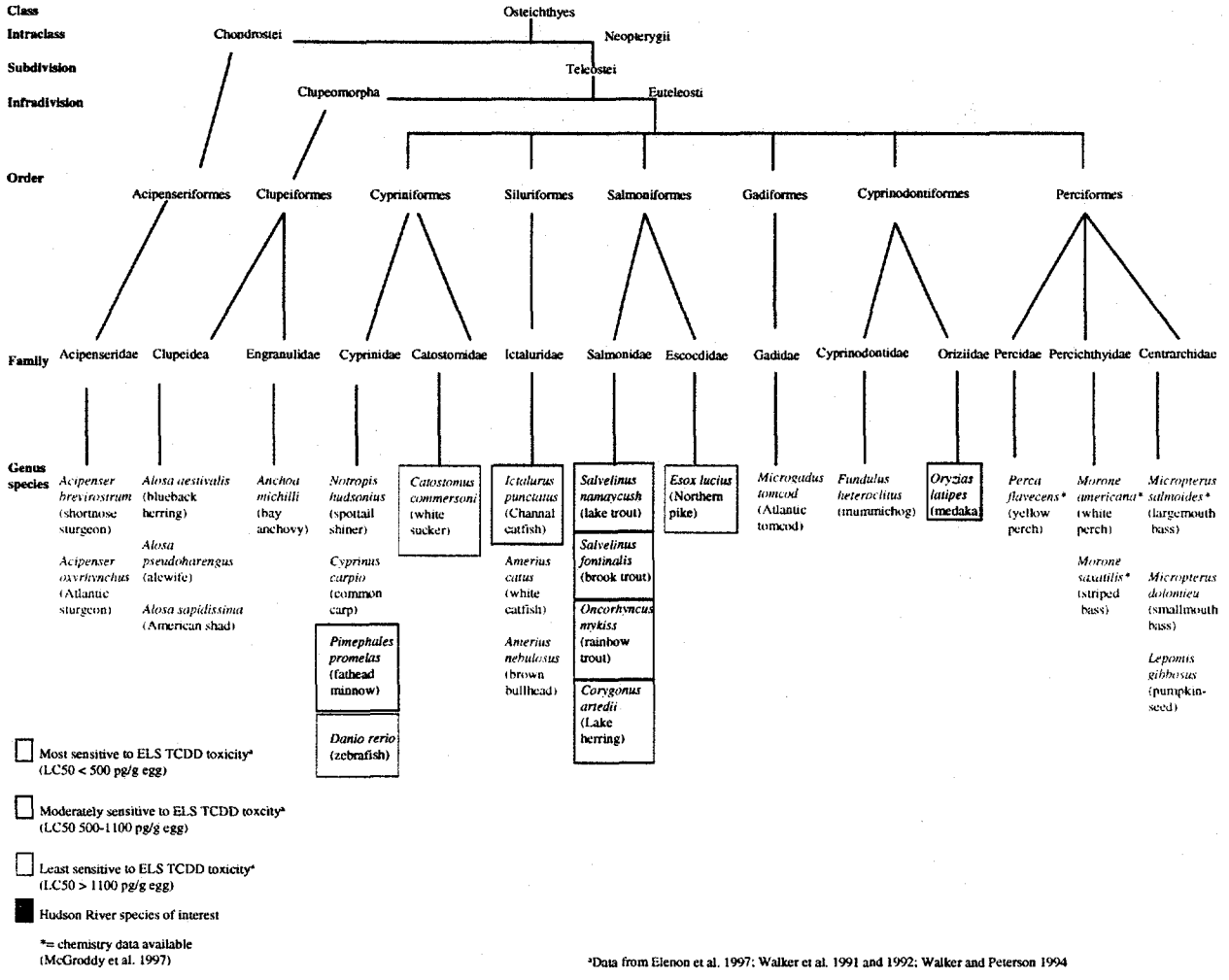
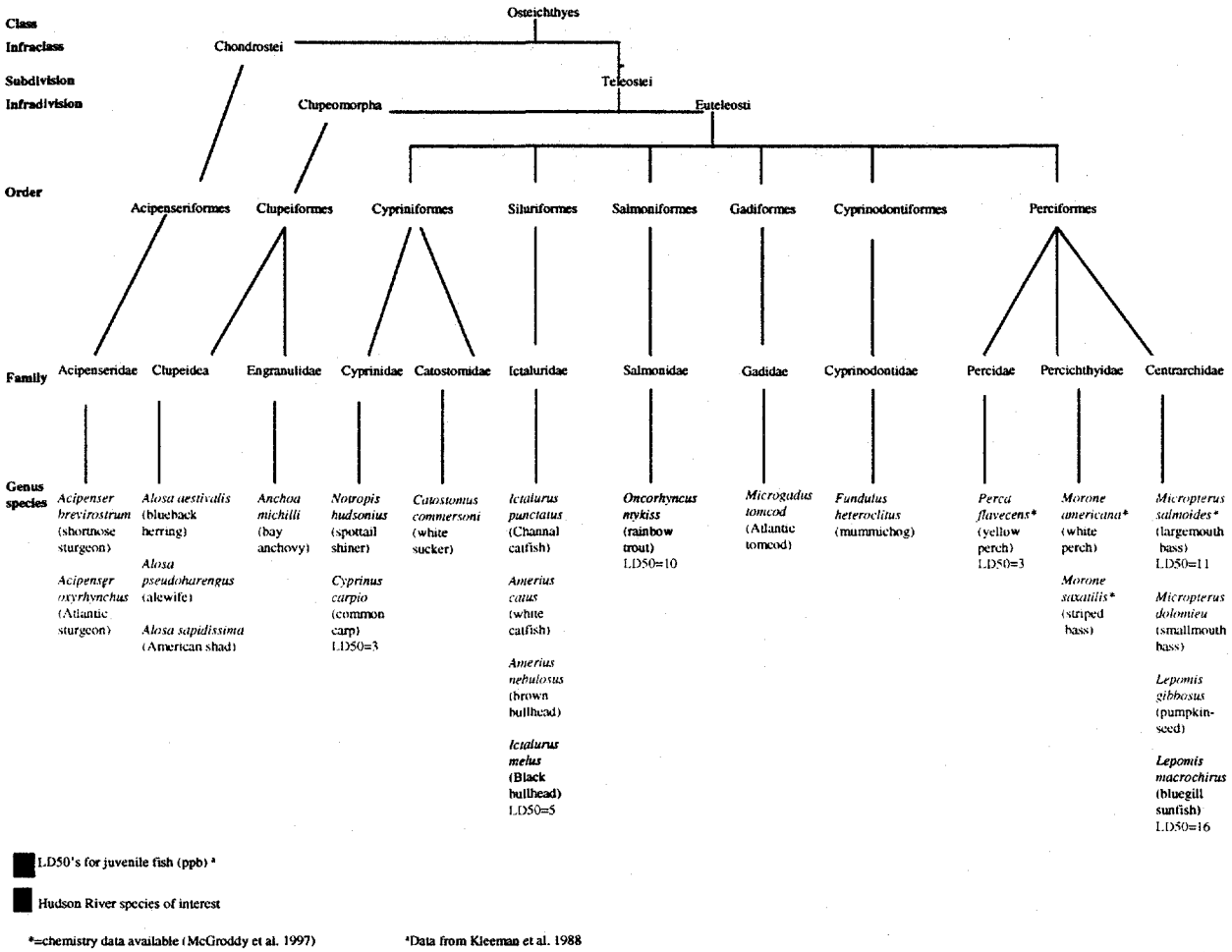


Figure 12 shows that the acute toxicity of dioxin to juvenile fish is known for three species of Hudson River fish (common carp, yellow perch and largemouth bass). It is interesting to note that the very large interspecies differences reported for early life stage mortality are not apparent at the juvenile stage for the species tested, with LD50s ranging from 3-16 ppb (Kleeman et al., 1988). In addition, the juvenile fish are much less sensitive to dioxin toxicity than the larvae.

Figure 12

GENETIC HIERARCHY OF SPECIES USED FOR TOXICITY TESTS WITH DIOXIN (AT THE JUVENILE STAGE) AND HUDSON RIVER SPECIES OF INTEREST



Considering the large interspecies differences in early life stage toxicity, and the incomplete data set for PCB congeners, it is currently not possible to evaluate the risk to Hudson River fish larvae from exposure to co-planar PCBs using the TEQ method.

6. Effects of PCBs on Immune Function

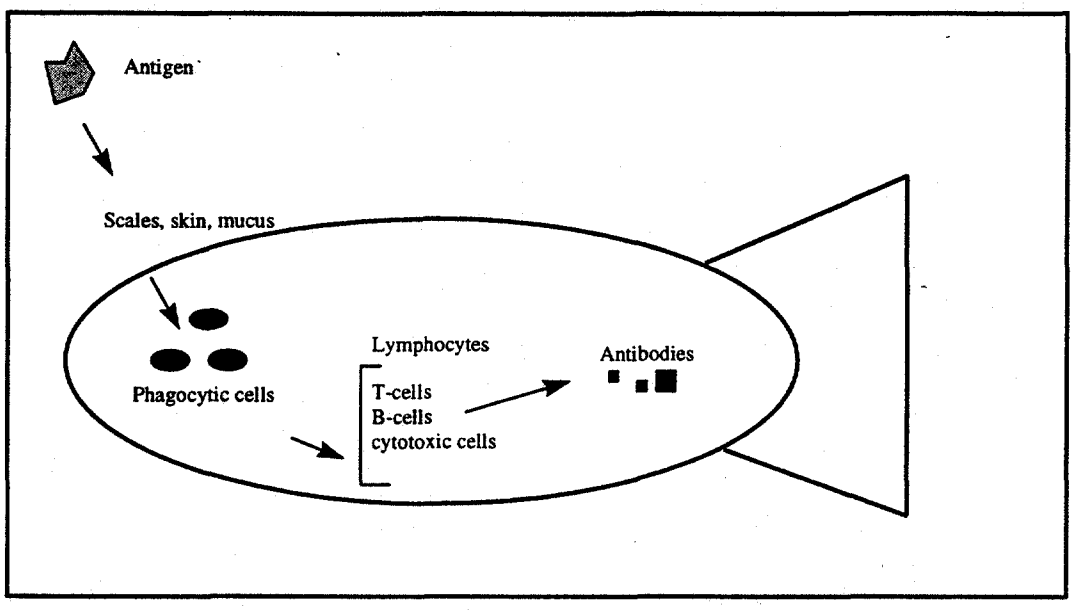
Background

The immune system in fish is comparable to the immune system in other vertebrates, including humans. Several reviews describe the immune system in fish, and effects of pollutants on the immune system in fish (Dunier et al., 1993; Anderson 1990; Kennedy-Stoskopf, 1993; Zeeman and Brindley, 1981). Fish have both nonspecific and specific defense systems (Figure

13). The nonspecific defense system includes physical barriers such as scales, skin, and mucus, as well as phagocytic cells which may respond to infiltration by foreign organisms by engulfing them.

Figure 13

THE IMMUNE SYSTEM IN FISH
(Adapted from Anderson 1990)



The specific defense system in fish, like mammals, is based on cellular and humoral response. In fish, lymphoid tissue (B and T lymphocytes) is present in the thymus, spleen, and kidney. There are many different roles for T-cells including enhancement or suppression of the immune response, or direct destruction of foreign organisms. Humoral immunity results from the production of antibodies by B-cells following a complex interaction between other components of the immune system, which may include T-cells. The humoral response can be a primary response or a secondary response. Production of antibodies following a first time exposure to an antigen is the primary response, the secondary response occurs when a second exposure to the same antigen occurs. The secondary response is sometimes referred to as memory, and is measured as a larger production of antibodies in contrast to the primary response. The secondary response is assessed by first priming the animals with a selected antigen, and after several weeks, reexposing the animals to the same antigen. If there is memory, the secondary antibody response should be much greater than the primary response.

Antigens can generally be categorized as T-cell dependent or T-cell independent. A T-independent antigen interacts directly with the B-cells, whereas the T-dependent antigen requires processing by the T-cell, and then presentation to the B-cell. An example of a T-independent antigen often used in laboratory studies is trinitrophenyl-lippopolysaccharide (TNP-LPS), whereas TNP-keyhole limpet hemocyanin (TNP-KLH) is a T-dependent antigen. Whole organisms (such as those likely to be encountered in the wild) are likely to elicit a combination of T-dependent and T-independent responses, since the whole organism may first interact and be digested by T-cells, releasing both kinds of antigens.

Although there is a large amount of research on the effects of contaminants on the immune system in fish (Dunier et al., 1993; Zeeman and Brindley, 1981), there are very few studies detailing the effects of PCBs on immune function. As a result, I was not able to develop effective concentrations for immunotoxicity.

Results: Immune Function

The results of the literature search for effects of PCBs on immune function are presented in Table 11. Five of these studies examine A1254, two examine Clophen A50 and one examines PCB congener 126. There are some common findings among these studies. Specifically, long-term exposure (2 months to a year) to A1254 at concentrations of approximately 80 ppm in the whole body causes a reduction of lymphoid tissue (white pulp) in the spleen (Hendricks et al,. 1977; Nestel and Budd, 1974). In addition, two studies report that PCBs reduce the amount of antibodies produced following exposure to a T-cell independent antigen (Thuvander and Carlstein, 1991; Arkoosh et al., 1994). Thuvander and Carlstein (1991) report that whole body concentrations of 40 ppm Clophen A50 result in reduced primary antibody response in fish exposed via the diet. Similarly, Arkoosh et al. (1994) report that A1254 exposure reduces both the primary and secondary antibody response. I estimate tissue concentrations in this study to be approximately 54 ppm in the whole body. Given the similarity between A1254 and Clophen A50, these studies are in agreement. Two studies report that similar (or higher) concentrations of PCBs (both A1254 and Clophen A50) are not effective in reducing antibody production when fish are challenged with a T-cell dependent antigen, suggesting differential responses to A1254 between the subpopulations of immune cells (Thuvander et al., 1993; Cleland et al., 1988).

Table 11. Effects of PCBs on Immune Function

Species	PCB	Dose (ppm)	Tissue Concentration[a]	General Effects	Specific Immunity	Nonspecific Immunity	References
Rainbow trout	Clophen A50	5 (i.p.)	10 in whole body (est 10 in liver)	No effect on spleen, head-kidney, thymus for all doses	None	No effect on leukocytes	Thuvander and Carlstein., 1991
		50 (i.p.)	30-40 in whole body (est 40 in liver)		Trend towards reduced antibody response to T independent antigen	No effect on leukocytes	
		500 (diet)	40 in whole body (est 40 in liver)		Reduced antibody response to T independent antigen (by ~50%)	No effect on leukocytes	
		Ten week exposure					
Rainbow trout	Clophen A50	40	140 (est 40 in liver)	None	None	Not tested	Thuvander et al., 1993
		80	296 in lipid (est 80 in liver)	Depletion and degeneration of thymus and spleen	Increased responsiveness of splenocytes to B and T cell mitogens following immunisation with a T-dependent antigen		
		I.p. nine week exposure					
Rainbow trout	A1254	5	Unable to estimate		Not tested[c]	Not tested[c]	Spitsbergen et al., 1988
		50-500 in diet for 30 days		Depletion of lymphoid tissue in spleen			
Rainbow trout	A1254	3	Unable to estimate	None	No effect of any dose on humoral response to a T-dependent antigen	Not tested	Cleland et al., 1988
		30		None			
		300		Weight loss, increased liver somatic index			
		In diet, twelve month exposure					

Table 11. Effects of PCBs on Immune Function (continued)

Species	PCB	Dose (ppm)	Tissue Concentration[a]	General Effects	Specific Immunity	Nonspecific Immunity	References
Chinook salmon	A1254	54 I.p. for ten weeks	54 est in liver	No difference in condition factor or in histology of lymph tissues	Suppression of immunological memory in splenic and anterior kidney tissues (e.g., secondary response) Primary response suppressed to T-cell independent antigen	Not tested	Arkoosh et al., 1994
Channel catfish	PCB 126	0.01 0.1 1.0 (i.p.)	(0.01 est. in liver) (0.1 est. in liver) (1.0 est. in liver)	No change in liver somatic index for all doses	Increase in number of specific antibody secreting cells No effect No effect	No effect Reduced head kidney phagocytosis after 7 days Reduced head kidney phagocytosis after 3 days	Rice and Schlenk 1995
Rainbow trout	A1254	100 in diet for 12 months	75.2 whole fish[b]	Reduced white pulp in spleen	Not tested	Not tested	Hendricks et al,. 1977
Rainbow Trout	A1254	1 10 100 in diet for 330 days	1.3 2.3 81.1 whole body	 reduced white pulp in spleen reduced white pulp in spleen	Not tested	Not tested	Nestal and Budd, 1974

[a] Tissue concentrations, where reported, are in parts per million (ppm) wet weight. Where no concentrations are reported, they were estimated in the liver (est. liver) as described in the text.

[b] Estimated from PCB concentrations per whole fish, and weight of whole fish at end of experiment.

[c] Authors tested resistance to an infectious virus. Mortality caused by virus exposure was not significantly affected by PCB exposure.

Recent *in vitro* assays indicate that the structure activity relationship for AhR-active PCBs can be applied to immunotoxicity in fish (Noguchi et al., 1996). One study tested the effects of non-ortho congener PCB126 *in vivo* (Rice and Schlenk, 1995). Exposure to this congener reduced the nonspecific immune response (phagocytosis in the anterior kidney) but did not affect specific immunity to *Eswardsiella ictaluri*, which is a natural pathogen of catfish (Rice and Schlenk, 1995). Since exposure was to a whole organism, this form of exposure was likely more similar to an exposure to a T-dependent antigen rather than to a T-independent antigen (C. Rice, pers. comm).

There are few field studies relating exposure to PCBs in the field to immunosuppression. Arkoosh et al. (1997) reports reduced immunologic memory in leukocytes from fish collected from a site contaminated with PCBs and other chemicals, suggesting that immune function can be compromised in the field.

A1254 concentrations could be estimated for the three studies that examined the effects of A1254 on immune function (Table 12). These studies suggest that concentrations of A1254 above 50 ppm can suppress the humoral response, and exposure to higher concentrations may result in reduced white pulp in the spleen.

Table 12. Summary of the Effects of A1254 on the Immune System

Concentration of A1254 in liver (ppm)	Effects	References
2.3-81[a]	Reduced white pulp in spleen	Nestel and Budd 1974
54[b]	Suppression of primary and secondary response to a T-independent antigen	Arkoosh et al., 1994
75[a]	Reduced white pulp in spleen	Hendricks et al., 1977

a. A1254 concentration based on whole body concentrations.
b. A1254 concentration estimated in liver.

Discussion and Conclusion: Immune Function

Compared to the body of work on reproduction and development, there are very few cstudies on the immunotoxicity of PCBs in fish. PCB mixtures appear to suppress T-independent antibody response, but not the T-dependent response. However, as noted earlier, exposure to "pure" T-dependent or T-independent antigens commonly used in laboratory studies may not mimic conditions in the field where fish must respond to whole organisms. In addition, PCB mixtures appear to cause splenic degeneration.

The relationship between these effects and disease susceptibility is unclear. One study (Arkoosh et al. 1991) reports suppressed secondary immune response and increased disease susceptibility in fish from a contaminated site. Thus, I am unable to assess the potential impact of PCBs on immune function in fish. An accurate assessment of the relationship between PCB exposure and immune function will require further laboratory and field investigation.

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Appendix 1. TEQ Calculations for Hudson River Fish

This appendix presents the calculation of TEQs for Hudson River fish. In addition, this appendix includes calculation of the means and standard deviations for TEQs used in Figure 9. This worksheet is a modified version of the worksheet provided in McGroddy et al., 1997. The columns of the table are described below:

SAMPLE:	McGroddy et al. sample number for each fish
RMILE:	River mile of sample
SPECIES:	Species (YP is yellow perch, LMB is large mouth bass, STB is striped bass and WP is white perch).
SEASON:	Season of sampling
SEX:	Sex (when determined)
%LIPID:	percent lipid
PCB077:	PCB congener 77, in ppb
PCB126:	PCB congener 126 as used for calculation, in ppb
PCB126:	PCB congener 126 as listed by McGroddy et al., a "U" indicates detection limit (ppb)
TEQ fillet:	TEQ calculation for the fillet. The TEF for PCB 77=0.0001; and the TEF for PCB 126=0.005. TEQ fillet = (G(N)*0.0001 + H(N)*0.005)*1000; where samples are below detection limit for PCB 126 column H is H/2 (i.e., half the detection limit is used in the calculation).
lipid TEQ:	TEQ calculation for lipid TEQ lipid = (((G(N)*0.0001 + H(N)*0.005)*1000))/(F(N)/100)), where samples are below detection limit for PCB 126 column H is H/2 (i.e., half the detection limit is used in the calculation).

The averages and standard deviations used in Figure 9 are included at the bottom of this worksheet. The mean (AVG TEQ) and standard deviation (StdTEQ) fillets are listed by fish (YP, STB, WP, LMB) site (RM27-190) and season (S=spring, F=fall). The mean TEQ for lipid (AVG TEQL) and standard deviations for lipid (StdTEQL) are also included for each species and site in this worksheet.

TEQs calculated from McGroddy et al., (1997) Study of Hudson River Fish 1995 Data compiled by EVS Consultants, 1996/97										
SAMPLE	RMILE	SPECIES	SEASON	SEX	%LIPID	PCB077	PCB126	PCB126	TEQ fillet	lipid TEQ
F284070	190	YP	SPR		4.8	23.00	1.50	1.50000 U	6.05	126.04
F284075	190	YP	SPR		2.6	16.00	0.75	0.75000	5.35	205.77
F284076	190	YP	SPR		2.1	9.20	1.00	1.00000 U	3.42	162.86
F284077	190	YP	SPR		3.5	78.00	2.03	2.03040	17.95	512.91
F284078	190	YP	SPR		2.5	84.00	4.00	4.00000 U	18.40	736.00
F284079	190	YP	SPR		3.6	23.00	2.50	2.50000 U	8.55	237.50
F309710R1	190	LMB	SPR	M	2.9	200.00	5.70	5.70000	48.50	1672.41
F309711R1	190	LMB	SPR	M	0.2	26.00	1.30	1.30000	9.10	4550.00
F309712R1	190	LMB	SPR	M	0.3	33.00	0.00	0.00000 U	3.30	1100.00
F309713R1	190	LMB	SPR	M	0.5	72.00	2.00	2.00000	17.20	3440.00
F309714R1	190	LMB	SPR	M	0.4	11.00	0.00	0.00000 U	1.10	275.00
F283146	175	YP	SPR		3	11.00	0.64	0.63630	4.28	142.72
F284071	175	YP	SPR		1.8	2.60	4.00	4.00000 U	10.26	570.00
F284072	175	YP	SPR		3.1	9.40	1.00	1.00000 U	3.44	110.97
F284073	175	YP	SPR		2.[illegible]	9.50	1.00	1.00000 U	3.45	138.00
F284074	175	YP	SPR		0.7	[illegible].70	3.00	3.00000 U	7.67	1095.71
F309700R1	175	LMB	SPR	M	0.1	[illegible]50	0.00	0.00000 U	0.35	350.00
F309701R1	175	LMB	SPR	M	0.3	14.00	0.00	0.00000 U	1.40	466.67
F309702R1	175	LMB	SPR	M	0.3	5.40	0.00	0.00000 U	0.54	180.00
F309703R1	175	LMB	SPR	M	0.3	5.70	0.00	0.00000 U	0.57	190.00
F309704R1	175	LMB	SPR	M	0.1	16.00	0.00	0.00000 U	1.60	1600.00
F282158	152	YP	FALL		4.2	8.20	1.00	1.00000 U	3.32	79.05
F282159	152	YP	FALL		3.5	9.90	5.00	5.00000 U	13.49	385.43
F282168	152	YP	FALL		2.7	8.40	4.00	4.00000 U	10.84	401.48
F282169	152	YP	FALL		4.8	12.00	5.00	5.00000 U	13.70	285.42
F282170	152	YP	FALL		3.2	8.90	5.00	5.00000 U	13.39	418.44
F283142	152	YP	SPR		1.1	1.70	0.00	0.00000 U	0.17	15.45
F283143	152	YP	SPR		0.7	2.50	0.00	0.00000 U	0.25	35.71
F283144	152	YP	SPR		5	8.10	0.44	0.44000	3.01	38.20
F283145	152	YP	SPR		1.6	2.50	0.00	0.00000 U	0.25	15.63
F282160	152	WP	FALL		3.7	11.00	5.00	5.00000 U	13.60	367.57
F282171	152	WP	FALL		3.4	12.00	5.00	5.00000 U	13.70	402.94
F282172	152	WP	FALL		4.8	8.70	5.00	5.00000 U	13.37	278.54
F282173	152	WP	FALL		2.7	3.40	2.50	2.50000 U	6.59	244.07
F282174	152	WP	FALL		2.3	12.00	7.30	7.30110	37.71	845.77
F283137	152	WP	SPR		3.9	7.10	0.00	0.00000 U	0.71	18.21
F283138	152	WP	SPR		2.7	5.00	0.00	0.00000 U	0.50	18.52
F283139	152	WP	SPR		2.8	2.90	0.00	0.00000 U	0.29	10.36
F283140	152	WP	SPR		5.6	6.90	00000 J	.00000 UJ		
F283141	152	WP	SPR		4.4	4.30	0.00	0.00000 U	0.43	9.77
F284087	152	STB	FALL		2.8	3.10	2.50	2.50000 U	6.56	234.29
F284088	152	STB	FALL		0.6	1.60	1.00	1.00000 U	2.66	443.33
F284089	152	STB	FALL		0.9	1.50	1.50	1.50000 U	3.90	433.33
F284134	152	STB	FALL		0.6	0.96	0.00	0.00000 U	0.10	16.00
F284135	152	STB	FALL		0.6	1.10	0.00	0.00000 U	0.11	18.33
F293913	152	STB	SPR	M	3	5.50	0.00	0.00000 U	0.55	18.33
F293914	152	STB	SPR	M	1.9	5.10	4.50	4.50000	23.01	618.95
F293915	152	STB	SPR	M	3	5.00	0.00	0.00000 U	0.50	16.67
F293916	152	STB	SPR	M	4.4	7.10	0.66	0.66000	4.01	91.14
F293917	152	STB	SPR	M	3.8	10.82	1.45	1.44700	8.32	123.67

TEQs calculated from McGroddy et al., (1997) Study of Hudson River Fish 1995 Data compiled by EVS Consultants, 1996/97										
SAMPLE	RMILE	SPECIES	SEASON	SEX	%LIPID	PCB077	PCB126	PCB126	TEQ fillet	lipid TEQ
F300490	152	STB	FALL	M	4.2	1.60	2.50	2.50000 U	6.41	152.62
F300491	152	STB	FALL	M	2.6	5.00	5.00	5.00000 U	13.00	500.00
F300492	152	STB	FALL	M	0.3	1.40	1.50	1.50000 U	3.89	1296.67
F300493	152	STB	FALL	M	2.1	6.60	5.00	5.00000 U	13.16	626.67
F300494	152	STB	FALL	M	1.4	5.80	2.50	2.50000 U	6.83	487.86
F309705R1	152	LMB	SPR	M	0.2	0.00	0.00	0.00000 U	0.00	0.00
F309706R1	152	LMB	SPR	M	1.2	3.20	0.00	0.00000 U	0.32	26.67
F309707R1	152	LMB	SPR	M	0.6	1.50	0.00	0.00000 U	0.15	25.00
F309708R1	152	LMB	SPR	M	1.1	1.40	0.00	0.00000 U	0.14	12.73
F309709R1	152	LMB	SPR	M	0.1	0.00	0.00	0.00000 U	0.00	0.00
F283127	115	YP	SPR		1.8	4.00	0.00	0.00000 U	0.40	22.22
F283128	115	YP	SPR		0.9	0.58	0.00	0.00000 U	0.06	6.44
F283129	115	YP	SPR		0.4	1.50	0.00	0.00000 U	0.15	37.50
F283130	115	YP	SPR		2.8	5.00	0.00	0.00000 U	0.50	17.86
F283131	115	YP	SPR		0.6	1.00	00000 J	.00000 UJ		
F283132	115	WP	SPR		3.1	2.10	50000 J	.50000 UJ		
F283133	115	WP	SPR		3.3	2.20	0.00	0.00000 U	0.22	6.67
F283134	115	WP	SPR		4.4	1.50	50000 J	.50000 UJ		
F283135	115	WP	SPR		2	1.40	0.00	0.00000 U	0.14	7.00
F283136R1	115	WP	SPR		2.1	5.20	0.00	0.00000 U	0.52	24.76
F300480	115	STB	SPR	F	2.8	3.20	2.00	2.00000	10.32	190.00
F300481	115	STB	SPR	M	0.8	0.60	1.00	1.00000 U	2.56	320.00
F300482	115	STB	SPR	M	1.4	1.90	1.00	1.00000 U	2.69	192.14
F300483	115	STB	SPR	F	4	1.00	1.00	1.00000 U	2.60	65.00
F300484	115	STB	SPR	F	3.5	1.00	1.00	1.00000 U	2.60	74.29
F300485	115	STB	SPR	M	6.3	1.40	1.00	1.00000 U	2.64	41.90
F300486	115	STB	SPR	F	2.1	2.10	1.50	1.50000 U	3.96	188.57
F300487	115	STB	SPR	M	4.3	1.00	1.00	1.00000 U	2.60	60.47
F300488	115	STB	SPR	F	2.4	0.85	1.50	1.50000 U	3.84	159.79
F300489	115	STB	SPR	M	0.1	1.30	0.00	0.00000 U	0.13	130.00
F309695R1	115	LMB	SPR	M	0.5	1.40	0.00	0.00000 U	0.14	28.00
F309696R1	115	LMB	SPR	M	1.8	3.90	0.00	0.00000 U	0.39	21.67
F309697R1	115	LMB	SPR	M	1	1.80	0.00	0.00000 U	0.18	18.00
F309698R1	115	LMB	SPR	M	1.9	6.60	0.00	0.00000 U	0.66	34.74
F309699R1	115	LMB	SPR	M	0.9	2.30	0.00	0.00000 U	0.23	25.56
F293910	75	STB	SPR	M	3.6	2.60	0.00	0.00000 U	0.26	7.22
F293918	75	STB	SPR	M	3.5	1.60	0.00	0.00000 U	0.16	4.57
F293919	75	STB	SPR	M	3.5	2.50	0.00	0.00000 U	0.25	7.14
F293920	75	STB	SPR	M	9	2.90	0.00	0.00000 U	0.29	3.22
F293921	75	STB	SPR	M	4.9	2.40	0.00	0.00000 U	0.24	4.90
F282161	59	WP	FALL	U	6.6	6.90	5.00	5.00000 U	13.19	199.85
F282162	59	WP	FALL		6.5	6.30	5.00	5.00000 U	13.13	202.00
F282163	59	WP	FALL		3	5.60	1.00	1.00000 U	3.06	102.00
F282164	59	WP	FALL		2.8	5.20	5.00	5.00000 U	13.02	465.00
F282165	59	WP	FALL		5.8	3.20	2.50	2.50000 U	6.57	113.28
F284080	59	STB	FALL		1.1	1.40	1.50	1.50000 U	3.89	353.64
F284081	59	STB	FALL		1	0.95	1.00	1.00000 U	2.60	259.50
F284131	59	STB	FALL		0.9	0.87	0.00	0.00000 U	0.09	9.67
F284132	59	STB	FALL		0.7	0.82	0.00	0.00000 U	0.08	11.71
F284133	59	STB	FALL		0.9	1.60	0.00	0.00000 U	0.16	17.78

TEQs calculated from McGroddy et al., (1997) Study of Hudson River Fish 1995 Data compiled by EVS Consultants, 1996/97										
SAMPLE	RMILE	SPECIES	SEASON	SEX	%LIPID	PCB077	PCB126	PCB126	TEQ fillet	lipid TEQ
F282155	27	WP	FALL		6.9	3.60	1.50	1.50000 U	4.11	59.57
F282156	27	WP	FALL		9.7	3.00	2.50	2.50000 U	6.55	67.53
F282157	27	WP	FALL		8.6	4.80	2.50	2.50000 U	6.73	78.26
F282166	27	WP	FALL		5.7	2.20	1.50	1.50000 U	3.97	69.65
F282167	27	WP	FALL		10.8	5.40	2.50	2.50000 U	6.79	62.87
F284082	27	STB	FALL		0.6	0.73	0.73	0.73000 U	1.90	316.33
F284083	27	STB	FALL		1.1	0.97	0.50	0.50000 U	1.35	122.45
F284084	27	STB	FALL		1	0.56	0.50	0.50000 U	1.31	130.60
F284085	27	STB	FALL		0.6	0.50	0.50	0.50000 U	1.30	216.67
F284086	27	STB	FALL		0.8	0.32	0.50	0.50000 U	1.28	160.25
F293907	27	STB	SPR	M	4.2	3.10	0.00	0.00000 U	0.31	7.38
F293908	27	STB	SPR	M	4.2	2.70	0.00	0.00000 U	0.27	6.43
F293909	27	STB	SPR	M	5.5	5.00	0.00	0.00000 U	0.50	9.09
F293911	27	STB	SPR	M	3.4	1.10	0.00	0.00000 U	0.11	3.24
F293912	27	STB	SPR	M	4.2	2.50	0.00	0.00000 U	0.25	5.95
F300495	27	STB	FALL	M	2.4	2.50	2.50	2.50000 U	6.50	270.83
F300496	27	STB	FALL	M	3.4	1.50	1.50	1.50000 U	3.90	114.71
F300497	27	STB	FALL	M	4.7	1.80	1.50	1.50000 U	3.93	83.62
F300498	27	STB	FALL	M	6	1.00	1.00	1.00000 U	2.60	43.33
F300499	27	STB	FALL	M	1.5	1.00	1.00	1.00000 U	2.60	173.33
FISHSITE		AVGTEQ	STDTEQ			AVGTEQ	STDTEQL			
		fillet	fillet			lipid	lipd			
YP190S		9.95	6.58			330.18	241.59			
LMB190S		15.84	19.29			2207.48	1750.27			
YP175S		5.82	3.03			411.48	429.39			
LMB175S		0.89	0.57			557.30	594.90			
YP152F		10.95	4.42			313.96	141.14			
YP152S		0.92	1.39			26.25	12.41			
WP152F		16.99	11.97			427.78	242.37			
WP152S		0.48	0.18			14.21	4.80			
STB152F		2.67	2.73			229.06	210.63			
STB152S		7.28	9.36			173.75	253.16			
STB152F		8.66	4.19			612.76	420.70			
LMB152S		0.12	0.13			12.88	12.93			
YP115S		0.28	0.21			21.01	12.85			
WP115S		0.29	0.20			12.81	10.35			
STB115S		3.39	2.64			142.21	85.84			
LMB115S		0.32	0.21			25.59	6.37			
STB75S		0.24	0.05			5.41	1.73			
WP59S		9.79	4.71			216.42	146.63			
STB59F		1.36	1.78			130.46	164.20			
WP27F		5.63	1.45			67.57	7.15			
STB27F		1.43	0.26			189.26	80.07			
STB27S		0.29	0.14			6.42	2.15			
STB27F		3.91	1.59			137.16	88.53			

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