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Use of Traditional Foods in a Healthy Diet in Alaska: Risks in Perspective

Second Edition:

Volume 1. Polychlorinated Biphenyls (PCBs) and Related Compounds

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Executive Summary

Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and polybrominated diphenyl ethers (PBDEs) are lipophilic, persistent, usually man-made chemicals. Due to concerns over potential adverse ecological and human health effects, the manufacture of PCBs was banned several decades ago by many industrial nations. However, trace amounts of PCDDs and PCDFs continue to be unintentionally produced during some industrial processes. PBDEs are currently used as fire retardants in many consumer products, although several PBDEs will soon be banned by the European Union and the State of California. Efforts are being made to dispose of PCB-like chemicals in a responsible manner, but some have been accidentally released into the environment by industrial nations.

Due to their environmental persistence, PCB-like chemicals have become distributed in small quantities throughout the globe. These Persistent Organic Pollutants (POPs) have been transported from temperate regions to the arctic through the atmosphere, oceans and the marine food chain. In aquatic environments, POPs partition from water into organic material and biomagnify up the food chain.

In Alaska and throughout the Arctic, people who consume large quantities of subsistence foods from the sea are exposed to these potentially toxic chemicals, as are consumers of many other foods. The focus of this chapter is to review what is known about the levels of PCB-like chemicals in subsistence foods in Alaska and the potential hazards they may pose to human health, using the most recent data available. A preliminary assessment of subsistence food safety is presented, and key knowledge gaps are identified. Although information about the concentrations of POPs in subsistence foods in Alaska is limited, recent studies included in this revision have broadened our knowledge.

Data that are available from several Alaskan studies are of limited utility due to poor or undocumented analytical quality, particularly in older research. It is important to consider the quality and limitations of existing POP data, because an uncritical interpretation of POP data can result in misleading conclusions. For the purposes of this review, the quality of existing Alaskan data was scrutinized. While all available data were carefully considered, more weight was placed on POP data from studies that met rigorous standards of analytical quality.

Our knowledge of POP concentrations in the blood of humans in Alaska is increasing. In addition to the Alaska Native serum bank study mentioned in our original monograph (Rubin et al., 2001), several additional investigations have since been conducted or are ongoing. In general, these investigations have documented the extent to which Alaskans have been exposed to POPs. Serum concentrations of PCBs in those Alaskans who have been tested were higher than those documented in the general population from the Lower 48, although they were similar to Great Lakes fish-eaters. Serum concentrations of dioxins, furans and coplanar PCBs in Alaskans were similar to other Americans. In Alaska, as elsewhere, serum POP concentrations were strongly associated with age and were higher in older persons. Serum POP concentrations were relatively low in women of childbearing age. All POP exposures documented in Alaska were far below concentrations associated with known adverse health effects.

There are a number of potential human health concerns related to exposure to PCB-like chemicals. Some consequences of acute, accidental high-dose PCB exposure are obvious; the skin disorder chloracne is particularly diagnostic. Doses of PCBs that cause such obvious effects are orders of magnitude greater than the background exposures encountered by Alaskans through the food chain. Risks about which public health officials are most concerned when considering subsistence food issues in Alaska are chronic, long-term or subtle effects that may occur at very low PCB dose concentrations. In particular, cancer, immunotoxicity, reproductive toxicity, and developmental/neurobehavioral toxicity have been considered as potential endpoints of exposure to PCB-like chemicals. Due to the controversy and confusion surrounding these endpoints and their relationships with exposure to PCB-like chemicals, this report considers these issues in some detail.

Thousands of studies have examined the potential health effects of PCBs and related compounds. The results of these studies have often been conflicting and difficult to interpret. Overall, we conclude that there is some small, unproven but theoretical risk of subtle health effects related to low-level exposure to PCB-like chemicals. These subtle effects may be impossible to detect with existing scientific and medical technology. Alternatively, there may be no adverse effects resulting from low-level PCB exposures such as those encountered through consumption of subsistence foods or store-bought foods.

The potential risks associated with POP exposure through subsistence food consumption are smaller than the risks associated with a decreased use of traditional foods, or the risks associated with many other aspects of Alaskan life. A decreased reliance on traditional foods would have a negative net effect on human health in native Alaskan communities. Traditional foods have important nutritional benefits as well as cultural and economic benefits. The Division of Public Health strongly encourages the continued unrestricted consumption of traditional foods.

Concentrations of PCB-like chemicals vary substantially among species and tissues. The highest concentrations of PCBs are likely to be found in the fatty tissues of animals that occupy the highest trophic levels of the marine food chain. In marine mammals, tissue concentrations are often higher in older animals, and in male animals relative to female animals. Recent studies of Alaskan fish have documented very low concentrations of PCB-like chemicals. Alaskan fish can be consumed safely in unlimited quantities. Most Alaskan fish and seafood have lower PCB concentrations than fish from the Lower 48, which reflects the relatively remote, nearly industry-free environment of many regions of Alaska. The highest current concentrations of PCBs known in Alaska are in the blubber of transient killer whales, and relatively high concentrations have also been detected in stellar sea lion blubber. Concentrations of PCBs in beluga whale blubber from Alaska are somewhat higher than the concentrations found in Great Lakes fish, although they are within the same order of magnitude. Marine mammal blubber is often consumed in combination with epidermis; this "muktuk" has lower POPs concentrations than blubber alone.

All Alaskan human biomonitoring data to date provides evidence that women of childbearing age have been exposed to concentrations of contaminants far below those associated with adverse health effects to the fetus. Therefore, in view of the known health benefits of traditional food consumption to the mother and infant, the continued unrestricted consumption of all Alaskan traditional foods is recommended.

Future research should focus on addressing the following key knowledge gaps:

- Monitoring of subsistence species for POP concentrations in tissues should focus on six species: the beluga whale, Stellar sea lion, northern fur seal, Pacific walrus, ringed seal and bearded seal. Among Alaskan subsistence foods, the first three species have the potential to accumulate the greatest concentrations of PCBs in their tissues. The Pacific walrus is an important subsistence species, and PCB concentrations have the potential for elevation in "rogue" animals that prey on seals (it is unknown whether this behavior is common in Pacific walrus in Alaska). The ringed seal is significant due to its moderate level of contamination and high rate of consumption by Alaskan natives. Monitoring the bearded seal is important because it is a preferred native food source, and very few samples have been analyzed for POP concentrations to date.

- Monitoring of POP concentrations in human tissues such as serum, adipose tissue or breast milk has only recently taken place in Alaska, and more data are needed. Exposure measurements are especially needed for polybrominated diphenyl ethers (PBDEs), which have not yet been analyzed for in Alaskans. As the most direct indicator of human exposure to POPs, this information is essential in order for health officials to estimate the risks associated with the consumption of traditional foods. Measurement of POP concentrations in Alaskans will enable a comparison of their exposures and risks relative to people in other circumpolar areas that have previously been characterized, such as the Inuit of Quebec and Greenland.

- POP concentrations in prepared traditional foods should be characterized, and village-specific dietary surveys conducted to assess dietary exposure to these chemicals. This would provide information on how food preparation methods influence POP concentrations, and help us to determine which foods contribute most to dietary exposures. This information would be essential to any efforts to reduce future POP exposures, if desired, while continuing to enjoy a healthy subsistence lifestyle.

- The nature of POP exposure through the Alaska marine food chain needs to be characterized by use of sophisticated analytical methods that have only recently been employed for Alaska samples. Patterns of PCB congeners vary significantly among species as a function of trophic level and metabolic capacity and among geographic areas, and these patterns influence toxicity. Congener-specific profiles which include the bioactive coplanar PCBs, PCDDs and PCDFs are needed for human tissues and for the more contaminated subsistence food species. In order to achieve adequate detection of important trace congeners, these coplanar analyses should focus on fatty tissues such as marine mammal blubber and human milk.

General Background Information on Polychlorinated Biphenyls (PCBs) and Related Compounds

Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins ("dioxins") and dibenzofurans ("furans"), and polybrominated diphenyl ethers (PBDEs) are structurally similar POP chemicals (Figure 1). Complex mixtures of these chemicals are present as trace environmental contaminants in water, soil, sediment, air and biota throughout the world. Structural features common to this chemical group include two aromatic rings and some degree of halogen substitution, and within each class the basic carbon structure is the same. Congeners within each class differ by the degree and position(s) of halogen substitution, most commonly by chlorine or bromine. There are 209 PCB congeners, 75 dibenzo-*p*-dioxin congeners, 135 dibenzofuran congeners and 209 PBDE congeners theoretically possible, although they are not all present in the environment.

Sources

Thousands of tons of PCBs were manufactured in many countries throughout the Northern hemisphere from the late 1920s through the early 1970s for a variety of commercial purposes (Kimbrough, 1980). PCBs are useful as heat transfer fluids, dielectric fluids for transformers and capacitors, plasticizers, hydraulic lubricants, flame retardants, and adhesives, in addition to a variety of other applications (Safe, 1994b). Commercial PCB mixtures were usually marketed according to their percentage of chlorine content by weight. In the United States, the Monsanto Chemical Company manufactured PCBs under the trade name Aroclor. Products included Aroclors 1016, 1221, 1232, 1242, 1248, 1254 and 1260, where the last two digits denoted the percentage of chlorine content. Commercial PCBs were also produced by other companies in other countries under different trade names, including Clophen (Germany) and Kanechlor (Japan) (Safe, 1994b). The United States explicitly banned the production and use of PCBs in the Toxic Substances Control Act of 1976 (Silbergeld and DeFur, 1994), although the compounds are still present in older equipment manufactured before that time. In many other countries, including most members of the Organization for Economic Cooperation and Development (OECD), PCBs have also been banned or their uses restricted in commerce and industry (Silbergeld and DeFur, 1994).

In contrast to the PCBs, dioxins and furans have not been intentionally manufactured. Rather, they are created as unintentional byproducts during the manufacture of other chemicals or as a result of some industrial processes. Trace amounts of these chemicals are formed by the pulp and paper industry when pulp is bleached with chlorine (Hrutfiord and Negri, 1992), and during certain types of metal processing (Oehme et al., 1989). Spent graphite electrodes used in the chloralkali industry can be important localized sources of polychlorinated dibenzofurans (Zook and Rappe, 1994). Chlorinated dioxins and furans are produced as unwanted byproducts during the manufacture of chemicals such as the wood preservative pentachlorophenol and certain herbicides that include 2,4-D and 2,4,5-T (Webster and Commoner, 1994). In the United States, the burning of household waste in backyard burn barrels may be a major source of airborne dioxin emissions (Lemieux et al., 2003). Chlorinated dioxins and furans can be formed during the combustion of virtually any organic material when chlorine is present, and their production has been associated with the burning of coal and the incineration of wastes. Chlorinated dioxins and furans are also created by natural processes, both by microorganisms and as a byproduct of combustion (for example, from forest fires) (Gribble, 1994). Forest and brush fires may be major sources of chlorinated dioxins and furans in the environment (Nestrick and Lamparski, 1982; Sheffield, 1985), although there is considerable evidence that anthropogenic inputs may be more significant than these natural sources (Kjeller et al., 1991; Tong et al., 1990; Webster and Commoner, 1994). Because dioxins and furans were never intentionally manufactured, efforts to reduce their creation have not focused on "banning" their production. Instead, regulations have focused on source abatement. Source abatement involves the alteration of production methods in problem industries to reduce dioxin and furan formation, as well as improved cleanup prior to the release of water or air from industrial processes into the environment.

Polybrominated diphenyl ethers (PBDEs) are flame retardants used in a wide variety of materials, most commonly the polyurethane foam used in seat cushions (Betts, 2001). They are also common components of building materials, textiles, and electronic devices such as computers and televisions (Darnerud et al., 2001). PBDEs are thought to enter the environment via waste incineration, leaching from landfills, and volatilization into the surrounding air from electrical components and other products (Darnerud et al., 2001). Three commercial mixtures are widely used (penta-BDE, octa-BDE, and deca-BDE), which are impure mixtures of PBDE congeners (Ikonomou et al., 2002). Large-scale production of PBDEs began in the early 1970s (Ikonomou et al., 2002), and PBDE concentrations in the environment have increased substantially since that time. In the mid-1990s, documentation of rapidly rising concentrations of PBDEs in the breast milk of Swedish women led to sharply reduced usage, and eventually a ban, on many PBDE formulations in the European Union (Darnerud et

al., 2001). There are preliminary data indicating that PBDE exposures in the United States and Canada may be the highest in the world, and that breast milk concentrations there are increasing exponentially (Betts, 2002), but a similar ban has not yet occurred in North America. The State of California has announced that it will ban two PBDE congeners shown to accumulate in humans scheduled to take effect in 2008.

Environmental Chemodynamics of PCB-like Chemicals

PCBs are an environmental problem because they are persistent and lipophilic. Because of their stability and resistance to biodegradation, many congeners undergo cycling and transport within the various compartments of the global ecosystem (Safe, 1994b). Within aquatic systems, these chemicals partition from the water to organic material such as marine zooplankton (Hoekstra et al., 2002b). The PCBs then bioaccumulate in the fatty tissues of marine predators, increasing in concentration at each level of the food chain (Muir et al., 1992c).

Factors unique to arctic ecosystems may enhance the deposition of organochlorines from the atmosphere and increase their environmental persistence. Polar regions may act as "cold traps" for some of the more volatile organochlorine compounds. Volatile, lower-chlorinated PCBs can be transported by the atmosphere from industrial nations in temperate regions to the arctic, where cold temperatures cause them to "distill" and settle (Wania and Mackay, 1993). The more highly chlorinated PCBs are less volatile and are less likely to remain in the atmosphere to reach the Arctic, but they may still arrive in the arctic in the bodies of migrating wildlife.

Migrating wildlife can carry ("biotransport") POPs to remote areas of Alaska. In one study, sockeye salmon accumulated POPs during their ocean life stage. Upon returning to their freshwater spawning areas via the Copper River, they transported these POPs to remote inland Alaskan lakes. The POPs from the salmon were incorporated into the freshwater food web and were found in the bodies of the lake's arctic grayling (Ewald et al., 1998). The POPs concentrations measured in the individual fish were far below those thought to be harmful to fish health or reproduction and did not pose any health risk to human consumers of the fish.

Distributions of PCB congeners in Canadian arctic fish and marine mammals appear to be regulated by trophic level biomagnification properties, as they do not reflect the different physical-chemical properties (such as volatility) of individual congeners (Muir et al., 1988). Animals at lower trophic levels (such as arctic cod) contain patterns of PCBs similar to commercial PCB mixtures. At higher trophic levels (such as marine mammals), lower chlorinated PCB congeners are not detectable, and more highly chlorinated congeners are dominant in PCB patterns (Muir et al., 1988). This may be due to the ability of some marine mammal species to metabolize and excrete the lower chlorinated PCB congeners.

Outside of biological systems, persistence of PCB-like chemicals is enhanced in the arctic environment due to slower reaction rates at low temperatures, reduced photolysis due to a low sun angle, and decreased biological activity (such as reduced scavenging of chemicals sorbed to sediments) relative to that of temperate climates (Wania and Mackay, 1993).

In Alaska, the highest concentrations of POPs have been found in the fatty tissues of animals that occupy the highest trophic levels of aquatic food chains. In particular, POPs accumulate in the blubber and fatty tissues of marine mammals near the top of the marine food chain, such as polar bears, orcas, and beluga whales (Muir et al., 1992c). In fish, POP concentrations are higher in species that consume other fish, and in fatty species compared to leaner species. POPs accumulate in the body over time, so that concentrations are usually higher in older, larger fish. The same holds true for male marine mammals (Norstrom and Muir, 1994). However, adult female marine mammals have the ability to transport POPs to the fetus and to excrete these contaminants in their breast milk; it is possible for their POP body burden to decrease following the birth and nursing of young. Therefore, in adult marine mammals males often have higher blubber POP concentrations than do females (Muir et al., 1992a; Tanabe et al., 1987).

Chemical Analysis and Reporting of POP Concentrations in Environmental Samples

Methods for analyzing POPs in environmental samples are continually being developed and improved. Different methods are used in various laboratories to isolate or "extract" PCBs from an environmental sample, and then to separate and quantify them. Data produced by different analytical methods often are not directly comparable. It is essential to consider the quality of quantitative chemical analyses prior to their use in risk assessment.

A gas chromatograph is usually used to separate or "resolve" the individual PCB congeners, which are detected with either electron capture or mass spectroscopy. Many early analyses (pre-1980s) utilized low-resolution packed column chromatography to separate the congeners, which produced a relatively

small number (5-12) of poorly resolved peaks. This method has largely fallen out of favor. Many of these older analyses are of marginal use today, as PCB peaks were poorly resolved and often erroneously included non-PCB compounds such as toxaphene congeners, chlordanes and DDT-related chemicals.

Modern methods of chemical separation use higher resolution capillary columns that more adequately separate most PCB congeners. With capillary column chromatography, 80-90 organochlorine peaks can be accurately identified from typical environmental extracts, and toxaphenes, chlordanes and DDTs can be distinguished from PCBs.

Following chemical separation, different methods can be used to quantify PCBs in a chromatogram. "Total PCBs" can be calculated by matching the pattern of PCB peaks from a sample with the pattern produced by commercial Aroclor mixtures, with use of pattern recognition algorithms such as COMSTAR (Burkhard, 1987). The pattern of PCB peaks is matched with use of multiple regression procedures, and quantitation is performed by comparison to Aroclor response factors. While this method provides a good approximation of "total PCBs", it is not ideal because the congener mixtures that are present in the environment are not the same as the commercial mixtures that were originally released. Some congeners are more persistent than are others. As a result, their relative abundance increases in the environment over time (McFarland and Clarke, 1989; Safe, 1994b).

Since PCB mixtures in the environment differ from their original formulations, most modern analytical approaches involve the quantitation and summing of targeted individual PCB congeners in the mixture. This approach tends to lead to lower PCB concentrations than the "total PCB" approach (Giesy et al., 1997). All PCB congeners may not be included in the summation process. This is partly due to the fact that some congeners do not separate well on the gas chromatograph (Niimi et al., 1996). Summed congener data may not be directly comparable from laboratory to laboratory, particularly if the same congeners are not chosen for quantitation, the same analytical standards are not utilized, or if procedures for data analysis and interpretation are different.

Detection limits and large differences in the abundance of individual congeners can also present analytical challenges. A particular dilution of environmental extract may contain some congeners below the limit of detection, while other congeners are so abundant that their concentrations exceed the linear range of quantitation. There are also different approaches toward the statistical treatment of non-detected congeners. In a sample with a non-detectable chemical concentration, the true concentration of the chemical is a non-zero, non-measureable value that is known to be below a defined threshold. When calculating statistics such as the mean, the concentration of a non-detected chemical in a sample may be treated as a zero, or as an estimated value such as half the detection limit (Hornung and Reed, 1990). The choice of how to treat non-detectable values affects the reported results, particularly if the chemical was not detected in a large proportion of the total samples taken.

In all of the procedures discussed so far, the most toxic congeners (i.e., the flat or "coplanar" congeners) are generally not included in these analyses. While coplanar congeners are usually only present in small quantities in a mixture, because of their potency they often contribute the vast majority of the overall toxicity of the mixture (Johansen et al., 1994). Coplanar PCBs are an important component of overall dioxin-like toxicity in marine ecosystems, and the bioaccumulation of coplanar PCB congeners in carnivorous marine mammals is of particular concern (Kannan et al., 1989). A special extraction procedure and sophisticated instrumental analysis are required for coplanar PCB analysis. Few coplanar analyses have been performed for Alaskan environmental samples, but these analyses are becoming more common, and our knowledge of coplanar PCB concentrations in Alaska should rapidly increase.

Dioxins, furans and coplanar PCBs all express their toxicity through a common mechanism. It is common to add all of the "dioxin-like" activity of the individual chemicals together to arrive at a single number that represents its overall toxicity. With this approach, the potency of each individual dioxin, furan and coplanar PCB congener is scaled to the potency of the most toxic congener, which is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The potency of each coplanar PCB congener can be expressed in terms of a "TCDD equivalency factor" (TEF). For example, a PCB congener that is half as potent as TCDD would have a TEF of 0.5. If congener-specific data are available, the overall toxicity of a mixture can be estimated by multiplying the concentration of each congener by its TEF and then summing the toxicities to calculate TCDD-equivalents (TEQs). The TEFs are periodically updated as new toxicological research increases our knowledge of dioxin-like toxicity. Therefore, several "sets" of TEFs are available, and TEQs calculated with different TEFs are not directly comparable. The most recent, internationally accepted TEFs were published in 1998 (Van den Berg et al., 1998).

Quality assurance and control (QA/QC) are essential aspects of PCB analysis. Without good QA/QC, there can be little confidence in the analytical data that are generated. During the process of PCB extraction, trace

quantities of these chemicals are isolated and concentrated from samples. Background PCB contamination in the laboratory can therefore be a serious problem, and blank samples must be periodically analyzed in order to assure that such contamination does not exist. Care must be taken to ensure that samples are not contaminated during the sampling process, during storage or during analysis. It is also important to analyze some samples more than once, to determine analytical precision or "repeatability". Another effective QA/QC procedure is to "spike" a subsample with a known quantity of a PCB congener and then determine how much of that spike is recovered and quantitated during the analytical process.

The accuracy and precision of analytical measurements vary as the concentration of the analyte in the sample changes. Accuracy refers to the ability to quantify the concentration of an analyte correctly, while precision refers to the ability to obtain the same value when analyses are repeated (regardless of whether that measurement was "accurate"). Each analytical method has a limit of detection for each analyte, below which the detected concentration is not significantly different from zero. Analytical methods also have a range of analyte concentrations for which accuracy and precision are optimized. As the concentration of an analyte diminishes and approaches the method detection limit, accuracy and precision of analytical results are decreased. In the optimal concentration range for an analyte the accuracy of a measurement should be ± 20%, but (by definition) near the limit of detection a detected concentration approaches an error of ± 200% (Taylor, 1989). Since POP analyses often involve trace quantities of analyte, it is important to investigate and report limits of detection and the relative confidence of values in different data ranges.

It is desirable to obtain a sufficient quantity of sample in order to achieve analyte concentrations within the optimal analytical range whenever possible. This allows the collection of robust analytical data rather than a host of "non-detects". In order to accurately determine the concentration of trace POP concentrations in biota, it is often necessary to analyze fatty tissues that are most likely to contain the highest concentrations of these chemicals.

Instrument detection limits are related to the concentration of analyte in a final extract. Consequently, detection of analyte in a sample can be enhanced by extracting a larger amount of sample in order to obtain more analyte molecules, and/or by reducing the final extract to a smaller volume. Pilot studies can be helpful to determine the sufficiency of proposed sample quantities.

Rather than analyzing tissues that do not accumulate POPs to a significant extent (such as plants), limited resources can be more effectively used by increasing the sample size for animal species of concern. In marine mammals, POP concentrations are much higher in blubber than in internal organs, making their quantitation more robust. In humans, adipose tissue and breast milk (Needham and Wang, 2002) are two fatty tissues that are likely to contain higher POP concentrations. Because the lipid content is low in human newborn cord blood, POP quantitation is difficult in this tissue.

Concentrations of POPs in biological tissues can be reported in whole weight, wet weight, dry weight, or "lipid adjusted" terms. The choice of reporting method greatly changes the resulting value. Direct comparisons of chemical concentrations should never be made between results that have been expressed in different terms unless data are provided to allow conversion to equivalent units. For example, POP concentrations reported in "dry weight" terms will be higher than those reported in "wet weight" terms, because chemical concentrations have been concentrated in "dry weight" samples as all moisture was removed. However, if data for percent moisture have been included for each sample, it is possible to convert data between the two reporting methods.

Biological samples are often reported in "lipid-adjusted" terms, such as "ng/g lipid". This practice allows researchers to account for differences in lipid (fat) content between various tissues, and for differences in fasting and feeding status (Phillips et al., 1989). POPs are highly lipophilic, and they partition among various tissues depending on their lipid content. For example, the whole weight concentration of POPs in a fatty tissue such as adipose will be much higher than the whole weight POP concentration in a lean tissue such as blood, but adipose and blood POP concentrations in an individual will be very similar when compared on a "lipid-adjusted" basis. Similarly, wet weight concentrations of POPs in blood will increase following consumption of a fatty meal, as POPs partition from other tissues into the fat-enhanced bloodstream. These changes in feeding status can be corrected for by expressing POP concentrations in "lipid-adjusted" terms. It is very important not to directly compare results that are not reported in the same terms, because "lipid-adjusted" concentrations of POPs will be higher than values that are expressed in whole weight, or wet weight, units.

Due to the varied methods that are used to quantitate and report POPs in environmental samples, caution must be taken when interpreting values. In particular, it can be difficult to compare the results obtained by different laboratories, especially when the analyses were performed during significantly different time periods. Small differences in POP quantities reported in various

samples from different studies may not be meaningful, as they may represent measurement variability rather than inherent differences between samples. It is imperative that analytical methodologies be reviewed in detail, including the quality assurance and control programs, in order to have confidence in the data and its interpretation. Current efforts are emphasizing the certification of standard reference materials (Schantz et al., 1995a), collaboration among analytical laboratories, and rigorous analytical methodology and QA/QC protocols so that results can be more directly comparable (Becker et al., 1993; Becker et al., 1997b).

The Importance of Congener-Specific PCB and Dioxin Data and Its Interpretation

PCBs, dioxins, furans, PBDEs and related chemicals are quantitated and reported in many different ways. For PCBs, laboratories may measure and report the individual values of a subset of the 209 possible congeners. The specific list and number of included congeners varies widely among laboratories. "Total PCBs" can be estimated in a variety of ways, such as summing the values of the measured congeners, summing the measured congeners and applying a correction factor, or performing pattern analysis and multiple regression techniques. In some analyses non-detected congeners are treated as zero values, while in others a positive value is estimated based on the detection limit of the congener. These quantitative complexities create challenges for data comparison between studies. Great care and meticulous scrutiny of detail must be taken to assure that comparisons are scientifically valid and appropriate.

The use of "total PCB" concentrations during the risk assessment process imposes an error on subsequent estimates of the toxicity of environmental samples. "Total PCBs" generally do not include or consider the coplanar PCBs, dioxins or furans in environment samples. These planar congeners can represent a significant proportion of the total dioxin-like toxicity in terms of TEQs. Estimates of risk can vary significantly, depending on whether total PCBs or calculated TCDD-equivalents from coplanar dioxin-like congeners are used. For example, the derived potency (with use of USEPA risk assessment procedures) of a PCB mixture extracted from Great Lakes salmon was 3.7 times greater when calculated as TEQs from coplanar PCBs than when calculated as total PCBs based on Aroclor pattern matching (Williams et al., 1992). The problem becomes even more severe when "total PCBs" are used to compare the relative toxicity of various subsistence foods from the marine environment. Patterns of PCB congeners vary significantly among arctic marine species, and these patterns may profoundly influence their overall toxicity.

The relative abundance of various PCB congeners in the arctic environment and biota has been determined. Animal species vary in their metabolic capabilities to depurate chemicals. In arctic cod from Canada, the pattern of PCB congeners was remarkably similar to an Aroclor standard mixture (1242:1254:1260, 0.6:3:1) (Muir et al., 1988). Lower-chlorinated congeners such as penta- and hexachlorobiphenyls were well represented in the arctic cod samples. In contrast, these lower-chlorinated congeners were less common in ringed seal blubber, and were virtually absent in polar bear fat. PCB congener profiles of ringed seal and polar bear were dominated by higher-chlorinated congeners such as hepta-, octa- and nona/decachlorbiphenyls. These data indicate that the ringed seal and polar bear were able to preferentially metabolize and eliminate the lower-chlorinated PCB congeners, in contrast to the arctic cod which could not. Interestingly, PCB congener profiles from narwhal and beluga blubber resembled those from cod, and contained a substantial proportion of lower-chlorinated congeners (Norstrom and Muir, 1994).

Differences in PCB congener profiles among marine species have been attributed to differences in metabolic capabilities related to specific cytochrome P450 enzymes. Small cetaceans such as dolphin, porpoise, beluga and narwhal do not metabolize PCBs with adjacent non-chlorinated *meta* and *para* positions efficiently. This deficiency in cetaceans has been attributed to a low activity of CYP 2B, the enzyme responsible for metabolism of most PCB congeners in higher animals (Tanabe et al., 1988). Bowhead whales collected by subsistence hunters in Barrow, Alaska exhibited little (Hoekstra et al., 2003) to no (Hoekstra et al., 2002c) CYP 2B-like biotransformation of PCB congeners, similar to other cetaceans.

Patterns of coplanar dioxin-like congeners also vary among marine species, and their relative contributions to TEQs vary accordingly. In general, concentrations of non-ortho PCBs were similar between narwhal, beluga and ringed seal from the Canadian Arctic (Ford et al., 1993). In contrast, concentrations of mono-ortho PCBs were much greater in narwhal and beluga than in ringed seal. Chlorinated dioxins and furans were found to contribute 37 to 42% of total TEQs in ringed seals, but less than 5% of total TEQs in narwhal and beluga (Ford et al., 1993). Another study confirmed that beluga have an exceptional ability to metabolize non-ortho PCB congeners and TCDD (Norstrom et al., 1992), a capacity attributed to high levels of CYP-1A activity in cetaceans (Watanabe et al., 1989). The bowhead whale can also metabolize PCBs via CYP1A-related pathways, but the structural determinants of PCB biotransformation in that species are complex (Hoekstra et al., 2002c).

Metabolic differences and subsequent POP congener profiles can have a dramatic influence on the toxicity of POP mixtures found in arctic animals. The implications of these differences for our risk assessment are profound. In particular, it is possible that our risk assessment may have overestimated the relative toxicity of beluga blubber but underestimated the relative toxicity of ringed seal blubber. This is because beluga blubber is likely to contain a lower proportion of the most toxic coplanar dioxin-like congeners than ringed seal blubber does.

Due to this dilemma, collection of congener-specific data is becoming increasingly common in environmental studies. While total PCBs have been used successfully to predict TEQs within a defined system (Williams et al., 1992), location-specific background data are initially needed to define applicable congener-specific relationships. Congener-specific relationships must be determined on a location-by-location basis, because there is major geographic variability in the ratio of TCDD to total PCBs among arctic marine mammals (Norstrom and Simon, 1990). In a place as vast and varied as Alaska, background knowledge is insufficient and congener-specific data are more useful for toxicologic interpretation.

Concentrations of PCBs in Alaskan Subsistence Foods and Other Wildlife

Although data about the concentrations of POPs in subsistence foods in Alaska are far more limited than we would like, recent studies (included in this revision) have contributed substantially to our knowledge. Far more comprehensive studies have been performed in the Canadian Arctic (Jensen et al., 1997; Kuhnlein et al., 1995; Murray, 1992; Murray et al., 1996; Murray and Shearer, 1993; Murray and Shearer, 1994). Despite the relative paucity of data from Alaska, we are able to compare available Alaskan data to Canadian data in order to see whether they are in the same general range. While small differences in numbers may not be meaningful, as discussed above, it is probably quite safe to compare relative orders of magnitude between Canadian and Alaskan studies. In fact, some of the Alaskan samples have been analyzed in Canadian laboratories, and in these cases the data are directly comparable.

We conducted an exhaustive review of the literature to investigate PCB concentrations in Alaskan fish and marine mammals. Peer-reviewed publications, government documents and accessible unpublished research reports were reviewed. The quality of data from each study was carefully evaluated by examining the analytical methodology, methods and limits of quantitation, and quality assurance provisions. Although all data available were carefully considered, we did not include some data (particularly from older research) in this report because of their inadequate quality. Problems with excluded studies included a lack of information about quality assurance or analytical methodology, outdated methodology and/or unacceptably high limits of detection for PCBs (McFall et al., 1986; Miles et al., 1992; Taylor et al., 1989).

Selected PCB data for marine mammals and freshwater fish from Alaska and Canada that were obtained with use of similar analytical methods and quality assurance provisions through 1997 are summarized in Tables 1 and 2 respectively. Table 3 presents more recent PCB data for Alaskan marine mammal subsistence species, salmon, and bird eggs, while Table 4 presents recent PCB data for Alaskan wildlife species or tissues not typically consumed by humans. In the selected studies, high-resolution chromatography was used to separate individual PCB congeners, which were then summed to estimate total PCBs.

PCBs and other contaminants were recently evaluated in two salmon species from the Yukon and Kuskokwim Rivers (Y-K) (USFWS, unpublished data). PCB concentrations in chinook and chum salmon muscle from the Y-K region were more than 100-fold lower than concentrations typically found in salmon from the Great Lakes, and more than 150-fold lower than the FDA action limit of 2 ppm for fish sold in commerce (Table 3, Figure 2). PCB concentrations were particularly low in chum salmon from the Kuskokwim River, where they were only detectable in 3 of 19 fish. Low PCB concentrations have also been observed in freshwater fish from Schrader Lake in the northern Interior region of Alaska (Wilson et al., 1995).

Coplanar PCBs, dioxins and furans have recently been measured in a few Alaskan samples. Dioxin TEQs in flatfish from Dutch Harbor were similar to concentrations found in freshwater fish from U.S. supermarkets, while dioxin TEQs in mussels and urchins from nearby bays were lower than concentrations found in many supermarket and fast foods (Figure 3) (Alaska Section of Epidemiology, 2001; Schecter et al., 1997; Schecter and Li, 1997). Dioxin TEQs derived from coplanar PCB analysis were very low in chinook and chum salmon muscle from the Yukon and Kuskokwim Rivers, averaging 1.8 ppt and 0.02 ppt, respectively (USFWS, unpublished data). PCB and dioxin concentrations are quite high in a few Alaskan wildlife species/tissues that are not typically consumed for subsistence, including polar bear fat and liver and killer whale blubber (Table 4). It is not surprising that POP concentrations are relatively high in these fatty tissues from species at the top of the marine food chain.

The concentrations of PCBs presented in this report were determined from freshly caught animals prior to preparation for human consumption. Preparation methods can significantly reduce the concentration of PCBs in fish, particularly if fat and skin are removed or if the fish is cooked (USEPA, 1996). PCB content was reduced by an average of 30% when Great Lakes fish were cooked (USEPA, 1996). When fish are smoked their organochlorine contaminant burden can also be significantly reduced. In one study, PCB concentrations were decreased by 46% in Great Lakes Lake Trout that were smoked (skin-on) (USEPA, 1996).

The effect that traditional food preparation methods unique to Alaskan Natives may have on POP concentrations has not been directly investigated. In a study of Canadian Inuit food preparation methods, the boiling of marine mammal blubber appeared to cause a modest decrease in PCB concentrations (Chan et al., 1996). In contrast, the omega-3 fatty acid content of walrus blubber was not changed by boiling or frying compared to raw blubber. Future studies should investigate how traditional methods of subsistence food preparation affect the concentrations of POPs in fish and marine mammals as they are consumed by Native Alaskans.

Species-Specific Data Gaps

Future studies of POP content in Alaskan subsistence foods should initially focus on marine mammal species of most concern. Additional information is needed on POP concentrations in belugas, which are rather high in Alaska. Data from Point Lay belugas suggest that POP concentrations may be greater in male than female belugas (Krahn et al., 1999). However, in belugas sampled from the Southern Beaufort Sea in Canada, POPs were high in both males and females (Muir, 1996). This is of concern because belugas from the Mackenzie River Delta and Beaufort Sea migrate to Alaskan waters (O'Corry-Crowe et al., 1997) and are hunted by Alaskan natives along the north slope (Robert Suydam, personal communication). Concentrations of POPs were lower in belugas from Cook Inlet than in belugas from the Chukchi Sea. Further research is needed to clarify the relationship between POP contamination, location, sex and age in belugas.

Research should also focus on the ringed seal, harbor seal and bearded seal, because they are commonly consumed by Alaskan Natives. A determination of TEQs in ringed seal blubber following analysis for coplanar congeners is particularly needed, especially as it is processed for food.

In the prior version of this monograph, we recommended prioritized analysis of Pacific walrus in Alaska. Since that time, two studies have been published that documented low POP concentrations in Pacific Walrus blubber from the Bering Sea, relative to POP concentrations in beluga blubber (Seagars and Garlich-Miller, 2001; Struntz and Kucklick, 2000). In the Canadian Arctic, some Pacific walrus had unexpectedly high concentrations of POPs in blubber (Muir et al., 1992b). Walrus at Inukjuak with high POP blubber concentrations (an average of 11.5 ppm PCBs in males, wet weight) were thought to have been feeding at a higher trophic level than usual, and predation on ringed seals was suspected (Muir et al., 1995). Although seal predation was once thought to be an uncommon behavior confined to large male walrus, the behavior may be more common than previously believed. Although seal predation has also been observed in Pacific walrus in Alaska (Lowry and Fay, 1984), it is unknown how common that behavior might be. Ecological research to determine the incidence of seal predation among walrus in Alaska would be helpful, as only these “rogue walrus” are likely to have elevated POP blubber concentrations.

Additional information is needed on blubber POP concentrations in northern fur seals. A recent study has measured comparatively high PCB concentrations in fur seals in Alaska, which the authors speculated may have been due to their higher trophic level and more extensive annual migrations in potentially contaminated areas relative to other Alaskan seal species (Krahn et al., 1997).

Finally, a sixth marine mammal that warrants focused research is the Stellar sea lion. Although few samples have been analyzed, available data indicate that Stellar sea lion blubber contains some of the highest PCB concentrations among marine mammals in Alaska. Stellar sea lions have the potential to bioaccumulate higher concentrations of organic contaminants, because they have a marine mammal component to their diet. Stellar sea lions are known to eat northern fur seal pups, sometimes in large numbers (Hoover, 1988). There is also speculation that Alaskan Stellar sea lions may become exposed to PCBs along their migration route, which encompasses offshore areas of southern California (Varanasi et al., 1993).

For all marine mammal species consumed by humans, there is a need to investigate the distribution of POP concentrations among individual animals in a population. Some contaminants, such as heavy metals, are highly skewed in marine mammal populations. A few individuals have very high contaminant concentrations, while most individuals have much lower concentrations. The extent to which this is true for POP concentrations in marine mammal tissues such as blubber requires further research.

Time Trends of POP Concentrations in the Arctic Environment

There are insufficient data to conclude whether concentrations of PCB-like chemicals in the Alaskan environment have been increasing or decreasing over time, although available data indicate that PCB concentrations are declining. For example, decreasing PCB concentrations have been observed in Peregrine Falcons in Alaska over the last several decades (Ambrose et al., 2000). Data collection of PCB concentrations in the Canadian arctic environment has been more comprehensive and long-term than in Alaska. Time trend information is emerging for the Canadian Arctic, and this may shed light on what might be happening in Alaska. On Ellesmere Island in Nunavut, air samples were collected weekly and analyzed for PCBs (Hung et al., 2001). During the time period from 1993-1997, there was evidence of a declining trend for several of the lighter, less chlorinated PCB congeners. However, with the exception of PCB 180, the more chlorinated PCB congeners did not decline over that time period. This was in marked contrast to temperate sites, indicating a lag time for decline between the Arctic and source regions. Half-lives of PCBs were longer at Nunavut relative to temperate sites, perhaps due to the lower temperatures and darkness at Nunavut, and the process of global fractionation.

A lack of decline of PCB concentrations has also been observed in biota from arctic Canada and Greenland. A decline in PCB concentrations was not observed between 1978 and 1988 in walrus from Greenland (Muir et al., 2000). In the Western Canadian Arctic, PCB concentrations in ringed seal blubber decreased significantly from 1972 to 1981, but then did not decrease further between 1981 and 1991 (Addison and Smith, 1998). Concentrations of PCBs in polar bears in the eastern Canadian Arctic appear to have increased form the 1970s to the 1980s, while PCB concentrations in ringed seal blubber showed no significant change from the mid-1980s to 1990s (Muir and Norstrom, 2000). Further work on time trends in polar bears and ringed seals with samples collected from the late 1990s has been urged to confirm anticipated declining trends in PCBs (Muir and Norstrom, 2000).

Concern is emerging worldwide regarding increasing concentrations of polybrominated diphenyl ethers (PBDEs) in wildlife (and humans, to be discussed later). Exponential increases in PBDE concentrations have recently been demonstrated in Canadian and Great Lakes wildlife. In Canadian arctic ringed seal blubber, PBDEs increased exponentially during the period 1981 – 2000 (Ikonomou et al., 2002). PBDE concentrations in arctic ringed seals are currently far lower than PCB and dioxin concentrations, but if current rates of bioaccumulation continue, PBDEs will surpass PCBs to become the most prevalent POP compound in Canadian arctic ringed seals by the year 2050 (Ikonomou et al., 2002). PBDEs are also increasing exponentially in Great Lakes Herring Gulls, with a doubling time of around 3 years for the Penta-BDE congeners (Norstrom et al., 2002) (Figure 4). If current PCB and PBDE trends continue, it will only take 10 –15 years for PBDEs to become the most abundant POP contaminant in the Great Lakes (Norstrom et al., 2002). To our knowledge, PBDEs have not yet been measured in the Alaskan environment or human population. These chemicals of emerging concern should be a high priority for investigation in Alaska.

Potential Health Effects of PCB-like Chemicals

There are a number of vexatious and contentious public health concerns related to exposure to PCBs, dioxins and related chemicals. Biological changes following PCB or dioxin exposure can be measured using a variety of different endpoints. Some biochemical changes, such as the induction of certain enzymes, are quite specific to this class of compounds and are expected responses. However, the functional significance of such alterations is often not clear. Other potential endpoints that are functionally more relevant, such as cancer or immunosuppression, can be caused or influenced by a variety of factors and cannot, with current scientific technology and understanding, be unambiguously attributed to low-level POP exposures in free-ranging wildlife and humans.

Some of the adverse biological effects that are associated with exposure to PCB-like chemicals have been observed primarily in laboratory animals treated with relatively high doses. It is difficult, and in some cases not valid, to extrapolate results obtained from high dose animal laboratory studies to the possible effects that might occur in humans exposed to chronic low doses. “Chronic” effects such as cancer that are observed in animal studies at high doses may be related to frank cellular toxicity and resultant cell proliferation, whereas the subtle long-term effects of low doses may be related to a complex alteration of hormonal systems involved in cell proliferation and differentiation. There is a large degree of variability in susceptibility to PCB-like chemicals among species, and there can also be great inter-individual variability in susceptibility within a species (DeVito et al., 1995).

The most toxic PCBs exert their effects on organisms through a common mechanism (Poland and Knutson, 1982). In the cell, these dioxin-like chemicals bind to the aromatic hydrocarbon receptor (AhR) (Landers and Bunce, 1991), and the dioxin/AhR complex interacts with DNA. This interaction results in an alteration of

gene expression, which mediates the responses of the organism to dioxin-like chemicals (Landers and Bunce, 1991). The toxicity of individual congeners is determined by their relative affinities for the AhR. Congeners that can assume a coplanar configuration have a greater affinity for the AhR, and are thus the more toxic PCBs. Relatively few congeners are coplanar, and they are usually minor components of PCB mixtures in the environment.

As discussed earlier, it is common to compare the AhR-mediated potency of individual coplanar PCB congeners relative to the potency of the most toxic congener, in terms of a "TCDD equivalency factor" (TEF). This approach assumes that the toxicities of the congeners are additive, and that the congeners do not interact in an antagonistic or synergistic manner. The non-planar PCB congeners or their metabolites elicit some toxic responses, such as neurobehavioural, neurochemical, carcinogenic and endocrinological changes, that do not appear to be mediated by the AhR (Ahlborg et al., 1992). The TEQ approach cannot presently be applied to these non-AhR responses.

The degree of hazard associated with human exposure to PCBs and dioxins is of scientific controversy, and scientific opinions have changed over time (Hanson, 1991). In early assessments, TCDD was dubbed "the most toxic synthetic chemical known to man". This was largely due to its great potency in guinea pigs, which die following exposure to minute concentrations of TCDD (the LD50 is approximately 0.6 μg/kg for this species).

With further study, we learned that there are dramatic differences in species sensitivity to TCDD. For example, about a 1,000 to 10,000-fold greater dose of TCDD is required to kill a hamster than a guinea pig (DeVito and Birnbaum, 1994). On the comparative scale of species sensitivity, some scientists conclude that humans are relatively insensitive to the adverse effects of TCDD and other planar dioxin-like chemicals.

Following several large accidental PCB, dioxin and furan exposure incidents, the only observed adverse effects in humans that have been unequivocally linked to PCB- and dioxin-like chemicals have been chloracne (Suskind, 1985) and other skin disorders (Lu and Wu, 1985); there may also be an association with increased cancer incidence in heavily exposed populations (Bertazzi et al., 1987; Bertazzi et al., 1993; Fingerhut et al., 1991). Following an industrial accident in Seveso, Italy at which TCDD was released in large amounts, animal mortality was about 25% in the most directly impacted zone although none of the 733 persons present in the most contaminated zone were killed (Bertazzi and Di Domenico, 1994; Pocchiari et al., 1979). Current analyses continue the scientific controversy over the degree of human sensitivity to the toxic effects of dioxin-like chemicals (DeVito et al., 1995). Concern continues because exposure to chronic, low concentrations of dioxins may produce subtle toxic effects that are difficult to detect.

The industrial and occupational incidents that produced obvious deleterious effects in humans involved exposures to PCBs or dioxins that were orders of magnitude greater than the background exposures in the United States, or exposures related to the consumption of traditional foods in the Arctic. For example, adverse birth outcomes such as decreased birth weights, delayed developmental milestones and skin disorders occurred in the offspring of Taiwanese women who consumed rice oil contaminated with PCBs and furans. The average body burden of the women involved in that poisoning incident known as Yu-Cheng was 2130 ng TEQ/kg body weight, which was 164 times greater than the average human background body burden of 13 ng TEQ/kg body weight (DeVito et al., 1995).

The PCB/dioxin risks about which public health professionals and Alaska citizens are most concerned are chronic, long-term or subtle effects that may occur at very low dose levels from subsistence foods. The following evaluation will discuss four possible chronic effects that are of primary concern with regard to PCB/dioxin exposure: cancer, neurobehavioral changes, reproductive impairment and immunosuppression. In general, these negative health outcomes can all be caused or influenced by a variety of genetic, nutritional, physiologic, lifestyle, and other factors and are impossible to attribute unambiguously to low-level PCB or dioxin exposure in humans.

Cancer

Cancer is a group of many related diseases. All forms of cancer involve out-of-control growth and spread of cells (Alaska Cancer Registry, 2002). Cancer is classified by the part of the body in which it began, and by its appearance under a microscope. Different types of cancer vary in their rates of growth, patterns of spread, and responses to different types of treatment. Cancers occur in all human populations, and the incidence of cancer increases greatly with age.

In the United States, cancer is second only to heart disease as a cause of death, accounting for 22% of all deaths (Fraumeni et al., 1993). In 1998, cancer was the leading cause of death in Alaska, accounting for 25.2% of all Alaska resident deaths (Alaska Cancer Registry, 2002). Cancers have increased greatly in Americans in the past 40 years, due to a large increase in life expectancy and to the high incidence of cigarette smoking since the 1940s. In the United States, smoking accounts for about 40% of all cancer deaths in men and

about 20% of all cancer deaths in women (Fraumeni et al., 1993).

PCBs have been classified by the USEPA as probable human carcinogens. If PCBs cause cancer in humans, PCB-caused cancers are rare and account for only a tiny to negligible proportion of all cancers. Only a small proportion of cancers are related to exposure to hazardous chemicals from the workplace or environment (Ames et al., 1995).

PCBs and dioxins are known to cause cancer in laboratory animals that are experimentally exposed to high doses. The more highly chlorinated PCB mixtures cause liver cancer in rodents, probably through a promotion mechanism (Safe, 1989). The increased incidence of liver cancer in rodents usually occurs at high doses that are toxic to liver cells (Kociba et al., 1978; Tatematsu et al., 1979). The most toxic dioxin congener, TCDD, acts as a tumor promoter in laboratory animals (Pitot et al., 1980) but has weak or no initiation activity (Shu et al., 1987). That is, PCB- and dioxin-like chemicals may "promote" the growth of cells that have already been damaged by a different, initial insult during the first stage of carcinogenesis.

Tumor promotion appears to be mediated by the Ah receptor, and likely results from modifications in hormonal systems involved in cell growth and differentiation such as the epidermal growth factor and estrogen receptor. Coplanar PCBs with dioxin-like activity may act through a similar Ah-mediated tumor promotion mechanism. The doses of dioxin-like chemicals that were required to induce cancer in experimental animals were large, and involved an estimated body burden (in terms of ng TEQ/kg body weight) that was 100 to 10,000 times higher than the background body burdens of TEQs found in humans today (DeVito et al., 1995). A recent analysis has convincingly shown that humans are significantly less susceptible than rats to TCDD-induced carcinogenesis, and that low-level background exposures to TCDD are not associated with an increased cancer risk in humans (Aylward et al., 1996).

PCBs and dioxins can indirectly modulate the incidence of cancer caused by other chemicals. The induction of phase I and phase II drug-metabolizing enzymes can lead to either an increase or a decrease in the toxicity of a variety of chemicals. In some cases, potent carcinogens are metabolized and cleared from the body more rapidly following PCB- or dioxin-induced enzyme induction, or adduct formation is otherwise reduced, such that dioxin-like chemicals can be protective and act as anti-carcinogens. For example, aflatoxin B_1-induced hepatocellular carcinomas in trout can be inhibited by pre-initiation treatment with PCBs (Hendricks et al., 1977; Makura et al., 1974; Shelton et al., 1986). Exposure of women to high levels of TCDD has also been associated with a slight decrease in the incidence of estrogen-dependent cancers of the breast and uterus (Bertazzi et al., 1993), which could possibly be related to the antiestrogenic properties of TCDD (Safe et al., 1991).

A number of epidemiological studies have been performed to examine the incidence of cancer in human populations that have been accidentally exposed to high levels of PCBs or dioxins (Hardell et al., 1994). In general, it has been difficult to detect statistically significant differences in the incidence of relatively rare forms of cancer between PCB- or dioxin-exposed and control populations. Very large numbers of study subjects are required to detect such changes, because the risk is so low. For example, in a population of 4,824 people exposed to high levels of TCDD during a chemical plant explosion in Seveso, Italy (Zone B), six cases of hepatobiliary cancer were detected among those who had lived in the zone for at least five years (Bertazzi et al., 1993). This was a statistically significant increase in incidence from the 2.1 cases expected. Even following the extreme TCDD exposures experienced in Seveso, detecting a health impact was difficult because of the rarity of cancer incidence, the small number of exposed individuals, and the short length of follow-up.

A number of studies have been conducted to assess cancer risk in people with occupational PCB or dioxin exposures. In a large study of electric utility workers occupationally exposed to PCBs, mortality from malignant melanoma increased monotonically with increasing cumulative exposure to PCB insulating fluids (Loomis et al., 1997). A separate examination of the same cohort did not reveal a significant association between PCB exposure and mortality from prostate cancer (Charles et al., 2003). A recent meta-analysis of three cohorts occupationally exposed to dioxin-like compounds revealed an increase in total cancer mortality associated with a lifetime intake rate of 7 pg TCDD-TEQ/kg body weight/day, with no increased risk at 6 pg TEQ/kg body weight/day (Crump et al., 2003). For comparison, the U.S. EPA estimates the average current lifetime human exposures to dioxin to be approximately 1 pg TEQ/kg/day, with 99% of Americans being exposed to less than 3 pg TEQ/kg body weight/day (Crump et al., 2003).

Exposure to PCBs or dioxins has not been consistently associated with one particular form of cancer, but instead has been associated with different types of cancers in various studies. This observation confirms that if they cause human cancer, PCBs and dioxins are not directed towards one specific target organ, but exert a pleiotropic response that affects the endogenous regulation of cell differentiation and proliferation. However, certain types of cancer are more commonly associated with PCB or

dioxin exposure, including soft tissue sarcoma, cancers of the hematopoietic system, and cancers of the liver and extrahepatic biliary system.

In humans, occupational doses of PCBs or dioxins have been associated with cancer of the liver and extrahepatic biliary system, including the bile ducts and gall bladder (Brown, 1987). Among capacitor plant workers the geometric mean serum concentration of Aroclor 1242 was 1470 ppb versus 6.6 ppb in controls; 5 cancers were observed versus 1.9 expected. Liver cancer has also been observed in experimental animals treated with high doses of TCDD (Kociba et al., 1978). However, PCBs and dioxins are considered to be minor risk factors for hepatocellular carcinoma (HCC) in comparison to other known causes. It is estimated that approximately 75% of HCC cases worldwide can be attributed to one of three causes: hepatitis B virus, alcohol, or aflatoxin (a natural product of mold that can contaminate foods) (Falk, 1982). Cancers of the biliary tract are usually associated with the incidence of gall stones, although hormonal, nutritional and genetic factors are also important (Fraumeni and Kantor, 1982).

Limited data suggest that liver and gall bladder cancer rates may be elevated among Alaskan natives compared to the overall white population of the United States (Nutting et al., 1993). It is unlikely that PCB-like chemicals are involved in the etiology of these diseases, because exposures of Alaskan natives to PCBs and dioxins are much lower than those experienced by accidentally exposed human populations in which carcinogenic effects have been observed. The higher rate of liver cancer in Alaska Natives relative to the total U.S. population is due to a greater prevalence of hepatitis B infection among Alaskan Natives (Lanier et al., 1989).

It has been hypothesized that background exposures to organochlorines (such as PCBs or persistent pesticides) may increase the risk of breast cancer (Davis et al., 1993; Krieger, 1989). Many organochlorines have very weak estrogenic or anti-estrogenic activity, and exposure to endogenous estrogens is a known risk factor for development of breast cancer. A number of epidemiological studies have been conducted to determine whether organochlorine exposure is a significant risk factor for development of breast cancer. Some preliminary studies with small sample sizes reported higher organochlorine exposures in breast cancer patients relative to controls (Dewailly et al., 1994a; Falck et al., 1992; Wolff et al., 1993). However, several larger, recent, well designed studies have since shown that organochlorine exposures were not associated with an increased breast cancer risk (Hunter et al., 1997; Safe, 2000). However, one preliminary report indicated a possible increase in breast cancer risk among women with both elevated organochlorine exposure and a genetic polymorphism of the cytochrome P4501A1 gene (Moysich et al., 1999); further research is needed on this topic.

There are a number of reasons why a hypothesized breast cancer/organochlorine exposure link is not plausible (Safe, 1995; Safe, 2000). First, several epidemiological studies of women occupationally exposed to relatively high levels of DDT (Higginson, 1985) or PCBs (Brown, 1987) have not shown a higher incidence of breast cancer. Second, most organochlorines are not estrogenic, and the estrogenic activity of the others is very weak. The relative contribution of estrogenic organochlorines to total exogenous estrogen exposure is very small. For example, Safe calculated that, in µg/day, the birth control pill may contribute 16,675 estrogen equivalents per day, bioflavonoids naturally present in many foods contribute about 102 estrogen equivalents per day, and environmental organochlorine estrogens may contribute 0.0000025 estrogen equivalents per day (Safe, 1995). Some organochlorines such as TCDD are antiestrogenic, and dietary levels of antiestrogen equivalents (industrial or natural) are significantly higher than the estrogen equivalents of organochlorine pesticides or PCBs (Safe, 1995). Several researchers who have recently reviewed the organochlorine/breast cancer literature have reached the same conclusion: in the general population, the weight of evidence does not support a causative association between organochlorine exposure and breast cancer (Adami et al., 1995; Ahlborg et al., 1995; Laden and Hunter, 1998; Safe, 2000).

A substantial body of evidence has accumulated indicating that the incidence of testicular cancer in men has increased significantly since the 1960s (Crisp et al., 1998). There are marked differences in testicular cancer incidence levels between countries and between races. The incidence level of testicular cancer in Denmark is particularly high; it is about 5 times higher than in Finland. Cryptorchidism, a condition in which one or both testicles have not descended, is a known risk factor for testicular cancer. It has been suggested that exposure to environmental contaminants such as organochlorines may cause cryptorchidism and/or testicular cancer, through a process called endocrine disruption (discussed in detail in a later section of this report) (Harrison et al., 1997). The hypothesis that exposure to organochlorines may be responsible for the observed increase in testicular cancer incidence is not well supported, based on several lines of reasoning (Safe, 2000). First, while the overall incidence of testicular cancer has increased in all Scandinavian countries during the last 25-30 years, there has been an 80-90% decrease in average breast milk DDE concentrations, showing an inverse relationship between testicular cancer and DDE concentration (Ekbom et al., 1996). Second, the Scandinavian countries do not have major differences in human or environmental concentrations of organochlorines, yet their incidence

levels of testicular cancer are dramatically different. The environmental and lifestyle factors, including diet and occupational exposures, that are responsible for this disease are unknown and should be investigated (Safe, 2000).

Information available to date does not support the existence of a causal relationship between POP exposure and cancer incidence among Alaska Natives. In a recent study, no relationship was observed between the incidence of breast cancer and serum concentrations of PCBs or other organochlorine chemicals among Alaska Native women (Rubin et al., 1997). However, it is important to note that this study had limited power to detect such a relationship due to its relatively small sample size, and additional research is needed.

Immunotoxicity

The immune system may be the most sensitive target for PCB and dioxin toxicity in experimental animals. The evidence for clinically relevant immunotoxicity in PCB- or dioxin-exposed humans is less consistent (DeVito et al., 1995). However, there is concern that low levels of PCBs or dioxins may have subtle immunosuppressive effects in exposed humans, making them less able to avoid or combat infectious diseases or cancer. Alternatively, an enhanced immune response could have negative repercussions such an increased incidence of allergic reactions or autoimmune diseases. The immune system involves a complex interaction of many cell types and soluble mediators, and immune responses are time-dependent relative to antigen exposure. Immuno-toxicological assessments must consider these levels of complexity in order to produce interpretable results. A wide variety of immunological endpoints have been studied with regard to the toxicity of PCBs and dioxins.

Immunosuppressive effects of PCBs and dioxins are largely modulated through the Ah receptor (Kerkvliet, 1994; Silkworth and Grabstein, 1982). The immuno-toxicity of PCB/dioxin mixtures are often not additive, as certain PCBs antagonize the immunotoxic effects of other PCBs and dioxins including those of TCDD (Harper et al., 1995). Therefore, the TEQ approach cannot be accurately used to estimate the immunotoxic potency of PCB/dioxin mixtures at this time (Tryphonas, 1994).

Immunotoxic effects have been observed in marine mammals fed fish from contaminated areas. In a 2.5 year feeding study, captive harbor seals fed fish from the heavily polluted Baltic Sea exhibited an impairment of T cell mediated immune responses (De Swart et al., 1995) and a suppression of natural killer cell activity (Ross et al., 1996) in comparison to seals fed fish from the relatively uncontaminated Atlantic Ocean. Natural killer cells are an important first line of defense against viral infections (Golub and Green, 1991). Consumption of dioxin-like chemicals was about ten times higher in the Baltic herring-fed than in the Atlantic herring-fed seals (288 ng TEQ and 29 ng TEQ per day respectively) (Swart et al., 1994), and total TEQs in the blubber of test subjects following two years on the different diets were approximately 3.4 times greater in the Baltic than Atlantic-fed seals (Ross et al., 1996). Although these chemicals might have contributed to the immuno-suppression observed, it is possible that other immunosuppressive agents may have been present in the fish as well.

Consumption of Baltic Sea fish may also affect the human immune system, since reduced numbers of natural killer cells were found in the blood of 23 adult males with high fish consumption relative to a group of 20 men who did not eat fish (Svensson et al., 1994). Differences in natural killer cell numbers were small, however, and all other immune system parameters measured were not significantly different between the two groups. A number of constituents that can impair the activity of natural killer cells were present in the fish and were highly intercorrelated, including methyl mercury, PCBs and dioxins, p,p'-DDT, and omega-3 polyunsaturated fatty acids. Therefore, the specific causative agent of natural killer cell impairment could not be identified. Furthermore, the observed differences were not likely to have functional significance. It should be emphasized that concentrations of POPs are much lower in Alaskan fish than in fish from the highly contaminated Baltic Sea. In one study, concentrations of PCBs and DDTs were ten times lower in cod from the Western Tana Fjord (Barents Sea) than in cod from the Gulf of Finland (Baltic Sea) (Vuorinen et al., 1989).

There is some concern that contaminant-induced immunosuppression may have contributed to a number of epizootics in recent years among seals and dolphins inhabiting polluted coastal waters (Aguilar and Borrell, 1994; Sarokin and Schulkin, 1992). In mice, enhanced susceptibility to influenza virus was observed following a single dose of 10 ng TCDD/kg body weight, making viral host resistance the most sensitive adverse effect yet reported for TCDD in this species (Burleson et al., 1996). In Europe, a large number of marine mammals died from infections with morbillivirus, and it is hypothesized that environmental contaminants may have rendered the stricken animals less immunocompetent to fight the disease (Hall et al., 1992). If such trends were global in nature, a decrease in marine mammal populations due to reduced immunocompetence could negatively affect Alaskan natives by reducing their traditional food supply. Fortunately, most Alaskan marine mammals are not exposed to the same degree of contamination as are

marine mammals from industrial coastal areas. For example, PCBs in common seals from the North and Baltic Seas were 34 times higher than PCBs in ringed seals from the arctic island of Spitzbergen (Luckas et al., 1990). Large-scale marine mammal epizootics such as those described in Europe and the east coast of the continental U.S. have not been observed in Alaska.

Different approaches have been used to study immunological endpoints of PCB and dioxin exposure in humans. Endpoints such as the incidence of infections and the response to vaccinations are integrated measurements of immune function that are highly relevant to human health, but they are non-specific to PCB or dioxin exposures. The number and relative quantities of various subsets of immune-related cells (lymphocytes) can function as specific markers of immune function, and they are often quantified in the blood. Immune cells from PCB- or dioxin-exposed humans can be cultured, and their proliferative response to challenge with specific mitogens or antigens can be assessed. Investigations of the *in vitro* function of immune cells in culture can diagnose specific aspects of the immune system, but are more difficult to relate to *in vivo* relevance.

Most immunological parameters have a very broad range of normal values, and small differences are often not biologically meaningful (Kerkvliet, 1994). Many of the *in vitro* assays that have been performed with immune cells from PCB- or dioxin-exposed humans have produced conflicting results in different studies. There are at least two possible reasons for this. First, *in vitro* assays can be greatly influenced by laboratory procedures and culture conditions. For example, when 23 commercial lots of serum were tested as components of cell culture media for *in vitro* assays, five of the serum lots supported a suppression of T-dependent humoral immune response while the remaining lots demonstrated an apparent protective effect against the TCDD exposure (Morris et al., 1991). Second, *in vitro* studies remove the complex influence of non-lymphoid factors on immune function, such as circulating endocrine hormones. Endocrine hormones such as glucocorticoids, sex steroids, thyroxine, growth hormone and prolactin are involved in the regulation of the immune response, and many of these hormones are influenced by PCBs and dioxins (Kerkvliet, 1994). The *in vivo* response to an antigen challenge such as sheep red blood cells (SRBD) can also be measured. One advantage of this approach is that it integrates the interactions of many immune systems components as well as non-lymphoid factors such as the endocrine system.

Epidemiological investigations of immunological characteristics have been performed in several human populations that were accidentally exposed to relatively high concentrations of PCBs or dioxins. The epidemiological studies were often limited by small sample sizes, and exposures to PCBs and dioxins were often not measured. The studies were conducted at very different times post-exposure. In some cases several decades had elapsed between the time of exposure and the time of evaluation. This could be a problem because immunological parameters could recover over time following an accidental exposure. Representative studies are presented in Table 5, which illustrates only a fraction of the wide variety of endpoints that have been measured and the inconsistency of the results obtained among various studies.

The incidence of infections has been related to accidental PCB, dioxin and/or furan exposures in several human populations. In Taiwanese Yu-Cheng patients accidentally exposed to rice oil contaminated with PCBs and furans, “frequent” infections of the respiratory tract and skin were observed, although the incidence was not compared with a control group (Lu and Wu, 1985). In a follow-up study, Yu-Cheng children exposed prenatally to the contaminated rice oil had a significantly higher incidence of middle-ear diseases than did controls, and middle-ear disease incidence was correlated with serum dibenzofuran concentrations (Chao et al., 1997). Sixteen years after the Yu-Cheng incident, no dose-response relationship was found between 27 Yu-Cheng children’s serum PCB/furan concentrations and any immunologic markers (Yu et al., 1998). Following the accidental release of large quantities of TCDD in Seveso, Italy, an increase in reports of infectious childhood diseases occurred, but it was thought to be due to increased reporting by doctors rather than to TCDD exposure per se (Pocchiari et al., 1979).

Several larger epidemiological studies have recently been conducted in Europe to examine the possible relationship between immunocompetence and background levels of PCB- and dioxin-like exposures in children. In a population from the Netherlands with a relatively high background exposure to PCBs and dioxins, there was no significant correlation between pre- and post-natal exposure to these chemicals and the number of infections during the first 18 mo of life, or in vaccination effectiveness in the infants (Weisglas-Kuperus et al., 1995). In a follow-up study of the same children, plasma PCB concentrations at 42 months were associated with a higher prevalence of recurrent middle-ear infections and chicken pox, and a lower prevalence of allergic reactions (Weisglas-Kuperus et al., 2000). In a study of 200 teenagers from Belgium with background PCB/dioxin exposures, dioxin TEQ concentrations in serum were also negatively associated with allergic responses to house dust mites, cat dander and grass pollen (Van Den Heuvel RL, 2002). These results are consistent with a laboratory experiment in which rats exposed to 2,3,7,8-

TCDD exhibited a suppression of allergic immune responses to house dust mite allergen (Luebke et al., 2001).

The possibility of PCB- or dioxin-induced immunosuppression among the Canadian Inuit was proposed, related to the incidence of infectious diseases such as otitis (Julien et al., 1987) and meningitis (Proulx, 1988). The incidence of these diseases has been much greater in infant Inuit from northern Quebec than in infants from other populations, and there has been speculation that PCBs and/or dioxins in Inuit food might have been responsible via immunosuppressive mechanisms (Dewailly et al., 1989; Dewailly et al., 1993). In a recent study of the Nunavik population, prenatal exposure to some organochlorines (as measured in immature breast milk of the mother) was associated with an increased risk of developing acute or recurrent otitis media (middle-ear infection) (Dewailly et al., 2000). The organochlorines most commonly associated with an increased risk of otitis media included the pesticides hexachlorobenzene, p,p'-DDE and dieldrin; a statistically significant relationship with PCBs was not observed. Dioxins, furans and coplanar PCBs were not measured in the study.

A substantial body of scientific evidence reveals that other known risk factors are actually responsible for the high incidence of otitis media among the Inuit. These risk factors for otitis media include low socioeconomic status, family history, house-crowding, anatomical factors such as morphology of the Eustachian tube, exposure to tobacco smoke, and genetic factors (Infante-Rivard and Fernandez, 1993; Julien et al., 1987; Lim et al., 1998; Stathis et al., 1999). Race may be an important risk factor for otitis media. Historically, American Indians, Canadian Eskimos and Native Alaskans have experienced a much greater prevalence of otitis media than have white children, while black children seem to be at lesser risk than white children (Infante-Rivard and Fernandez, 1993).

Confounding factors make assignment of causality difficult for otitis media cases. Breast feeding has been shown in many studies to be a significantly protective factor against the development of otitis media (Infante-Rivard and Fernandez, 1993), despite the fact that infants may be exposed to POPs in breast milk. Also, there are potential confounding immunosuppressive influences within the fish diet itself, such that it would be difficult to separate the influence of POPs. For example, the omega-3 polyunsaturated fatty acids found in fish are potent immunosuppressive agents (Blok et al., 1996; Kelley and Daudu, 1993).

No clear pattern of PCB- or dioxin-mediated immunotoxicity in humans has emerged from epidemiological studies (Table 5). Parameters such as the CD4/CD8 ratio, immunoglobulin levels and lymphocyte proliferation were decreased in PCB- and/or dioxin-exposed individuals in some studies, but increased or unaffected in exposed individuals in other studies. It is also important to recognize that the effects of chronic low-level exposures to PCBs or dioxins may be fundamentally different from those that occur following accidental high-dose exposures. In marmoset monkeys, the effect of repeated low exposures of TCDD on a T cell subpopulation (helper-inducer or "memory" cells) was the opposite of that which occurred at higher exposures (Neubert et al., 1992). Therefore, extrapolations from data obtained at high TCDD dose levels to much lower exposures are probably not justified with respect to immune system effects, and the "possible effects induced by high occupational exposures or in victims of accidents are not necessarily to be expected .... at the much lower exposures of the general population" (Neubert et al., 1992).

Reproductive and Developmental Toxicity; "Endocrine Disruption"

Human reproduction and fetal development are regulated by the endocrine system, and involve a complex interplay of hormonal signals that can produce their effects at minute doses. Chemicals that interfere with the normal functioning of hormonal signals have been called "endocrine disruptors". The developing fetus is considered the most vulnerable and sensitive member of the population to endocrine disruption, because hormones play such a crucial role in fetal development. One important difference between exposure to endocrine disruptors during critical periods in development versus during adulthood is the irreversibility of an effect during development (Bigsby et al., 1999).

Xenobiotic chemicals (that is, chemicals originating from outside the body) can interfere with hormonal signals in a variety of ways. Some chemicals interact with hormone receptors. At times the chemical interacting with the receptor acts as an agonist, and mimics the hormone to "turn on" the receptor and induce biological effects. In other cases the chemical interacting with the receptor acts as a hormone antagonist. Effectively, it does not "turn on" the receptor but instead blocks the hormone from the receptor site, such that the hormone can not carry out its intended function (Klinge et al., 1992). Xenobiotics can also interfere with signals by altering the production, metabolism or clearance kinetics of hormones, or by influencing the regulation of hormone receptor levels.

It has long been recognized that exposure to some xenobiotic chemicals can interfere with hormonal signals and result in adverse consequences (Birnbaum, 1994). Some plants found in nature produce chemicals that can cause sterility in the livestock or wildlife that consume

them (Cheeke and Shull, 1985). Also, the drug diethylstilbestrol (DES) produced vaginal cancer and other abnormalities of the reproductive organs in female offspring of mothers who took the drug during pregnancy (Herbst, 1981). These adverse outcomes were not expressed until the daughters reached puberty. This drug is a potent mimic of the female hormone 17-B-estradiol, and it produced its negative effects by altering the delicate hormonal balance of sex hormones in the womb during the critical period for sexual differentiation and development.

More recently, environmental contaminants have been implicated as one of the causes of reproductive abnormalities in wildlife. Severe developmental abnormalities of the reproductive system were observed among hatchling alligators from a pesticide-contaminated Florida lake, including abnormal gonadal morphology, abnormal sex steroid concentrations, elevated neonatal mortality, and significantly reduced phallus size in male juveniles (Guillette, 1995). Low female reproductive activity and success were observed in belugas from the St. Lawrence Estuary in Canada, along with reproductive tissue disorders such as ovarian tumors and mastitis (Beland et al., 1993). Beluga blubber from the St. Lawrence estuary population was found to contain very high concentrations of PCBs and organochlorine pesticides (Martineau et al., 1987; Muir et al., 1990), as well as PAHs and heavy metals. Environmental contaminants are a suspected cause of the St. Lawrence beluga's reproductive and other health problems (De Guise et al., 1995), although some feel the problem has been overstated, and population estimates and cancer rates for St. Lawrence beluga are controversial (Hammill et al., 2003; Kingsley, 1998).

Hermaphrodism (a full set of both male and female sexual organs) and pseudohermaphrodism (ambiguity only in the external or internal genitalia, but not the gonads) have been documented in several arctic marine mammal individuals. A true hermaphrodite was discovered in the St. Lawrence beluga population (De Guise et al., 1994), and four female pseudohermaphrodite polar bears were recorded at Svalbard (Wiig et al., 1998). Relatively high organochlorine concentrations have been measured in both of those populations, and organochlorine-induced endocrine disruption has been suggested as a potential cause of the abnormalities. Two male bowhead whales taken by subsistence hunters near Barrow, Alaska were also classified as pseudohermaphrodites (O'Hara et al., 2002). It is unlikely that organochlorine contaminants caused pseudohermaphrodism in the bowhead, because organochlorine concentrations are quite low in that filter-feeding species (Table 3).

The process of sexual differentiation is particularly sensitive to hormone alterations. The differentiation of sex organs from bipotential gonadal tissue occurs during early prenatal development and is determined by the milieu of sex hormones present during a critical period (Crews et al., 1995; Loomis, 1986). In experimental animals, sexual differentiation of the brain and many aspects of adult sexual behavior are also determined by sex hormones present in the womb during finite critical periods of development. For example, early sex hormone administration can have profound permanent sex reversing effects on adult behavior in birds (Adkins-Regan, 1987). When male Japanese quail embryos are injected with 1 μg estradiol or 500 μg testosterone during a critical period of incubation, they can be completely behaviorally sex reversed. As adults they fail to mount, crow, or strut; they are completely demasculinized and are behaviorally indistinguishable from females (Adkins, 1979). This effect is due to a fundamental change in the neural substrate underlying behavior.

Recently there has been great concern that environmental contaminants, including PCBs and dioxins, may "disrupt" the endocrine system and cause deleterious reproductive and developmental effects in exposed wildlife and humans (Birnbaum, 1994; Brouwer et al., 1995; Brouwer et al., 1999; Harrison et al., 1997). Although much attention has been paid to the "estrogenic" activity of various xenobiotic chemicals (perhaps due to the model toxicity displayed by DES), this is an overly simplistic approach to the issue.

Chemicals may have estrogenic, anti-estrogenic, androgenic or anti-androgenic activities, which can by different mechanisms each alter the effective hormonal milieu in the womb (Crisp et al., 1998). TCDD and structurally related chemicals displayed anti-estrogenic properties in human breast cancer cells (Krishnan and Safe, 1993). The complex mixture of estrogenic and anti-estrogenic chemicals humans are exposed to through the environment and diet may be contra-active, and result in an insignificant overall effect (Safe, 1994a). A more holistic approach to the problem of POP-induced endocrine disruption recognizes the profound interdependence of hormones, other soluble factors and immune system parameters in the body. Through alterations in gene expression PCBs and dioxins can influence a wide variety of hormones and soluble regulatory factors and alter the communication between cells, possibly by influencing gap junctions (Trosko et al., 1981). They therefore have the ability to influence reproduction and development not only by mimicking or blocking sex hormone activity, but also by altering processes of cell differentiation and growth during critical periods.

It is necessary to consider several factors when evaluating the potential for xenobiotics to interfere with the endocrine system. The potency of the xenobiotic and

the timing of the exposure at the relevant target cell or organ are both crucial. The dramatic disruption of a process such as sexual differentiation can only happen during a very limited time period, which may only last a few days. The nature of the exposure can greatly influence the effect observed. Some hormones are only active when presented as pulses, while slow steady exposures are not active (Gangong, 1985). Due to the complexity of the biological systems involved, information obtained from *in vitro* screening assays (for example, for estrogen receptor binding) should be interpreted with caution until the chemical in question has been confirmed to produce reproductive or developmental toxicity *in vivo* using realistic exposure concentrations and scenarios.

Endocrine disruptive potency and the nature of dose/response relationships are critical to understanding potential effects. Many of the pesticides that have been termed "estrogenic" exhibit activity that is at least a thousand-fold weaker than endogenous estradiol, and very high doses of the pesticides were required to elicit observable estrogenic effects in experimental animals (Eroschenko, 1981; Kupfer and Bulger, 1980). The intake of environmental contaminant-related "estrogen equivalents" is minuscule in comparison to the quantity of "natural" estrogens produced by the body or consumed in food, and under most conditions it is unlikely that trace contaminants could contribute significantly to the body's estrogen balance (Safe, 1995). However, there is some evidence that endocrine disruption effects do not always display a monotonic dose-response relationship (monotonic means that as the dose increases, the response either increases or stays the same) (Bigsby et al., 1999; vom Saal and Sheehan, 1998; Welshons et al., 2003). For example, high doses of estrogens inhibited an effect (enlargement of the fetal mouse prostate) that was stimulated by much lower doses, demonstrating an inverted U-shaped dose-response curve (vom Saal et al., 1997). In an *in vitro* bioassay several natural phytoestrogens were anti-estrogenic at low concentrations (via aromatase inhibition), but estrogenic at high concentrations, exhibiting U-shaped dose-response curves (Almstrup et al., 2002). These experiments demonstrate the importance of performing dose-response assessments for endocrine disruptors across a wide range of doses, from levels encountered in the environment through doses that produce acute toxicity. Since standard toxicity testing protocols call for in vivo testing at maximum tolerable dosages (Daston et al., 1997), over typically a maximum of a 50-fold dosage range, they may be inadequate to characterize relevant low-dose endocrine disruptive effects (Bigsby et al., 1999).

Dioxins have exhibited reproductive and/or developmental toxicity in several animal models (Theobald and Peterson, 1994). For example, in the rat a single maternal oral dose of TCDD on day 15 of gestation resulted in an impairment of several reproductive parameters in male offspring. Maternal doses as low as 0.16 μg TCDD/kg body weight produced significant dose-related delays in testicular descent, decreases in seminal vesicle and ventral prostate weights at several stages of sexual development (Mably et al., 1992c), and sexual behavior during adulthood was demasculinized in male offspring (Mably et al., 1992b). Decreases in epididymis and cauda epididymis weight, daily sperm production, and caudal epididymal sperm number were observed at the lowest maternal dose tested (0.064 μg TCDD/kg body weight) (Mably et al., 1992a). Despite these alterations, reproductive outcomes of matings between the male offspring and control female rats were not significantly impaired during this study, even at the highest dose tested (1.0 μg TCDD/kg body weight) (Mably et al., 1992a).

Endpoints related to reproduction have been investigated in human males exposed to PCBs, dioxins and/or furans. Some sperm quality deficits were observed in Yu-Cheng males exposed to PCBs and PCDFs relative to controls, including abnormal morphology, oligospermia, and reduced oocyte penetration (Hsu et al., 2003). It has been reported that sperm counts have dramatically decreased in humans during the past 50 years throughout the world (Carlsen et al., 1992), and it was suggested that environmental contaminants might be to blame (Colborn et al., 1996). It has similarly been noted that testicular abnormalities have increased in recent decades, and might also have an environmental cause (Giwercman et al., 1993). Endocrine-modulating chemicals such as POPs are often implicated as possible culprits of male reproductive toxicity in the literature (Colborn et al., 1996). The evidence in support of POP-induced sperm count declines is, however, nonexistent. There is serious debate as to whether a decline in sperm count has even occurred (Bromwich et al., 1994; Lipshultz, 1996). Sperm counts vary dramatically among geographic areas, and many of the differences originally detected were related to geographic location rather than to time (Fisch and Goluboff, 1996; Paulsen et al., 1996).

Several studies have investigated the effect of TCDD exposure on testosterone and gonadotropin concentrations in human serum. Testosterone concentrations were lower in industrial workers exposed to TCDD than in a reference population, while luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations were higher in the TCDD-exposed workers than in the reference population (Egeland et al., 1994). The hormone differences measured were of no biological significance, as the magnitude of the measured hormone differences was very small. Primary gonadal failure was not involved, because low testosterone and high LH and FSH

were not observed in the same individuals. The workers in that study had rather high concentrations of TCDD in serum (63% had concentrations above 33.3 ppt). Testosterone and gonadotropins were measured in another group of TCDD-exposed males, the Ranch Hand veterans involved in herbicide application in Vietnam (Henriksen et al., 1996). In that cohort TCDD body burdens were lower (only 26% had TCDD concentrations above 33.3 ppt in serum), and no consistent or meaningful associations between TCDD and hormone concentrations were found. In a related study of the Ranch Hand veterans, an association between paternal dioxin concentrations and reproductive outcomes such as birth defects and developmental disabilities was not apparent (Wolfe et al., 1995).

Several epidemiological studies of dioxin-exposed cohorts have documented apparent sex ratio skews in their offspring, with an abnormally low proportion of male babies born. The mechanism for a possible sex-ratio skew is unknown, although a modification of hormonal balance may be involved. A differential ovopathy mechanism has also been suggested (Jongbloet et al., 2002). A sex ratio skew was noted in the offspring of the Seveso population, who were exposed to high concentrations of TCDD following an industrial accident (Mocarelli et al., 1996). High TCDD exposure in both parents, as measured in serum samples collected the year of the accident, was associated with an excess of female offspring. In the 74 total births occurring in the "A-zone" during the first 7 years after the accident, 26 were males and 48 were females. This ratio declined (60 males vs 64 females) in the years from 1985 to 1994 and was no longer significant. Further study of the Seveso cohort revealed that the effect was associated with paternal, not maternal, TCDD exposure (Mocarelli et al., 2000). Similarly, a recent study of an occupationally-exposed cohort in Russia documented an excess of female children associated with their fathers' exposure to dioxins (Ryan et al., 2003). The sex ratio was normal in offspring of TCDD-exposed mothers, but for 150 fathers exposed to dioxins at the pesticide production plant, the subsequent sex ratio of offspring was 0.38 males/(total males + females) (the normal ratio is 0.51). However, a sex ratio skew was not observed in offspring of a large occupationally-exposed U.S. cohort of fathers (Schnorr et al., 2001).

Several lines of evidence point to an association between endometriosis and exposure to dioxin-like compounds (Birnbaum and Cummings, 2002). Endometriosis is characterized by the growth and proliferation of endometrial cells at sites outside the uterus, and occurs exclusively in menstruating species. Both mild and severe forms are associated with infertility and chronic pain. One study involving chronic, low-level exposure of rhesus monkeys to TCDD detected an elevated and dose-related incidence of moderate to severe endometriosis in monkeys from both dioxin treatment groups (Rier et al., 1993). This negative outcome was discovered over seven years after termination of dioxin treatment, when several monkeys died from fulminating endometriosis. In the same experiment, compromised reproductive outcomes were observed in the high dose group (25 parts per trillion in food for four years) (Bowman et al., 1989). Although five of eight females in that group conceived, only one gave birth to a viable infant. Unlike dioxin, PCBs do not appear to cause endometriosis. In a recent reproductive toxicology study, ingestion of PCB Aroclor 1254 did not increase the incidence or severity of endometriosis in rhesus monkeys (Arnold et al., 1996). More research is needed to definitively determine whether dioxin exposure is a risk factor for endometriosis in humans (Birnbaum and Cummings, 2002).

Reproductive outcomes in humans have been assessed for relationships with POP exposure. Exposure to POPs was often not adequately measured in study subjects in these epidemiological studies (Sweeney, 1994). The possible relationship between fetal mortality and POP exposure has been examined in several studies. Many early resorptions occur prior to the clinical recognition of pregnancies, which makes it very difficult to quantify any early-stage mortality that might be associated with POP exposure. The contamination of the Michigan food supply with polybrominated biphenyls in the mid-1970's did not have a detectable impact on the rate of late spontaneous abortions (after 20 weeks gestation) (Humble and Speizer, 1984). In New York state, consumption of Lake Ontario fish that contained PCBs and other environmental contaminants was not associated with an increased risk of spontaneous fetal death (Mendola et al., 1995).

Several studies have reported an association between POP exposures and altered sexual maturation in pubertal children. Among Yu-Cheng children exposed in utero to PCBs and PCDFs, girls were significantly shorter, and boys aged 11 to 14 had a significantly shorter penis length, compared to their matched controls (Guo et al., 1993). In Belgium, PCB exposure has been associated with delayed genital development in boys, while dioxin exposure has been associated with delayed breast development in girls (Hond et al., 2002). The children in the Belgian study were only exposed to background POP levels. Women who were exposed to TCDD as pre-pubertal children in the Seveso, Italy industrial accident may have experienced altered menstrual cycles as adults. For women who had been pre-menarcheal at the time of the explosion, a 10-fold increase in serum TCDD concentration was associated with an increase in menstrual cycle length of almost 1 day (Eskenazi et al., 2002).

Birth size and gestational age have also been examined in relation to POP exposure, because decreased prenatal growth has been observed in animals treated with TCDD (Theobald and Peterson, 1994). Small decreases in gestational age (6.6 days) were noted among female workers occupationally exposed to PCBs (Taylor et al., 1984). Birthweights were also reduced in infants born to the occupationally exposed women, but most of that reduction was explained by the decreased gestational age. An association between PCB exposure and decreased infant birth weight was also observed in a population of women who consumed large quantities of Lake Michigan fish (Fein et al., 1984), but the influence of other chemicals present in the fish could not be adequately determined due to the low resolution analytical methodology employed. In a population in North Carolina with background PCB exposure, there was no relationship observed between PCB concentrations in maternal milk fat at birth and infant birth weight (Rogan et al., 1986).

Hydroxylated PCB metabolites can disrupt thyroid hormone and vitamin A homeostasis, which can affect many aspects of metabolism and prenatal development. The effects of PCBs on fetal and neonatal growth and development may be related to thyroid regulation (Feeley, 1995), although the relationship between thyroid hormone concentrations and PCB exposure has been inconsistent among studies of human infants (Koopman-Esseboom et al., 1994b; Nagayama et al., 1996; Pluim et al., 1993). Hydroxylated PCB metabolites have a thyroid hormone-like affinity for the serum transport protein transthyretin (TTR) (Cheek et al., 1999). Transthyretin is involved in the transport of vitamin A (retinol) to target tissues, and is also a carrier of thyroid hormones. When hydroxylated PCBs bind to TTR, unbound vitamin A is cleared from the body rather than being delivered to target tissues, and plasma concentrations of vitamin A drop rapidly (Brouwer and Van Den Berg, 1986). Similarly, serum thyroxine (T4) plasma concentrations drop when hydroxylated PCBs compete with T4 for TTR binding (Brouwer and Van Den Berg, 1986). Treatment of rats with 2,3,7,8-TCDD also induced an increased mobilization of retinoids from storage sites into serum, accompanied by an enhanced elimination via the kidney into the urine (Brouwer et al., 1989). When vitamin A homeostasis is disturbed in this manner, vitamin A storage in the liver is ultimately reduced. Vitamin A plays an important role in reproduction, prenatal development, and disease resistance, and many toxic symptoms of PCB exposure resemble those of vitamin A deficiency (Murk et al., 1998). In European otters environmentally exposed to PCBs, otters with an internal dose of more than 2 ng TCDD-TEQs/g lipid had strongly reduced hepatic retinoid concentrations, which coincided with a higher incidence of infectious diseases (Murk et al., 1998). Recently, some brominated flame retardant metabolites were found to bind to human TTR *in vitro* with greater affinity than did thyroxin (T4), suggesting that they may affect thyroid hormone homeostasis *in vivo* similar to hydroxylated PCBs (Meerts et al., 2000).

In conclusion, exposure of humans to high levels of PCBs, dioxins and/or furans following industrial accidents or severe poisoning incidents has resulted in some adverse reproductive outcomes. Skin discoloration and eye discharge were observed in infants born to women who consumed PCB- and furan-contaminated rice oil during the Yusho and Yu-Cheng poisoning incidents (Hsu et al., 1994; Masuda, 1994). Following the Yu-Cheng incident in Taiwan, children exposed to PCBs and furans *in utero* exhibited increased abnormalities of the gums, skin, nails, teeth and lungs, as well as developmental delays and reduced cognitive function, relative to controls (Rogan et al., 1988). Other adverse outcomes are less well documented but may have occurred following these extreme exposures, including increased rates of spontaneous abortion, stillbirths and birth defects. On the other hand, low level, background exposures such as those experienced in the Arctic are not likely to present a significant risk to human reproductive outcomes. Epidemiological studies focused on fish-eaters or others with background POP exposures have not shown consistent results, and any effects observed have been very minor.

Neurotoxicity

PCB-like chemicals have caused a number of changes in the neurochemistry and neurobehavioral development of laboratory animals. Interestingly, it appears that many of the neurotoxicological effects of PCBs may not be regulated by interaction with the Ah receptor. In fact, many of the neurotoxicological effects have been attributed to the non-Ah active PCB congeners that have chlorine atoms at two or more ortho positions. While TCDD and coplanar congeners have been observed to affect the nervous system, the effects are qualitatively and quantitatively different from those caused by PCB mixtures (Schantz and Widholm, 2001; Seegal and Schantz, 1994b). In this important respect, the neurotoxicity of PCBs, dioxins and related chemicals is quite different from other endpoints of toxicity that have been previously discussed.

Feeding studies with non-human primate adults and rodent adults have demonstrated that ortho-substituted PCB congeners can cross the blood-brain barrier and induce changes in the concentration and activity of the neurotransmitter dopamine in the brain (Seegal et al., 1991; Seegal et al., 1994). The relationship between PCB exposure and dopamine concentrations is complex, and appears to be dependent upon the magnitude of the dose, the age at exposure, and perhaps the composition of the

PCB mixture. For example, adult nonhuman primates fed 3.2 mg Aroclor 1016/kg body weight daily for 20 weeks exhibited a decrease in brain dopamine (Seegal et al., 1994), while female rats born to mothers fed 100 ppm Aroclor 1016 exhibited an increase in brain dopamine and other neurotransmitters (Seegal and Schantz, 1994b). Some studies with rats have shown that ortho-substituted PCB congeners reduce brain dopamine concentrations in both the adult and developing nervous systems, while coplanar, dioxin-like congeners are active only during development (Brouwer et al., 1995). It has been hypothesized that PCBs may cause deficits in spatial learning and memory by altering dopamine input to the dorsolateral area of the prefrontal cortex (Seegal and Schantz, 1994b).

PCBs are also suspected of causing neurotoxic effects via other mechanisms. Some ortho-substituted congeners cause acute neuronal cell death in cerebellar granule cells (Carpenter et al., 1997; Kodavanti and Tilson, 1997), perhaps by interfering with calcium homeostasis (Kodavanti et al., 1996). Exposure of rats to PCB 153 has also been found to reduce long-term potentiation in the hippocampal area of the brain, which may adversely affect learning ability (Hussain et al., 2000). Others suspect that endocrine disruption and hormonal factors may play an important role in PCB neurotoxicity (Brouwer et al., 1999; Porterfield and Hendry, 1998). For example, similar detriments in auditory-evoked potentials can be induced by fetal hypothyroidism and by perinatal exposure to PCB-like chemicals. In one important experiment, hearing deficits induced in rats perinatally exposed to PCBs appeared to be directly linked to alterations in the thyroid hormone system (Goldey et al., 1995).

Animal behavioral studies have been undertaken to determine the functional significance of PCB- and dioxin-induced changes in the nervous system. It is clear from laboratory animal studies that developmental exposure to PCB mixtures or ortho-substituted PCB congeners results in long-lasting deficits in learning and memory (Schantz and Widholm, 2001). Spatial learning and memory are particularly impaired by ortho-substituted PCB congeners. In contrast, animals exposed to dioxin or coplanar PCBs often exhibit improved performance on spatial learning tasks, but are impaired on object learning tasks (Seegal and Schantz, 1994a). In general, the cognitive effects of dioxins and coplanar PCBs are limited in scope, with the primary effect being an improvement in working memory (Schantz and Widholm, 2001).

In a series of experiments in which monkeys were exposed perinatally to either TCDD or PCBs, learning was impacted in both cases but in qualitatively different ways (Seegal and Schantz, 1994b). Monkeys born to mothers fed 1.0 ppm Aroclor 1016 exhibited impaired spatial discrimination-reversal learning but facilitated object discrimination-reversal learning (Schantz et al., 1989), while the exact opposite effect was observed in monkeys born to mothers fed 5 ppt TCDD (Bowman et al., 1990; Schantz and Bowman, 1989). In addition, monkeys born to mothers fed 2.5 ppm Aroclor 1248 exhibited impaired performance on delayed spatial alternation tests at 4 to 6 years of age, although they had not been exposed since they were weaned at 4 months of age (Levin et al., 1988). In contrast, these deficits were not seen in TCDD-exposed monkeys (Seegal and Schantz, 1994b).

Clear impairments of spatial learning were also seen in 3 to 4-year-old monkeys that had been exposed to a PCB mixture from birth to 20 weeks of age, which was formulated to represent the PCBs typically found in human breast milk (Rice, 1997; Rice and Hayward, 1997). Those results are of particular concern because exposure was to an environmentally relevant PCB mixture, and fat and blood PCB concentrations in the exposed monkeys were similar to those typically found in human populations. Impaired spatial learning has also been observed in ortho PCB-exposed rats (Schantz et al., 1995b), but not in coplanar PCB-exposed rats (Rice, 1999; Schantz et al., 1996). Impairments in nonspatial, cue-based discrimination-reversal learning (object learning) have been observed in dioxin-exposed rats (Seo et al., 1999) and monkeys (Seegal and Schantz, 1994a).

Recently, the developmental neurotoxicity of several brominated flame retardants was investigated (Eriksson et al., 2001). Neonatal mice were exposed to a single oral dose of either polybrominated diphenyl ether (PBDE) 47, PBDE 99, or tetrabromo-bis-phenol-A (TBBPA) on postnatal day 10. The animals were then subjected to several neurobehavioral tests at 2 and 4 months of age. Exposure to TBBPA did not cause any significant change in performance. However, exposure to PBDE 99, and to a lesser degree PBDE 47, affected spontaneous behavior, habituation capability, and learning and memory in adult mice. These effects were induced at doses similar to those used in PCB studies, and the animals' weight gain was not affected.

Several large epidemiological studies have been undertaken in an attempt to determine what effect PCB- and dioxin-like exposure may have on the neurological system of exposed humans. These efforts have largely focused on the neurological development and cognitive functioning of children exposed *in utero* to PCBs, dioxins and/or furans. In the Yu-Cheng poisoning incident in Taiwan, children that received high doses of heat-degraded PCBs and dibenzofurans *in utero* displayed a significant decrease in cognitive function when compared with matched controls (Chen et al., 1992). Yu-Cheng children scored approximately 5 points

lower than controls on several standard intelligence tests, an effect that remained consistent during yearly tests from 2.5 to 7 years of age. In contrast to the Yu-Cheng study of a highly exposed population, several other neurodevelopment studies have focused on children exposed to lower, background concentrations of PCBs and dioxins.

In one series of studies, the maternal consumption of fish from Lake Michigan was found to be associated with impaired intellectual function in young children (Jacobson et al., 1990; Jacobson et al., 1992; Jacobson and Jacobson, 1996; Jacobson et al., 1985). This impairment was attributed to *in utero* exposure to PCBs from the fish. The maternal consumption of fish from Lake Ontario was also associated with neonatal behavioral test deficits in offspring, although the causative agent in the fish was not identified (Lonky et al., 1995). In another study, the relationship between background PCB exposure and neurodevelopment was examined in children from North Carolina (Gladen et al., 1988; Rogan and Gladen, 1991). Estimated prenatal exposures to PCBs were associated with decreased psychomotor scale scores at 6, 12, 18 and 24 months of age.

Various epidemiology studies have produced inconsistent results regarding whether POP exposures from breastfeeding are associated with neurological deficits in children. In both the Lake Michigan and North Carolina cohorts, neurological deficits were not associated with POP exposure from breastfeeding. In fact, in a small cohort from the Netherlands, perinatal exposure to background dioxin levels was associated with enhanced neuromotor maturation (Ilsen et al., 1996). In a large Dutch study, prenatal exposure to PCBs and dioxin was not associated with neurological development, while post-natal exposure to PCBs and dioxins from breast feeding was associated with reduced neurological optimality and hypotonia in neonates (Huisman et al., 1995). However, in a follow-up study at 42 months age, cognitive performance in the same Dutch children was negatively correlated with *in utero* PCB exposure, but lactational and current PCB exposures had no effect on cognitive functioning (Patandin et al., 1999). In fact, the Dutch children who were breast-fed performed better on cognitive tests than did their formula-fed counterparts, suggesting that substances in breast milk or factors associated with breast-feeding may have counteracted any negative influence of prenatal PCB exposure on cognitive development (Patandin et al., 1999). A study of 171 mother-infant pairs in Germany found that prenatal PCB exposure, and to a lesser extent postnatal PCB exposure through breastfeeding, both had a negative impact on mental and motor development between 7 and 42 months of age (Walkowiak et al., 2001). However, the quality of the home environment had a stronger effect on neurodevelopment than did PCB exposure, such that the positive impact of a quality home environment could counteract the slight negative effects attributed to neonatal PCB exposure.

Although the developing fetus is most sensitive to the neurological effects of PCBs, other people may also be at risk of adverse effects. In a recentudy of older, frequent Great Lakes fish consumers, PCB exposure during adulthood was associated with impairments of certain aspects of memory and learning (Schantz et al., 2001). Other contaminants in the fish, including DDE, mercury, and lead, did not appear to have any negative impact on cognitive functioning.

Interestingly, in another cohort exposed to multiple contaminants through seafood consumption, PCBs were not found to be the principle contaminant correlated with observed neurobehavioral deficits. In a study of 7-year-old children from the Faroe Islands, prenatal exposure to methylmercury was more strongly associated with neurobehavioral decrements than was prenatal exposure to PCBs (Grandjean et al., 2001). However, the researchers found that PCBs might possibly augment the slight neurobehavioral deficits seen at increased levels of methylmercury exposure. Similarly, in a separate cohort from the Faroe Islands, increased methylmercury exposures were associated with slightly decreased neurologic optimality scores in neonates, while PCB exposures had no effect (Steuerwald et al., 2000).

Epidemiological studies that explore the relationships between neurological development and PCB exposure must be evaluated with a great deal of caution (Kimbrough, 1997). Most of the studies performed to date have had methodological problems. In the Lake Michigan and North Carolina studies, the quantitation of PCB exposure was weak. Although maternal serum, cord blood and breast milk were collected in these studies, analytical data were not available for many samples and PCB concentrations were often estimated. Analytical methods were crude (low resolution packed-column chromatography), individual congeners were not quantified, and detection limits were too high to enable quantification of the trace concentrations of PCBs present in many samples. In these early studies the lipid content of serum was not considered when PCB concentrations were evaluated, although this is an important determinant of PCB concentrations in biological tissues (Phillips et al., 1989). Variability of quantitation at low concentrations of PCBs is a fundamental problem in the early studies, and the small differences of PCB concentration measured (or merely estimated!) were probably meaningless (Kimbrough, 1997). The Lake Michigan study was further weakened by an inadequate explanation of methodology, possible selection bias, and inadequate control of possible

confounding factors (Middaugh and Egeland, 1997). Another problem common to most of the epidemiological studies was the inability to rule out the influence of other chemicals or environmental factors that might have been correlated with exposure to PCBs.

In conclusion, the epidemiological evidence for neurodevelopmental toxicity following background exposure to PCBs or dioxins is weak. The weight of the evidence suggests that exposure to low levels of PCBs or dioxins (or an environmental correlate) might possibly be associated with a slight detriment to neurological development in infants, but due to the methodological difficulties inherent to epidemiological studies this link may never be conclusively demonstrated. Severe neurological effects have never been observed in children in any epidemiological study that has investigated POP exposures at levels comparable to those encountered by Alaskans through the marine food chain. Furthermore, several factors have been found to have a positive effect on cognitive development that can outweigh any slight negative influence of PCB exposure, including the healthful practice of breastfeeding and the provision of a positive, nurturing home environment.

Epidemiological Studies related to Human Health and PCBs in the Arctic

There is concern for the welfare of humans that consume large quantities of animals from the top of aquatic food chains, due to their potential exposure to PCBs and other bioaccumulative contaminants. Some indigenous peoples from the Arctic consume large quantities of fish and/or marine mammals, and these organisms have the potential to bioaccumulate organic contaminants. Few major environmental epidemiological studies have been conducted to assess possible human health effects of POPs in the Arctic specifically. This is due to logistical difficulties such as the climate, small population sizes, the remoteness of communities, confounding social and behavioral factors, and the difficulty of extrapolating Western scientific methods to unique Arctic cultures. However, several smaller-scale studies have been conducted to assess the human health implications of PCBs and dioxins in the arctic environment; these are presented below.

Breast Cancer

A recent study conducted by the Centers for Disease Control, the Alaska Native Health Board and the Alaska Area Native Health Service determined the concentrations of PCBs and other organochlorines in the serum of 126 Alaska Native women (Rubin et al., 1997). The concentrations of environmental chemicals found in the serum of breast cancer patients were compared with the concentrations observed in women without breast cancer. The mean year of serum collection was 1985, and the serum was banked 3-8 years prior to breast cancer diagnosis. The mean serum concentration of PCBs found in the 126 women was 4.6 parts per billion (ppb), with 17.7 ppb being the highest individual value. After accounting for other risk factors for breast cancer in Alaska Natives, no relationships between breast cancer incidence and exposure to environmental chemicals were observed in this study. This study was an excellent preliminary effort to examine possible relationships between exposure to organochlorines and disease incidence in Alaskans, and more research is needed in this area.

Immune System Function

The relationship between organochlorine exposure and infectious disease incidence was investigated in Inuit infants from Nunavik (Arctic Quebec) (Dewailly et al., 2000). The occurrence of selected infectious diseases was documented during the first year of life for 171 participating newborns. Organochlorine analysis (10 PCB congeners and 8 pesticides) was performed on breast milk early in lactation for 94 of those infants, as a measure of prenatal exposure. Breastfeeding was a protective risk factor for several diseases in this study, as the 98 breast-fed infants experienced fewer episodes of several infectious diseases during the first year of life than did the 73 bottle-fed infants. This is consistent with a large body of scientific evidence documenting the protection breastfeeding provides against infection (Oddy, 2001).

While the research did not show an association between PCB exposure and infectious disease, the researchers did report a greater relative risk of acute otitis media (middle ear infection) in infants with higher prenatal exposures to several other organochlorines (the pesticides hexachlorobenzene, DDE and dieldrin) (Dewailly et al., 2000). However, several important methodological problems with the study make it inadvisable to place too much weight on these findings. Most importantly, the researchers failed to control for critical confounding factors, especially smoking. The study did not collect any information on maternal smoking, despite the fact that smoking is a very important risk factor for otitis media in children (Stathis et al., 1999). Other methodological issues included inadequate diagnostic criteria for acute otitis media, and likely inconsistencies in disease diagnosis among multiple practitioners.

Cytochrome P450-1A1 enzyme activity

Cytochrome P450-1A1 (CYP1A1) activity is increased following exposure to PCBs or dioxins. CYP1A1-mediated ethoxyresorufin *o*-deethylase (EROD) activity is a convenient and sensitive biomarker often used to assess whether PCB or dioxin exposure is affecting biochemical function (Safe, 1990). Placenta collected

from Inuit women giving birth in Arctic Quebec in 1995 did not exhibit PCB- or dioxin-mediated elevated EROD activity in comparison to women from Southern Quebec (Ayotte, 1996). Elevation of EROD activity is a sensitive subclinical response to PCB or dioxin exposure, and the fact that the "PCB body burden of Inuit women may not be high enough to induce EROD activity" indicates that their PCB/dioxin exposure has not been extreme, and is of limited biological significance. Interestingly, elevated EROD activity was observed in some women from both Arctic and southern Quebec, and that response was directly attributable to maternal cigarette smoking. Similar results have been seen in two subsequent studies involving newborns from Nunavik (Arctic Québec), in which PCB body burden did not significantly influence placental CYP1A1 activity (Lagueux et al., 1999) (Pereg et al., 2002). In both studies, smoking during pregnancy emerged as the major modulating factor for placental CYP1A1 activity.

Thyroid hormone status in newborns

A recent study examined the relationship between thyroid hormone status and exposure to pentachlorophenol and hydroxylated PCB metabolites in newborns, in two Canadian subsistence populations compared to southern Quebec (Sandau et al., 2002). When individual chemical residue data from umbilical cord plasma were compared to thyroid hormone markers, only pentachlorophenol was negatively correlated to T3, free T4, and thyroxine-binding globulin concentrations. It is unknown whether the observed decreases of these thyroid hormone markers are of functional biological significance, or if the decreases were actually caused by pentachlorophenol.

Governmental Agency Guidelines

Daily Intake-Based Guidelines

There are wide variations in the consumption guidelines developed for PCBs, dioxins and related chemicals among different governmental organizations. These variations reflect the scientific uncertainties and ongoing controversy of PCB/dioxin toxicity at very low levels of exposure, and the different methods and assumptions used during the risk assessment process. Various governmental agencies have established threshold exposure values, below which no adverse health effects would be expected to occur. These values are based on average daily intake levels, and have different names such as "Minimal Risk Level" (U.S. ATSDR), "Reference Dose" (U.S. EPA), and "Tolerable Daily Intake" (European countries; Canada). The daily intake guidelines for PCBs, Dioxin Equivalents and PBDEs in several countries are presented in Tables 6a, 6b and 6c, respectively.

Differences among daily intake guidelines are illustrated by comparing the risk levels established in the United States and Canada (Table 6a). The Canadian Tolerable Daily Intake of PCBs is 1 µg/kg-bw/d (Kuhnlein, 1995). This value is fifty-fold higher (less conservative) than the U.S. EPA reference dose of 0.02 µg/kg-bw/d, but still incorporates a 5-fold safety factor above the lowest observed adverse effect level for PCBs from animal studies (ocular effects and distorted nail growth in monkeys). Some of this difference reflects the conservative, risk-based approach of the U.S. EPA, versus the balanced risk/benefit approach of Health Canada.

Differences in governmental agency guidelines are generally less dramatic for dioxin equivalents. There is a ten-fold difference between the U.S. ATSDR Minimal Risk Level (1 pg/kg-bw/day) (US ATSDR, 2000) and the Health Canada Tolerable Daily Intake (10 pg/kg-bw/day) (Health Canada, 1996), with the levels established by Japan and European countries generally falling in between those two extremes (European Commission, 2001; Johansson and Hanberg, 2000; Ministerial Council on Dioxin Policy, 1999; World Health Organization, 2001) (Table 6b). However, the U.S. EPA is working to reassess the risk of dioxins, and their calculations have produced a theoretical reference dose that is 100 to 1,000 times lower than current background exposure levels (which are currently approximately 0.5 – 1.0 pg/kg-bw/day) (USEPA, 2000a). The U.S. EPA has not yet set a reference dose for dioxin, but it appears that if they do, it may be orders of magnitude more conservative than those established by other countries.

In order to determine the non-carcinogenic risks associated with PCB exposure, the U.S. EPA considered a large body of literature related to chronic, developmental, immunological and neurobehavioral toxicity from human epidemiological and animal studies. Risk calculations were performed using data from the strongest studies that showed effects at the lowest doses. The analysis was ultimately based on data from a study in which adult female monkeys were fed low doses of PCB (Aroclor 1254) over a long period of time (ongoing; over 4 years). At the lowest dose tested, 0.005 mg/kg-bw/day, subtle ocular effects were observed such as eye exudate, inflammation and/or prominence of the eyelid. The monkeys also exhibited changes in finger and toe nails, and some changes in immunological parameters were observed such as decreased IgG and IgM concentrations (IRIS, 1996).

To calculate the daily reference dose that is likely to be without an appreciable risk of deleterious effects during a lifetime, this lowest observable adverse effect level (LOAEL) of 0.005 mg/kg-bw/day was divided by a safety factor of 300. This safety factor included a factor

of ten to protect the most sensitive members of the population, and three factors of 3 to account for uncertainties associated with (1) the extrapolation of data from monkeys to humans, (2) from subchronic toxicity to lifetime chronic exposure, and (3) the fact that a LOAEL was used instead of a NOAEL (no observable adverse effect level). By this conservative approach, an oral reference dose (RfD) of 2×10^{-5} mg/kg-bw/day was derived.

When a chemical is associated with both carcinogenic and non-carcinogenic health effects, the USEPA conducts two separate risk assessments based on the two types of endpoints (USEPA, 1994). Both types of risk assessments have been performed by the USEPA for PCBs. The USEPA's risk assessment of carcinogenicity was based on studies with rats treated with high doses of the commercial PCB mixture Aroclor 1260 (25 to 100 ppm). For PCBs, the carcinogenic endpoint was calculated to be more sensitive than chronic systemic endpoints such as reproductive, developmental and immunological health. The reason why the carcinogenic endpoint turned out to be the most sensitive is that the USEPA uses a very conservative method to calculate the risks posed by environmental carcinogens. With their approach, it is assumed that there is no threshold below which an increased cancer risk does not occur. Extrapolation of effects from high-dose laboratory studies to low environmental levels is based on a linearized multistage no-threshold model. This approach has been widely criticized because it is unrealistically conservative and fails to take evidence of thresholds for carcinogenic endpoints into account, particularly for chemicals that act through a promotion mechanism such as PCBs and dioxins (Ames et al., 1987; Covello and Merkhofer, 1993; Hanson, 1991; Shu et al., 1987). For the carcinogenic endpoint, the USEPA has adopted a high risk and persistence upper-bound slope factor of 2.0 per (mg/kg)/day for PCBs (IRIS, 1996). The USEPA concedes that this slope factor drives a currently recommended seafood screening value for PCBs that "will result in widespread exceedance in waterbodies throughout the country and will drive virtually all fish and shellfish contaminant monitoring programs into the risk assessment phase for PCBs" (USEPA, 1995).

In our opinion, a risk assessment for PCBs and dioxins based on chronic systemic endpoints such as reproductive, developmental and immunological health is more appropriate than a risk assessment based on a carcinogenic end point, because the chronic end point risk assessment has a stronger foundation of scientific evidence behind it. Animal cancer studies were performed at high doses, at which the mechanisms of carcinogenicity may have involved cell proliferation as a result of cellular toxicity. This mechanism of toxicity would not be applicable to low-dose exposures. Furthermore, the linearized multistage no-threshold model used for extrapolation is inappropriate for use in PCB or dioxin risk assessment. The USEPA's focus on carcinogenicity as the most sensitive endpoint for PCBs and dioxins is not in accordance with human epidemiological evidence or laboratory animal studies, which both suggest that developmental and immunological deficits may occur at lower PCB or dioxin doses than does cancer (DeVito et al., 1995; Hanson, 1991). Therefore, for the remainder of this paper our risk assessment will focus on chronic systemic health endpoints of PCB/dioxin exposure, using a very conservative approach with a large margin of safety.

Guidelines for Fish Advisories

Individual states usually assume primary responsibility for establishing fish consumption advice for recreational and subsistence-caught fish within their boundaries. The U.S. EPA has published fish consumption guidelines based on contaminant concentrations, as a tool for states working to establish their criteria (USEPA, 1994). Guidelines for fish consumption vary widely from state to state, due to uncertainties of PCB- and dioxin-associated health effects, differences in risk assessment methods, and varying social, political and economic factors that contribute to risk management decisions. For large bodies of water that border multiple states and countries, such as the Great Lakes of North America, several different and conflicting fish advisories may be in force simultaneously (Kamrin and Fischer, 1999). Guidelines for fish consumption based on PCB concentrations can span several orders of magnitude, as illustrated in Table 7. Fish advisories are informational rather than regulatory, such that compliance with them is voluntary.

The U.S. FDA has established regulations for the maximum allowable PCB concentrations in edible portions of food in commerce, called "Tolerances". In contrast with fish advisories, U.S. FDA Tolerances carry the force of law, and prohibit the sale of food items that exceed those concentrations. The maximum allowable concentrations vary by food type, as shown in Table 8. The U.S. FDA has also established guidelines for dioxin content in fish; these guidelines are not formal tolerances that carry the force of law. The U.S. FDA guidelines state that no serious health effects are expected following consumption of fish with less than 25 parts per trillion (ppt) 2,3,7,8-TCDD, while fish with 2,3,7,8-TCDD concentrations greater than 50 ppt should not be consumed (ATSDR, 2003).

Dietary Intake/Risk Assessment

For the present purpose, risk assessment involves the consideration of toxicity, exposure scenarios and

chemical concentration data in order to evaluate the safety of subsistence food consumption. When developing consumption-oriented recommendations for public health purposes, it is also critical to evaluate the beneficial aspects of traditional food consumption. These include physical health benefits such as an apparent reduced risk of heart disease due to the omega-3 polyunsaturated fatty acids found in fish and marine mammals, as well as the benefits of exercise associated with the harvest of traditional foods. There are also important social and cultural benefits associated with the harvest, sharing and consumption of traditional foods (Usher et al., 1995).

In addition, it is important to perform a relative risk assessment between traditional foods and the market foods that would replace them in the Alaskan Native diet. For example, risks associated with trace contaminants in traditional foods should be compared against the risks associated with a reduced nutrient intake or an increased intake of saturated fats associated with market food consumption. Market foods also contain trace levels of contaminants, and their risks should be factored into any relative risk assessment. A nutritional study has demonstrated the superior nutritional quality of traditional foods in the Alaskan Native diet, and these foods were hypothesized to play a protective role against chronic diseases in the Alaskan Native population (Nobmann et al., 1992). Since concentrations of coplanar PCBs, dioxins and furans are poorly characterized in Alaskan subsistence foods, the following risk assessment will focus on the summed PCB congener data that is available.

We performed a conservative risk assessment using US EPA methodology to calculate the "maximum allowable daily fish consumption", based on PCB concentrations in Alaska salmon from Table 3. These calculations are for discussion purposes only, and should not be interpreted as our actual advice since they do not take the benefits of traditional food consumption into account. Also, the calculations are based on limited fish data, which are not sufficient to represent the state as a whole. To perform the calculations, the US EPA Reference Dose (RfD) was used in the following equation:

$$\mathbf{CR_{lim} = [RfD \bullet BW] / C_m}$$

where

CR_{lim} = maximum allowable daily consumption rate of the fish species (kg/d)
RfD = reference dose
BW = consumer body weight (kg)
C_m = measured concentration of contaminant *m* (mg/kg)

A body weight of 70 kg was used in our calculations, which is the average weight of an adult male.

Figure 5 illustrates the calculated daily consumption limits that would result for the freshwater fish species from Schrader Lake, Alaska, based on the analysis of samples collected in 1992 (Wilson et al., 1995), and for chinook and chum salmon from the Yukon-Kuskokwim region (USFWS, unpublished data). Dietary surveys have revealed that Native Alaskan adults consume an average of 4 ounces of fish and shellfish daily, which is six times greater than the U.S. national average (Nobmann et al., 1992). The concentrations of PCBs in Y-K salmon and in Schrader Lake fish are so low that they are very safe to eat, even at the high rates of consumption typical for rural Alaskan communities.

The recent data available for Alaskan marine mammal tissue concentrations (Table 3) were also subjected to a risk assessment. In this analysis we focused on the consumption of blubber, as this tissue contains the highest concentration of PCB-like compounds. This is an overly conservative approach, because marine mammal blubber is often not eaten in isolation, but as "maktak", a combination of blubber and epidermis with lower concentrations of lipophilic contaminants (Todd O'Hara, personal communication).

Since marine mammal tissue is consumed by Alaskan Natives much less frequently than are fish or shellfish (Nobmann, 1989), a maximum monthly consumption limit was calculated rather than a daily consumption limit. The monthly consumption quantity of Alaskan marine mammal blubber deemed safe by U.S. EPA standards was quite low. We compared the U.S. EPA risk assessment method with the PCB intake standard utilized in Canada (Figure 6). The Canadian Tolerable Daily Intake of PCBs is 1 μg/kg/d (Kuhnlein, 1995). This value is fifty-fold higher (less conservative) than the USEPA reference dose of 0.02 μg/kg/d, but still incorporates a 5-fold safety factor above the lowest observed adverse effect level for PCBs from animal studies (ocular effects and distorted nail growth in monkeys). These results demonstrate how dramatically the risk assessments performed by different governmental agencies can vary, and how relevant these differences are to Native Alaskan subsistence food safety issues. Using the Canadian guidelines, which we feel incorporate a reasonable consideration of both risks and benefits, it is apparent that most blubber from Alaskan marine mammals can be safely consumed in large quantities.

It is important to keep a relative perspective on the concentrations of PCBs found in Alaskan fish and marine mammals. The concentration of PCBs found in Alaskan beluga whale blubber was similar to the PCB

concentration found in Steelhead trout from the Manistee River, Michigan in 1990, while concentrations of PCBs in blubber from other Alaskan marine mammals were often similar to or below the concentrations found in fish from the Great Lakes (Table 9). PCB concentrations are far lower in blubber from baleen whales, such as the gray whale and bowhead whale, than in blubber from toothed whales such as the beluga (Tables 3 and 4). In a survey of PCB concentrations in sediments and liver of bottom-feeding fish from bays of the U.S. West Coast, fish from Alaska and Oregon were significantly less contaminated than fish from California and Washington (Varanasi et al., 1989). PCB concentrations in chinook and chum salmon from the Yukon and Kuskokwim were far lower than those observed in more industrialized parts of the world, and appear to reflect the remote, nearly industry-free environment of Alaska (Figure 2).

Blubber PCB concentrations of most marine mammals in Alaska are far lower than the PCB concentrations found in blubber of long-finned pilot whales hunted near the Faroe Islands. Mean PCB concentrations (total PCBs quantified by Aroclor matching) in the blubber of 53 Faroe Islands long-finned pilot whales harvested in 1986 were 20 ppm (20,000 ng/g) wet weight (Simmonds et al., 1994). Mean DDE concentrations in the blubber (12 ppm wet weight) (Simmonds et al., 1994) and mean methylmercury concentrations in various tissues (Julshamn et al., 1987) were also elevated in long-finned pilot whales from the Faroe Islands. Pilot whale tissue is commonly consumed by the people of the Faroe Islands, and several major health studies have been conducted there to look for possible contaminant-related health effects. In that population, prenatal methylmercury exposure was more closely related to the slight neurobehavioral deficits reported than was prenatal PCB exposure (Grandjean et al., 2001). However, the researchers found that PCBs might possibly augment the neurobehavioral deficits seen at increased levels of methylmercury exposure. Similarly, in a separate cohort from the Faroe Islands, increased methylmercury exposures were associated with decreased neurologic optimality scores in neonates, while PCB exposures had no effect (Steuerwald et al., 2000). These studies are interesting, because they probably present a "worst-case" scenario for any possible health risks associated with subsistence food consumption in Alaska. Interested readers are referred to this monograph's Methylmercury chapter for additional information regarding the Faroe Islands studies.

Another research group investigated the comparative risks and benefits of traditional native diets in Canada. Their approach focused on a documentation of dietary intake, complemented by detailed chemical analysis of traditional food items for their content of both nutrients and environmental contaminants. A community in the Baffin Islands was chosen as a sentinel population for study, due to a heavy reliance on marine species consumption by the inhabitants.

In an initial study of the community on Broughton Island (Kinloch and Kuhnlein, 1988), the average daily intake of PCBs (as summed congeners) was calculated to be 74 μg/day per individual. Although PCB concentrations were low in most food items, marine mammal blubber and skin was found to contain over 1 ppm PCBs. Consumption of various food items and dietary PCB intake were found to vary seasonally. No correlations were observed between calculated PCB intakes based on food consumption and actual PCB blood concentrations in individuals. Similar results were obtained in another recent study of the Canadian Inuit, in which traditional food intake during pregnancy was unrelated to PCB body burden (Muckle et al., 2001). PCB body burden is most closely associated with lifetime consumption patterns, so temporary dietary changes during pregnancy may not have much impact on prenatal PCB exposure levels.

Interestingly, in the 1985 study, three of four breast milk samples contained PCBs within the same range reported for average southern Canadian women (13, 16 and 19 ppb PCBs in whole milk, in comparison to the southern Canadian average of 15.9 ppb PCBs in whole milk) (Kinloch and Kuhnlein, 1988). A breast milk sample from a fourth Inuit woman contained 69 ppb PCBs in whole milk, which was above the Canadian 'tolerable level' of 50 ppb PCBs in whole milk. A larger followup study (Kinloch et al., 1992) documented the substantial nutritive value of traditional foods in the Inuit community.

Although marine mammal blubber samples were found to contain the greatest PCB concentrations among the traditional foods studied, blubber was also documented to be an excellent and important source of retinol and omega-3 fatty acids for the Inuit diet. A balanced approach was urged toward the assessment of traditional food safety. Health risks might well be associated with a decreased reliance on traditional foods in native communities and a concomitant decline in nutritional status.

Results from the above community on Broughton Island should not be extrapolated to represent the Canadian indigenous situation in general, or the situation in Alaska. The Broughton Island community was non-randomly selected from harvest data as a population with a relatively high risk of PCB contamination, and was intended to represent a worst-case scenario among the Inuit (Kinloch and Kuhnlein, 1988). Organochlorine exposure in the Broughton Island Inuit has been compared with that of two Sahtu Dene/Metis communities from western Canada that relied heavily on traditional foods from a terrestrial food chain (Kuhnlein

et al., 1995; Kuhnlein, 1995). Exposure to PCBs and other organochlorines was found to be very low in the Sahtu Dene/Metis, and no traditional food item of the Sahtu Dene/Metis was found to contain over 0.1 ppm PCBs. Traditional foods of the Sahtu Dene/Metis contained an abundant supply of many nutrients, and contributed much more protein, iron, zinc, magnesium and copper to the diet than did market foods (Kuhnlein, 1995).

It should not be assumed that dietary intake of PCBs is elevated in Native Alaskan communities. Rather, research is needed to determine PCB exposure levels in Alaskan communities before risks can be assessed. Community-specific dietary intake levels, contaminant concentrations in traditional foods, and human bio-monitoring data would be very useful to determine the percent contribution of various foods to total human exposure levels. This information would be useful to develop optimal consumption advice. This approach has been very successful in Canada, where extended contaminants research was conducted over the course of a decade under the Northern Contaminants Program (Van Oostdam et al., 1999).

Concentrations of PCBs, Dioxins and Related Chemicals in Humans – Status and Trends

PCB, Dioxin and Furan Concentrations in Alaskans

Information about POP concentrations in Alaskans has increased substantially since our original monograph was published in 1998. Two major investigations of serum organochlorine concentrations in Alaskans have been completed, while a third is ongoing. The Centers for Disease Control and Prevention (CDC), the National Cancer Institute, and the Indian Health Service collaborated with the Alaska Area Native Health Service to analyze PCBs and pesticides in 131 banked serum samples from Alaska Native women (Rubin et al., 2001). In 1999, the Alaska Division of Public Health and the CDC collaborated to provide serum PCB and organochlorine pesticide testing to 166 adult participants from five Aleutian and Pribilof Island Villages (Alaska Division of Public Health, 2001). Samples from the three Aleutian Island villages were also analyzed for dioxins, furans and coplanar PCBs. In a large ongoing study, the Alaska Native Tribal Health Consortium and the CDC are collaborating with a number of other agencies to monitor contaminant exposures in pregnant women from several Alaskan villages, as well as contaminant exposures and health outcomes in their newborn babies. The CDC's National Center for Environmental Health provided analytical laboratory services for all three projects, so analytical methodology and data quality were both state-of-the-art and comparable.

Serum PCB results for comparable sub-populations were similar among the three Alaskan studies. For example, the arithmetic mean total PCB concentration in Alaska Native women (mean age 57 years old) from the serum bank study was 7.56 ppb, while the mean total PCB concentration in Aleutian/Pribilof volunteers (mean age 49 years old) was 7.69 ppb. In the Aleutian/Pribilof Islands exposure assessment, women of childbearing age had an average total PCB serum concentration of 2.9 ppb, while pregnant women in the ANTHC study had an average total PCB serum concentration of 1.29 ppb in Bethel and 0.77 ppb in Barrow (Dr. Jim Berner 2002, personal communication). Serum PCB concentrations in Aleutian/Pribilof women of childbearing age were also similar to maternal plasma PCB concentrations from other arctic countries (AMAP, 1998) (Figure 7).

Age- and sex-related differences were observed in PCB concentrations among Aleutian/Pribilof Island participants. PCB concentrations were strongly associated with age, with higher PCB concentrations observed among older participants. In most age groups, PCB concentrations were higher in male participants than in female participants (Figure 8). Serum PCB concentrations were low in women of childbearing age relative to the older persons sampled (Figure 9). Since the developing fetus is the most sensitive member of the human population to the adverse health effects of PCBs, it is most important to minimize PCB exposures in women who are or may become pregnant.

The CDC has recently published national reference range data for individual PCB, dioxin and furan congeners (CDC, 2003). In 1999-2000, the serum of over 1200 randomly-selected American adults was collected and analyzed. These NHANES results are challenging to compare with many studies, because they are only presented as selected percentiles for individual congeners on a lipid-adjusted basis. Many PCB, dioxin and furan congeners were not detected in the national NHANES sample, so no numbers are available for them with which to perform comparative calculations. We were able to compare the NHANES data to our Aleutian/Pribilof data for eight non-planar PCB congeners (Table 10). Results varied among congeners, but PCB concentrations were consistently higher in the Aleutian/Pribilof data relative to the national reference data. This was to be expected, because Alaska Natives consume far more fish than the national average (Nobmann et al., 1992). We were also able to compare the NHANES data to our Aleutian/Pribilof data for two dioxin congeners, one furan congener, and two coplanar PCB congeners (Table 11). Results varied among congeners, but in general the national data and Aleutian/Pribilof data were similar for these dioxin-like chemicals. In general, PCB concentrations in Aleutian/Pribilof volunteers were similar to those of Great Lakes fish consumers, while

average dioxin, furan and coplanar PCB concentrations in Aleutian/Pribilof volunteers were about half those found in Great Lakes fish consumers (Anderson et al., 1998; Humphrey et al., 2000) (Table 12).

PCB, Dioxin and Furan Concentrations in Canadians

Inuit communities from Arctic Quebec have a heavy reliance on marine species consumption, and their exposure to POPs has been investigated. In one study, breast milk fat from the Inuit women of east Hudson Bay contained an average of 1 ppm PCBs (as summed congeners), which was similar to the PCB concentration found in beluga blubber from the region (Dewailly et al., 1993). Average concentrations of PCBs in breast milk fat of Inuit women were 6.7 times higher than PCB concentrations found in breast milk fat of 96 Caucasian women from southern Quebec, when expressed as summed PCB congeners (Dewailly et al., 1993).

Comparisons between Arctic and southern Quebec have also been made for dioxin, furan and coplanar PCB concentrations in breast milk. The data were expressed as TCDD-equivalents for the dioxins, furans and non-ortho PCB congeners measured (Dewailly et al., 1992; Dewailly et al., 1994b). The Toxic Equivalency Factors used to calculate TCDD-equivalents (TEQs) have been updated since those papers were published. When the most current TEFs from the World Health Organization are used (Van den Berg et al., 1998), the average TEQs in Inuit and Caucasian breast milk fat were 52 and 26 ppt, respectively: a 2-fold difference (Dewailly et al., 1992).

Although PCB exposure was greater in Inuit women relative to Caucasian women, differences in exposure to polychlorinated dioxins and furans were slight between the two populations. The results demonstrate how data interpretations and study conclusions can vary based upon the type of POP analysis chosen.

The results of the above study were interpreted by the investigators to evidence a "surprisingly high organo-chlorine body burden" (Dewailly et al., 1993) in Inuit women, as a result of receipt of "an unusually high dose of dioxin-like compounds through their traditional diet" (Ayotte et al., 1996). In fact, the degree of elevation of PCB- and dioxin-like concentrations in the Inuit was overstated. The average concentrations of PCBs reported in milk fat of these Inuit women (1 ppm expressed as summed congeners) were not elevated above the background concentrations found in human milk fat in industrial countries throughout the world, which averaged 0.5 to 1.5 ppm PCBs (Jensen, 1991). When expressed as total TEQs using the most recent TEFs (Van den Berg et al., 1998), the concentrations of dioxin-like chemicals were similar in Canadian Inuit breast milk fat and in background breast milk fat from women in the Netherlands (52 ppt and 54 ppt respectively, Figure 10) (Dewailly et al., 1992; Koopman-Esseboom et al., 1994a).

Time Trends for POP Concentrations in Humans

PCB concentrations in humans around the world are declining. Declining PCB concentrations have been observed at lower latitudes for over a decade (Schade and Heinzow, 1998; Tee et al., 2003), and are now being documented in the Arctic as well. Total PCB concentrations have dropped precipitously in human breast milk in Sweden during the past 30 years (Noren and Meironyte, 2000) (Figure 11). Steady declines in concentrations of PCBs and organochlorine pesticides have been observed in human infants from an eastern arctic Canadian community from 1993 to 2000 (Dallaire et al., 2002) (Figure 12). The reason for the organochlorine decline in umbilical cord blood was not determined, but a decline in maternal fish consumption was unlikely, as omega-3 fatty acid concentrations in cord blood declined only slightly over time. Declining organochlorine concentrations in umbilical cord blood were hypothesized to be due to lower PCB concentrations in traditional food species, or perhaps by modified consumption of seabird eggs (the community's principle source of organochlorine exposure). Continued human biomonitoring in Alaska is needed to assess our long-term exposure trends.

In contrast to PCBs, which are declining in humans, polybrominated diphenyl ether (PBDE) concentrations are increasing exponentially in some sampled populations. For example, total PBDEs increased exponentially in Swedish breastmilk during the period 1972 to 1997 (Meironyte et al., 1999; Noren and Meironyte, 2000) (Figure 13). PBDEs also increased exponentially in human serum from Norway during the period from 1977 to 1999 (Thomsen et al., 2002). Two recent studies showed that serum concentrations of the predominant PBDE congener, PBDE-47, were much higher in Indiana (Mazdai et al., 2003) and in California (Petreas et al., 2003) than in Sweden (Guvenius et al., 2003) (Figure 14). Another preliminary assessment of PBDEs in the breast milk of North American women indicated that the body burden of PBDEs in Americans and Canadians may be the highest in the world, and breast milk concentrations in North America appear to be increasing at an exponential rate. Average North American breast milk concentrations in 2000 were 40 times greater than the highest concentrations reported for women in Sweden (Betts, 2002). Also, the relative ratio of PBDEs to PCBs in humans appears to be different in Sweden than in America. Considering the concentration of the predominant PBDE congener (PBDE-47) relative

to the predominant PCB congener (PCB-153), recent studies have shown a 67-fold PCB 153/PBDE 47 ratio in Sweden (Guvenius et al., 2003), but only a 4-fold PCB 153/PBDE 47 ratio in California (Petreas et al., 2003). These results indicate that PBDE contamination in North America may be a large, emerging problem that may soon overtake PCB contamination as a public health concern. This is particularly true because PCBs have been banned in the U.S. since 1976, but no restrictions are yet in place on PBDE production or use in North America.

In a Norway time trend study, PBDE concentrations were not related to gender or age in a manner similar to PCBs (Thomsen et al., 2002). The current body burden of brominated flame retardants (including PBDEs) in Norway appeared to be independent of age, except for in infants (0-4 years old), who had 1.6-3.5 times higher concentrations than other age groups.

At present, we have no data on PBDE concentrations in Alaskans. It is a top environmental public health priority to assess PBDE exposure levels and trends in Alaskans.

Public Health Evaluation for Alaska

Alaskans have been exposed to POPs at levels similar to those found in other arctic countries, and in fish-eating populations from the Lower 48. Several comprehensive efforts have been undertaken to evaluate the health risks of contaminants in traditional foods in the arctic, balancing risks against the nutritional, social, spiritual and economic benefits of traditional foods. The Arctic Monitoring and Assessment Programme (AMAP, 2003) and Canada's Northern Contaminants Program (Arnold et al., 2003) are large, long-term projects involving many scientific experts who have been working for many years to investigate arctic contaminants and their human health implications.

In general, these projects have concluded that while some small risks may exist related to possible adverse health effects from POP exposures, these risks are vastly outweighed by the many benefits of traditional food consumption. Traditional foods provide inexpensive and readily available nutrients, essential fatty acids, antioxidants, calories and protein, and many health benefits such as protection from diabetes, cardiovascular disease, improved maternal nutrition and neonatal and infant brain development. Market replacement foods are often nutritionally inferior, are high in saturated fat, sugar and salt, and also contain contaminants. Unhealthful market replacement foods present their own health risks, and may contribute to the rising rates of diabetes, heart disease, and other health problems in villages that reduce their traditional food consumption.

The traditional lifestyle and diet are also of great importance to the self-definition, self-determination, cultural and socio-economic, and overall health and well-being of indigenous peoples. Recommendations to restrict traditional food consumption have caused cultural disruptions and have unintended adverse consequences in Native communities.

Fortunately, the POP levels documented in Alaska to date are not expected to cause adverse health effects. We continue to recommend the unrestricted consumption of traditional foods.

Despite a lack of any clear evidence of adverse health effects at low POP exposure levels, some individuals may choose to limit their exposure to POPs. Individuals may lessen their exposure to POPs while still enjoying a traditional diet by choosing smaller, younger animals that are lower in the food chain. Exposure can be further reduced by choosing lean tissues rather than fatty tissues from marine mammals.

A long-term human biomonitoring program in Alaska is critical to assess trends in contaminant exposure and nutrient intake, and to continually verify that our consumption advice is optimally protective of human health. The Section of Epidemiology and the Alaska Public Health Laboratory within the Alaska Division of Public Health are currently collaborating to establish such a biomonitoring program. The Alaska Public Health Laboratory is developing the capacity to measure persistent organic pollutants, including PCBs, dioxins, furans, and PBDEs, in human serum. This analytical support will enable the Section of Epidemiology's Environmental Public Health Program to offer blood testing to Alaskans who are concerned about potential POP exposures. This will be a valuable extension to the Division's biomonitoring efforts, which include the statewide Maternal Hair Mercury Biomonitoring Program (Alaska Division of Public Health, 2002). The Maternal Hair Mercury program was reviewed by the Alaska Area Institutional Review Board and was determined to be standard public health practice, not research.

Conclusions and Future Directions

Traditional foods are an important and healthful component of the diet of Native Alaskans. The Division of Public Health strongly endorses the consumption of subsistence foods. PCB concentrations in Alaskan fish are far lower than in most fish from the Lower 48, reflecting the relatively remote, nearly industry-free environment of many regions of Alaska. Wild Alaska salmon are a particularly nutritious food, and have undetectable to negligible contaminant concentrations.

The benefits of a traditional food diet far outweigh the potential relative risks posed by trace quantities of POPs in traditional foods. We encourage the consumption of a varied diet consisting of a number of different species and tissues. Exposure to POPs can be lessened by choosing animals from a lower trophic level (for example, baleen whales rather than toothed whales) and by avoidance of older male animals. Additional information should be obtained regarding the POP content of the beluga whale, ringed seal, bearded seal, Pacific walrus, northern fur seal and Stellar sea lion, to better assess human exposure.

Alaskans who have traditionally consumed marine mammals in their diet should continue to enjoy their foods. Marine mammal blubber-containing foods are excellent sources of monounsaturated fatty acids, omega-3 fatty acids, and fat- soluble vitamins. Risks associated with avoidance of marine mammal consumption are greater than the small potential risk of subtle health effects from POPs in blubber. For example, avoidance of marine mammal blubber and replacement with foods high in saturated fat (such as Crisco, fat products from cattle and pigs, and dairy products such as butter and cheese) would increase the prevalence of heart disease, diabetes, and certain cancers in Alaska Natives.

Key knowledge gaps must be the focus of future studies of subsistence food safety. There is a pressing need to obtain additional information regarding PCB concentrations in Alaskan subsistence foods and sport fish. The State of Alaska needs to conduct comprehensive evaluations of subsistence foods. While progress has been made on fish sampling and analysis in Alaska, comparable surveys are needed for marine mammal tissues.

To protect public health, we need information about concentrations of POPs in subsistence species, including data on the age, sex and tissue type of the animals. It is also necessary to measure how various preparation methods influence PCB concentrations in subsistence foods as they are actually consumed by people. Village-specific dietary surveys are also needed to determine the identity and quantity of the foods people are eating. We need to refine our chemical analyses and obtain congener-specific information, including data on coplanar congeners, dioxins, furans, and PBDEs.

Of most importance, Alaska must measure human PCB exposure. Information regarding PCB concentrations in Alaskans is limited. We have no information about PCB concentrations in the adipose tissue or breast milk of Alaskans. A top priority is to analyze PBDEs in the serum of Alaskans and to monitor PBDE exposure trends over time. We know that PBDE concentrations are increasing rapidly in North American wildlife. Human exposure information will provide public health officials with the most relevant data possible regarding POP exposure through the subsistence food chain. A long-term human biomonitoring program is needed to comprehensively evaluate contaminant exposures and their public health implications in Alaska.

Table 1. PCB concentrations in Alaskan marine mammals and freshwater fish (summed congeners, ng/g wet weight): Older studies published 1993-1997

Species	Location	Collection Date	Tissue	Sex	n	ΣPCB[1]		Reference
Beluga Whale	Pt. Lay, Chukchi Sea, AK	1990	Blubber		10	3,808.1	(1,496.4)	Schantz et al. 1993
Beluga Whale	Pt. Lay, AK	July 1992	Blubber	F	5	680	(216)	Tarpley, 1994
				M	2	2,986-6,406		
Beluga Whale	Cook Inlet	1992-95	Blubber		12	977	(484)	Becker et al. 1997a
Bowhead Whale	Barrow, AK	1992	Blubber		11	689	(226)	Becker, 1993a
Gray Whale	Kodiak Island,AK	May-June 1989	Blubber		2	150-1,200		Varanasi et al. 1994
	Tugidak Island		Liver			79-880		
Ringed Seal	Barrow, AK	July 1988	Blubber		2	686-686		Schantz et al. 1993
			Liver			18-28		
			Kidney			10-17		
Ringed Seal	Nome, AK	May 1989	Blubber		2	371-415		Schantz et al. 1993
			Liver			8-9		
Ringed Seal	Bering Sea, AK	May 1989 & 94	Blubber	F	2	330-363		Krahn et al. 1997
		May 1993-95	Blubber	M	6	249	(75)	
Northern Fur Seal	St. Paul Island, AK	July 1987	Blubber		2	275-590		Schantz et al. 1993
			Liver			18-48		
			Kidney			17-87		
			Muscle			14-30		
Northern Fur Seal	St. Paul Island, AK	July 1990	Blubber	M	7	1,343	(522)	Krahn et al. 1997
Northern Fur Seal	Alaska	1990	Liver		9	150	(69)	Varanasi et al. 1993
			Blubber		9	2,100	(1,080)	
Harbor Seal	Prince William Sound, AK	September 1993	Blubber	F	2	225-240		Krahn et al. 1997
				M	3	599	(143)	
Harbor Seal	Alaska	1989-1990	Liver		9	21	(6)	Varanasi et al. 1993
			Blubber		7	340	(110)	
Bearded Seal	Bering Sea, AK	May 1993-95	Blubber	F	1	199		Krahn et al. 1997
				M	5	153	(110)	
Steller Sea Lion	Alaska	1976-1978	Blubber	M	12	12,580		Lee, 1996
				F	17	4,346		
			Liver	M	13	513		
				F	15	236		
Steller Sea Lion	Alaska	1985, 1989, 1990	Liver		8	290	(340)	Varanasi et al. 1993
			Blubber		8	23,000	(37,000)	
Lake Trout	Schrader Lake, AK (inland)	August 1992	Muscle		11	6.6		Wilson et al. 1995
			Liver		5	22.8		
Grayling	Schrader Lake, AK (inland)	August 1992	Muscle		5	1.3		Wilson et al. 1995
			Liver		5	3.2		

1 = Mean value with standard deviation in parenthesis when n > 2 (when available)
Both actual values listed when n = 2

Table 2. PCB concentrations in Canadian marine mammals and fish (summed congeners, ng/g wet weight): Older studies published 1988-1996

Species	Region	Collection Date	Tissue[1]	Sex	N	PCBs*		Reference
Ringed seal	W Hudson Bay	1992	B	F	24	1115	(425)	Muir, 1994a
Ringed seal	W Hudson Bay	1992	B	M	35	1852	(1359)	Muir, 1994a
Ringed seal	E Baffin Is	1994	B	F	10	467	(195)	Muir, 1994a
Ringed seal	E Baffin Is	1994	B	M	10	675	(597)	Muir, 1994a
Ringed seal	E Hudson Bay	1989-92	B	F	6	1457	(1648)	Muir, 1994a
Ringed seal	E Hudson Bay	1989-92	B	M	4	1234	(636)	Muir, 1994a
Ringed seal	Lancaster S	1993	B	F	10	535	(154)	Muir, 1996a
Ringed seal	Lancaster S	1993	B	M	10	655	(184)	Muir, 1996a
Ringed seal	Admirality Inlet	1983	B	M	10	794	(879)	Muir et al, 1988
Ringed seal	Admirality Inlet	1983	B	F	16	308	(138)	Muir et al, 1988
Ringed seal	Admirality Inlet	1975-76	B	F	5	600	(99)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	B	M	19	568	(287)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	B	F	14	375	(172)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	L	M	19	6	(4)	Muir et al, 1988
Ringed seal	Barrow Strait	1984	L	F	14	4	(3)	Muir et al, 1988
Ringed seal	Arviat	1991	B	M	13	1760	(1200)	Muir, 1993a
Ringed seal	Arviat	1991	B	F	9	846	(310)	Muir, 1993a
Walrus	E Hudson Bay	?	B	F	3	5604	(1941)	Muir, 1994a
Walrus	E Hudson Bay	?	B	M	2	10403	(13916)	Muir, 1994a
Beluga	Western Greenland	?	K	M	10	169	(60)	Muir, 1993a
Beluga	Western Greenland	?	K	F	10	75	(38)	Muir, 1993a
Beluga	Western Greenland	?	T	M	10	323	(265)	Muir, 1993a
Beluga	Western Greenland	?	T	F	10	411	(178)	Muir, 1993a
Beluga[2]	MacKenzie Delta	?	B	F	5	5299	(1460)	Muir, 1996a
Beluga[2]	MacKenzie Delta	?	B	M	20	4882	(1878)	Muir, 1996a
Beluga[2]	MacKenzie Delta	?	T	F	5	218	(60)	Muir, 1996a
Beluga[2]	MacKenzie Dalta	?	T	M	6	317	(96)	Muir, 1996a
Beluga	E Hudson Bay	1984-85	B	M	8	2770	(510)	Muir et al, 1990
Beluga	E Hudson Bay	1984-85	B	F	8	1230	(840)	Muir et al, 1990
Beluga	W Hudson Bay	1986	B	M	4	3120	(340)	Muir et al, 1990
Beluga	W Hudson Bay	1986	B	F	4	960	(1000)	Muir et al, 1990
Beluga	Cumberland Sound	1983	B	M	6	4910	(250)	Muir et al, 1990
Beluga	Cumberland Sound	1983	B	F	6	1150	(410)	Muir et al, 1990
Beluga[2]	Beaufort Sea	1983, 1987	B	M	10	3330	(850)	Muir et al, 1990
Beluga[2]	Beaufort Sea	1983, 1987	B	F	2	830 - 1640		Muir et al, 1990
Beluga	Jones Sound	1984	B	M	8	2530	(570)	Muir et al, 1990
Beluga	Jones Sound	1984	B	F	7	2460	(1980)	Muir et al, 1990
Beluga	St Lawrence Estuary	1986-87	B	M	4	75800	(15300)	Muir et al, 1990
Beluga	St Lawrence Estuary	1986-87	B	F	5	37300	(22000)	Muir et al, 1990
Arctic char	Cornwallis Island	1991	M		12	72.5	(40.4)	Muir & Lockhart, 1993b
Arctic char	Alex Heiberg	1992	M		10	6.8	(2.7)	Muir & Lockhart, 1993b
Arctic char	Resolute	1993	M		5	290	(118)	Muir & Lockhart, 1993b
Arctic char	W Hudson Bay	1994	M		6	11.4	(3.5)	Muir & Lockhart, 1996b
Burbot	Yellowknife	1993	L		5	26.9	(18.0)	Muir & Lockhart, 1994b
Burbot	Mackenzie River	1994	L		11	56.6	(18.1)	Muir & Lockhart, 1996b
Lake trout	Banks Island	1993	M		5	31.9	(15.5)	Muir & Lockhart, 1996b
Lake trout	Rankin Inlet	1993-94	M		12	19.0	(14.1)	Muir & Lockhart, 1996b
Lake trout	Banks Island	1993	M		6	33.5	(9.9)	Muir & Lockhart, 1996b
Lake trout	Mackenzie Delta	1993	M		6	8.8	(3.7)	Muir & Lockhart, 1994b
Walleye	Hay River	199?	M		3	1.4	(0.3)	Muir & Lockhart, 1996b

*Summed congeners mean value with standard deviation in parenthesis; both actual values listed when n = 2

1: B = Blubber, L = Liver, M = Muscle + Skin, K = Kidney, T = Muktuk

2: Shared population with Alaska

Table 3. PCB concentrations in Alaskan marine mammal subsistence species, fish, and bird eggs (summed congeners, ng/g wet weight): Recent data published 1999-2004

Species	Location	Collection Date	Tissue	Sex	n	PCBs[1]		Reference
Beluga Whale	Cook Inlet	1992-1996	Blubber	M	10	1,490	(700)	Krahn et al. 1999
	Cook Inlet	1994-1997	Blubber	F	10	790	(560)	
	Point Hope	1989	Blubber	F	2	1,880 - 2,560		
	Point Lay	1990-1996	Blubber	M	11	5,200	(900)	
	Point Lay	1990-1996	Blubber	F	8	1,500	(1,120)	
Beluga Whale	Point Lay	1999-2000	Blubber		20	2,809	(263)	Hoekstra et al. 2003[3]
Bowhead Whale	Barrow	1992-1993	Blubber	M	14	327	(202)	O'Hara et al. 1999
			Blubber	F	12	377	(208)	
			Liver	M	8	39.5	(42.1)	
			Liver	F	3	20.8	(8.8)	
Bowhead Whale	Barrow	1999-2000	Blubber		25	379	(32)	Hoekstra et al. 2003[3]
Bowhead Whale	Barrow	1997-2000	Blubber		71	410	(29)[2]	Hoekstra et al. 2002
			Liver		23	9.1	(0.9)[2]	
Pacific Walrus	Bering Sea	1991	Blubber	M	6	480	(440)	Seagars et al. 2001
			Blubber	F	14	150	(160)	
Pacific Walrus	Bering Sea	1993-1996	Blubber		10	60.4	(27.0)	Struntz et al. 2000
Ringed Seal	Barrow	1996	Blubber	M	5	901	(244)	Kucklick et al. 2002
			Blubber	F	3	519	(21)	
Ringed Seal	Barrow	1999-2000	Blubber		20	588	(99)	Hoekstra et al. 2003[3]
Bearded Seal	Barrow	1999-2000	Blubber		7	303	(25)	Hoekstra et al. 2003[3]
Chum Salmon	Alaska, marine or river mouths	Summer 2002	Muscle		18	2.52	(1.20)	Alaska DEC 2004[6]
Chinook Salmon		Summer 2002	Muscle		17	8.17	(4.58)	
Sockeye Salmon		Summer 2002	Muscle		24	10.0	(4.26)	
Halibut		Summer 2002	Muscle		11	1.15	(0.94)	
Sablefish		Summer 2002	Muscle		11	4.79	(3.87)	
Sheefish		Winter 2001	Muscle		8	2.47	(1.17)	
Chinook Salmon	Yukon, Kuskokwim Rivers	2001	Muscle		48	12	(.987)[4]	USFWS 2003
Chum Salmon	Yukon River	2001	Muscle		40	3.3	(.229)[4]	
Chum Salmon	Kuskokwim River	2001	Muscle		19	see footnote 5		
Pink Salmon	Elson Lagoon, Barrow AK	1999-2000	Whole fish		7	2.6	(1.3)	Hoekstra et al. 2003[3]
Arctic Char					5	2.3	(0.4)	
Arctic Cod					12	2.5	(0.4)	
Fourhorn Sculpin					7	3.5	(0.7)	
Common Murre	St. Lazaria Isl. (Gulf of AK)	1999	Egg		10	241	(99)	Vander Pol et al. 2004
Common Murre	E. Amatuli Isl. (Gulf of AK)	1999	Egg		11	99.1	(31)	
Common Murre	St. George Isl. (Bering Sea)	1999	Egg		11	86.4	(45)	
Murre spp.	Little Diomede I. (Bering Sea)	1999	Egg		9	92.8	(25)	
Common Murre	Bogoslof I. (Aleutian Islands)	2000	Egg		9	76.2	(25)	
Thick-billed Murre	Bogoslof I. (Aleutian Islands)	2000	Egg		10	90.6	(29)	
Thick-billed Murre	St. George Isl. (Bering Sea)	2000	Egg		7	88.8	(22)	

1=Mean value with standard deviation in parenthesis unless otherwise indicated (both actual values listed when n = 2)
2=geometric mean with standard error in parenthesis
3=Mean with standard error in parenthesis; converted from reported lipid concentration to wet weight using mean lipid % value
4=Mean with standard error in parenthesis; USFWS unpublished data
5=PCBs only detected in 3 of 19 fish; range in detected fish was 2.9 to 8.0 ng/g wet weight
6=Alaska Dept. of Environmental Conservation, http://www.state.ak.us/dec/eh/docs/vet/FMP%20Organic%20data%20release3.pdf

Table 4. PCB concentrations in Alaskan wildlife species or tissues not typically used for subsistence (summed congeners unless otherwise noted, ng/g wet weight)

Species	Location	Collection Date	Tissue	Sex	n	PCBs[a]		Reference
Polar Bear	Barrow	1996	Subcutaneous fat	M	5	3,592	(1,442)	Kucklick et al. 2002
Polar Bear	Alaska	1997-1999	Liver	M	5	2,110	(1,870)	Corsolini et al. 2000
Killer Whale	Prince William Sound	1994-1999	Blubber	resident[b]	64	3,900	(4,500)	Ylitalo et al. 2001
				transient[b]	13	59,000	(43,000)	
Gray Whale	Russia - Bering Sea	1994	Blubber	F-juvenile	13	680	(98)[d]	Krahn et al. 2001
				M-juvenile	4	480	(130)[d]	
Sea Otter	Southeast Alaska	1991	Liver	M	7	8	(14)	Bacon et al. 1999
	Aleutian Islands	1991-1992		mixed	7	310	(480)	
Northern Fur Seal	St. George Island	1996	Milk	F	22	433	(198)	Beckman et al. 1999
			Dam blood	F	19	14.5	(2.6)	
			Pup blood	mixed	48	20.6	(6.9)	
Bald Eagle	Adak Island	1993-1994	Egg		10	2,100[c]		Anthony et al. 1999
	Tanaga Island				5	700[c]		
	Amchitka Island				4	1,700[c]		
	Kiska Island				6	2,000[c]		

a=mean value with standard deviation in parenthesis unless otherwise indicated
b=whales divided into two distinct eco-types named 'resident' and 'transient'; they have different morphology, diet and habitat use
c=geometric mean concentration of Aroclor 1260
d=mean value with standard error in parenthesis

Table 5. Selected epidemiological studies of immunotoxicity in humans exposed to PCBs and/or dioxins

Nature of Exposure	n (exposed group)	Exposure Measured?	Time Between Exposure & Study	DTH[1]	CD4/CD8	IgA	IgM	Lymphocyte Proliferation	MLR[2]	Reference
Yu-Cheng incident, Taiwan. Consumption of rice oil contaminated with PCBs and furans	varied; 30-143	unclear	1 and 3 yr	* ↓	* ↓	* ↓	* ↓	* ↑		Lu et al, 1985
Lactational; fish-eating population, Japan	37	yes - TEQ in breast milk 120 pg/kg median daily intake	none		* ↑					Nagayama et al, 1996
Industrial workers (TCDD)	11	workers only, not controls. 43-874 ppt TCDD/blood fat	20 years		nd			nd	* ↓	Knutsen, 1984
Chemical plant explosion (TCDD) Seveso, Italy	45 (children)	no, but high (21 with chloracne)	2 mo, repeat every 4 mo			nd	nd	nd	nd	Pocchiari et al, 1979
Missouri - TCDD in soil	68	no	unclear; none?		↓			nd		Stehr, 1986
Industrial workers - polybrominated dioxins and furans	42	workers only, not controls blood TEQ median 83 ppt	several months		nd	nd	* ↑			Zober, 1992
Times Beach Missouri TCDD in soil	50	no	unclear	(in sub-↓ set)	nd			(in subset) ↓		Knutsen, 1984

* = statistically significant, $p \leq .05$
nd = no difference
ppt = parts per trillion
1: delayed-type hypersensitivity
2: mixed lymphocyte response

Table 6a. Daily intake guidelines for polychlorinated biphenyls (PCBs)

Agency	Level (µg/kg-bw/day)	Guideline description
U.S. ATSDR	0.03	Minimal Risk Level - intermediate duration oral
U.S. ATSDR	0.02	Minimal Risk Level - chronic duration oral
U.S. EPA	0.02	Oral Reference Dose for Aroclor 1254
Health Canada	1	Tolerable Daily Intake

Table 6b. Daily intake guidelines for Dioxin Equivalents

Agency	Level (pg/kg-bw/day)	Guideline description
U.S. ATSDR	1	Minimal Risk Level - chronic
Health Canada	10	Tolerable Daily Intake
European Commission	2	Temporary Tolerable Daily Intake
Japan	4	Tolerable Daily Intake
Nordic Countries	5	Tolerable Daily Intake
UN/WHO JECFA	2.3	Average Tolerable Daily Intake
Health Council-Netherlands	1	Health-based Exposure Limit

Table 6c. Daily intake guidelines for Polybrominated Diphenyl Ethers (PBDEs)

Agency	Level (µg/kg-bw/day)	Guideline description
U.S. ATSDR	7	Minimal Risk Level - intermediate-duration oral
U S. EPA	10	Oral Reference Dose for decabromodiphenyl ether
U S. EPA	3	Oral Reference Dose for octabromodiphenyl ether
U S. EPA	2	Oral Reference Dose for pentabromodiphenyl ether

Table 7. Guidelines for Fish Advisories Based on PCB Levels in Fish (ppm)

Consumption Category	U.S. EPA[1]	Great Lakes Task Force[2]	Province of Ontario[2]
Unrestricted Consumption	0 - 0.0059	0 - 0.05	0 - 0.5
One Meal/Week	0.023-0.047	0.06 - 0.2	0.5 - 1.0
Two Meals/Month	0.063-0.094	NA	1.0 - 2.0
One Meal/Month	0.094-0.19	0.21 - 1.0	NA
One Meal/month for less sensitive only	NA	NA	2.0 - 4.0
One Meal/Two Months	NA	1.1 - 1.9	NA
No Consumption/Sensitive persons	NA	NA	>2.0
No consumption for anyone	>0.38	>1.9	>4.0

1: Monthly Consumption Limits for Chronic Systemic Health Endpoints, based on 8 Oz meal size
All values for adults. Source: U.S. EPA 2000b
2: Kamrin and Fischer, 1999

Table 8. U.S. FDA regulations for Maximum Allowable PCB Levels in Edible portions of Food in Commerce

Food Item	Level
Infant and Junior Foods	0.2 ppm
Eggs	0.3 ppm
Milk, other Dairy	1.5 ppm lipid
Fish and Shellfish	2.0 ppm
Poultry and Red Meat	3.0 ppm lipid

Table 9. PCB concentrations in freshwater fish from the Great Lakes (mean, ng/g wet weight)

Species	Location	Collection Date	Tissue	n	PCB	Reference
Walleye	Saginaw Bay	1990	Whole fish	13	2300[1]	Giesy, 1997
Chinook Salmon	Au Sable River, Mich[3]	1990	Whole fish	1 composite of 5 fish	1700[2]	Giesy, 1994
Pike	Au Sable River, Mich[3]	1990	Whole fish	1 composite of 5 fish	720[2]	Giesy, 1994
Walleye	Au Sable River, Mich[3]	1990	Whole fish	1 composite of 5 fish	2200[2]	Giesy, 1994
Steelhead	Manistee River, Mich[3]	1990	Whole fish	1 composite of 5 fish	3900[2]	Giesy, 1994
Perch	Muskegan River, Mich[3]	1990	Whole fish	1 composite of 5 fish	770[2]	Giesy, 1994
Chinook Salmon	Lake Michigan (by Ludington MI)	1988	fillet (no skin)	81	940[2]	Williams, 1992
Walleye	Apostle Islands Region, Lake Superior	1991-1992	Fillet (no skin)	1 composite	193[1]	Gerstenberger, 1997
Siscowet Lake Trout	Apostle Islands Region, Lake Superior	1991-1992	Fillet with skin	1 composite	370[1]	Gerstenberger, 1997
Carp	Lake Michigan tributary near Oshkosh,WI	1991-1992	Fillet (no skin)	1 composite	1404[1]	Gerstenberger, 1997
Whitefish	Apostle Islands Region, Lake Superior	1991-1992	Fillet with skin, scaled	1 composite	154[1]	Gerstenberger, 1997
Whitefish liver	Apostle Islands Region, Lake Superior	1991-1992	Liver	1 composite	224[1]	Gerstenberger, 1997
Lake Trout	Lake Superior	1996	Whole fish	2	250-430	Kannan, 2000
Lake Trout	Siskiwit Lake, Isle Royale	1996	Fillet (no skin)	3	40-87	Kannan, 2000

1 = Summed congeners
2 = Totals based on Arochlor pattern matching
3 = Great Lakes - influenced zone of river

Table 10. Individual PCB Congener Levels (ppb Lipid-Adj) in 166 Aleutian/Pribilof Residents in Comparison to U.S. National Averages for Adults, from NHANES 2003

Congener	10th	25th	50th	75th	90th	95th
A/P[1], PCB 74	<LOD[2]	<LOD	27.3	57.7	89.9	124.95
NHANES[3], PCB 74	<LOD	<LOD	<LOD	13.4	23.3	30.4
A/P, PCB 99	<LOD	6.7	29.5	74.4	122.7	176.6
NHANES, PCB 99	<LOD	<LOD	<LOD	<LOD	13.9	19.9
A/P, PCB 118	<LOD	2.1	36.8	90.6	160.5	246.5
NHANES, PCB 118	<LOD	<LOD	<LOD	16.3	28.7	43.8
A/P, PCB 153	<LOD	72.275	185	392.75	614.5	949
NHANES, PCB 153	<LOD	<LOD	<LOD	<LOD	83.2	120
A/P, PCB 156	<LOD	3.75	9.8	16.275	22.1	33.525
NHANES, PCB 156	<LOD	<LOD	<LOD	<LOD	13.8	17.4
A/P, PCB 170	<LOD	14.5	32.95	59.875	93.6	119.25
NHANES, PCB 170	<LOD	<LOD	<LOD	<LOD	25.1	32.6
A/P, PCB 180	<LOD	51.825	101	192.75	313	387.75
NHANES, PCB 180	<LOD	<LOD	<LOD	42.7	66.6	83.5
A/P, PCB 187	<LOD	8.6	22.15	38.575	63.8	104
NHANES, PCB 187	<LOD	<LOD	<LOD	<LOD	19.2	25.2

1 = Middaugh et al, 2001 – "Assessment of Exposure to Persistent Organic Pollutants (POPs) in 5 Aleutian and Pribilof Villages"
2 = Below Limit of Detection
3 = CDC 2003 – Second National Report on Human Exposure to Environmental Chemicals, NHANES

Table 11. Individual Detected Polychlorinated Dioxin, Furan, and Coplanar PCB Congener Levels (ppt Lipid-Adj) in Aleutian Island Residents (n=37-52) in Comparison to U.S. National Averages for Adults, from NHANES 2003

Congener	10th	25th	50th	75th	90th	95th
A/P[1] 1,2,3,4,6,7,8-HeptaCD-dioxin	< LOD[2]	29.75	56.5	84.5	116	203
NHANES[3] 1,2,3,4,6,7,8-HeptaCD-dioxin	<LOD	<LOD	<LOD	63.6	93	123
A/P OctaCD-dioxin	235.3	310.25	372	548	615.9	649.6
NHANES OctaCD-dioxin	<LOD	<LOD	<LOD	452	727	952
A/P 2,3,4,7,8-PentaCD-furan	<LOD	<LOD	7.6	11	14	16
NHANES 2,3,4,7,8-PentaCD-furan	<LOD	<LOD	<LOD	<LOD	13	16.3
A/P PCB 126	18.4	35	52	86.5	129.5	235.3
NHANES PCB 126	<LOD	<LOD	<LOD	31.8	58.7	91.4
A/P PCB 169	17.1	22	38	60	73.9	80.5
A/P PCB 169	<LOD	<LOD	<LOD	<LOD	37.3	48.3

1 = Middaugh et al, 2001 – "Assessment of Exposure to Persistent Organic Pollutants (POPs) in 5 Aleutian and Pribilof Villages"
2 = Below Limit of Detection
3 = CDC 2003 – Second National Report on Human Exposure to Environmental Chemicals, NHANES

Table 12. Mean Levels of Individual PCB, Dioxin and Furan Congeners in Serum from Aleutian/Pribilof Residents in Comparison to Great Lakes Residents

A. PCB Congeners in Serum, ppb wet weight

	Aleutian/Pribilof[1]	Great Lakes Fisheaters[2]	Elder Great Lakes Fisheaters[3]	Elder Great Lakes Non-fisheaters[3]	Comparison Group[2]
PCB 74	0.33	0.3	0.64	0.22	0.009
PCB 99	0.42	0.4	0.54	0.16	<LOD
PCB 118	0.52	0.4	0.83	0.16	0.03
PCB 153	2.29	1.1	2.13	0.75	0.4
PCB 180	1.12	0.4	2.00	0.79	0.4
PCB 187	0.24	0.3	0.58	0.19	0.04

1 = Middaugh et al, 2001; 5 Aleutian and Pribilof Villages, n = 166
2 = Anderson 1998; GL fisheater n = 30; Unexposed comparison group n = 41
3 = Humphrey 2000; All participants >50 yrs old, GL fisheaters n = 101; GL non-fisheaters n = 78

B. Polychlorinated Dioxins, Furans and Coplanar PCBs in Serum, ppt Lipid-Adjusted

	Aleutian/Pribilof[4]	Great Lakes Fisheaters[5]	Comparison Group[5]
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin	64.3	134	124
Octachlorodibenzo-p-dioxin	412	777	971
2,3,4,7,8-Pentachlorodibenzofuran	6.41	17.7	5.5
PCB 126	73.2	148	18.4
PCB 169	41.1	80.8	17.9

4 = Middaugh et al, 2001; 3 Aleutian Villages, n = 37-52
5 = Anderson 1998; GL fisheater n = 31; Unexposed comparison group n = 70

Figure 1. Structure, nomenclature and numbering for polyhalogenated biphenyls (a & b), dioxins (c) furans (d) and diphenyl ethers (e).

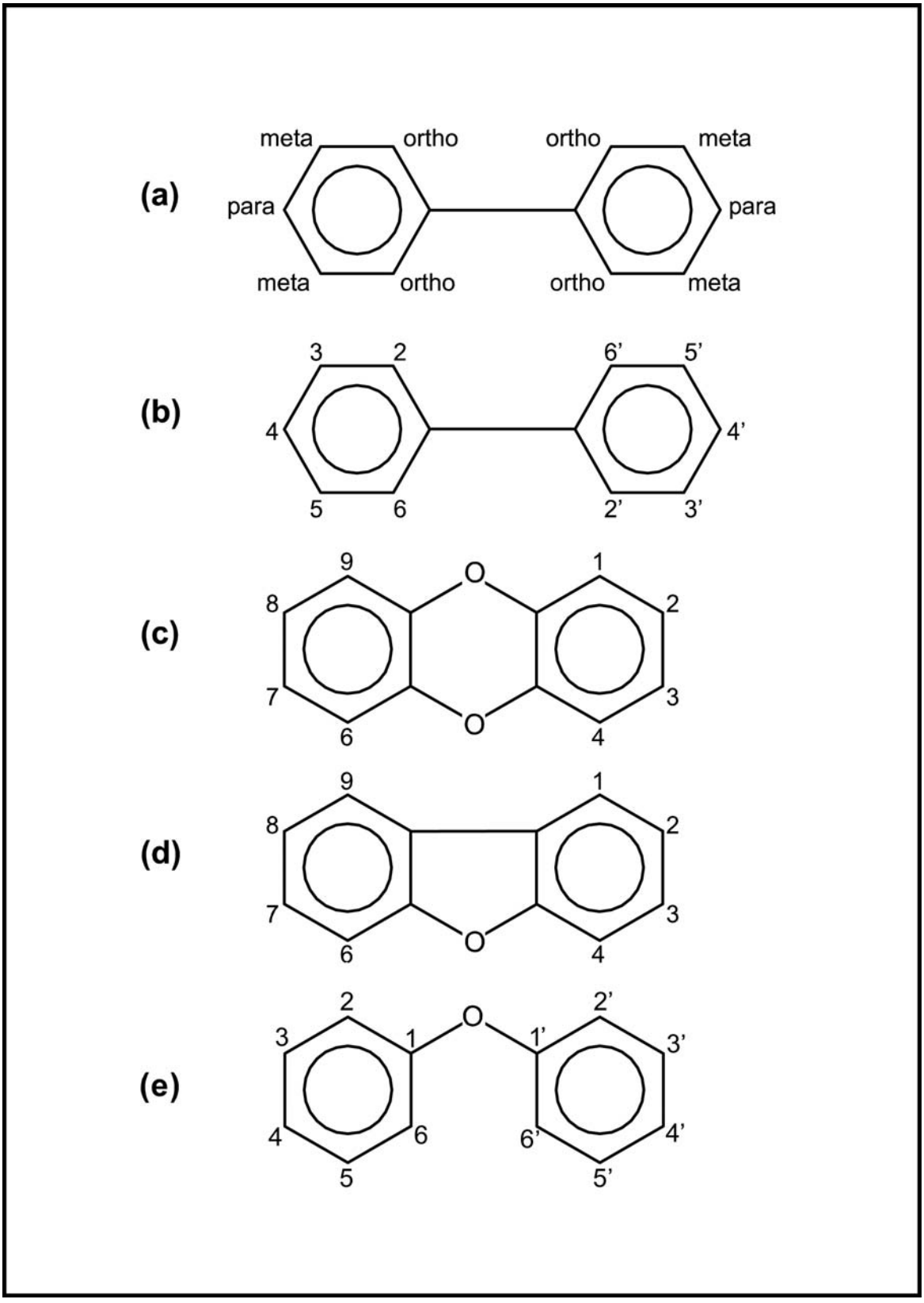
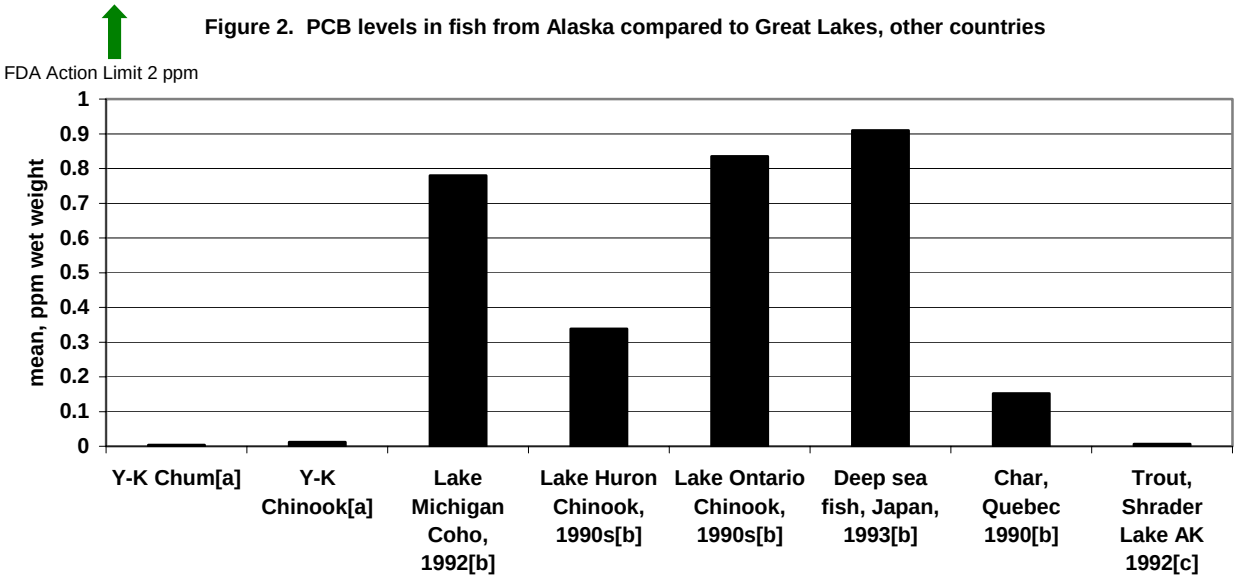
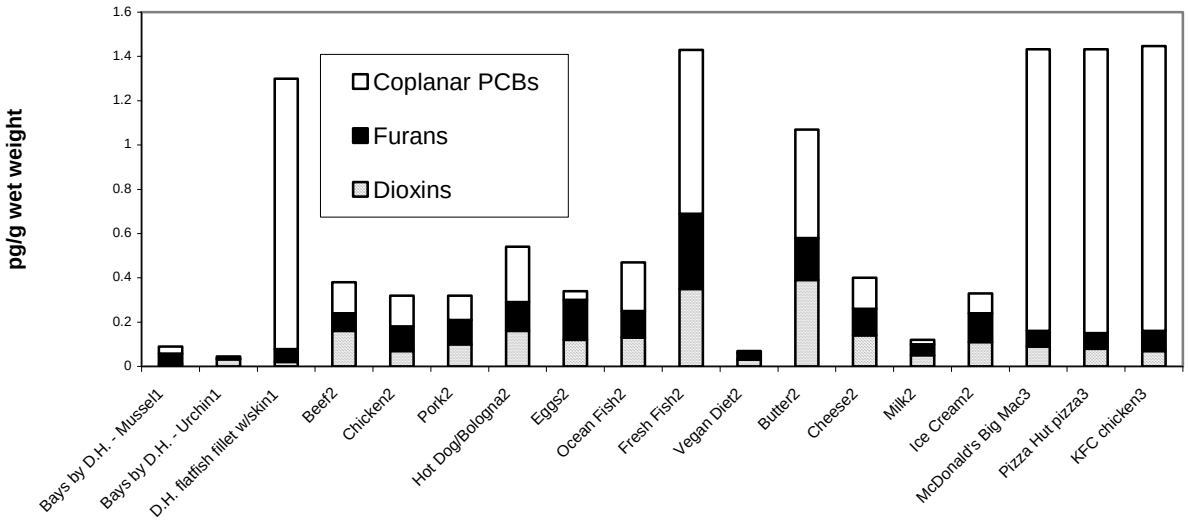


Figure 2. PCB levels in fish from Alaska compared to Great Lakes, other countries



[a] USFWS, unpublished data
[b] ATSDR, 2000
[c] Wilson et al., 1995

Figure 3. Dioxin TEQs in Biota from Dutch Harbor area vs. U.S. Supermarket/Fast Food



[1] Alaska Section of Epidemiology, 2001: TEQs calculated using WHO 1998 Toxic Equivalency Factors (TEFs) from van den Berg et al., 1998
[2] Schecter et al., 1997: TEQs calculated using 1988 International TEFs
[3] Schecter and Li, 1997: TEQs calculated using 1988 International TEFs

Figure 4. Time Trends of Polybrominated Diphenyl Ether (PBDE) Levels in Great Lakes Herring Gull Egg Pools

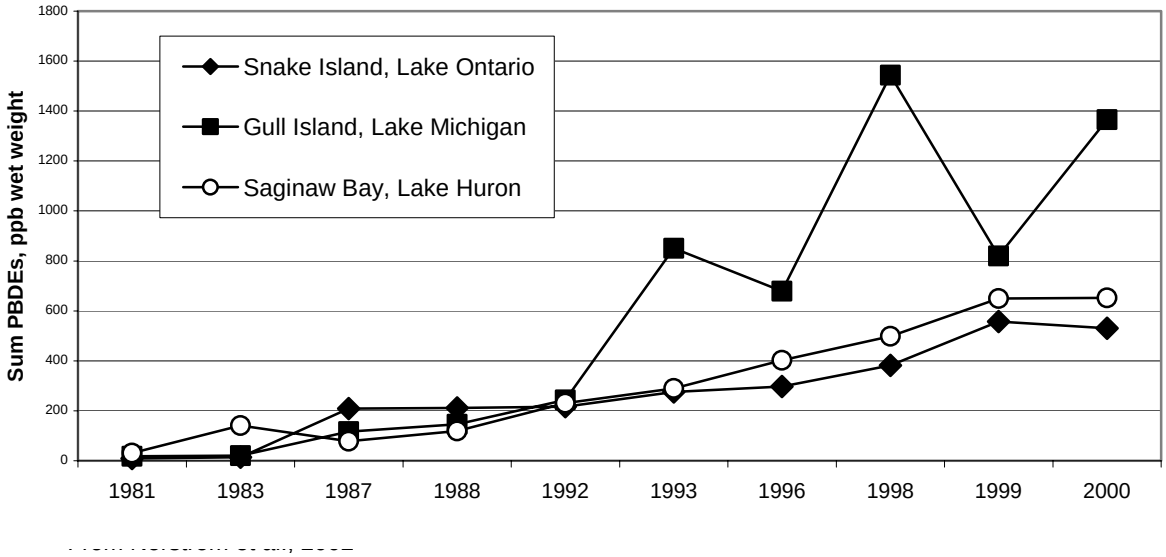
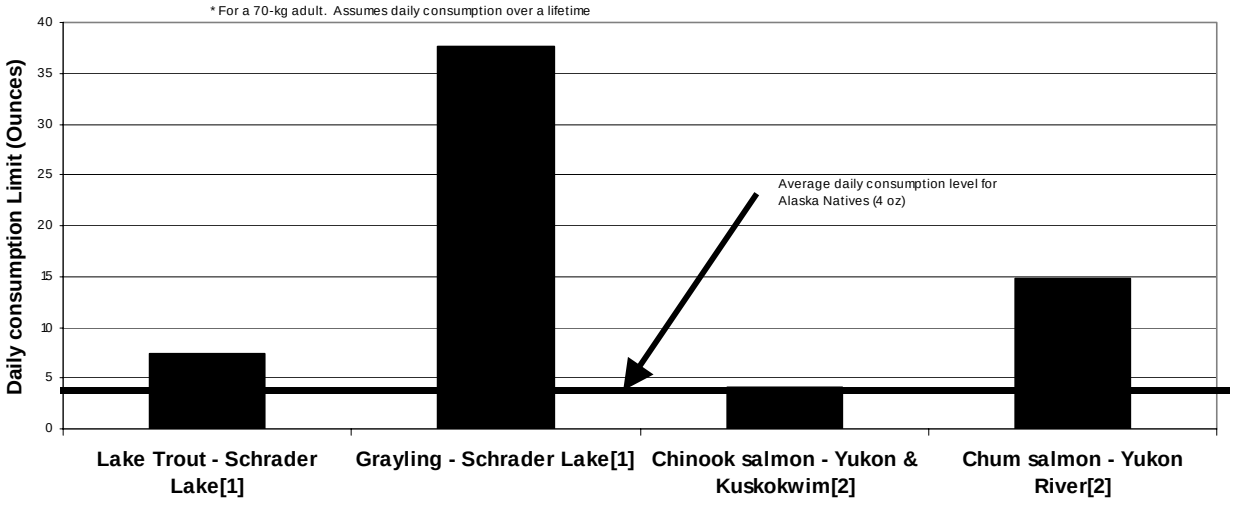
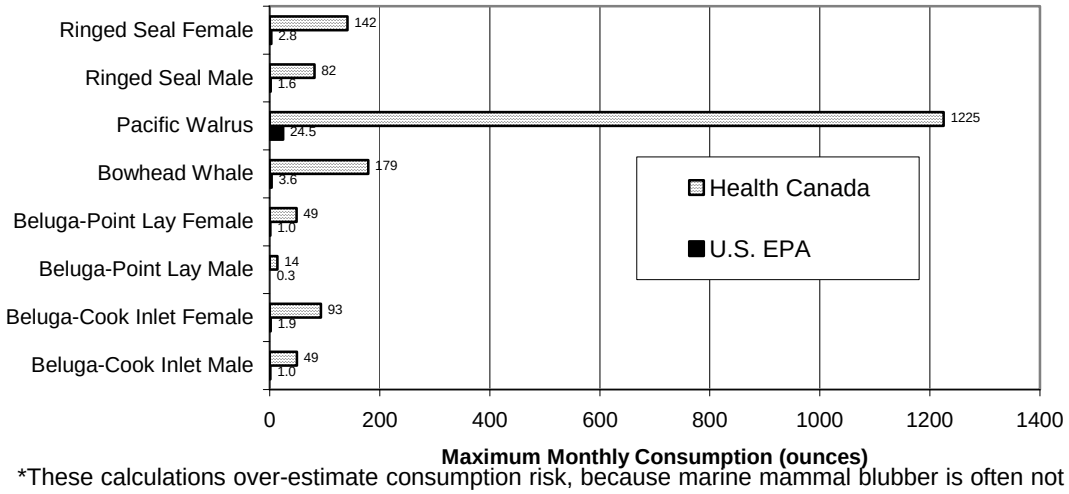


Figure 5. Maximum allowable daily consumption* of fish flesh based on PCB content (chronic systemic health endpoint, USEPA)



[2] USFWS, unpublished data

Figure 6. Maximum allowable monthly consumption limit for Alaskan marine mammal blubber*, based on total PCB content in animals sampled during the 1990s (chronic system health endpoint, for a 70-kg adult)



*These calculations over-estimate consumption risk, because marine mammal blubber is often not eaten in isolation or without extensive processing. Blubber is often eaten as "maktak", a combination of blubber and epidermis that has lower concentrations of lipophilic contaminants.

Figure 7: Serum PCB Levels in Women of Childbearing Age from 5 Aleutian/Pribilof Island Villages in Comparison to maternal plasma from other Arctic Countries (AMAP)

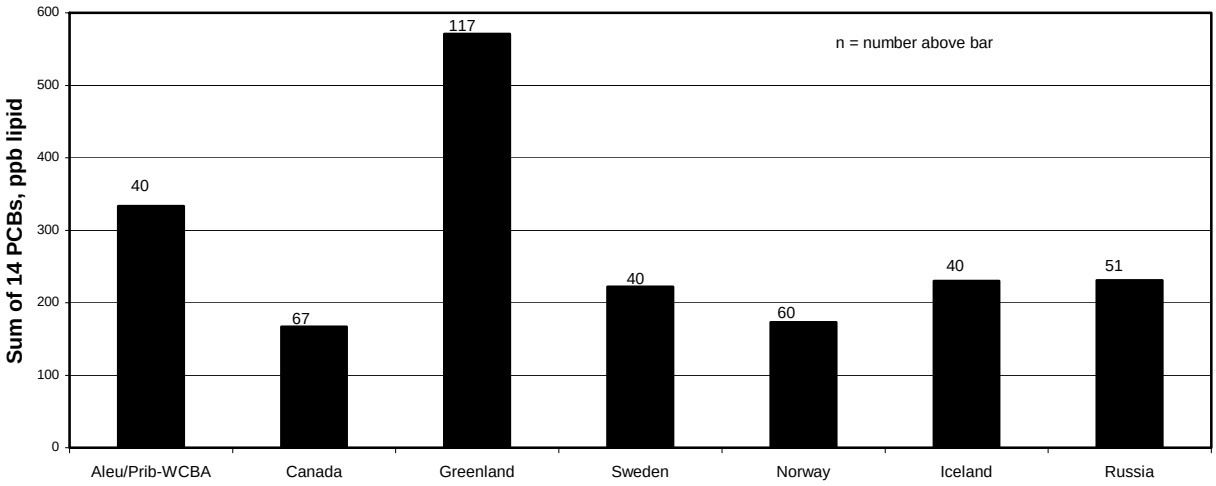
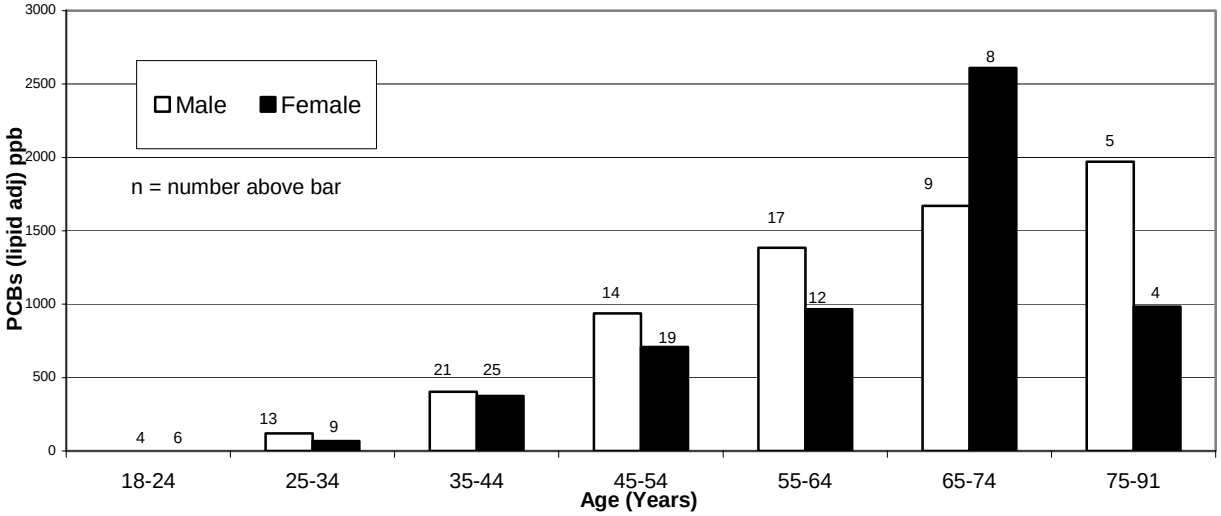


Figure 8. Median PCB levels in 5 Aleutian/Pribilof Villages



Alaska Division of Public Health, 2001

Figure 9. Lipid-adj. Total PCB serum levels and Age, for Women of Childbearing Age and All Other Participants, in 5 Aleutian/Pribilof Island Villages, 1999

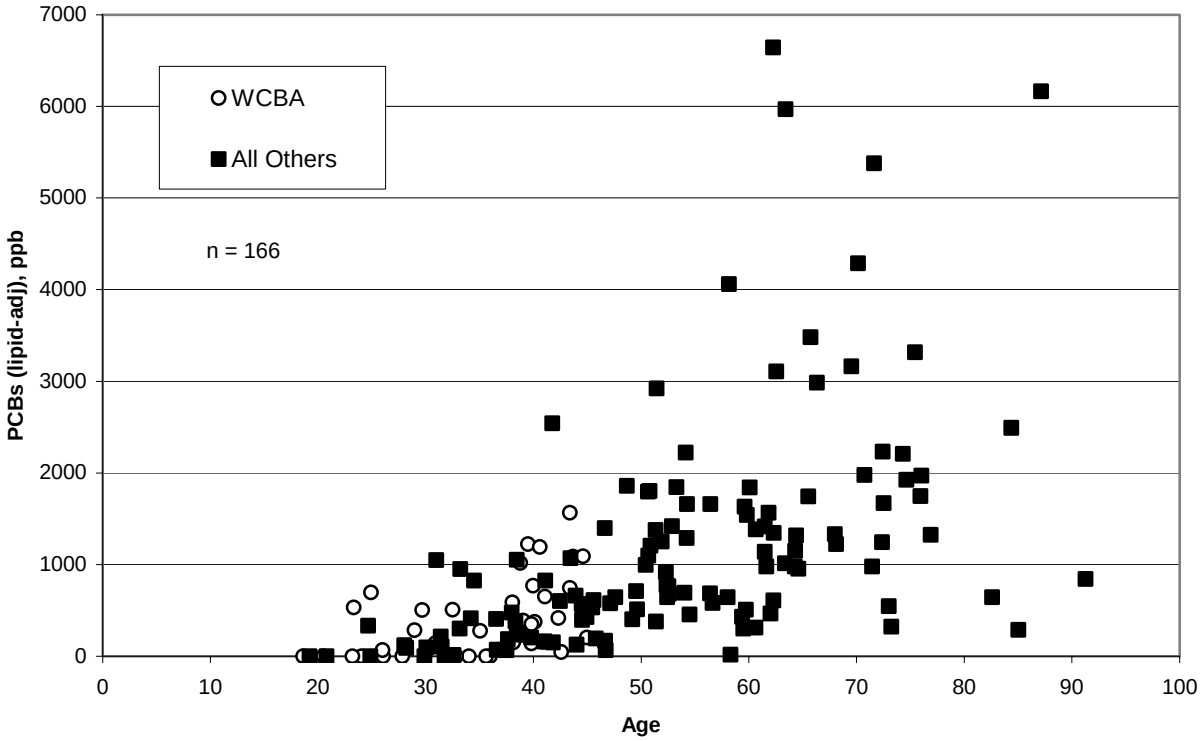
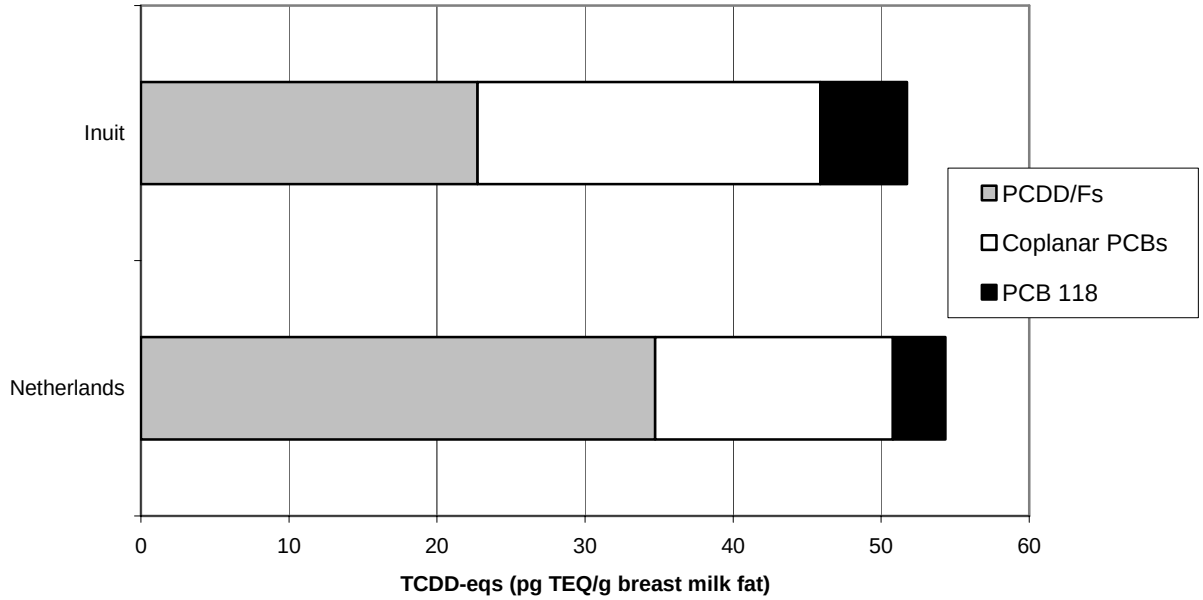


Figure 10. Direct comparison of TCDD-equivalents in breast milk fat of women from the Netherlands and Arctic Quebec, as calculated with identical congeners and TEF values.



Congener-specific data for the Netherlands is from Koopman-Esseboom et al., 1994a; and data for arctic Quebec is from Dewailly et al., 1992. All dioxin Toxic Equivalents (TEQs) were re-calculated for this figure using the most recent WHO Toxic Equivalency Factors (TEFs) from van den Berg et al., 1998.

Figure 11. Time Trend of Total PCB Levels in Pooled Swedish Breastmilk Samples

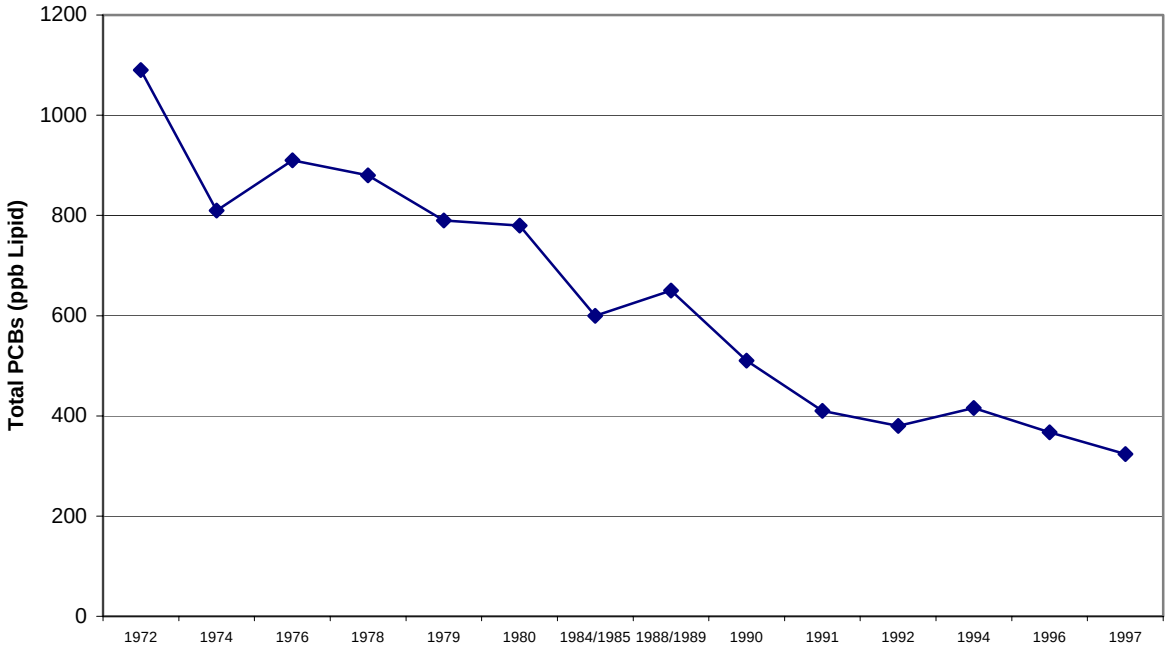


Figure 12. Time Trends of PCBs in Cord Blood, Canadian Lower North Shore of St. Lawrence River (Quebec)

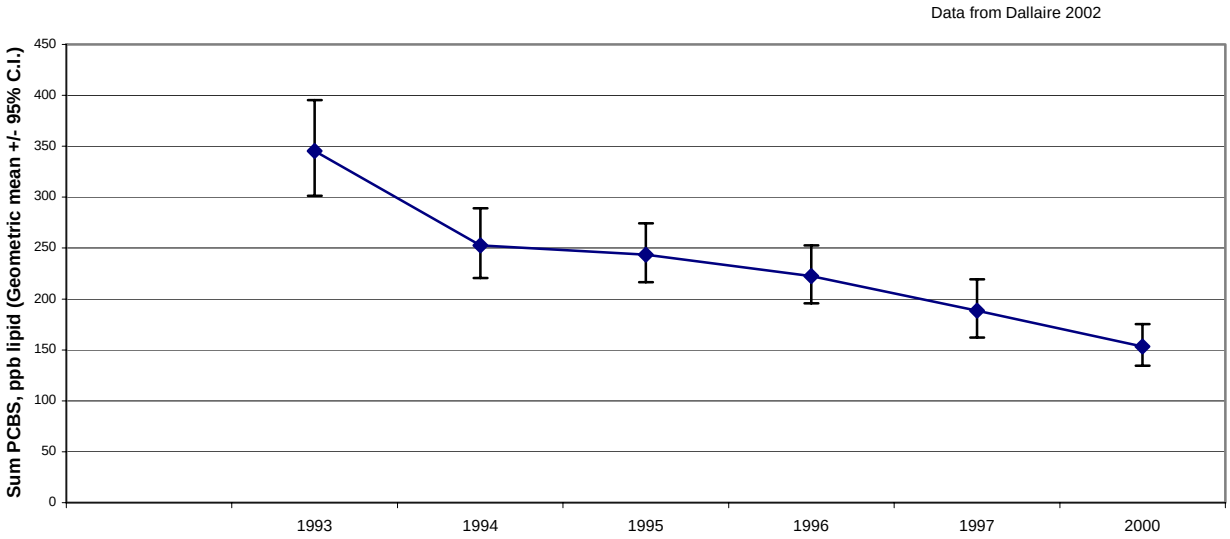
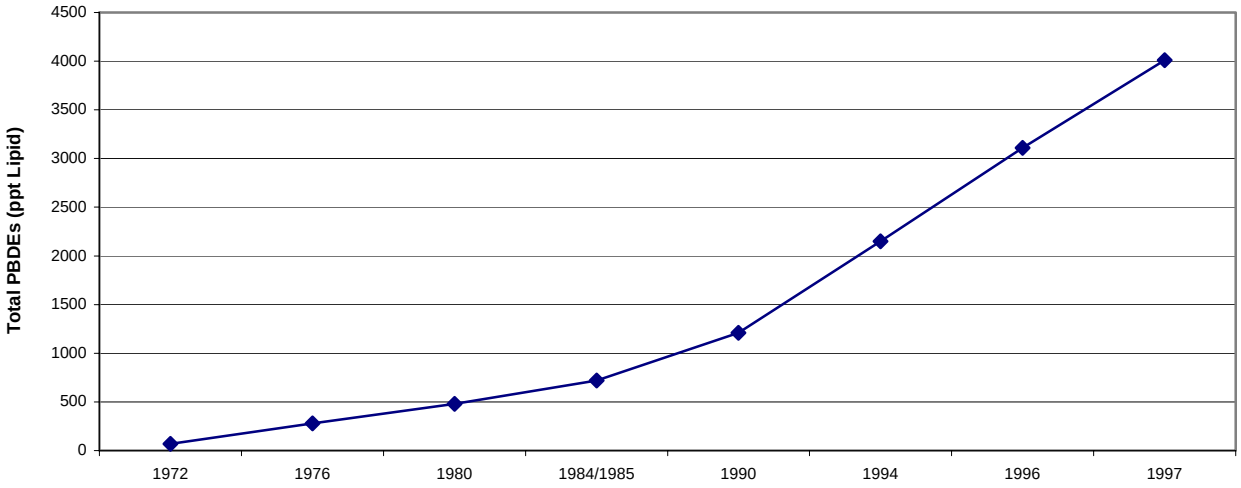
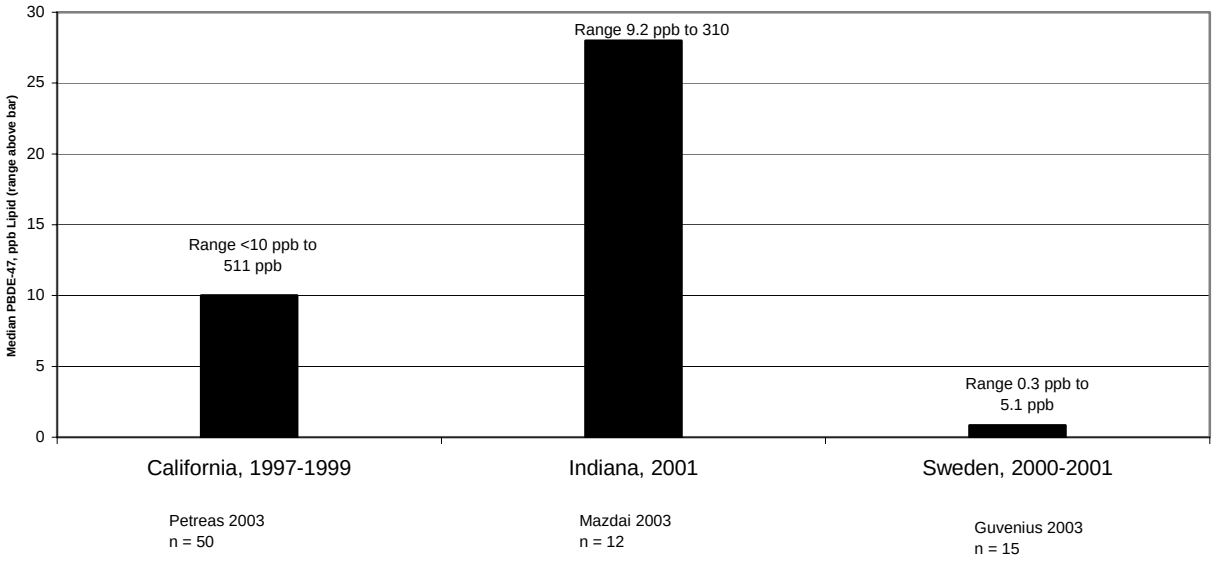


Figure 13. Time Trend of Total Polybrominated Diphenyl Ether Levels in Pooled Swedish Breastmilk Samples



Data from Norén and Meironyte, 2000

Figure 14. Median PBDE-47 Level in Serum from Women of Childbearing Age, USA and Sweden



UNITS OF MEASURE

Milligram	**10^{-3}**	**one thousandth**	**0.001**
Microgram	**10^{-6}**	**one millionth**	**0.000001**
Nanogram	**10^{-9}**	**one billionth**	**0.000000001**
Picogram	**10^{-12}**	**one trillionth**	**0.000000000001**

parts per million = ppm = µg/g = mg/kg = ng/mg

parts per billion = ppb = µg/kg = ng/g = µg/L

parts per trillion = ppt = pg/g = ng/kg

0.01 mg/L = 10 µg/L

1 µmol mercury = 200 µg mercury = 1 µmol methylmercury

Reference List

Adami,H.-O., Lipworth,L., Titus-Ernstoff,L., Hsieh,C., Hanberg,A., Ahlborg,U. et al. (1995) Organochlorine compounds and estrogen-related cancers in women. *Cancer Causes Control* **6:** 551-566.

Addison,R.F. and Smith,T.G. (1998) Trends in organochlorine residue concentrations in ringed seal (Phoca hispida) from Homan NWT, 1972-1991. *Arctic* **51:** 253-261.

Adkins,E.K. (1979) Effect of embryonic treatment with estradiol or testosterone on sexual differentiation of the quail brain. *Neuroendocrinology* **29:** 178-185.

Adkins-Regan,E. (1987) Sexual differentiation in birds. *TINS* **10:** 517-522.

Aguilar,A. and Borrell,A. (1994) Abnormally high polychlorinated biphenyl levels in striped dolphins (Stenella coeruleoalba) affected by the 1990-1992 Mediterranean epizootic. *Sci Total Environ* **154:** 237-247.

Ahlborg,U.G., Becking,G.C., Birnbaum,L.S., Brouwer,A., Derks,H.J.G.M., Feeley,M. et al. (1994) Toxic equivalency factors for dioxin-like PCBs. *Chemosphere* **28:** 1049-1067.

Ahlborg,U.G., Brouwer,A., Fingerhut,M.A., Jacobson,J.L., Jacobson,S.W., Kennedy,S.W. et al. (1992) Impact of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept. *Eur J Pharmacol* **228:** 179-99.

Ahlborg,U.G., Lipworth,L., Titus-Ernstoff,L., Hsieh,C., Hanberg,A., Baron,J. et al. (1995) Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence. *Crit Rev Toxicol* **25:** 463-531.

Alaska Cancer Registry . 1998 Cancer in Alaska: Cancer Incidence and Mortality. 2002. Alaska Division of Public Health.

Alaska Division of Public Health (2001) Assessment of Exposure to Persistent Organic Pollutants (POPs) in 5 Aleutian and Pribilof Islands. *Epidemiology Bulletin* **5**.

Alaska Division of Public Health (2002) Alaska Maternal Hair Mercury Biomonitoring Program: Initial Results. *Epidemiology Bulletin*.

Alaska Section of Epidemiology . Evaluation of the Public Health Significance of Chemical Concentrations Found in Mussel, Urchin, Fish and Sea Lion samples/Dutch Harbor, Alaska. 10-25-2001. Anchorage AK, State of Alaska Department of Health & Social Services, Division of Public Health, Section of Epidemiology, Environmental Public Health Program.

Almstrup,K., Fernandez,M.F., Petersen,H.P., Olea,N., Skakkebaek,N.E., and Leffers,H. (2002) Dual Effects of Phytoestrogens Result in U-Shaped Dose-Response Curves. *Environ Health Perspect* **110:** 743-748.

AMAP (1998) *AMAP Assessment Report: Arctic Pollution Issues.* Oslo, Norway: Arctic Monitoring and Assessment Programme.

AMAP . AMAP Assessment 2002: Human Health in the Arctic. 2003. Oslo, Norway, AMAP.

Ambrose,R.E., Matz,A., Swem,T., and Bente,P. Environmental contaminants in American and Arctic peregrine falcon eggs in Alaska, 1979-95. NAES-TR-00-02. 5-31-2000. AK, US Fish and Wildlife Service, US Department of the Interior.

Ames,B.N., Gold,L.S., and Willett,W.C. (1995) The causes and prevention of cancer. *Proc Natl Acad Sci USA* **92:** 5258-65.

Ames,B.N., Magaw,R., and Gold,L.S. (1987) Ranking possible carcinogenic hazards. *Science* **236:** 271-280.

Anderson,H.A., Falk,C., Hanrahan,L., Olson,J., Burse,V.W., Needham,L. et al. (1998) Profiles of Great Lakes critical pollutants: a sentinel analysis of human blood and urine. *Environ Health Perspect* **106:** 279-289.

Arnold,D., Ayotte,P., Bondy,G., Chan,L., Dewailly E., Donaldson,S. et al. Canadian Arctic Contaminants Assessment Report II. 2003.

Arnold,D.L., Nera,E.A., Stapley,R., Tolnai,G., Claman,P., Hayward,S. et al. (1996) Prevalence of endometriosis in Rhesus (Macaca mulatta) monkeys ingesting PCB (Aroclor 1254): Review and evaluation. *Fund Appl Toxicol* **31:** 42-55.

ATSDR (2000) *Toxicological profile for polychlorinated biphenyls (PCBs).* Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

ATSDR . Toxilogical Profile for Chlorinated Dibenzo-*p*-Dioxins. 2003. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

Aylward,L.L., Hays,S.M., Karch,N.J., and Paustenbach,D.J. (1996) Relative susceptibility of animals and humans to the cancer hazard posed by 2,3,7,8-tetrachlorodibenzo-p-dioxin using internal measures of dose. *Environ Sci Technol* **30:** 3534-3543.

Ayotte,P. (1996) Biomarkers of early biological responses induced by organochlorine exposure in women giving birth in Arctic Quebec. *Environmental Studies, Northern Contaminants Program* **73:** 309-312.

Ayotte,P., Carrier,G., and Dewailly,E. (1996) Health risk assessment for Inuit newborns exposed to dioxin-like compounds through breast feeding. *Chemosphere* **32:** 531-542.

Becker,P.R. Alaska Marine Mammal Tissue Archival Project: Annual Report. Interagency Agreement No. 17909, Amendment No. 2. 1993. U.S. DOC, National Marine Fisheries Service.

Becker,P.R., Koster,B.J., Wise,S.A., and Zeisler,R. (1993) Biological Specimen Banking in Arctic Research: An Alaska Perspective. *Sci Total Environ* **139/140:** 69-95.

Becker,P.R., Mackey,E.A., Demiralp,R., Schantz,M.M., Koster,B.J., and Wise,S.A. (1997a) Concentrations of chlorinated hydrocarbons and trace elements in marine mammal tissues archived in the U.S. National Biomonitoring Specimen Bank. *Chemosphere* **34:** 2067-2098.

Becker,P.R., Wise,S.A., Thorsteinson,L., Koster,B.J., and Rowles,T. (1997b) Specimen banking of marine organisms in the United States: current status and long-term prospective. *Chemosphere* **34:** 1889-1906.

Beland,P., DeGuise,S., Girard,C., Lagace,A., Martineau,D., Hichaud,R. et al. (1993) Toxic compounds and health and reproductive effects in St. Lawrence beluga whales. *J Great Lakes Res* **19:** 766-775.

Bertazzi,P.A. and Di Domenico,A. (1994) Chapter 18: Chemical, Environmental, and Health Aspects of the Seveso, Italy, Accident. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 587-632.

Bertazzi,P.A., Pesatori,A.C., Consonni,D., Tironi,A., Landi,M.T., and Zocchetti,C. (1993) Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. *Epidemiology* **4:** 398-406.

Bertazzi,P.A., Riboldi,L., Pesatori,A., Radice,L., and Zocchetti,C. (1987) Cancer mortality of capacitor manufacturing workers. *Am J Ind Med* **11:** 165-176.

Betts,K.S. (2001) Mounting concern over brominated flame retardants. *Environ Sci Technol* 274A-275A.

Betts,K.S. (2002) Rapidly rising PBDE levels in North America. *Environ Sci Technol* **36:** 50A-52A.

Bigsby,R., Chapin,R.E., Daston,G.P., Davis,B.J., Gorski,J., Gray,L.E. et al. (1999) Evaluating the effects of endocrine disruptors on endocrine function during development. *Environ Health Perspect* **107:** 613-618.

Birnbaum,L.S. and Cummings,A.M. (2002) Dioxins and Endometriosis: A Plausible Hypothesis. *Envir Health Perspectives* **110:** 15-21.

Birnbaum,L.S. (1994) Endocrine effects of prenatal exposure to PCBs, dioxins, and other xenobiotics: implications for policy and future research. *Environ Health Perspect* **102:** 676-679.

Blok,W.L., Katan,B., and van der Meer,J.W. (1996) Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. *J Nutr* **126:** 1515-1533.

Bowman,R.E., Schantz,S.L., Ferguson,S.A., Tong,H.Y., and Gross,M.L. (1990) Controlled exposure of female rhesus monkeys to 2,3,7,8-TCDD; cognitive behavioral effects in their offspring. *Chemosphere* **20:** 1103-1108.

Bowman,R.E., Schantz,S.L., Weerasinghe,N.C.A., Gross,M.L., and Barsotti,D.A. (1989) Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 5 or 25 parts per trillion in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity. *Chemosphere* **18:** 243-252.

Bromwich,P., Cohen,J., Stewart,I., and Walker,A. (1994) Decline in sperm counts: An artefact of changed reference range of normal. *Br Med J* **309:** 19-22.

Brouwer,A., Hakansson,H., Kukler,A., Van Den Berg,K.J., and Ahlborg,U.G. (1989) Marked alterations in retinoid homeostasis of Sprague-Dawley rats induced by a single i.p. dose of 10 micrograms/kg of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicology* **58:** 267-283.

Brouwer,A. and Van Den Berg,K.J. (1986) Binding of a Metabolite of 3,4,3,4- Tetrachlorobipheny to Transthyretin Reduces serum Vitamin A Transport by Inhibiting the Formation of the Protein Complex Carrying Both Retinol and Thyroxin . *Toxicol Appl Pharmacol* **85:** 301-312.

Brouwer,A., Ahlborg,U.G., Van den Berg,M., Birnbaum,L.S., Boersma,E.R., Bosveld,B. et al. (1995) Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimentsl animals and human infants. *Eur J Pharmacol* **293:** 1-40.

Brouwer,A., Longnecker,M.P., Birnbaum,L.S., Cogliano,J., Kostyniak,P., Moore,J. et al. (1999) Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. *Environ Health Perspect* **107:** 639-649.

Brown,D.P. (1987) Mortality of workers exposed to polychlorinated biphenyls - An update. *Arch Environ Health* **42:** 333-339.

Burkhard,L.P. (1987) Determination of polychlorinated biphenyls using multiple regression with outlier detection and elimination. *Anal Chem* **59:** 1187-1190.

Burleson,G.R., Lebrec,H., Yang,Y.G., Ibanes,J.D., Pennington,K.N., and Birnbaum,L.S. (1996) Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on influenza virus host resistence in mice. *Fund Appl Toxicol* **29:** 40-47.

Carlsen,E., Giwercman,A., Keiding,N., and Skakkeback,N.E. (1992) Evidence for the decreasing sperm quality of semen during the past 50 years. *Br Med J* **305:** 609-612.

Carpenter,D.O., Stoner,C.R.T., and Lawrence,D.A. (1997) Flow cytometric measurements of neuronal death triggered by PCBs. *NeuroToxicology* **18:** 507-514.

CDC. Second National Report on Human Exposure to Environmental Chemicals. 02-0716. 2003. http://www.cdc.gov/exposurereport/

Chan,L.H.M., Receveur,O., and Kuhnlein,H.V. (1996) Assessment of effects of preparation on levels of organic contaminants in Inuit traditional food. Environmental Studies Northern Contaminants Program Centre for Nutrition and the Environment of Indigenous Peoples (CINE), McGill University **73:** 323-332.

Chao,W.-Y., Hsu,C.-C., and Guo,Y.L. (1997) Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. *Arch Environ Health* **52:** 257-262.

Charles,L.E., Loomis,D., Shy,C.M., Newman,B., Millikan,R., Nylander-French,L.A., and Couper,D. (2003) Electromagnetic Fields, Polychlorinated Biphenyls, and Prostate Cancer Mortality in Electric Utility Workers. *Am J Epidemiol* **157:** 683-691.

Cheek,A.O., Kow,K., Chen,J., and McLachlan,J.A. (1999) Potential mechanisms of thyroid disruption in humans: interacttion of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. *Environ Health Perspect* **107:** 273-278.

Cheeke,P.R. and Shull,L.R. (1985) Natural Toxicants in Feeds and Poisonous Plants. Westport CT: AVI Publishing.

Chen,Y.-C.J., Guo,Y.-L., Hsu,C.-C., and Rogan,W.J. (1992) Cognitive development of Yu-Cheng ('Oil Disease') children prenatally exposed to heat-degraded PCBs. *JAMA* **268:** 3213-3218.

Colborn,T., Dumanoski,D., and Myers,J.P. (1996) Our Stolen Future Are We Threatening Our Fertility, Intelligence, and Survival? - A Scientific Detective Story. New York: Dutton.

Corsolini,S., Kannan,K., Evans,T., Focardi,S., and Giesy,J.P. (2000) Polychlorinated biphenyls in Arctic and Antarctic organisms: Polar bear, krill, fish, Weddell seal and skua. *Organohalogen Compounds* **46:** 314-317.

Covello,V.T. and Merkhofer,M.W. (1993) Risk Assessment Methods Approaches for Assessing Health and Environmental Risks. New York: Plenum Press.

Crews,D., Bergeron,J.M., and McLachlan,J.A. (1995) The role of estrogen in turtle sex determination and the effect of PCBs. *Environ Health Perspect* **103:** 73-77.

Crisp,T.M., Clegg,E.D., Cooper,R.L., Wood,W.P., Anderson,D.G., Baetcke,K.P. et al. (1998) Environmental endocrine disruption: an effects assessment and analysis. *Environ Health Perspect* **106:** 11-56.

Crump,K.S., Canady,R., and Kogevinas,M. (2003) Meta-analysis of Dioxin Cancer Dose Response for Three Occupational Cohorts. *Environ Health Perspect* **111:** 681-687.

Dallaire,F., Dewailly E., Laliberte,C., Muckle,G., and Ayotte,P. (2002) Temporal Trends of Organochlorine Concentrations in Umbilical Cord Blood of Newborns from the Lower North Shore of the St. Lawrence River (Qeubec, Canada). *Environ Health Perspect* **110:** 835-838.

Darnerud,P.O., Eriksen,G.S., Johannesson,T., Larsen,P.B., and Viluksela,M. (2001) Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. *Environ Health Perspect* **109:** 49-68.

Daston,G.P., Gooch,J.W., Breslin,W.J., Shuey,D.L., Nikiforov,A.I., Fico,T.A., and Gorsuch,J.W. (1997) Environmental estrogens and reproductive health: a discussion of the human and environmental data. *Reprod Toxicol* **11:** 465-481.

Davis,D.L., Bradlow,H.L., Wolff,M., Woodruff,T., Hoel,D.G., and Anton-Culver,H. (1993) Medical Hypothesis: Xenoestrogens as preventable causes of breast cancer. *Environ Health Perspect* **101:** 372-377.

De Guise,S., Lagace,A., and Beland,P. (1994) True hermaphrodism in a St. Lawrence beluga whale (Delphinapterus leucas). *J Wildlife Dis* **30:** 287-290.

De Guise,S., Martineau,D., Beland,P., and Fournier,M. (1995) Possible mechanisms of action of environmental contaminants on St. Lawrence beluga whales (Delphinapterus leucas). *Environ Health Perspect* **103:** 73-77.

De Swart,R.L., Ross,P.S., Timmerman,H.H., Vos,H.W., Reijnders,P.J.H., Vos,J.G., and Osterhaus,A.D.M.E. (1995) Impaired cellular immune response in harbour seals (Phoca vitulina) feeding on environmentally contaminated herring. *Clin Exp Immunol* **101:** 480-486.

DeVito,M.J., Birnbaum,L.S., Farland,W.H., and Gasiewicz,T.A. (1995) Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals. *Environ Health Perspect* **103:** 820-831.

DeVito,M.J. and Birnbaum,L.S. (1994) Chapter 5: Toxicology of Dioxins and Related Compounds. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 139-162.

Dewailly,E., Ayotte,P., Bruneau,S., Gingras,S., Belles-Isles,M., and Roy,R. (2000) Susceptibility to Infections and Immune Status in Inuit Infants Exposed to Organochlorines. *Environ Health Perspect* **108:** 205-211.

Dewailly,E., Dodin,S., Verreault,R., Ayotte,P., Sauve,L., Morin,J., and Brisson,J. (1994a) High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J Natl Cancer Inst* **86:** 232-4.

Dewailly,E., Nantel,A., Bruneau,S., Laliberte,C., Ferron,L., and Gingras,S. (1992) Breast milk contamination by PCDDs, PCDFs and PCBs in Arctic Quebec: a preliminary assessment. *Chemosphere* **25:** 1245-1249.

Dewailly,E., Ayotte,P., Bruneau,S., Laliberte,C., Muir,D.C.G., and Norstrom,R.J. (1993) Inuit exposure to organochlorines through the aquatic food chain in arctic Quebec. *Environ Health Perspect* **101:** 618-620.

Dewailly,E., Nantel,A., Weber,J.-P., and Meyer,F. (1989) High levels of PCBs in breast milk of Inuit women from Arctic Quebec. *Bull Environ Contam Toxicol* **43:** 641-646.

Dewailly,E., Ryan,J.J., Laliberte,C., Bruneau,S., Weber,J.-P., Gingras,S., and Carrier,G. (1994b) Exposure of remote maritime populations to coplanar PCBs. *Environ Health Perspect* **102:** 205-209.

Egeland,G.M., Sweeney,M.H., Fingerhut,M.A., Wille,K.K., Schnorr,T.M., and Halperin,W.E. (1994) Total serum testosterone and gonadotropins in workers exposed to dioxin. *Am J Epidemiol* **139:** 272-281.

Ekbom,A., Wicklund-Glynn,A., and Adami,H.-O. (1996) DDT and Testicular cancer. *Lancet* **347:** 553-554.

Eriksson,P., Jakobsson,E., and Fredriksson,A. (2001) Brominated Flame Retardants: A Novel Class of Developmental Neurotoxicants in Our Environmnent? *Environ Health Perspect* **109:** 903-908.

Eroschenko,V.P. (1981) Estrogenic activity of the insecticide chlordecone in the reproductive tract of birds and mammals. *J Toxicol Environ Health* **8:** 731-742.

Eskenazi,B., Warner,M., Mocarelli,P., Samuels,S., Needham,L.L., Patterson Jr.,D.G. et al. (2002) Serum Dioxin Cocentrations and Menstrual Cycle Concentrations. *Am J Epidemiol* **156:** 383-392.

European Commission . Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxin-like PCBs in food. 5-30-2001. European Commission Health & Consumer Protection Directorate-General Scientific Committee on Food.

Ewald,G., Larsson,P., Linge,H., Okla,L., and Szarzi,N. (1998) Biotransport of organic pollutants to an inland Alaska lake by migrating sockeye salmon *(oncorhynchus nerka)*. *Arctic* **51:** 40-47.

Falck,F.Jr., Ricci,A.Jr., Wolff,M.S., Godbold,J., and Deckers,P. (1992) Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health* **47:** 143-146.

Falk,H. (1982) Chapter 37: Liver. In *Cancer Epidemiology and Prevention*. Schottenfeld,D. and Fraumeni,J.F. (eds). Philadelphia: W. B. Saunders Company, 668-681.

Feeley,M.M. (1995) Workshop on perinatal exposure to dioxin-like compounds. III. Endocrine effects. *Environ Health Perspect* **103:** 147-150.

Fein,G.G., Jacobson,J.L., Jacobson,S.W., Schwartz,P.M., and Dowler,J.K. (1984) Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age. *J Pediatr* **105:** 315.

Fingerhut,M.A., Halperin,W.E., Marlow,D.A., Piacitelli,L.A., Honchar,P.A., Sweener,M.H. et al. (1991) Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* **324:** 212-218.

Fisch,H. and Goluboff,E.T. (1996) Geographic variations in sperm counts: a potential cause of bias in studies of semen quality. *Fertil Steril* **65:** 1044-1046.

Ford,C.A., Muir,D.C.G., Norstrom,R.J., Simon,M., and Mulvihill,M.J. (1993) Development of a semi-automated method for non-ortho PCBs: application to Canadian Arctic marine mammal tissues. *Chemosphere* **26:** 1981-1991.

Fraumeni,J.F. and Kantor,A. (1982) Chapter 38: Biliary Tract. In *Cancer Epidemiology and Prevention*. Schottenfeld,D. and Fraumeni,J.F. (eds). Philadelphia: W. B. Saunders Company, 683-691.

Fraumeni,J.F.Jr., Hoover,R.N., Devesa,S.S., and Kinlen,L.J. (1993) Chapter 9: Epidemiology of Cancer. In *Cancer: Principles & Practice of Oncology*. DeVita,V.T.Jr., Hellman,S., and Rosenberg,S.A. (eds). Philadelphia: J. B. Lippincott Co, 150-181.

Gangong,W.F. (1985) The gonads: development & function of the reproductive system. Review of Medical Physiology Appleton & Lange publishers, pp. 342-347.

Giesy,J.P., Verbrugge,D.A., Othout,R.A., Bowerman,W.W., Mora,M.A., Jones,P.D. et al. (1994) Contaminants in fishes from Great Lakes-influenced sections and above dams of three Michigan rivers. I: Concentrations of organo chlorine insecticides, polychlorinated biphenyls, dioxin equivalents, and mercury. *Arch Environ Contam Toxicol* **27:** 202-212.

Giesy,J.P., Jude,D.J., Tillitt,D.E., Gale,R.W., Meadows,J.C., Zajieck,J.L. et al. (1997) Polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents in fishes from Saginaw Bay, Michigan. *Environ Toxicol Chem* **16:** 713-724.

Giwercman,A., Carlsen,E., Keiding,N., and Skakkebaek,N.E. (1993) Evidence for increasing incidence of abnormalities of the human testis: a review. *Environ Health Perspect Supp* **101:** 65-71.

Gladen,B.C., Rogan,W.J., Hardy,P., Thullen,J., Tingelstad,J., and Tully,M. (1988) Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. *Journal of Pediatrics* **113:** 991-995.

Goldey,E.S., Kehn,L.S., Lau,C., Rehnberg,G.L., and Crofton,K.M. (1995) Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. *Toxicol Appl Pharmacol* **135:** 77-88.

Golub,E.S. and Green,D.R. (1991) *Immunology: A Synthesis*. Sunderland MA: Sinauer Assoc Inc.

Grandjean,P., Weihe,P., Burse,V.W., Needham,L.L., Storr-Hansen,E., Heinzow,B. et al. (2001) Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol Teratol* **23:** 305-317.

Gribble,G.W. (1994) The natural production of chlorinated compounds. *Environ Sci Technol* **28:** 311-319.

Guillette,L.J.Jr. (1995) Endocrine disrupting environmental contaminants and developmental abnormalities in embryos. *Hum Ecol Risk Assess* **1:** 25-36.

Guo,Y.L., Lai,T.J., Ju,S.H., Chen,Y.C., and Hsu,C.C. (1993) Sexual Developments and Biological Findings in Yucheng Children. *Organohalogen Compounds* **14:** 235-238.

Guvenius,D.M., Aronsson,A., Ekman-Ordeberg,G., Bergman A., and Noren,K. (2003) Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols, and pentachlorophenol. *Environ Health Perspect* **111:** 1235-1241.

Hall,A.J., Law,R.J., Wells,D.E., Harwood,J., Ross,H.M., Kennedy,S. et al. (1992) Organochlorine levels in common seals (Phoca vitulina) which were victims and survivors of the 1988 phocine distemper epizootic. *Sci Total Environ* **115:** 145-162.

Hammill,M.O., Lesage,V., and Kingsley,M.C.S. (2003) Cancer in beluga from the St. Lawrence estuary. *Environ Health Perspect* **111:** A77-A78.

Hanson,D.J. (1991) Dioxin toxicity: new studies prompt debate, regulatory action. Chemical & Engineering News 7-14.

Hardell,L., Eriksson,M., Axelson,O., and Zahm,S.H. (1994) Chapter 16: Cancer Epidemiology. In Dioxins and Health. Schecter,A. (ed). New York NY: Plenum Press, 525-548.

Harper,N., Connor,K., Steinberg,M., and Safe,S. (1995) Immunosuppressive activity of polychlorinated biphenyl mixtures and congeners: Nonadditive (antagonistic) interactions. *Fund Appl Toxicol* **27:** 131-139.

Harrison,P.T., Holmes,P., and Humfrey,C.D. (1997) Reproductive health in humans and wildlife: are adverse trends associated with environmental chemical exposure? *Sci Total Environ* **205:** 97-106.

Health Canada,E.H.D.H.P.B. Health-based tolerable daily intakes/concentrations and tumorigenic doses/concentrations for priority substances. 1996.

Hendricks,J.D., Putman,T.P., Bills,D.D., and Sinnhuber,R.O. (1977) Inhibitory effect of a polychlorinated biphenyl (aroclor 1254) on aflatoxin B carcinogenesis in rainbow trout (Salmo gairdneri). *J Natl Cancer Inst* **59:** 1545-1551.

Henriksen,G.L., Michalek,J.E., Swaby,J.A., and Rahe,A.J. (1996) Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand. *Epidemiology* **7:** 352-357.

Herbst,A.L. (1981) Clear cell adenocarcinoma and the current status of DES-exposed females. *Cancer* **48:** 484-488.

Higginson,J. (1985) DDT: Epidemiological evidence. In *IARC Scientific Publication no. 65*. Lyon: International Agency for Research on Cancer, 105-117.

Hoekstra,P.F., Letcher,R.J., O'Hara,T.M., Backus,S.M., Solomon,K.R., and Muir,D.C.G. (2003) Hydroxylated and Methylsulfone-Containing Metabolites of Polychlorinated Biphenyls in the Plasma and Blubber of Bowhead Whales (*Balaena mysticetus*). *Environ Toxicol Chem* **22:** 2650-2658.

Hoekstra,P.F., OHara,T.M., Pallant,S.J., Solomon,K.R., and Muir,D.C. (2002a) Bioaccumulation of organochlorine contaminants in bowhead whales (Balaena mysticetus) from Barrow, Alaska. *Arch Environ Contam Toxicol* **42:** 497-507.

Hoekstra,P.F., OHara,T.M., Teixeira,C., Backus,S., Fisk,A.T., and Muir,D.C.G. (2002b) Spatial trends and bioaccumulation of organochlorine pollutants in marine zooplankton from the Alaskan and Canadian Arctic. *Environmental Toxicology and Chemistry* **21:** 575-583.

Hoekstra,P.F., Wong,C.S., OHara,T.M., Solomon,K.R., Mabury,S.A., and Muir,D.C.G. (2002c) Enantiomer-specific accumulation of PCB atropisomers in the bowhead whale (Balaena mysticetus). *Environ Sci Technol* **36:** 1419-1425.

Hond,E.D., Roels,H.A., Hoppenbrouwers,K., Nawrot,T., Thijs,L., Vandermeulen,C. et al. (2002) Sexual Maturation in Relation to Polychlorinated Aromatic Hydrocarbons: Sharpe and Skakkebaek's Hypothesis Revisited. *Environ Health Perspect* **110:** 771-776.

Hoover,A.A. (1988) Steller Sea Lion - *Eumetopias jubatus*. In *Selected Marine Mammals of Alaska*. Lentfer,J.W. (ed). Washington DC: Marine Mammal Commmission, 159-194.

Hornung,R.W. and Reed,L.D. (1990) Estimation of average concentration in the presence of nondetectable values. *Appl Occup Hyg* **5:** 46-51.

Hrutfiord,B.F. and Negri,A.R. (1992) Dioxin sources and mechanisms during pulp bleaching. *Chemosphere* **25:** 53-56.

Hsu,C.-C., Yu,M.-L., Chen,Y.-C.J., Guo,Y.-L.L., and Rogan,W.J. (1994) Chapter 20: The Yu-Cheng Rice Oil Poisoning Incident. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 661-684.

Hsu,P.-C., Huang,W., Wei-Jen,Y., Meng-Hsing,W., Yueliang,L.G., and Lambert,G.H. (2003) Sperm Changes in Men Exposed to Polychlorinated Biphenyls and Dibenzofurans. *JAMA* **289:** 2943-2944.

Huisman,M., Koopman-Esseboom,C., Fidler,V., Hadders-Algra,M., Van der Paauw,C.G., Tuinstra,L.G.M.Th. et al. (1995) Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Hum Dev* **41:** 111-127.

Humble,C.G. and Speizer,F.E. (1984) Polybrominated biphenyls and fetal mortality in Michigan. *Am J Public Health* **74:** 1130-1132.

Humphrey,H.E.B., Gardiner,J.C., Pandya,J.R., Sweeney,A.M., Gasior,D.M., McCaffrey,R.J., and Schantz,S.L. (2000) PCB congener profile in the serum of humans consuming Great Lakes fish. *Environ Health Perspect* **108:** 167-172.

Hung,H., Halsall,C.J., Blanchard,P., Li,H.H., Fellin,P., Stern,G., and Rosenberg,B. (2001) Are PCBs in the Canadian Arctic atmosphere declining? Evidence from 5 years of monitoring. *Environ Sci Technol* **35:** 1303-1311.

Hunter,D.J., Hankinson,S.E., Laden,F., Colditz,G.A., Manson,J.E., Willett,W.C. et al. (1997) Plasma organochloirne levels and the risk of breast cancer. *N Engl J Med* **337:** 1253-1258.

Hussain,R.J., Gyori,J., Decaprio,A.P., and Carpenter,D.O. (2000) In vivo and in vitro exposure to PCB 153 reduces long-term potentiation. *Environ Health Perspect* **108:** 827-831.

Ikonomou,M.G., Rayne,S., and Addison,R.F. (2002) Exponential increases of the brominated flame retardants, polybrominated diphenyl ethers, in the Canadian Arctic from 1981 to 2000. *Environ Sci Technol* **36:** 1886-1890.

Ilsen,A., Briet,J.M., Koppe,J.G., Pluim,H.J., and Oosting,J. (1996) Signs of enhanced neuromotor maturation in children at 2 years and 7 months due to perinatal load with background levels of dioxins. *Organohalogen Compounds* **30:** 237-241.

Infante-Rivard,C. and Fernandez,A. (1993) Otitis media in children: frequency, risk factors, and research avenues. *Epidemiol Rev* **15:** 444-465.

IRIS . IRIS Integrated Risk Information System. 1996. Denver CO, Micromedex Inc.

Jacobson,J.L. and Jacobson,S.W. (1996) Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N Eng J Med* **335:** 783-789.

Jacobson,J.L., Jacobson,S.W., and Humphrey,H.E.B. (1990) Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicol Teratol* **12:** 319-326.

Jacobson,J.L., Jacobson,S.W., Padgett,R.J., Brumitt,G.A., and Billings,R.L. (1992) Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. *Dev Psychol* **28:** 297-306.

Jacobson,S.W., Fein,G.G., Jacobson,J.L., Schwartz,P.M., and Dowler,J.K. (1985) The effect of intrauterine PCB exposure on visual recognition memory. *Child Dev* **56:** 853-860.

Jensen,A.A. (1991) Levels and Trends of Environmental Chemicals in Human Milk. In *Chemical Contaminants in Human Milk*. Jensen,A.A. and Slorach,S.A. (eds). Boca Raton: CRC Press Inc, 45-198.

Jensen,J., Akare,K., and Shearer,R. Canadian Arctic Contaminants. QS-8525-000-EE-A1, Catalogue No R72-260/1997E, ISBN 0-662-25704-9. 1997. Ottawa, Indian and Northern Affairs Canada. 1997.

Johansen,H.R., Becher,G., Polder,A., and Skaare,J.U. (1994) Congener-specific determination of polychlorinated biphenyls and organochlorine pesticides in human milk from Norwegian mothers living in Oslo. *J Toxicol Environ Health* **42:** 157-171.

Johansson,N. and Hanberg,A. (2000) Report form a Nordic meeting on the 1998 WHO consultation on assessment of the health risks of dioxins; re-evaluation of the tolerable daily intake (TDI). *Organohalogen Compounds* **48:** 252-255.

Jongbloet,P.H., Roeleveld,N., and Groenewoud,H.M.M. (2002) Where the boys aren't: dioxin and the sex ratio. *Environ Health Perspect* **110:** 1-3.

Julien,G., Baxter,J.D., Crago,M., Ilecki,H.J., and Therien,F. (1987) Chronic otitis media and hearing deficit among Native children of Kuujjuaraapik (Northern Quebec): a pilot project. *C J Public Health* **78:** 57-60.

Julshamn,K., Andersen,A., Ringdal,O., and Morkore,J. (1987) Trace elements intake in the Faroe Islands. I. Element levels in edible parts of pilot whales *(Globicephalus meleanus)*. *Sci Total Environ* **65:** 53-62.

Kamrin,M.A. and Fischer,L. (1999) Current status of sport fish consumption advisories for PCBs in the Great Lakes. *Regul Toxicol Pharm* 29: 175-181.

Kannan,K., Yamashita,N., and Imagawa,T. (2000) Polychlorinated naphthalenes and polychlorinated biphenyls in fishes from Michigan waters including the Great Lakes. *Environ Sci Technol* **34:** 566-572.

Kannan,N., Tanabe,S., Ono,M., and Tatsukawa,R. (1989) Critical evaluation of polychlorinated biphenyl toxicity in terrestrial and marine mammals: increasing impact of non-ortho and mono-ortho coplanar polychlorinated biphenyls from land to ocean. *Archives Environ Contam Toxicol* **18:** 850-857.

Kelley,D.S. and Daudu,P.A. (1993) Fat intake and immune response. *Prog Food Nutr Sci.* **17:** 41-63.

Kerkvliet,N.I. (1994) Chapter 7: Immunotoxicology of Dioxins and Related Chemicals. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 199-226.

Kimbrough,R.D. (1980) *Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products*. Amsterdam: Elsevier North-Holland Biomedical Press.

Kimbrough,R.D. (1997) Studies in children: polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans. *Hlth and Environ Digest* **10:** 61-63.

Kingsley,M.C.S. (1998) Population index estimates for the St. Lawrence belugas, 1973-1995. *Mar Mammal Sci* **14:** 508-530.

Kinloch,D. and Kuhnlein,H. (1988) Assessment of PCBs in Arctic foods and diets. *Arct Med Res* **47:** 159-162.

Kinloch,D., Kuhnlein,H., and Muir,D.C.G. (1992) Inuit foods and diet: a preliminary assessment of benefits and risks. *Sci Total Environ* **122:** 247-278.

Kjeller,L.-O., Jones,K.C., Johnston,A.E., and Rappe,C. (1991) Increases in the polychlorinated dibenzo-p-dioxin and -furan content of soils and vegetation since the 1840s. *Environ Sci Technol* **25:** 1619-1627.

Klinge,C.M., Bambara,R.A., and Hilf,R. (1992) What differentiates antiestrogen-liganded vs estradiol-liganded estrogen receptor action? *Oncol Res* **4:** 137-144.

Knutsen,A.P. (1984) Immunologic effects of TCDD exposure in humans. *Bull Environm Contam Toxicol* **33:** 673-681.

Kociba,R.J., Keyes,D.G., Beyer,J.E., Carreon,R.M., Wade,C.E., Dittenber,D.A. et al. (1978) Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. *Toxicol Appl Pharmacol* **46:** 279-303.

Kodavanti,P.R.S. and Tilson,H.A. (1997) Structure-activity relationships of potentially neurotoxic PCB congeners in the rat. *NeuroToxicology* **18:** 425-442.

Kodavanti,P.R.S., Ward,T.R., McKinney,J.D., and Tilson,H.A. (1996) Inhibition of microsmal and mitochondrial Ca+2 - sequestration in rat cerebellum by polychlorinated biphenyl mixtures and congeners. Structure-activity relationships. *Arch Toxicol* **70:** 150-157.

Koopman-Esseboom,C., Huisman,M., Weisglas-Kuperus,N., Van der Paauw,C.G., Tuinstra,L.G.M.Th., Boersma,E.R., and Sauer,P.J.J. (1994a) PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. *Chemosphere* **28:** 1721-1732.

Koopman-Esseboom,C., Morse,D.C., Weisglas-Kuperus,N., Lutkeschipholt,I.J., Van der Paauw,C.G., Tuinstra,L.G.M. et al. (1994b) Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediat Res* **36:** 468-473.

Krahn,M.M., Burrows,D.G., Stein,J.E., Becker,P.R., Schantz,M.M., Muir,D.C., and OHara,T.M. (1999) White whales *(Delphinapterus leucas)* from three Alaskan stocks: concentrations and patterns of persistent organochlorine contaminants in blubber. *J Cetacean Res Manage* **1:** 239-249.

Krahn,M.M., Ylitalo,G.M., Burrows,D.G., Calambokidis,J., Moore,S.E., Gosho,M. et al. (2001) Organochlorine contaminant concentrations and lipid profiles in eastern North Pacific gray whales (*Eschrichtius robustus*). *J Cetacean Res Manage* **3:** 19-29.

Krahn,M.M., Becker,P.R., Tilbury,K.L., and Stein,J.E. (1997) Organochlorine contaminants in blubber of four seal species: integrating biomonitoring and specimen banking. *Chemosphere* **34:** 2109-2121.

Krieger,N. (1989) Exposure, susceptibility, and breast cancer risk:

A hypothesis regarding exogenous carcinogens, breast tissue development, and social gradients, including black/white differences, in breast cancer incidence. *Breast Cancer Res Tr* **13:** 205-223.

Krishnan,V. and Safe,S. (1993) Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: quantitative structure-activity relationships. *Toxicol Appl Pharmacol* **120:** 55-61.

Kucklick,J.R., Struntz,W.D., Becker,P.R., York,G.W., OHara,T.M., and Bohonowych,J.E. (2002) Persistent organochlorine pollutants in ringed seals and polar bears collected from northern Alaska. *Sci Total Environ* **287:** 45-59.

Kuhnlein,H.V., Receveur,O., Muir,D.C.G., Chan,H.M., and Soueida,R. (1995) Arctic indigenous women consume greater than acceptable levels of organochlorines. *J Nutr* **125:** 2501-2510.

Kuhnlein,H.V. (1995) Benefits and risks of traditional food for indigenous peoples: focus on dietary intakes of Arctic men. *Can J Physiol Pharmacol.* **73:** 765-771.

Kupfer,D. and Bulger,W.H. (1980) Estrogenic properties of DDT and its analogs. In *Estrogens in the Environment*. McLachlan,J.A. (ed). New York: Elsevier/North-Holland, 239-262.

Laden,F. and Hunter,D.J. (1998) Environmental risk factors and female breast cancer. *Annu Rev Publ Health* **19:** 101-123.

Lagueux,J., Pereg,D., Ayotte,P., Dewailly,E., and Poirier,G.G. (1999) Cytochrome P450 CYP1A1 enzyme activity and DNA adducts in placenta of women environmentally exposed to organochlorines. *Environ Res* **80:** 369-382.

Landers,J.P. and Bunce,N.J. (1991) The Ah receptor and the mechanism of dioxin toxicity. *Biochem J* **276:** 273-287.

Lanier,A.P., Bulkow,L.R., and Ireland,B. (1989) Cancer in Alaskan Indians, Eskimos, and Aleuts, 1969-83: implications for etiology and control. *Public Health Reports* 658-664.

Lee,J.S., Tanabe,S., Umino,H., Tatsukawa,R., Loughlin,T.R., and Calkins,D.C. (1996) Persistent organochlorines in Steller sea lion *(Eumetopias jubatus)* from the bulk of Alaska and the Bering Sea, 1976-1981. *Mar Pollut Bull* **32:** 535-542.

Lemieux,P.M., Gullett,B.K., Lutes,C.C., Winterrowd,C.K., and Winters,D.L. (2003) Variables affecting emissions of PCDD/Fs from uncontrolled combustion of household waste in barrels. *J Air Waste Manag Assoc* **53:** 523-531.

Levin,E.D., Schantz,S.L., and Bowman,R.E. (1988) Delayed spatial alternation deficits resulting from perinatal PCB exposure in monkeys. *Arch Toxicol* **62:** 267-273.

Lim,D.J., Demaria,T.F., and Bakaletz,L.O. (1998) Current concepts of pathogenesis of otitis media: a review. *Acta Otolaryngol* Suppl. 48**:** 174-180.

Lipshultz,L.I. (1996) The debate continues - the continuing debate over the possible decline in semen quality. *Fertil Steril* **65:** 909-911.

Lonky,E., Reihman,J., Darvill,T., Mather,J.Sr., and Daly,H. (1995) Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. *J Great Lakes Res* **22:** 198-212.

Loomis,D., Browning,S.R., Schenck,A.P., Gregory,E., and Savitz,D.A. (1997) Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med* 720-728.

Loomis,W.F. (1986) Chapter 12: Sex Differentiation. In *Developmental Biology*. New York: Collier Macmillan Publishers, 275-282.

Lowry,L.F. and Fay,F.H. (1984) Seal eating by walruses in the Bering and Chukchi Seas. *Polar Biol* **3:** 11-18.

Lu,Y.-C. and Wu,Y.-C. (1985) Clinical findings and immunological abnormalities in Yu-Cheng patients. *Environ Health Perspect* **59:** 17-29.

Luckas,B., Vetter,W., Fischer,P., Heidemann,G., and Plotz,J. (1990) Characteristic chlorinated hydrocarbon patterns in the blubber of seals from different marine regions. *Chemosphere* **21:** 13-19.

Luebke,R.W., Copeland,C.B., Daniels,M., Lambert,A.L., and Gilmour,M.I. (2001) Suppression of Allergic Immune Responses to House Dust Mite (HDM) in Rats Exposed to 2,3,7,8-TCDD. *Toxicol Sci* 71-79.

Mably,T.A., Bjerke,D.L., Moore,R.W., Gendron-Fitspatrick,A., and Peterson,R.E. (1992a) In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin 3. Effects on spermatogenesis and reproductive capability. *Toxicol Appl Pharmacol* **114:** 118-126.

Mably,T.A., Moore,R.W., Goy,R.W., and Peterson,R.E. (1992b) In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood. *Toxicol Appl Pharmacol* **114:** 108-117.

Mably,T.A., Moore,R.W., and Peterson,R.E. (1992c) In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin 1. Effects on androgenic status. *Toxicol Appl Pharmacol* **114:** 97-107.

Makura,S., Aoe,H., Sugihara,S., Hirao,K., Arai,M., and Ito,N. (1974) Inhibitory effect of polychlorinated biphenyls on liver tumorigeneses in rats treated with 3'-methyl-4-dimethylaminoazobenzene, N-2-fluorenylacetamide, and diethylnitrosamine. *J Natl Cancer Inst* **53:** 1253-1257.

Martineau,D., Beland,P., Desjardins,C., and Lagace,A. (1987) Levels of organochlorine chemicals in tissues of beluga whale *(Delphinapterus leucas)* from the St. Lawrence estuary, Quebec, Canada. *Arch Environ Con Tox* **16:** 137-148.

Masuda,Y. (1994) Chapter 19: The Yusho Rice Oil Poisoning Incident. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 633-660.

Mazdai,A., Dodder,N.G., Abernathy,M.P., Hites,R.A., and Bigsby,R.M. (2003) Polybrominated diphenyl ethers in maternal and fetal blood samples. *Environ Health Perspect* **111:** 1249-1252.

McFall,J.A., Antoine,S.R., and Overton,E.B. Organochlorine compounds and Polynuclear Aromatic Hydrocarbons In tissues of Subsistence Harvested Bowhead Whales, *Balaena mysticetus*. 1986. Center for Bio-Organic Studies, University of New Orleans. 1986.

McFarland,V.A. and Clarke,J.U. (1989) Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. *Environ Health Perspect* **81:** 225-239.

Meerts,I.A., van Zanden J.J., Luijks E.A., van Leeuwen-Bol I., Marsh G., Jakobsson E. et al. (2000) Potent competitive interactions of some brominated flame retardants and related comounds with human transthyretic in vitro. *Toxicol Sci* **56:** 95-104.

Meironyte,D., Noren,K., and Bergman,A. (1999) Analysis of Polybrominated diphenyl ethers in Swedish human milk. A time-related trend study, 1972-1997. *J Toxicol Environ Health A* **58:** 329-341.

Mendola,P., Buck,G.M., Vena,J.E., Zielezny,M., and Sever,L.E. (1995) Consumption of PCB-contaminated sport fish and risk of spontaneous fetal death. *Environ Health Perspect* **103:** 498-502.

Middaugh,J.P. and Egeland,G.M. (1997) Intellectual function of children exposed to polychlorinated biphenyls in utero. *N Engl J Med* **336:** 660-661.

Miles,A.K., Calkins,D.G., and Coon,N.C. (1992) Toxic Elements and Organochlorines in Harbor Seals (*Phoca vitulina richardsi*), Kodiak, Alaska, USA. *Bull Environ Contam Toxicol* **48:** 727-732.

Ministerial Council on Dioxin Policy . Dioxins - Informational Brochure. 1999. Japan.

Mocarelli,P., Gerthoux,P.M., Ferrari,E., Patterson Jr.,D.G., Kieszak,S.M., Brambilla,P. et al. (2000) Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* **355:** 1858-1863.

Mocarelli,P., Brambilla,P., Gerthoux,P.M., Patterson,D.G.Jr., and Needham,L.L. (1996) Change in sex ratio with exposure to dioxin. *Lancet* **348:** 409.

Morris,D.L., Jordan,S.D., and Holsapple,M.P. (1991) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on humoral immunity: I. Similarities to Staphylococcus aureus Cowan Strain I (SAC) in the in vitro T-dependent antibody response. *Immunopharmacology* **21:** 159-170.

Moysich,K.B., Shields,P.G., Freudenheim,J.L., Schisterman,E.F., Vena,J.E., Kostyniak,P. et al. (1999) Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* **8:** 41-44.

Muckle,G., Ayotte,P., Dewailly,E., Jacobson,S.W., and Jacobson.J.L. (2001) Determinants of polychlorinated biphenyls and methylmercury exposure in inuit women of childbearing age. *Environ Health Perspect* **109:** 957-963.

Muir,D. (1993) Spatial and Temporal Trends of Organochlorines in Arctic Marine Mammals. In *Synopsis of Research Conducted Under the 1992/93 Northern Contaminants Program*. Murray,J.L. and Shearer,R.G. (eds). Ottawa: Browes, Pauline, Minister of Indian Affairs and Northern Development, 88-94.

Muir,D. (1994) Spatial and temporal trends of organochlorines in arctic marine mammals. *Environmental Studies, Northern Contaminants Program* **72:** 189-196.

Muir,D. (1996) Spatial and temporal trends of organochlorines in arctic marine mammals. *Environmental Studies, Northern Contaminants Program* **73:** 143-146.

Muir,D., Grift,B., Ford,C., and Segstro,M. (1992a) Circumpolar survey of PCBs in beluga. *Environmental Studies, Northern Contaminants Program* **68:** 104-109.

Muir,D., Grift,B., Ford,C., and Segstro,M. (1992b) Spatial trends in organochlorines in arctic ringed seal and walrus. *Environmental Studies, Northern Contaminants Program* **68:** 73-76.

Muir,D. and Lockhart,W.L. (1993) Contaminant Trends in Freshwater Biota. In *Synopsis of Research Conducted Under the 1992/93 Northern Contaminants Program*. Murray,J.L. and Shearer,R.G. (eds). Ottawa: Browes, Pauline; Minister of Indian Affairs and Northern Development, 167-173.

Muir,D. and Lockhart,W.L. (1994) Contaminant trends in freshwater and marine fish. *Environmental Studies, Northern Contaminants Program* **72:** 264-271.

Muir,D. and Lockhart,W.L. (1996) Contaminant trends in freshwater and marine fish. *Environmental Studies, Northern Contaminants Program* **73:** 189-194.

Muir,D.C., Born,E.W., Koczansky,K., and Stern,G.A. (2000) Temporal and spatial trends of persistent organochlorines in Greenland walrus (Odobenus rosmarus rosmarus). *Sci Total Environment* **245:** 73-86.

Muir,D.C., Wagemann,R., Hargrave,B.T., Thomas,D.J., Peakall,D.B., and Norstrom,R.J. (1992c) Arctic marine ecosystem contamination. Sci Total Environ **122:** 75-134.

Muir,D.C.G., Ford,C.A., and Steward,R.E.A. (1990) Organochlorine contaminants in belugas, *Delphinapterus leucas* , from Canadian waters. *Can B Fish Aquat Sci* **224:** 165-190.

Muir,D.C.G., Segstro,M.D., Hobson,K.A., Ford,C.A., Stewart,R.E.A., and Olpinski,S. (1995) Can seal eating explain elevated levels of PCBs and organochlorine pesticides in walrus blubber from eastern Hudson Bay (Canada)? *Environ Pollut* **90:** 335-348.

Muir,D.C.G. and Norstrom,R.J. (2000) Geographical differences and time trends of persistent organic pollutants in the Arctic. *Toxicol Lett* **112/113:** 93-101.

Muir,D.C.G., Norstrom,R.J., and Simon,M. (1988) Organochlorine contaminants in Arctic marine food chains: accumulation of specific polychlorinated biphenyls and chlordane-related compounds. *Environ Sci Technol* **22:** 1071-1079.

Murk,A.J., Leonards,P.E.G., van Hattum,B., Luit,R., van der Weiden,M.E.J., and Smit,M. (1998) Application of biomarkers for exposure and effect of polyhalogenated aromatic hydrocarbons in naturally exposed European otters (Lutra lutra). *Environ Toxicol Phar* **6:** 91-102.

Murray,J.L. Synopsis of Research Conducted Under the 1991-92 Northern Contaminants Program. Murray, J. L. and Shearer, R. G. 68, 213. 1992. Ottawa, Ontario, Tom Siddon, PC MP Minister of Indian Affairs and Northern Development. Environmental Studies.

Murray,J.L. and Shearer,R.G. Synopsis of Research Conducted Under the 1992/93 Northern Contaminants Program. QS-8490-000-EF-A1 Catalogue No. R71-19/70-1993E ISBN 0-662-21037-9. 1993. Northern Affairs Program. 1993.

Murray,J.L. and Shearer,R.G. Synopsis of Research Conducted Under the 1993/94 Northern Contaminants Program. QS-8500-000-EF-A1 Catologue No. R71-19/72-1994E ISBN 0-662-22692-5. 1994. Hon. Ronald A. Irwin, P.C., M.P., Minister of Indian Affairs and Northern Development. 1994.

Murray,J.L., Shearer,R.G., and Han,S.L. Synopsis of Research Conducted Under the 1994/95 Northern Contaminants Program. QS-8519-000-EF-A1 Catalogue No. R71-19/73-1995E ISBN 0-662+24414-1. 1996. Hon. Ronald A. Irwin, P.C., M.P. Minister of Indian Affairs and Northern Development. 1996.

Nagayama,J., Ilda,T., Hirakawa,H., Matsueda,T., Tsuji,H., Okamura,K. et al. (1996) Effects of lactational exposure to chlorinated dioxins and related chemicals on lymphocyte subpopulations and thyroid function in Japanese babies. In *Organohalogen Compounds*. Van den Berg,M., Brouwer,A., Birnbaum,L., Bueno-de-Mesquita,B., Koppe,J., Lambert,G. et al. (eds). 228-233.

Needham,L.L. and Wang,R.Y. (2002) Analytic Considerarions for Measuring Enviromental Chemicals in Breast Milk. *Environ Health Perspect* **110:** A317-A324.

Nestrick,T.J. and Lamparski,L.L. (1982) Isomer-specific determination of chlorinated dioxins for assessment of formation and potential environmental emission from wood combustion. *Anal Chem* **54:** 2292-2299.

Neubert,R., Golor,G., Stahlmann,R., Helge,H., and Neubert,D. (1992) Polyhalogenated dibenzo-p-dioxins and dibenzofurans and the immune system. 4. effects of multiple-dose treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on peripheral lymphocyte subpopulations of a non-human primate *(Callithrix jacchus)*. *Arch Toxicol* **66:** 250-259.

Niimi,A.J., Lee,H.B., and Muir,D.C.G. (1996) Environmental assessment and ecotoxicological implications of the co-elution of PCB congeners 132 and 153. *Chemosphere* **32:** 627-638.

Nobmann,E.D. Dietary Intakes of Alaska Native Adults 1987-1988. 1989. Anchorage AK, Alaska Area Native Health Service. 1989.

Nobmann,E.D., Byers,T., Lanier,A.P., Hankin,J.H., and Jackson,M.Y. (1992) The diet of Alaska Native adults: 1987-1988. *Am J Clin Nutr* **55:** 1024-1032.

Noren,K. and Meironyte,D. (2000) Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20-30 years. *Chemosphere* **40:** 1111-1123.

Norstrom,R.J., Muir,D.C.G., Ford,C.A., Simon,M., Macdonald,C.R., and Beland,P. (1992) Indications of P450 Monooxygenase Activities in Beluga (*Delphinapterus leucas*) and Narwhal (*Monodon monoceros*) from Patterns of PCB, PCDD and PCDF Accumulation. *Mar Environ Res* **34:** 267-272.

Norstrom,R.J. and Simon,M. (1990) Polychlorinated dibenzo-p-dioxins and dibenzofurans in marine mammals in the Canadian north. *Environ Pollut* **66:** 1-19.

Norstrom,R.J., Simon,M., Moisey,J., Wakeford,B., and Weseloh,D.V.C. (2002) Geographical Distribution (200) and Temporal Trends (1981-2000) of Brominated Diphenyl Ethers in Great Lakes Herring Gull Eggss. *Environ Sci Technol* **36:** 4783-4789.

Norstrom,R.J. and Muir,D.C.G. (1994) Chlorinated Hydrocarbon Contaminants in Arctic Marine Mammals. *Sci Total Environ* **154:** 107-128.

Nutting,P.A., Freeman,W.L., Risser,D.R., Helgerson,S.D., Paisano,R., Hisnanick,J. et al. (1993) Cancer incidence among American Indians and Alaska Natives, 1980 through 1987. *Am J Public Health* **83:** 1589-1598.

O'Corry-Crowe,G.M., Suydam,R.S., Rosenberg,A., Frost,K.J., and Dizon,A.E. (1997) Phylogeography, population structure and dispersal patterns of the beluga whale *Delphinapterus leucas* in the western Nearctic revealed by mitochondrial DNA. *Mol Ecol* **6:** 955-970.

O'Hara,T.M., George,J.C., Tarpley,R.J., Burek,K., and Suydam,R.S. (2002) Sexual maturation in male bowhead whales (*Balaena mysticetus*) of the Bering-Chukchi-Beaufort Seas stock. *J. Cetacean Res. Manage.* **4:** 143-148.

O'Hara,T.M., Krahn,M.M., Boyd,D., Becker,P.R., and Philo,L.M. (1999) Organochlorine contaminant levels in Eskimo harvested bowhead whales of arctic Alaska. *J Wildlife Dis* **35:** 741-752.

Oddy,W.H. (2001) Breastfeeding protects against illness and infection in infants and children: a review of the evidence. *Breastfeed Rev* **9:** 11-18.

Oehme,M., Mano,S., and Bjerke,B. (1989) Formation of polychlorinated dibenzofurans and dibenzo-p-dioxins by production processes for magnesium and refined nickel. *Chemosphere* **18:** 1379-1389.

Patandin,S., Lanting,C.I., Mulder,P.G.H., Boersma,E.R., Sauer,P.J.J., and Weisglas-Kuperus,N. (1999) Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J Pediatr* **134:** 33-41.

Paulsen,C.A., Berman,N.G., and Wang,C. (1996) Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform. *Fertil Steril* **65:** 1015-1020.

Pereg,D., Dewailly,E., Poirier,G.G., and Ayotte,P. (2002) Environmental exposure to polychlorinated biphenyls and placental CYP1A1 activity in Inuit women from northern Quebec. *Environ Health Perspect* **110:** 607-612.

Petreas,M., She,J., Brown,F.R., Winkler,J., Windham,G., Rogers,E. et al. (2003) High Body Burdens of 2,2,4,4 -Tetrabromodiphenyl Ether (BDE-47) in California Women. *Environ Health Perspect* **111:** 1175-1179.

Phillips,D.L., Pirkle,J.L., Burse,V.W., Bernert,J.T.Jr., Henderson,L.O., and Needham,L.L. (1989) Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. *Arch Environ Con Tox* **18:** 495-500.

Pitot,H.C., Goldsworthy,T., Campbell,H.A., and Poland,A. (1980) Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. *Cancer Res* **40:** 3616-3620.

Pluim,H.J., De Vijlder,J.J.M., Olie,K., Kok,J.H., Vulsma,T., Van Tijn,D.A. et al. (1993) Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. *Environ Health Perspect* **101:** 504-508.

Pocchiari,F., Silano,V., and Zampieri,A. (1979) Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. *Annals of the New York Academy of Sciences* **320:** 311-320.

Poland,A. and Knutson,J.C. (1982) 2,3,7,8-Tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity. *Annual Reviews in Pharmacology and Toxicology* **22:** 517-554.

Porterfield,S.P. and Hendry,L.B. (1998) Impact of PCBs on thyroid hormone directed brain development. *Toxicol Ind Health* **14:** 103-120.

Proulx,J.F. (1988) Meningitis in Hudson's Bay, Northern Quebec, Canada. *Arct Med Res* **47:** 686-687.

Rice,D.C. (1997) Effect of postnatal exposure to a PCB mixture in monkeys on multiple fixed interval-fixed ratio performance. *Neurotoxicol Teratol* **19:** 429-434.

Rice,D.C. (1999) Effect of exposure to 3,3',4,4',5-pentacholorobiphenyl (PCB 126) throughout gestation and lactation on development and spatial delayed alternation performance in rats. *Neurotoxicol Teratol* **21:** 59-69.

Rice,D.C. and Hayward,S. (1997) Effects of postnatal exposure to a PCB mixture in monkeys on nonspatial discrimination reversal and delayed alternation performance. *NeuroToxicology* **18:** 479-494.

Rier,S.E., Martin,D.C., Bowman,R.E., Dmowski,W.P., and Becker,J.L. (1993) Endometriosis in rhesus monkeys (Macaca mulatta) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fund Appl Toxicol* **21:** 433-441.

Rogan,W.J., Gladen,B.C., Hung,K.-L., Koong,S.-L., Shih,L.-Y., Taylor,J.S. et al. (1988) Congenital Poisoning by Polychlorinated Biphenyls and Their Contaminants in Taiwan. *Science* **241:** 334-336.

Rogan,W.J. and Gladen,B.C. (1991) PCBs, DDE, and child development at 18 and 24 months. *Ann Epidemiol* **1:** 407-413.

Rogan,W.J., Gladen,B.C., McKinney,J.D., Carreras,N., Hardy,P., Thullen,J. et al. (1986) Neonatal effects of transplacental exposure to PCBs and DDE. *J Pediatr* **109:** 335-341.

Ross,P.S., De Swart,R.L., Timmermann,H.H., Reijnders,P.J.H., Vos,J.G., Van Loveren,H., and Osterhaus,A.D.M.E. (1996) Suppression of natural killer cell activity in harbour seals (Phoca vitulina) fed Baltic Sea herring. *Aquat Toxicol* **34:** 71-84.

Rubin,C., Lanier,A.P., and Harpster,A. Environmental Chemicals and Health, Report of Pilot Study of Breast Cancer and Organochlorines in Alaska Native Women. 1997. Anchorage AK, CDC. 1997.

Rubin,C.H., Lanier,A., Socha,M., Brock,J.W., Kieszak,S., and Zahm,S. (2001) Exposure to persistent organochlorines among Alaska Native women. Int J *J Circumpolar Health* **60:** 157-169.

Ryan,J.J., Amirova,Z., and Carrier,G. (2003) Sex Ratios of Children of Russian Pesticide Producers Exposed to Dioxin. *Environ Health Perspect* **110:** A 699-A 701.

Safe,S., Astroff,B., Harris,M., Zacharewski,T., Dickerson,R., Romkes,M., and Biegel,L. (1991) 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds as antiestrogens: characterization and mechanism of action. *Pharmacol Toxicol* **69:** 400-409.

Safe,S.H. (1995) Environmental and dietary estrogens and human health: is there a problem? *Environ Health Perspect* **103:** 346-51.

Safe,S.H. (2000) Endocrine disruptors and human health--is there a problem? An update. *Environ Health Perspect* **108:** 487-493.

Safe,S. (1989) Polychlorinated biphenyls (PCBs): mutagenicity and carcinogenicity. *Mut Res* **220:** 31-47.

Safe,S. (1990) Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit Rev Toxicol* **21:** 51-88.

Safe,S.H. (1994a) Dietary and environmental estrogens and antiestrogens and their possible role in human disease. *Environ Sci Pollut R* **1:** 29-33.

Safe,S.H. (1994b) Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *Crit Rev Toxicol* **24:** 87-149.

Sandau,C.D., Ayotte,P., Dewailly,E., Duffe,J., and Norstrom,R. (2002) Pentachlorophenol and Hydroxylated Polychorinated Biphenyl Metabolites in Umbilical Cord Plasma of Neonates from Coastal Populations in Québec. *Environ Health Perspect* **110:** 411-418.

Sarokin,D. and Schulkin,J. (1992) The role of pollution in large-scale population disturbances Part 1: Aquatic populations. *Environ Sci Technol* **25:** 1476-1484.

Schade,G. and Heinzow,B. (1998) Organochlorine pesticides and polychlorinated byphenyls in human milk of mothers living in northern Germany: current extent of contamination, time trend from 1986 to 1997 and factors that influence the levels of contamination. *Sci Total Environ* **215:** 31-39.

Schantz,M.M., Koster,B.J., Wise,S.A., and Becker,P.R. (1993) Determination of PCBs and Chlorinated Hydrocarbons in Marine Mammal Tissues. *Sci Total Environ***139/140:** 323-345.

Schantz,M.M., Koster,B.J., Oakley,L.M., Schiller,S.B., and Wise,S.A. (1995a) Certification of polychlorinated biphenyl congeners and chlorinated pesticides in a whale blubber standard reference material. *Anal Chem* **67:** 901-910.

Schantz,S.L., Gasior,D.M., Polverejan,E., McCaffrey,R.J., Sweeney,A.M., Humphrey,H.E.B., and Gardiner,J.C. (2001) Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of Great Lakes fish. *Environ Health Perspect* **109:** 605-611.

Schantz,S.L., Moshtaghian,J., and Ness,D.K. (1995b) Spatial learning deficits in adult rats exposed to ortho-substitued PCB congeners during gestation and lactation. *Fund Appl Toxicol* **26:** 117-126.

Schantz,S.L., Seo,B.W., Moshtaghian,J., Peterson,R.E., and Moore,R.W. (1996) Effects of gestational and lactational exposure to TCDD or coplanar PCBs on spatial learning. *Neurotoxicol Teratol* **18:** 305-313.

Schantz,S.L. and Widholm,J.J. (2001) Cognitive Effects of Endocrine-Disrupting Chemicals in Animals. *Environ Health Perspect* **109:** 1197-1206.

Schantz,S.L. and Bowman,R.E. (1989) Learning in monkeys exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Neurotoxicol Teratol* **11:** 13-19.

Schantz,S.L., Levin,E.D., Bowman,R.E., Heironimus,M.P., and Laughlin,N.K. (1989) Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. *Neurotoxicol Teratol* **11:** 243-250.

Schecter,A., Cramer,P., Boggess,K., Stanley,J., and Olson,J.R. (1997) Levels of dioxins, dibenzofurans, PCB and DDE congeners in pooled food samples collected in 1995 at supermarkets across the United States. *Chemosphere* **34:** 1437-1447.

Schecter,A. and Li,L. (1997) Dioxins, dibenzofurans, dioxin-like PCBs, and DDE in U.S. fast food, 1995. *Chemosphere* **34:** 1449-1457.

Schnorr,T.M., Lawson,C.C., Whelan,E.A., Dankovic,D.A., Deddens,J.A., Piacitelli,L.A. et al. (2001) Spontaneous Abortion, Sex Ratio, and Paternal Occupational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. *Environ Health Perspect* **109:** 1127-1131.

Seagars,D.J. and Garlich-Miller,J. (2001) Organochlorine compounds and aliphatic hydrocarbons in Pacific walrus blubber. *Mar Pollut Bull* **43:** 122-131.

Seegal,R.F. and Schantz,S.L. (1994a) Neurochemical and behavioral sequelae of exposure to dioxins and PCBs. In *Dioxins and Health*. Schecter,A. (ed). New York: Plenum Press, 409-447.

Seegal,R.F., Bush,B., and Brosch,K.O. (1991) Comparison of effects of Aroclors 1016 and 1260 on non-human primate catecholamine function. *Toxicology* **66:** 145-163.

Seegal,R.F., Bush,B., and Brosch,K.O. (1994) Decreases in dopamine concentrations in adult, non-human primate brain persist following removal from polychlorinated biphenyls. *Toxicology* **86:** 71-87.

Seegal,R.F. and Schantz,S.L. (1994b) Chapter 13: Neurochemical and Behavioral Sequelae of Exposure to Dioxins and PCBs. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 409-448.

Seo,B.W., Sparks,A.J., Medora,K., Amin,S., and Schantz,S.L. (1999) Learning and memory in rats gestationally and lactationally exposed to 2,3,7,8,-tetrachlorodibenzo-p-dioxin (TCDD). *Neurotoxicol Teratol* **21:** 231-239.

Sheffield,A. (1985) Sources and releases of PCDD's and PCDF's to the Canadian environment. *Chemosphere* **6/7:** 811-814.

Shelton,D.W., Goeger,D.E., Hendricks,J.D., and Bailey,G.S. (1986) Mechanisms of anti-carcinogenesis: the distribution and metabolism of aflatoxin B1 in rainbow trout fed Araclor 1254. *Carcinogenesis* **7:** 1065-1071.

Shu,H.P., Paustenbach,D.J., and Murray,F.J. (1987) A critical evaluation of the use of mutagenesis, carcinogenesis, and tumor promotion data in a cancer risk assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Regul Toxicol Pharmacol* **7:** 57-58.

Silbergeld,E.K. and DeFur,P.L. (1994) Chapter 2: Risk Assessments of Dioxinlike Compounds. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 51-78.

Silkworth,J.B. and Grabstein,E.M. (1982) Polychlorinated biphenyl immunotoxicity: dependence on isomer planarity and the Ah gene complex. *Toxicol Appl Pharmacol* **65:** 109-115.

Simmonds,M.P., Johnson,P.A., French,M.C., Reeve,R., and Hutchinson,J.D. (1994) Organochlorines and mercury in pilot whale blubber consumed by Faroe islanders. *Sci Tot Environ* **149:** 97-111.

Stathis,S.L., O'Callaghan,M., Williams,G.M., Najman,J.M., Anderson,M.J., and Bor,W. (1999) Maternal Cigarette Smoking During Pregnancy Is an Independent Predictor for Symptoms of Middle Ear Disease at Five Years' Postdelivery. *Pediatrics* **104:** 1-6.

Stehr,P.A., Stein,G., Webb,K., and Schramm,W. (1986) A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contaminations in Missouri. *Arch Environ Health* **41:** 16-22.

Steuerwald,U., Weihe,P., Jorgensen,P.J., Bjerve,K., Brock,J., Heinzaw,B. et al. (2000) Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *J Pediatr* **136:** 599-605.

Struntz,W.D.J. and Kucklick,J.R. Polychlorinated Biphenyl Congeners and Organochlorine Pesticides in Pacific Walrus Samples Analyzed by the NIST Charleston Laboratory in 1999. 839.02-00-009. 4-19-2000. Gaithersburg, Maryland, US Department of Comerce, National Institute of Standards and Technology, Chemical Science and Technology Laboratory, Analytical Chemistry Division.

Suskind,R.R. (1985) Chloracne, "the hallmark of dioxin intoxication". *Scand J Work Env Hea* **11:** 165-171.

Svensson,B.G., Hallberg,T., Nilsson,A., Schutz,A., and Hagmar,L. (1994) Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. *Int Arch Occ Env Hea* **65:** 351-358.

Swart,R.d.L., Ross,P.S., Vedder,L.J., Timmerman,H.H., Heisterkamp,S., Van Loveren,H. et al. (1994) Impairment of immune function in harbor seals *(Phoca vitulina)* feeding on fish from polluted waters. *Ambio* **23:** 155-159.

Sweeney,A. (1994) Chapter 17: Reproductive Epidemiology of Dioxins. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 549-586.

Tanabe,S., Loganathan,B.G., Subramanian,A., and Tatsukawa,R. (1987) Organochlorine Residues in Short-Finned Pilot Whale: Possible Use as Tracers of Biological Parameters. *Mar Pollut Bull* **18:** 561-563.

Tanabe,S., Watanabe,S., Kan,H., and Tatsukawa,R. (1988) Capacity and mode of PCB metabolism in small cetaceans. *Mar Mammal Sci* **4:** 103-124.

Tarpley,R.J., Wade,T.L., and Haubold,E.M. Toxicological Studies in Tissues of the Beluga Whale *Delphinapterus leucas* along Northern Alaska with an Emphasis on Public Health Implications of Subsistence Utilization. 1994. Department of Veterinary Anatomy & Public Health Geochemical and Environmental Research Group Marine Mammal Research Program. 1994.

Tatematsu,M., Nakanishi,K., Murasaki,G., Mlyata,Y., Hirose,M., and Ito,N. (1979) Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by N-2-fluorenylacetamide in rats. *J Natl Cancer Inst* **63:** 1411-1416.

Taylor,D.L., Schliebe,S., and Metsker,H. (1989) Contaminants in blubber, liver, and kidney tissue of Pacific walruses. *Mar Pollut Bull* **20:** 465-468.

Taylor,J.K. (1989) *Quality Assurance of Chemical Measurment.* Chelsea MI: Lewis Publishers.

Taylor,P.R., Lawrence,C.E., Hwang,H.-L., and Paulson,A.S. (1984) Polychlorinated biphenyls: influence on birthweight and gestation. *Am J Public Health* **74:** 1153-1154.

Tee,P.G., Sweeney,A.M., Symanski,E., Gardiner,J.C., Gasior,D.M., and Schantz,S.L. (2003) A longitudinal examination of factors related to changes in serum polychlorinated biphenyl levels. *Environ Health Perspect* **111:** 702-707.

Theobald,M. and Peterson,R.E. (1994) Chapter 10: Developmental and Reproductive Toxicity of Dioxins and Other Ah Receptor Agonists. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 309-346.

Thomsen,C., Lundanes,E., and Becher,G. (2002) Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. *Environ Sci Technol* **36:** 1414-1418.

Tong,H.Y., Gross,M.L., Schecter,A., Monson,S.J., and Dekin,A. (1990) Sources of dioxins in the environment: second stage study of PCDD/Fs in ancient human tissue and environmental samples. *Chemosphere* **20:** 987-992.

Trosko,J.E., Dawson,B., and Chang,C.-C. (1981) PBB inhibits metabolic cooperation in Chinese hamster cells in virto: its potential as a tumor promoter. *Environ Health Perspect* **37:** 179-182.

Tryphonas,H. (1994) Immunotoxicity of polychlorinated biphenyls: present status and future considerations. *Exp Clin Immunogenet* **11:** 149-62.

US ATSDR (2000). Minimal risk levels (MRLs) for hazardous substances. [On-Line]. [WWW document]. URL Available: http://www.atsdr.cdc.gov/mrls.html

USEPA . Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Volume II: Risk Assessment And Fish Consumption Limits. EPA 823-B-94-004. 1994. Washington DC, United States Environmental Protection Agency Office of Water. 1994.

USEPA . Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Volume 1: Sampling and Analysis, Second Edition. EPA 823-R-95-007. 1995. United States Environmental Protection Agency Office of Water (4305). 1995.

USEPA . Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories Supplement to Volume II: Risk Assessment And Fish Consumption Limits. EPA-823-B-96-004. 1996. EPA Office Of Water (4305). 1996.

USEPA . Exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds, Part III: Integrated summary and risk characterization for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds (DRAFT). 2000a.

USEPA . Guidance for assessing chemical contaminant data for use in fish advisories. Volume 2: Risk assessment and fish consumption limits, Third Edition. EPA 823-B-00-008. 2000b. Office of Water (4305).

Usher,P.J., Baikie,M., Demmer,M., Nakashima,D., Stevenson,M.G., and Stiles,M. Communicating About Contaminants in Country Food: The Experience in Aboriginal Communities. ISBN 0-9699774-0-9. 1995. Research Department Inuit Tapirisat of Canada. 1995.

Van den Berg,M., Birnbaum,L., Bosveld,A.T.C., Brunstrom,B., Cook,P., Feeley,M. et al. (1998) Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ Health Perspect* **106:** 775-792.

Van Den Heuvel RL, Koppen G, Staessen JA, Hond ED, Verheyen G, Nawrot TS, et al. (2002) Immunologic Biomarkers in Releation to Exposure Markers of PCBs and Dioxins in Flemish Adolescents (Belgium). *Environ Health Perspect* **110:** 595-600.

Van Oostdam,J.V., Gilman,A., Dewailly,E., Usher,P., Wheatley,B., Kuhnlein,H. et al. (1999) Human health implications of environmental contaminants in Arctic Canada: a review. *Sci Total Environ* **230:** 1-82.

Vander Pol,S.S., Becker,P.R., Kucklick,J.R., Pugh,R.S., Roseneau,D.G., and Simac,K.S. (2004) Persistent organic pollutants in Alaskan Murre (*Uria* spp.) eggs: geographical, species, and temporal comparisons. *Environ Sci Techno.* **38:** 1305-1312.

Varanasi,U., Stein,J.E., Tilbury,K.L., Meador,J.P., Sloan,C.A., Clark,R.C., and Chan,S.L. (1994) Chemical contaminants in gray whales *(Eschrichtius robustus)* stranded along the west coast of North America. *Sci Total Environ* **145:** 29-53.

Varanasi,U., Chan,S.-L., McCain,B.B., Landahl,J.T., Schiewe,M.H., Clark,R.C. et al. National Benthic Surveillance Project: Pacific Coast Part II Technical Presentation of the Results for Cycles I to III. 1989. Seattle, Washington, Environmental Conservation Division Northwest Fisheries Center National Marine Fisheries Service National Oceanic and Atmospheric Administration. 1989.

Varanasi,U., Stein,J.E., Tilbury,K.L., Brown,D.W., Meador,J.P., Krahn,M.M., and Chan,S.-L. Contaminant Monitoring for NMFS Marine Mammal Health and Stranding Response Program. Magoon, O. T., Wilson, W. S., Converse, H., and Tobin, L. T. 2516-2530. 1993. New Orleans LA, ASCE. 1993.

vom Saal,F.S., Timms,B.G., Montano,M.M., Palanza,P., Thayer,K.A., Nagel,S.C. et al. (1997) Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. *Proc Natl Acad Sci USA* **94:** 2056-2061.

vom Saal,F.S. and Sheehan,D.M. (1998) Challenging Risk Assessment. *Forum for applied research and public policy* **13:** 11-18.

Vuorinen,J.P., Paasivirta,J., and Reistinen,J. Comparison of the levels of organochlorines in Arctic and Baltic wildlife samples. 1989. Oslo. 9-18-1989.

Walkowiak,J., Wiener,J.A., Fastabend A., Heinzow,B., Kramer,U., Schmidt,E. et al. (2001) Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *Lancet* **358:** 1602-1607.

Wania,F. and Mackay,D. (1993) Global fractionation and cold condensation of low volatility ogranochlorine compounds in polar regions. *Ambio* **22:** 10-18.

Watanabe,S., Shimada,T., Nakamura,S., Nishiyama,N., Yamashita,N., Tanabe,S., and Tatsukawa,R. (1989) Specific profile of liver microsomal cytochorme P-450 in dolphin and whales. *Marine Environmental Research* **27:** 51-65.

Webster,T. and Commoner,B. (1994) Chapter 1: Overview: The Dioxin Debate. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 1-50.

Weisglas-Kuperus,N., Patandin,S., Berbers,G.A.M., Sas,T.C.J., Mulder,P.G.H., Sauer,P.J.J., and Hooijkaas,H. (2000) Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. *Environ Health Perspect* **108:** 1203-1207.

Weisglas-Kuperus,N., Sas,T.C.J., Koopman-Essenboom,C., Van der Zwan,C.W., De Ridder,M.A.J., Beishuizen,A. et al. (1995) Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. *Pediatric Res* **38:** 404-410.

Welshons,W.V., Thayer,K.A., Judy,B.M., Taylor,J.A., Curran,E.M., and vom Saal,F.S. (2003) Large Effects from Small Exposures. I. Mechanisms for Endocrine-Disrupting Chemicals with Estrogenic Activity. *Envionr Health Perspect* **111:** 994-1006.

Wiig,O., Derocher,A.E., Cronin,M.M., and Skaare,J.U. (1998) Female pseudohermaphrodite polar bears at Svalbard. *Journal of Wildlife Diseases* **34:** 792-796.

Williams,L.L., Giesy,J.P., DeGalan,N., Verbrugge,D.A., Tillitt,D.E., and Ankley,G.T. (1992) Prediction of concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents from total concentrations of polychlorinated biphenyls in fish fillets. *Environmental Science & Technology* **26:** 1151-1159.

Wilson,R., Allen-Gil,S., Griffin,D., and Landers,D. (1995) Organochlorine contaminants in fish from an Arctic lake in Alaska, USA. *Sci Total Environ* **160/161:** 511-519.

Wolfe,W.H., Michalek,J.E., Miner,J.C., Rahe,A.J., Moore,C.A., Needham,L.L., and Patterson,D.G. (1995) Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand. *Epidemiology* **6:** 17-22.

Wolff,M.S., Toniolo,P.G., Lee,E.W., Rivera,M., and Dubin,N. (1993) Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst* **85:** 648-652.

World Health Organization . Joint UN FAO/WHO Expert Committee on Food Additives, Fifty-seventh Meeting, Rome 5-14, 2001. 2001.

Ylitalo,G.M., Matkin,C.O., Buzitis,J., Krahn,M.M., Jones,L.L., Rowles,T., and Stein,J.E. (2001) Influence of life-history parameters on organochlorine concentrations in free-ranging killer whales (Orcinus orca) from Prince William Sound, AK. *Sci Total Environ* **245:** 183-203.

Yu,M.-L., Hsin,J.-W., Hsu,C.-C., Chan,W.-C., and Guo,Y.L. (1998) The immunologic evaluation of the Yucheng children. *Chemosphere* **37:** 1855-1865.

Zober,M.A., Ott,M.G., Papke,O., Senft,K., and Germann,C. (1992) Morbidity study of extruder personnel with potential exposure to brominated dioxins and furans. I results of blood monitoring and immunological tests. *British Journal of Industrial Medicine* **49:** 532-544.

Zook,D.R. and Rappe,C. (1994) Chapter 3: Environmental Sources, Distribution, and Fate of Polychlorinated Dibenzodioxins, Dibenzofurans, and Related Organochlorines. In *Dioxins and Health*. Schecter,A. (ed). New York NY: Plenum Press, 79-114.