The Role of Persistent Organic Pollutants in the Worldwide Epidemic of Type 2 Diabetes Mellitus and the Possible Connection to Farmed Atlantic Salmon (*Salmo salar*)

Walter J. Crinnion, ND

Abstract

Rates of type 2 diabetes mellitus (T2DM), both in the United States and worldwide, have been rising at an alarming rate over the last two decades. Because this disease is viewed as primarily being attributable to unhealthy lifestyle habits, a great deal of emphasis has been placed on encouraging increased exercise, better dietary habits, and weight loss. Recent studies reveal that the presence of several persistent organic pollutants (POPs) can confer greater risk for developing the disease than some of the established lifestyle risk factors. In fact, evidence suggests the hypothesis that obesity might only be a significant risk factor when adipose tissue contains high amounts of POPs. Chlorinated pesticides and polychlorinated biphenyls, in particular, have been strongly linked to the development of metabolic syndrome, insulin resistance, and T2DM. In addition to reviewing the evidence associating POPs to these conditions, this article explores the possible contribution of farmed Atlantic salmon – a significant and common dietary source of POPs – with blood sugar dysregulation conditions.

(Altern Med Rev 2011;16(4):301-313)

Walter J. Crinnion, ND – 1982 graduate of Bastyr University; practice since 1982 with a special focus on treating chronic diseases caused by environmental toxic burden; conducts post-graduate seminars in environmental medicine; professor and chair of the Environmental Medicine Program, Southwest College of Naturopathic Medicine, Tempe, AZ; Environmental Medicine Editor, *Alternative Medicine Review*
Email: w.crinnion@scnm.edu

Background

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood sugar levels. There are three main types of diabetes: type 1 diabetes (also referred to as insulin-dependent diabetes mellitus [IDDM] or juvenile diabetes); type 2 diabetes (T2DM; formerly referred to as non-insulin-dependent diabetes mellitus [NIDDM] or adult onset diabetes); and gestational diabetes. The emphasis in this review will be on type 2 diabetes mellitus. T2DM is characterized by high blood glucose levels in the context of insulin resistance and/or relative insulin deficiency. It is one of the most common and fastest growing worldwide health problems, causing significant morbidity and mortality.

A 2004 study estimated that 2.8 percent of all persons worldwide had diabetes (i.e., 171 million persons). This study also predicted global prevalence rates to increase to 4.4 percent by 2030 (i.e., 366 million persons).[1] A newer study estimated worldwide diabetes prevalence in adults ages 20-79 years at 6.4 percent for 2010 and predicted it would increase to 7.7 percent (i.e., 439 million adults) by 2030.[2] This study also estimated that the prevalence of T2DM will increase more rapidly in developing (69% increase) compared to developed (20% increase) countries over the next two decades.[2] In the United States, the prevalence of diabetes increased from 0.93 percent in 1958 to 2.04 percent in 1973. It took another 20 years for the prevalence to increase by an additional one percent (i.e., an increase above three percent in 1993), but increased by another one percent in just six years (i.e., an increase to four percent in 1999 – just six years later). By 2009 (the most current figures available from the U.S. Centers for Disease Control [CDC]) the prevalence of reported diabetes in the U.S. population was 6.6 percent, an increase of more than 50 percent in just 10 years.[3]

Established risk factors for T2DM include obesity, sedentary lifestyle, poor diet, family history of diabetes, race/ethnicity, age, a history of gestational diabetes, and metabolic syndrome. In

Key words: diabetes, T2DM, DM, metabolic syndrome, glucose, insulin, triglycerides, HDL, obesity, salmon, POPs, PCBs, pollutants, pesticides, farmed fish, fish oil, EFA

addition to being a risk factor, metabolic syndrome has been considered a precursor to T2DM.[4] Metabolic syndrome is a clustering of symptoms. The criteria established by the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (2001) for the diagnosis of metabolic syndrome is the presence of at least three of the following: central obesity (waist circumference ≥102 cm or 40 in [male], ≥88 cm or 36 in [female]), impaired fasting glucose (≥6.1 mmol/L [110 mg/dL]), high blood pressure (≥130/85 mmHg), decreased high-density lipoprotein (HDL) cholesterol values (<40 mg/dL [male], <50 mg/dL [female]), and increased triglycerides (≥1.7 mmol/L [150 mg/dL]).[5] While the NCEP criteria are frequently used to define metabolic syndrome, other definitions have also been used. These include definitions by the International Diabetes Federation (IDF) and the World Health Organization (WHO). The prevalence of metabolic syndrome in a population varies slightly depending upon the definition used.[6]

A number of studies have been published in the last 14 years linking insulin resistance, metabolic syndrome, and T2DM to persistent organic pollutants (POPs). (Note: See sidebar for definition and examples of POPs.) As an example, U.S. Air Force veterans, who participated in Operation Ranch Hand from 1962-1972 during the Vietnam War, were exposed to Agent Orange in the course of their duties. Agent Orange was contaminated with a dioxin-like POP called 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The veterans exposed to Agent Orange had average blood levels of 2,3,7,8-TCDD that were three times higher than in the control group. They were also 40 percent more likely to have glucose abnormalities and 50 percent more likely to have T2DM. As blood levels of 2,3,7,8-TCDD increased, the length of time it took to develop T2DM decreased.[7] After this study was published in 1997, other researchers began to study potential associations between POPs (and more recently some non-persistent environmental pollutants) and conditions such as metabolic syndrome, insulin resistance, and T2DM. This article reviews these findings.

Metabolic Syndrome/Insulin Resistance Associations with POPs

A study was conducted on 1,374 Japanese citizens ages 15-73, none of whom had any known occupational exposures to dioxins, furans, or dioxin-like polychlorinated biphenyls (PCBs). The study group was evenly divided across the five regions of Japan, and further divided to recruit equal numbers of those living in cities, farms, and fishing villages from each of the regions. Prevalence of metabolic syndrome in the study participants was 11.6 percent. A strong statistical association was found between the presence of metabolic syndrome and higher lipid-adjusted toxic equivalents (TEQs) of dioxin and dioxin-like POPs (e.g., polychlorinated dibenzo-p-dioxins [PCDDs or dioxins], polychlorinated dibenzofurans [PCDFs or furans], and dioxin-like polychlorinated biphenyls [PCBs]). Using quartile 1 (i.e., the lowest TEQ for the POP) as the referent (with an odds ratio of 1), the adjusted odds ratio for developing metabolic syndrome was 2.2 for the 2nd quartile and

Persistent Organic Pollutants

Persistent organic pollutants (POPs) are organic compounds that are resistant to environmental degradation. Because of this, they persist in the environment, bioaccumulate in human and animal tissue, and biomagnify in food chains. The United Nations Environment Programme Governing Council (GC) originally created a list of 12 POPs – known as the "dirty dozen." These were aldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDD or dioxins), polychlorinated dibenzofurans (PCDF or furans), and toxaphene. In recent years, this list has been expanded to include polycyclic aromatic hydrocarbons (PAHs), polybrominated diphenyl ethers (PBDE), and tributyltin (TBT). The groups of compounds that make up POPs are also classed as persistent, bioaccumulative, and toxic (PBTs) or toxic organic micro pollutants (TOMPs). These terms are essentially synonyms for POPs.

increased to 3.2 for the 4th quartile for dioxin TEQs; 4.0 (2nd quartile) and increased to 4.4 (4th quartile) for furan TEQs; and 1.9 (2nd quartile) and increased to 4.8 (4th quartile) for total TEQs of dioxin-like PCBs.[8]

Note: Because dioxins, furans, and dioxin-like POPs are almost invariably found in complex mixtures, the concept of TEQ has been developed to facilitate risk assessment and regulatory control. Compounds with higher toxicity are assigned a higher toxic equivalence factor (TEF) on a scale from 0 to 1. TEF is multiplied by the concentration of a specific dioxin or dioxin-like chemical in the serum to produce the TEQ for that compound. To generate the TEQ for furans, for example, the TEQ of the different furan congeners are added together. Two people could conceptually have an equal TEQ of furans, with one person having larger concentrations of less toxic furans and the other person having smaller concentrations of more toxic furans.

Table 1. Odds Ratios for Metabolic Syndrome by Specific PCB Congeners in Japanese Individuals

PCB congener	2nd quartile	3rd quartile	4th quartile	p value
PCB-126	2.5	4.9	9.1	<0.01
PCB-105	1.9	4.6	7.3	<0.01
PCB-114	3.1	3.6	6.4	<0.01
PCB-118	2.5	3.8	6.5	<0.01
PCB-123	1.8	3.4	5.9	<0.01
PCB-167	2.3	2.7	4.1	<0.01

Adapted from Uemura H, Arisawa K, Hiyoshi M, et al. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. *Environ Health Perspect* 2009;117:568-573.

Uemora et al also reported statistically significant associations between metabolic syndrome and specific PCB congeners (i.e., specific PCBs that differ based on the number and position of the chlorine atoms around the biphenyl rings). Persons with the highest concentrations of PCB-126 and PCB-105 (i.e., the 4th quartile) had odds ratios for metabolic syndrome of 9.1 and 7.3, respectively. Associations between different dioxin-like PCB congeners and metabolic syndrome by quartile of congener are listed in Table 1.[8]

Uemura et al provided odds ratios for the various metabolic syndrome criteria by quartile of TEQs of serum dioxin-like PCBs. All TEQs of PCDDs (dioxins), PCDFs (furans), and dioxin-like PCBs, and total TEQs for all three combined, were associated with high blood pressure and elevated triglycerides (tests of trend were all significant). TEQs of dioxin-like PCBs were statistically associated with each of the metabolic syndrome criteria, with higher concentrations producing higher odds ratios for each criteria (Table 2)

An association between hypertension and POPs was also reported in a study of 294 residents of Anniston, Alabama, living near a Monsanto plant. Individuals were assessed for PCBs and chlorinated pesticides. A significant association between the presence of PCBs and the development of hypertension was found – the greatest association being with congeners PCB-156, -157 and -189.[9]

The relationship between POPs and insulin resistance has been investigated. The homeostasis model assessment (HOMA-IR) was used to assess insulin resistance (Note: HOMA-IR utilizes fasting insulin and glucose and calculates insulin resistance with the equation: [fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5]). HOMA-IR was calculated for 749 non-diabetic individuals who participated in the 1999-2002 National Health and Nutrition Examination Survey (NHANES). Serum from these participants was also assessed for 19 chemicals from five POP subclasses – PCDDs (dioxins), PCDFs (furans), dioxin-like PCBs, nondioxin-like PCBs, and organochlorine (OC) pesticides.

OC pesticides, specifically oxychlordane and *trans*-nonachlor (both are chlordanes commonly used for termite treatment), along with the nondioxin-like PCB congeners PCB-170 and PCB-187 showed strong and statistically significant associations with insulin resistance. The other subclasses of POPs investigated in this study – PCDDs, PCDF, and dioxin-like PCBs – had increased odds ratios compared with the lowest quintile; however, odds ratios did not increase linearly for increasing quartiles of exposure and the positive trends did not reach statistical significance.[10]

A subset of participants from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort (a study that focused on development of cardiovascular disease risk in individuals who enrolled in the trial when they were between

ages 18 and 30) was used to investigate interactions with POPs and the development of aspects of metabolic syndrome.[11] The CARDIA trial began in 1985 with five follow-up examinations conducted at years 2, 5, 7, 10, 15, and 20 (ending in 2005-2006). A total of 55 POPs were measured during the second year: nine OC pesticides, 35 PCB congeners, 10 polybrominated diphenyl ether (PBDE) congeners, and one polybrominated biphenyl (PBB) congener.

Dichlorodiphenyldichloroethylene (DDE) – an OC pesticide – had the greatest association with increased body mass index (BMI) at year 20. Three PCBs – PCB-170, -180, and -206 – also predicted greater BMI at study conclusion. Oxychlordane, *trans*-nonachlor, hexachlorobenzene, and DDE predicted future triglycerides at year 20, after adjusting for triglycerides at year 2; however, only DDE was significantly associated with increased triglyceride levels at year 20. Low HDL was significantly associated with levels of DDE and PCBs-170, -180, -195, -199, and -206. Insulin resistance (utilizing HOMA-IR) was significantly associated with DDE and PCB-99. In this study, some OC pesticides and PCBs predicted excess adiposity, dyslipidemia, and insulin resistance among participants without diabetes; however, these associations were not linear across increasing quintiles of exposure. Low-dose exposure to OC pesticides and PCBs showed strong associations (e.g., 2nd and 3rd quintiles), with highest exposure (e.g., 4th quintile) often producing an inverted U-shaped dose-response curve.[11] This U-shaped pattern was different from the linear dose-response found in the Uemura study,[8] and might indicate that some of these adverse effects occur with lower, rather than higher, POP exposure.

Associations Between Type 2 Diabetes Mellitus and POPs

While dose-response curves were not always linear, the previously reviewed studies showed a strong association between POP levels above reference levels and the onset of metabolic

Table 2. Odds Ratios for the Specific Metabolic Syndrome Criteria by Quartile of TEQs of Dioxin-like PCBs in the Serum in Japanese Individuals[8]

Criteria	TEQs of PCB 2nd quartile	TEQs of PCB 3rd quartile	TEQs of PCB 4th quartile	p value
BMI ≥ 25 kg/m2	1.7	1.8	2.6	<0.01
Blood pressure ≥ 130/85 mmHg (or a history of physician-diagnosed hypertension)	1.0	1.1	1.9	<0.01
Triglycerides ≥150 mg/dL	2.4	3.4	5.2	<0.01
HDL <40 mg/dL males, <50 mg/dL females	1.1	1.9	2.1	0.06
HbA1c ≥ 5.6% (or physician diagnosis of T2DM)	2.1	3.1	8.0	<0.01

Adapted from Uemura H, Arisawa K, Hiyoshi M, et al. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. *Environ Health Perspect* 2009;117:568-573.

Table 3. Odds Ratio of T2DM by Individual POPs with Average Concentration of each POP in Participants from NHANES[12]

POP	<25th percentile	25th-50th percentile	50th-75th percentile	75th-90th percentile	>90th percentile	p value
PCB-153	14.3 ng/g; (2.5)	36.7 ng/g; (4.3)	60.2 ng/g; (5.9)	93.6 ng/g; (5.9)	164 ng/g; (6.8)	<0.001
HCDD	20.7 pg/g; (1.0)	37.8 pg/g; (1.7)	60.8 pg/g; (1.8)	97.5 pg/g; (1.6)	170 pg/g; (2.7)	0.007
OCDD	194 pg/g; (1.7)	323 pg/g; (2.2)	514 pg/g; (1.6)	805 pg/g; (2.7)	1,485 pg/g; (2.1)	0.094
Oxychlordane	8.5 ng/g; (0.8)	15.4 ng/g; (1.9)	25.1 ng/g; (3.1)	39.1 ng/g; (4.5)	65.5 ng/g; (6.5)	<0.001
trans-Nonachlor	11.0 ng/g; (1.2)	21.7 ng/g; (2.5)	35.7 ng/g; (4.9)	60.6 ng/g; (7.6)	114 ng/g; (11.8)	<0.001
DDE	112 ng/g; (1.0)	292 ng/g; (1.5)	717 ng/g; (1.6)	1,560 ng/g; (2.3)	3,700 ng/g; (4.3)	<0.001
OR for the Sum of all 6 POPs	1.0	14.0	14.7	38.3	37.7	<0.001

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

syndrome (or its criteria) and insulin resistance. Since these conditions are risk factors for T2DM, studies of the association between POPs and T2DM will be explored.

Utilizing NHANES data, Lee et al investigated the association between T2DM and PCB-153, two dioxins (1,2,3,4,7,8-hexachlorodibenzo-p-dioxin [HCDD] and octachlorodibenzo-p-dioxin [OCDD]), oxychlordane, DDE, and *trans*-nonachlor. All six POPs were detectable in 80 percent of samples from participants. T2DM was strongly associated with all six POPS. Interestingly, BMI was not predictive of a high burden of these POPs; instead, their presence was correlated with increasing age.[12]

Table 3 lists the odds ratios for developing T2DM for each of the six studied POPs. Results are divided into percentiles from lowest to highest blood levels (i.e., 90th percentile represents participants in the top 10 percent with respect to concentrations of the specific POP). For each POP the average concentration in the blood (either in ng/g lipid or in pg/g lipid) is listed first, followed by the odds ratio (OR) in parenthesis. Odds ratios were corrected for age, gender, race/ethnicity, as well as BMI and waist circumference.

While not perfectly linear, PCB-153, the two chlordanes (oxychlordane and *trans*-nonachlor), and DDE all showed statistically significant dose-response associations with T2DM.

Summing the six POPs together also resulted in a statistically significant dose-response association with T2DM. Interestingly, while these POPs had strong associations with diabetes in obese persons, obese subjects who did not have high POP levels did not have any higher risk for diabetes.[12] This finding suggests that the total amount of POPs stored in adipose tissue, rather than the amount of adipose tissue per se, might be the greatest risk and best predictor for T2DM.

Lee et al also investigated a subset of participants from the CARDIA study to see if POPs were associated with the development of T2DM over an 18-year period. Specifically, these researchers wanted to determine whether lower levels of POPs were more likely to be associated with T2DM than higher levels. Criteria for a diagnosis of T2DM included histories of taking anti-diabetic medications or fasting blood glucose ≥126 mg/dL at two or more examinations. After 18 years of follow-up, 116 members of the CARDIA trial fit that definition and, of those, 90 were selected by Lee to participate in this study. Blood samples of these subjects and their matched controls, taken during the second year of the trial, were measured for 55 POPs. Odds ratios for T2DM per quintile of specific POP are listed in Table 4, with the concentration of the POP listed in pg/g, followed by the OR in parenthesis; p values for individual POPs were not provided in the study.[13]

Table 4. Average Blood Concentrations of Selected POPs and Odds Ratio for T2DM in a Subset of Persons from the CARDIA Cohort[13]

POP	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Oxychlordane	≤110 pg/g; (1.0)	111-157 pg/g; (2.0)	158-200 pg/g; (1.3)	>200 pg/g; (2.6)
trans- Nonachlor	≤109 pg/g; (1.0)	110-174 pg/g; (4.8)	175-250 pg/g; (2.7)	>250 pg/g; (3.7)
DDE	≤2,153 pg/g; (1.0)	2,154-3,312; (1.3)	3,313-5,731; (1.6)	> 5,731 pg/g; (0.9)
PCB-74	≤58 pg/g; (1.0)	59-98 pg/g; (2.8)	99-144 pg/g; (1.4)	> 144 pg/g; (2.6)
PCB-153	≤204 pg/g; (1.0)	205-349 pg/g; (2.4)	350-466 pg/g; (0.8)	>466 pg/g; (1.6)
PCB-178	≤8 pg/g; (1.0)	9-15 pg/g; (3.2)	16-21 pg/g; (0.7)	>21 pg/g; (2.0 OR)
PCB-187	≤44 pg/g; (1.0)	45-78 pg/g; (3.2)	79-104 pg/g; (0.5)	>104 pg/g; (1.9)

Adapted from: Lee DH, Steffes MW, Sjödin A, et al. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. *Environ Health Perspect* 2010;118:1235-1242.

Oxychlordane showed a strong association (it was the only one of the chlorinated pesticides in this study to show statistical significance) with T2DM – as it had in Lee's previous study.[12] Similarly, PCB-153 also again showed an increased risk, but risk was most notable for those in the 2nd quartile. This pattern of increased risk for individuals in the second quartile of POP concentrations is one of the hallmark findings of this study. This finding led the researchers to conclude that the association of certain POPs to T2DM might be nonlinear and that increased risk may occur at low levels of exposure to certain POPs.[13]

The association between specific PCBs and T2DM was studied in 117 middle-aged, overweight and obese Japanese individuals who were participating in the Saku Control Obesity Program. Two different diagnostic distinctions were used to determine T2DM. The term "definite diabetes" was used for individuals who had a hemoglobin A1c (HbA1c) level ≥6.9 percent or who were taking medication for diabetes. The term "all diabetes" was used for people who had an HbA1c level ≥6.5 percent, a fasting plasma glucose level ≥126 mg/dL (single measurement), or a history of doctor-diagnosed diabetes. As shown in Table 5, changing the definition of diabetes altered the OR associated with the different PCBs.[14]

Table 5. Odds Ratios for "Definite Diabetes" and "All Diabetes" and Lipid-adjusted Levels of Specific PCBs from Participants in the Saku Control Obesity Program[14]

PBC	OR for Definite Diabetes	OR for All Diabetes
PCB-74	0.67	1.16
PCB-99	2.2	1.70
PCB-146	137	29.2
PCB-153	0.64	0.73
PCB-156	20.2	0.94
PCB-180	5.32	1.76
PCB-182/187	1.21	1.15

Adapted from: Tanaka T, Morita A, Kato M, et al. Congener-specific polychlorinated biphenyls and the prevalence of diabetes in the Saku Control Obesity Program (SCOP). *Endocr J* 2011;58:589-596.

In this study, only 13 PCB congeners and no organochlorine pesticides were measured (i.e., some POPs previously associated with T2DM were not assessed in this study). Table 5 lists seven of the PCBs measured (with PCB-182 and -187 combined). The four with the greatest statistical significance were PCB-99, -146, -156, and -180. Three PCB congeners that showed a significant association with T2DM in the Lee et al study[13] – PCB-74, -153, and -187 – did not have a significant association in this study. The most noteworthy association in this study was between PCB-146 and "definite diabetes" (OR=137) and "all diabetes" (OR=29.2).[14]

Highlighting the point that findings can change from study to study, PCB-153, previously shown to have a statistically significant association with T2DM,[12,13] appeared to have the opposite (protective) effect in this study.[14] However, in a study of 544 Swedish women, PCB-153 was again shown to be significantly associated with an increased risk of T2DM (OR=1.6). In this study, DDE also had a significant association with risk for T2DM (OR=1.3).[15]

Lee et al also worked with 725 Swedish participants in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Blood samples, taken from participants when they reached age 70, were measured for 19 POPs, including 14 PCBs and three chlorinated pesticides. Follow-up was conducted when participants turned 75, at which point 36 were found to have developed T2DM. Presence of POPs in the blood five years prior was strongly predictive of risk for developing T2DM. Table 6 shows the OR for the six specific POPs that showed statistical significance and for five other POPS that just missed statistical significance (defined as $p \leq 0.5$).[16]

A large cohort of 1,988 persons from Helsinki, Finland, born between 1934 and 1944 (before PCBs were environmentally ubiquitous, but who lived through a period of steep environmental POP exposure), were assessed in 2003 for the presence of T2DM and POPS – OC pesticides (oxychlordane and *trans*-nonachlor), DDE, PCB-153, and polybrominated diphenyl ethers (PBDE-47 and -153).[17] All persons over the 50th percentile for OC pesticides, DDE, and PCB-153 had an increased risk for the development of T2DM. OR increased linearly with exposure, and highest exposure levels were associated with approximately double the risk for T2DM. No association was detected for the two PDBEs. Analysis also detected that, among the normal-weight participants (BMI <25 kg/m^2), POP exposure did not increase the risk of T2DM. Data is provided in Table 7. In individuals with low POP exposure, being overweight or obese was not associated with T2DM risk. This finding is consistent with the report by Lee et al,[12] and provides more evidence to suggest that POPs stored in adipose tissue, not quantity of adipose tissue, might be the actual risk factor for T2DM.

While Airaksinen et al did not design this study to assess actual sources of POP exposure, human exposure to POPs is thought to occur primarily through diet, with foods of animal origin being the largest contributor. In Finland, the most important source of POPs is Baltic Sea fatty fish, such as Baltic herring (*Clupea harengus membras*) and salmon (*Salmo salar*).[18]

Fish and Marine Life as Sources of Exposure to POPs and the Possible Connection to T2DM

Except for individuals living or working around industrial sites where PCBs were used or dumped, the most common source of exposure to PCBs is from diet, with foods of animal origin, especially seafood, identified as high sources of exposure.[19] In a dietary study, the highest content of PCBs was found in dairy products, meat, and fish.[20] The estimated dietary intake of PCBs in the United States for an average adult peaked in 1978 at 0.027 µg/kg/day, and had declined to an average of <0.001 µg/kg/day by 1991.[21] Great Lakes sport fishermen, who eat what they catch, consume more than the average U.S. resident and demonstrate very elevated blood levels of PCBs.[22] In another report, consuming fish from PCB-contaminated waters was linked to higher-than-average PCB blood levels, as well as elevated fasting blood glucose values.[23]

Because fish consumption is such a major source of both PCBs and OC pesticides, a few studies have compared the rate of T2DM between heavy fish consumers and those who do not consume much fish. A study of 692 Greenland Inuit, who consume a diet high in fish and marine mammals, examined whether there was an association between POP blood levels and glucose intolerance.[24] A prevalence of 10.3 percent and 10.5 percent was reported for diabetes and impaired glucose tolerance, respectively (this is higher than worldwide diabetes rates[1,2]). The average POP burden was about 10-fold higher than those found in any of the other studies reviewed in this article. In this study, despite overall concentrations of POPs, and the high concentrations of several specific POPs, there were no associations found between POPs and stages of glucose intolerance, markers of insulin resistance, or diabetes. POPs were actually inversely associated with stimulated insulin concentrations and homeostasis model assessment of beta-cell function. If there is a U-shaped dose-response curve between POPs and T2DM (some evidence suggests this non-linear pattern), low levels might in theory produce the greatest risk for glucose intolerance, metabolic syndrome, and T2DM. More work is required to better understand why such high levels of POPs were not associated with increased risk of T2DM in this population.

Table 6. Adjusted Odds Ratios for Development of T2DM by Quintiles of Specific POPs in the PIVUS Study[16]

POP	OR for 2nd quintile	OR for 3rd quintile	OR for 4th quintile	OR for 5th quintile	p value
PCB-74	7.7	8.5	11.5	9.0	0.05
PCB-99	2.5	4.3	6.9	3.3	0.04
PCB-138	1.5	2.5	5.9	3.2	0.01
PCB-153	0.8	1.5	3.4	1.7	0.06
PCB-157	2.1	2.3	3.5	2.9	0.07
PCB-170	2.8	5.6	5.0	3.6	0.06
PCB-180	4.6	2.8	4.6	4.8	0.07
PCB-194	1.4	3.5	2.2	6.0	<0.01
PCB-206	3.2	2.1	5.5	5.0	0.02
PCB-209	3.9	7.1	3.8	6.2	0.06
trans–Nonachlor	1.2	0.5	4.2	1.8	0.03

Adapted from: Lee DH, Lind PM, Jacobs DR Jr, et al. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of Type 2 Diabetes in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care* 2011;34:1778-1784.

A group of Great Lakes sport fish consumers were followed for an average of 8.4 years to investigate whether there was any correlation between certain POPs and the development of T2DM. The criterion used for determining diabetes was "self-reported diagnosis of diabetes" – a far-less stringent criterion than those used in previously mentioned studies. Since objective data was not used, and many people with T2DM can actually be unaware that they have this condition, individuals with T2DM might have been placed in the control group instead of the study group. Even

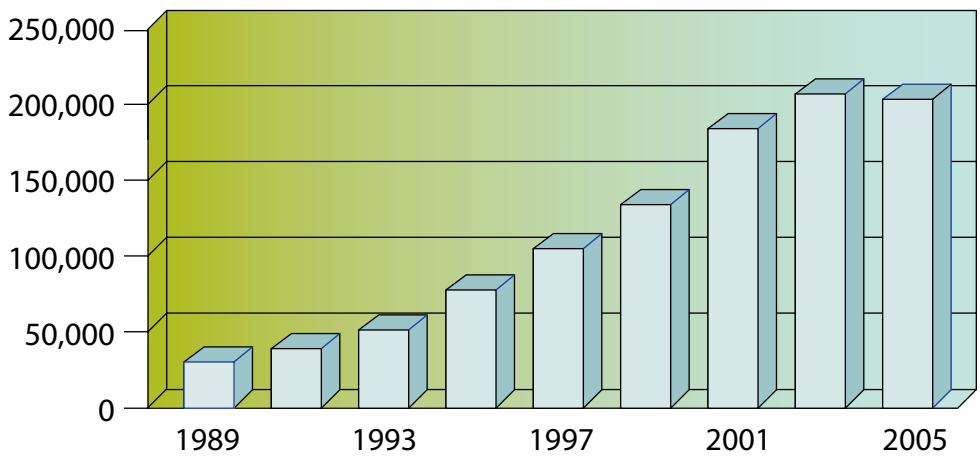
Table 7. Concentration of POPs and OR (in parenthesis) for T2DM in Finnish Study[17]

POP	10th percentile	10th-50th percentile	50th-90th percentile	>90th percentile	p value
Oxychlordane	5.4 ng/g; (1.0)	8.9 ng/g; (1.03)	14 ng/g; (1.42)	23 ng/g; (2.08)	0.17
trans-Nonachlor	11 ng/g; (1.0)	22 ng/g; (1.21)	36 ng/g; (1.52)	65 ng/g; (2.24)	0.067
DDE	120 ng/g; (1.0)	320 ng/g; (1.0)	710 ng/g; (1.62)	1500 ng/g; (1.75)	<0.0001
PCB-153	140 ng/g; (1.0)	230 ng/g; (1.0)	360 ng/g; (1.19)	590 ng/g; (1.64)	0.20

Adapted from: Airaksinen R, Ratakokko P, Eriksson JG, et al. Association between type 2 diabetes and exposure to persistent organic pollutants. *Diabetes Care* 2011;34:1972-1979.

with this major confounding factor, DDE levels were significantly associated with the development of T2DM. Prior to adjusting for smoking, alcohol use, and elevated lipids, PCB-118 also showed significant association. The researchers found that the geometric means of DDE, PCB-118, and total PCBs, rather than years of sport fish consumption, were higher in participants who subsequently developed T2DM. OC pesticide levels, which have been associated with T2DM in other studies, were not assessed.[25]

Figure 1. Consumption of Farmed Salmon in the United States from 1989-2005[35]



Adapted from: The Great Salmon Run. (http://www.iser.uaa.alaska.edu/iser/people/knapp/pubs/TRAFFIC/The_Great_Salmon_Run.pdf)

A third study looked at the rates of T2DM among Native American Mohawks who eat a lot of fish from the St. Lawrence River. The inclusion criterion for a diagnosis of T2DM was either fasting blood glucose >125 mg/dL or a prescription for anti-diabetic medication. The prevalence of T2DM in this group of 352 adults was 20.2 percent.[26] This rate was twice that of the Greenland Inuit study,[24] and over three times that of the general U.S. adult population.[3] In this study, blood was tested for the presence of 101 PCB congeners, along with DDE, mirex, and hexachlorobenzene (HCB). When looked at individually, after adjusting for gender, age, BMI, and lifetime smoking status, significant associations were found between T2DM and total PCBs (OR=3.9), DDE (OR=6.4), HCB (OR=6.2), PCB-153 (OR=3.2), and PCB-74 (OR=4.9).[26]

The three groups in the studies cited above ate fish that were caught for sustenance, and all showed high concentrations of some POPs (presumably as a direct result of their high fish consumption). In the two studies that largely investigated fresh-water fish from the Great Lakes or the St. Lawrence River, higher levels of at least some

POPs were associated with increased T2DM. In the Inuit study, the extremely high levels of POPs were not associated with blood sugar abnormalities.

Farmed Atlantic Salmon Consumption as a Source of Exposure to POPs

In 2009 the global production of farmed Atlantic salmon (*Salmo salar*) topped 1.4 million tons, with commercial sales of $6.5 million.[27] Salmon has been called a "functional food," because of its content of omega-3 essential fatty acids (EFAs) and their potential benefits for cardiovascular disease risk reduction.[28,29] Despite the potential benefit of EFAs, farmed salmon is also a significant, and possibly the greatest, source of dietary POPs, including PCBs.

A pilot study compared levels of POPs in farmed and wild salmon. Total PCBs were found to average 51,216 pg/g wet weight in farmed Atlantic salmon, versus an average of 5,302 in wild Pacific salmon – a 10-fold difference. The farmed salmon also had far higher levels of OC pesticides and PDBE (brominated flame retardants) than their wild counterparts.[30]

Two larger studies compared farmed Atlantic salmon from around the world and wild salmon from the Northeast Pacific. The studies used close to 600 whole salmon and filets (totaling about 2 million metric tons each), along with samples of the feed used in the farming operations for these fish. Concentrations of POP contaminants, especially certain PCB congeners, were significantly higher in farmed Atlantic salmon than in wild-caught salmon. European-raised farmed salmon had significantly greater contaminant loads than those farm-raised in North and South America. Although Chinook salmon (also known as King salmon) had the highest PCB content of any of the wild fish, levels were still far below those found in farmed salmon.[31,32] An earlier study also reported that the mean concentration of total PCBs in farmed salmon was 41.5 ng/g wet weight, while the wild salmon only averaged 3.2 ng/g wet weight.[33]

The PCB congener profiles detected in wild salmon were significantly different from those in farmed salmon. Upon investigation, the PCB congener profiles found in farmed salmon often closely corresponded to samples of commercial feed purchased in the same region. In other words, evidence indicated that feed was the likely source of some of the characteristic PCBs found in the farmed salmon.[31] While the wild fish had PCBs with fewer chlorine molecules, making the POPs more water-soluble (which helps explain why they might be more likely to be consumed in the ocean), the farmed salmon had PCBs with more chlorine atoms,[31] consistent with the types of PCBs that have been detected in some samples of fish food.[31,33] Interestingly, it was PCB congeners containing more attached chlorine molecules that were most strongly associated with T2DM in the CARDIA cohort study conducted by Lee et al.[13]

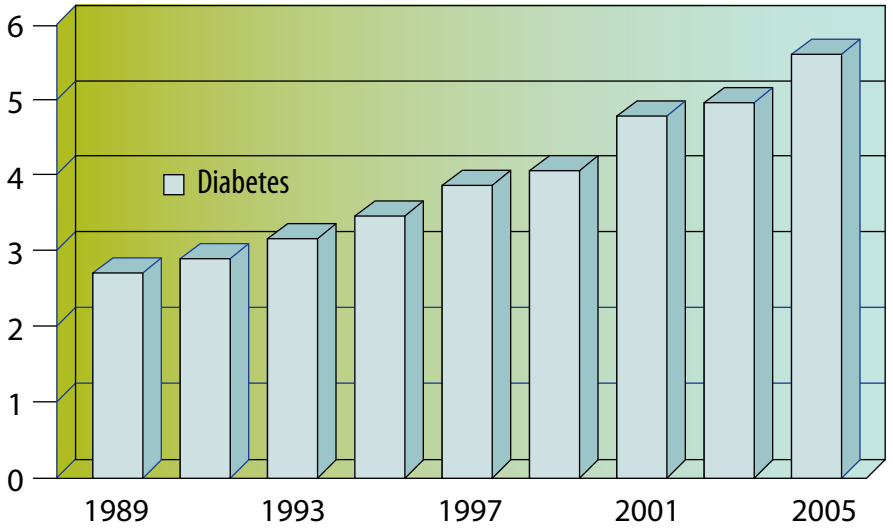
Utilizing data from these studies and from the Environmental Protection Agency calculation for cancer risk, it has been recommended that no one should eat more than one meal of farmed salmon a month.[32,34]

Figure 1 shows the annual consumption totals of farmed Atlantic salmon in the United States from 1989 through 2005 (amounts are in metric tons).[35]

During the time of this large increase in farmed salmon consumption, the rates of T2DM in the United States also significantly increased. Figure 2 shows the percentage of U.S. adults diagnosed with diabetes in the same years (1989-2005).[3]

A study by Storlein et al found that rats fed saturated fats or the omega-6 EFA linoleic acid had higher rates of insulin resistance, while those fed omega-3 fish oils were protected from developing insulin resistance.[36] While this study suggests that

Figure 2. Rates (in percent) of Diabetes in the United States from 1989-2005[3]



Adapted from: CDC National Diabetes Surveillance System

Table 8. Non-fasting Serum PCB Values from a Regular Consumer of Farmed Atlantic Salmon

PCB	Patient serum levels in ppb*	CDC percentile for serum in ppb†	Patient lipid-adjusted levels in ng/g lipid	CDC 95th percentile for lipid-adjusted levels in ng/g lipid†	Estimated OR for T2DM based on Lee et al studies[12,16]
PCB-138	0.35	90th	46.2	75th-90th	1.5
PCB -153	0.51	90th	67.3	75th-90th	1.5
PCB -156	0.05	50th-75th	6.6	75th-90th	NA
PCB -180	0.29	75th-90th	38.2	50th-75th	4.6

*ppb=Parts per billion; †Reference values based on *4th National Report on Human Exposure to Environmental Chemicals*[41]

fish oils should help protect against the insulin resistance characteristic of T2DM, a newer animal study suggests the presence of POPs in fish oil would more than cancel this benefit. Rats were fed one of four diets for 28 days – either regular rat chow or one of three high-fat diets (with added corn oil, crude Atlantic salmon oil, or Atlantic salmon oil that had been highly purified to remove all POPs). The crude salmon oil contained a similar omega-3 EFA profile to the purified salmon oil, but contained significantly higher concentrations of POPs.[37] In this study, rats fed the crude Atlantic salmon oil accumulated visceral adipose tissue. Histological examination also revealed severe hepatosteatosis (fatty liver). Rats fed the purified salmon oil lost weight and had a reduced amount of lipids in the liver. The rats fed the POP-laden crude salmon oil also developed insulin resistance. This study demonstrated a causal link between dietary POPs and visceral obesity, fatty liver, and insulin resistance in rats. The author pointed out that the blood level and adipose tissue concentrations of POPs achieved after 28 days of feeding rats the crude salmon oil were consistent with levels generally found in human studies.[37]

In an eight-week study, mice were fed one of several different diets – control diet, high-fat diet, high-fat diet with farmed Atlantic salmon, Western diet, Western diet with farmed Atlantic salmon, and a high-fat diet with farmed Atlantic salmon with reduced POP content – and monitored for weight and glycemic control. The findings implicated the POP-contaminated farmed Atlantic salmon as the dietary cause of increased rates of insulin resistance and obesity. Mice fed the contaminated salmon (with either the high-fat diet or the Western diet) had exaggerated insulin resistance, visceral fat accumulation, glucose intolerance, and a reduction in muscle glucose uptake in response to insulin. Mice fed the same diet, but with the reduced-POP salmon showed much better insulin sensitivity and glucose tolerance.[38]

POPs are considered persistent because they all have exceptionally long half-lives. As an example, the half-life of a PCB can vary between 10 and 15 years.[39] Some of the same high-chlorine PCBs (i.e., congeners with more chlorines attached) that have been associated with T2DM have extremely long half-lives. For example, PCB-170 has a half-life of 15.5 years, PCB-153 has a half-life of 14.4 years, and PCB-180 has a half-life of 11.5 years. This means that persons consuming regular (even monthly) meals of Atlantic salmon not only might consume high concentrations of POPs, but some of these POPs might take between 50 and 75 years to clear from the body.

To illustrate the potential impact frequent farmed-salmon consumption can have on human POP levels, blood work for specific PCBs from a 58-year-old male patient of the author's is presented in Table 8. Patient history revealed no prior non-dietary exposure to PCBs. Diet history indicated a high intake of farmed Atlantic salmon

(patient had consumed seven bagel and lox breakfasts during the two-week period preceding PCB testing). Compared to other PCB panels ordered by this author in the previous two-year time period, only one other patient had a greater number and higher blood levels of PCBs than this patient. PCBs detected were high chlorine congeners, suggesting the source was farmed salmon (presumably because of contaminated feed fed to these farmed fish). While the patient did not have fasting blood glucose or insulin abnormalities, based upon Lee's studies,[12,16] this individual has an elevated risk for developing metabolic syndrome and T2DM; thus, he will be monitored closely.

Summary

Rates of metabolic syndrome (and its co-morbidities including hypertension, obesity, and low HDL levels), insulin resistance, dysglycemia, and T2DM are continuing to increase worldwide. A growing body of evidence links these problems to *in vivo* levels of POPs – OC pesticides and certain PCB congeners, specifically.

Evidence has been mixed in terms of whether the association has a linear dose-response curve. Some evidence links lower levels of certain POPs with the greatest risk for blood sugar dysregulation, while higher levels are not as strongly associated. More research is required to better understand dose-responses to POPs and risk for metabolic syndrome and T2DM.

Certain PCB congeners have been consistently linked to risk for blood sugar abnormalities, while others have been inconsistently linked, and still others do not appear to have any association with risk. Evidence suggests that certain PCBs, especially those with a greater number of chlorine molecules, have the strongest association with increased risk of developing T2DM. Exposure to these congeners can double to quadruple the risk over a 12-20 year period.

Obesity is one of the most well-known risk factors associated with developing T2DM. The evidence on POPS and T2DM suggests that increased body fatness with low *in vivo* POPs levels does not place a person at increased risk, while increased adiposity with high levels of POPs does. Although more work is needed to verify these finding, this evidence suggests that obesity might only be a risk factor for T2DM in persons with high levels of POPs.

For individuals who do not live or work in areas that have been industrially contaminated with PCBs and OC pesticides, the greatest ongoing exposure to these compounds is generally accepted to be through diet, specifically foods of animal origin and seafood. The evidence discussed in this review implicates farmed Atlantic salmon, presumably because of contaminants in the feed, as possibly being the single largest dietary source of these POPs. Farmed Atlantic salmon are the most commonly available salmon in grocery stores and restaurants throughout the United States and Canada. Although salmon does have many health benefits (primarily connected with its omega-3 EFA content), it is prudent to minimize exposure to the chemical compounds found in farmed salmon because of their connection to T2DM. The documented lower content of POPs in wild Alaskan salmon makes wild-caught salmon a better choice than farmed varieties.

Because certain POPs are risk factors for T2DM, and because these POPs generally have long half-lives, physicians, especially those concerned with prevention, may want to include toxicant testing, along with HbA1c and comprehensive blood panels, as part of a basic laboratory screening for risk of T2DM.

References

1. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-1053.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4-14.
3. Centers for Disease Control and Prevention, National Center for Health Statistics. Crude and age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes, United States, 1980–2009.
4. http://www.cdc.gov/diabetes/statistics/prev/national/figage.htm [Accessed August 11, 2011]
5. Lorenzo C, Okoloise M, Williams K, et al. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio Heart Study. *Diabetes Care* 2003;26:3153-3159.
6. NCEP ATP-III. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
7. Qiao Q, DECODE Study Group. Comparison of different definitions of the metabolic syndrome in relation to cardiovascular mortality in European men and women. *Diabetologia* 2006;49:2837-2846.
8. Henriksen GL, Ketchum NS, Michalek JE, Swaby JA. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. *Epidemiology* 1997;8:252-258.

9. Uemura H, Arisawa K, Hiyoshi M, et al. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. *Environ Health Perspect* 2009;117:568-573.
10. Goncharov A, Pavuk M, Foushee HR, Carpenter DO. Blood pressure in relation to concentrations of PCB congeners and chlorinated pesticides. *Environ Health Perspect* 2011;119:319-325.
11. Lee DH, Lee IK, Jin SH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care* 2007;30:622-628.
12. Lee DH, Steffes MW, Sjödin A, et al. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. *PLoS One* 2011;6:e15977.
13. Lee DH, Lee IK, Song K, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. *Diabetes Care* 2006;29:1638-1644.
14. Lee DH, Steffes MW, Sjödin A, et al. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. *Environ Health Perspect* 2010;118:1235-1242.
15. Tanaka T, Morita A, Kato M, et al. Congener-specific polychlorinated biphenyls and the prevalence of diabetes in the Saku Control Obesity Program (SCOP). *Endocr J* 2011;58:589-596.
16. Rignell-Hydbom A, Rylander L, Hagmar L. Exposure to persistent organochlorine pollutants and type 2 diabetes mellitus. *Hum Exp Toxicol* 2007;26:447-452.
17. Lee DH, Lind PM, Jacobs DR Jr, et al. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care* 2011;34:1778-1784.
18. Airaksinen R, Rantakokko P, Eriksson JG, et al. Association between type 2 diabetes and exposure to persistent organic pollutants. *Diabetes Care* 2011;34:1972-1979.
19. Kiviranta H, Ovaskainen ML, Vartiainen T. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. *Environ Int* 2004;30:923-932.
20. Hopf NB, Ruder AM, Succop P. Background levels of polychlorinated biphenyls in the U.S. population. *Sci Total Environ* 2009;407:6109-6119.
21. Zuccato E, Calvarese S, Mariani G, et al. Level, sources and toxicity of polychlorinated biphenyls in the Italian diet. *Chemosphere* 1999;38:2753-2765.
22. Gunderson EL. FDA Total Diet Study, July 1986-April 1991, dietary intakes of pesticides, selected elements, and other chemicals. *J AOAC Int* 1995;78:1353-1363.
23. Anderson HA, Falk C, Hanrahan L, et al. Profiles of Great Lakes critical pollutants: a sentinel analysis of human blood and urine. The Great Lakes Consortium. *Environ Health Perspect* 1998;106:279-289.
24. Langer P, Kocan A, Tajtaková M, et al. Fish from industrially polluted freshwater as the main source of organochlorinated pollutants and increased frequency of thyroid and dysglycemia. *Chemosphere* 2007;67:S379-S385.
25. Jørgensen ME, Borch-Johnsen K, Bjerregaard P. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. *Diabetologia* 2008;51:1416-1422.
26. Turyk M, Anderson H, Knobeloch L, et al. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. *Environ Health Perspect* 2009;117:1076-1082.
27. Codru N, Schymura MJ, Negoita S, et al. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans. *Environ Health Perspect* 2007;115:1442-1447.
28. Food and Agriculture Organization of the United Nations, Global Aquaculture production for *Salmo salar*. http://www.fao.org/figis/servlet/SQServlet?ds=Aquaculture&k1=SPECIES&k1v=1&k1s=2929&outtype=html [Accessed on August 14, 2011]
29. Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. *Arch Intern Med* 2001;161:2185-2192.
30. Stone NJ. Fish consumption, fish oil, lipids, and coronary heart disease. *Am J Clin Nutr* 1997;65:1083-1086.
31. Easton MD, Luszniak D, Von der GE. Preliminary examination of contaminant loadings in farmed salmon, wild salmon and commercial salmon feed. *Chemosphere* 2002;46:1053-1074.
32. Carlson DL, Hites RA. Polychlorinated biphenyls in salmon and salmon feed: global differences and bioaccumulation. *Environ Sci Technol* 2005;39:7389-7395.
33. Hites RA, Foran JA, Carpenter DO, et al. Global assessment of organic contaminants in farmed salmon. *Science* 2004;303:226-229.
34. Shaw SD, Brenner D, Berger ML, et al. PCBs, PCDD/Fs, and organochlorine pesticides in farmed Atlantic salmon from Maine, eastern Canada, and Norway, and wild salmon from Alaska. *Environ Sci Technol* 2006;40:5347-5354.
35. Huang X, Hites RA, Foran JA, et al. Consumption advisories for salmon based on risk of cancer and noncancer health effects. *Environ Res* 2006;101:263-274.
36. Knapp G, Roheim CA, Anderson JL. The great salmon run: competition between wild and farmed salmon. TRAFFIC North America; 2007. http://www.iser.uaa.alaska.edu/iser/people/knapp/pubs/TRAFFIC/The_Great_Salmon_Run.pdf [Accessed on August 14, 2011]
37. Storlien LH, Kraegen EW, Chisholm DJ, et al. Fish oil prevents insulin resistance induced by high-fat feeding in rats. *Science* 1987;237:885-888.
38. Ruzzin J, Petersen R, Meugnier E, et al. Persistent organic pollutant exposure leads to insulin resistance syndrome. *Environ Health Perspect* 2010;118:465-471.
39. Ibrahim MM, Fjaere E, Lock EJ, et al. Chronic consumption of farmed salmon containing persistent organic pollutants causes insulin resistance and obesity in mice. *PLoS One* 2011;6:e25170.
40. Ritter R, Scheringer M, MacLeod M, et al. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. *Environ Health Perspect* 2011;119:225-231.
41. National Report on Human Exposure to Environmental Chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport/ [Accessed on August 14, 2011]