

Relationship of polychlorinated biphenyls with type 2 diabetes and hypertension

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Diabetes and hypertension are important contributors to morbidity and mortality worldwide. Both of these conditions are caused by some combination of genetic and environmental factors which may include exposure to persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs). Studies have shown an association between elevated serum PCBs and the metabolic syndrome, insulin sensitivity and insulin secretion. Cross-sectional studies have shown associations between diabetes or hypertension and certain PCB congeners or classes, while those same studies show no association between diabetes or hypertension and several other PCB congeners. In animal and human cell studies, various PCBs and dioxins appear to alter glucose and insulin metabolism. These studies specifically show effects on the glucose transporter (GLUT-4) gene and protein; insulin-like growth factor binding protein-1 (IGFBP-1); nuclear transcription factor kappa B (NF κ B); tumor necrosis factor alpha (TNF- α); and insulin production. There are a few longitudinal studies examining the association of diabetes or hypertension and PCBs with no consensus conclusion. Some longitudinal studies have found there to be an association, others have not and a gender difference has also been noted. Prospective studies are needed to determine if PCBs and other POPs contribute to development of diabetes and hypertension.

I. Introduction

Diabetes and hypertension are common health conditions that lead to significant morbidity and mortality worldwide. Diabetes affects 285 million people worldwide, there are almost 4 million deaths attributable to diabetes annually and diabetes is among the top five leading causes of death in many countries. The prevalence of diabetes is increasing dramatically and is estimated to reach over 430 million by 2030.¹ Risk factors for type 2 diabetes include obesity, sedentary lifestyle, poor diet, family history of diabetes, race/ethnicity (in the USA, African Americans, Hispanics, and Native Americans have higher rates; in the UK, South Asians have higher rates), age, impaired fasting glucose, high blood pressure, low high-density lipoprotein (HDL) cholesterol, high triglycerides, metabolic syndrome and history of gestational diabetes. Complications from diabetes include heart disease and stroke; kidney disease; retinopathy; and peripheral neuropathy.

Diabetes is characterized by elevated blood sugar levels that are either the result of the body's inability to produce adequate amounts of insulin; the body's inability to adequately utilize insulin that is produced; or a combination of these factors. Diabetes is diagnosed based on the measurement of serum blood glucose levels or hemoglobin A1C which represents the average blood sugar over a three month period. Diabetes is categorized as either type 1 (also known as insulin dependent) or type 2 (non-insulin dependent). Type 1 diabetes is usually the result of an autoimmune process whereby the insulin producing, pancreatic β -cells are damaged and can no longer produce adequate amounts of insulin; this form of diabetes usually develops earlier in life. Type 2 diabetes results from decreased insulin sensitivity in peripheral tissues and more often develops later in life.

The underlying cause of diabetes has not been conclusively determined, but there are genetic and environmental factors involved in the development of type 2 diabetes. Individuals with impaired fasting glucose or metabolic syndrome are considered to have pre-diabetes and are at higher risk for developing diabetes. Metabolic syndrome is a term used to describe the co-occurrence of several common diabetes risk factors. These risk factors are more likely to occur together than they are to occur separately. The presence of three of the following five risk factors

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Environmental impact

This paper reviews the impact of PCBs on the common human diseases of type 2 diabetes and hypertension. Cross-sectional studies are compelling, but the few longitudinal studies tend not to confirm the results of the cross-sectional studies. If PCBs were proven to contribute to type 2 diabetes and hypertension, we would have to acknowledge a serious environmental impact involving humans directly. This in turn could lead to an increased concern worldwide that would ultimately lead to new PCB regulations. There could be greater urgency for remediation of areas known to be heavily contaminated, and there could be tougher regulations regarding cleaning up any accidental spills. Therefore, the environmental impact would be in the overall reduction of PCBs in the environment.

classifies a person as having metabolic syndrome. (1) Abdominal obesity, defined as the waist circumference >102 cm in men and >88 cm in women. (2) Serum triglycerides $\geq 1.7 \text{ mmol l}^{-1}$. (3) Serum high-density lipoprotein (HDL) cholesterol $< 1.1 \text{ mmol l}^{-1}$ in men or $< 1.5 \text{ mmol l}^{-1}$ in women. (4) Blood pressure $\geq 130 \text{ mmHg}$ systolic or $\geq 85 \text{ mmHg}$ diastolic, or taking anti-hypertensive medication. (5) Impaired fasting glucose, defined as serum glucose $\geq 5.6 \text{ mmol l}^{-1}$ and $< 7.0 \text{ mmol l}^{-1}$. Diabetes and hypertension are closely associated; three-quarters of diabetics also have blood pressure problems.

Hypertension affected almost 1 billion people worldwide in 2000; more than a quarter of the adult population at the time. That number is projected to grow to more than 1.5 billion in the next fifteen years which will represent almost 30% of the population.² Hypertension leads to 7.1 million or 13% of global deaths annually.³ Risk factors for hypertension are similar to those for diabetes and include obesity, sedentary lifestyle, high sodium or low potassium diet, family history of hypertension, race/ethnicity (in the USA, African Americans, Hispanics, and

Native Americans have higher rates), age, tobacco use, and excessive alcohol intake. Complications related to hypertension include heart disease and stroke; congestive heart failure; kidney disease; retinopathy; and peripheral arterial disease. Hypertension is characterized by elevated blood pressure readings ($\geq 140 \text{ mmHg}$ systolic blood pressure or $\geq 90 \text{ mmHg}$ diastolic blood pressure). In some cases of hypertension a cause can be determined such as renal artery stenosis, but the underlying cause of hypertension is unknown in over 90% of cases. Environmental contaminants such as polychlorinated biphenyls have been found to be associated with both hypertension and diabetes.

Polychlorinated biphenyls (PCBs) were manufactured in the USA during a fifty year period that ended in 1977 when their production was banned due to concerns about adverse health effects and environmental persistence.⁴ PCBs are synthetic compounds that were used in a wide variety of industrial and commercial applications ranging from electrical capacitors to floor finish. There are no known natural sources of PCBs and they are considered persistent organic pollutants (POPs). There are 209 possible PCB congeners which are categorized based on structural properties such as the number of chlorine atoms in the compound. A common classification divides PCBs into dioxin-like and nondioxin-like based on their structural and toxicological similarity with the dioxin molecule.

Historically, PCBs were released into the environment during the manufacturing process, from accidental spills or leaks associated with the end-use products, and when PCB containing products were disposed of in landfills. PCB release into the environment continues today from improperly maintained hazardous waste sites, leaks from PCB containing devices, improper disposal of materials in landfills and from municipal waste incinerators. PCBs are found all over the world due to their capacity for long range dispersal and due to their environmental persistence, PCBs will remain a health concern for many years to come. Human exposure is mainly from consumption of PCB-containing foods and from inhalation of contaminated air. Fish (especially when taken from lakes or rivers with high levels of PCBs), meat and dairy products are the main dietary sources for PCBs. This paper will review the evidence supporting an



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association between serum polychlorinated biphenyl levels and both diabetes and hypertension.

II. Relative importance of PCBs and literature search strategy

The term, persistent organic pollutants, refers to several classes of chemicals including dioxins, furans, PCBs and organochlorine pesticides. These chemicals are lipophilic and migrate together making it difficult to distinguish actions of each. In many studies, elevated levels of organochlorine pesticides show stronger associations with diabetes than do PCBs. The subject of pesticide exposure and diabetes has been reviewed by Everett and Matheson,⁵ and a follow-up article published by the same authors.⁶

We conducted two literature searches in October 2010 to identify articles pertinent to our critical review. The first search used Ovid Medline. Search terms were “polychlorinated biphenyls or PCB or persistent organic pollutants” and “diabetes or hypertension.” The second search used ISI Web of Science and was a cited reference search. Articles that cited Lee *et al.*⁷ and mentioned polychlorinated biphenyls were selected. For both searches only articles that included data on PCBs were selected. Articles on PCB poisoning were excluded from our critical review. We also reviewed references for the identified articles to find pertinent literature. For information on potential mechanisms by which PCBs may contribute to diabetes, we included information on dioxins (cited by Carpenter⁸ and Wang *et al.*⁹) because of their similarity to dioxin-like PCBs.

III. Diabetes

IIIA. Associations of PCBs with common diabetes risk factors

The National Health and Nutrition Examination Survey (NHANES) 1999–2002, conducted in the USA, has been used for a number of pertinent cross-sectional studies. One study of 721 non-diabetic NHANES participants focused on the association of POPs in blood with metabolic syndrome.¹⁰ Several compounds were evaluated including four dioxin-like PCBs (74, 118, 126, and 169) and 5 non-dioxin-like PCBs (138, 153, 170, 180, and 187). These congeners were examined using multiple comparisons that included: association of PCB by class with metabolic syndrome; association of PCB by class with individual components of the metabolic syndrome; and association of individual congeners with metabolic syndrome. Non-detectable lipid-adjusted PCBs were used as the reference categories and detectable PCBs divided into quartiles.

When examined as a class, both dioxin-like and non-dioxin-like PCBs showed an association with metabolic syndrome. However, neither displayed a linear dose–response relationship. The dioxin-like PCBs show an increasing association to the third quartile where a plateau is reached, while non-dioxin-like PCBs showed a significant inverted U-shaped association. When individual non-dioxin-like PCBs were examined, the inverted U-shaped association was seen in each of them. Some dioxin-like PCBs, but not non-dioxin-like PCBs, were found to be associated with central obesity, elevated triglycerides, impaired fasting glucose, elevated blood pressure and/or low HDL. This study found a positive association between metabolic syndrome and

both dioxin-like and non-dioxin-like PCBs with non-linear dose–response trajectories.

Uemura *et al.*¹¹ studied the association of dioxins, furans and dioxin-like PCBs with metabolic syndrome among a cross-section of the general population of Japan. All of the POPs tested had toxic equivalent factors¹² which were used to calculate toxic equivalents (TEQs) for each class of chemical analyzed. Dioxin-like PCBs included non-*ortho*-substituted PCBs 77, 81, 126, and 169, and mono-*ortho*-substituted PCBs 105, 114, 118, 123, 156, 157, 167, and 189. For the definition of metabolic syndrome this study used body mass index $\geq 25 \text{ kg m}^{-2}$ instead of waist circumference, and glycohemoglobin (HbA1c) $\geq 5.6\%$ instead of fasting glucose. The other components of metabolic syndrome were the same as described previously. There were 1374 participants, 65 had diabetes either doctor diagnosed or undiagnosed with HbA1c $>6.1\%$.¹³ Of the 65 participants with diagnosed or undiagnosed diabetes, 38 had metabolic syndrome. For most of the analyses the diabetics were included, making the study representative of Japan. When the analyses were limited to the 1309 non-diabetics there were 122 subjects with metabolic syndrome. Dioxin TEQs, furan TEQs, dioxin-like PCBs TEQs and total TEQs were all associated with metabolic syndrome in age, gender, smoking habit, drinking habit, regional block, residential area (urban, farming village, or fishing village), and survey year adjusted analyses among non-diabetic participants. Dioxin-like PCB ≥ 12.87 TEQs had an odds ratio of 7.3 (95% CI 2.9–20) compared to referent group with <4.28 TEQs in an adjusted logistic regression. In this study, there were increasing odds ratios as one progressed from the first quartile to the fourth quartile of dioxin-like PCBs.

IIIB. Associations of PCBs with insulin resistance and insulin secretion

The NHANES 1999–2002 has been used to study the association of PCBs and insulin resistance in 749 non-diabetic participants.¹⁴ Insulin resistance precedes the development of diabetes, but the degree of insulin resistance associated with diabetes varies from person to person. A simple measure of insulin resistance which is based on fasting insulin and fasting glucose is the homeostasis model assessment (HOMA-IR). HOMA-IR is calculated by the following equation: (fasting insulin [mU l^{-1}] \times fasting glucose [mmol l^{-1}]/22.5). The same 9 lipid-adjusted PCBs evaluated for metabolic syndrome⁵ were tested for associations with insulin resistance. Multiple comparisons were performed that included association of PCBs by class with insulin resistance (HOMA-IR) and individual PCB congeners with insulin resistance. There were no significant associations with dioxin-like or non-dioxin-like PCBs, and 7 of the individual congeners with HOMA-IR. Only the non-dioxin-like PCBs 170 and 187 were associated with insulin resistance (HOMA-IR $>90^{\text{th}}$ percentile).

In a study of 692 Inuits living in Greenland, 3 dioxin-like PCB congeners (105, 118, and 156) and 10 non-dioxin-like PCB congeners (28, 52, 99, 101, 128, 138, 153, 163, 170, and 180) were evaluated for association with impaired glucose tolerance, insulin resistance and homeostasis model assessment of β -cell function (HOMA-B). A 75 g oral glucose tolerance test (OGTT) was used to evaluate impaired glucose tolerance (two-hour glucose levels of 7.8 to 11.0 mmol l^{-1}) and HOMA-B, was calculated by the

equation: (fasting insulin [pmol l⁻¹] × 3.33)/(fasting glucose [mmol l⁻¹] – 3.5). Statistical analyses were adjusted for age, sex, ethnicity, waist circumference, physical activity, alcohol consumption, smoking, and education level. No association with insulin resistance markers or impaired glucose tolerance was found, but a significant negative association with indices of insulin secretion, that is stimulated insulin, and HOMA-B was found. The results of this study suggest PCBs affect insulin secretion rather than the development of insulin resistance.¹⁵

IIIC. Cross-sectional studies of PCBs and type 2 diabetes

IIIC.1. Studies of *ortho*-substituted PCBs and pesticides. Here we will review the literature produced in the last ten years on the association of PCBs with type 2 diabetes. Relevant reviews have been published by Carpenter^{8,16} and Wang *et al.*,⁹ and Table 1 summarizes the cross-sectional and longitudinal studies reviewed here. Mono-*ortho*-substituted and non-*ortho*-substituted PCB congeners have been assigned dioxin toxic equivalency factors (TEFs) ranging from 0.1 for PCB 126 to 0.00003 for mono-*ortho*-substituted PCBs relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).¹⁷ Dioxins such as TCDD, and dioxin-like PCBs, bind aryl hydrocarbon (Ah) receptors that in turn antagonize peroxisome proliferator-activated receptors (PPAR) and affect glucose homeostasis. Early studies looking at TCDD were reviewed by Longnecker and Daniels.¹⁸ None of the studies “showing an unequivocally positive association, (were) very convincing on close examination.”

Glynn *et al.*¹⁹ conducted a study including 205 elderly Swedish women, 7 of whom had diabetes. Individual PCB congeners 105, 118, 138, 153, 156, 167, and 180 were evaluated in this study with no evaluation of PCBs as a class. The mean age of participants in this study was 62.8 ± 7.4. None of the congeners studied were significantly associated with diabetes in age, BMI, weight change, and region adjusted analyses. The results of this study should be considered hypothesis generating.

Rylander *et al.*²⁰ reported on 380 Swedish fishermen and their wives with 22 having type 2 diabetes. Only PCB congener 153 and *p,p'*-DDE were measured. In unadjusted analyses, an increase of 100 ng g⁻¹ PCB 153 had an odds ratio of 1.16 (95% CI 1.03–1.32) overall, and 1.20 (95% CI 1.04–1.39) for men. The odds ratio for diabetes was not significant for women. Adjustment for gender, age and BMI at 25 years of age changed the odds ratios only slightly. This study found diabetics overall to have significantly higher levels of PCB 153 compared to non-diabetics; however, there was a gender difference as this trend was not seen among women. The results of this study should also be considered hypothesis generating.

In a follow-up study, Rignell-Hydbom *et al.*²¹ studied 543 Swedish fishermen's wives for an association between diabetes and PCB 153, and *p,p'*-DDE. In this study, 15 participants had type 2 diabetes. In unadjusted analyses, increasing quartiles of PCB 153 had 0.7%, 0%, 5.5% and 5.4% type 2 diabetes (*p* for trend = 0.004). However, in age adjusted analysis using 100 ng g⁻¹ increases in concentration, there was not a significant association with PCB 153 and diabetes. This study also found that there was not an association between the time since diagnosis of diabetes and serum concentrations of either POP studied. This study should be considered a hypothesis generating investigation.

Three additional studies have been done using the NHANES 1999–2002, this time to evaluate the association of PCBs with type 2 diabetes.^{7,22,23} In a study by Lee *et al.*,⁷ 2016 participants in the NHANES 1999–2002 were evaluated for an association of 6 different POPs including non-dioxin-like PCB congener 153 with diabetes (diagnosed and undiagnosed). Undiagnosed diabetes was determined by glucose concentration in serum, ≥7.0 mmol l⁻¹ in fasting participants and ≥11.1 mmol l⁻¹ in non-fasting participants. In an age, gender, race/ethnicity, poverty income ratio, BMI, and waist circumference adjusted logistic regression; PCB 153 was associated with diabetes.

Philibert *et al.*²⁴ studied 101 participants in a First Nation Community in Northern Ontario, Canada for associations between diabetes and several PCBs and *p,p'*-DDE. Aroclor 1254 (PCB congeners 99, 118 and 153), and Aroclor 1260 (PCB congeners 99, 153 and 180) were assessed along with individual PCB congeners (74, 99, 118, 153, 138, 187, 180, and 170) and the sum of PCB congeners. Covariates included gender, age, place of birth, current smoking status, and total serum lipids; but not BMI. Both wet weight and lipid-standardized PCBs were tested. PCB 74, PCB 153, Aroclor 1254, Aroclor 1260, and total sum of PCB congeners were associated with diagnosed diabetes. Among this population, an important source of PCB exposure is from fish consumption, yet consumption of trout and white fish was negatively associated with diabetes.

Turyk *et al.*²⁵ conducted a cross-sectional study to examine the association of diabetes and several POPs among a group of 503 Great Lakes sport fish consumers who were surveyed and had blood collected in 2004–2005. Sum of PCB congeners 74, 99, 118, 146, 180, 194, 201, 206, 132/153/105, 138/163, 170/190, 182/187, and 196/203 was analyzed along with sum of dioxin-like PCBs 118 and 167. Undiagnosed diabetes was assessed using glycohemoglobin (HbA1c) >6.3% and HbA1c >6.1%. The sum of PCB congeners was not associated with diagnosed diabetes or with diagnosed diabetes plus undiagnosed diabetes (either definition) in age, BMI, gender, triglycerides and total cholesterol adjusted analyses. The sum of dioxin-like PCBs was associated with diagnosed diabetes plus those with HbA1c >6.3% in age, BMI, gender, triglycerides and total cholesterol adjusted analyses, but not when further adjusted for DDE (*p,p'*-diphenyldichloroethene).

Ukropec *et al.*²⁶ studied the association of 15 PCBs and 4 pesticides and pesticide metabolites with prediabetes and diabetes among 2047 adults living in a heavily polluted area of Eastern Slovakia. Eight mono-*ortho*-substituted PCBs with toxic equivalent factors (PCB 105, 114, 118, 123, 156/171, 157, 167, and 189) and 7 other PCBs (28, 52, 101, 138/163, 153, 170 and 180) were evaluated. Of the 2047 participants, all had a fasting plasma glucose and 1220 underwent an oral glucose tolerance test (OGTT). Prediabetes was defined as impaired fasting glucose (fasting plasma glucose >5.6 but <7.0 mmol l⁻¹) and/or impaired glucose tolerance (2 hour glucose >7.8 but <11.1 mmol l⁻¹). Diabetes was defined as fasting plasma glucose >7.0 mmol l⁻¹ or 2 hour glucose >11.1 mmol l⁻¹. The fifth quintile of PCBs (≥2330 ng g lipids⁻¹) had odds ratios of 2.74 (95% CI 1.92–3.90) and 1.86 (95% CI 1.09–3.17) compared to the first quintile of PCBs (148–627 ng g lipids⁻¹) for prediabetes and diabetes, respectively. Stepwise logistic regressions for prediabetes and diabetes showed age, gender and body mass index were

Table 1 Epidemiology of PCBs and metabolic syndrome, insulin resistance, diabetes and hypertension

Article	Substances	Total <i>N</i> (disease)	PCB positive associations
Lee <i>et al.</i> , ⁷ <i>Diabetes Care</i> , 2006	PCB 153, dioxins (HpCDD, OCDD), oxychlorodane, <i>trans</i> -nonachlor, DDE	2016, 217 diabetics (diagnosed and undiagnosed).	Diabetes and PCB 153.
Lee <i>et al.</i> , ¹⁰ <i>Diabetologia</i> , 2007	PCDDs, PCDFs, dioxin-like PCBs (4), non-dioxin-like PCBs (5), organochlorine pesticides	721, 175 metabolic syndrome.	Metabolic syndrome and dioxin-like PCBs (class) and individual dioxin-like PCB congeners 74, 118, 126, non-dioxin-like PCBs (class) and individual non-dioxin-like PCB congeners 153, 170, 180, 187.
Uemura <i>et al.</i> , ¹¹ <i>Environmental Health Perspectives</i> , 2009	PCDDs, PCDFs, dioxin-like PCBs (12), used TEQs	1374, 160 metabolic syndrome includes 38 diabetics (diagnosed and undiagnosed).	Metabolic syndrome and PCB TEQs, total TEQs.
Lee <i>et al.</i> , ¹⁴ <i>Diabetes Care</i> , 2007	PCDDs, PCDFs, dioxin-like PCBs (4), non-dioxin-like PCBs (5), organochlorines	749, HOMA-IR.	HOMA-IR and individual non-dioxin-like PCB congeners 170, 187.
Jorgensen <i>et al.</i> , ¹⁵ <i>Diabetologia</i> , 2008	Dioxin-like PCBs (3), non-dioxin-like PCBs (10), organochlorines	692 Greenland Inuits-eat marine mammals, (HOMA-IR with diabetics excluded) (HOMA-B with diabetics excluded) (diabetes 10.3%) (IGT 10.5%).	HOMA-B and non-dioxin-like PCBs, dioxin-like PCBs.
Glynn <i>et al.</i> , ¹⁹ <i>Environmental Health Perspectives</i> , 2003	PCBs (7), organochlorines/metabolites	205 elderly Swedish women, 7 diabetics (diagnosed).	No association with PCBs and diabetes. Positive association with PCBs and age.
Rylander <i>et al.</i> , ²⁰ <i>Environmental Health: A Global Access Science Source</i> , 2005	PCB 153, <i>p,p'</i> -DDE	380 Swedish fishermen and their wives, 22 diabetics (diagnosed).	Diabetes and PCB 153 overall, PCB 153 and men, NOT PCB 153 and women, time since diabetes diagnosis and PCB 153, negative for men (sig.) not sig. for women.
Rignell-Hydbom <i>et al.</i> , ²¹ <i>Human and Experimental Toxicology</i> , 2007	PCB 153, <i>p,p'</i> -DDE	544 Swedish women, 16 diabetics (diagnosed).	No associations in adjusted models.
Lee <i>et al.</i> , ²² <i>Diabetes Care</i> , 2007	PCDDs, PCDFs, dioxin-like PCBs (4), non-dioxin-like PCBs (5), organochlorine pesticides	1721, 179 diabetics (diagnosed and undiagnosed).	Diabetes and dioxin-like PCBs.
Everett <i>et al.</i> , ²³ <i>Environmental Research</i> , 2007	HxCDD, PCB 126, <i>p,p'</i> -DDT	1830, 226 diabetics (diagnosed and undiagnosed).	Diabetes and PCB 126.
Philibert <i>et al.</i> , ²⁴ <i>International Journal of Environmental Research and Public Health</i> , 2009	PCBs (8), <i>p,p'</i> -DDE	101, 25 diabetics (diagnosed).	Diabetes and PCB congeners 74, 153.
Turyk <i>et al.</i> , ²⁵ <i>Chemosphere</i> , 2009	PBDEs, PCBs (13), dioxin-like PCBs (2), <i>p,p'</i> -DDE	503, 61 diabetics, 11 undiagnosed.	Diabetes and dioxin-like PCBs (not when adjusted for DDE).
Ukropec <i>et al.</i> , ²⁶ <i>Diabetologia</i> , 2010	PCBs (15), <i>p,p'</i> -DDE, <i>p,p'</i> -DDT, HCB, β -HCH	2047, 296 diabetics (32% undiagnosed), 973 pre-diabetics.	Pre-diabetes and PCBs, diabetes and PCBs.
Fierens <i>et al.</i> , ²⁷ <i>Biomarkers</i> , 2003	PCDDs, PCDFs, PCBs (4 coplanar and 12 markers)	257 subjects living near industrial facilities. 9 diabetics (diagnosed).	Diabetes and coplanar PCB TEQs, 12 PCB markers.
Codru <i>et al.</i> , ²⁸ <i>Environmental Health Perspectives</i> , 2007	DDE, HCB, PCBs (101), mirex	352, 71 diabetics (diagnosed and undiagnosed).	Diabetes and total PCBs (wet weight), PCB 153 (wet weight), PCB 74 (wet weight), not lipid adjusted.
Uemura <i>et al.</i> , ²⁹ <i>Environmental Research</i> , 2008	PCDDs, PCDFs, dioxin-like PCBs (12)	1374, 65 diabetics (diagnosed and undiagnosed).	Diabetes and total dioxin-like PCB TEQ.
Patel <i>et al.</i> , ³⁰ <i>PLoS One</i> , 2010	266 environmental factors	Minimum of 503 subjects per analysis. Used fasting glucose alone to determine diabetes.	Diabetes and non-dioxin-like PCB 170.
Chen <i>et al.</i> , ³¹ <i>Environmental Research</i> , 2008	PCDDs, PCDFs, PCBs (12)	40 pregnant women, insulin sensitivity.	Insulin sensitivity and total PCBs TEQ, PCBs 123, 126 and 169 using HOMA-IR, not using QUICKI.
Longnecker <i>et al.</i> , ³² <i>Diabetes Care</i> , 2001	PCBs (total)	2201 pregnant women with blood collected 1959–1966, 44 diabetics—mostly type 1.	Diabetes and total PCBs.
Vasiliu <i>et al.</i> , ³³ <i>Epidemiology</i> , 2006	PBBs, PCBs (Aroclor 1016, 1254, and 1260)	1384, 180 incident diabetes cases.	Incident diabetes and PCBs (wet weight) in women, not in men.
Turyk <i>et al.</i> , ³⁵ <i>Environmental Health Perspectives</i> , 2009	PBDE, PCBs (13), DDE	471, 36 incident diabetes cases.	No associations in adjusted models.
Rignell-Hydbom <i>et al.</i> , ³⁶ <i>PLoS One</i> , 2009	PCB 153, <i>p,p'</i> -DDE	742, 371 incident diabetes cases, case control study.	No associations in adjusted models.
Lee <i>et al.</i> , ³⁷ <i>Environmental Health Perspectives</i> , 2010	PCBs (22), organochlorines, PBB	180, 90 incident diabetes cases, Case control study.	No association at high levels of PCBs.

Table 1 (Contd.)

Article	Substances	Total <i>N</i> (disease)	PCB positive associations
Kreiss <i>et al.</i> , ⁵² <i>JAMA, the Journal of the American Medical Association</i> , 1981	PCBs (total)	458 subjects living in Triana, AL, USA, 191 with hypertension by blood pressure.	Log (PCBs) associated with log (diastolic blood pressure), but not with log (systolic blood pressure) in fully adjusted analyses.
Everett <i>et al.</i> , ⁵³ <i>Environmental Research</i> , 2008	Dioxin-like PCBs (5), non-dioxin-like PCBs (6)	2074 subjects, 890 hypertension by doctor diagnosis or by blood pressure.	3 dioxin-like PCBs and 4 non-dioxin-like PCBs associated with hypertension.
Everett <i>et al.</i> , ⁵⁴ <i>Environmental Research</i> , 2008	Dioxin-like PCBs (5), non-dioxin-like PCBs (6)	3326 subjects, 1377 hypertension by doctor diagnosis or by blood pressure.	3 dioxin-like PCBs associated with hypertension.
Ha <i>et al.</i> , ⁵⁵ <i>Journal of Human Hypertension</i> , 2009	PCDDs (3), PCDFs (3), dioxin-like PCBs (5), non-dioxin-like PCBs (6), organochlorine pesticides (4)	524 subjects, diagnosed hypertension or diabetes excluded. 123 with hypertension by blood pressure.	PCB 156, in men, associated with newly diagnosed hypertension. Other dioxin-like PCBs and non-dioxin-like PCBs not associated with newly diagnosed hypertension.
Goncharov <i>et al.</i> , ⁵⁶ <i>Journal of Hypertension</i> , 2010	PCBs (35)	365 subjects on anti-hypertension medication. 394 not on medication, of which 72 had hypertension by blood pressure. All living in Anniston, AL, USA.	Total PCBs associated with clinical hypertension, diastolic and systolic blood pressure among those not on medications.
Ha <i>et al.</i> , ⁵⁷ <i>Environmental Health Perspectives</i> , 2007	PCDDs (3), PCDFs (3), dioxin-like PCBs (5), non-dioxin-like PCBs (6), organochlorine pesticides (4)	889 subjects, persons with diabetes excluded. 108 with prevalent self-reported cardiovascular disease.	Dioxin-like PCBs and non-dioxin-like PCBs associated with prevalent cardiovascular disease, among women, but not men.

significant factors. For prediabetes, PCBs were also a significant factor ($p < 0.001$) and for diabetes *p,p'*-DDT was also a significant factor ($p < 0.0049$). These analyses showed a strong association of PCBs with prediabetes. The concentrations of PCBs in the this study were considerably higher than those reported for the NHANES²² and some persons in the referent group of the study by Ukropec *et al.* would be considered a part of an elevated PCB group in the NHANES.

IIIC.2. Studies including non-ortho-substituted or coplanar PCBs. In a population-based study in Belgium, 257 participants were assessed, including 9 with diabetes.²⁷ This was a case-control study that recruited subjects from areas immediately surrounding sites producing PCB and/or dioxin emissions in addition to some from areas with no known emission source. Since there were only 9 persons with diabetes included, the results of this study should be considered hypothesis generating. Four dioxin-like coplanar PCB congeners 77, 81, 126 and 169 and twelve PCB markers 3, 8, 28, 52, 101, 118, 138, 153, 180, 194, 206 and 209 were evaluated. PCB concentrations were expressed as pg TEQ g fat⁻¹ for coplanar PCBs and as ng g⁻¹ for the 12 PCB markers. In age, BMI, fat intake, fish consumption, and place of residence adjusted logistic regressions, coplanar PCBs above the 90th percentile, and 12 PCB markers above the 90th percentile had odds ratios for diabetes of 13.3 (95% CI 3.31–53.2) and 7.58 (95% CI 1.58–36.3), respectively. This case-control study found an association between coplanar PCBs and a group of 12 PCB congeners with diabetes.

In a follow-up study, Lee *et al.*²² studied 1721 persons and 19 different POPs in the NHANES 1999–2002. Dioxin-like PCB congeners 74, 118, 126, 156 and non-dioxin-like PCB congeners 138, 153, 170, 180, and 187 were evaluated for their association with diabetes (diagnosed and undiagnosed). Undiagnosed

diabetes was determined by serum glucose concentration ≥ 7.0 mmol l⁻¹ in fasting participants and ≥ 11.1 mmol l⁻¹ in non-fasting participants. In age, gender, race/ethnicity, poverty income ratio, BMI, and waist circumference adjusted logistic regressions; all 9 PCB congeners were associated with diabetes. The summed ranks of the 4 dioxin-like PCB congeners, the 5 non-dioxin-like PCB congeners, 3 polychlorinated dibenzo-*p*-dioxins, 3 polychlorinated dibenzofurans, and 4 organochlorine pesticides were also tested in a single logistic regression. Summed ranks $\geq 75^{\text{th}}$ percentile for the dioxin-like PCB congeners had an odds ratio of 15.7 (95% CI 3.4–71.2) compared to dioxin-like PCB congener summed ranks $< 25^{\text{th}}$ percentile. Summed ranks $\geq 75^{\text{th}}$ percentile for the organochlorine pesticides had an odds ratio of 6.8 (95% CI 2.2–21.3) compared to values $< 25^{\text{th}}$ percentile, and summed ranks $\geq 75^{\text{th}}$ percentile for polychlorinated dibenzofurans had an odds ratio of 2.2 (95% CI 1.1–4.7) compared to values $< 25^{\text{th}}$ percentile. The non-dioxin-like PCB congeners and polychlorinated dibenzo-*p*-dioxins were not associated with diabetes in the combined logistic regression.

Everett *et al.*²³ evaluated 1830–2090 participants in the NHANES 1999–2002 for an association between diabetes and 3 different POPs including PCB congener 126. The association of dioxin-like PCB congener 126 with diagnosed diabetes, undiagnosed diabetes (HbA1c $> 6.1\%$) and total diabetes (diagnosed plus undiagnosed) was assessed in age, gender, race, country of birth, education, poverty income ratio, BMI, waist circumference, and physical activity adjusted logistic regressions. Lipid-standardized PCB 126 was associated with diagnosed diabetes, undiagnosed diabetes (non-fasting glycohemoglobin [HbA1c] $> 6.1\%$), and total diabetes.

When the logistic regression for total diabetes was also adjusted for DDT and a dibenzo-*p*-dioxin the odds ratio for total diabetes was 2.57 (95% CI 1.33–4.95) for PCB 126, > 83.8 pg g

lipid⁻¹ compared to PCB 126 ≤ 31.2 pg g lipid⁻¹. PCB 126 remained significantly associated with total diabetes when participants with decreased liver function and decreased kidney function, those most likely to have impaired metabolism and excretion, were removed from the analysis. PCB 126 was also not correlated with the number of years since the diagnosis of diabetes was made (undiagnosed diabetes = 0 years) suggesting metabolism and excretion of PCB 126 were not increasingly impaired over time in participants with diabetes. However, information on time since diagnosis of diabetes is often not precise or reliable indicator as many diabetes cases go undiagnosed for a long period of time.

Codru *et al.*²⁸ conducted a study that included 352 adult Native-American (Mohawk) participants from New York, USA, with a 20.2% prevalence of diabetes. A total of 101 PCB congeners were evaluated for (see Table 1 in ref. 8) relationships with diabetes using tertiles of several groupings of PCB congeners and adjusting for age, gender, BMI, and smoking. Wet-weight total PCBs, PCB 153 and PCB 74 were significantly associated with diagnosed plus undiagnosed (fasting glucose ≥ 7.0 mmol l⁻¹) diabetes in gender, age, BMI, lifetime smoking status, and total lipid concentration adjusted logistic regressions. When further adjusted for DDE, hexachlorobenzene and mirex only wet-weight PCB 74 was significantly associated with diabetes. Lipid-standardized total PCBs, PCB 153 and PCB 74 were not associated with diabetes in fully adjusted analyses.

In a population-based study, 1374 participants from throughout Japan were evaluated for an association between several POPs and diabetes.²⁹ There were 65 subjects who had diagnosed or undiagnosed (glycohemoglobin [HbA1c] > 6.1%) diabetes. Dioxin-like PCB congeners 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189 were expressed as pg TEQ g lipid⁻¹. Compared to the first and second quartile of dioxin-like PCBs, the third quartile had an odds ratio of 3.07 (95% CI 1.16–8.81) and the fourth quartile had an odds ratio of 6.82 (95% CI 2.59–20.1) for diagnosed plus undiagnosed diabetes in age, gender, log (BMI), smoking, regional block, residential area, and survey year adjusted logistic regression. log (HbA1c) was also correlated with log (dioxin-like PCBs).

Patel *et al.*³⁰ investigated 266 environmental factors using the NHANES 1999–2006. Only participants who were fasting were included in their study, and fasting glucose ≥ 7.0 mmol l⁻¹ was used to identify those with diabetes. Persons with diagnosed diabetes and fasting glucose < 7.0 mmol l⁻¹ were characterized as not having diabetes. In logistic regression models adjusted for age, gender, BMI, ethnicity and socioeconomic status, non-dioxin-like PCB 170, heptachlor epoxide, γ -tocopherol (a form of vitamin E), and β -carotenes were significantly associated with diabetes. One standard deviation of change of PCB 170 had an odds ratio of 2.2 ($p < 0.001$) for fasting glucose ≥ 7.0 mmol l⁻¹.

The majority of these cross-sectional studies show associations between PCBs and diabetes. Perhaps the most compelling are Fierens *et al.*²⁷ (a hypothesis generating study), Everett *et al.*,²³ Lee *et al.*,²² Uemura *et al.*²⁹ and Philibert *et al.*²⁴ These studies show associations between dioxin-like PCBs and diabetes, and Ukropec *et al.*²⁶ show an association of PCBs with prediabetes. Notably, Glynn *et al.*¹⁹ and Codru *et al.*²⁸ did not find associations between PCB 153 and diabetes in fully adjusted analyses. Turyk *et al.*²⁵ found no association between PCBs and diabetes

and Lee *et al.*²² found associations for individual non-dioxin-like PCBs, but no association for non-dioxin-like PCBs as a class. Statistical adjustment for pesticides or pesticide metabolites appears to negate any association of non-dioxin-like PCBs and diabetes.^{22,28}

IIID. Studies of insulin sensitivity and diabetes among pregnant women

In Taiwan, 40 pregnant women living in an area with high levels of POP exposure were tested to determine associations between insulin sensitivity and POPs. Multiple comparisons were made in this study using insulin sensitivity based on the inverse of HOMA-IR and quantitative insulin-sensitivity check index (QUICKI) methods; toxic equivalents (TEQ) and concentrations of POPs were used. Analysis was performed using PCBs as a class and individual PCB congeners 81, 77, 123, 118, 114, 105, 126, 167, 156, 157, 169, 189. Toxic equivalents of PCBs 123, 126 and 169, and sum of PCBs TEQ were negatively associated with insulin sensitivity in age and pre-pregnancy BMI adjusted correlations using inverse HOMA-IR, but not with the QUICKI method.³¹ Hence, this small study supports the theory that PCBs are associated with decreased insulin sensitivity.

Longnecker *et al.*³² published a study on 2245 pregnant women of whom 44 had diabetes (primarily type 1). This study examined PCBs overall and does not include analysis of individual congeners. Mean age 28 ± 7 for diabetic subjects and 24 ± 6 for control subjects. Total PCBs ≥ 5.00 $\mu\text{g l}^{-1}$ had an adjusted odds ratio of 5.1 (95% CI 1.9–13.8) compared to total PCBs < 2.50 $\mu\text{g l}^{-1}$. Logistic regressions were adjusted for age, socioeconomic index, serum triglycerides, serum cholesterol and race. Further adjustment for prepregnancy BMI had no appreciable effect on the association. This study showed a significant association between diabetes and PCB levels in a specific population.

IIIE. Longitudinal studies of PCBs and type 2 diabetes

While cross-sectional studies can show associations, they do not prove that PCBs cause type 2 diabetes. Longitudinal studies, however, bring us closer to showing cause and effect, particularly in studies with long follow-up times. The Michigan polybrominated biphenyls (PBB) cohort was established in 1976 and included 1384 participants with 25 years of follow-up. Three different standards were used: Aroclor 1016, 1254, and 1260. Serum PCBs (wet weight) were associated (elevated incidence density ratios) with incident diabetes among women, but not among men. Covariates were polybrominated biphenyls, age, BMI, smoking status, and alcohol consumption.³³

In a commentary on the Michigan PBB cohort study, Longnecker³⁴ said investigators need to consider “differences in metabolism and excretion.” Associations of PCBs with diabetes may be due to decreased excretion in diabetics. As described above, authors such as Everett *et al.*²³ have attempted to address the issue of decreased excretion in persons with diabetes and have not found evidence supporting Longnecker’s view.

Conducting an additional study of the Great Lakes sport fish consumers, Turyk,³⁵ followed 471 participants from 1994–1995 to 2004–2005. The sum of PCB congeners 74, 99, 118, 146, 180, 194, 201, 206, 132/153, 138/163, 170/190, 182/187, and 196/20 was

analyzed along with PCB 118 by itself. PCB 118 was the only dioxin-like PCB congener included in the study (these authors considered PCB 74 to be non-dioxin-like). The sum of the PCBs and PCB 118 was not associated with incident diabetes in age, gender and BMI adjusted analyses. In 289 participants with biomarker analyses in both 1994–1995 and 2001–2005 there was no difference in the unadjusted and adjusted geometric mean PCB 132/153 annual percent change between those with diabetes at any time during the study, and those without diabetes.

Rignell-Hydbom *et al.*³⁶ studied the association of PCB 153 and *p,p'*-DDE with type 2 diabetes among Swedish women 50–59 years old at baseline. This was a case-control study with 371 women who developed diabetes matched with 371 controls. Serum concentrations of PCB 153 and *p,p'*-DDE were used rather than lipid adjusted values. Criteria for matching cases and controls were similar age, calendar year, body mass index and whether or not they had any features of the metabolic syndrome. A majority of the cases (56%) were diagnosed with diabetes within one year after baseline examination. When the 742 cases and controls were evaluated, PCB 153 and *p,p'*-DDE were not associated with development of diabetes. When the analyses were restricted to the 39 cases diagnosed more than 7 years after baseline and the 39 controls matched to these persons *p,p'*-DDE, but not PCB 153, was associated with development of diabetes. DDE is a metabolite of DDT, and these results suggest that DDT is related to type 2 diabetes, but that PCBs, as indicated by PCB 153, are not.

Lee *et al.*³⁷ conducted a longitudinal case-control study using the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Ninety cases, diabetes-free in 1987–1988 that developed diabetes by 2005–2006 were matched with 90 controls that remained diabetes-free. PCB congeners 74, 87, 99, 105, 118, 146, 153, 156, 157, 138/158, 167, 170, 178, 180, 183, 187, 194, 195, 199, 196/203, 206, and 209 were measured in sera. In age, gender, race, BMI, triglyceride, and total cholesterol adjusted logistic regressions, only the second quartiles of PCB congeners 74, 178, 180, and 187 were significantly associated with incident diabetes. The third and fourth quartiles of all of the PCB congeners were not significantly associated with incident diabetes.

The longitudinal studies of PCBs and incident diabetes do not support the results of the cross-sectional studies. Vasiliu *et al.*³³ found relationships of PCBs and diabetes among women, but not men, whereas Turyk *et al.*,³⁵ Lee *et al.*,³⁷ and Rignell-Hydbom *et al.*³⁶ found elevated PCBs to not to be associated with incident diabetes. More longitudinal studies are needed to either confirm the negative findings reported to date, or to support the positive results of the cross-sectional studies.

IIIF. Potential mechanisms by which PCBs may contribute to diabetes

While much research points to the relationships between PCB exposure and diabetes, the mechanism underlying this connection is not well understood. We can turn to animal studies to give us some insight into potential mechanisms for how PCBs may contribute to the development or worsening of diabetes, as well as some *in vitro* human cell studies. Much toxicology research has been done with the dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and many PCBs are dioxin-like compounds in terms of

their toxicology profiles. Hence, we have included mechanism studies with TCDD in addition to four studies with results specific to PCBs.

One potential mechanism is the effect on regulation and metabolism of glucose and insulin. Enan and Matsumura showed that the dioxin, TCDD, reduces glucose uptake in various animal models including mice, rats and guinea pigs.³⁸ The effect was likely on glucose transport where a dose-dependent reduction was seen. An important gene and protein in glucose regulation is the GLUT-4 protein. GLUT-4 is a glucose transporter protein in muscle and adipose cells that functions in the insulin mediated transport of glucose into cells. Mice studies have shown that the lack of GLUT-4 resulted in insulin resistance.³⁹ Olsen *et al.* showed that TCDD, and the PCBs 3,3',4,4' tetrachlorobiphenyl (PCB 77) and 2,2',5,5' tetrachlorobiphenyl (PCB 52) reduced functional GLUT-4 in preadipocyte cells lines by binding to the aryl hydrocarbon (Ah) receptors.⁴⁰

TCDD administered to rats inhibited insulin-like growth factor 1 (IGF-1), a compound important in glucose metabolism.⁴¹ In another study looking at insulin-like growth factor binding protein-1 (IGFBP-1), a protein involved in glucose homeostasis, TCDD induced IGFBP-1 mRNA in human hepatocytes which may in part account for its effects on glucose metabolism and regulation.⁴² Additionally, in human adipose tissue of Vietnam veterans exposed to dioxin, GLUT-4 to nuclear transcription factor kappa B (NFκB) ratio was a marker for diabetes.⁴³ The proposed mechanism is that dioxin upregulates tumor necrosis factor alpha (TNF-α) which activates NFκB. This increased NFκB acts to down-regulates GLUT-4 causing its effects on glucose.⁴⁴

Other animal models have shown that PCBs Aroclor 1254, 2,2',4,4'-tetrachlorobiphenyl (PCB 47) and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) induce insulin release from rat insulinoma cells⁴⁵ and this release of insulin is due in part to the increase in intracellular free calcium caused by PCB exposure.⁴⁶ This PCB stimulated increase in insulin production may play a role in the development of insulin resistance. Ruzzin *et al.*⁴⁷ studied the development of insulin resistance in adult male rats exposed to crude salmon oil containing persistent organic pollutants. Insulin-stimulated glucose uptake in primary adipocytes was reduced in rats fed with a high-fat diet containing crude fish oil compared to rats fed with just a high-fat diet without fish oil. The contribution of dioxins, furans, non-*ortho*-substituted PCBs, mono-*ortho*-substituted PCBs and organochlorine pesticides to insulin resistance was then confirmed using differentiated adipocytes. Insulin action in cultured adipocytes was inhibited by several POP mixtures, especially by organochlorine pesticides. Of interest in this review, relative glucose uptake in adipocytes was reduced by non-*ortho*-substituted PCBs and mono-*ortho*-substituted PCBs. Ruzzin *et al.* proposed that POPs affect nuclear receptors (aryl hydrocarbon receptors, constitutive androstane receptor, and pregnane X receptor) which increase chronic low-grade inflammation, decrease mitochondrial function and fatty acid oxidation, and increase lipogenesis leading to insulin resistance syndrome. Lim *et al.*⁴⁸ reviewed the literature surrounding the effect of persistent organic pollutants on mitochondrial function and metabolic/insulin resistance syndrome. They concluded that mitochondrial dysfunction plays a key role in the association of POPs and insulin resistance or type 2 diabetes.

Another important potential mechanism in which PCBs may contribute to diabetes involves gene regulation. TCDD has been shown to affect expression of hundreds of genes.⁴⁹ In rat liver studies, TCDD affected the mRNA expression of numerous genes related to glucose and insulin sensitivity including decreases in glucokinase and fructose-6-phosphatase transport protein 1.⁵⁰ Other studies have focused on peroxisome proliferator-activated receptors (PPAR) and aryl hydrocarbons. PPAR function has a role in glucose homeostasis including translation of the important glucose transporter protein GLUT-4. Dioxins such as TCDD bind Ah receptors that in turn antagonize PPAR and its associated functions, providing another potential mechanism between PCBs and diabetes.⁵¹

It is important to note that none of these potential explanations prove that dioxins and PCBs cause diabetes. These genetic and biochemical processes and dysregulations do, however, provide some potentially compelling explanations for the associations seen between PCBs and diabetes. Further and ongoing studies are needed to fully elucidate if PCB exposure induces insulin resistance and diabetes and the underlying genetic and biochemical processes.

IV. Hypertension

In an early study, Kreiss *et al.*⁵² investigated the association of PCBs with hypertension among 458 participants in Triana, AL, USA. Measurement of PCB concentration used Aroclor 1260 as the calibration standard. In age, gender, BMI, social class, total cholesterol, triglyceride, smoking and race adjusted multiple regression analyses, log PCB values were not significantly associated with log systolic blood pressure, but were associated with log diastolic blood pressure.

More recently, Everett *et al.*⁵³ studied 2074–2556 participants in the NHANES 1999–2002. The association of 11 PCB congeners with hypertension (diagnosed and undiagnosed [$\geq 140/90$ mmHg]) was assessed in age, gender, race, smoking status, body mass index, exercise, total cholesterol, and family history of coronary heart disease adjusted logistic regressions. Both dioxin-like PCBs congeners 74, 118, 126, 156, and 169, and non-dioxin-like PCBs 99, 138/158, 153, 170, 180, and 187 were evaluated. The congeners found to be associated with hypertension were PCBs 126, 74, 118, 99, 138/158, 170, and 187. In a follow-up commentary, Everett *et al.*⁵⁴ studied 3326–3712 participants in the NHANES 1999–2004. The associations of the same 11 PCB congeners with hypertension were evaluated again using 2 years additional data. Only dioxin-like PCB congeners 74, 118, and 126 were significantly related to hypertension in the expanded analysis. The prevalence in the USA of one or more of these PCBs being elevated was 30.4%. When the number of PCBs elevated was analyzed as a continuous variable (0–3 elevated PCBs) the odds ratio per elevated PCB was 1.26 (95% CI 1.07–1.47).

Ha *et al.*⁵⁵ evaluated newly diagnosed (*i.e.* undiagnosed) hypertension among 524 participants ≥ 40 years old in the NHANES 1999–2002. Diagnosed hypertension and diagnosed diabetes were excluded. Dioxin-like PCB congeners 74, 118, 126, 156, and 169 were assessed along with non-dioxin-like PCB congeners 99, 138, 153, 170, 180, and 187. Men and women were evaluated separately and logistic regressions were adjusted for age, race, poverty income ratio, BMI, smoking status, serum

cotinine, alcohol consumption and exercise. Only lipid-adjusted PCB 156, among men, was significantly associated with undiagnosed hypertension, with an odds ratio of 3.3 (95% CI 1.2–3.0) for $\geq 75^{\text{th}}$ percentile.

Goncharov *et al.*⁵⁶ studied 365 participants on anti-hypertensive medication and 394 not on medication, in Anniston, AL, USA. A total of 35 PCB congeners were evaluated. There was no association of total PCBs (wet weight) with hypertension among those on anti-hypertensive medication. Among those not on medication, the third tertile of total PCBs had odds ratios of 3.87 (95% CI 1.13–13.17) for systolic hypertension and 4.49 (95% CI 1.34–14.99) for diastolic hypertension, compared to the first tertile, in age, BMI, total serum lipids, gender, race, smoking status and physical activity adjusted logistic regressions.

Diabetes and hypertension can lead to cardiovascular disease (CVD). In another study of the NHANES 1999–2002, Ha *et al.*⁵⁷ investigated CVD among 889 participants ≥ 40 years old. Dioxin-like PCBs congeners (74, 118, 126, 156, and 169) and non-dioxin-like PCBs congeners (99, 138, 153, 170, 180, and 187) were studied. Dioxin-like PCBs, as a class, and non-dioxin like PCBs, as a class, were not associated with self-reported CVD among males, but were associated with CVD among females. Congeners 156, 138, 153, and 170 were associated with self-reported CVD among females. Covariates were age, race, poverty income ratio, BMI, cigarette smoking, serum cotinine, alcohol consumption, exercise, HDL cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein. Additional, longitudinal studies are needed to evaluate the relationship between PCB congeners and CVD.

V. Discussion

Several commentaries have been published in response to the articles by Lee *et al.*^{7,22} and more recent studies of persistent organic pollutants (POP) and diabetes. Porta⁵⁸ commented there was “no association between obesity and diabetes in individuals with non-detectable levels of POPs” in the study by Lee *et al.*⁷ Lee⁵⁹ himself commented “As people get fatter, the retention and toxicity of POPs related to the risk of diabetes may increase.” In 2008, Jones *et al.*⁶⁰ commented “The expected association between obesity and diabetes was absent in people with low concentrations of POPs in their blood. The association between obesity and diabetes became stronger as the concentrations of such pollutants in the blood increased.” In 2010, Lee and Jacobs⁶¹ expanded the discussion commenting that studies of fish consumption show inconsistent results, which may be due to differences in chemical contamination.

Determination of causality is ultimately the goal of research into any environmental exposure and subsequent development of disease. The question will always come back to if there is something about diabetes that reduces the body's ability to metabolize and excrete PCBs thereby leading to increased serum concentrations; or if the increased serum concentrations of PCBs actually cause diabetes. As Lee points out, a large scale epidemiological argument against POPs as a cause of diabetes is the fact that diabetes prevalence continues to increase while levels of POPs have been steadily declining. However, two of the studies cited above reported that the length of time from diagnosis of diabetes was not associated with increasing serum levels of POPs

as would be expected if the association between diabetes and POPs was due to a change in the metabolism of diabetics. Only large scale prospective studies will be able to determine if POPs contribute to development of diabetes.

VI. Conclusions

The relationship of PCBs with diabetes and hypertension has been investigated in several cross-sectional studies and a few longitudinal studies. In cross-sectional studies the evidence tends to support associations of dioxin-like PCBs with diabetes (diagnosed plus undiagnosed diabetes). Associations of non-dioxin-like PCBs and diabetes are reported, but when tested as classes, with other POPs, were not significant.²² Longitudinal studies of PCBs and diabetes are few. One study concludes that women, but not men, show an association between PCBs and diabetes, and three studies show no association for elevated PCBs and diabetes. Investigations of PCBs and hypertension are limited in number. Goncharov *et al.*⁵⁶ found associations between total PCB concentrations and the third tertile of clinical hypertension, systolic blood pressure, and diastolic blood pressure among persons not on hypertension medication. Everett *et al.*⁵⁴ found associations between dioxin-like PCB congeners 74, 118, and 126 and clinical hypertension in a representative sample of the US population. More longitudinal studies are needed to illuminate the relationships of PCBs with diabetes and hypertension.

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