Environmental Contaminants as Risk Factors for Developing Diabetes

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Abstract: The contribution of exposure to persistent organic pollutants (POPs) to the incidence of diabetes has received little attention until recently. A number of reports have emerged, however, concerning elevated diabetes in persons occupationally exposed to dioxin. United States (US) Air Force personnel in Vietnam who sprayed Agent Orange containing dioxin as a contaminant had elevated rates of diabetes, leading to US government compensation for diabetes in these veterans. Recent studies in populations exposed to polychlorinated biphenyls (PCBs) and chlorinated pesticides found a dose-dependent elevated risk of diabetes. An elevation in risk of diabetes in relation to levels of several POPs has been demonstrated by two different groups using the National Health and Nutrition Examination Survey (NHANES), a random sampling of US citizens. The strong associations seen in quite different studies suggest the possibility that exposure to POPs could cause diabetes. One striking observation is that obese persons that do not have elevated POPs are not at elevated risk of diabetes, suggesting that the POPs rather than the obesity *per se* is responsible for the association. Although a specific mechanism is not known, most POPs induce a great number and variety of genes, including several that alter insulin action. Because diabetes is a dangerous disease that is increasing in frequency throughout the world, further study of the possibility that exposure to POPs contributes to the etiology of diabetes is critical.

Keywords: dioxins, furans, polychlorinated biphenyls, chlorinated pesticides, type 1 diabetes, type 2 diabetes, obesity, arsenic

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INTRODUCTION

Diabetes, characterized by high levels of sugar in the blood, is a very serious and lifelong metabolic disease that can be caused either by too little insulin—a hormone produced by the pancreas that allows glucose to penetrate cells—or by insulin resistance (non-responsiveness), or both. Traditionally, two distinct forms of diabetes have been distinguished: type 1 (insulin dependent), resulting from the loss of function of the beta cells of the pancreas that produce insulin; and type 2 (non-insulin dependent), due to a loss of insulin sensitivity in peripheral tissues. More recently, a continuum in the forms of diabetes has become apparent in that type 2 diabetes is often accompanied by dysfunctional pancreatic beta cells and peripheral insulin resistance, with beta-cell dysfunction predating insulin resistance /1/. Type 1 diabetes usually develops as an autoimmune disease, in which the immune system creates antibodies against the beta cells. The trigger for the immune response is unknown. Symptoms develop when only 10% to 20% of insulin-producing cells remain viable. This form of diabetes is often called *early onset diabetes*, because it typically develops in adolescence although it can occur at any age. In contrast, diabetes associated with insulin insensitivity usually develops later in life and therefore is called *adult onset* or type 2 diabetes.

Although genetic susceptibility is involved in the etiology of type I diabetes to a certain extent (see Vaarala /2/ and Knip /3/ for details), many reasons exist for believing that environmental factors play a more important role.

- Monozygotic twins have only a 13% to 33% concordance.
- Type 1 diabetes varies according to geographic region, and individuals moving from a low-incidence to a high- incidence region acquire the rates in their new area of residence over time.
- Risk factors that have been considered include viral infections, gluten in the diet, vitamin D, abnormally high weight/height in childhood, as well as reduced microbial load in early life (the 'hygiene hypothesis').
- The incidence of type 1 diabetes is increasing significantly throughout the world /4/.
- Certain drugs directly damage the beta cells of the pancreas and cause type 1 diabetes (see Longnecker and Daniels /5/ for details).

Type 2 diabetes is genetically complex, involving multiple genes and multiple gene-environment interactions. In contrast to type 1 diabetes twin studies, for example, almost 100% of siblings of persons with type 2 diabetes were found to have diabetes.

A great deal of study has not been conducted on traditional environmental contaminants and type 1 diabetes, although Longnecker et al /6/ reported that in pregnant women with diabetes (primarily type 1), their mean serum polychlorinated biphenyl (PCB) levels were 30% higher than those of control subjects. The authors reported a linear relation between serum PCB levels and risk of diabetes.

The prevalence of diabetes is increasing rapidly in most developed countries for reasons that are not completely clear, particularly for type 2 diabetes. Insulin-resistant diabetes is increasing at an alarming rate and occurs at younger ages than was common in the past. The general wisdom is that the increasing rate of type 2 diabetes is a reflection of a 'western life-style', characterized by an un-healthy diet, obesity, and lack of physical activity /7/. Strong evidence has been presented that the incidence of diabetes increases with obesity, physical inactivity, age, and genetic factors /8-11/. The disease occurs at higher rates in certain ethnic groups, including Native Americans and African Americans /12-13/. Little evidence is available for an elevation in rates of diabetes among Africans, however. In the United States (US), the lifetime risk of developing diabetes has been estimated at 32.8% for males and 38.5% for females /14/.

The Centers for Disease Control and Prevention has estimated that 14.4% of the US population over 20 years of age either have frank diabetes or impaired fasting glucose, among which fully 29% are undiagnosed. The prevalence increases with age, reaching 15% among persons 60 years of age and older /10/. Yet, the increase in persons with diabetes is by no means limited to the US. Zimmet et al /15/ project a global increase in diabetes between 2000 and 2010 of 46%, with a 23% increase in North America, a 44% increase in South America, a 24% increase in Europe, a 50% increase in Africa, a 57% increase in Asia, and a 33% increase in Australia!

In addition to the risk factors mentioned above (genetic susceptibility, age, physical inactivity, obesity), individuals born of low birth weight are at an increased risk for type 2 diabetes /16/. Leibson et al /17/ showed that mortality from diabetes was significantly affected by birth weight, with those born with a weight of 4 to 5.5 pounds showing a 7-fold elevation in the ratio of observed to expected mortality. Several studies have shown that PCBs and perhaps other persistent organic pollutants (POPs) exposures increase the risk of babies having low birth weight /18-22/.

Taylor et al /19/ showed that women working in a capacitor plant in areas where they were presumed exposed to PCBs gave birth to children 153 gm lower in weight and with an average of 6.6 days shorter gestation. This effect has been seen in a number of other studies and appears greater in

male than female infants. Rylander et al /21/ reported a significant increase in the odds ratios (OR) for low birth weight in Swedish infants whose mothers had consumed fatty fish from the Baltic Sea, and that the rates increased with the concentration of PCB 153.

Sagiv et al /23/ investigated 722 infants born to mothers living near a PCB-contaminated site in the state of Massachusetts and found a negative association between maternal PCB levels, but not with either p,p'-dichlorodiphenyltrichloroethane (DDE), the major metabolite of DDT, or hexachlorobenzene. We showed that maternal residence in a zip code containing or abutting a PCB-contaminated site significantly increases risk of giving birth to a low birth weight infant and that risk is greater for male than for female infants /24/.

In utero exposure to a diabetic environment appears to predispose an individual to type 2 diabetes /25/. Type 2 diabetes is a central component of the *metabolic syndrome*—insulin resistance, dyslipidemia, hypertension, obesity, and cardiovascular disease /26-27/. Abnormalities of lipid metabolism are central to the pathogenesis of diabetes and may even precede the development of diabetes /28/. Noteworthy is that evidence has been reported for a relation between exposure to POPs and dyslipidemia and hypertension, as well as diabetes /29-30/. Therefore, a great deal of interest is being shown at the moment in the possible relation between exposure to POPs and risk of the full metabolic syndrome, although no or only a few publications to date have focused on this question.

ENVIRONMENTAL CONTAMINANTS AND DIABETES

Some evidence has emerged for an increased risk of diabetes in individuals exposed to arsenic, although many of the individual studies are limited. This information has been reviewed by Navas-Acien et al /31/, who examined 19 epidemiologic studies, of which several were conducted in the high-arsenic areas of Bangladesh and Taiwan. The authors identified a pooled relative risk (RR) of 2.52 [95% confidence interval (CI) = 1.69-3.75], while acknowledging that methodology issues limit the interpretation of the association. Several reports have been published of a correlation between smoking and diabetes /32-33/, although this relation does not appear to be strong. On the other hand, the relation between diabetes and exposure to POPs is much better documented.

Some of the earliest evidence for a relation between the rates of diabetes and exposure to POPs came from study of US Air Force personnel who sprayed the herbicide and defoliant Agent Orange, which was contaminated with a dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD), during the Vietnam War. A highly significant relation between exposure to dioxin and young age of onset and severity of diabetes was found in those individuals with the greatest exposure /34. Michalek et al /35/ studied US Air Force veterans who were involved in aerial spraying to destroy enemy foliage cover in Vietnam during 1962 to 1971, called *Operation Ranch Hand* (for details see http://www.airpower.maxwell.af.mil/airchronicles/aureview/1983/Jul-Aug/buckingham.html.) The investigators found that the mean of the logarithm of insulin concentration in non-diabetic veterans increased significantly with dioxin concentration.

Longnecker and Michalek /36/ examined the association between the serum dioxin level and the prevalence of diabetes and levels of serum insulin and glucose in 1,197 veterans of *Operation Ranch Hand* and calculated the OR for diabetes in the highest to lowest quartile of dioxin exposure to be 1.71 (95% CI =1.00-2.91). These reports led to a report by a committee of the National Academy of Sciences' Institute of Medicine, which concluded that there was suggestive evidence of an association between dioxin exposure and diabetes /37/. Steenland et al /38/ reported a positive dose-response relation between serum levels of dioxin and risk of diabetes in this population. These observations led the US Department of Veterans

Affair to recognize type 2 diabetes as a disease related to herbicide exposure in 2001 (http://www.vva.org/Benefits/vvgagent.html). In a later study of 343 Ranch Hand veterans, Michalek et al /39/ found no relation between the rate of dioxin elimination and the occurrence or time to onset of diabetes, which they take as evidence that the relation is not just secondary to some effect on the process of dioxin metabolism.

Pesatori et al /40/ and Bertazzi et al /41/ studied individuals exposed to dioxins at Seveso, Italy and found significantly elevated deaths from diabetes among women living in the zone with intermediate exposure (OR = 1.9, 95% CI = 1.1-3.2). Vena et al /42/ analyzed data reported from 36 international cohorts of workers in phenoxyacid herbicide and chlorophenol plants, where dioxins were an unintended byproduct. This group reported a RR of 2.25 (95% CI = 0.53-9.50) for diabetes in these workers. Calvert et al /43/ reported on diabetes in workers in two US chemical plants. Although the authors did not find an overall elevation in diabetes in workers as compared with referents, 60% of workers with elevated TCDD concentrations had diabetes, and workers with the highest extrapolated TCDD concentrations had a significantly increased mean serum glucose concentration. Steenland et al /44/, however, did not find an increase in diabetes when analyzing mortality data from 5,132 workers in 12 US chemical plants at which dioxin exposure was presumed.

Cranmer et al /45/ studied a population of individuals exposed to dioxin from a pesticide manufacturing site having inadequate production controls and waste disposal. The group studied 69 subjects who lived within 25 miles of the site but showed normal glucose levels during a glucose tolerance test. They demonstrated that plasma insulin concentrations were significantly higher in individuals with elevated dioxin levels and concluded that high serum dioxins levels (> 15 ppt) were associated with insulin resistance.

As mentioned before, Longnecker et al /6/ studied 2,245 pregnant women, 44 of whom had diabetes. How many of these women had type 2 diabetes is not clear. The mean serum PCB level in the women with diabetes (3.77 ppb) was 30% higher than in the controls (2.79 ppb), and the relation of PCB level to the adjusted OR for diabetes was linear. Taking PCB levels < 2.50 ppb to have an OR of 1.0, the OR was 2.9 for PCB levels 2.50-3.75, 4.4 for PCB levels 3.75-5.00, and 5.1 for PCB levels > 5.0. All values were statistically significant. This study is excellent for showing a dose-response relation.

Support for a relation between exposure and diabetes is also found in a population-based study of Fierens et al /46/ in which they found, after adjustment for age and other covariates, that total TEF and 12 marker PCB concentrations were respectively 62% and 39% higher than in controls. The ORs were 5.1 (95% CI = 1.18-21.7) for dioxins, 13.3 (95% CI = 3.31-53.2 for coplanar PCBs, and 7.6 (95% CI = 1.58-36.3) for 12 marker PCBs in the top decile of concentration. Vasiliu et al /47/ investigated a Michigan cohort that had elevated exposure to polybrominated biphenyls (PBB) in relation to risk of diabetes and found a significant relation with PCB concentrations (OR = 2.33, 95% CI = 1.25-4.34), but not with PBB concentrations.

In a population living near a PCB manufacturing plant in Eastern Slovakia, Radikova et al /48/ reported on studies of 2,050 adults. The authors reported an elevated incidence of diabetes and impaired glucose regulation in individuals in the second and third tertiles of PCB levels, but apparently did not control for age or BMI.

The PCBs can have 209 different configurations or *congeners*, defined by the number of chlorine substitutions and the position of the substitutions on the biphenyl rings. Rylander et al /49/ reported a significant elevated risk of diabetes in Swedish fisherman and their wives in relation to concentrations of the PCB 153 congener (2,4,5,2', 4',5'-hexachlorobiphenyl). A more recent report from the same Swedish groups studied 544 women and a significant association between elevated levels of PCB 153 and incidence of diabetes (OR = 1.6,

95% CI = 1.0-2.7) /50/. The authors also found a positive relation with serum levels of DDE (OR = 1.3, 95% CI = 1.1-1.6).

Kouznetsova et al /51/ investigated the rates of hospitalization for diabetes in individuals in New York State, except for New York City, who lived in zip codes containing or abutting an identified hazardous waste site in which POPs were known to be significant contaminants. After adjustment for age, race, gender, income, and urban/rural residence, the investigators found a significant elevation in the frequency of diagnosis of diabetes in residents in POPs-contaminated zip codes as compared with zip codes not containing any hazardous waste site (OR = 1.23, 95% CI = 1.15-1.32). In a subset of zip codes along the PCB-contaminated Hudson River, where average income was higher with less smoking, a better diet, and more frequent exercise, Kouznetsova and coworkers found the rates of hospitalization for diabetes to be even higher (OR = 1.36, 95% CI = 1.26-1.47). Although the exposure assessment in this study is weak (only residence in a zip code with or without an identified waste site), the very large numbers of hospitalized patients (about 2.5 million per year for 8 years) gives significant power to the study.

Strong evidence for the relation between PCB or other organochlorine exposure and diabetes has emerged from use of data from the US National Health and Examination Survey (NHANES). The NHANES study was designed to be a random survey of health of Americans, and the data were collected between 1999 and 2002. The information available included demographic characteristics, medical history, and the results of a physical examination. Blood samples were drawn for a variety of contaminants, including a large number of persistent organochlorine compounds, and for clinical chemistry, including fasting glucose and serum lipid levels.

In the first report using the data, Lee et al /52/ examined the relation between levels of PCB 153, two dioxin congeners [1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (HpCDD), and 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin (OCDD)], and three pesticide levels (oxychlordane, DDE, and trans-nonachlor) and risk of diabetes in a study of 2,016 adults 20 years of age or older, 217 of whom had diabetes. These compounds were selected for analysis because they were found in > 80% of persons at levels greater than the level of detection. Levels of all of these POPs increased with age and were, in general, lower in Caucasians and men. The body mass index (BMI) was positively correlated with levels of HpCDD, OCDD, and DDE but negatively correlated with levels of PCB 153.

Lee et al /52/ found a striking relation between the sum of levels of these six POPs and risk of diabetes. In relation to the lowest quartile ORs increased to 14.0 (95% CI = 3.0-65.0), 14.7 (95% CI = 3.4-63.9) and 38.3 (95% CI = 8.0-183.1) with increasing quartile of exposure. For PCB 153, the OR for individuals with serum levels in the greater than 90th percentile was 6.8 (95% CI = 3.0-15.5), and the p for trend was <0.001 with increasing concentration. Comparable values for HpCDD were 2.7 (95% CI = 1.3-5.5), p for trend = 0.007 and for OCDD were 2.1 (95% CI = 0.9-5.2), p for trend = 0.094. Values for the three pesticides were stronger. For oxychlordane OR = 6.5 (95% CI = 2.0-32.4), p for trend = < .001, for DDE OR = 4.3 (95% CI = 1.8-10.2), p for trend < .001, and for trans-nonachlor OR = 11.8 (95% CI = 4.4-31.3), p for trend < .001.

In this and the other reports discussed below, it is important to understand that all of these POPs are lipid-soluble compounds that migrate together. Figure 1, from a study by Huang et al /53/, shows the relations among levels of 11 different contaminants in wild and farmed salmon. What is clear is that the level of any single contaminant is directly correlated with the level of every other contaminant. In this case, the contaminant levels reflect the food taken by the salmon, whether wild or farmed. As farmed salmon are fed a fish meal/oil mixture made from pelagic fish, this pattern reflects that of the oceans and is the same in the many different sites from which these fish were either caught or raised.

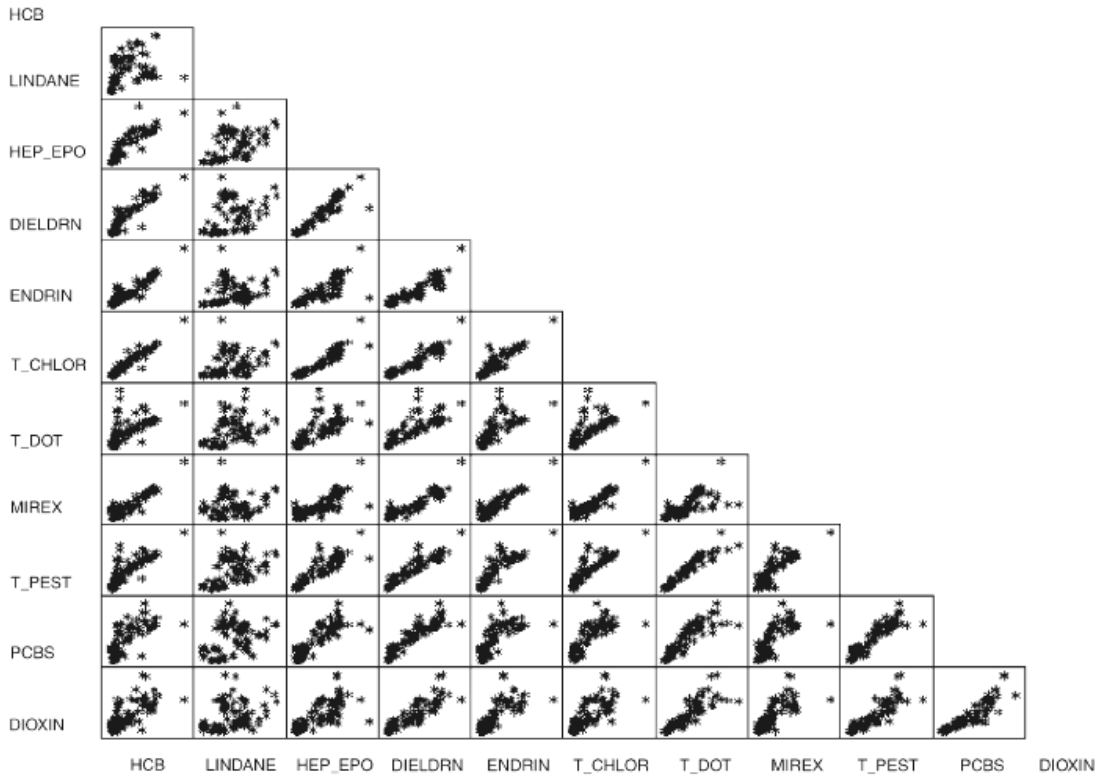

Fig. 1: Scatter-plot matrix for the content of pairs of 10 contaminants and total pesticides measured in salmon from various locations where the salmon were produced or purchased. HEP_EPO, heptachlor; T_CHLOR, total chlordane; T_DDT, total DDT; T_PEST, total pesticide. From Huang et al /53/. Reproduced with permission.

Whereas significant differences occur in the magnitude of the contamination in the various geographic areas, little or no difference is seen in the pattern. This is not to deny that frequently very local sources of contamination with one chemical come from, for example, a manufacturing site. On a more global scale, however, these chemicals migrate together.

Thus, finding an association with one particular compound does not necessarily implicate that compound as being responsible for the relation because a given compound might be only a marker for a different compound, the levels of which are correlated with the quantified compound. For example, HpCDD and OCDD are not potent activators of the Ah receptor but can be markers for other dioxin-like compounds that are more toxic. Although most POPs are persistent in the human body, the half-lives of individual chemicals are not always the same. TCDD is usually considered to have a half-life of about 7 to 9 years, but even for this substance, the half-life is known to vary with concentration, being significantly briefer at high levels of exposure and faster in men than in women /54/.

Different PCB congeners vary significantly in half-life, with lower chlorinated congeners having half lives of weeks to months, and some more highly chlorinated congeners having half lives of decades /55/. Thus, levels in the blood of any particular substance will reflect both recent and distant past intake and the rate of metabolism and excretion. This variation, however, does not mean a lack of important information in the correlation

with rates of disease in relation to levels of specific contaminants.

In a later report, Lee et al /56/ analyzed the NHANES data in relation to five categories of POPs: the sum of three dioxin congeners, the sum of four furans, the sum of four dioxin-like PCBs, the sum of five non-dioxin-like PCBs, and the sum of four organochlorine pesticides, each of which was detected in at least 60% of a population of 1,721 persons. Almost all of the 19 individual POPs were positively associated with an elevated prevalence of diabetes. When modeled simultaneously, however, positive associations were found only for the dioxin-like PCBs and the chlorinated pesticides. The dioxins and non-dioxin-like PCBs did not show any significant relation and that for the furans was weak. The results of these studies led Lee et al /58/ to propose that background levels of POPs contribute to the burden of diabetes.

Everett et al /57/ independently analyzing data similar to that used by Lee et al /52, 56/ investigated 1,830 persons in relation to levels of 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (HxCDD); PCB 126, the most potent dioxin-like PCB congener; and p,p'-DDT. After adjustment for age, gender, race, country of birth, education, poverty income ratio, BMI, waist circumference, physical activity, and other contaminants, PCB 126 levels > 83.8 pg g^{-1} lipid showed an OR for diabetes of 3.68 (95% CI=2.09-6.49) as compared with PCB 126 levels < 31.2 pg g^{-1} lipid. DDT, after all of these adjustments, showed an OR of 2.46 (95% CI = 1.45-4.15). The HxCDD was not significantly associated with elevated risk of diabetes.

Codru et al /59/ reported serum PCB levels and fasting glucose levels in 352 adult Native Americans, Mohawks, who live just downstream of three aluminum foundries on the St. Lawrence River and its tributaries at the New York-Canadian border. These individuals were exposed to PCBs primarily through the consumption of local fish that were contaminated but also through inhalation of the vapor-phase PCBs /60/. Fasting blood samples were obtained for clinical chemistry and determination of 101 PCB congeners, plus DDE, hexachlorobenzene, and mirex. Individuals with diabetes were identified based on either reporting that they were diabetic and were regularly taking anti-diabetes medication, or having fasting blood sugar levels greater than 125 mg dL^{-1}, a level presently used by physicians to diagnose diabetes. In this population, 20.2% of the subjects were diagnosed as diabetic. Serum PCB concentrations ranged from 0.51 to 48.32 ppb wet weight. Age and BMI were found to be significant risk factors for diabetes, but gender and smoking status were not in this study. Total serum lipid levels were modestly related to diabetic status.

After adjustment for age, gender, BMI, and smoking status, the rate of diabetes in Mohawks in the highest third total PCB levels was compared with those in the lowest third. For total PCBs, the OR was 3.9 (95% CI = 1.5-10.6). This elevation in risk was significant whether wet weight or lipid adjusted total PCB concentration was used. Many investigators report lipid-adjusted PCB concentrations based on the lipophilicity of the PCBs, substances found in the lipid layer of serum. Schisterman et al /61/, however, recently demonstrated that lipid adjustment confers a significant bias in the relation, so the finding of similar relations, with or without lipid adjustment, is significant. Codru et al /59/ reported relations for only two individual congeners, 2,4,5,4'-tetrachlorobiphenyl (PCB 74), a congener with some dioxin-like activity, and PCB 153, a non-dioxin-like congener. PCB 74 is the congener most tightly correlated with history of fish consumption, and showed an OR of 4.9 (95% CI = 1.7-13.7) for the top-to-bottom tertile of wet weight concentration /62/. After adjustment for all other contaminants, a significant OR of 3.6 (95% CI = 1.0-13.4) still remained. A significant relation with PCB 153 (OR = 3.2, 95% CI = 1.3-8.2) was also seen, but after adjustment for other contaminants, was no longer significant (OR = 3.0, 95% CI = 0.7-12.8).

Table 1. *Association between diabetes and tertiles of concentration of various groupings of PCB congeners after controlling for age, gender, body mass index and smoking*. (Unpublished data of Codru et al /59/)

PCB Groupings	Lowest	Middle	Highest
Anti-estrogenic	1	1.59 (0.62-4.10)	3.77 (1.48-9.57)
Estrogenic	1	2.14 (0.90-5.09)	2.75 (1.15-6.58)
Phenobarbital Induce	1	1.81 (0.67-4.89)	4.25 (1.56-11.59)
Dioxin Like	1	1.53 (0.58-4.00)	3.81 (1.44-10.09)
Highly Chlorinated	1	12.77(0.98-7.86)	7.06 (2.46-20.29)
Low Chlorinated	1	2.28 (0.95-5.51)	3.06 (1.29-7.28)
Non-*ortho*	1	0.87 (0.41-1.84)	1.36 (0.68-2.27)
Mono-*ortho*	1	1.91 (0.75-4.88)	4.06 (1.64-10)
Di-*ortho*	1	1.9 (0.73-4.93)	3.81 (1.46-10.05)
Tri- and tetra-*ortho*	1	2.04 (0.78-5.34)	4.29 (1.62-11.39)

Anti-estrogenic: PCB congeners 74, 105, 118, 156, 170
Estrogenic: PCB congeners 44, 52, 70, 177, 187, 201
Phenobarbitol Inducers: PCB congeners 99, 153, 180, 183, 203
Dioxin-like: PCB congeners 77, 105, 114, 118, 156, 170, 180, 147+109, 123+149
Highly chlorinated: PCB congeners 83, 84, 87, 91, 92, 95, 97, 99, 110, 123, 128, 129, 130, 132, 134, 136, 137, 141, 144, 146, 147, 151, 153, 158, 170, 171, 174, 172, 176, 177, 179, 180, 183, 185, 187, 190, 194, 195, 196, 199, 200, 201, 203, 206.
Low chlorinated: PCB congeners 1, 3, 6, 7, 8, 9, 10, 13, 15, 17, 19, 22, 25, 26, 28, 29, 31, 33, 40, 42, 44, 45, 46, 49, 51, 52, 53, 56, 63, 64, 66, 67, 70, 71, 74, 77
Non-ortho: PCB congeners 3, 13, 15, 77
Mono-ortho: PCB congeners 1, 6, 7, 8, 9, 22, 25, 26, 28, 29, 31, 33, 56, 63, 66, 67, 70, 74, 105, 114, 118, 156,
Di-ortho: PCB congeners 2+4, 10, 17, 18, 19, 24+27, 32+16, 40, 42, 44, 47+59, 49, 52, 64, 71, 83, 87, 90+101, 92, 97, 99, 110, 128, 129, 130, 137 163+164+138, 141, 146, 153, 158, 170, 172, 180, 190, 194.
Tri- plus tetra-ortho: 45, 46, 51, 53, 84, 91, 95, 1342, 134, 136, 144, 151, 171, 174, 176, 179, 183, 185, 187, 195, 196, 199, 200, 201, 203, 206.

An effort by Codru et al /59/ to determine other major groups of PCBs as risk factors for diabetes is presented in Table 1 (previously un-published). From the data, we can see that all major PCB groups clearly show a relatively similar relation with diabetes, even though the groups have different modes of action. These observations only reinforce the point made above, that because these persistent compounds are all lipophilic and migrate together, to be confident in attributing any particular effect to one group at the exclusion of others is very difficult. The relation between diabetes and contaminant concentration was even stronger for DDE and hexachlorobenzene. For DDE the wet weight OR was 6.4 (95% CI = 2.2-18.4), and for hexachlorobenzene OR = 6.2 (95% CI = 1.2-16.9). After adjustment for all other contaminants, the DDE OR was 2.6 (95% CI = 0.8-8.8), and the hexachlorobenzene OR was 4.5 (95% CI = 1.4-14.3). The relation for mirex was surprising, in that it did not show any relation to diabetes before adjustment for other contaminants. After adjustment for all other contaminants, however, mirex appeared to be protective with an OR of 0.3 (95% CI = 0.1-0.8).

ANIMAL AND CELLULAR STUDIES:

Experimental animal studies are consistent with the evidence that PCB and dioxin exposure increases risk of diabetes. Nishizume et al /63/ showed that rats given Kanechlor-400 (a Japanese equivalent to Aroclor) showed depressed insulin sensitivity that increased with the duration of PCB exposure, as well as disturbed glucose and lipid metabolism and elevated serum lipids /63/. Several older studies demonstrated morphological changes in the structure of beta cells in the pancreas (where insulin is made) upon PCB exposure /64-65/. Stahl /66/ reported that dioxin alters enzyme activity related to glucose metabolism in rat liver cells. Boll et al /67/ demonstrated that both lipogenic and gluconeogenic enzymes in rat liver are altered upon PCB exposure. A clear relation exists between the abnormalities of lipid metabolism and glucose regulation /28/.

POSSIBLE MECHANISMS

The information presented above provides strong evidence for an association between exposure to POPs and diabetes. The major unresolved question remains whether exposure to POPs causes diabetes, and if so, what are the mechanisms? The notion that diabetes, secondary to other factors, would alter the metabolism of POPs in such a way as to retard their removal from the body, leading to an apparent association that did not reflect causation, is certainly conceivable, but has not been demonstrated. The results of Michalek et al /39/ revealing no change in the rate of elimination of dioxin in Ranch Hand veterans with or without diabetes provide evidence against this possibility. The most likely mechanism is one involving gene induction because most of these compounds up-regulate and down-regulate a variety of genes, including some that influence glucose tolerance. This mechanism has been best studied for POPs that bind to the Ah receptor. Puga et al /68/ demonstrated that TCDD alters the expression of 310 of 4,076 known genes by a factor of twofold or more in human hepatoma cells. Of the genes altered, 114 were up-regulated and 196 were down-regulated. The affected genes are involved in a large number of different processes, from signaling pathways and transcription factors to genes involved in cell-cycle regulation, xenobiotic metabolism, and development.

Fletcher et al /69/ investigated mRNA expression of genes associated with cholesterol and bile function in rat liver after TCDD administration and found that concentrations as low as 0.4 $\mu g\ kg^{-1}$ body weight altered a great variety of genes, including transcripts relating to lipid, carbohydrate, and nitrogen metabolism. At 40 $\mu g\ kg^{-1}$, 57 probesets were altered by greater than twofold at 6 h; at 7 d, 236 probesets were altered, with 107 upregulated and 129 downregulated. Of particular relevance to glucose metabolism, glucokinase decreased about threefold at 6 h and 7 d, and glucose-6-phosphatase transport protein 1 decreased about 2.5-fold at 24 h and 7 d. Glucose-6-phosphate dehydrogenase levels increased 3.3-fold at 24 h and 3.5-fold at 7 d, but how these alterations might relate to insulin insensitivity is unclear.

Croutch et al /70/ administered TCDD and HxCDD to rats and determined the levels of circulating insulin, glucose, and insulin-like growth factor-1 (IGF-1), as well as hepatic levels of phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression. The authors found that both TCDD and HxCDD inhibit IGF-1, with less inhibition of PEPCK, and attributed the weight loss seen in the animals to these actions. No changes in levels of either insulin or glucose were seen.

Olsen et al /71/ and Enan et al /72/ reported that TCDD causes a reduction of glucose transport in preadipocyte and in luteinizing granulosa cells, respectfully, in a time and dose-dependent manner. The action is dependent upon activating the Ah receptor and is mediated through cAMP-dependent protein kinase activity. These transporters are insulin-sensitive and important parts of the insulin response at a cellular level. In the Olsen et al /71/

report, TCDD had a greater action on the GLUT 4 low-affinity glucose transporter found in adipose cells than on GLUT 1, a transporter found in endothelial cells. Liu and Matsumura /73/ showed that this action on GLUT 4 is regulated at the mRNA level. GLUT 4 appears to play a central role in type 2 diabetes. Minokoshi et al /74/ found that lack of GLUT 4 in adipose tissue resulted in insulin resistance and diabetes in mice. Garvey et al /75/ reported an 80% decrease in GLUT 4 in the adipocytes of diabetics, which was associated with a 56% decrease in glucose uptake.

Another central factor involved in insulin resistance is tumor necrosis factor alpha (TNFα). TNFα is over-expressed in adipose tissue and either directly or indirectly inhibits the action of insulin /76/. Fujiyoshi et al /77/ analyzed adipose tissues from Vietnam veterans in an attempt to determine molecular mechanisms for the diabetic action of dioxin. The authors found the ratio of mRNA for GLUT 4 to that of nuclear transcription factor kappa B (NFκB) to be a reliable marker. NFκB expression in adipocytes in increased by TNFα, which in turn down-regulates GLUT 4 /78/.

Hokanson et al /79/ investigated the dioxin-induced alteration of estrogen-regulated gene expression in a human breast cancer cell line (MCF-7). Of 2,400 genes on the gene chip, 317 were significantly up-regulated and 488 were significantly down-regulated. The gene encoding insulin receptor substrate-1 (IRS-1), which has been reported to be decreased, missing, defective, or altered in persons with type 2 diabetes, was found to be down-regulated /80-81/.

Lipid accumulation in muscle results in increased serine phosphorylation and reduced tyrosine phosphorylation at important sites on IRS-1, which together inhibit the binding and activation of phosphoinositol 3-kinase, which in turn results in reduced insulin-stimulated glucose transport /28/. Thus, IRS-1 may play a central role in insulin insensitivity.

A number of polymorphorisms of IRS-1 have been reported to be associated with type 2 diabetes as well /82/, and polymorphorisms of the glucose transporter genes also occur /81/. This information is important in that it may be at least as a partial explanation for genetic susceptibility to type 2 diabetes. Johnson et al /83/ reported on gene networks showing interactions between the Ah receptor, cytochrome P450 1B1, insulin-like growth factor-binding protein-5 (IGFBP-5), lysyl oxidase, and osteopontin. Their study demonstrates how complex the relations are in such a network, even on consideration of only five functions.

Vezina et al /84/ performed an important study in rats by administering TCDD, a pentachlorodibenzofuran, PCB 126, and PCB 153 for 13 weeks and then investigating hepatic gene-expression profiles. The first three compounds are Ah receptor agonists, whereas PCB 153 is not. Two important results were obtained. Although the genes altered by the Ah-receptor agonists showed some similarity, they were strikingly not identical. Their finding that furan and PCB 126 gene-expression profiles were significantly different from those of TCDD indicates that not all Ah-receptor agonists have identical actions. The gene-expression profile for PCB 153 was extensive and very different from those by each of the Ah receptor agonists. The altered expression for all these substances included genes regulating a great variety of cellular functions.

Other studies have focused on specific genes. Marchand et al /85/ demonstrated that TCDD induces IGFBP-1 expression in human hepatocytes and hepatoma cells. This factor is known to modulate blood glucose levels, and therefore may be important in susceptibility to diabetes. Michalek et al /35/ suggested that dioxin alters the activity of pancreatic nitric oxide synthase.

UNANSWERED QUESTIONS

Many questions concerning POPs exposure and risk of diabetes that remain uncertain to various degrees are very important. Among them are the following:

Table 2. *Rates of diabetes as a function of BMI in relation to percentile of the sum of six POPs* (data from Lee et al /52/)

BMI	< 25th	25th-50th	50th-75th	75th-90th	> 90th
<25 kg/m2	0/176	6/171	4/145	8/71	9/60
25-<30 kg/m3	1/158	14/181	20/206	25/117	23/106
> 30 kg/m2	1/129	14/153	29/176	32/87	31/80

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- *Do certain POPs contribute to the etiology of diabetes or rather does the apparent relation merely reflect an effect of the metabolic perturbation caused by diabetes?* This question is one of causation as compared to mere association. Mickalek et al /39/ found no difference in the rates of the half-life of TCDD in veterans, regardless of whether they had diabetes, which argues against significantly different pharmacodynamics of metabolism and removal of POPs in diabetes. A definitive answer to this question, however, will await a clear identification of a mechanism explaining how POPs may cause diabetes.
- *What is the mechanism whereby POPs causes diabetes?* The studies listed above provide several possible mechanisms for altered insulin sensitivity, but much more still remains to be learned to identify which mechanisms are most important. Because of the very considerable numbers of different genes that are altered upon exposure to the various POPs, possibilities are not lacking. At present, however, to say with confidence which of the proposed mechanisms, if any, is responsible for such a relation is not possible.
- *Which POPs are responsible*? This question cannot be answered at present because of the complication that these lipophilic substances exist together in humans and in most environmental samples as well but vary in their rates of metabolism and excretion. Such compounds are also widely distributed in the food supply. Because expecting ever to find human populations that have been exposed to only one POP is unrealistic, the definitive answer must come from animal studies. Yet, even that research is not possible without an animal model of type 2 diabetes having a clearly identifiable endpoint. Such studies are extremely expensive and difficult, and this sort of information will not be available at any time soon. Interestingly, the data that we have at present implicates the chlorinated pesticides as showing the most consistently elevated ORs. The chlorinated pesticides have not received the attention given to dioxin or PCBs, but may be deserving of more.
- *What is the role of obesity?* One striking observation in the report of Lee et al /52/ was the finding that individuals with obesity who did not have elevated levels of POPs did not appear to be at elevated risk of diabetes. Their results are shown in Table 2, with data taken from their publication. This finding is consistent with the possibility that the PCBs and related compounds could be what cause the diabetes, not obesity (see Porta /86/). This observation runs counter to almost every current report on risk factors for diabetes and is of great importance for further study because of the significant implications for the prevention and treatment of diabetes. Yet, there may be a reasonable explanation for the apparent association between obesity and diabetes, even if the real culprits are the POPs. Most obesity comes

from an excessive consumption of animal fats, and animal fats contain most of the POPs that are taken in with our diet. Reducing the consumption of animal fats is good for health in any case, but a more difficult problem is in finding ways to reduce the POPs content of animal fats, much of which results from the global practice of recycling waste animal fats back into feed for animals that are meant for human consumption /87/. Yet, if the POPs, not the obesity, is the major risk factor for diabetes, then explaining how exercise can help prevent diabetes is very difficult. The American Diabetes Association has stated, "*…the recently completed Diabetes Prevention Program study conclusively showed that people with pre-diabetes can prevent the development of type 2 diabetes by making changes in their diet and increasing their level of physical activity. They may even be able to return their blood glucose levels to the normal range.*" (http://www. diabetes.org/diabetes-prevention/how-to-prevent-diabetes.jsp).

It is not obvious how exercise could alter levels of POPs. This question requires much greater study and is critical to understanding the disease.

- *Does POPs exposure alter the risk for other components of the "metabolic syndrome" (heart disease, hypertension, hyperlipidemia)?* Some evidence has already emerged that POPs exposure increases the risk of heart disease, hypertension, and hyperlipidemia /29, 30, 53, 88-90/. These diseases, however, have been much less studied than diabetes and further research is essential. Lee et al /91/ published a preliminary analysis of the relation between POPs and the metabolic syndrome and found that the organochlorine pesticides showed the strongest association, with ORs of 1.0, 1.5, 2.3, and 5.3 (p for trend < .01), with dioxin-like PCBs also showing a positive relation (ORs of 1.0, 1.1, 2.2, and 2.1 (p for trend = 0.01). Although confirming that organochlorine pesticides and total PCBs are strongly related to impaired fasting glucose levels, the studies did not find significant associations with dioxins or furans. Nevertheless, additional research is needed to understand exactly which POPs cause what and how they do it.
- *If POPs do in fact cause type 2 diabetes, how important is this exposure in relation to other traditional risk factors, including age, genetic factors, exercise, exposure to other chemicals, and diet?* This question is extremely important, given the significant increase in the rates of diabetes seen throughout the world and the importance of finding ways to prevent and treat the disease.

SUMMARY AND CONCLUSIONS

Diabetes is a very dangerous disease that is rapidly increasing throughout the world. Contrary to past belief, recent research demonstrates a significant role of exposure to POPs as a likely etiologic cause of type 2 diabetes. Much additional research is necessary for determining the possible mechanism(s) involved. Nevertheless, if this preliminary information is correct in documenting POPs exposure as a possible cause of diabetes, then this finding has very important implications on both diabetes prevention and treatment.

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