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Chronic Exposure To Persistent Organic Pollutants(POPs) And Diabetes Incidence:

A Systematic Review

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**A Systematic Review**

By

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An abstract of

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**ABSTRACT**

**Chronic Exposure to Persistent Organic Pollutants (POPs) and Diabetes Incidence: A Systematic Review**

By Likita aminu

*Aim*: The aim of this study was to conduct a review of the published studies assessing the association of diabetes with persistent organic pollutants (POPs).
*Methods***:** A systematic review of existing literature was conducted. Original publications were retrieved from Medline data base using search engines such as Pubmed, Google scholar or Web of Science. The author retrieved 123 articles on diabetes and POPs. Out of these 54 publications were considered complete and were reviewed. Relevant information including age, sex, measures of association, population studied, and year/place of publication, statistical methods as well as exposure characteristics were extracted from the articles. These information were entered into Excel spreadsheet. Because there was significant heterogeneity in the data quantitative analysis was considered inappropriate and a qualitative analysis was conducted.
*Results*: The result showed adult women bear the brunt of the burden of diabetes associated with POPs. PCBs topped the list of persistent organic pollutants (POPs) associated with diabetes. PCBs was closely followed by *p*, *p'*-DDE and OC pesticides. There was significant association between persistent organic pollutants (POPs) and diabetes.
As much as 82% of the studies had OR of 1.5 or more, with the highest OR being 26(Son 2010). The confidence interval was significant in 53.66% of the studies that reported on confidence intervals. These findings support an association of POPs and diabetes.
As much as two-thirds of the studies adjusted for confounders. The top ten confounding factors adjusted for (in order of frequency) were age, sex, BMI, tobacco smoking, race/ethnicity, income, alcohol consumption, serum cholesterol, waist circumference and triglycerides. These potential confounders should be considered in future studies of the association between diabetes and POPs.

*Conclusion*
This review used systematic review methodology to provide an evidence-based evaluation of the relationship between persistent organic pollutants and diabetes. The result of this review shows the possibility of significant association between persistent organic pollutants and diabetes. Although methodologically sound methods of studies are needed to evaluate causality between persistent organic pollutants and diabetes, much has been gained from previous studies to establish the link between persistent organic pollutants and diabetes.

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First, I praise and thank the Almighty God for giving me the knowledge and strength to do this work

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**Table of contents**

**Introduction**

Globally, the burden of diabetes is rising. In the most burdened nations the prevalence is expected to double between 2000 and 2030(Wild 2004). Therefore it is important to investigate the risk for diabetes. The outcome will inform efforts and methods to prevent the disease. Previous studies have shown growing evidence that exposure to persistent organic pollutants (POPs) may contribute to diabetes epidemic. No systematic analysis of the literature involving POPs and diabetes has been done. To add to the growing body of literature a systematic analysis was carried out. The aim was to conduct a systematic analysis of the literature on exposure to POPs and its association with diabetes incidence.

**Background and Literature review**

Diabetes is a significant and growing concern, with over 246 million people around the world living with the disease and another 308 million with impaired glucose tolerance(Ceriello 2008). The disease is chronic and potentially disabling that represents a major public health concern(Muir 2001). Muir's study revealed the cost in diabetes care(in USA) to be as much as $128 billion per year(Muir 2001).This high cost was corroborated by Kouznetsova(New York study) where she reported the total direct and indirect healthcare cost for people with diabetes amounted to $132 billion(Kouznetsova 2007). The prevalence of all types of diabetes in the US is 6.3%. Type 2 Diabetes makes up 95% of all persons with diabetes(Kouznetsova 2007). It is a major source of morbidity and mortality in USA, Canada and other industrial nations. The prevalence for diabetes worldwide is expected to double by 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366million in 2030(Wild 2004). This study indicated India, has the greatest number of diabetic persons (31.7 million), followed by China (20.8 million) and the United States with 17.7 million. Furthermore the 2030 projected number of diabetics for these countries are: India 79.4 million, followed by China 42.3 million and the US with 30.3 million(Wild 2004). Codru's report of 2007 revealed that the number of Americans with Diabetes was more than doubled between 1980 and 2004; rising from 5.8 million in 1980 to 14.7 million in 2004(Codru 2007).

Rignell-Hydbom's study of 544 women in 2007 revealed 16 women (3%) had diabetes; 15 out of the 16 women had type 2 diabetes. The study confirmed a strong positive trend between 2,2_,4,4_,5,5_-hexachlorobiphenyl( CB-153) and type 2 diabetes(P value=0.004)(Rignell-Hydbom 2007). It is concerning that recent rise in use of organochlorines pesticides (OCP) in Asia may be related to the risk of metabolic syndrome (insulin resistance, dyslipidemia, hypertension, obesity, and cardiovascular disease), a precursor to diabetes. This risk is growing into significant public health problem(Carpenter 2008; Park 2010). Carpenter's report indicated 57% increase in diabetes prevalence in Asia between 2000 and 2010(Carpenter 2008). In India organochlorines are extensively used for control of agricultural pest and disease-vector control. Residue such as gamma-HCH were as high as 9.8ug/l in Arumbakam wells. Also found in the wells were *pp'*- DDT(dichloro-diphenyl-trichloro-ethane) and OP-DDT at concentrations of 14.3ug/l and 0.8ug/l respectively(Jayashree 2007). These persist and accumulate in animals and plants tissues causing disease in man(Jayashree 2007). This is concerning. It reflects pollution of ground water exposing the population to POPs. In addition Tanabe's report showed India leads the rest of the Asian Nations in high breast milk concentrations of biphenyls( PCBs), hexachlorocyclohexane(HCHs), and polychlorinated dibenzo-p-dioxins( PCDDs)(Tanabe 2007).

Furthermore, worldwide consumption of pesticides is about 2 million tonnes per year. As of 2004,the USA alone consumes 24% of this amount, Europe 45%, the rest of the world 25%(Gupta 2004). It's worth noting that production of basic pesticides began in India in 1952 with manufacture of benzene hexachloride (BHC), followed by DDT. Since then the production of pesticides has increased tremendously such that by 1958, India produced over 5000 metric tonnes of pesticides (especially DDT and BHC). By the mid 1990s 145 pesticides were registered and production rose to 86,000 metric tonnes (Gupta 2004). In India 51% of food commodities are contaminated with pesticides residues. India is undergoing rapid industrialization. It is faced with giant task of feeding 1000 million people and a huge cattle population. In addition , the control of insects, weeds and other pests is of utmost importance, to India(Gupta 2004). This partly explains the increased production and use of pesticides in India.

Despite the ban on organochlorine pesticides use in developed countries, India has continued to use them liberally. Pesticide has become a necessary part of agricultural husbandry. The harmful residues that remain on the edible portion of crops and the amount which reach water bodies has become a cause for concern(Bakore 2004). In addition Subramania's report of 2007 highlighted the presence of pesticides, in significant levels, in human breast milk in Chennai. This study detected all organochlorine compounds in all the 46 mothers' breast milk, with HCH having the highest concentration. The levels of HCH and DDT were comparatively higher than the levels found in China(Subramanian 2007).

Tanabe found that in India levels of dioxin(in breast milk) and related compounds in mothers living around the open dumping site were notably higher than other Asian countries(Tanabe 2007). It is clear therefore that widespread use of pesticides in India is alarming, and therefore need attention.

**Role of POPs**

Factors associated with diabetes include diet, obesity and the environment(Montgomery 2008; Latini 2009). It is becoming clearer that most common non-communicable diseases are a result of complex combination of genetic processes and the environment(Patel 2010). Earlier studies to link POPs as etiologic factor in type2 diabetes were suggestive but inconclusive (Calvert 1999; kogevinas 2001; Longnecker 2001). However, recent epidemiological studies indicated background exposure to POPs was strongly associated with type 2 diabetes(Park 2010). In addition several epidemiologic studies have also shown that dioxin exposure is associated with elevated rates of diabetes and dysglycemia (Steenland 2001; Codru 2007). POPs such as polychlorinated dibenzo-p-dioxins(dioxins, PCDDs), dibenzofurans, polychlorinated biphenyls(PCBs), and organochlorines pesticides(OCPs) are stored in the adipose tissues of various living organisms because of their persistence in the environment and highly bioaccumulative nature (Park 2010). Over the years, the evidence of POPs contributing to development of diabetes is on the rise, as revealed by several studies ((Turyk 2009);(Son 2010) ;(Uemura 2009);(Cox 2007);(Fujiyoshi 2006) ;(Rylander 2005);(Longnecker 2001) (kogevinas 2001; Glynn 2003)).

**Exposure to POPs**

The principal method of exposure to POPs is by ingestion. The US Environmental protection Agency(EPA) estimates that over 95% of dioxin intake comes through dietary intake of animal fats(Everett 2007). Most human populations are exposed to

POPs through consumption of fat-containing food such as fish, dairy products and meat(Ruzzin 2010). POPs accumulate in lipid rich fraction of fish, and fish consumption represents a significant source of exposure to humans(Glynn 2003).

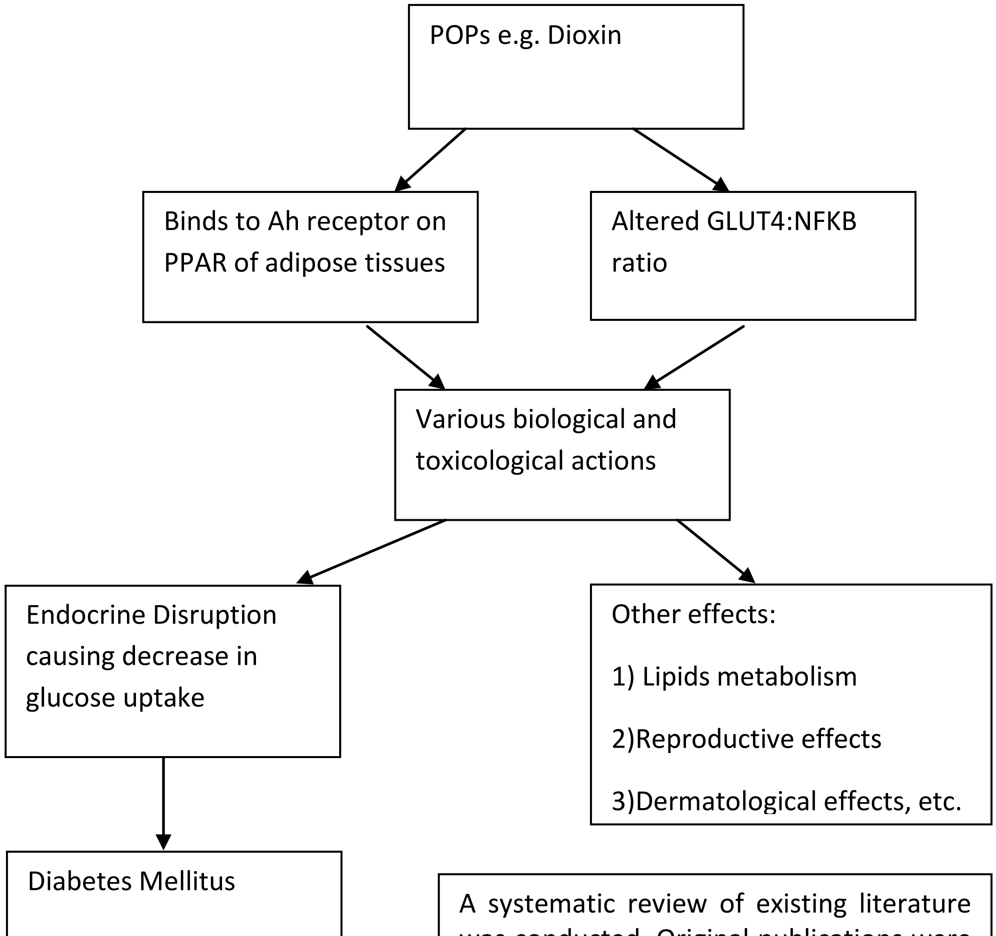
Bakore reported in 2004 that all the wheat and water samples were found to be contaminated with various organochlorine pesticides and their metabolites(Bakore 2004). He also emphasized the fact that pollutants released in the air, water, and soil find their way into the human body by breathing, eating and drinking. Jayashree confirmed this when he found the ground water samples were highly contaminated with organochlorine residues(Jayashree 2007). The contamination of food and water is explained by increase in modern agricultural practices resulting in increased use of pesticides and fertilizers to meet food demand of an increasing population. This results in the contamination of the environment including food and water(Jayashree 2007). Turyk's 2009 report alluded to exposure by great lakes sports fish consumption(Turyk 2009). Concentrations of POPs amongst the Inuits are among the highest in the world. Jorgensen highlighted the high intake of marine mammals by the Inuits population in Greenland leading to rapid increase of diabetes(Jorgensen 2008). The Mohawks of Akwesasne are traditionally a fish eating community that were significantly exposed(Codru 2007). Humans bioaccumulate these lipophilic and hydrophobic pollutants in fatty tissues for many years because POPs are highly resistant to metabolic degradation(Ruzzin 2010).

Since the 1930s, PCBs and Dichlorodiphenyltrichloroethane (DDT) have been manufactured and released into the environment. The pollutants are highly lipophilic, hence bioaccumulate in the food chain and due to their long half-lives they are still detected in humans even though they were banned in most countries in the 1970s and 1980s(Rignell-Hydbom 2009). Eskenazi supported this report by stating ‘DDT was used worldwide until 1970s, when concern about its toxic effects, its environmental persistence and its concentration in food supply led to its use restrictions and prohibitions’(Eskenazi 2009). As many as 100 countries signed the Stockholm convention on POPs which is committed to eliminate the use of 12 POPs of greatest concerns. However DDT continued to be used, for disease vector control (indoor residual spraying), till today, especially in developing nation like India.

**Mechanism of Diabetes: Endocrine Disruption**

Although Carpenter had reported that specific mechanism for association of POPs and diabetes is not known(Carpenter 2008) , today there is a better understanding of the molecular mechanism involved. Several chemicals including POPs, especially OC(organochlorines) pesticides, nondioxin-like polychlorinated biphenyls, 2,3,7,8,tetrachlorodibenzo-*p*-dioxin(TCDD) and phthalates interfere with function of the endocrine system and are suspected of having endocrine disrupting or modulating effects(Latini 2009). Several congeners of polychlorinated dibenzo-*p*-dioxins( PCDDs) and polychlorinated dibenzonfurans(PCDFs) exhibit various biological and toxic actions such as dermal, reproductive and endocrine toxicities(fig. 1)(Uemura 2008). TCDD has been shown to dramatically reduce glucose uptake in guinea pigs, mice and rats and in epidemiological studies(Everett 2007). Wang's study revealed PCBs and Dioxins were POPs with long half-lives in humans and they may act as endocrine disruptors and exhibit endocrine effects(Wang 2008).

## Hypothesized Mechanism of Association of POP with diabetes




Key:

POPs= Persistent Orgaanic Pollutants

Ah=Aryl Hydrocarbon

PPAR=Peroxisome proliferator-activated receptor

GLUT4=Glucose transporter 4

NFKB=Nuclear transcription factor beta

**Figure 1**: Showing hypothesized mechanism of diabetes.

A systematic review of existing literature was conducted. Original publications were retrieved from Medline data base using search engines such as Pubmed, Google scholar or Web of Science. The author retrieved 123 articles on diabetes and POPs. Out of these 54 publications were considered complete and were reviewed. Relevant information including age, sex, measures of association, population studied, and year/place of publication, statistical methods as well as exposure characteristics were extracted from the articles. These information were entered into Excel spreadsheet. Because there was significant heterogeneity in the data quantitative analysis was considered inappropriate and a qualitative analysis was conducted.

Based on studies on guinea pigs, Remillard(Fig. 1) suggested that aryl carbohydrate(Ah) receptor functions may antagonize peroxisome proliferator-activated receptor(PPAR) functions, and that the Ah receptor may promote diabetogenesis through a mechanism of PPAR antagonism(Remillard 2002; Everett 2007). Fujiyoshi found that the most reliable and sensitive molecular indicator of dioxin-induced diabetes to be the ratio of mRNA of glucose transporter 4(Glut 4) and nuclear transcription factor Kappa B (NFkB), i.e. GLUT4: NFkB (Fujiyoshi 2006).

While POPs are associated with diabetes, conversely, type 2 diabetes is also known to cause dysregulation of fat metabolism, which in turn might influence the distribution and elimination of lipophilic compounds such as dioxins and PCBs(Fierens 2003; Glynn 2003). Experimental studies have shown that TCDD could cause hypoinsulinemia through alteration of pancreatic membrane tyrosine phosphorylation suggesting that POPs may be involved in the pathogenesis of type 1 diabetes as well as type 2 diabetes(Glynn 2003; Lee 2006). Experimental evidence indicate that TCDD inhibits total 2-deoxyglucose transport in a dose dependent fashion resulting in inhibition of glucose transport(Kern 2002). Sankurai's 2004 finding was different. He found that in mice, Bisphenol A caused enhanced insulin-stimulated glucose uptake in the body and also caused increased amount of GLUT 4 protein(Sakurai 2004).

**Risk Factors for diabetes**

Established risk factors for diabetes include age, hyperinsulinemia, obesity, genetic factors and sedentary lifestyle(Kouznetsova 2007). Imbeault's report established that reduction in weight resulted in increased level of organochlorines(OC) in both men and women with effect being more pronounced in men(Imbeault 2002). This resulted in low insulin and therefore may contribute to diabetes.

**Organic Pollutants of Interest**

Pollutants of interest , that have been implicated in diabetes include POPs such as polychlorinated dibenzo-p-dioxin(PCDD)**,** dibenzofurans(PCDFs), polychlorinated biphenyls(PCBs), and organochlorines Pesticides(OCP)(Turyk 2009; Park 2010; Ruzzin 2010). In this study, Pops included included the 'dirty dozen': aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, polychlorinated biphenyls, Polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and toxaphene(Wikipedia 2010)

**Previous Studies: strengths and weaknesses**

Table 1: Showing some previous studies and main findings.

| Study | Study design/Population | Main findings |
|---|---|---|
| Park et al, 2010 | **Case-control** study, of Residents aged>40yrs old in Uljin county South Korea, A community based survey, 50 diabetics and 50 nondiabetics. Insulin resistance was measured byHOMA-IR. Eight OCPs analyzed | B-HCH and Heptachlor epoxide were positively associated with metabolic syndrome. |
| Rignell-Hydbom et al, 2009 | **case-control**, cohort of women aged 50-59 yrs Southern Sweden. Serum POPs biomarkers were analyzed | The case-control study, including a follow-up design, confirmed that p,p9-DDE exposure can be a risk factor for type 2 diabetes |
| Son et al 2010 | **Case-control** , South Koreans(40 cases, 40 controls),ten OCs were evaluated in relation to diabetes | Low dose background exposure to OCs pesticides was strongly associated with diabetes. Asian may be susceptible to adverse effects of OC pesticides than others. |
| Uemura et al, 2008 | **Cross-sectional**, Japanese aged 15-73yrs, exposure to seven POPs were analyzed. | HbA1C correlated with accumulated TEQ of PCDD + PCDFs, Dioxin-like PCBs and total dioxins-indicating strong association between dioxin exposure and diabetes. |
| Lee et al, 2006 | **Cross sectional**, NHANES 1999/2002, Serum POPs and HOMA-IR) were investigated in 749 nondiabetic participants aged 20yrs. | Nineteen POPs from 5 classes selected, detectable in 60% participants. Data suggest OC pesticides and Nondioxin-like PCBs may be associated with type 2 diabetes risk, by increasing resistance. POPs may interact with obesity to increase the risk of type 2 diabetes. |
| Turyk et al, 2009 | **cohort** of 471 participants. Tested serum for DDE and PCB congeners. Assessed diabetes diagnosis, fish consumption etc. Association of diabetes and exposure examined prospectively. | DDE exposure was associated with incident diabetes. |

**Cross-sectional-studies:**

While the current literature have shed more light in the relationship between POPs and diabetes there are limitations that need to be addressed. One such limitation is that most studies were cross-sectional in design (Bertazzi 1998; Jorgensen 2008; Lang 2008; Lee 2008; Rantakoko 2009; Uemura 2009; Patel 2010). A cross-sectional study is incapable of demonstrating whether pesticide accumulation was greater before or after the onset of diabetes(Fierens 2003). Randomized clinical trial (RCT) would have been the best study to do in order to establish etiology. Since doing RCT will be unethical, the best study design to establish causation is observational case-control study. However a case-control study will not fit into the time frame that the author has. A systematic study of the literature is considered appropriate.

**A) Self-reporting:**

A number of previous studies used self-report method to collect data on diabetes status (Beard 2003; Dellinger 2004; Jorgensen 2008; Uemura 2008; Uemura 2009). Jorgensen's report indicated only 30% of participants were aware they were diabetics. In phase 3 of the CURES only 39.2% of the diabetics were self reported(Martin 2009). The problem with this is that diabetic cases may be misclassified as controls(Lee 2006; Vasiliu 2006). Substantial bias to the null would be evident.

**B) Type 1 or type2 diabetes:**

Previous studies did not differentiate between type 1 and type 2 diabetes, and the association of POPs levels with diabetes prevalence might differ by diabetes type(Lee 2006). Experimental studies have shown that TCDD could cause hypoinsulinemia through alteration of pancreatic membrane tyrosine phosphorylation suggesting that POPs may be involved in the pathogenesis of type 1 diabetes as well as type 2 diabetes(Lee 2006). Though not within the scope of this study, this is a plausible concept which needs to be researched more.

**Conclusion: The case for this study**

Previous cross-sectional studies have stimulated the need for further work on diabetes and POPs. No systematic analysis of the literature has been done on the relation between POPs exposure and diabetes incidence. The literature reviewed showed both the exposure and the disease have substantial prevalence and the Public Health significance could be marked(Lee 2006). It is therefore necessary to carry out a systematic analysis to inform efforts on use of appropriate public health resource in a manner that is efficient, effective and ethically responsible and beneficial to people-especially Americans of Indian descent. It is hoped that this will also stimulate future research, such as a case-control study, to validate the result of this study.

**Methods**

The aim of this work was to study the association of diabetes and exposure to persistent organic pollutant(POPs)s using published studies **.** The purpose of this systematic study was to analyze the association of diabetes incidence and exposure to POPs. Search engines engines such as Pubmed, Google scholar or Web of Science and the data base Pubmed were used to retrieve as many relevant publications as could be obtained. Most previous studies reviewed between 20-and 50 articles. The author retrieved 123 articles on diabetes and POPs. Variables evaluated included socio-demographics, medical history, biochemical characteristics etc(Mohan 2007). The outcome of this study was expected to add to existing knowledge on POPs-diabetes relationship.

**Conceptual Framework**

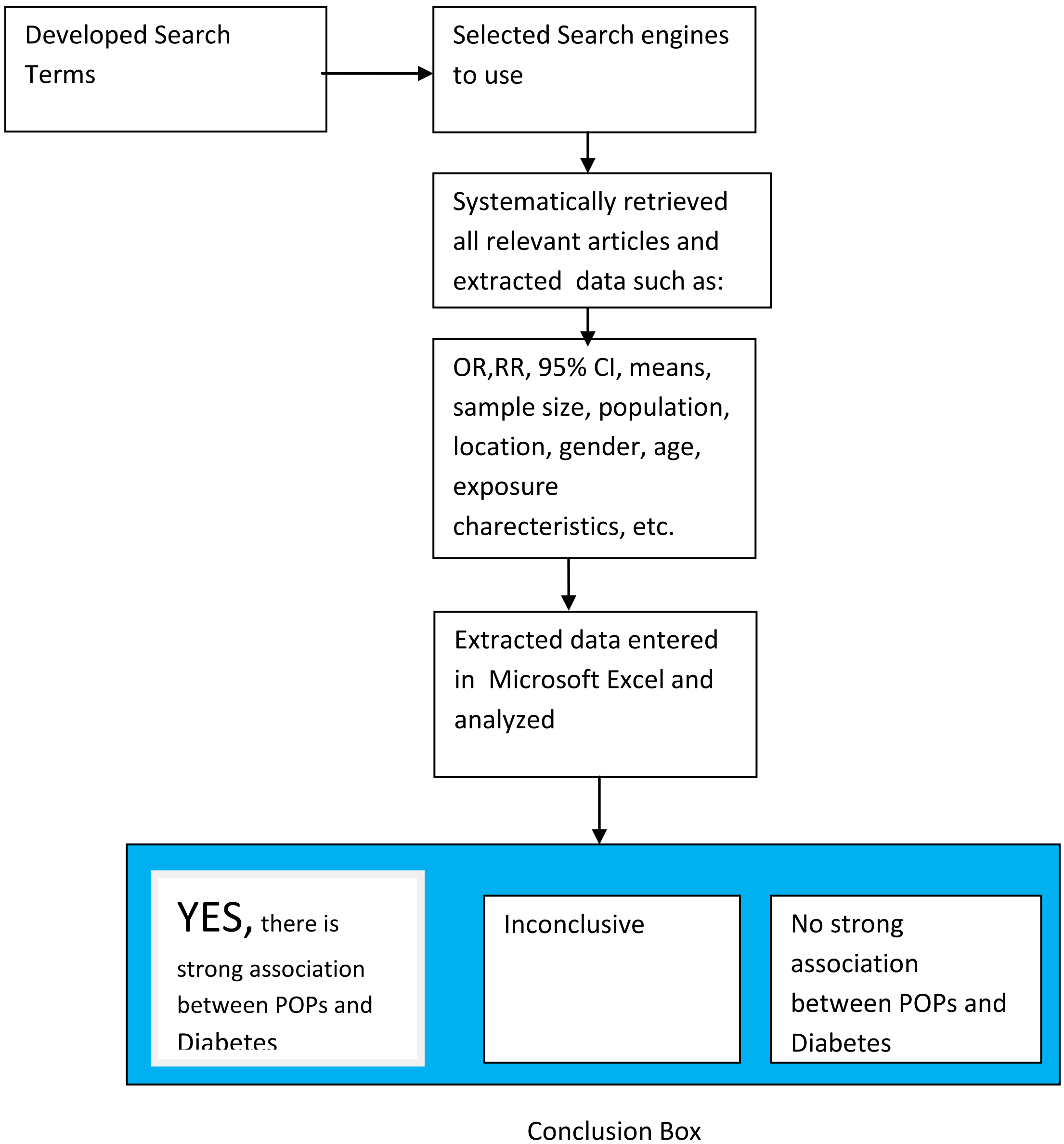



**Fig 2-**Showing Conceptual framework.

**1-1 Strategies:**

a) Used search engines such as Pubmed, Google scholar, Web of Science to retrieve original relevant scientific papers, between December 2010 and February 2011.

b) Search terms included persistent organic pollutants, pesticides, diabetes, pesticides and diabetes, organochlorine pesticides, dioxins etc.

c) Created Endnote library. From endnote library obtained abstracts and downloaded citations.

d) Bibliographies of retrieved references were scanned for further relevant publications.

e) Information abstracted from the retrieved articles were: Odds ratios (OR), Relative Risks (RR), means, age, gender and exposure characteristics. Others are were statistical methods used(including study design, inclusion criteria, variables adjusted for), population studied and, location, year of study and the Author

**1-2 Procedure:**

**a)** From search term articles were retrieved, from Pubmed, first, then Google scholar followed by Web of science**.**

**b)** Articles selected on basis of title and/or abstract

**c)** If title and/or abstract was relevant, full paper was retrieved.

**d)** Excel spread sheet was created**.** A separate excel spreadsheet was created for studies that had OR as measure of effect (as these were the majority).

**e)** Full articles were studied and the relevant information abstracted (such as ORs RRs, Mean, SD, P values)and entered into Excel spreadsheet(Navas-Acien 2006).

**f)** As much as possible the Gantt chart created for this study was adhered to.

**Statistical Methods:**

Inclusion criteria: **a**ll the relevant publications on POPs and diabetes were retrieved from the data bases. There was no date restriction. Only studies in English were retrieved. Relevant articles were selected serially. Exclusion Criteria included articles on experimental/animal studies, as these cannot be applicable to humans yet. Chemicals other than POPs, e.g. arsenic, were excluded. Although arsenic exposure is implicated in diabetes it was not included, firstly, because it is not the focus of this study and secondly, it is not a pesticide. Also excluded were case reports, case series and non-research letters. These would not represent a significant population exposure, as the context will be outside the scope of this study.

Measures of association such as odds ratios (OR), relative risks (RR), standardize d mortality ratios (SMR) and incidence density ratios (IDR) were retrieved from the articles. In articles where these were not recorded effort was made to compute these indices. The data were entered into excel and reviewed thoroughly. There was significant heterogeneity in the data retrieved. The studies were not similar in characteristics and methods(Khan 2003). There was significant variation in statistical methods, populations studied, locations of the studies, confounding factors, demographic as well as exposure characteristics. Consequently, quantitative analysis was considered inappropriate. A qualitative analysis was therefore carried out. The information from the excel spreadsheet was used to make tables of results.

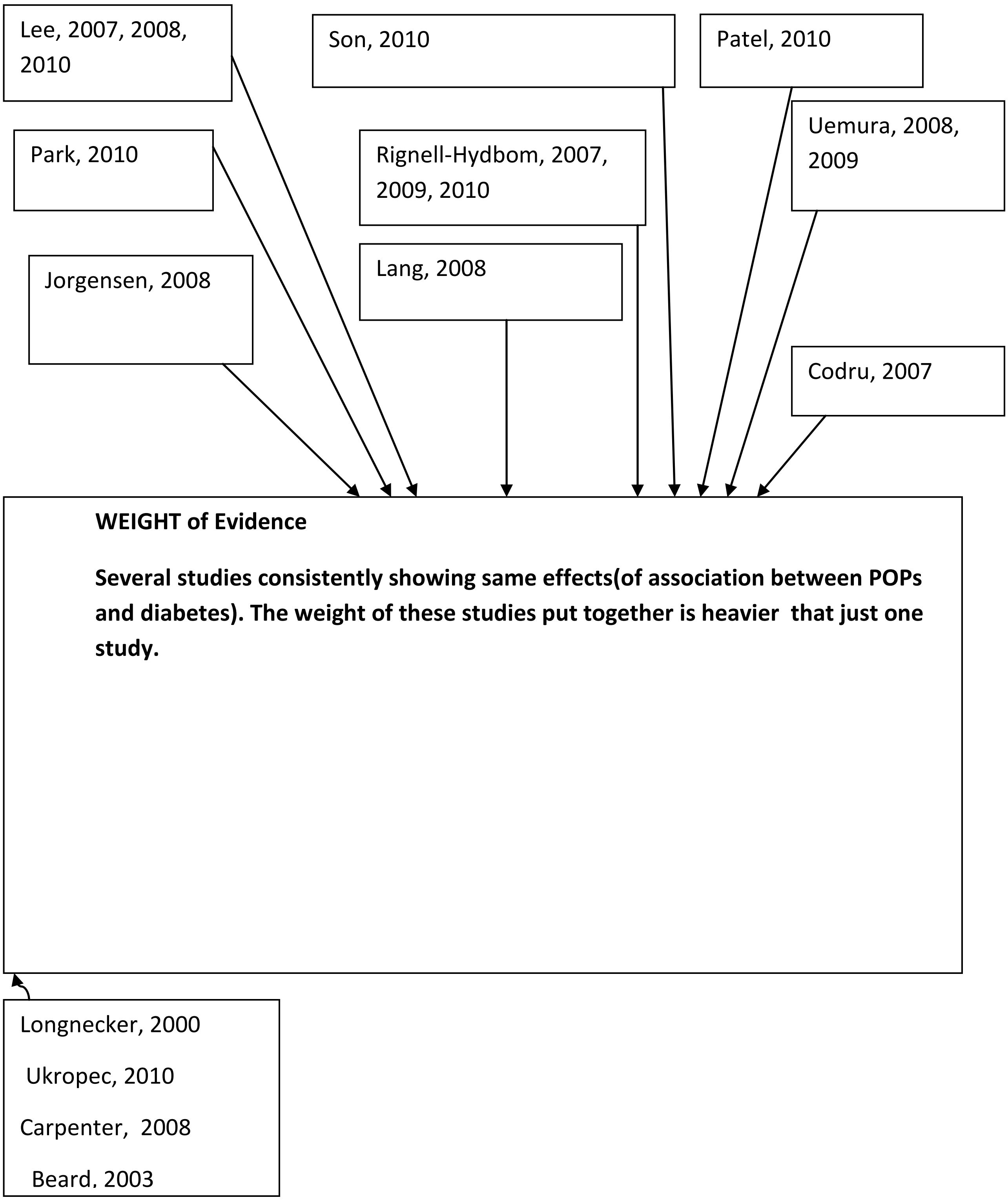
**Limitations:** The main limitation of the study is methodological. This method does not establish strong causal relationship between POPs and diabetes. In addition, reviews of articles and data extraction were carried out by the author, largely, alone. This was subject to missing information or bias. The ideal situation would have been to have at least two persons review the articles and extract information independently(BRIDLE 2005; Navas-Acien 2009). This will eliminate bias or reduce missing information to minimum. Furthermore, only English studies were evaluated. This limited the scope of the literature that would have been covered.

**Strengths:** This pilot study has the advantage of being the first of its kind. There is no previous systematic analysis of relationship between POPs and diabetes incidence. It is hoped that this will pave the way for subsequent and better studies. The outcome added to the body knowledge as related to POPs and diabetes.

**Protection of Human Subjects:** There was no contact with human subjects for this systematic analysis. Thus, no consent was required. However IRB exemption was still obtained.

**Results:**

Putting Pieces of evidence together



Following the methodology outlined for this study the following results were obtained. There were 123 articles published between 1997 and 2010(13 years period) on POPs and diabetes. These were retrieved. Following review of the titles and abstracts 69 articles were excluded and 54 were considered complete for analysis. Fifty percent of the selected publications were cross-sectional studies (table 1), 22.2% were case-control studies, 14.8% cohort studies and literature review accounted for 7(12.96%).

Table1: showing distribution of study designs

| **Study Designs** | | | | |
|---|---|---|---|---|
| Case Control | Cross-sectional | cohort | Literature review | Total |
| 12 | 27 | 8 | 7 | 54 |
| 22.20% | 50% | 14.80% | 12.96% | 100% |

With regard to gender, 22(40.74%) publications reported proportion of men who participated in their studies. Sixty-eight percent (of 22 publications) had proportion of men<50%. Six publications involved only female participants, accounting for 11.11% of studies.

**Table 2: showing number of articles that indicated proportion of men**

| **Proportion of men stated** | |
|---|---|
| YES=22 | No=26 |

Proportion Range (men): 28% to 95%. Studies involving all women=6(11.11%)

Only 23 studies indicted average age of participants accounting for 42.56% of the studies (table 3). The average age range in all studies under consideration was 20-68 years.

**Table3: Showing number of studies that indicated average age.**

| **age stated** | |
|---|---|
| YES=23 | No=31 |

Age range=20years to 68 years

Table 4 shows distribution of different statistical methods. Logistic regression was the most common model used for statistical analysis accounting for 18(33.34%) of the studies reviewed. Two (3.7%) studies used conditional regression modeling, 7(12.96%) studies did not report any statistical method.

**Table 4:** Showing description of statistical methods: Showed significantly, varied statistical methods

| **Description of statistical methods** | **Number of articles** |
|---|---|
| Logistic regression | 18 |
| conditional Logistic regression | 2 |
| Unconditional logistic regression | 1 |
| Spearman's correlation | 1 |
| Cox proportional Hazards regression | 1 |
| Multiple regression | 1 |
| poison regression | 1 |
| Binomial regression | 1 |
| multivariate data analysis | 1 |
| Mann-Whitney test | 1 |
| General Linear regression | 1 |
| Descriptive statistic | 1 |
| Pearson correlation | 1 |
| Stepwise regression | 1 |
| Scatter plots | 1 |
| Database search engines | 1 |
| partial least square regression | 1 |
| No statistical method stated | 7 |

Forty eight (88.89%) studies stated sample size while 6(11.11%) did not. For Cross-sectional and Cohorts studies, sample sizes ranged between 46 and 1,428.

**Table 5**: showing number of articles that stated Sample size

| Sample size stated | |
|---|---|
| Yes=48 | No=6 |

United States reported the highest number of studies (26) accounting for 48.25%, closely followed by Sweden with 9 publications, with Japan coming third with 4 publications.

**Table 6**: Showing Study by country

| Study by country | Number of studies |
|---|---|
| South Korea | 2 |
| Sweden | 9 |
| USA | 26 |
| Japan | 4 |
| Italy | 2 |
| Greenland | 1 |
| Singapore | 2 |
| Taiwan | 1 |
| India | 3 |
| Scotland | 1 |
| Canada | 1 |
| Australia | 1 |
| Slovakia | 1 |

The USA studies had 10 studies from NHANES cohorts accounting for 38.46% of the US publications, followed by reports from NY with 4(table 7).

**Table 7: showing studies in USA alone**

| Studies in USA(26) | Number of studies |
|---|---|
| Wisconsin | 1 |
| NY | 4 |
| NHANES | 10 |
| IOWA/NC | 1 |
| California | 1 |
| Michigan/Minesota/Wisconsin | 1 |
| NIOSH/Airforce | 1 |
| New Jersey/Missouri | 1 |
| Ranch(Vietnam) | 3 |
| Michigan | 1 |
| Minnesota | 1 |
| Total | 26 |

The list of population of participants is indicated by Table 8.

**Table 8: Showing List of study Populations:**

| | |
|---|---|
| Seveso | Michigan PBB cohort |
| Vietnam Air force Veterans | Wives of Fishermen only |
| NIOSH study | Farmers |
| Agricultural workers | Swedish men |
| NHANES | Malmo city University Hospital |
| Chennai Cohort | Yuchen |
| NY Data | The Intuits |
| Lactating Mothers | Great Lakes sport-fishers |
| Slovakia Residents | Children |
| New Jersey Mission | Diabetics |

NHANES=National health and Nutrition Examination Survey. NIOSH=National Institute for Occupational Safety and health.PBB=Polybrominated biphenyls

Diagnosis of diabetes was based on serum blood sugar level. Only 22 studies reported blood sugar levels accounting for 40.74 %( table 9). Out of these serum blood sugar of

126mg/dl or more was the most commonly used blood sugar level, the least used level being >7.8mmol/l and HBA1C >5.6%.

**Table 9: Showing Diagnosis of Diabetes on basis of Blood sugar level criteria**

| **Glucose Levels** | **Number of studies** |
|---|---|
| >7.8mmol/l | 1 |
| 11.1mmol/l(2hrs post-prandial) | 2 |
| >=7.0mmol/l | 2 |
| >126.omg/dl | 4 |
| 126.0mg/dl | 4 |
| >125.0mg/dl | 3 |
| OGTT(Oral glucose tolerance test) | 2 |
| >200.0mg/dl(2hrs post-prandial) | 3 |
| HBA1C >5.6% | 1 |
| Total | 22 |

32 studies had no serum sugar levels.

Forty-eight studies indicated exposure routes accounting for 88.89% of the studies, while 8 studies did not report on exposure routes (table 10).

**Table 10: Exposure Routes**

| **Exposure Routes Stated** | |
|---|---|
| YES=48 | No=8 |

Table 11 shows routes of exposure by number of studies. The most common route of exposure was ingestion in 35 studies accounting for 72.92% of the studies. Out of these 19 studies indicated exclusive ingestion routes, the other 16 other studies were mixture of ingestion and other routes such as inhalational and/or dermal. Twenty-five papers( 52.1%)reported inhalational routes of exposure with 9 papers indicating exclusive inhalational routes, the other 16 papers were mixture of inhalational , dermal, and/or ingestional routes of exposure .Only 4 studies indicated exclusive dermal exposure accounting for 8.34%.

**Table 11: Number of studies by exposure routes.**

| **Exposure Routes by Number of studies** | |
|---|---|
| Inhalational | 25(9/25 inhalation alone) |
| Dermal | 4 |
| Ingestion | 35(19/35 ingestion alone) |

Because ingestion was the most common route of exposure, food types were classified into crops/plants foods, Fish/meat foods and water/diary (Table 12). Thirty-four studies (70.83%) indicated foods were fish, marine and poultry; crops/plants food sources were noted in 23(47.92%) studies and water/diary accounted for 18 studies (37.50%). Studies with all foods groups implicated were 15 accounting for 31.25% of the studies, while 16 studies did not indicate any food types.

**Table 12: showing ingestion exposure by food types**

| **Food group** | **Number of studies** |
|---|---|
| Fish, marine, poultry (alone) | 34 |
| water/diary (alone) | 18 |
| Crops/plants foods (alone) | 23 |
| All groups of foods | 15 |
| Studies with no indication | 16 |

The levels of exposure and comparison or referent groups varied across studies (Table 13). While some studies compared quartile, some compared tertiles. Others used various descriptive terms for comparisons. Fourteen studies (42.42%) compared quartiles (highest versus lowest); 5 studies (15.15%) compared tertiles. In 21 studies (38.89%) no comparison group and referent not stated.

**Table 13: Exposure levels compared to referents**

| Level of exposures Vs Referent | Number of studies |
|---|---|
| Highest tertile vs lowest tertile | 5 |
| Highest quartile vs lowest quartile | 14 |
| upper cut point vs lower cut point | 1 |
| workers vs referent | 1 |
| High/medium/low vs referent | 2 |
| Highest vs lowest | 4 |
| highest quintile vs lowest quintile | 1 |
| percentile(90th, 75th, 50th, 25th) | 1 |
| Cases vs control | 3 |
| Diabetes vs No diabetes | 1 |
| Exposure levels compared to referents not stated | 21 |

Forty-seven studies (87.03%) reported on POPs associated with diabetes while 7(12.96%) studies did not (Table 14). PCBs topped the list of those most associated with diabetes; it was listed in 11 studies (23.40%). PCBs was closely followed by *p, p'*-DDE with 8 studies accounting for 17.02% of the studies. TCDD was third in rank with 7 studies while OC pesticides were fourth with 4 studies.

**Table 14: Most common POPs implicated in Diabetes**

| POPs listed as Most common | Number of studies |
|---|---|
| P,P'-DDE | 8 |
| CB-153 | 2 |
| PCBs | 11 |
| PBDE | 1 |
| Oxychlordane | 1 |
| PCDD | 3 |
| DL-PCB | 1 |
| OC Pesticides | 4 |
| BPA | 2 |
| Organophosphates | 1 |
| H-HCH | 2 |
| TCDD | 7 |
| DDT | 2 |
| PCDFs | 2 |

Pls, see Appendix 2 for names of these chemicals.

Forty-four studies stated measure of effects accounting for 81.48% of the studies (Table 15). Out of these odds ratios (OR) was the most commonly reported measure of effects with 31 studies accounting for 70.45% of the studies. This was followed by relative risk (RR) with 5 studies (11.36%) and correlation coefficient(r) with 3 studies. In 10 studies (18.52%) there was no report on measure of effects.

**Table 15: Measure of Effect**

| Measure of effect | Number of studies |
|---|---|
| OR | 31 |
| RR | 5 |
| r | 3 |
| r2 | 2 |
| IDR | 1 |
| SMR | 1 |
| IRR | 1 |
| total | 44 |

No measure of association stated=10studies

**Key**:OR=odds ratio, RR= Relative risk, r=linear correlation coefficient, r2=coefficient of determination, IDR=Incidence density ratio.., SMR=Standardized mortality ratio, IRR=Incidence Rate Ratio

The ORs were categorized as shown in Table 16(a) and reviewed further. Two studies(with the lowest OR) had OR 0.85 and 0.73(not shown on table 16(a)) respectively; while the highest OR was 26. The most common OR range was 1.5-2.0 and 6.5-7.0accounting for 22.58% each. As much as 25 studies (80.65%) had OR greater than 1.5.

**Table 16(a): Odds Ratio (OR)**

| OR strength | Number of studies |
|---|---|
| <1 | 2 |
| 1-1.5 | 4 |
| 1.5-2.0 | 7 |
| 2.0-2.5 | 3 |
| 2.5-3.0 | 3 |
| 3.0-3.5 | 0 |
| 3.5-4.0 | 1 |
| 4.0-4.5 | 1 |
| 4.5-5.0 | 1 |
| 5.0-5.5 | 2 |
| 5.5-6.0 | 1 |
| 6.0-6.5 | 1 |
| 6.5-7.0 | 7 |
| 7.0-7.5 | 1 |
| 7.5-8.0 | 0 |
| 8.0-8.5 | 0 |
| 8.5-9.0 | 0 |
| 9.0-9.5 | 0 |
| 9.5-10.0 | 0 |
| >10 | 3 |
| total | 31 |

Range of OR: 0.73-26

Forty-one studies reported on confidence interval accounting for 75.93% of the studies (Table17). Out of these the confidence interval was significant in 22 studies (53.66%), as shown in table 17. It was not significant in 19 studies (46.34%). The confidence interval was not reported in 13 out of 54 studies (24.1%).

**Table16 (b): Showing measure of effect (OR only) and Population studied**

| Source(Author) | year | Design | population | Diagnosis diabetes(serum glucose level) | OR/RR Diabetes(95%CI) |
|---|---|---|---|---|---|
| | | | | | |
| **Park** | 2010 | CC | Nondiabetic cases with metablic sym | 126 mg/dL | OR=6.0 |
| **Rignell-Hydbom** | 2007 | CS | Fishermen's wives | | OR=1.6(95%CI 1.0, 2.7) |
| **Rignell-Hydbom-1** | 2009 | CC | women aged 50-59yrs | OGTT | OR=5.5 [95% CI 1.2, 25] |
| **Rignell-Hydbom-2** | 2010 | CC | Children | | OR=95%CI 0.85, 0.45, 1.63) |
| **Turyk(b)(Chemo)** | 2009 | CS | Great Lake sport fish consumers. | >125 mg/ dL | OR=1.9 |
| **Son** | 2010 | CC | comm survey | ≥126 mg/dl | OR=26.0 (95%CI 1.3–517.4) |
| **Uemura(b) Assoc** | 2008 | CS | Japanese public | >126mg/dl | OR=6.82(95% CI 2.59,20.1) |
| **Uemura** | 2009 | CS | Japanese | HbA1c ≥ 5.6% | OR=5.4 (CI 3.1–10) |
| **Jørgensen** | 2008 | CS | The Inuits | OGTT | OR=2.1 (0.9–5.2) |
| **Lang** | 2008 | CS | USA(NHANES) | | OR=2.43 (95% CI1.35-4.38) |
| **Montgomery** | 2008 | CC | Iowa/NC | | OR = 1.06 (95%CI0.83-1.35) |
| **WANG** | 2008 | CC | yuchen | | OR= 2.1 [95% CI 1.1– 4.5] |
| **Codru** | 2007 | CS | NY(Native-American) | > 125 mg/dL | OR=3.9(95% CI1.5–10.6). |
| **Cox** | 2007 | CS | NHANES(HISPANIC) | | OR=7.5 (95%CI3.6–15.8) |
| **Everett** | 2007 | CS | NHANES | >126 mg/dl | OR=2.57 (95% CI 1.33–4.95) |
| **Rignell-Hydbom** | 2010 | CC | Malmo Univ Hosp. | | OR= 0.73 (95%CI0.42- 1.27) |
| **Rignell-Hydbom** | 2007 | co | women | >126 mg/dl | OR=1. 6(95%CI 1.0-2.7) |
| **Rylander** | 2005 | CS | Swedish men | | OR= 1.16(95%CI 1.03, 1.32) |
| **Steenland** | 2001 | CS | Niosh/Airforce vets | 126 mg/dl | OR=1.2(95%CI o.9,1.5) |
| **Calvert** | 1999 | CS | NJ/Missoiuri | >7.8 mmol/l | OR=1.49(95% CI 0.77, 2.91) |

**Table16 (b): Measure of effect (OR only) and Population studied-continued**

| Source(Author) | year | Design | population | Diagnosis diabetes(serum glucose level) | OR/RR Diabetes(95%CI) |
|---|---|---|---|---|---|
| **Beard** | 2003 | CC | agric workers | | OR=10.39(95%CI 6.15,17.54) |
| **Carpenter** | 2008 | lit Rev. | all | | OR=1.71 (95% CI =1.00,2.91) |
| **Kang** | 2006 | CC | vietnam Vets | | OR=1.50 (95%CI 1.15, 1.95) |
| **Lang** | 2010 | CS | NHANES 2003-04 | | OR=1.39(95% CI 1.21, 1.60) |
| **Patel** | 2010 | CS | NHANES 1999-2006 | 126 mg/dL. | OR=4.5(95%CI 2.1,9.9) |
| Ukropec | 2010 | CS | Residential area | >7.0 mmol/l | OR=2.7495%CI 1.92, 3.90) |
| **Longnecker** | 2000 | CS | Air Force(vietnam Vets non-exposed group) | >200 mg/dL | OR=1.71 (95% CI 1.00, 2.91). |
| **LEE(Extended)** | 2007 | CS | NHANES 99-02 | >126mg/dl | OR=24.3 (95%CI 7.0,84.5) |
| **Lee** | 2010 | CC | CARDIA cohort. | ≥ 126 mg/dL | OR=2.6(95%CI 1.0, 7.0) |
| **Lee(Relationship)** | 2007 | CS | NHANES 99-02 | ≥5.6 mmol/l. | OR=5.9 (95%CI 2.8,12.2) |
| **Lee** | 2008 | CS | NHANES | | OR=5.0(95%CI 1.8–13.4 |

**Table 17: Confidence interval**

| **Confidence Interval** | **Number of studies** |
|---|---|
| Significant | 22 |
| Not significant | 19 |
| Confidence interval Not stated | 13 |
| Total | 54 |

In 47 studies (87.04%) inclusion criteria were clearly stated while in 7 studies did not have inclusion criteria stated (table 18).

**Table 18: Inclusion Criteria**

| Inclusion Criteria stated | |
|---|---|
| Yes=47 | no=7 |

Thirty-six studies (66.67%) had factors adjusted for clearly stated while 18 studies did not report on factors adjusted for (table 19).

**Table 19: Factors adjusted stated for by number of articles.**

| 'Adjusted for' stated | |
|---|---|
| Yes=36 | no=18 |

Table 20 shows the list of factors adjusted for. Table 21 showed the list of top ten factors adjusted for , with age being the most common factor adjusted in 21(38.89%) of the studies, followed by BMI in 16(29.63%) studies with sex being third in 14(25.93%) studies.

**Table 20: List of Factors adjusted for.**

| |
|---|
| age, sex, BMI, ethnicity, Socioeconomic status, Smoking, race/ethnicity, education, income, Waist circumference, urine creatine concentration, military occupation (officer, enlisted flyer, or enlisted ground crew), family history of diabetes (no or yes), duration of diabetes, alcohol consumption, exercises, triglyceride, cholesterol, poverty income ratio, half life of serum TCDD, region, body fat, Residential Latitude, sun reaction, population density (urban/rural), sport fish meals. |

**Table 21: Top ten factors adjusted by studies:**

| Factor adjusted for | Number of studies it appeared |
|---|---|
| Age | 21 |
| BMI | 16 |
| sex | 14 |
| Tobacco smoking | 11 |
| Race/Ethnicity | 9 |
| Income | 8 |
| Alcohol consumption | 7 |
| Serum cholesterol | 6 |
| Waist circumference | 5 |
| Triglycerides | 4 |

**DISCUSSION**

The objective of this study was achieved. There is a strong concensus among the studies, of a positive association between POPs and diabetes. That 50% of the studies identified (table 1)were cross-sectional is in agreement with other previous findings(Bertazzi 1998; Jorgensen 2008; Lang 2008; Rantakoko 2009; Uemura 2009; Patel 2010). The number of studies used for this study is above the range in the literature reviews. The number of literature reviews articles considered in this study was 7. These reviewed previous publications ranging between 24 and 40. Arisawa reviewed 24 articles, Eskinazi 26 and Wild 40. This study identified 54 articles for review. This indicates a growing body of knowledge and literature on the subject. One limitation of cross-sectional studies, as pointed out by Fierens, is the inability of establishing causality(Fierens 2003).

Established risk factors for diabetes include age(Kouznetsova 2007). The age range noted in this study was 20-68 years. Lee's NHANES study had the oldest average age of 68 years(Lee 2006). Her study and others' indicated most diabetic cases associated with POPs were in adults. Uemura and Lang had the youngest average age of 20 years each(Lang 2008; Uemura 2009). This does not mean that diabetes associated with POPs does not affect individuals whose ages are below 20 years. Further research is needed, considering the fact that children also live in the same environment where the adults affected live and are exposed. However Lee had suggested that the association of POPs and diabetes prevalence might differ in diabetes type(I or II)(Lee 2006).

Majority studies reported the proportion of men which ranged between 28% and 95%.

Most of the 22 papers reported the proportion of men was less than 50%. This suggests that the female gender is the most impacted by diabetes due to POPs exposure. This is corroborated by Subramanian's and Tanabe's studies(Subramanian 2007; Tanabe 2007). Tanabe found that in India levels of dioxin(in breast milk) and related compounds in mothers living around the open dumping site were notably higher than other Asian countries(Tanabe 2007). In addition Subramania's report of 2007 highlighted the presence of pesticides, in significant levels, in human breast milk in Chennai(Subramanian 2007). Furthermore, Glynn noted, that POPs accumulate in lipid rich fraction of fish, and fish consumption represents a significant source of exposure to humans (Glynn 2003). Since women generally have more fat in their body than men, this might explain why their numbers are higher than men. Conclusively, the female gender bears the brunt of diabetes due to POPs exposure. Could this be the same in the US? Could Americans of Indian descent benefit from this knowledge? Answers to this questions will better inform policies on public health related to POPs and diabetes. Also the public will be better advised on prevention and reduction of morbidity and mortality due to this problem.

More than half of the studies were carried in western world with US topping the list (Table 6). In Asia Japan and India are leading. This trend does not establish causality, it suggests the increasing awareness of the association between POPs and diabetes. In the US the NHANES data is the major source of information on pesticides and diabetes accounting for 38.46% of the US publications on POPs and diabetes(Table 7)(Lee 2006; Cox 2007; Lang 2008; Lee 2010; Patel 2010). This presents an opportunity to explore the subject further. India is rising in agricultural activities to feed its high population(Gupta

2004). This provides an encouragement to study the association between diabetes and POPs in such an environment.

Making a diagnosis of diabetes was largely based on serum sugar levels(Longnecker 2000; Mohan 2007; Tanabe 2007; Turyk 2009; Park 2010; Patel 2010; Ukropec 2010). Forty-one percent (Table 9) of the studies reported on diabetes based on blood studies. Out of these, serum blood sugar of 126mg/dl or more was the most commonly used blood sugar level, for diagnosis. This underscores the importance of blood sugar evaluation in the prevention of diabetes or reduction of morbidity/mortality due to the disease which may arise from POPs exposure.

The most common route of exposure was ingestion in 35 studies accounting for 72.92% of the studies (Table 11). This is in agreement with previous studies(Glynn 2003; Codru 2007; Everett 2007; Jayashree 2007; Jorgensen 2008; Rignell-Hydbom 2009; Turyk 2009). This knowledge should inform public health departments, organizations or personnel to counsel the public on diabetes prevention through what a person ingests.

PCBs was the lead chemical associated with diabetes, listed in 23.4% of the studies(table 14) including the reports by Uemura and Patel(Vasiliu 2006; Tanabe 2007; Uemura 2008; Rantakoko 2009; Turyk 2009; Patel 2010; Rignell-Hydbom 2010; Ukropec 2010). This list of the chemicals identified in these studies underscore the importance of POPs and diabetes.

The most common measure of association was OR followed by RR (Table 16). Only 2 studies had OR<1. Eighty-one percent of the studies had OR of 1.5 or more, with the highest OR being 26(Son 2010). The OR was strongly supported by the confidence intervals, which was significant in 53.66% of the studies that reported on confidence intervals (Table 17). These findings suggest a significant causal association of POPs and diabetes, as concluded by several authors(Longnecker 2000; Longnecker 2001; Beard 2003; Codru 2007; Cox 2007; Patel 2010). Codru concluded PCBs, DDE, and HCB were positively associated with diabetes, though mirex had a negative association. Codru's conclusion was strongly supported by Uemura and Park(Uemura 2008; Park 2010).

Several Confounding factors were noted in several studies (Table 20). As much as two-thirds of the studies adjusted for confounders (Table 19). The top ten (Table 21) confounding factors adjusted for (in order of frequency), were age, sex, BMI, tobacco smoking, race/ethnicity, income, alcohol consumption, serum cholesterol, waist circumference and triglycerides. This suggests that though POPs may be blamed for diabetes in those exposed to them, these factors should not be ignored in determining association.

**Conclusion**

This review used systematic review method to provide an evidence-based evaluation of the relationship between persistent organic pollutants and diabetes. The result of this review shows the possibility of significant association between persistent organic pollutants and diabetes. Thus exposure to these chemicals could be listed as risk factors for the disease. This has great implication for public health and research. Because the prevalence of diabetes is expected to double worldwide by 2030 it is imperative that public health advocates and researchers should take this threat serious. Concerted efforts should be made by all concerned to prevent and /or reduce diabetes prevalence and its debilitating and fatal consequences. One of such measures must include aggressive efforts to reduce or stop use of persistent organic pollutants, while providing alternatives. Although methodologically sound methods of studies are needed to evaluate causality between persistent organic pollutants and diabetes, much has been gained from previous studies to establish the link between POPs and diabetes, as established in this study.

The strength of this study is that it is the first of its kind. It is hoped that this will be an eye opener to conduct better research to establish causality. The outcome of this study has added to the body of knowledge as related to persistent pollutants and diabetes. The main limitation of the study is methodological. Systematic review does not establish strong causal relationship between persistent organic pollutants and diabetes. In addition, reviews of articles and data extraction were carried out by the author, largely, alone. This was subject to missing information or bias. The ideal situation would have been to have at least two persons review the articles and extract information independently(BRIDLE 2005; Navas-Acien 2009). This will eliminate bias or reduce missing information to minimum. Furthermore, only English studies were evaluated.

This limited the scope of the literature and the body of evidence that would have been covered.

**Recommendations**

On the basis of this work, the following recommendations are made:

1) Exposure to POPs should be listed as a risk factor for diabetes.
2) It is recommended that serious health policy efforts should be made in education and enlightenment campaign of the public on association between POPs and diabetes.
3) Discourage or reduce exposure to POPs
4) More studies to uncover the exact mechanisms in which POPs cause diabetes in humans. Animal studies have been carried out(Remillard 2002), but their relevance to human populations has not been determined.
5) Further investigation of the association of POPs and diabetes is recommended. Susceptible populations may be identified and followed up.

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EMORY UNIVERSITY | Institutional Review Board

TO: Likita Aminu
Principal Investigator

DATE: December 14, 2010

RE: **Notification of Submission Determination: No IRB Review Required**
IRB00048037
Chronic exposure to Persistent Organic pollutants (POPs) and diabetes incidence: A systematic review

The above-referenced study has been vetted by the Institutional Review Board (IRB), and it was determined that it does not require IRB review because it does not meet the definition of "Research involving Human Subjects" under applicable federal regulations. Based on the information included in the submission, the PI will only conduct a systematic review of the current literature to study exposure to POPs and its relationship with diabetes incidence. At no time will the PI interact with human subjects or obtain identifiable private information from human subjects. Accordingly, IRB review is not required.

45 CFR Section 46.102(f)(2) defines "Research involving Human Subjects" as follows:

> Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:
>
> (1) data through intervention or interaction with the individual, or
> (2) identifiable private information
>
> Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Please note that any changes to the protocol could conceivably alter the status of this research under the federal regulations cited above. Accordingly, any substantive changes in the protocol should be presented to the IRB for consideration prior to their implementation in the research.

Sincerely,

Carol Corkran, MPH, CIP
Senior Research Protocol Analyst
*This letter has been digitally signed*

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**Appendix 2: List of Persistent organic pollutants and Uses**

a) Persistent Organic Pollutants (POPs): What are POPs? In 1995 the UN governing Council gave a short list of POPs (12 chemicals) and called it the 'dirty dozen'.

These included :

Aldrin

Chlordane

DDT

Dieldrin

Endrin

Heptachlor

Hexachlorobenzene

Mirex

Polychlorinated biphenyls (PCBs)

Polychlorinated dibenzo-p-dioxins (PCDD)

Polychlorinated dibenzofurans (PCDDFs)

toxaphene(Wikipedia 2010).

Their properties include low water solubility, high lipid solubility, high molecular masses, often halogenated with chlorine. The more the chlorine the more the resistant to degradation.

**b) Uses of POPs:**

1) **PCBs** are good insulators and are used as coolants and lubricants in transformers and capacitors(Pelletier 2003; ATSDR 2010).
2) Found in : hydraulic oils, old microscope, old fluorescent bulbs and electrical devices
3) **DDT,** for agricultural and public health purposes from 1940s until 1970s when it was banned because of its toxicity((Eskenazi 2009) ;(Gupta 2004)).
4) Other than agriculture and public health use pesticides have other uses such as industrial(fumigation of buildings and ships), domestic(household and garden spray), and personal application(control of ectoparasites such as fleas or lice)(Gupta 2004).
5) DDT continues to be used for malaria vector control in parts of Africa, Latin America and Asia including India((Cox 2007); (Eskenazi 2009); (Son 2010)).
6) Polychlorinated dibenzo-p-dioxins are chlorinated chemicals commonly called dioxins. They are produced as by-products in bleaching of paper products(Everett 2007).

**References**

ATSDR (2010). ""Polychlorinated Biphenyls (PCBs)"." ATSDR-agency for Toxic Substances and Dusease Registry 2010. http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=26. **07/06/2010**.

Bakore, N. (2004). "Organochlorine Pesticide Residues In Wheat And Drinkingwater Samples Jaipur. Rajastan , India." Environmental Monitoring and Assessment **98**: 381–389.

Beard, J. (2003). "Health Impacts of Pesticide Exposure in a Cohort of Outdoor Workers." Environmental Health Perspectives **111**(5): 724-730.

Bertazzi, P. A. (1998). "The Seveso studies on early and long-term effects of dioxin exposure: a review." Environ Health Perspect **106(2)**: 625-633.

BRIDLE (2005). "Systematic review of the effectiveness of health behavior interventions based on the transtheoretical model." Psychology and Health **20** ( 3 ): 283–301.

Calvert, G. M. (1999). "Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin." Occup Environ Med **56**(4): 270-276.

Carpenter, D. O. (2008). "Environmental Contaminants as Risk Factors for Developing Diabetes." Reviews On Environmental Health **23**(1): 59-71.

Ceriello, A. (2008). "International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations." Diabetic Medicine **25**: 1151–1156.

Codru, N. (2007). "Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans." Environ Health Perspect **115**(10): 1442-1447.

Cox, S. (2007). "Prevalence of Self-Reported Diabetes and Exposure to Organochlorine Pesticides among Mexican Americans: Hispanic Health and Nutrition Examination Survey, 1982–1984." Environmental Health Perspectives **115**(12): 1747–1752.

Dellinger, J. A. (2004). "Exposure assessment and initial intervention regarding fish consumption of tribal members of the Upper Great Lakes Region in the United States." Environmental Research **95**: 325-340.

Eskenazi, B. ( 2009). "The Pine River Statement: Human Health Consequences of DDT Use." Environmental Health Perspectives **117**(9).

Everett, C. J. (2007). "Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999–2002 National Health and Nutrition Examination Survey." Environmental Research **103**: 413-418.

Fierens, S. (2003). "Dioxin/polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium." Biomarkers **8**(6): 529-534.

Fujiyoshi, P. T. (2006). "Molecular epidemiologic evidence for diabetogenic effects of dioxin exposure in U.S. Air force veterans of the Vietnam war." Environ Health Perspect **114**(11): 1677-1683.

Glynn, A. W. (2003). "Organochlorines in Swedish women: determinants of serum concentrations." Environ Health Perspect **111**(3): 349-355.

Gupta, P. K. (2004). "Pesticide exposure—Indian scene." Toxicology and Industrial Health **198**: 83–90.

Imbeault, P. (2002). "Increase in Plasma Pollutant Levels in Response to Weight Loss Is Associated With the Reduction of Fasting Insulin Levels in Men But Not in Women." Metabolism **51**(4): 482-486.

Jayashree, R. (2007). "Organochlorine pesticide residues in ground water of Thiruvallur district, India." Environ Monit Assess **128**: 209–215.

Johnson, B. L. (2007). "Environmental Policy And Public Health." CRC Press **1**: 1-441.

Jorgensen, M. E. (2008). "A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit." Diabetologia **51**(8): 1416-1422.

Kern, P. (2002). "The Stimulation of Tumor Necrosis Factor and Inhibition of Glucose Transport and Lipoprotein Lipase in Adipose Cells by 2,3,7,8-Tetrachlorodibenzo-p-Dioxin." Metabolism **51**(1): 65-68.

Khan, S. K. (2003). "systematic Reviews to support Evidence-based Medicine: How to Review and Apply Findings of Healthcare Research." **1**: 1-131.

kogevinas, M. (2001). "human health effects of dioxin:cancers,reproductive and endocrine system effects." Human reproduction update **7**(3): 331-339.

Kouznetsova, M. (2007). "Increased rate of hospitalization for diabetes and residential proximity of hazardous waste sites." Environ Health Perspect **115**(1): 75-79.

Lang, I. (2008). "Association of UrinaryBisphenolAConcentration With Medical Disorders and Laboratory Abnormalities in Adults." JAMA www.jama.com **300**(11): 1303-1310.

Latini, G. (2009). "Influence of environment on insulin sensitivity." Environment International **35**: 987-993.

Lee (2008). "Association of organochlorine pesticides with peripheral neuropathy in patients with diabetes or impaired fasting glucose." Diabetes **57**(11): 3108-3111.

Lee, D.-H. (2010). "Low Dose of Some Persistent Organic Pollutants

Predicts Type 2 Diabetes: A Nested Case-Control Study." ENVIRONMENTAL

HEALTH

PERSPECTIVES: 1 of 31.

Lee, D. (2006). "A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes." Diabetes Care **29**(7): 1634-1644.

Longnecker, M. (2001). "Environmental contaminants as etiologic factors for diabetes." Environ Health Perspect **109(l 6)**: 871-876.

Longnecker, P. M. (2000). "Serum Dioxin Level in Relation to Diabetes Mellitus among Air Force Veterans with Background Levels of Exposure " Epidemiology **11**: 44-48.

Martin, M. (2009). "NIH RO3 Grant Proposal: Nested case-control study of chronic exposure to persistent organic pollutants (POPs) and diabetes incidence." A thesis submitted to the Hubert Department of Global Health.: 1-26.

Mohan, V. (2007). "A diabetes risk score helps identify metabolic syndrome and cardiovascular risk in Indians – the Chennai Urban Rural Epidemiology Study (CURES-38)." Diabetes, Obesity and Metabolism **9**: 337–343.

Montgomery, M. P. (2008). "Incident Diabetes and Pesticide Exposure among Licensed Pesticide Applicators: Agricultural Health Study, 1993–2003." Am J Epidemiol **167**(1235-1246).

Muir, T. (2001). "Societal Costs of Exposure to Toxic Substances: Economic and Health Costs of Four Case Studies That Are Candidates for Environmental Causation." Environmental Health Perspectives **109**(6): 885-903.

Navas-Acien (2006). "Arsenic Exposure and Type 2 Diabetes: A Systematic Review of the Experimental and Epidemiologic Evidence." Environmental Health Perspectives **114** (5 ): 641-648.

Navas-Acien, A. (2009). "Rejoinder: Arsenic Exposure and Prevalence of Type 2 Diabetes." Epidemiology **20**(6): 816-820.

Park, S. (2010). "Relationship Between Serum Concentrations of Organochlorine Pesticides and Metabolic Syndrome Among Non-Diabetic Adults." J Prev Med Public Health **43**(1): 1-8.

Patel, C. J. (2010). "An Environment-Wide Association Study (EWAS) on Type 2 Diabetes Mellitus." PLoS ONE | www.plosone.org 1 May 2010 **5**(5): 1-10.

Pelletier (2003). "Energy balance and pollution by organochlorines and

polychlorinated biphenyls." obesity reviews in Endocrine & Metabolic Disorders **4**: 17–24.

Rantakoko (2009). "A simple and fast liquid–liquid extraction method for the determination of

2,2 ,4,4 ,5,5 -hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-

bis(p-chlorophenyl)-ethylene (p,p -DDE) from human serum for epidemiological

studies on type 2 diabetes." Journal of Chromatography **1216**(A): 897-901.

Rantakoko, P. (2009). "A simple and fast liquid–liquid extraction method for the determination of 2,2 ,4,4 ,5,5 -hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2- bis(p-chlorophenyl)-ethylene (p,p -DDE) from human serum for epidemiological studies on type 2 diabetes." Journal of Chromatography **1216**(A): 897-901.

Remillard (2002). "Linking Dioxins to Diabetes: Epidemiology and Biologic Plausibility." Environmental Health Perspectives **110**(9): 853-858.

Remillard, R. (2002). "Linking Dioxins to Diabetes: Epidemiology and Biologic Plausibility." Environmental Health Perspectives **110**(9): 853-858.

Rignell-Hydbom (2010). "A Nested Case-Control Study of Intrauterine Exposure to

Persistent Organochlorine Pollutants in Relation to Risk

of Type 1 Diabetes." PLoS ONE | www.plosone.org **5**( 6 ): 1-6.

Rignell-Hydbom, A. (2007). "Exposure to persistent organochlorine

pollutants and type 2 diabetes mellitus." Human & Experimental Toxicology **26** 447–452.

Rignell-Hydbom, A. (2009). "Exposure to p,p'-DDE: a risk factor for type 2 diabetes." PLoS One **4**(10): 1-6.

Ruzzin, J. (2010). "Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome." Environmental Health Perspectives **118**(4): 465-471.

Rylander, L. (2005). "A cross-sectional study of the association between persistent organochlorine pollutants and diabetes." Environ Health **4**: 28.

Sakurai, K. (2004). "Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes." Br J Pharmacol **141**(2): 209-214.

Son, H. (2010). "Strong associations between low-dose organochlorine pesticides and type 2 diabetes in Korea." Environment International **30**(30): 1-5.

Steenland, K. (2001). "Dioxin and diabetes mellitus: an analysis of the combined NIOSH and Ranch Hand data." Occup Environ Med **58**(10): 641-648.

Subramanian, A. (2007). "High levels of organochlorines in mothers' milk from Chennai (Madras) city, India." Chemosphere **68**: 928–939.

Tanabe, S. (2007). "Persistent organic pollutants in human breast milk from Asian countries." Environmental Pollution **146**(2): 400-413.

Turyk, M. (2009). "Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers." Environ Health Perspect **117**(7): 1076-1082.

Uemura, H. (2008). "Associations of environmental exposure to dioxins with prevalent diabetes among general inhabitants in Japan." Environmental Research **108**: 63-68.

Uemura, H. (2008). "PCDDs/PCDFs and dioxin-like PCBs: Recent body burden levels and their determinants among general inhabitants in Japan." Chemosphere **73**: 30-37.

Uemura, H. (2009). "Prevalence of Metabolic Syndrome Associated with Body Burden Levels of Dioxin and Related Compounds among Japan's General Population." Environmental Health Perspectives **117**(4): 568-573.

Ukropec (2010). "High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail." Diabetologia

**53** 899–906.

Vasiliu (2006). "Polybrominated Biphenyls, Polychlorinated Biphenyls, Body Weight, and Incidence of Adult-Onset Diabetes Mellitus " Epidemiology **17**( 4): 352-359.

Wang, S. (2008). "Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort." Diabetes Care **31**(8): 1574-1579.

Wikipedia (2010). "Persistent organic pollutant." http://en.wikipedia.org/wiki/Persistent_organic_pollutants accessed 10/10/2010.

Wild, S. (2004). "Global Prevalence of Diabetes." Diabetes Care **27**(5): 1047-1053.