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Review

Persistent organic pollutants and diabetes: A review of the epidemiological evidence

D.J. Magliano^{a,b,*}, V.H.Y. Loh^a, J.L. Harding^{a,b}, J. Botton^{c,d}, J.E. Shaw^{a,b}

^a Baker IDI Heart and Diabetes Institute, Melbourne, Australia

^b Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

^c Inserm, CESP (Centre of Research for Epidemiology and Population Health), U1018, Lifelong Epidemiology of Obesity, Diabetes and Kidney Diseases Team, 94807 Villejuif, France

^d UMR-S 1018, University Paris-Sud, 94807 Villejuif, France

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Abstract

The prevalence of diabetes and obesity has increased rapidly over the last few decades in both developed and developing countries. While it is intuitively appealing to suggest that lifestyle risk factors such as decreased physical activity and adoption of poor diets can explain much of the increase, the evidence to support this is poor. Given this, there has been an impetus to look more widely than traditional lifestyle and biomedical risk factors, especially those risk factors, which arise from the environment. Since the industrial revolution, there has been an introduction of many chemicals into our environment, which have now become environmental pollutants. There has been growing interest in one key class of environmental pollutants known as persistent organic pollutants (POPs) and their potential role in the development of diabetes. This review will summarise and appraise the current epidemiological evidence relating POPs to diabetes and highlight gaps and flaws in this evidence.

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Keywords: Persistent organic pollutants; Diabetes; Polychlorinated biphenyls; Dioxin

Résumé

Polluants organiques persistants et diabète : revue des données épidémiologiques.

La prévalence du diabète et de l'obésité a augmenté rapidement au cours de quelques dernières décennies, à la fois dans les pays développés et en voie de développement. Bien qu'il soit suggéré que les facteurs de risque relatifs au mode de vie comme la diminution de l'activité physique et une mauvaise alimentation puissent expliquer la majeure partie de cette augmentation, il y a eu un intérêt récent pour l'étude du rôle des facteurs de risque environnementaux. Depuis la révolution industrielle, de nombreux composés chimiques ont été introduits dans notre environnement et sont maintenant devenus des polluants environnementaux. Un intérêt s'est développé pour une classe particulière connue comme polluants organiques persistants (POPs) et leur rôle potentiel dans le développement du diabète. Cette revue résume et évalue les preuves actuelles dans le domaine environnemental concernant les associations entre les POPs et le diabète, en soulignant les lacunes et les défauts.

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1. Introduction

The last few decades have seen epidemics of diabetes and obesity, which are not fully explained by changes in the prevalence of established risk factors, such as physical inactivity and poor diet [1]. In fact, the reasons for the extremely rapid increase in diabetes and obesity over the past few decades remain unclear.

Given this, there has been a thrust to look more widely than traditional lifestyle and biomedical risk factors. One key avenue of novel risk factors are those arising from the external environment. Since the industrial revolution, we have introduced many chemicals, (intentionally and unintentionally) into our environment and while these are many and varied, there has been growing interest in the potential health effects of particular environmental toxicants such as persistent organic pollutants (POPs).

Persistent organic pollutants are a class of compounds, which are characterised by their ability to persist in the

* Corresponding author. Level 4, 99, Commercial Road, Melbourne VIC 3004, Australia. Tel.: +613 8532 1826; fax: +613 8532 1100.

E-mail address: dianna.magliano@bakeridi.edu.au (D.J. Magliano).

environment, their low water and high lipid solubility and their bio-magnification in the food chain [2]. POPs include many of the first generation organochlorines (OC), pesticides such as dieldrin, dichlorodiphenyltrichloroethane (DDT), toxaphene and chlordane, and several industrial chemical products or by-products including polychlorinated biphenyls (PCBs), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated dibenzo-p-dioxin (PCDD), dibenzo-p-furans (PCDFs) and polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), polybrominated biphenyls (PBB) and perfluorinated compounds (PFCs) such as perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA). Given the large number of POPs which have been identified, a nomenclature has been derived based on the number of halogenated atoms that each compound has. Each individual POP is referred to as a congener and the name of a congener specifies the total number of halogenated substituents and their position. It is believed that POPs with fewer chlorine atoms persist in the environment for less time and are less toxic [3]. Many of these congeners have been and continue to be used in large quantities in chemical and related industries and now represent a global health problem [4].

POPs are either used as pesticides or generated as by-products of industrial or combustion processes. Dioxin, a key class of POPs, is produced as a by-product in the bleaching of paper products and during certain types of chemical synthesis [5]. POPs can travel great distances and become widely distributed by wind and can end up in countries other than those in which they were produced [6]. Once in the environment, POPs accumulate in the fatty tissue of living organisms, reaching the greatest concentrations at the top of the food chain in fish, mammals and predatory birds [7]. Although humans can be exposed to POPs through direct exposure, occupational accidents and the environment, most of the human exposure nowadays is from the ingestion of contaminated food as a result of bioaccumulation in the food chain. The main source (around 95%) of POPs intake is through dietary intake of animal fats [2].

The mechanisms linking POPs exposure to diabetes have not been fully elucidated, but several pathways have been proposed. *In vitro* and *in vivo* experiments show that TCDD affects glucose homeostasis by reducing glucose uptake by adipose tissue, liver and the pancreas, which is accompanied by decreases in insulin production and secretion by beta cells. The primary mechanism by which these effects are proposed to occur is via the binding of TCDD to the aryl hydrocarbon receptor (AhR) [8]. This binding causes changes in translational and transcriptional mechanisms resulting in decreased glucose transporter (GLUT) expression [9–11]. TCDD has also been suggested to affect pancreatic nitric oxide synthase, the function of which is not yet understood [12], and it has also been shown to increase expression of tumour necrosis factor (TNF) α [13], which linked to insulin resistance. The effects of other POPs such as PCBs are less studied although Baker et al. [14] showed using mice studies that coplanar PCBs cause rapid and sustained impairment of glucose and insulin tolerance through an AhR-dependent mechanism associated with an adipose-specific increase in TNF- α expression.

Further, some of the POPs act as endocrine disrupting chemicals (EDC). EDCs bind to nuclear receptors such as androgen receptors, peroxisome proliferator-activated receptor (PPAR) α and estrogen receptor (ER) α and β . This binding, often at high affinity, can interfere with the synthesis, secretion, transport, binding, action, or elimination of a range of hormones in the body that are responsible for normal cell metabolism. For example, the E₂ receptor is involved with the maintenance of insulin sensitivity. Abnormal binding to this receptor by the EDC may promote insulin resistance [15]. Further PPAR α , which has a role in fatty acid synthesis, is activated *in vivo* by PFOA but the *in vivo* consequences of this appear to be species specific and thus remain controversial. Similarly, dioxins and pesticides can modulate PPAR activity, although little is known about the molecular mechanisms and physiological output from this binding [15].

Most of the current epidemiological data linking POPs to disease is related to dioxins, which have been suggested to be the most toxic pollutant [3]. In a range of animal experiments, TCDD, the most toxic of all dioxins, has been linked to many severe adverse effects including cancer, liver disease and diabetes. Since the 1990s, evidence has accumulated associating POPs with diabetes, high blood glucose levels, insulin resistance and obesity [5]. Such evidence has arisen from occupational cohorts exposed during work or chemical accidents, cohorts who are at high-risk of exposure due to consumption of contaminated fish, and general-population studies. While the data are accumulating in this area, there are conflicting reports and thus a review of the diverse information sources is needed. This review will summarise and appraise the current evidence relating POPs to diabetes and highlight gaps and flaws in the evidence.

2. Methods

PubMed, OVID (Medline) and Web of Science databases were searched to identify potential studies published from 1950 to March 2013. The Medical Subject Heading (MeSH) terms ‘diabetes’, ‘insulin resistance’, and ‘glucose intolerance’ were combined with the operator ‘OR’. The MeSH term ‘persistent organic pollutant’, ‘polychlorinated biphenyls’, ‘organofluorine’, ‘organobromine’ and ‘organo pesticides’ were entered and combined with the former using the operator ‘AND’ and the search was limited to human studies published in English. We also reviewed bibliographies and references lists. Our inclusion criteria comprised any cross-sectional, cohort or case-control studies, which explored the relationship between POPs or pesticides and diabetes, insulin resistance, glucose intolerance or HOMA-IR in adults. We excluded studies which used death from diabetes, gestational diabetes or metabolic syndrome as the outcome.

Studies were broadly categorized into high-risk occupational cohorts, non-occupational high-risk cohorts, and general population studies. This was based on the study design employed and whether the paper focused on participants expected to be at high risk of higher POPs exposure for occupational or other reasons.

3. Results

After removal of duplicate studies and reviews, our search identified a total of 388 publications. Review of reference lists identified an additional 8 articles. Among these, a total of 74 articles were identified as potentially eligible and were reviewed in full text (DJM, VHYL) and 41 articles met our inclusion criteria and were included in the systematic review.

The characteristics and results of the studies reviewed for this work are summarised in [Table 1](#) and [Table S1 \(Table S1; see supplementary material associated with this article online\)](#). Given the large heterogeneity in the way the data on POPs were reported and analysed, it was not possible to undertake any formal meta-analyses. Studies are grouped according to the population type.

4. High-risk occupational cohorts

Some of the earliest data linking POPs with diabetes come from occupational cohorts studies, where exposure to pollutants occurred in relation to employment. The most well known of these is the study of US veterans of Operation Ranch Hands from the Vietnam war [16]. During the war, veterans were exposed to Agent Orange, which contained the dioxin TCDD. Compared to age, race and occupational-matched controls, cases of diabetes had average levels of POPs three times higher after ten years follow-up. Ranch Hand veterans with serum dioxin level (derived by back calculations) above the median also had a higher incidence of diabetes (Relative Risk [RR]: 1.5 [95% CI 1.2–2.0]) compared to those below the median. In similar, but separate analyses on the same cohort, it was also found that increased serum dioxin was related to a broader definition of glucose abnormalities (impaired glucose metabolism and diabetes) (RR: 1.4 [95% CI: 1.1–1.8]). Further, it was found that as blood levels of dioxin increased, the time to present with diabetes decreased [17], but this was not confirmed in another study of the same cohort [16]. In a different follow-up of the same cohort, plasma insulin was significantly increased (suggesting insulin resistance) in those of the highest dioxin category [12]. Similarly, a different group of Vietnam veterans exposed to herbicides, compared to non-exposed veterans, also were at an increased risk of diabetes (Odds Ratio [OR] 1.5 [95% CI: 1.15–1.95]) over 30 years [18]. Interestingly, the toxic effects of TCDD also extended to those living near the plant (Vertac-Hercules Superfund site) in Arkansas where TCDD was produced. In individuals living near the plant, it was found that plasma insulin concentrations correlated with levels of dioxins [19].

Several other studies carried out from occupational cohorts exposed have shown an association of POPs, in particular dioxin, with diabetes. In 1987, the National Institute of Occupational Safety and Health (NIOSH) conducted a study of US workers who were exposed to TCDD during employment 15 years earlier. In this study, it was found that the overall prevalence of diabetes was not different in workers compared to the reference group (workers from another industry). However, workers in the group with the highest TCDD concentrations (derived from half-life back calculations) had an increased mean serum glucose

concentration compared to the reference group after adjustment for other risk factors [20]. Another analysis from same cohort comparing workers ($n = 281$) to the reference group ($n = 260$) showed a small increase in the risk of diabetes (OR 1.12, $P < 0.003$) and high fasting glucose ($P < 0.001$) with increasing serum concentration of dioxins. It should be noted however that the point estimate was still increased but key adjustments were not made. Interestingly, this study also measured exposure to other dioxin-like chemicals and found that concentrations of these were similar in cases and controls. This is one of the only studies to adjust for other chemicals [21,22]. The reasons why the Ranch Hand studies and the NIOSH have different findings has never been resolved. It has been suggested that the Ranch Hand subjects may have been exposed to insecticides and herbicides and these insecticides may have caused diabetes preferably among those with higher TCDD or that these subjects were inadvertently exposed to other diabetes induced chemicals such as arsenic. Conversely, the NIOSH subjects may have been exposed to other factors which provided protection against the development of diabetes [22].

The Agricultural Health Study is a large prospective cohort of 30,000 people recruited in the 1990s [23]. It studied the cumulative exposure to 50 pesticides (by questionnaire, tracing the exposure over the life-course), and found that 7 pesticides were associated with an increased incidence of diabetes over 5 years. A retrospective occupational cohort study in Australia of 2000 workers compared to a similar number of population controls showed that exposure to herbicides (measured by questionnaire) was associated with an increased risk of diabetes [24].

A major limitation of studies using occupational cohorts is that in many cases, the exposure occurs many years before the analysis is undertaken and thus dioxin levels are estimated by questionnaires or by back calculation from serum concentrations measured many years later. This calculation uses the whole-body half-life of the pollutant which can be somewhat variable, being between 5.8 and 8.6 years [25]. The consequence of this limitation is not known, but if we assume that those with diabetes metabolise POPs in a similar way to those without diabetes, this misclassification would most likely be non-differential and the effect would be an underestimate of the observed association. Further, in these studies, while the worker cohorts are exposed to TCDD, they are also exposed to other chemicals such as dioxin-like chemicals, often in large concentrations. These other chemicals are rarely measured and therefore the results could be confounded by exposure to other chemicals. Lastly, with occupational cohort studies, the choice of reference group (allegedly unexposed workers of the general population) can be an issue.

Overall, the evidence relating exposure to dioxin and the incidence of diabetes from occupational cohorts is suggestive of there being an increased risk of diabetes associated with past exposure to PCBs/dioxins, but the data are not fully consistent. In particular, the fact that the NIOSH studies are inconsistent with the Ranch Hand studies has never been resolved [22]. It should be noted that exposures in both studies were large in magnitude.

Table 1
Characteristics of studies which examine the relationship between POPs and diabetes/insulin resistance.

| Reference | Cohort name/Country | Sample size | Sample population | Types of POPs measured | Gender | Race/ethnicity % | Age (y), range |
|--|--|---|--|--|--|--|--|
| <i>High risk (cross sectional and prospective) occupational cohorts of POPs and diabetes/insulin resistance</i> | | | | | | | |
| Henriksen et al. 1997/ Michalek et al. 1999 [12,17] | US Air Force veterans, USA | 2602 | 20 years prospective study of Operation Ranch Hand compared to other air force veterans who served in Southeast Asia during the same period but were not involved with spraying herbicides | TCDD | M: 100 | Not reported | Comparison: 53.5 Ranch hand: 54.6 Low: 54.9 High: 50.9 |
| Kang et al. 2006 [18] | National Personnel Records Center in St Louis, MO | Vietnam Non-Vietnam | Case-control study of Army Vietnam veterans who were occupationally exposed to the herbicide versus non-Vietnam veteran who were not exposed to the herbicide | TCDD | M: 100 | Vietnam veterans: White: 81.2 Non-white: 18.8 Non-Vietnam veterans: White: 86.5 Non-white: 13.5 | Vietnam veterans: <46: – 46–50: 16.6 51–55: 52.9 >55: 30.5 Non-Vietnam veterans: <46: 2.5 46–50: 39.2 51–55: 46.1 >55: 12.3 |
| Cranmer et al. 2000 [19] | Vertac/Hercules Superfund site in Arkansas, USA | 69 | Cross-sectional study of subjects living close to Vertac/Hercules Superfund site in Jacksonville, Arkansas | TCDD | TCDD > 15 ppt M: 42.8 F: 57.2 TCDD < 15 ppt M: 40.3 F: 59.7 | Not reported | TCDD > 15 ppt 55 ± 11.6 TCDD < 15 ppt 51 ± 13.2 |
| Calvert et al. 1999/Sweeney et al. 1997 [20,21] | Workers employed in one of two plants located in Newark, New Jersey, and Verona, Missouri. 1951–1969 | 281 exposed workers 260 unexposed referent | Cross-sectional study of workers employed > 15 years earlier in the manufacture of 2, 4, 5–trichlorophenol or one of its derivatives at two US chemical plants | TCDD | M: 94.3 F: 5.7 | White: 88.7 Others: 11.3 | Mean: 55.7 |
| Montgomery et al. 2008 [23] | Licensed pesticide applicators, USA | 33457 | Prospective study of licensed pesticide applicators in the US. Follow-up of 5 years | Aldrin Chlordane Heptachlor Dichlorvos Trichlorform Alachlor cyanazine | M:98 F: 2 | Predominantly non-Hispanic white | Under 40: 13% 41–50: 28% 61–70: 22% over 70: 4% |
| Beard et al.2003 [24] | Agricultural workers with high pesticides exposures, New South Wales, Australia | 776 exposed workers 391 control workers | Cohort study to examine health outcomes of agricultural workers (employed by Board of Tick Control 1935–1995) with high occupational pesticides exposures | Arsenic DDT Modern chemical | M: 100 | Australian | Not reported |
| <i>Non-occupational (cross-sectional and prospective) high-risk population studies of POPs and diabetes/insulin resistance</i> | | | | | | | |
| Airaksinen et al. 2011 [4] | Helsinki Birth Cohort Study 1934–1944 Finland | 1988 | Cross-sectional study, residents born in 1934 and 1944 in Finland | Oxychlordan <i>p,p'</i> -DDE PCB 153 BDE 47 BDE 153 | M: 46.3 F: 53.7 | Whites: 100 | 62 |

Table 1 (Continued)

| Reference | Cohort name/Country | Sample size | Sample population | Types of POPs measured | Gender | Race/ethnicity % | Age (y), range |
|---------------------------------|--|-------------|---|---|--------------------|----------------------------------|------------------------------|
| Codru et al. 2007 [27] | Native-American (Mohawk) population USA/ Canada | 352 | Cross-sectional study of Mohawk adults who resided at or near Akwesasne for at least 5 years | PCBs PCB 153 PCB 74 DDE HCB Mirex | M: 38.1 F: 61.9 | Native American: 100 | ≥ 30 |
| Turyk et al. 2009 [28] | Cohort of Great Lakes sport fish consumers, USA | 471 | Prospective study of participants without diabetes in 1994–1995 that consume Great Lakes sport fish, followed through 2005 | <i>p,p'</i> -DDE PCBs | M: 59.3 F: 40.7 | Not reported | 25–76 |
| Grandjean et al. 2011 [29] | Residents of the Faroe Islands, Sweden | 712 | Cross-sectional study of elderly subjects from a fishing population with elevated contaminant exposures from seafood species high in the food chain | PCB DDE | M: 50.7 F: 49.3 | Faroese: 100 | 70–74 |
| Jorgensen et al. 2008 [30] | Greenland population-based study, 1999–2002 | 692 | Population-based study drawn from the central population register and consisted of Greenlanders living in three areas of West Greenland | Dioxin-like PCB Non-dioxin-like PCB OC pesticides | M: 44.1 F: 55.9 | Inuit: 90 Others: 10 | ≥ 35 |
| Philibert et al. 2009 [31] | Health Canada Assessment 1999 cohort, Canada | 101 | Exploratory study among the First Nation Community | <i>p,p'</i> -DDE PCBs PCB 74 PCB 153 A1254 A1260 | M: 48.5 F: 51.5 | Indigenous people of Canada: 100 | 15–86 |
| Rignell-Hydbom et al. 2007 [32] | Fishermen's wives in Sweden | 543 | Case-control study among fishermen's wives from the Swedish east and west coast | CB-153 <i>p,p'</i> -DDE | F: 100 | Swedish | Median age: 50 |
| Rylander et al. 2005 [33] | Swedish population | 380 | Cross sectional study of men and women who consume fatty fish from the Baltic sea | CIB-153 <i>p,p'</i> -DDE | M: 51.5 F: 48.5 | Swedish | Median age M: 60 F: 64 |
| Vasiliu et al. 2006 [35] | Michigan PBB cohort, USA | 1384 | Prospective study of 25 years follow-up in the Michigan cohort established in 1976 and surveyed again in 1991–1993 and in 2011 | PBB PCB | M: 49.7 F: 50.3 | White: 99.8 Others: 0.2 | ≥ 20 |
| Silverstone et al. 2012 [36] | Anniston Community Health Survey, Alabama 1929–1971, USA | 774 | Cross-sectional study of randomly selected households and adults who completed the Anniston Community Health Survey | PCBs | M: 30 F: 70 | Whites: 53 Nonwhite: 47 | Mean age: 54.8 ± 15.9 |

Table 1 (Continued)

| Reference | Cohort name/Country | Sample size | Sample population | Types of POPs measured | Gender | Race/ethnicity % | Age (y), range |
|--|---|---|--|--|--------------------|--|-----------------|
| Ukropec et al. 2010 [37] | PCBRISK cross-sectional survey, Slovakia | 2047 | Cross-sectional study of men and women from 28 primary care physicians from heavily polluted Slovakian district of Michalovce, Svidnik and Stropkov | PCB <i>p,p'</i> -DDT <i>p,p'</i> -DDE B-HCH HCB | M: 38.9 F: 56.5 | Slovakian: 100 | 21–75 |
| Fierens et al 2003 [38] | Individuals living in five areas of Belgium | 257 | Population based study in Belgium during 2000–2001. | 17 PCDD/Fs 4 coplanars 12 PCBs | M: 44.7 F: 55.3 | Flemish | 21–80 |
| Wang et al. 2008 [39] | Yucheng cohort, Taiwan | 748 | Prospective study of 24-year follow-up in Yucheng cohort against neighborhood reference subjects | PCBs PCDFs | M: 41.1 F: 58.9 | Taiwanese: 100 | > 30 |
| MacNeil et al. 2009 [40] | C8 Health project 2005–2006, Ohio USA | Case control: 13,922 Cross-sectional: 21,642 | Case control study, plus cross sectional analyses conducted among the C8 health project, a population exposed to drinking water contaminated with PFOA | PFOA | M: 47.5 F: 52.6 | Whites: 97.3 Non whites: 2.7 | ≥ 20 |
| <i>General (cross sectional) population studies of POPs and diabetes</i> | | | | | | | |
| Lee et al. 2006 [2] | NHANES 1999–2002, USA | 2016 | Cross-sectional study, civilian non-institutionalized United States population | PCB-153 HpCDD OCDD Oxychlordane <i>p,p'</i> -DDE <i>trans</i> -nonachlor | M: 44.7 F: 55.3 | Non-Hispanic Whites: 48.0 Others: 52.0 | ≥ 20 |
| Everett et al. 2007 [7] | NHANES 1999–2002 USA | 1830 | Cross-sectional study, civilian non-institutionalized United States population | HxCDD PCB 126 <i>p,p'</i> -DDT | M: 44.7 F: 55.3 | Non-Hispanic Whites: 48.0 Others: 52.0 | Aged ≥ 20 years |
| Everett et al. 2010 [41] | NHANES 1999–2004 USA | 3049 | Cross-sectional study, civilian non-institutionalized United States population | β-HCH <i>p,p'</i> -DDE <i>p,p'</i> -DDT Oxychlordane <i>trans</i> -Nonachlor Heptachlor Mirex Dieldrin | Not stated | Not reported | Aged ≥ 20 years |
| Lim et al. 2008 [42] | NHANES 2003–2004, USA | 1367 | Cross-sectional study, civilian non-institutionalized United States population | PBB 153 PBDE 28 PBDE 47 PBDE 99 PBDE 100 PBDE 153 | M: 47.3 F: 52.7 | White: 53.3 Others: 46.7 | ≥ 20 |
| Cox et al. 2007 [43] | Hispanic Health and Nutrition Survey USA | 1303 | Cross-sectional study of three Hispanic subgroups of the Mexican Americans population residing in the United States | β-HCH HCB <i>p,p'</i> -DDE <i>p,p'</i> -DDT Oxychlordane <i>trans</i> -Nonachlor Heptachlor Mirex Dieldrin | M: 40.5 F: 59.5 | Hispanic | 20–74 |

Table 1 (Continued)

| Reference | Cohort name/Country | Sample size | Sample population | Types of POPs measured | Gender | Race/ethnicity % | Age (y), range |
|-----------------------------|--|-------------|---|--|--------------------|--|---|
| Melzer et al.2010 [44] | NHANES 1999–2000 2003–2004 2005–2006 USA | 3966 | Cross-sectional study, civilian non-institutionalized United States population | PFOS PFOA | M: 48 F: 52 | Non-Hispanic Whites: 73.5 Non-Hispanic Blacks: 9.9 Mexican Americans: 8.3 Other Hispanics: 4.2 Others: 4.1 | ≥ 20 |
| Nelson et al. 2010 [45] | NHANES 2003–2004, USA | 2094 | Cross-sectional study, civilian non-institutionalized United States population | PFOS PFOA PFHxS PFNA | M: 52 F: 48 | Mexican American/Other Hispanics: 24 NH White/Other inc. Multi-Racial: 54 NH Black: 22 Catalonian | 20–80 |
| Gasull et al. 2012 [46] | Catalan Health Survey (CHIS), Catalonia, Spain | 886 | Cross-sectional study of the general adult population of Catalonia | PCBs HCB <i>p,p'</i> -DDT <i>p,p'</i> -DDE β -HCH | M: 42.9 F: 57.1 | Catalonian | 18–74 |
| Longnecker et al. 2001 [47] | CPP USA | 2245 | Cross-sectional study of pregnant women in the United States population | PCBs | F: 100 | Diabetic subject: White: 84 Others: 16 Control: White: 45 Others: 55 Koreans | Diabetic subject: 28 ± 7 Control: 24 ± 6 |
| Son et al. 2010 [48] | Community Health study in Uljin County, South Korea | 80 | Sub sample from cross-sectional study in Uljin County | β -HCH HCB <i>p,p'</i> -DDE <i>p,p'</i> -DDT <i>p,p'</i> -DDD <i>o,p'</i> -DDT Oxychlorane <i>trans</i> -Nonachlor Heptachlor Mirex | M: 52.5 F: 47.5 | Koreans | Mean: 55.6 |
| Tanaka et al. 2011 [49] | Saku Control Obesity Program (SCOP)– an intervention study Japan | 117 | The lifestyle arm of intervention trial among middle-aged, overweight and obese Japanese participants | PCB 74 PCB 99 PCB 118 PCB 138 PCB 146 PCB 153 PCB 156 PCB 163/164 PCB 170 PCB 180 PCB 182/187 | M: 50.4 F: 49.6 | Japanese | 40–64 |
| Uemura et al. 2008 [50] | General inhabitants of Japan | 1374 | Cross-sectional study among general inhabitant in Japan from 2002 to 2006 | TCDD PeCDD HxCDD HpCDD OCDD PCDDs TCDF PeCDF HxCDF HpCDF OCDF PCDFs PCBs | M: 45.6 F: 54.4 | Japanese | 15–73 |

Table 1 (Continued)

| Reference | Cohort name/Country | Sample size | Sample population | Types of POPs measured | Gender | Race/ethnicity % | Age (y), range |
|--|--|--|---|---|---|---|----------------|
| Chen et al. 2008 [51] | | 40 | Cross-sectional study of non-diabetic pregnant women in Tainan City | 17 PCDD/PCDFs 12 PCBs | F: 100 | Taiwanese | 21–39 |
| Lee et al. 2007 [52] | NHANES 1999–2002, USA | 749 | Cross-sectional study, civilian non-institutionalized United States population | 3 PCDDs 3 PCDFs 4 dioxin-like PCBs 5 non-dioxin-like PCBs 4 OC | M: 46.3 F: 53.7 | White: 49.7 Others: 50.3 | 20–85 |
| <i>Prospective studies of POPs and diabetes/insulin resistance</i> | | | | | | | |
| Lee et al. 2010 [3] | Coronary Artery Risk Development in Young Adults (CARDIA) cohort USA | 180 | Nested case-control study among participants free of diabetes in 1987–1988 | 9 OC pesticides 35 PCBs 10 PBDE 1 PBB | Case: M: 31.1 F: 68.9 Control: M: 45.6 F: 54.4 | Case: White: 51.1 Others: 48.9 Control: White: 31.1 Others: 68.9 | 18–30 |
| Lee et al. 2011 [34] | Coronary Artery Risk Development in Young Adults (CARDIA) USA | 5115 | Prospective study of POPs among free-diabetes people on 5 occasion over 20 years | OC Pesticides PCBs PBB | M: 31.1 F: 68.9 | White: 51.1 African American: 48.9 | 18–30 |
| Lee et al. 2011 [53] | PIVUS, community of Uppsala, Sweden | Cross-sectional: 989 Prospective: 725 | Cross-sectional and prospective study of elderly living in the community of Uppsala | 3PCBs 3 organochlorine pesticides 1 brominated diphenyl ether 1 dioxin | M: 50 F: 50 | Caucasian: 100 | 70 |
| Rignell-Hydbom et al. 2009 [55] | Women's Health in the Lund Area cohort study 1995–2000 Sweden | 742 | Case-control study on women aged 50–59 years living in the five municipalities in the Lund area | CB-153 <i>p,p'</i> -DDE | F: 100 | Caucasians: 100 | 50–59 |
| Wu et al. 2013 [56] | Two samples from the Nurses' Health study (Non Hodgkins lymphoma and breast cancer), USA | NHL study: 422 Breast cancer study: 673 | Two independent nested case-control study: a non-Hodgkin lymphoma (NHL) study and a breast cancer study | PCBs <i>p,p'</i> -DDE HCB | F: 100 | Caucasians: 76.6 Others: 23.4 | 30–55 |

5. Non-occupational high-risk population studies

Many studies of POPs exposure and diabetes have been performed on populations who are at increased risk of POPs exposure because they consume large amounts of fish or live near to heavily polluted areas. Other than occupational exposure, the most common source of exposure to POPs is via dietary intake of foods from animals such as seafood [26]. In a study of 352 Native American Mohawk (high consumers of fish from the St Lawrence River) adults ≥ 30 years of age who were tested for PCBs, *p,p'*-DDE and HCB, the ORs (95% CI) of having diabetes in the highest quartiles of PCB, *p,p'*-DDE and HCB compared to the lower quartiles were 3.9 (1.5–10.6), 6.4 (2.2–18.4) and 6.2 (2.3–16.9), respectively. Upon adjustment for other analytes, the OR for HCB remained significant, while ORs for PCB and *p,p'*-DDE remained elevated but lost significance [27]. In another study of Great Lakes sport fish consumers followed up for 8.4 years, mean levels of *p,p'*-DDE, PCB-118 and total PCBs were

higher in participants who developed type 2 diabetes than those who did not. Diabetes was measured by self-report in this study [28].

In a group of 712 septuagenarians living on Faroe Island in the North Atlantic, those with type 2 diabetes or impaired fasting glycaemia tended to have higher PCB concentrations and higher past intake of traditional foods, especially during childhood and adolescence. It was also shown that in non-diabetic subjects, the fasting insulin concentration decreased by 7% for each doubling of the PCB concentration after adjustment for sex and body mass index (BMI). The fasting glucose concentration increased by 6% for each doubling in PCB [29].

POPs were also measured in a cross-sectional study of 692 men and women of Inuit descent from Greenland. In this study, while no associations were found between POPs and stages of glucose tolerance or markers of insulin resistance, concentrations of dioxin-like PCBs and non-dioxin-like PCBs were significantly inversely associated with HOMA-B (a marker of

beta cell function) with a decrease in HOMA-B of 8.5% to 14.2% with increasing quartiles of dioxin-like PCBs and non-dioxin-like PCBs [30]. POPs have been associated with diabetes in other ethnic minorities such as in First National Canadians [31]. In a study of 100 Native First Nation Canadians, ORs of having diabetes in the top quartile of *p,p'*-DDE and of total PCBs compared to the remaining population were 3.5 (95% CI 1.0–13.8) and 4.9 (95% CI 1.4–19.0), respectively [31].

Several studies [4,32,33] from Finland and Sweden deserve particular note as the diets of these participants were enriched with fatty fish from local seas. In a study of 1988 persons from Helsinki born during 1934–1944 (before the global emission peak of POPs), the presence of type 2 diabetes and serum levels of several POPs were assessed in 2003. It was found that people who had levels over the 50th percentile for OC pesticides, *p,p'*-DDE and PCB, had an increased risk of diabetes with ORs ranging from 1.64–2.24 [4]. The increase in diabetes risk was linear [3]. Exposure to BDE 47 and BDE 153 were not related to diabetes risk. [4] When the results were stratified by BMI, the results suggested that POPs exposure may not be related to diabetes risk in normal weight individuals. In obese individuals, the OR for diabetes was greater in those with high POPs exposure than those with low POPs exposure. This phenomenon has been reported previously in another study [34].

In one Swedish study, 196 men and 184 women were tested for CB-153 and *p,p'*-DDE. CB-153 and *p,p'*-DDE were related to diabetes prevalence after adjustment for conventional risk factors (OR 1.16 [95% CI 1.03–1.32] and OR 1.05 [95% CI 1.01–1.09] respectively per 100 ng/g lipid increase) [33]. In the second Swedish study of 544 fisherman and their wives living by the Baltic sea, significant associations with type 2 diabetes were observed for both CB-153 (OR 1.60 [95% CI 1.00–2.7]) and *p,p'*-DDE [OR 1.3 (95% CI 1.1–1.5)] per 100 ng/g lipid [32].

A study in Michigan of over 1300 subjects living in an area of known contamination, assessing participants for the development of diabetes over 25 years, showed that compared to the lowest quintile of a summary measure of PBB, women and men in the highest quintile were 2.3 and 1.7 times more likely to develop diabetes; only the results in women were significant [35]. In Anniston, Alabama, which is noted for being one of the most highly exposed areas to PCBs in the world, a 1 SD increase in log PCB levels was associated with an increased risk of diabetes (OR 1.52 [95% CI 1.01–2.28]) in women only [36]. Diabetes and pre-diabetes have also been associated with POPs exposure in heavily polluted towns in Slovakia. In a representative sample of 2,122 participants from 28 areas in Slovakia, both pre-diabetes and diabetes were significantly associated with a range of POPs and pesticides [37].

In a population-based study conducted in Belgium of 257 individuals who were environmentally exposed, compared to those living in areas with no known exposure, the risk of diabetes was significantly increased in subjects in the top decile of dioxin exposure (OR 5.1 [95% CI 1.18–21.7]), coplanar PCBs (OR 13.3 [95% CI 3.31–53.2]), or PCBs (OR 7.6 [95% CI 1.58–36.6]), compared to the bottom decile of each POP. However the

number of cases of diabetes in this study was small ($n = 9$) which is reflected by the wide 95% confidence intervals [38]. In the 1970s, a group of Taiwanese were exposed to high levels of POPs following consumption of rice bran oil that had been contaminated with PCBs due to an accident. This is now known as the Yucheng incident. In a study following up 1054 Yucheng victims, it was found that exposed individuals ($n = 370$) had an increased risk of diabetes (OR 2.1 [95% CI 1.1–4.5]) compared to the reference population (neighbouring subjects) after adjustment for traditional factors. However this was only shown in women. In this same study, women diagnosed with chloracne (an acne-like condition associated with exposure to halogenated aromatic compounds) had an adjusted OR of 5.5 (95% CI 2.3–13.4) for diabetes compared to controls [39]. MacNeil et al. failed to demonstrate a link between serum levels of PFOA and diabetes or fasting glucose in the C8 health project, a project, which measured the health of populations who were exposed to water contaminated with PFOAs [40].

Among these studies reviewed here, the data are very suggestive of an independent association of POPs exposure with diabetes, the notable exceptions being the study in the Greenland Inuits and those exposed to PFOAs.

6. General population studies

The data showing a link between POPs and diabetes from general, population-based studies mainly comes from the US National Health and Nutrition Examination Survey (NHANES). Lee et al. used the 1999–2002 NHANES data and investigated the relationship of type 2 diabetes (defined using fasting glucose) with PCB 153, two dioxins (HCDD and OCDD), oxychlorane, *p,p'*-DDE and trans-nonachlor. They showed that 80% of participants had detectable levels of these chemicals and diabetes was strongly associated with all POPs. Exposure to individual POPs were summed and the bottom quartile of summed POPs was compared to the 25–50th, 50–75th, 75–90th and >90th percentiles after adjustment for age, gender, BMI, waist circumference and ethnicity. Compared to the bottom quartile, the ORs for each comparison were 14.0, 14.7, 38.3 and 37.7, respectively. All ORs were significant. Furthermore, PCB 153, two chlordanes and *p,p'*-DDE showed statistically significant linear dose-response associations with diabetes [2].

Using a similar sample of the NHANES population, Everett et al. [7] showed that PCDD, PCB and *p,p'*-DDT were all associated with diagnosed diabetes. PCB 126 and *p,p'*-DDT were associated with undiagnosed diabetes using $HbA1c \geq 6.1\%$ adjusted for age, race, socioeconomic status, education, physical activity and BMI while HCDD was not. In a model of total diabetes (diagnosed and undiagnosed diabetes combined) and including all three POPs, exposure to elevated PCB 126 and *p,p'*-DDT was associated with increased risk of diabetes (OR 2.57 [95% CI 1.33–4.95] and OR 2.74 [95% CI 1.44–5.23], respectively). HCCD was not related to diabetes. In a related NHANES study, Everett et al. [41] showed that pesticide metabolites were associated with diabetes, and the relationship was strongest for heptachlor and oxychlorane, intermediate for

p,p'-DDT, and least for beta-hexachlorocyclohexane, *p,p'*-DDE, and trans-nonachlor while mirex and dieldrin were not associated with diabetes. Using the 2003–2004 sample of the NHANES study, PBBs were related to an increased odds of diabetes. Compared to those who had undetectable levels of PBBs, those in the 25–50th percentile and 50–70th percentile had ORs for diabetes of 2.6 (95% CI 1.2–5.8) and 2.7 (95% CI 1.2–6.0), respectively, after adjustment for age, sex, race and poverty [42]. In line with these results from NHANES, several pesticides were associated with self-reported diabetes in the Hispanic Health and Nutrition Examination Survey from 1982–1984, but only *p,p'*-DDT remained significant after adjustment for lipids [43]. In yet another study using the NHANES 1999–2004 datasets, self-reported diabetes was not associated with serum levels of PFOA and perfluorooctane sulfonic acid (PFOS) [44] nor were they associated with insulin resistance in the 2003–2004 NHANES population [45].

In a general population study in Catalonia, Spain, 886 people were tested for PCB 118, 138, 153, 180 and HCB, *p,p'*-DDT, *p,p'*-DDE and β -HCH. Diabetes and pre-diabetes were related to PCB 118, 138, 153, 180 and HCB and the statistically significant ORs for the fourth quartile of exposure ranged from 2.0–2.8 for the POPs tested (all *P* values for linear trend < 0.05) compared to the first quartile. The other POPs tested were not related to diabetes [46]. In pregnant women, Longnecker et al. found a dose-dependent relationship between PCBs and type 1 diabetes [47]. POPs have also been associated with diabetes in a small (*n* = 80) cross-sectional study in Korea. Compared with subjects in the lowest tertile of each OC pesticide, adjusted ORs in the 3rd tertile for oxychlorane, for *p,p'*-DDT and for *p,p'*-DDE were 26.0 (95% CI 1.3–517.4), 10.6 (95% CI 1.3–84.9) and 12.7 (95% CI 1.9–83.7), respectively [48]. In a Japanese population, PCBs 146 and 180 were positively associated with diabetes, while PCB 163 and 164 were negatively associated with diabetes [49]. In another study from Japan, dioxin-like PCBs were associated with diabetes (OR for 3rd vs. 1st tertile, 6.82 [95% CI 2.59–20.1]) [50].

In two studies measuring insulin resistance and POPs (congeners 123, 125 169), Chen et al. [51] showed that PCBs may be associated with decreasing insulin sensitivity in non-diabetic pregnant women and Lee et al. [52] showed that among five POPs classes, organochlorine pesticides and two non-dioxin-like PCBs were strongly associated with HOMA-IR, but PCDDs, PCDFs and dioxins-like PCBs were not related to these measures.

Among these studies reviewed here, the data are suggestive of an independent association of POPs exposure to diabetes. However, although cross-sectional studies do not allow us to determine the direction of causality between the POPs exposure and diabetes outcome, Lee et al. [53] and Devito et al. [54] argue that it is unlikely in most cases that diabetes preceded POPs because of the metabolism of POPs in mammalian systems is extremely slow; the half life of the compound ranging from 7–10 years [53].

7. Prospective studies

Prospective data on POPs and diabetes are limited. In a nested case-control study of diabetes with 20 years follow-up from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort, Lee et al. [3] showed a non-linear relationship between POPs and diabetes. This study reported unusual findings. First, some individual POPs displayed statistically significantly highest ORs of diabetes in the second quartile. In addition, upon summing 31 POPs including trans-nonachlor, oxychlorane, mirex, highly chlorinated PCBs and PBB153, the adjusted OR in the second sextile versus the first sextile was 5.4 (95% CI 1.6–18.4) and the risk of diabetes then decreased as the value of the summary score increased. In those who were obese, the risk in the second sextile was even higher (OR 20.1) [3]. These results lead to an inverted U shape relating POPs exposure to diabetes risk; a relationship, which has been previously described between other endocrine disruptors and diabetes risk. One possible explanation of this is that at high dose exposure, there is a down regulation of receptors, which reduces the impact of the agent. Thus at that high doses, hormonally active chemicals can exert inhibitory effects on processes that are observed at much lower doses resulting in an inverted U-shape dose response. The main study, which showed this, was carried out with a small number of subjects in each exposure group and thus needs to be replicated in larger populations. In another study by the same author, Lee et al. [34] showed that *p,p'*-DDE predicted HOMA-IR as did PCBs with more than 7 chlorines, after 20 years of follow-up.

POPs have been linked to diabetes in two longitudinal studies from Sweden. In a case-control study of women age 50–59, neither *p,p'*-DDE nor CB-153 were associated with increased risk of diabetes in cases diagnosed after 3 years, but by 6 years, *p,p'*-DDE was related to increased diabetes risk (quartile 4th versus 1st, OR 5.5 [95% CI 1.2–25]) [55]. In a more recent study, the prospective investigation of the Vasculature in Uppsala Senior study, the ORs (95% CI) for type 2 diabetes, according to quintiles of a summary measure of PCBs (vs. lowest quintiles) were 4.5 (0.9–23.5), 5.1 (1.0–26.0), 8.8 (1.8–42.7) and 7.5 (1.4–38.8) (*P*trend < 0.01) after adjustment for known risk factors. There were also significant relationships with the organochlorins, but neither PBB nor dioxin were related to diabetes. However, with only 36 cases of diabetes, the confidence intervals around the ORs are large so there is some uncertainty relating to the effect size [53].

The relationships of plasma HCB and other POPs with diabetes have been recently studied in the Nurses' Health Study in two separate nested case control studies. After multivariable adjustment, plasma HCB concentration was positively associated with incident type 2 diabetes (pooled OR 3.59 [95% CI 1.49–8.64], *P*trend = 0.003 comparing extreme tertiles). Other POPs were not significantly associated with diabetes. Further, a meta-analysis of six published prospective studies measuring HCB and diabetes that included 842 diabetes cases found that both HCB and total PCBs were associated with diabetes. The pooled ORs were 2.00 (95% CI 1.13–3.53) and 1.70 (95% CI

1.28–2.27), respectively [56]. Though the prospective data are limited, the data suggest that POPs exposure is an independent risk factor for diabetes.

8. Discussion

In general, the majority of evidence reviewed in this study from occupationally exposed, high-risk populations, and general-population studies is consistent with an independent relationship between POPs exposure and diabetes.

The data from studies of occupational cohorts exposed to dioxins and diabetes are suggestive of a link between diabetes and dioxin exposure. The notable exceptions to this are the studies of US workers from NIOSH. Some of the limitations, which may influence these inconsistencies, include the estimation of dioxin levels using back calculations and the choice of reference group. Among cross-sectional studies reviewed here, many show an independent relationship between most POPs, (especially those which are highly chlorinated) and diabetes. Among the five general population prospective studies reviewed here (not including the prospective studies of chemical accidents of POPs and diabetes), all studies report some positive associations of PCB/HCB with diabetes after adjustment for traditional risk factors, although the choice of POP tested varied considerably and the findings were not always significant in both sexes.

In terms of which POPs are more likely to cause disease, while it is difficult to be definitive, the majority of the studies examining TCDD or dioxins showed they were associated with an increased risk of diabetes. Similarly, the *p,p'*-DDE, *p,p'*-DDT, trans-achlor, HCB and the PCBs, especially PCB 153 were also likely to be associated with diabetes in the majority of studies which tested them. In contrast, two of the three of the studies of PFCs (PFOA, PFNA and PFOS) failed to show a relationship with diabetes [40,44,45].

There are several limitations with the current prospective POPs and diabetes data which may preclude clear cut statements of harm. First, the current number of prospective studies in the area is small. Second, the sample sizes in most of the studies are small, the one exception being the Nurses' Health study. Small study size leads to increased uncertainty around the effect size of the estimate. Study samples are presumably kept small because of the high analytical costs required to test these chemicals. In addition, all the studies reviewed here test for different congeners making cross-study comparisons difficult. This is also compounded by the large number of different congeners, which are produced and could be potentially related to diabetes. Certain PCB congeners are more consistently linked to diabetes than others. It has been suggested that those POPs with the greatest number of chlorine atoms may be more likely associated with greater diabetes risk as these persist in the environment longer, though it is important to note that those with the highest number of chlorines are no longer produced and have been replaced with brominated and fluorinated compounds [57]. In this review, we noted a trend of highly chlorinated POPs such as β -HCH and HCB being linked with an increased risk of diabetes.

Diabetes was assessed in a variety of ways in the reviewed studies. This might have influenced some of the relationships

noted, particularly in relation to the estimated effect sizes, but given that significant findings were observed across many studies, any differences are unlikely to have an important effect on the associations seen.

Some other issues should be highlighted. POPs are generally highly correlated with each other, and it is not always possible to determine the independent effect of each POP on the outcome. This is compounded by the fact that individuals are often exposed to many POPs but only a few are tested for in studies. In terms of other confounders, the majority of the studies did adjust for several confounding factors, but almost none of them adjusted for covariates such as family history of diabetes, which is a potentially important confounder. The possibility that unmeasured confounders, particularly lifestyle factors, such as diet, could be the real causative factor underlying the observed associations must be recognised, and can, in fact, never be excluded when considering observational studies. It has also been argued that it is difficult to disentangle the effect of POPs from the effect of age due to the cumulative exposure to these pollutants as we age. This notion has been explored for obesity and Hue et al. showed that organochlorines concentrations were not associated with obesity, but strongly correlated with age [58]. Similar studies have not been conducted for diabetes. In addition, the studies reviewed here report results as lipid standardised measurements, as wet concentrations without adjustment for lipids or as wet concentrations with adjustment for measurements. Since POPs are lipophilic, high lipid levels will give rise to high measured POPs levels, and if this is not accounted for, risk may be overestimated. However, it is also known that exposure to some POPs can lead to increased lipids and elevated lipid is associated with diabetes. This would imply that lipids could lie in the causal pathway and thus models should not adjust for these factors [59]. It is clear that more research is required to understand how best to account for lipids in these models. The magnitude of effects of the relationship between POPs and diabetes is large, especially in the population-based studies. This is potentially very relevant to human health. Even though many may argue that with wide confidence intervals, the uncertainty is too great to discern a reliable estimate of effect, we argue that these large effect sizes should not be ignored. Related to this is whether the observed association between POPs and diabetes has a linear dose–response curve or inverted U-shape. Evidence is mixed in this regard. Lee et al. suggest that adverse effects of POPs on diabetes are greater at very lower doses especially those seen in general populations compared to occupational cohorts. Lee et al. argue that for the estimation of relative risk of low-dose effects, a reference group of extremely low concentration of POPs is required and this does not appear to exist. While different POPs are correlated with each other, the correlation is not perfect and an individual who has low levels of one POP may have a higher levels of another which may leads to an artificial increase of risk in this reference group and therefore an underestimation of risk relative to this group [3].

There is also a possibility that the association of POPs and diabetes is due to confounding. For example, POPs are stored in fat and the association that is observed in cross-sectional studies could be confounded by fat mass. Other potential confounders

include intake of a high-fat diet, which is related to both obesity and increased POPs levels. However a study by Lim et al. showing that weight loss leads to increases serum concentrations of POPs whereas weight gain can decrease them suggests that adipose tissue serves as a reservoir for POPs reducing the circulating levels of POPs. It has also been suggested that the diabetes state could change metabolism of POPs, which leads to a different distribution or a concentration of POPs [60]. However, a study has cast doubt on this showing that diabetes does not change excretion of POPs [16]. Well-conducted cohort studies should help disentangle the possibility of reverse causation.

Another interesting issue is the notion that the relationship between POPs and diabetes differs across BMI categories. In stratified analyses, high POPs exposure was not related to diabetes in normal weight individuals [4]. Further among individuals with low POPs/non-detectable POPs, overweight and obesity did not seem to increase the prevalence of diabetes as much as among individuals with high POPs exposure [2,4]. This raises the possibility that adipose and POPs exposure may have a synergistic effect on the risk of type 2 diabetes. Other studies are required to confirm this finding.

It is noteworthy that the majority of the studies use quantiles (e.g. tertiles or quintiles) in the modelling of the POPs exposure. This approach may fail to describe some of the complex relationships between POPs and outcome. We recommend that future analyses should examine other models POPs exposures using continuous data and spline analyses so that it is possible to explore the nature of the relationship between exposure and outcome. This is especially important since there is increasing evidence to suggest that non-monotonic dose relationships are not uncommon with compounds which act as endocrine disruptors such as POPs [61].

The key strength of this review is the inclusion of various study types, which have explored the relationships between POPs and diabetes. The limitation of this review is that due to the variation in the way the data were reported, we were unable to perform any formal meta-analyses. This means that the actual magnitude of effect of POPs exposure for the outcome of diabetes remains unknown. Even if the true magnitude of the association is small, the prevalence of diabetes in society and the ubiquity of POPs suggest that even a small increased risk of diabetes among the susceptible individuals will have public health significance. It is also important to recognise that within each of the three major categories of studies reported, there could have been substantial variation in actual POPs exposure, and this may have influenced the variability of findings between studies.

If the associations between POPs and diabetes can be proven and POPs are found to account for some of the excess risk of diabetes, this will drive further bans on the use of POPs, help to explain the rising prevalence of diabetes, and suggest novel avenues for the prevention of diabetes. Furthermore, a full comprehension of the risk relationship between diabetes and POPs is very important because the diabetes epidemic is worldwide, and is observed in the developing world at least at the same rate (if not greater) than in developed countries. Westernised countries are implementing bans on use of POPs and no longer require insecticides to be used in large volumes. In contrast, developing

countries may still be using many of the POPs to control disease and thus their exposure may still be high for decades to come.

In summary, while the overall evidence is strongly suggestive of an independent relationship between POPs and diabetes, some inconsistencies exist. Additional studies with a greater number of diabetes cases, which can confirm or refute the link between POPs exposure and diabetes, are needed. In particular, studies, which have measured POPs as well as other chemicals, should be conducted. Further studies in those with type 1 diabetes, lean type 2 diabetes, which are prospective in design, will be useful in progressing this research further. Studies are also needed to explore, in greater detail, the characteristics of the dose–response between POPs and diabetes and the possible synergistic relationship of obesity and POPs exposure with diabetes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary material

Supplementary material (Table S1) associated with this article can be found at <http://www.sciencedirect.com> at <http://dx.doi.org/10.1016/j.diabet.2013.09.006>.

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