Chlorinated Persistent Organic Pollutants, Obesity, and Type 2 Diabetes

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Persistent organic pollutants (POPs) are lipophilic compounds that travel with lipids and accumulate mainly in adipose tissue. Recent human evidence links low-dose POPs to an increased risk of type 2 diabetes (T2D). Because humans are contaminated by POP mixtures and POPs possibly have nonmonotonic dose-response relations with T2D, critical methodological issues arise in evaluating human findings. This review summarizes epidemiological results on chlorinated POPs and T2D, and relevant experimental evidence. It also discusses how features of POPs can affect inferences in humans. The evidence as a whole suggests that, rather than a few individual POPs, background exposure to POP mixtures—including organochlorine pesticides and polychlorinated biphenyls—can increase T2D risk in humans. Inconsistent statistical significance for individual POPs may arise due to distributional differences in POP mixtures among populations. Differences in the observed shape of the dose-response curves among human studies may reflect an inverted U-shaped association secondary to mitochondrial dysfunction or endocrine disruption. Finally, we examine the relationship between POPs and obesity. There is evidence in animal studies that low-dose POP mixtures are obesogenic. However, relationships between POPs and obesity in humans have been inconsistent. Adipose tissue plays a dual role of promoting T2D and providing a relatively safe place to store POPs. Large prospective studies with serial measurements of a broad range of POPs, adiposity, and clinically relevant biomarkers are needed to disentangle the interrelationships among POPs, obesity, and the development of T2D. Also needed are laboratory experiments that more closely mimic real-world POP doses, mixtures, and exposure duration in humans. **(*Endocrine Reviews* 35: 557–601, 2014)**

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I. Introduction

Over the past three decades, the number of people with type 2 diabetes (T2D) has more than doubled globally, making it one of the most important public health

Abbreviations: AhR, aryl hydrocarbon receptor; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; EDC, endocrine-disrupting chemical; GSH, glutathione; MGC, multinucleated giant cells; NHANES, National Health and Nutrition Examination Survey; OC, organochlorine; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated dibenzofurans; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; POP, persistent organic pollutant; SD, standardized deviates; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; T1D, type 1 diabetes; T2D, type 2 diabetes; TEF, toxic equivalency factor; TEQ, toxic equivalent.

challenges to all nations (1). T2D and prediabetes are increasingly observed among children and adolescents (2). A common assumption is that lifestyle changes characterized by excess energy intake and a lack of exercise have led to the obesity epidemic and, in turn, to the diabetes epidemic. However, there is considerable evidence suggesting that individuals with similar degrees of obesity can have strikingly different risks of T2D (3). It is particularly noteworthy that whereas 80% of T2D patients are obese, approximately 75–80% of obese people never develop T2D (4). Insulin resistance, a prediabetic state, varies 6-fold among obese persons (5). Although causal relationships between genetic factors and T2D have been eagerly sought, the data from genome-wide association studies have shown that genetic variants might explain statistically only about 10% of the phenotypic variability (6). Thus, obesity itself is not a sufficient cause of T2D. Neither is genetics sufficient in the vast majority of cases.

Recently, evidence has linked environmental chemicals with obesity, insulin resistance, and T2D. In January 2011, the US National Toxicology Program and the National Institute of Environmental Health Sciences held a workshop that evaluated the science assessing exposure to certain chemicals with the development of these disorders (7). A main conclusion was that persistent organic pollutants (POPs) have generated particularly strong evidence as a risk factor for T2D in humans (8).

POPs have several unique features that distinguish them from other common chemicals. First, POPs include various lipophilic compounds that accumulate mainly in lipid-containing tissues like adipose tissue and move within the body bound to lipids. Metabolic disturbances of both adipose tissue and lipids are key to the pathophysiology of T2D (9). Therefore, an interesting question is whether the concurrent and continuous presence of POPs in these sites is harmless? Another interesting aspect is that the change of adipose tissue mass is one factor determining the pharmacodynamics of POPs in humans (10, 11).

The second feature is that POPs are always present as chemical mixtures due to mixing in the environment, food webs, and long-term retention in fat tissue. The same difficulties that pertain to evaluating any chemical mixture (12) are therefore relevant to the evaluation of POPs. There are positive correlations among concentrations of many POPs, although some pairs of POPs are weakly correlated (13). In studies performed in general populations with only background exposure to POPs, findings for a specific compound cannot be interpreted as due solely to that compound; rather, they likely reflect the properties of the POP mixture of which the compound is part. Therefore, focusing on individual POPs can be misleading. In this review, we often use the word "POPs" to denote a POP mixture. Also, organochlorine (OC) pesticides, polychlorinated biphenyls (PCBs), and dioxins are terms referring to chemical mixtures of each POP subclass.

A third key feature arises from the possibility of nonlinear and nonmonotonic dose-response relationships between POPs and T2D. The discussion on nonmonotonicity in POPs and T2D associations is a major focus of this paper. Traditional approaches to summarize results from epidemiological studies, including meta-analyses, typically pool single parameters, such as a linear slope or risk ratio between the highest and lowest categories of the exposure. However, these approaches are limited for describing nonlinear dose-response relations. As we will discuss in *Section V*, nonlinearities may lead to differing associations across the range of exposure, which in turn may lead to apparent inconsistencies across studies with different exposure ranges. Therefore, data analytic pooling may in many cases blur estimates of true associations.

Finally, there is no population group without any exposure to POPs; virtually everyone in modern society has some POP exposure, given contamination of the environment and food webs (14). Therefore, a major point in the evaluation of the health effects of POPs is how to form a reference group that is as close as possible to unexposed.

This review has two main purposes: first, to summarize the available epidemiological findings on POPs and T2D; and second, to discuss how features of POPs can affect inferences relevant for human health. The two aims are closely linked because the first purpose cannot be validly achieved without an appropriate understanding of the second. After a discussion of the epidemiological evidence, we will present experimental evidence from studies that used POP mixtures similar to the pattern of human internal POP contamination. Such studies provide insights into plausible mechanisms for the relationships between POPs and T2D.

Although a pathway starting with obesity, leading to insulin resistance, and ultimately to T2D is commonly regarded as the natural pathogenesis of T2D, we discuss issues related specifically to obesity after the section concerned with T2D. The current prevailing concept is that chemicals inducing obesity (obesogens) can also predispose individuals to T2D due to the role of obesity in the development of T2D. However, when assessing such relationships, it should be considered that adipose tissue mass may play a dual role in the biological effects of POPs, which will be discussed in *Section IV*.

II. Human Evidence Linking POPs and T2D

A. What are POPs?

POPs encompass a variety of lipophilic chemicals resistant to environmental degradation that bioaccumulate

in food webs and living organisms (14). OC pesticides such as dichlorodiphenyltrichloroethane (DDT), lindane, chlordane, and hexachlorobenzene are typical examples of POPs. Other POPs are produced as industrial chemicals or byproducts, including PCBs, polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polybrominated diphenyl ethers. Characteristics of common POPs and their estimated half-lives are listed in Table 1.

Among all POPs, those with chloride atoms have long been suspected to have a deleterious effect on humans and wild animals (14). They were thus banned several decades ago in most developed countries, and the emission of dioxins is strictly regulated in many countries (15). On the other hand, brominated POPs are still commonly used, and their exposure patterns are different from those of chlorinated POPs (16). In addition, because human evidence regarding brominated POPs is scarce compared to that for chlorinated POPs, we focus here on chlorinated POPs.

Despite regulation, the exposure to chlorinated POPs by the general population continues, mostly through consumption of fatty foods of animal origin (14). The resistance of POPs to chemical and metabolic degradation entails that they become more concentrated as they move up through food webs (17). Biomagnification can lead to concentrations in humans several orders of magnitude higher than in the general environment. In addition, POPs that accumulate in adipose tissue during life become a source of chronic internal exposure because they are continuously released from adipose tissue to the circulation and vital organs with lipid content (18, 19).

B. Earlier puzzling findings linking POPs and T2D

The first human evidence about the possible harmfulness of a chemical often comes to light after high-dose exposures in an occupational or accidental setting. Among various POPs, exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in workers or residents near accidental spills became the focus of researchers because TCDD was known to be highly toxic from traditional toxicological studies (20). Although direct comparison of results was difficult due to the diverse methodologies of studies, positive, inverse, and null associations were observed in the earliest human studies on TCDD and T2D (Table 2). There were also some puzzling findings, described below.

The most extensive study was performed among US Air Force veterans of Operation Ranch Hand (Air Force Health Study), the unit responsible for aerial spraying of herbicides, including Agent Orange contaminated with TCDD, during the Vietnam War from 1961 to 1971 (21). Compared with other US Air Force veterans without exposure to Agent Orange, exposed veterans had a serum dioxin level approximately three times higher in serum collected in 1987; exposed veterans also had a 40% higher risk of fasting or 2-hour postprandial glucose abnormalities, as well as a 50% higher risk of T2D (22). Based on the combined evidence from reports about the Air Force Health Study, T2D was listed as a compensable disease for Vietnam veterans exposed to Agent Orange (23).

However, subsequent reports on the Air Force Health Study revealed puzzling results. The new analyses excluded veterans exposed to Agent Orange and included only the comparison group of veterans who never had contact with TCDD-contaminated herbicides in Vietnam (24). Their serum TCDD levels were within the range of background exposure typical of the US general population. Unexpectedly, dose-response relationships between TCDD and T2D tended to be clearer than in the earlier study, which compared veterans with Agent Orange exposure to the comparison group (22).

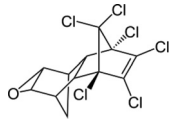
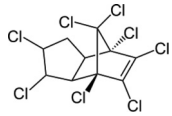
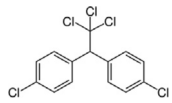
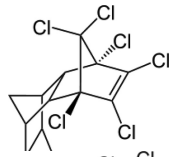
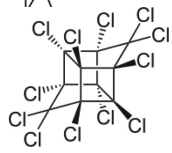
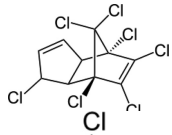
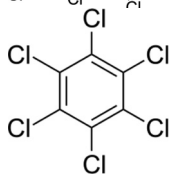
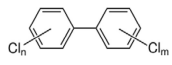
The chemical plant accident near the town of Seveso, Italy, in 1976 also provided an opportunity to examine the association between exposure to TCDD and T2D (25). Although the interpretation was limited because death due to T2D was used as the study outcome, one puzzling finding was that residents living in the medium-exposure area showed a higher risk of T2D mortality than those living in the high-exposure area (25). In addition, studies among workers with occupational exposures to TCDD in factories mainly showed no association with T2D relative to the respective general populations used as reference groups, although these workers had about 10 times higher serum levels of TCDD than Operation Ranch Hand veterans with exposure to Agent Orange (26–28).

These earlier findings may be interpreted as providing insufficient evidence to conclude that there was an association between TCDD exposure and T2D; traditional causal reasoning postulates higher risk of disease among higher exposure groups. Furthermore, data from the Air Force Health Study were recently reanalyzed, and the original conclusion of a positive association between Agent Orange contaminated with TCDD and T2D was questioned (29). This issue will be revisited in *Section II.D*.

C. Recent evidence linking POPs and T2D: cross-sectional and case-control studies

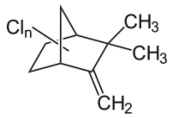
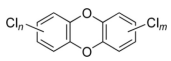
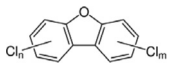
Despite some evidence linking TCDD with T2D from the Air Force Health Study, POPs like OC pesticides or PCBs without dioxin activity were not immediately considered possible risk factors for T2D in the general population. Perhaps the focus on TCDD to the exclusion of other POPs was partly the result of believing that the pathway for adverse

Table 1. List of Common Chlorinated POPs

Compounds	Historical Use/Source	Structure	Characteristics
Aldrin/Dieldrin	-Insecticides used on crops such as corn, cotton, and citrus crop; also used for termite, mosquito, and locust control -Banned for the use on crops in the U.S.: 1974 -Voluntarily termination of production for the use on termites by manufacturers in the U.S.: 1987		-Half life in human: 9–12 months -Estrogenic
Chlordane	-Insecticide used on crops, including small grains, vegetables, potatoes, fruits, nuts, citrus, and cotton. Used on home lawn and garden pests. Also used extensively to control termites -Banned for the use on crops in the U.S.: 1978 -Banned for the use on termite in the U.S.: 1988		-A mixture of many related chemicals (major components: *trans*-chlordane, *cis*-chlordane, *β*-chlordane, and *trans*-nonachlor, *cis*-nonachlor) -Metabolites: oxychlordane -Half life in human: 1–3 months
Dichlorodiphenyltrichloroethane (DDT)	-Insecticide used on agricultural crops, primarily cotton, and insects that carry diseases such as malaria and typhus. -Banned in the U.S.: 1972 -Still used in South America, Africa, and Asia for malaria control		-Technical grade DDT is a mixture of *p,p*;-DDT (85%), *o,p'*-DDT (15%), *o,o'*-DDT (trace) -Contaminants or metabolites: DDE, DDD -Half-life in human: 4 −6 yr -*p,p'*-DDT, estrogenic; *o,p'*-DDT: estrogenic; DDE, anti-androgenic
Endrin	-Insecticide used on crops such as cotton and grains; also used to control rodents and birds -Banned in the U.S.: 1986		-Contaminants or metabolites: endrin aldehyde, endrin ketone -Half life in human: 2–6 days
Mirex	-Insecticide used to combat fire ants and termites; also used as a fire retardant in plastics, rubber, and electrical products. -Banned in the U.S.: 1978		-Half life in soil: ∼10 yr
Heptachlor	-Insecticide used primarily against soil insects and termites; also used against some crop pests and to combat malaria -Banned in the U.S.: 1988		-Metabolites: Heptachlor epoxide -Half life in soil: ∼ 3.5 yr
Hexachlorobenzene	-Fungicide used for seed treatment; an industrial chemical used to make fireworks, ammunition, synthetic rubber, and other substances; unintentionally produced during combustion and the manufacture of certain chemicals; an impurity in certain pesticides -Banned in the U.S.:1984		-Half life in soil: ∼6 yr
Polychlorinated biphenyls (PCBs)	Used for a variety of industrial processes and purposes, including in electrical transformers and capacitors, as heat exchange fluids, as paint additives, in carbonless copy paper, and in plastics Also unintentionally produced during combustion -Banned in the U.S.: 1977		-A family of 209 congeners -Half life in human: months to years (increases as the number of chlorines increased) -PCB44, PCB49, PCB52, PCB101, PCB187: estrogenic; PCB64, PCB74, PCB77, PCB105, PCB118, PCB128, PCB138, PCB170: anti-estrogenic

(*Continued*)

Table 1. Continued

Compounds	Historical Use/Source	Structure	Characteristics
Toxaphene	-Insecticide used to control insect pests on cotton and other crops; other uses included controlling insect pests on livestock and killing unwanted fish in lakes		-A mixture of hundreds of different chlorinated compounds
	-Banned in the U.S.: 1990		-Half life in soil: ~ 14 yr
Polychlorinated dibenzo-p-dioxins (PCDDs)	-Not intentionally manufactured by industry except for research purposes -Unintentionally produced during the chlorine bleaching process at pulp and paper mills; also formed during chlorination by waste and drinking water treatment plants, combustion of municipal wastes, and industrial processes; also can be found as trace contaminants in certain herbicides, wood preservatives, and in PCB mixtures		-A family of 75 congeners -TCDD is known as the most toxic one and most studied -Half life in human: 7–12 yr for 2,3,7,8-TCDD), several years to decades for other PCDDs depending on congeners
Polychlorinated dibenzo-p-furans (PCDFs)	-Not intentionally manufactured by industry expect for research purposes -Unintentionally produced as undesirable by-products of certain processes, such as manufacturing other chemicals or bleaching at paper and pulp mills; also released from incinerators		-A family of135 congeners -Half life in human: several years depending on congeners

Abbreviation: DDD, dichlorodiphenyldichloroethane.

Source: All contents are extracted from the Agency for Toxic Substances and Disease Registry (http://www.atsdr.cdc.gov/).

Unless otherwise specified, information on half lives is primarily in humans. When there is no information on humans, half lives in soil are provided.

health effects of TCDD, including diabetes, was known, namely binding to the aryl hydrocarbon receptor (AhR), an intracellular ligand-dependent transcriptional factor expressed in most tissues of mammals (30). AhR-binding affinity and toxic potency are highly correlated in different congeners of POPs with dioxin activity (31). Because OC pesticides and non-dioxin-like PCBs have no affinity to AhR (32), they were supposed to be less harmful than dioxins. In addition, because the association between TCDD and T2D was not consistent even among persons with high exposure, as discussed above, the traditional toxicological viewpoint implied that any relation of non-dioxin-like POPs (like OC pesticides and some common PCBs) with T2D would be smaller than that of TCDD, or even negligible.

More recently, cross-sectional and case-control epidemiological studies have reported strong associations of T2D with OC pesticides and PCBs (8). Cross-sectional studies evaluate the status of both exposure and disease at one specific time point (33); eg, serum concentrations of POPs and the presence of T2D are measured at the same time. Case-control studies compare past exposure to a suspected risk factor among persons with the disease of interest and among a control group of persons without the disease (33). Usually, information about suspected risk factors is collected to reflect the person's exposure or experience before disease development begins. In case-control studies of POPs and T2D, however, serum concentrations of POPs have often been measured after having selected for study the cases who had already been diagnosed with T2D; hence, the temporal relationship between such concentrations and the status of T2D has often been as difficult to determine as in cross-sectional studies. Given the long half-life of POPs, it is generally considered that serum concentrations of POPs are a good reflection of lifetime exposures, including those that occur long before blood was drawn for the study. However, a bias may arise when serum concentrations of POPs are measured after T2D onset because concentrations may then be altered by the disease and, hence, have no etiological significance (33), as we will discuss in *Section II.D*.

Most cross-sectional studies have been performed among the general population rather than among workers or veterans. Background exposure in the general population is characterized by being low dose and long term, mostly throughout the lifetime; and exposure is to various POP mixtures as opposed to high-dose exposures to one or several selected POPs in occupational or accidental exposure settings. Because the production and use of most OC pesticides and PCBs were banned several decades ago, their average absolute levels in recent epidemiological studies were low in most of the population compared to earlier years (34, 35).

Table 2. Summary of Epidemiological Findings on Associations Between TCDD and T2D in Workers in Occupational Settings or Residents Near Accidental Spills

Settings	First Author, Year (Ref.)	Study Population	Assessment of T2D	Results
Occupational exposure to Agent Orange in Vietnam	Henriksen, 1997 (22)[a]	US Air Force veterans exposed to Agent Orange during aerial spraying of herbicides from fixed wing aircraft	Physician diagnosis	Positive association
	Kim, 2003 (246)	Korean veterans exposed to Agent Orange	Self-report of physician diagnosis	Positive association
	Kang, 2006 (247)	US Army Chemical Corps veterans exposed to Agent Orange while handling herbicides around base camp and spraying from helicopters	Self-report of physician diagnosis	Positive association
Occupational exposure in plants	Steenland, 1999 (248)	Workers at 12 US plants that produced TCDD-contaminated products	Mortality	No or inverse association
	Calvert, 1999 (26)	Workers employed more than 15 y in the production of sodium trichlorophenol or one of its derivatives at 2 US plants	Fasting glucose or self-report of physician diagnosis	No or positive association
	Sweeney, 1997 (27)			
	Vena, 1998 (249)	Workers in phenoxy herbicide and chlorophenol production plants in 12 countries	Mortality	No association
Accidental exposure	Zober, 1994 (28)	Workers after autoclave accident during the production of trichlorophenol in Germany in 1953	Hospital admissions	Inverse association
	Bertazzi, 1998 (25)	Residents after accident of chemical plant in Seveso, Italy, in 1976	Mortality	No association in high-exposure area. Positive association in women living in medium-exposure area

[a] There are multiple reports from US Air Force veterans exposed to Agent Orange using different analytic approaches (24, 250, 251). We selected the most exemplary studies on T2D.

As shown in Table 3, evidence on T2D, OC pesticides, and PCBs has been reported from the United States, Canada, Sweden, Finland, Spain, Belgium, Japan, Korea, and the Slovak Republic. Most cross-sectional studies have reported a positive association for at least one POP, although the details have differed, especially relative to which POPs showed statistical significance. One noteworthy exception is a lack of association in a cross-sectional study of Greenland Inuits; however, the participants had much higher serum concentrations of POPs than in other populations (36). This study will be discussed in *Section V.A.2*.

The most striking evidence among studies with a cross-sectional design suggesting that POPs are associated with T2D was found in the US general population using the 1999–2002 dataset from the US National Health and Examination Survey (NHANES) (37). NHANES is well designed to be nationally representative of the noninstitutionalized US civilian population. In this study, the six POPs (two PCDDs, one PCB, and three metabolites of OC pesticides) most commonly detected in the US general population were strongly positively associated with the prevalence of T2D after adjusting for known risk factors, including obesity. The adjusted odds ratios for *trans*-nonachlor, oxychlordane, *p,p′*-dichlorodiphenyldichloroethylene (DDE) (the main metabolite of DDT), and PCB153 comparing the highest to lowest exposure categories were 6.5, 11.8, 4.3, and 6.8, respectively. When participants were classified by a measure summarizing the combined exposure to the six POPs, the prevalence of T2D rose to 10 to 40 times higher as the summary measure levels increased compared with subjects classified in the lowest quartile of the summary measure. Such strength of association is unusual in epidemiological studies.

In this study (37), the magnitude of association was much stronger with *trans*-nonachlor, oxychlordane, *p,p′*-DDE, and PCB153, which do not have dioxin activity, than with the PCDDs, which do have dioxin-like activity. In fact, the POPs' toxic equivalency factors (TEFs), which measure the ability of a given dioxin-like contaminant to bind to the AhR, were not related

to the strengths of the associations between POPs and T2D.

Another provocative finding was the interaction between POPs and obesity on the risk of T2D (37) (Figure 1A). The association between POPs and T2D was stronger among more obese persons. There was also a clear positive association between POPs and T2D among normal-weight persons (ie, with body mass index [BMI] < 25 kg/m^2). However, obesity was not associated with T2D among persons in the lowest quartile of the POPs summary measure, and T2D itself was very rare among individuals who had a low POP summary score, even if their BMI was ≥ 30 kg/m^2. These findings could mean that POPs that have accumulated in adipose tissue may play a more critical role in the pathogenesis of T2D than the adipose tissue itself (38, 39).

Recent studies from Finland and Spain (40, 41) showed that the positive associations of T2D with POPs became stronger as BMI increased, in line with the findings from the NHANES dataset. Also, in each category of BMI the prevalence of T2D increased with increasing concentrations of POPs (Figure 1, B and C). However, obesity was associated with T2D among subjects with both high and low POP concentrations (40, 41). In Finland and Spain, serum concentrations of POPs—in particular, PCBs—were substantially higher than in the United States. When low and high POP groups were defined in each study, classifications were based on the relative distributions of POP concentrations within each population. In fact, groups in Finland and Spain with lower concentrations of POPs had higher concentrations than groups in the United States with the lowest levels. Therefore, the fact that the

Table 3. Summary of Findings of Cross-sectional and Case-Control Epidemiological Studies on Associations Between Chlorinated POPs and T2D in General Populations With Background Exposure

Country	Author, Year (Ref.)	Study Participants	Assessment of T2D (No. of Cases)	Adjustment	Exposure -Measured Chemicals -Median Values[a] or Geometric Means	Results[b]
Cross-sectional studies						
Belgium	Fierens, 2003 (252)	257 men and women	Self-report of physician diagnosis (n = 10)	None	-17 PCDD/PCDF congeners -25.2 pg/g lipid TEQ-based summary measure	Based on TEQ-based summary measure OR = 5.1 (higher 10th % vs lower 90th %)
					-4 Dioxin-like PCB congeners (PCB77, PCB81, PCB126, PCB169) -7.2 pg/g lipid TEQ-based summary measure	Based on TEQ-based summary measure OR = 13.3 (higher 10th % vs lower 90th %)
					-12 Non-dioxin-like PCB congeners (PCB3, PCB8, PCB28, PCB52, PCB101, PCB118, PCB138, PCB153, PCB180, PCB194, PCB206, PCB209) -402 ng/g lipid for total of 12 PCBs	Based on absolute concentration-based summary measure OR = 7.6 (higher 10th % vs lower 90th %)
Canada	Philibert, 2009 (253)	101 First Nation community	Self-report of physician diagnosis (n = 25)	Age, sex, birthplace, smoking, total cholesterol, and triglycerides	-*p,p'*-DDE -3.1 ng/g	OR = 6.1 (>75th % vs ≤ 75th %)
					-8 PCB congeners (PCB74, PCB99, PCB118, PCB138, PCB153, PCB170, PCB180, PCB187) -4.0 ng/g	Based on absolute concentration-based summary measure OR = 4.9 (>75th % vs ≤ 75th %)
Finland	Airaksinen, 2011 (40)	1988 men and women	Fasting glucose, 2-h glucose, or DM medication (n = 308)	Age, sex, waist circumference, and mean arterial pressure	-PCB153 -310 ng/g lipid	OR = 1.6 (highest vs lowest decile)
					-Oxychlordane -12 ng/g lipid	OR = 2.1 (highest vs lowest decile)
					-*Trans*-nonachlor -32 ng/g lipid	OR = 2.2 (highest vs lowest decile)
					-*p,p'*-DDE -610 ng/g lipid	OR = 1.8 (highest vs lowest decile)

(*Continued*)

Table 3. Continued

Country	Author, Year (Ref.)	Study Participants	Assessment of T2D (No. of Cases)	Adjustment	Exposure -Measured Chemicals -Median Values[a] or Geometric Means	Results[b]
Greenland	Jørgensen, 2008 (36)	692 men and women	Fasting glucose, 2-h glucose, or DM medication (n = 71)	Age, sex, ethnicity, waist circumference, physical activity, alcohol consumption, smoking, education	-3 Dioxin-like PCB congeners (PCB105, PCB118, PCB156) -135 ng/g lipid for PCB118	Based on rank-based summary measure[c] Statistically nonsignificant
					-10 Non-dioxin-like PCB congeners (PCB28, PCB52, PCB99, PCB101, PCB128, PCB138, PCB153, PCB163, PCB170, PCB180)	Based on rank-based summary measure[c] Statistically nonsignificant
					-808 ng/g lipid for PCB153 -OCPs (Aldrin, Mirex, hexachlorobenzene, β-hexachlorocyclohexane, α-chlordane, γ-chlordane, oxychlordane, *trans*-nonachlor, *cis*-nonachlor, DDT, *p,p'*-DDE) -1500 ng/g lipid for *p,p'*-DDE	Based on rank-based summary measure[c] Statistically nonsignificant
Japan	Uemura, 2009 (254)	1374 men and women	HbA1C or self-report of physician diagnosis (n = 65)	Age, sex, BMI, smoking, regional block, residential area, and survey year	-17 PCDDs and PCDF congeners -12.0 pg/g lipid TEQ-based summary measure	Based on TEQ-based summary measure OR = 2.2 (1st vs 3rd tertile)
					-12 Dioxin-like PCBs (PCB77, PCB81, PCB105, PCB114, PCB118, PCB123, PCB126, PCB156, PCB157, PCB167, PCB169, PCB189) −7.6 pg/g lipid TEQ-based summary measure	Based on TEQ-based summary measure OR = 3.1 (2nd vs 1st tertile) OR = 6.8 (3rd vs 1st tertile)
Japan	Tanaka, 2011 (255)	117 men and women (participants of the Saku Control Obesity Program)	Fasting glucose, HbA1C, DM medication, or self-report of physician diagnosis (n = 32)	Age, sex, BMI, total cholesterol, and triglycerides	-PCB74 -0.029 ng/g	Statistically nonsignificant
					-PCB99 -0.022 ng/g	Statistically nonsignificant
					-PCB118 -0.054 ng/g	Statistically nonsignificant
					-PCB138 -0.074 ng/g	Statistically nonsignificant
					-PCB146 -0.022 ng/g	OR = 1.59 per 1 pg/g
					-PCB153 -0.15 ng/g	Statistically nonsignificant
					-PCB156 -0.016 ng/g	Statistically nonsignificant
					-PCB163/164 -0.036 ng/g	OR = 0.77 per 1 pg/g
					-PCB170 -0.020 ng/g	Statistically nonsignificant
					-PCB180 -0.076 ng/g	OR = 1.09 per 1 pg/g
					-PCB182/187 -0.039 ng/g	Statistically nonsignificant

(*Continued*)

Table 3. Continued

Country	Author, Year (Ref.)	Study Participants	Assessment of T2D (No. of Cases)	Adjustment	Exposure -Measured Chemicals -Median Values[a] or Geometric Means	Results[b]
Slovak Republic	Ukropec, 2010 (256)	2047 men and women	Fasting glucose, 2-h glucose, or DM medication (n = 296)	Age, sex, BMI	-15 PCB congeners (PCB28, PCB52, PCB101, PCB105, PCB115, PCB118, PCB123, PCB138 + 163, PCB153, PCB156 + 171, PCB157, PCB167, PCB170, PCB180, PCB189) -1123 ng/g lipid for total 15 PCBs	Based on absolute concentration-based summary measure OR = 1.77 (4th vs 1st quintile) OR = 1.86 (5th vs 1st quintile)
					- *p,p′*-DDE -1817 ng/g lipid	OR = 1.85 (3rd vs 1st quintile) OR = 1.94 (5th vs 1st quintile)
					- *p,p′*-DDT -49.5 ng/g lipid	OR = 1.84 (3rd vs 1st quintile) OR = 2.51 (4th vs 1st quintile) OR = 2.49 (5th vs 1st quintile)
					-Hexachlorobenzene -669 ng/g lipid	Statistically nonsignificant
					-β-Hexachlorocyclohexane -46.5 ng/g lipid	Statistically nonsignificant
Spain	Gasull, 2012 (41)	886 men and women	Fasting glucose, DM medication, or self-report of physician diagnosis (n = 143)	Age, sex, BMI, total cholesterol, and triglycerides	-7 PCB congeners (PCB28, PCB52, PCB101, PCB118, PCB138, PCB153, PCB180) -1.76 ng/g for total 7 congeners	Based on rank-based summary measure OR = 2.4 (4th vs 1st quartile)
					-Hexachlorobenzene -1.19 ng/g	OR = 2.8 (4th vs 1st quartile)
					-β-Hexachlorocyclohexane -0.67 ng/g	Statistically nonsignificant
					- *p,p′*-DDT -0.18 ng/g	Statistically nonsignificant
					- *p,p′*-DDE -2.63 ng/g	Statistically nonsignificant
Sweden	Rylander, 2005 (257)	380 fishermen and their wives	DM medication or self-report of physician diagnosis (n = 22)	Age, BMI (both were dropped from the final model)	-PCB153 -360 ng/g lipid for men -240 ng/g lipid for women	OR = 1.2 (per 100 ng/g lipid) for men Statistically nonsignificant for women
					- *p,p′*-DDE -570 ng/g lipid for men -590 ng/g lipid for women	Statistically nonsignificant for men OR = 1.05 (per 100 ng/g lipid) for women
Sweden	Rignell-Hydbom, 2007 (258)	543 women	DM medication or self-report of physician diagnosis (n = 15)	Age, BMI (BMI was dropped from the final model)	-PCB153 -82 ng/g lipid	Statistically nonsignificant
					- *p,p′*-DDE -140 ng/g lipid	OR = 1.3 (per 100 ng/g lipid)

(*Continued*)

Table 3. Continued

Country	Author, Year (Ref.)	Study Participants	Assessment of T2D (No. of Cases)	Adjustment	Exposure -Measured Chemicals -Median Values[a] or Geometric Means	Results[b]
United States	Lee, 2006 (37)	2016 men and women	Fasting glucose, nonfasting glucose, or self-report of physician diagnosis (n = 217)	Age, sex, race, poverty income ratio, BMI, and waist circumference	-PCB153 -48.5 ng/g lipid	OR = 2.5 (1st quartile vs nondetectable) OR = 4.3 (2nd quartile vs nondetectable) OR = 5.9 (3rd quartile vs nondetectable) OR = 5.9 (4th quartile to 90th % vs nondetectable) OR = 6.8 (≥90th % vs nondetectable)
					-Oxychlordane -20.3 ng/g lipid	OR = 3.1 (3rd quartile vs nondetectable) OR = 4.5 (4th quartile to 90th % vs nondetectable) OR = 6.5 (≥90th % vs nondetectable)
					-*Trans*-nonachlor -28.7 ng/g lipid	OR = 2.5 (2nd quartile vs nondetectable) OR = 4.9 (3rd quartile vs nondetectable) OR = 7.6 (4th quartile to 90th % vs nondetectable) OR = 11.8 (≥90th % vs nondetectable)
					- *p,p*′-DDE -504.5 ng/g lipid	OR = 2.3 (4th quartile to 90th % vs nondetectable) OR = 4.3 (≥90th % vs nondetectable) OR = 2.7 (≥90th % vs nondetectable)
					-1,2,3,4,6,7,8-PCDD -49.3 pg/g lipid	OR = 2.2 (2nd quartile vs nondetectable)
					-1,2,3,4,6,7,8,9-PCDD -418.5 pg/g lipid	OR = 2.7 (4th quartile to 90th % vs nondetectable)
United States	Everett, 2007 (259)	1830 men and women	HbA1C or self-report of physician diagnosis (n not provided)	Age, sex, race, country of birth, education, poverty income ratio, BMI, waist circumference, physical activity	-1,2,3,6,7,8-PCDD -70.6 ng/g lipid	OR = 1.77 (2nd vs 1st tertile)
					-PCB126 -57.5 pg/g lipid	OR = 1.67 (2nd vs 1st tertile) OR = 3.68 (3rd vs 1st tertile)
					- *p,p*′-DDT -23.7 ng/g lipid	OR = 2.69 (2nd vs 1st tertile) OR = 2.46 (3rd vs 1st tertile)

(*Continued*)

Table 3. Continued

Country	Author, Year (Ref.)	Study Participants	Assessment of T2D (No. of Cases)	Adjustment	Exposure -Measured Chemicals -Median Values[a] or Geometric Means	Results[b]
United States	Cox, 2007 (260)	1303 Mexican American men and women	Self-report of physician diagnosis (n = 89)	Age, BMI, and alcohol consumption	-Hexachlorobenzene -1.34 ng/g	Statistically nonsignificant
					-*Trans*-nonachlor -1.52 ng/g	OR = 2.9 (detectable vs nondectectable)
					- *p,p'*-DDT -3.22 ng/g	OR = 1.9 (detectable vs nondectectable)
					- *p,p'*-DDE -9.00 ng/g	OR = 2.4 (3rd vs 1st quartile) OR = 2.6 (4th vs 1st quartile)
					-β-Hexachlorocyclohexane -1.70 ng/g	OR = 2.1 (detectable vs nondectectable)
					-Oxychlordane -1.22 ng/g	OR = 3.1 (detectable vs nondectectable)
					-Dieldrin -1.50 ng/g	Statistically nonsignificant
United States	Cordu, 2007 (261)	352 Native American men and women	Fasting glucose or DM medication (n = 71)	Age, sex, BMI, smoking	-101 PCB congeners -580 ng/g lipid for 101 totalPCBs	OR = 3.2 (3rd vs 1st tertile)
					-PCB153 -78.3 ng/g lipid	OR = 2.4 (3rd vs 1st tertile)
					-PCB74 -28.0 ng/g lipid	OR = 4.5 (3rd vs 1st tertile)
					-*p,p'*-DDE -350 ng/g lipid	OR = 6.2 (3rd vs 1st tertile)
					-Hexachlorobenzene -11.1 ng/g lipid	OR = 6.8 (3rd vs 1st tertile)
					-Mirex -12.4 ng/g lipid	Statistically nonsignificant
United States	Turyk, 2009 (262)	503 men and women	HbA1C, DM medication, or self-report of physician diagnosis (n = 61)	Age, sex, BMI, total cholesterol, and triglycerides	-13 PCB congeners (PCB74, PCB99, PCB118, PCB146, PCB180, PCB194, PCB201, PCB206, PCB132/153/105, PCB138/163, PCB170/190, PCB182/187, PCB196/203) -2.17 ng/g for total 13 PCBs	Statistically nonsignificant
					-2 Dioxin-like PCB congeners (PCB118, 67) -0.15 ng/g for total of 2 PCBs	Based on absolute concentration-based summary measure OR = 2.1 (4th vs 1st tertile)
					-*p,p'*-DDE -3.01 ng/g	OR = 3.6 (4th vs 1st tertile)
United States	Silverstone, 2012 (263)	774 men and women (residents living in PCB-contaminated area)	Fasting glucose or self-report of physician diagnosis (n = 207)	Age, BMI, race/ethnicity, family history of DM, taking lipid-lowering medication, total cholesterol, and triglycerides	-35 PCB congeners (PCB28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 118, 128, 138 + 158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196 + 203, 199, 206, 209) -3.18 ng/g for total 35	Based on absolute concentration-based summary measure OR = 1.52 (per 1 SD increase) for women Statistically nonsignificant for men

(*Continued*)

Table 3. Continued

Country	Author, Year (Ref.)	Study Participants	Assessment of T2D (No. of Cases)	Adjustment	Exposure -Measured Chemicals -Median Values[a] or Geometric Means	Results[b]
Case-control study Korea	Son, 2010 (264)	40 cases and 40 controls	Fasting glucose or DM medication (n = 40)	Age, sex, BMI, alcohol consumption, smoking, total cholesterol, and triglycerides	- *p,p'*-DDE -1.6 ng/g	OR = 26.6 (3rd vs 1st tertile)
					-*p,p'*-DDD -0.027 ng/g	OR = 10.8 (3rd vs 1st tertile)
					-*p,p'*-DDT -0.13 ng/g	OR = 7.6 (3rd vs 1st tertile)
					-*o,p'*-DDT -0.013 ng/g	Statistically nonsignificant
					-Oxychlordane -0.047 ng/g	Statistically nonsignificant
					-*Trans*-nonachlor -0.096 ng/g	Statistically nonsignificant
					-Heptachlor epoxide -0.037 ng/g	Statistically nonsignificant
					-β-Hexachlorocyclohexane -0.22 ng/g	Statistically nonsignificant
					-Hexachlorobenzene -0.10 ng/g	OR = 28.4 (3rd vs 1st tertile)
					-Mirex -0.012 ng/g	OR = 6.5 (3rd vs 1st tertile)

Abbreviations: DM, diabetes mellitus; HbA1C, glycosylated hemoglobin; OCP, OC pesticide; OR, odds ratio.

[a] When only cutoff points by categories were provided in the original article, median values over all subjects were crudely estimated (the center value of 2nd tertile in tertile categories, the upper cutoff value of the 2nd quartile in quartile categories, the center value of 3rd quintile in quintile categories, etc). When median values of subjects with and without T2D were presented separately, values among subjects without T2D were cited.

[b] Statistically significant ORs were presented; nonsignificant findings were not presented.

[c] Summary measures were calculated by summing individual rank of individual POPs belonging to each category.

positive association between obesity and T2D was still observed even among low POPs groups in Finland and Spain may be attributable to a lack of subjects with very low concentrations of POPs similar to the low POP group in the United States. Alternatively, the complete lack of association between obesity and T2D among subjects with very low serum concentrations of POPs in the United States may be a chance finding that requires replication through studies examining a large number of people with relatively low serum concentrations of POPs across a wide range of obesity.

D. Reverse causality due to disease progression bias

Even when strong positive associations are observed in cross-sectional studies, attention should be paid to the possibility of "reverse causality," which may be due to mechanisms like "disease progression bias" (33). There is a possibility that subclinical or overt progress of T2D might alter the metabolism of POPs, slowing their excretion from the body or increasing release of POPs from adipose tissue. Under this hypothesis, T2D would increase serum levels of POPs, rather than POPs increasing the risk of T2D (11).

The possibility of T2D slowing the excretion of POPs from the body was not supported by two studies that revealed no change in the rate of elimination of POPs from blood in relation to the presence or duration of T2D (42, 43). Nevertheless, given that patients with T2D are often obese, one mechanism that might lead to increased serum concentrations of POPs in T2D in cross-sectional studies is increased lipolysis, which releases POPs stored in adipose tissue (18).

This issue was addressed in a recent article that reanalyzed associations between TCDD and T2D from the Air Force Health Study among veterans who had multiple blood samples drawn over a 20-year period (29). The reanalysis suggested that increases of serum TCDD levels (compared to previous levels measured during the monitoring period) were slightly more common in veterans with diabetes (33%; 44 of 135) than in veterans without diabetes (26%; 95 of 405), thus identifying a possible reverse causal pathway. These authors also presented trends of increasing incidence of T2D according to deciles of serum concentrations of TCDD within Vietnam veterans exposed to Agent Orange; such reported incidences were similar to the trends over deciles in comparison veterans, despite large differences in TCDD con-

Figure 1.

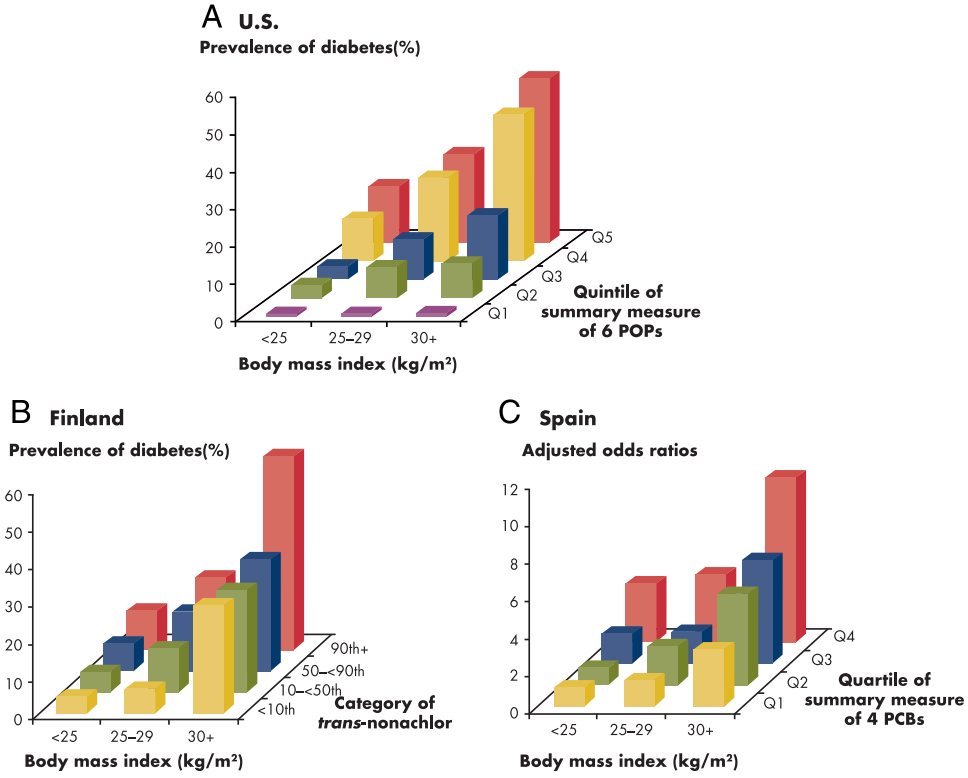


Figure 1. Interaction between BMI and POPs estimating the prevalence of T2D. A, United States (37): The summary measure of six POPs was calculated by summing individual rank of six POPs (1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin, *p,p'*-DDE, oxychlordane, *trans*-nonachlor, and PCB153). The summary measure was classified into five quintiles from Q1 to Q5. Among persons with the lowest quintile (Q1) of the summary POPs, BMI was not associated with the risk of T2D, and T2D itself was very rare even among obese. In addition, the risk of diabetes increased with increasing concentrations of POPs even among lean persons. The highest risk was observed in persons with high POPs and high BMI. B, Finland (40): Because only results based on individual POP, not summary measures of POPs, were presented in the paper, we selected *trans*-nonachlor, which showed the strongest association with T2D for this figure. Serum concentrations of *trans*-nonachlor were divided into <0th, 10-<50th, 50-<90th, and ≥ 90th percentiles. The positive associations of T2D with POPs became stronger as BMI increased, similar to those in the United States. However, obesity was associated with T2D even among persons with the lowest levels of *trans*-nonachlor. C, Spain (41): The summary measure of four PCBs was calculated by summing individual rank of four PCBs (PCB118, PCB138, PCB153, and PCB180). The summary measure was classified into four quartiles from Q1 to Q4. All odds ratios were computed with Q1 and normal weight as the reference category, with models adjusted by age, sex, total cholesterol, and triglycerides. Results were similar with those from Finland.

centrations between the two groups. The authors took these findings as evidence of reverse causality and further speculated that this finding applies to other persistent lipophilic chemicals such as OC pesticides or PCBs.

However, despite some evidence suggesting the existence of a reverse pathway (T2D causing elevated POPs), the magnitude of the reverse effect does not seem to be large, mainly because increases in serum TCDD levels during the monitoring period were common even among veterans without T2D. Furthermore, methodological issues like the inverted U-shaped association and/or the characteristics of POP mixtures need to be considered when interpreting findings of the Air Force Study, as will be done in *Section V*.

In general terms, the Air Force Health Study is classifiable as a prospective study. However, it is based on retrospective estimation of baseline levels of TCDD from about 1962 to 1972, derived from TCDD levels measured in 1987, and it evaluated associations with T2D diagnosed between the end of each veteran's Vietnam tour and 2002 (43). In some T2D patients, the TCDD measurement in 1987 could have been made after disease onset. Thus, similar to cross-sectional and case-control studies, in this study, it is difficult to evaluate temporality of presumed cause and effect. A full assessment of causality of POPs and T2D will require evidence from prospective epidemiological studies, as well as in vitro and in vivo experimental studies.

E. Prospective evidence linking POPs and T2D

Since publication of the cross-sectional associations of OC pesticides or PCBs with T2D, several prospective studies have been performed in general populations (42, 44–

Table 4. Prospective Studies Concerning Chlorinated POPs and the Risk of Incident T2D in General Populations With Background Exposure

Country	First Author, Year (Ref.)	Study Participants: -No. of Subjects -Characteristics -Age at Baseline	Baseline Year	Follow-Up Period	Outcome: -Diagnosis -No. of Cases	Adjustment	Exposure -Measured Chemicals -Median Values[a]	Results[b] -Relative Risk (RR) (95% Confidence Interval)
Prospective cohort studies								
Sweden	Lee, 2011 (44)	-725 men and women -General population -70 y old	2001–2004	~5 y	-36 cases -Fasting glucose or DM medication	Sex, BMI, smoking, alcohol consumption, physical activity, total cholesterol, and triglycerides	-PCB74, PCB99, PCB105, PCB118, PCB138, PCB153, PCB156, PCB157, PCB170, PCB180, PCB189, PCB194, PCB206, PCB209 -1.4 ng/g for PCB153	Based on rank-based summary measure of 14 PCBs[c] RR = 4.5 (0.9–23.5) (2nd vs 1st quintile) RR = 5.1 (1.0–26.0) (3rd vs 1st quintile) RR = 8.8 (1.8–42.7) (4th vs 1st quintile) RR = 7.5 (1.4–38.8) (5th vs 1st quintile)
							-*p,p′*-DDE, *trans*-nonachlor, hexachlorobenzene -2.0 ng/g for *p,p′*-DDE	Based on rank-based summary measure of 3 OCPs[c] RR = 1.1 (0.3–4.5) (2nd vs 1st quintile) RR = 1.6 (0.4–5.8) (3rd vs 1st quintile) RR = 1.5 (0.4–5.8) (4th vs 1st quintile) RR = 3.4 (1.0–11.7) (5th vs 1st quintile)
							-Octachlorodibenzo-p-dioxin -0.0025 ng/g	Statistically nonsignificant
United States	Vasiliu, 2006 (47)	-1384 men and women -Residents who consumed animal products that were exposed to PBBs -≥20 y old	1976	~25 y	-180 cases -Known DM	Age, BMI, smoking, alcohol consumption	-Total PCBs -7 ng/g	Only among women RR = 2.0 (1.1–3.8) (2nd vs 1st quartile) RR = 2.3 (1.2–4.3) (3rd vs 1st quartile) RR = 2.3 (1.3–4.3) (4th vs 1st quartile)
United States	Turyk, 2009 (42)	-471 men and women -Great Lakes Sport Fish Consumers -Mean age: ≈ 50 y old -3.2 ng/g	1994–1995	~11 y	-36 cases -2.4 ng/g -Self-report of physician diagnosis	Age, sex, BMI	-Total PCBs -2.4 ng/g	Statistically nonsignificant
							-PCB118 -0.15 ng/g	Statistically nonsignificant
							-*p,p′*-DDE -3.2 ng/g	RR = 5.5 (1.2–25.1) (2nd vs 1st tertile) RR = 7.1 (1.6–31.9) (3rd vs 1st tertile)

(*Continued*)

Table 4. Continued

Country	First Author, Year (Ref.)	Study Participants: -No. of Subjects -Characteristics -Age at Baseline	Baseline Year	Follow-Up Period	Outcome: -Diagnosis -No. of Cases	Adjustment	Exposure -Measured Chemicals -Median Values[a]	Results[b] -Relative Risk (RR) (95% Confidence Interval)
United States	Wu, 2013 (49)	-1095 women -Participants in two previous case-control studies (Breast Cancer Study and Non-Hodgkin Lymphoma Study) from the Nurses' Health Study -Mean age:: ≈ 59 y old	1989–1990	∼19 y	-48 cases -Known DM	Age, BMI, family history of DM, smoking, alcohol consumption, physical activity, case-control status	-PCB118, PCB138, PCB153, PCB180, total PCBs -104.5–106.1 ng/g lipid for PCB153	Statistically nonsignificant
							-*p,p*′-DDE -773.6–989.6 ng/g lipid	Statistically nonsignificant
							-*p,p*′-DDT -53.1–43.7 ng/g lipid	Statistically nonsignificant
							-Hexachlorobenzene -29.8–37.0 ng/g lipid	RR = 1.5 (0.6–3.9) (2nd vs 1st tertile) RR = 3.1 (1.3–7.7) (3rd vs 1st tertile)
Nested case-control studies								
Sweden	Rignell-Hydbom, 2009 (46)	-372 cases and 371 controls (men and women) -General population -50–59 y old	1995–2000	∼11 y	-372cases -Linkage with the Swedish inpatient and outpatient registers	Age, calendar year, BMI (through matching)	-PCB153 -1.3 ng/g	Statistically nonsignificant
							-*p,p*′-DDE -2.9 ng/g	Only 39 cases diagnosed ≥ 7 y after baseline RR = 5.5 (1.2–25.0) (≥75th % vs <75th %)
United States	Lee, 2010 (45)	-90 cases and 90 control (men and women) -General population -18–30 y old	1987–1988	∼18 y	-90 cases -Fasting glucose ≥126 mg/dL or known DM	Age, sex, race, BMI, total cholesterol, and triglycerides	-PCB74, PCB87, PCB99, PCB105, PCB118, PCB146, PCB153, PCB156, PCB157, PCB138–158, PCB167, PCB170, PCB178, PCB180, PCB183, PCB187, PCB194, PCB195, PCB199, PCB196–203, PCB206, PCB209 -0.4 ng/g for PCB153	Based on rank-based summary measure of 22 PCBs[c,d] RR = 4.4 (1.3–14.8) (2nd vs 1st sextile) RR = 2.7 (0.8–8.8) (3rd vs 1st sextile) RR = 1.7 (0.5–5.7) (4th vs 1st sextile) RR = 1.2 (0.3–4.4) (5th vs 1st sextile) RR = 1.1 (0.3–4.6) (6th vs 1st sextile)
							-*p,p*′-DDE, *p,p*′-DDT, *trans*-nonachlor, oxychlordane, hexachlorobenzene, *β*-hexachlorocyclohexane, γ-hexachlorocyclohexane, mirex -3.3 ng/g for *p,p*′-DDE	Based on rank-based summary measure of 8 OCPs[c,d] Statistically nonsignificant Results on *trans*-nonachlor RR = 4.3 (1.5–12.6) (2nd vs 1st quartile) RR = 2.3 (0.7–7.4) (3rd vs 1st quartile) RR = 2.0 (0.6–6.9) (4th vs 1st quartile)

Abbreviations: DM, diabetes mellitus; OCPs, OC pesticides; OR, odds ratio; PBB, polybrominated biphenyl.

[a] When only cutoff points by categories were provided in the original article, median values over all subjects were crudely estimated (the center value of the 2nd tertile in tertile categories, the upper cutoff value of the 2nd quartile in quartile categories, the center value of 3rd quintile in quintile categories, etc). When median values of subjects with and without T2D were presented separately, values among subjects without T2D were cited. Median values of the Wu et al study (49) were shown as ranges because they used datasets from two case-control studies and presented concentrations of POPs respectively.

[b] When there were statistically significant specific RRs, all RRs were presented with 95% confidence intervals.

[c] Summary measures were calculated by summing individual rank of individual POPs belonging to each category.

[d] Results not previously published. Findings were recalculated using the raw dataset because the original article reported results on summary measures over all POPs, not PCBs or OCPs separately. Summary measures were calculated by summing individual rank of individual POPs belonging to each category

Figure 2.

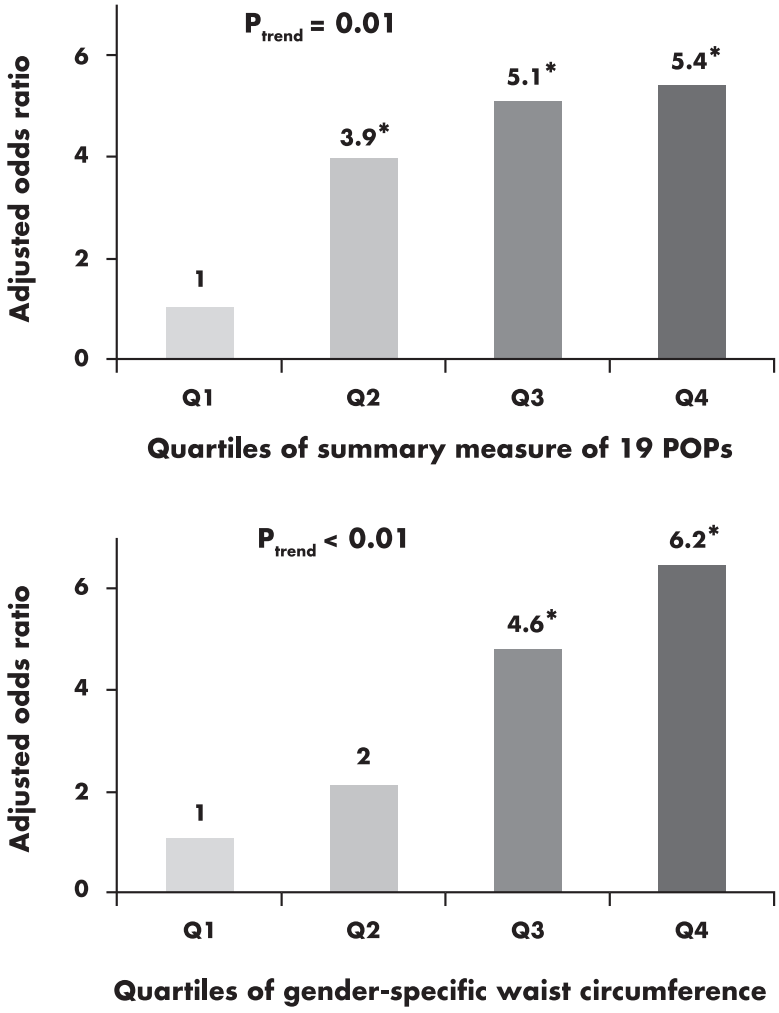


Figure 2. Comparison of strength of associations with T2D between a summary measure of 19 POPs and gender-specific waist circumference in the PIVUS (the Prospective Investigation of the Vasculature in Uppsala Seniors) cohort study (44). The summary measure was calculated by summing the individual rank of 19 POPs. Results were recalculated using the raw dataset because the original article (44) reported results on summary measures of subclasses of POPs (PCBs or OC pesticides), not all POPs. These findings use the methodology described in the original article (44) but have not been published before. Both POPs and gender-specific waist circumference were included in the same model and adjusted for gender, physical activity, cigarette smoking, alcohol consumption, total cholesterol, and triglyceride. Statistically significant odds ratios are indicated with asterisks.

49). In prospective studies, researchers can be fairly certain that exposure precedes the development of diseases (33) because serum concentrations of POPs are measured in serum collected from individuals years before the development of T2D. In Table 4, we have summarized the main findings from six prospective studies performed in general populations with background exposures to POPs.

Although all prospective studies concluded that some POPs or combinations of POPs predicted the future risk of T2D, no single POP significantly predicted T2D in all prospective studies. In the oldest cohort studies, just one or a few POPs were measured as a "surrogate marker" of all POPs (42, 46, 47), which is a significant limitation. By contrast, recent cohort studies have measured a much larger variety of POPs and used improved technology for such measurement (44, 45). Similar to cross-sectional or case-control studies, the interpretation of findings for individual POPs in human studies should also be cautious in prospective studies, given that humans are virtually always exposed to correlated POP mixtures. This issue will be discussed further in *Section V.B*.

Considering the characteristics of POPs as mixture, two prospective studies, Coronary Artery Risk Development in Young Adults (CARDIA) (45) and Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) (44), created a summary measure of POPs using the sum of ranks of various POPs rather than focusing on individual POPs. Results demonstrated that POP mixtures were associated with about three to five times higher T2D risk, depending on study subjects and exposure ranges. When the predictive power of POP mixture vs waist circumference was compared in the elderly, POPs were as strongly predictive of T2D as was waist circumference (Figure 2).

In the CARDIA study, subjects were categorized by sextiles, not conventional quartiles, in an attempt to isolate subjects with very low concentrations of multiple POPs in the lowest sextile of the summary measure. When the quartile approach was used, there was no association between POP mixture and T2D (the adjusted odds ratios were 1.0, 1.4, 0.7, and 0.5). However, the association became significant and stronger with the sextile approach, with adjusted odds ratios of 1.0, 2.8, 3.7, 1.2, 1.3, and 1.0 (*P* value for quadratic term = .04) (Figure 3). We will also discuss this issue in *Section V.B*.

On the other hand, whereas the CARDIA study showed an inverted U-shaped association (45), the other prospective study, PIVUS (44), did not show a clear inverted U-

Figure 3.

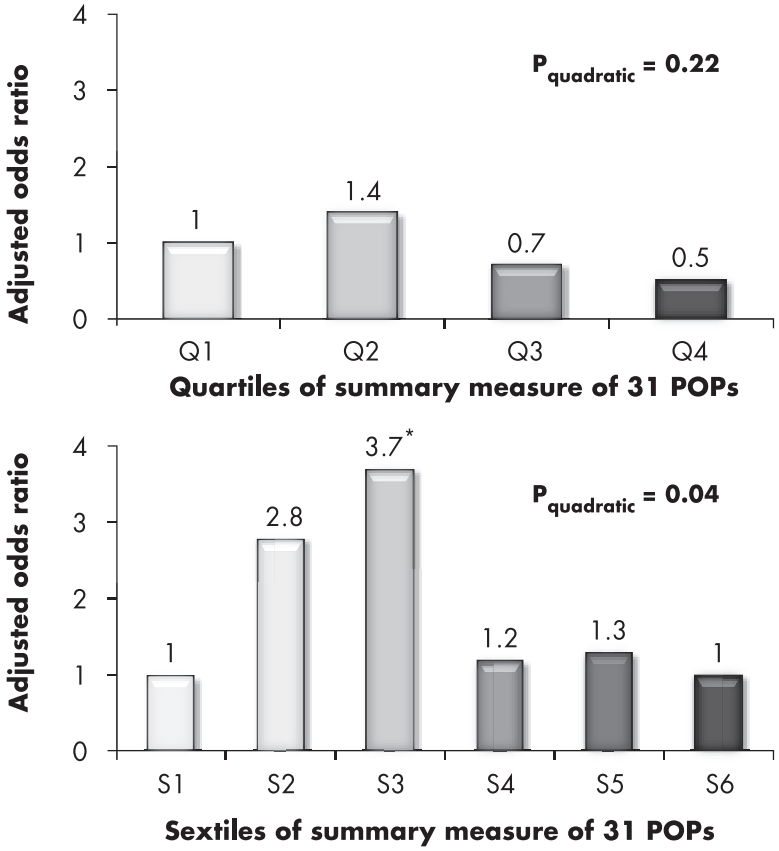


Figure 3. Comparison of quartile vs sextile approaches to the associations between a summary measure of 31 POPs on T2D in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study (45). The summary measure was calculated by summing individual rank of 31 POPs. When the summary measure was classified into quartiles, there was no association between POPs and T2D. However, with classification into sextiles, low-dose POPs significantly predicted the future risk of T2D. The authors interpret this finding to have occurred because the sextile reference group was closer to a true hypothetical reference group without exposure to POPs than the quartile reference group. Results were adjusted for age, gender, race, BMI, total cholesterol, and triglyceride. Statistically significant odds ratios are indicated with an asterisk.

shaped association (Figure 2). However, it did suggest nonlinearity; the risk of T2D was substantially increased with only a slight increase of concentrations of POPs within the lower dose range of POPs and only a slight increase in risk with increasing dose of POPs within higher doses of POPs.

One big difference between the CARDIA study and the PIVUS study was the age distribution of study subjects. At baseline, the PIVUS subjects were elderly adults aged 70 years, whereas the CARDIA subjects were young adults aged 18 to 30 years. Patients diagnosed with T2D at an advanced age have particular characteristics; they tend to be less obese and to have more β-cell dysfunction (50, 51). Thus, when the pathogenesis of T2D is classified into two stages, insulin resistance and insulin secretory defects, the relative importance of each stage might be different depending on the age at which T2D develops, which makes it difficult to produce exactly the same dose-response relations between these two prospective studies. In addition, physiological differences between the young and the elderly may play a mechanistic role, which will be discussed in *Section V.A*.

III. Experimental Evidence Linking POPs and T2D

In this section, we focus on experimental findings of subchronic/chronic exposure to low-dose POP mixtures that approximate current human exposure patterns. One recent in vivo and in vitro experimental study confirmed a causal relationship between POP mixtures and T2D- related metabolic dysfunction (52). In this experiment, scientists utilized POP-contaminated fish oil, not artificial mixtures of several POPs. Because POP-contaminated food is the main external exposure source of POPs for humans, this approach tends to mimic the current human exposure pattern in terms of mixture and doses of POPs. Adult rats were fed crude salmon oil containing environmental levels of POPs for 4 weeks. In this exposure period, the rats developed insulin resistance, visceral obesity, dyslipidemia, nonalcoholic fatty liver, and chronic low-grade inflammation, whereas animals fed salmon oil from the same source, but refined to achieve low POP concentrations, did not. Importantly, body burdens of POPs in these rats were similar to those observed in Northern Europeans at 40 to 50+ years of age (53), suggesting a strong relevance of these experimental findings to humans. Also, because this experiment was performed with adult rats, it suggests that chronic exposure to low-dose POP mixtures during adulthood can induce all of these T2D-related abnormalities.

These authors complemented their in vivo rat study with additional in vitro tests (52). They incubated differentiated 3T3-L1 adipocytes with artificially combined POP mixtures including OC pesticides, PCBs, PCDDs, and PCDFs within specified dose ranges. The authors ob-

served reduced insulin action after treatment with both OC pesticides and PCBs, whereas PCDDs or PCDFs with dioxin activity had no effect on this endpoint. Interestingly, impaired insulin action was observed with 1 nM of mixed OC pesticides and PCBs; there were no clear dose-response relations on insulin action with 10 or 100 times higher concentrations, suggesting low-dose effects and nonmonotonic dose-response curves. The authors' approach is appropriate for the study of POP mixtures because each treatment consisted of several compounds belonging to specific subclasses of POPs. However, these treatments differed from the mixture in the POP-contaminated fish oil, which was a combination of all subclasses of POPs. Therefore, the relevance of findings from the in vitro aspect of this experiment to humans may be less than those of the in vivo animal experiments. Despite this limitation, this study provides an opportunity to evaluate what kinds of POPs might be more relevant to the development of T2D and what dose-response relationships might be expected.

Two further experimental studies were performed by the same researchers (54, 55). One study evaluated the effects of chronic consumption of farmed-salmon fillet in mice (54), whereas the other fed animals whale meat (55). Unlike their earlier experimental study that focused on crude fish oil contaminated with POPs, these studies evaluated effects of fish or mammal consumption as a whole food, considering both possible harmful effects of POPs contaminating food and possible beneficial effects of nutrients naturally contained in the food. Feeding adult mice the farmed-salmon fillet containing POP contaminants for 8 weeks caused visceral obesity and accelerated the development of insulin resistance and glucose intolerance (54). When POP levels in farmed-salmon fillet were reduced by decontamination, the experimental mice had a lower body burden of POPs, less visceral fat, and better insulin sensitivity and glucose tolerance (54). In contrast, surprisingly, feeding animals POP-contaminated whale meat improved insulin sensitivity and glucose tolerance and reduced body weight (55). Importantly, the extent of POP contamination of the whale meat was 10 to 15 times higher than that of the farmed-salmon fillet. Although the different nutrient profiles between salmon and whale meat could contribute to these contradictory results, the authors interpreted that low-dose POPs can be more harmful than high-dose POPs, similar to the expectation from epidemiological studies that show inverted U-shaped relationships.

IV. POPs and Obesity

A. POPs as obesogens

In 2002, Paula Baillie-Hamilton (56) proposed a hypothesis linking exposure to chemicals with obesity, and this premise is now gaining credence. Historically, the main purpose of measuring the weight of experimental animals was to gather basic information on their general health, and toxicologists were mainly concerned about weight loss as a sign of toxicity. When a wide range of chemical concentrations were tested in animals, weight gain effects were observed after treatment at low concentrations to a variety of chemicals including POPs. However, a significant amount of this evidence was ignored in early studies (56).

In 2006, weight gain effects of chemicals were reformulated under the "obesogen hypothesis," a term coined by Bruce Blumberg (57). Obesogens can be functionally defined as chemicals that alter homeostatic metabolic setpoints, disrupt appetite controls, perturb lipid homeostasis to promote adipocyte hypertrophy, stimulate adipogenic pathways that enhance adipocyte hyperplasia, or otherwise alter adipocyte differentiation during development (57, 58). In particular, recent experimental studies have mainly focused on prenatal or early life exposure to chemicals during critical periods of cell and organ differentiation because these exposures can alter developmental programming of the endocrine controls of metabolism including the differentiation of adipocytes, resulting in obesity in the future (58). These proposed pathways include inappropriate modulation of nuclear receptor function; therefore, putative obesogens can be classified as endocrine-disrupting chemicals (EDCs).

Possible candidate obesogens encompass a wide range of compounds with different chemical and physical properties like organotins, organophosphates, bisphenol A, phthalates, and heavy metals (59). It is highly likely that there are many other chemicals in the environment that increase the risk of obesity but have yet to be recognized. Because a detailed analysis on various obesogens is outside the scope of this article, we will only focus on chlorinated POPs.

Earlier experimental studies on POPs mainly characterized a TCDD-related severe weight loss; one hallmark of TCDD systemic toxicity is a wasting syndrome (60). In vitro experiments have shown an inhibition of adipogenesis with the treatment of approximately 10 nM TCDD (61, 62). In fact, biological changes accompanying the wasting syndrome are diabetogenic phenotypes such as hyperlipidemia and decreased glucose uptake (63, 64). Because these treatment doses are close to overt toxicity levels, these findings are not relevant to the typical human population. However, the diabetogenic phenotype produced by inhibiting adipogenesis is important and will be discussed in *Section IV.B*.

On the other hand, a recent experimental study reported the importance of dose in inducing obesity (65).

Similar to findings from other obesogens, treatment of cultured cells with low-dose PCB77 with dioxin activity (3.4 μM) or TCDD (0.1 nM, a concentration 100 times lower than the earlier experimental studies) induced adipogenesis, whereas higher doses of either compound inhibited it. In this experiment, the effects of PCB77 were abolished by an AhR antagonist; thus, the authors interpreted their findings as suggesting that low-dose dioxin-like chemicals can induce weight gain through AhR-mediated responses.

However, experimental studies on OC pesticides with no dioxin-like activities also showed effects on weight, indicating that there could be AhR-independent mechanisms of POPs. For example, a study of *p,p′*-DDT reported a concentration-dependent increased adipogenesis from 1 to 50 μM (66). However, endrin (a cyclidiene pesticide) caused a dose-dependent inhibition of adipocyte differentiation from 0.1 to 30 μM (67). Other cyclidiene pesticides like aldrin and dieldrin also showed adipogenesis-inhibiting effects (67). Neither *p,p′*-DDE nor oxychlordane (2 or 20 μM) had a significant effect on adipogenesis itself, but both promoted adipocyte fatty acid uptake in mature adipocytes, leading to the promotion of adipocyte hypertrophy (68).

Different effects on adipogenesis—depending on the kind and dose of compound studied—make it very difficult to assess the relevance of experimental findings on one specific POP to humans. Therefore, we focused on recent animal studies that have utilized POP mixtures with human relevant doses. These studies have revealed that chronic exposure to POP mixtures in rats or mice during adulthood led to increased visceral fat (52, 54). In another experiment using a zebrafish model, lifelong exposure to POP mixtures induced weight gain (69, 70). Therefore, whatever effects specific individual POPs may have shown in experimental settings, the net result of POP mixtures similar to current human exposure levels may be weight gain.

Despite the experimental evidence on POP mixtures from laboratory animals, human evidence on POPs is diverse (Table 5). When human studies are classified into early life exposure (including intrauterine) and adult exposures, results on the association between POPs and obesity are less consistent with early life exposure than with adult exposure, although direct comparisons among studies are difficult due to substantial methodological differences.

A recent review explored the relationships between EDCs and obesity in humans (71). Regarding POPs, it concluded that OC pesticides may play a role in the development of obesity, whereas PCBs showed variable results depending on dose, timing, and gender. This study did not clearly separate studies characterizing intrauterine exposures from those examining adult exposures, except in considering the former ones as prospective studies and the latter ones as cross-sectional studies. In fact, the conclusions of the review (71) may be more appropriate for cross-sectional findings focusing on adult exposure than for findings on intrauterine exposure. However, any cross-sectional association between POPs and obesity in humans cannot be interpreted as evidence for or against obesogenic effects of POPs for the reasons detailed below.

First, positive cross-sectional associations between POP body levels and obesity among adults can be observed even in the absence of any POP-related obesogen effects because obesity itself can lengthen the half-lives of POPs. Kinetic studies indicate that fat mass is among the major determinants of half-lives of POPs in humans (72). On the other hand, if lean and obese persons have equal total body burden of POPs, serum concentrations of POPs in obese persons are expected to be lower than in lean persons due to the dilution effects of adipose tissue mass, hence leading to the inverse cross-sectional associations (73).

Also, there are complicated dynamics between a change in adipose tissue volume and toxicokinetics of POPs. Weight loss is responsible for increasing serum concentrations of POPs due to the reduction in storage capacity in the adipose tissue compartment, which consequently leads to the release of POPs into blood (10, 74). In contrast, weight gain leads to decreasing serum concentrations of POPs through remobilization of POPs into adipose tissue (10, 74). Two persons who have the same weight at age 50 may have had substantially different histories of weight change, which may have affected differently their serum concentrations of POPs at this age.

However, as the interrelated pharmacodynamics between POPs and adipose tissue we mentioned above affect all lipophilic chemicals similarly, an interesting issue remains; cross-sectional associations tend to differ depending on the type of POP. OC pesticides tend to be positively associated or not associated with obesity; to date, no study has reported an inverse association. However, PCBs showed inverse associations in many studies (Table 5), particularly highly chlorinated PCB congeners, whereas less chlorinated PCBs were often positively associated with obesity.

Possible reasons for the contrasting associations with obesity between OC pesticides and PCBs have been discussed by other researchers, again from the viewpoint of pharmacodynamics (75). They suggest dilution effects of adipose tissue when there are active external sources of exposure to POPs, leading to inverse associations between serum concentrations of POPs and obesity. However, when there were fewer active exposure sources (eg, after

banning of specific POPs), or the extent of external exposure was much lower than the amount already accumulated in the body, the direction of association between serum concentrations of POPs and obesity started to change from inverse to positive because of increased half-lives of POPs among obese persons. Different results between OC pesticides and PCBs may be due to the different balance between ongoing and past exposure levels. For example, average *p,p′*-DDE levels in 2000 were approximately one-tenth those in the 1970s, a much more precipitous decline than PCBs, whose concentrations are not declining in some populations (76, 77). Therefore, the di-

Table 5. Associations Between Chlorinated POPs and Obesity in Human Studies

	Summary of Results		
Compound	**Positive Associations**	**Inverse Associations**	**Null Associations**
Prenatal or early exposure			
PCBs	Hertz-Picciotto, 2005 (F) (265) Valvi, 2012 (F) (266) Verhulst, 2009 (267)	Blanck, 2002 (268) Burns, 2012 (M) (269) Jacobson, 1990 (270) Lamb, 2006 (F) (271)	Cupul-Uicab, 2010 (272) Gladen, 2000 (F) (273)[a] Gladen, 2000 (M) (273) Hertz-Picciotto, 2005 (M) (265) Karmaus, 2009 (F) (274) Lamb, 2006 (M) (271) Mendez, 2011 (275) Patandin, 1998 (276) Valvi, 2012 (M) (266)
DDT	Gladen, 2000 (*p,p′*-DDE) (M) (273) Karmaus, 2009 (*p,p′*-DDE) (F) (274) Mendez, 2011 (275) Valvi, 2012 (*p,p′*-DDT) (M) (266)[b] Valvi, 2012 (*p,p′*-DDE) (F) (266)[b] Verhulst, 2009 (*p,p′*-DDE) (267)[a]	Burns, 2012 (*p,p′*-DDE) (M) (269)	Cupul-Uicab, 2010 (*p,p′*-DDE) (M) (272) Cupul-Uicab, 2010 (272) Gladen, 2000 (*p,p′*-DDE) (F) (273) Gladen, 2004 (*p,p′*-DDE, *p,p′*-DDT) (M) (277) Jusko, 2006 (*p,p′*-DDE, *p,p′*-DDT, *o,p′*-DDT) (278) Valvi, 2012 (*p,p′*-DDE) (M) (266) Valvi, 2012 (*p,p′*-DDT) (W) (266) Warner, 2013 (*p,p′*-DDE, *p,p′*-DDT, *o,p′*-DDT) (279)
Hexachlorobenzene	Smink, 2008 (280)	Burns, 2012 (M) (269)	Cupul-Uicab, 2010 (272) Mendez, 2011 (275) Verhulst, 2009 (267)
β-Hexachlorocyclohexane		Burns, 2012 (M) (269)	Cupul-Uicab, 2010 (272) Mendez, 2011 (275)
Heptachlor epoxide			Cupul-Uicab, 2010 (272)
Chlordane			Cupul-Uicab, 2010 (oxychlordane, *trans*-nonachlor) (272)
Dieldrin	Cupul-Uicab, 2010 (272)		
TEQ		Burns, 2012 (M) (269)	Patandin, 1998 (276) Verhulst, 2009 (267)
PCDDs/PCDFs		Burns, 2012 (M) (269)	
Adult exposure, cross-sectional studies			
PCBs	Glynn, 2003 (PCB105, PCB118) (281) Hovinga, 1993 (M) (282) Hue, 2007 (PCB138) (283 Lee, 2012 (PCB72, PCB99, PCB105, PCB118) (M) (78) Pelletier, 2002 (PCB28, PCB99, PCB118, PCB138, PCB153) (284)	Bachelet, 2011 (285) De Roos, 2012 (PCB146, PCB153, PCB156, PCB170, PCB180, PCB183, PCB194, PCB196/203, PCB199, PCB206, PCB209) (286) Dirinck, 2011 (PCB153, PCB170, PCB180) (292) Glynn, 2003 (PCB156, PCB180) (281) Hue, 2007 (PCB153, PCB156, PCB170, PCB180, PCB187) (283) Ibarluzea, 2011 (PCB138, PCB153, PCB180) (287) Lee, 2006 (PCB153) (37)	De Roos, 2012 (PCB74, PCB99, PCB105, PCB118, PCB138/158, PCB187) (286) Glynn, 2003 (PCB138, PCB153, PCB167) (281) Hovinga, 1993 (F) (282) Hue, 2007 (PCB99, PCB118) (283) Lee, 2012 (PCB74, PCB99, PCB105, PCB118) (F) (78) Lee, 2012 (PCB126, PCB138, PCB153, PCB156, PCB157) (M) (78) Pelletier, 2002 (PCB156, PCB170, PCB180, PCB187) (284)

(*Continued*)

Table 5. Continued

Compound	Summary of Results		
	Positive Associations	**Inverse Associations**	**Null Associations**
		Lee, 2012 (PCB126, PCB138, PCB153, PCB156, PCB157, PCB169, PCB170, PCB180, PCB189, PCB194, PCB206, PCB209) (F) (78) Lee, 2012 (PCB169, PCB170, PCB180, PCB189, PCB194, PCB206, PCB209) (M) (78) Sandanger, 2007 (PCB153) (288)	
DDT	Bachelet, 2011 (*p,p*′-DDE) (285) Glynn, 2003 (*p,p*′-DDE) (281) Hovinga, 1993 (282) Hue, 2007 (*p,p*′-DDE) (283) Jakszyn, 2009 (*p,p*′-DDE) (289) Lee, 2006 (*p,p*′-DDE) (37) Lee, 2012 (*p,p*′-DDE) (M) (78) Lee, 2012 (*p,p*′-DDE) (F) (78) Pelletier, 2002 (*p,p*′-DDE) (284) Schildkraut, 1999 (*p,p*′-DDE) (290)		Bradman, 2007 (*p,p*′-DDE, *p,p*′-DDT, *o,p*′-DDT) (291) De Roos, 2012 (*p,p*′-DDE) (286) Dirinck, 2011 (*p,p*′-DDE) (292) Ibarluzea, 2011 (*p,p*′-DDE) (287) Pelletier, 2002 (*p,p*′-DDT) (284)
Chlordane	Hue, 2007 (oxychlordane) (283) Lee, 2012 (*trans*-nonachlor) (M) (78) Pelletier, 2002 (oxychlordane, *trans*-nonachlor) (284)		De Roos, 2012 (oxychlordane, *trans*-nonachlor) (286) Glynn, 2003 (281) Hue, 2007 (*trans* -nonachlor) (283) Lee, 2006 (oxychlordane, *trans*-nonachlor) (37) Lee, 2012 (*trans*-nonachlor) (F) (78)
Hexachlorobenzene	Glynn, 2003 (281) Ibarluzea, 2011 (287) Jakszyn, 2009 (289) Lee, 2012 (M) (78) Pelletier, 2002 (284)		Bradman, 2007 (291) Hue, 2007 (283) Lee, 2012 (F) (78)
β-Hexachlorocyclohexane	Dirinck, 2011 (292) Glynn, 2003 (281) Hue, 2007 (283) Ibarluzea, 2011 (287) Jakszyn, 2009 (289) Pelletier, 2002 (284)		Bradman, 2007 (291)
Mirex			Pelletier, 2002 (284)
PCDDs/PCDFs	Lee, 2006 (HpCDD, OCDD) (37)		Lee, 2012 (OCDD) (F) (78) Lee, 2012 (OCDD) (M) (78)
Adult exposure, prospective studies			
PCBs	Lee, 2011 (PCB153[b,c], PCB156, PCB170[b], PCB178[b,c], PCB180[b], PCB187[b,c], PCB194, PCB195[b,c], PCB199[b,c], PCB196–203[b], PCB206[b], PCB209) (79) Lee, 2012 (PCB74[b], PCB99[b,c], PCB118[b,c], PCB138[b], PCB153[b], PCB156) (F) (78) Lee, 2012 (PCB156[c], PCB157[b,c], PCB169[c], PCB180, PCB189[c], PCB209[b]) (M) (78)	Lee, 2012 (PCB156, PCB157[c], PCB169[c], PCB170, PCB180, PCB189, PCB194, PCB206 PCB209[b,c]) (F) (78) Lee, 2012 (PCB180) (M) (78)	Lee, 2011 (PCB74, PCB87, PCB99, PCB105, PCB118, PCB146, , PCB157, PCB138–158, PCB167, PCB183) (79) Lee, 2012 (PCB105, PCB126) (F) (78) Lee, 2012 (PCB74, PCB99, PCB105, PCB118, PCB126, PCB138, PCB153, PCB170, PCB194, PCB206) (M) (78)

(*Continued*)

Table 5. Continued

	Summary of Results		
Compound	**Positive Associations**	**Inverse Associations**	**Null Associations**
DDT	Lee, 2011 (*p,p′*-DDE[b], *p,p′*-DDT) (79) Lee, 2012 (*p,p′*-DDE[b]) (M) (78)		Lee, 2012 (*p,p′*-DDE) (F) (78)
Chlordane			Lee, 2011 (oxychlordane, *trans*-nonachlor) (79) Lee, 2012 (*trans* -nonachlor) (F) (78) Lee, 2012 (*trans* -nonachlor) (M) (78)
Hexachlorobenzene			Lee, 2011 (79) Lee, 2012 (F) (78) Lee, 2012 (M) (78)
β-Hexachlorocyclohexane			Lee, 2011 (79)
Mirex			Lee, 2011 (79)
PCDDs	Lee, 2012 (OCDD) (F) (78)		Lee, 2012 (OCDD) (M) (78)

Abbreviations: M, male; F, female; HpCDD, heptachlorodibenzo-p-dioxin; OCDD, octachlorodibenzo-p-dioxin. Data for summary of results are expressed as first author of study, year (specific compounds) (gender of subjects) (Ref.) When there were several compounds belonging to each POP, the kinds were listed. When male and female were separately reported, results by gender were presented using M or F. Otherwise, gender-specific results were not provided in original articles.

[a] In addition to gender-specific analyses, these studies performed further stratified analyses on race or cigarette smoking and reported different results among subgroups.

[b] Nonlinear dose-response relations.

[c] POPs with marginal significances. They were considered only in prospective studies because a sample size or numbers of incident cases of these studies were small.

lution effect of increased adiposity may still be observed with PCBs.

Due to the fundamental limitations of cross-sectional studies, the possible obesogenic effects of POPs need to be evaluated in cohort studies. There were two recent prospective studies on POPs and obesity among adults (78, 79). In each study, approximately 20 POP compounds or metabolites were measured, with variable results. In particular, sample sizes or numbers of incident cases were small; thus, some POPs showed only marginal statistical significance although the patterns of associations were very similar to those of other POPs. Therefore, in these prospective studies it is appropriate to focus on the consistency rather than on statistical significance.

One prospective study among young adults observed that *p,p′*-DDE and highly chlorinated PCBs were associated with increased BMI 18 years later (79). Importantly, the dose-response curves between serum concentrations of these POPs and BMI were inverted and U-shaped; as serum concentrations of POPs at the baseline increased, BMI increased until a critical low dose; above this dose, BMI did not increase, and it even started to decrease as serum concentration of POPs increased. Except for *p,p′*-DDE, OC pesticides did not predict future BMI. Another prospective study of elderly adults reported various associations with obesity endpoints depending on the POP examined and gender. *p,p′*-DDE, dioxin, or less chlorinated PCBs predicted the future risk of abdominal obesity (78), with some of these POPs showing inverted U-shaped associations. However, highly chlorinated PCBs strongly inversely predicted abdominal obesity. Although the findings from these two prospective studies suggest possible obesogenic effects of some POPs, the shape of the associations and kinds of POPs were inconsistent.

Despite the importance of testing hypotheses on the relationships between POPs and obesity in humans, such tests are particularly difficult because of the major roles that both diet and physical activity play in causing obesity. Even when sophisticated statistical methods are applied, it is very difficult to completely eliminate the strong effects of diet and physical activity on obesity— eg, because of unavoidable measurement errors in estimating energy intake and physical activity in human beings and because information on diet and physical activity during follow-up is not commonly collected. An additional difficulty stems from the fact that humans are continuously exposed to POPs through fatty animal foods, an intake that is often also closely linked to obesity.

B. Are obesogens unequivocally harmful?

When POPs have obesogenic effects as discussed in the previous section, one may ask whether the development of insulin resistance and T2D after exposure to POPs is the result of the obesogenic effects of POPs or a direct effect of POPs. One interesting example is obesogens that act as PPARγ agonists (57, 80); PPARγ is a receptor that regulates glucose metabolism, lipid uptake, and fatty acid storage, and promotes adipogenesis.

PPARγ-mediated proadipogenic effects of tributyltin and other EDCs have been proposed as the mechanistic basis for the environmental obesogen hypothesis (57). However, one group of PPARγ agonists, thiazolidinediones, are used to treat diabetes because PPARγ activation increases insulin sensitivity, even while these drugs promote fat accumulation (81). In this section, we will present evidence suggesting that the development of insulin resistance and T2D might not be directly related to the obesogenic effects of POPs.

As we stated in the introduction, obesity itself is not sufficient to cause insulin resistance and T2D. It is well-known that these metabolic abnormalities are accompanied by a state of chronic low-grade inflammation in adipose tissue (74). The presence of inflammation appears to be a main factor discriminating metabolically healthy obese and metabolically unhealthy lean persons (82). Which kinds of factors contribute to the inflammation of adipose tissue? Findings from experimental and human studies on adipose cell size provide a hint. In earlier studies with genetically obese mice or very obese persons, large adipose cell sizes were associated with the concentration of macrophages in the stromal vascular fraction of adipose tissue, which led to an inflammatory cascade (83, 84). Epidemiological studies also reported that enlarged mean adipocyte size is associated with increased risk of insulin resistance and T2D (85). However, there are recent reports that observed completely opposite associations; the increased proportion of small adipose cells, representing immature adipocytes with impaired ability to store triacylglycerol, was associated with inflammation in adipose tissue among moderately obese persons (86, 87). Also, impaired adipogenesis characterized with decreased expression of differentiation and/or fat storage genes was demonstrated in individuals with T2D or insulin resistance as compared with controls (88, 89).

Opposite results on adipose cell size can be at least partly explained by varying methodologies for measuring adipocyte size because earlier studies used a method that could not accurately separate small adipocytes (90). It is reported that the size distribution of adipocytes is bimodal, ie, cells primarily reside in either a large or a small cell fraction, with few in between (86). In this situation, the mean cell size estimated from total lipid extracted and total cell count is meaningless. Even after setting aside these methodological issues, the apparently contradictory results on adipocyte sizes may not be irreconcilable. An environment enriched with an excessive supply of food and lacking demand for physical activity requires so-called "adaptive responses" to buffer against metabolic imbalance. Normal adipose tissue functions adapt to this situation through adipocyte differentiation from precursor cells and maturation to triglyceride-loaded adipocytes of various sizes (91, 92). When adipose tissue expands in a healthy way, there is no insulin resistance. However, when there are inhibitors impairing adipocyte proliferation and/or differentiation, excess energy mainly leads to a serious enlargement of pre-existing adipocytes (93). In this situation, therefore, both an increased proportion of small immature adipocytes and an increased mean adipocyte size among mature adipocytes may coexist in adipose tissue.

Because there are limits to the size an adipocyte can achieve, if there is continuous excess energy intake, it will lead to consequent increase of fatty acid spillover into plasma and provide substrate availability for triglyceride synthesis in other tissues such as liver, skeletal muscle, myocardium, or even pancreas, increasing ectopic fat deposition, insulin resistance, and T2D (94). Therefore, certain factors that impair increased adipose tissue volume can be more problematic in inducing obesity-related metabolic dysfunction, under the current living conditions of excess energy intake (93). Supporting this idea, it is well-recognized that a lack of adipose tissue, the clinical state of lipodystrophy, is associated with insulin resistance and increased risk for development of T2D (95–98). The wasting syndrome and diabetogenic phenotype observed in TCDD-treated animals is an example of this type of T2D (60, 63, 64).

Under the situation of excess energy intake, hyperplasia and hypertrophy of adipocytes might be adaptive responses against metabolic imbalance, providing a means for the body to store extra energy. If this were true, chemical exposures that produce the same biological effects would not be harmful if they did not produce additional disturbances of other signaling pathways that are critical in the development of T2D. Given the same amount of excess energy intake, the presence of chemicals that *inhibit* adipogenesis—not obesogens that *promote* adipogenesis—could actually increase the risk of obesity-related metabolic dysfunction because they can exaggerate fat deposition in ectopic sites rather than within adipose fat pads. Although it may seem provocative, it may be time for a more nuanced approach; ie, it is perhaps too simplistic to suggest that the obesity-inducing effects of obesogens are themselves universally problematic. The worst-case scenario could be the combination of antiadipogenic chemicals and excess energy intake.

C. POPs and inflammation in adipose tissue

Regardless of obesogenic effects of POPs, POPs in adipose tissue can be involved in the inflammatory reaction in the adipose tissue, a critical condition for metabolically unhealthy adipose tissue. Direct proinflammatory effects

of POPs have been observed with several individual POPs with AhR affinities like TCDD, PCB77, or PCB126 in both in vitro and in vivo experimental studies; note that doses in these studies were much higher than human exposure doses (61, 65, 99, 100). Recently, chronic low-grade inflammation of adipose tissue developed in mice after chronic consumption of farmed salmon containing mixed POPs at concentrations similar to human exposure doses (54). Furthermore, a more fundamental possibility can be proposed: the presence of poorly biodegradable chemicals like POPs in adipose tissue may contribute to the development of chronic inflammation in such tissue.

Adipose tissue participation in inflammation is attributed largely to the proinflammatory actions of bone marrow-derived white adipose tissue macrophages (74). According to animal and human studies, most macrophages tend to localize to dead adipocytes, where they fuse to form syncytia that sequester and scavenge the residual free adipocyte lipid droplet and ultimately form multinucleated giant cells (MGCs), a characteristic of local chronic inflammatory states (83, 84, 101). Adipocyte death increases in proportion to BMI or adipocyte hypertrophy, and such adipose tissue mainly exhibits ultrastructural features of necrosis (83, 84, 101). Unlike apoptosis, in which cell constituents are packaged into inflammation-suppressive apoptotic bodies, during the process of necrosis, cell contents are released into the extracellular space where they evoke an inflammatory response (102).

Macrophage activation consists of biochemical, morphological, and functional changes that result in the secretion of preformed and/or newly synthesized constituents, such as cytokines and chemokines, leading to the inflammatory response (103). Macrophage activation at sites of inflammation is typically transient, giving way to repair processes that reestablish local tissue function (103). However, at sites of resistant infectious agents (eg, tuberculosis) or poorly biodegradable tissue irritants (ie, foreign bodies), macrophages remain activated and fuse to form MGCs surrounding the unresolved site (104). In fact, MGCs are a regular feature of granulomatous inflammation and are found in various organs after exposure to some poorly soluble, persistent, and nondegradable foreign bodies (105). One typical example is MGCs in pulmonary diseases associated with inhalation of environmental or occupational particulates (106). Furthermore, MGCs are commonly found on the surfaces of implanted biomaterials (107). At these sites, MGCs actively phagocytose debris and can acutely produce inflammatory cytokines until the insult is either cleared by phagocytosis or encapsulated (108).

Researchers have proposed that MGCs in adipose tissue are present to scavenge the residual free lipid droplets released from the necrotic adipocyte (83, 84, 101). However, lipid is not the sole content of adipocytes; POPs are also released from necrotic adipocytes. A pure lipid droplet (absent any POPs or other xenobiotics) that is released from a necrotic adipocyte may be easily scavenged by a macrophage and is unlikely to lead to the formation of MGCs because the pure lipid droplet is a natural body product that can be catabolized and excreted. To the contrary, a lipid droplet contaminated with POPs may not be so easily cleared by a macrophage, because POPs are highly resistant to biodegradation (109). Thus, the release of biodegradation-resistant POPs from necrotic adipocytes could promote formation and maintenance of MGCs, similar to resistant infectious agents or poorly biodegradable tissue irritants, which finally lead to chronic inflammation status in adipose tissue. Besides adipose tissue, because POPs universally exist in other tissues with lipids, similar inflammatory reactions might present in these other tissues as well.

D. POPs, gut microbiota, and obesity

Growing evidence reveals the importance of gut microbiota in developing obesity and obesity-related metabolic dysfunctions through nutrition acquisition, energy harvest, and a myriad of host metabolic pathways (110). There has been a great effort to understand the structure and function of gut microbial communities with a hope to develop prebiotic and/or probiotic interventions that will enable manipulation of the gut microbiota (111).

Recently, a hypothesis paper was published exploring possible interactions between gut ecology and environmental chemicals (112), postulating that variations in gut microbiota are likely to affect toxicodynamics of chemicals. However, there has been little interest in the possibility that chemicals like POPs directly influence the composition of gut microbiota. Unlike other common chemicals that are mainly excreted in urine, the main excretion route of POPs is feces through bile acid and the colon mucosa (113). Therefore, although most POPs are stored in adipose tissue, human gut is continuously exposed to POPs.

In fact, some microorganisms are known to biodegrade a large number of organic chemical substances such as petroleum hydrocarbons, halogenated and nitroaromatic compounds, phthalate esters, solvents, and pesticides that pollute soil and aquatic environments (114). These microorganisms naturally replicate in places with chemical contamination as one way of autopurification and have also been artificially introduced

to remove pollutants in environments (115). Because POPs are petroleum-based man-made chemicals, the continuous presence of these compounds in the human gut could alter the delicate balance of microorganisms present by increasing the number of microorganisms that survive via biodegradation of these chemicals. There is currently only one small-scale study that evaluated this possibility in humans (116); there were strong positive correlations between body burden of some POPs and methanogenic archaea levels in feces. Methanogenic archaea are a typical example of microorganisms that biodegrade PCBs or OC pesticides in the environment (117–119).

Methanogenic archaea may also be closely related to obesity. In mice, the presence of methanogenic archaea in the colon promotes obesity through improved efficiency of polysaccharide fermentation by the *Bacteroidetes* and the *Firmicutes,* the primary bacterial fermenters in the gut (120). The extent of methanogenic archaea colonization in the small bowel and the colon is predictive of the degree of weight gain in animal models, whereas total bacteria did not show this effect (121).

Despite clear experimental evidence from rodents, human studies on methanogenic archaea have reported inconsistent associations with obesity (116, 122–124). However, these discrepancies may be related to methodological issues because human studies measured methanogenic archaea in fecal samples. Because animal models revealed a higher abundance of methanogenic archaea in the small intestines, not the large intestines (121), methanogenic archaea measures in stool may not reflect their numbers in the remainder of the gut. In this sense, it is interesting that recent human studies measuring methane and hydrogen output via a breath test, a surrogate marker for colonization of methanogenic archaea, reported a consistent positive association with obesity (125, 126). Unlike methanogenic archaea in stools, methane and hydrogen on the breath test can better reflect the situation of the whole gut system, including both small and large intestines. The possible role of POPs affecting gut microbiota, which may itself be directly related to obesity, should be further studied.

E. Can the obesity paradox be explained by POPs?

Once POPs enter the bodies of humans or animals, they must be stored before excretion. Compared to other critical organs, adipose tissue, which is the natural lipid storage location, may be a relatively safe organ to accumulate POPs (19). Despite the side effects of increasing POP half-lives by storing them in adipose tissue and having a chronic internal exposure source of POPs, the accumulation of POPs in adipose tissue can reduce the acute burden of POPs on other critical organs. This idea is closely related to the concept that activation of the body's acute defense mechanisms can lead to long-term side effects (127), ie, there is a cost to "adaptation."

It is well-known that weight loss intervention studies found clear improvements in many metabolic profiles of patients with insulin resistance and/or T2D (128, 129), although weight loss increases serum concentrations of POPs. Because obesity and POPs appear to interact in the risk of T2D, as was discussed in *Section II.C*, and any harmful effects due to POPs may require a long time to develop, a decrease in adipose tissue mass itself could lead to an improvement of the metabolic profiles among patients with T2D. However, long-term effects of weight loss may be different from short-term effects.

Although overweight and obesity are well-established independent risk factors for various chronic diseases, overweight and obese patients with various conditions (including T2D, cardiovascular diseases, cancer, and chronic kidney diseases) or obese elderly have a better prognosis than do patients with ideal body weight (130–133). This phenomenon is called the "obesity paradox." Several mechanisms have been proposed for this phenomenon (130–133). Inaccurate assessment of body fatness by conventional BMI is one postulated mechanism. However, studies using directly measured body fat mass observed a similar obesity paradox (134). Other speculations include a survival effect, increased lean body mass, more aggressive treatment, or better nutritional reserve among obese patients or the elderly (130–133). However, these speculations lack supporting data.

POPs would help explain the obesity paradox if adipose tissue were shown to be a safe depot for POP storage relative to other critical organs. In this sense, the role of adipose tissue could well differ depending on POP levels. This hypothesis was recently tested in an elderly population showing the obesity paradox, using the NHANES 1999–2004 mortality follow-up database (135). Among subjects with relatively low serum concentrations of POPs, there was no obesity paradox: the risk of mortality among elderly with high fat mass was approximately two or three times higher than among those with low fat mass. On the other hand, the obesity paradox was strongly observed among elderly with high serum concentrations of POPs; among them, subjects with high fat mass showed a lower risk of mortality than those with low fat mass.

There is also experimental evidence suggesting possible protective effects of adipose tissue against POPs. For example, coplanar PCBs impaired glucose homeostasis in lean mice but not in obese mice; furthermore, obese mice developed impaired glucose homeostasis after weight loss (136). In rats, diet-induced obesity also significantly in-

creased survival time after exposure to a lethal dose of TCDD (137).

To our knowledge, only one human study has evaluated the role of POPs in the obesity paradox (135); therefore, the findings on the obesity paradox need to be replicated in other cohort studies. Importantly, the different associations between obesity and mortality by POP levels may be observed or not, depending on the distribution of POPs in a specific population. For example, if most people in a population had high POP concentrations, there may be no observable difference in associations between obesity and mortality by POP levels. This factor needs to be considered in future cohort studies.

V. Methodological Issues Crucial for Human Studies

One dilemma in interpreting recent epidemiological findings on POPs is how the strengths of the associations of T2D with OC pesticides and PCBs observed in recent general population studies could be so large when the earlier studies on TCDD or PCBs with much higher doses revealed no association or only a modest increase in risk of T2D. Another apparently puzzling aspect is that the average body burden of many chlorinated POPs has declined worldwide over recent decades (138). By contrast, T2D has more recently been unfolding as a worldwide epidemic. If chlorinated POPs are really important in the development of T2D, how can these apparent mismatches be reconciled?

A. Issue 1: inverted U-shaped associations

1. How can inverted U-shaped associations affect human findings?

A central hypothesis and line of thinking to explain these seemingly contradictory processes is that a low-dose exposure might be more harmful than a high-dose exposure, producing an inverted U-shaped dose response. We will discuss two possible mechanisms that can explain the inverted U-shaped associations in *Section VI*. Here, we will show how epidemiological studies can be affected by inverted U-shaped associations.

Consistency of research findings is a key factor when making causal inferences between exposures and the risk of human diseases (139). In addition, a dose-response relationship is generally considered to be an important condition that supports a causal association (139). The traditional toxicological dogma, "the dose makes the poison," has been actively debated in the field of toxicology and among environmental health scientists studying EDCs (140). However, a unique aspect of the inverted U-shaped association in human studies is that it can lead to varying association estimates among populations with different exposure distributions, even when the association is actually causal.

Unlike experimental studies, which can evaluate biological effects of a broad range of doses from zero to highly toxic levels, the exposure range in a specific human population is unique to that population and historical period; eg, it is influenced by the extent of industrialization, use of pesticides in agriculture, regulation of chemicals, and dietary patterns. The practical constraints inherent to studies in humans may directly influence epidemiological findings when an inverted U-shaped relationship truly exists.

Most importantly, human studies can observe different shapes of the dose-response relationship when there is an inverted U-shape over a wide dose range; inverted U-shaped, positive, inverse, and null associations are all possible depending on the exposure distribution of the population under study; this is illustrated and interpreted in Figure 4. In addition, although mean values of one specific POP may be generally similar between two populations, if the absolute concentrations in the reference category differ substantially among populations, the relative risk estimates will differ significantly as well.

The age distribution of each study may also influence the ability to unveil the whole spectrum of the dose-response relationship. Among the human studies on POPs and T2D, the only study that presented a clear inverted U-shaped association was CARDIA (45). One defining feature of this prospective study was that the participants had POPs measured as young adults. If POPs are involved in the development of T2D as EDCs or through mitochondrial dysfunction, this pattern would likely be clearer among young persons, who tend to have a more sensitive physiological system, such as the CARDIA subjects (young population in Figure 4). Considering that physiological system sensitivity decreases with aging (141), the inverted U-shaped dose-response curve can be blunted in elderly populations, as in the PIVUS subjects (44) (old population in Figure 4). Because most chronic diseases, including T2D, increase with age (142), in most epidemiological studies focusing on chronic diseases, incident cases are middle-aged or old. In such studies, therefore, inverted U-shaped associations may not be apparent.

2. Explanation for puzzling epidemiological findings on POPs

Inverted U-shaped associations can help to explain why the association from recent studies in general populations

Figure 4.

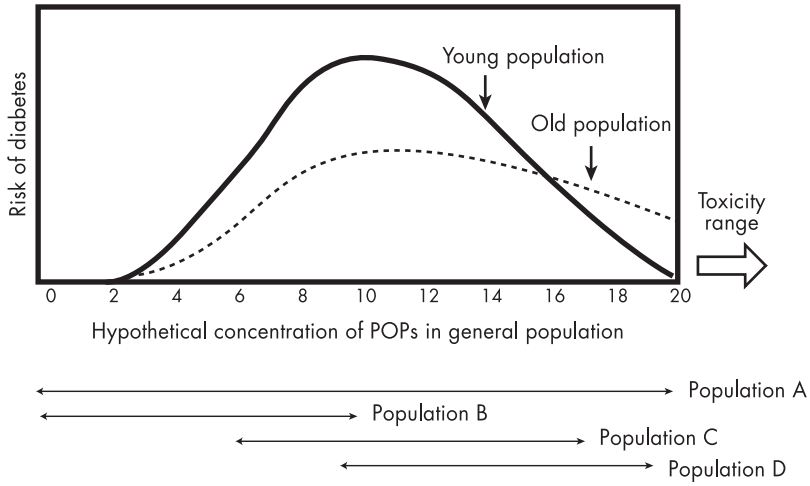


Figure 4. Hypothetical dose-response relationship between POPs and T2D. For simplicity, monotonically increasing doses are arbitrarily numbered starting from zero: 0–2 entails no significant response; doses 3–9 induce an increased risk of T2D; a decreased risk of T2D is observed from 10–20; toxicity (including strongly adverse effects) starts above dose 20. Let us assume that the dose range 0–20 represents a general population within environmental exposure to concentrations of chemicals within the presumed safety level, determined from the linear viewpoint of toxicology. The shape of the dose-response curve differs depending on the different distributions of POPs across populations. Population A shows an inverted U-shaped association (full range of doses 0–20); population B (doses 0–9) shows a strong positive association; population C (doses 5–15) shows a null association; and population D (doses 10–20) shows an inverse association. In addition, the shape of the dose-response curve can look different depending on the sensitivity of the physiological system. A young population is expected to show a sharper inverted U-shaped association (greater y-axis range), whereas an older population would show a blunted shape (less y-axis range). An additional feature made clear in Figure 4 is attenuation of risk estimation when there is a gradient of risk within the reference category. For example, in a population with exposure doses close to 0–12, relative risk for doses 8–12 (the "at risk" group) would have a much lower relative risk if the reference group were doses 0–7 than if doses 0–2 were taken as the reference group. In epidemiological studies, the most common shape of association we can observe may be the increase of risk within lower range of dose and flattening of the risk at higher doses.

with low concentrations of POPs is more consistent and stronger than in earlier studies with occupational or accidental high exposure. Often, occupationally or accidentally highly exposed persons provide the first human evidence about possible harmfulness of a chemical. Such human studies compare the disease risk among persons who had a high exposure to a suspected chemical in an occupational or accidental setting with the risk of subjects "occupationally unexposed or accidentally unexposed" (the reference groups).

However, this study design is problematic when a low concentration of the chemical increases the risk and a higher concentration does not further increase the risk or even decreases the risk. In the presence of an inverted U-shaped relationship, this approach may miss an existing true association. On the other hand, epidemiological studies among general populations can discriminate much more finely among exposure levels and therefore identify gradients of risks according to POP levels.

In fact, the Air Force Health Study examining only comparison veterans with only background exposures found a clearer dose-response relationship between dioxin and T2D than did the original study, which compared veterans exposed to Agent Orange with those unexposed to it. Also, no association with T2D was seen among workers with high occupational exposures to TCDD or PCBs (26–28, 143, 144). All these earlier findings on high exposure populations are consistent with our hypothesis on the inverted U-shaped association between POPs and T2D.

A molecular epidemiological finding within the Air Force Health Study also supported the existence of an inverted U-shaped association, specifically between the GLUT4:NFkB ratio, which was selected as a biomarker for possible diabetogenic action of TCDD, and serum dioxin levels (145). In this study, inverse relationships were observed only among the comparison group without exposure to Agent Orange, particularly in those with genetic (family history of diabetes) and physiological (obesity) risk factors. Also, when both comparison and exposed veterans were examined, the shape of the dose-response curve between serum dioxin and GLUT4:NFkB ratio was consistent with an inverted U-shaped association, a result the authors called "somewhat surprising" (145).

The most recent cross-sectional studies of OC pesticides or PCBs with T2D in the general population showed positive associations, yet no such relationship was seen in an Inuit population highly exposed to POPs (exposures that are mostly due to a high intake of contaminated marine mammals), although this population has experienced a rapid increase in T2D prevalence over the last 30 years (36). In this study, the average body burden of POPs such as PCBs and chlordanes was about 10–12 times higher than in the current US general population, whereas DDE concentrations were twice as high (37). Therefore, it is plausible that the Inuit population does not include a true unexposed reference group (similar to population C in

Figure 4); if almost all persons had high levels of POPs and the risk gradient were flat at higher exposure levels, it would be difficult to observe any positive association at the individual level, although the prevalence of T2D would be increased at the population level.

3. Inconsistent epidemiological findings on fish consumption

The inconsistency of the epidemiological evidence on effects of fish consumption in relation to T2D also illustrates several of the substantive and methodological issues that have been raised in this field of study. Some studies have reported beneficial effects of fish consumption on the risk of T2D (146–148), whereas other studies have reported that it increases such risk (149, 150). Interestingly, studies from Asian countries demonstrated beneficial effects, whereas those from North America or Europe showed detrimental effects on T2D (146). A recent review article on omega-3 fatty acid from seafood sources and T2D reported no harm or benefit on the risk of T2D, but omega-3 fatty acids from plant sources were possibly associated with a modestly lower risk (146, 151).

Fish, in particular oily species with omega-3 fatty acids, are a main dietary source of POPs in the general population (152). When two opposing forces, beneficial nutrients and harmful contaminants, simultaneously exist in the same food, inconsistent human data on the consumption of such food can be expected (153). In addition, if harmful effects of POPs on T2D truly occur at low doses, but beneficial effects of omega-3 fatty acids show linear dose-response relations, we can expect a nonlinear, or even nonmonotonic, dose-response relationship between fish consumption and T2D.

This hypothesis may explain different patterns of associations between studies from North America/Europe and Asia. Compared to persons living in North America or Europe, persons living in Asian countries tend to consume more fish. If the harmful effects due to POPs start to appear at low fish consumption and there is no further clear increase of risk with increasing doses of POPs, the harmful effects of low fish consumption may be difficult to observe among populations with high fish consumption like Asian people. In contrast, the possible beneficial effects due to omega-3 fatty acid could more prominently appear among a population with high fish consumption.

The widespread POP contamination of all animal fat, not just fish, should be considered when interpreting epidemiological findings concerning human consumption of fatty animal food. Moving forward, it will also be important to parse how much the animal fat itself, vs the POPs contained in this fat, contributes to chronic disease.

B. Issue 2: mixtures

A couple of recent animal studies have suggested that the low-dose POP mixture to which humans are currently exposed may be a more relevant research focus than studies examining single or even several specific POPs (52, 54). However, similar to traditional toxicological studies, most epidemiological studies were performed focusing on specific POPs, with interpretation of findings from the viewpoint of those POPs that emerge as statistically significant. However, one specific POP that is associated in a given study may partly or largely reflect the influence of other POPs rather than the role of that POP itself due to high correlations among serum concentrations of various POPs. In this sense, a recent meta-analysis on POPs and T2D, which focused on individual POPs, may be misleading (49).

Mixture issues become more complicated when combined with an inverted U-shaped association due to the common contamination of the reference group. Even Figure 4 presents an unrealistically simplified situation, using the example of just one chemical. In actuality, humans experience lifetime background exposure to several hundred POPs with various distributions. Given correlations among POPs and a multiplicity of POPs in background exposures, subjects who have low concentrations of a specific POP are likely to have higher concentrations of other POPs (13, 154). If these ranges of other POPs carry a high risk of T2D, the risk of T2D in the reference group for the specific POP would become high due to the contamination with other POPs. Consequently, relative risk for higher dose groups would be underestimated.

Unfortunately, an ideal reference group without any exposure to POPs does not exist in current human populations. Therefore, the isolation of a reference group that is as close as possible to having no exposure to POPs is critical. Summary POP measures using information on multiple POPs can be used to make a reference group that at least approximates such a true reference group that has low levels of as broad a set of POPs as possible.

In current human studies, there are several methods to form summary POP measures. In the field of toxicology, it has long been known that the AhR plays a major role in the onset of toxic effects of many POPs; this is the basis for the TEF concept that uses the relative potencies of individual congeners. TEFs multiplied by their concentrations are summed over all congeners in a mixture to achieve a sum-toxic potency, the toxic equivalent (TEQ) (31). Therefore, a TEF-based summary measure for POPs has been commonly used in many studies (31). Other summary measures have been formed according to underlying biological principles, such as PCB groupings by enzyme induction potential of cytochrome P450 subfamilies or

estrogenic/neurotoxic, antiestrogenic, etc (155, 156). However, this kind of *functional* approach only makes sense when the association between POPs and T2D is mediated by the corresponding biological mechanism. Also, strong positive correlations among individual POPs can lead to positive correlations among different summary POP measures, leading to a similar interpretive problem as for individual POPs.

Given that we do not know the exact biological mechanisms between POPs and T2D, we have proposed two data-driven approaches for forming summary measures based on either absolute concentrations or individual POP rank. Absolute concentration-based summary measures have intuitive appeal, but there are large absolute concentration differences among POPs. Simple summation of these would be mainly influenced by the concentrations of a couple of POPs with the highest concentrations. For example, a concentration-based summary measure would be very similar to *p,p′*-DDE alone because this POP has concentrations that are several times higher than levels of other POPs. Alternatives exist to decrease the influence of specific POPs with high concentrations. One is to combine logarithms of absolute concentrations. Another is to combine standardized deviates (SD), in effect assuming that a common scale for POPs is the population SD of each. Scaling to the SD on the logarithmic scale is yet another option. Finally, rank-based summary measures lead to a common scale for all POPs, ignoring all aspects of absolute concentrations except their ordering. Rank-based and standardized deviate-based scalings generally lead to similar inferences about POPs and T2D.

To fulfill the purpose of isolating a reference group that is as close as possible to a true unexposed reference group, summary measures based on individual POP rank appear to perform well. At the very least, this procedure assures that reference subjects have relatively lower values of the multiple POPs in the summary measure. Even in this approach, there should be a further effort to isolate the best reference group, for example, by using small groups such as sextiles, rather than larger groups such as quartiles, as we presented in Figure 3.

C. Issue 3: how can we deal with lipid profiles?

In human studies on POPs, how lipid profiles are handled is an important methodological issue. Lipid-standardized concentrations (eg, the concentrations of serum POPs divided by total serum lipid content) have generally been reported in studies because POPs are predominantly carried in the lipid component of the blood and because they have been regarded as a measure that better reflects POP body burden than wet-weight concentrations (157). However, experimental studies have reported that low-dose POP mixtures significantly affected the expression of critical genes involved in lipid homeostasis (52) and ectopic fat accumulation in muscle and liver (52, 54). Epidemiological studies have also reported that exposures to POPs can disturb lipid metabolism, leading to dyslipidemia (79). Because dyslipidemia is also closely involved in the pathogenesis of T2D (158), in this situation, lipid concentrations are an intermediate factor within the causal chain linking POPs and T2D.

The problem of lipid standardization of lipophilic chemicals was considered in one simulation study (159), and wet-weight concentrations adjusting for triglycerides and total cholesterol as covariates in models were recommended as a less statistically biased approach than lipid-standardized concentrations. In fact, there is substantial variation in how serum lipid levels have been dealt with in epidemiological studies, as presented in Tables 3 and 4. Among the six prospective studies examining relationships between POPs and T2D we discussed above, three studies did not consider serum lipid levels in their analyses (42, 46, 47), one study used lipid-standardized concentrations (49), and two studies used wet concentrations adjusting for serum lipid levels (44, 45). However, any statistical adjustment for lipid levels would underestimate true associations between POPs and T2D if lipid levels are in the causal pathway between POPs and T2D. At the same time, failure to consider lipid levels in analyses would overestimate true associations. Therefore, we suspect that true risk estimates are intermediate between risk estimates based on wet concentrations and those adjusting for lipid profiles. Future epidemiological studies should primarily use wet concentrations of POPs in their analyses and present both results based on models with and without adjustment for lipid profiles.

VI. Possible Mechanisms

A. Traditional endocrine disrupting-related mechanisms

A central hypothesis and line of thinking to explain the findings in humans about POPs and T2D—which may be considered intuitively contradictory from a toxicological perspective because they disobey the expectation of a linear dose-response model—is that a low but persistent exposure might be more harmful than high-dose acute exposures if POPs are involved in the pathogenesis of T2D as EDCs (38). Knowledge is now sufficient to suggest that EDCs can have biological effects at low doses that are not predicted by their effects at higher doses, because these chemicals follow the same biological "rules" as natural hormones, which also often display nonmonotonic responses (160). It should be noted that EDCs target many

endpoints, and thus the assumption that high doses are inherently "safe" is not true; although high doses may not be associated with a particular disease (ie, T2D), they do induce other forms of toxicity (161).

In biological systems, linear effects of hormones typically exist only up to a dose that occupies about 10% of receptors; at higher doses, occupancy rate does not linearly increase as the dose of the hormone increases (162). Furthermore, natural hormones display linear biological responses at much lower doses than those that produce linear responses in receptor occupancy. Thus, in the low-dose range, small increases in the concentration of hormones have large effects on the number of bound receptors, which also produces large biological effects; in contrast, in the high-dose range, the same increase in hormone concentration has small effects on the number of bound receptors, and further has very little effect on biological endpoints (160). Under high-dose exposure to hormones, there can be down-regulation of receptors as the dose further increases (163) as well as receptor desensitization (164–166). Thus, chemicals with endocrine-disrupting properties can produce nonmonotonic dose-response curves for certain biological endpoints.

Although POPs are well-known to be EDCs, it remains largely unknown what specific kinds of endocrine-disrupting properties of POPs may be involved in the pathogenesis of T2D. As a typical example of chemical mixtures, they have variable molecular and cellular targets and thus they cannot be considered to have a single mode of action. For example, DDT is known to have estrogen agonist activity (167), but its metabolite DDE has antiandrogenic properties (168). PCB products include mixtures of congeners with estrogenic and antiestrogenic effects (169, 170), and some PCBs alter thyroid hormone signaling (171). There are interactions between the AhR and estrogen receptor signaling pathways (172), suggesting that dioxins could have indirect effects on some estrogen-mediated endpoints as well.

A variety of hormones including estrogens, androgen, thyroid hormone, and glucocorticoids are involved in the homeostasis of glucose and lipid metabolism (173). Because humans are simultaneously exposed to various chemicals that have the capacity to function as antagonists or agonists to all these hormones (174), it is difficult to speculate about what kind of synergistic, additive, or antagonistic actions of EDC mixtures might occur. Importantly, biological effects of one EDC can differ widely depending on the presence of another EDC. For example, certain biological effects of tributyltin disappeared with a concurrent exposure to the DDT metabolite, DDE (175, 176). Other studies reveal that uterotrophic responses to relatively strong estrogens can be inhibited if weaker estrogens are coadministered, whereas other mixtures demonstrate intermediate uterotrophic responses to the effects of the individual components (177–179). The fact that hormone-related effects of EDCs are likely dependent on the endogenous hormonal milieu makes the issue even more complicated (180).

For many years, EDCs were commonly defined as chemicals that act as agonists or antagonists of nuclear receptors. However, this viewpoint is not sufficiently comprehensive; it is now accepted that EDCs can act via nonnuclear steroid membrane receptors as well as nonsteroid receptors (181). In addition, chemicals that can control the metabolism of endogenous hormones, including their breakdown, can also induce hormonal imbalances (182). Thus, any chemicals that are metabolized through the same metabolic pathways as endogenous hormones can act as EDCs, although these chemicals may not be direct agonists or antagonists of any receptor.

As a whole, experimental studies focusing on one EDC have demonstrated possible diabetogenic effects through traditional endocrine disruption-related mechanisms (183–186). However, the validity of extrapolating experimental findings in laboratory animals to humans is still largely unknown; although evolutionary theory predicts that chemicals will likely produce similar effects in various mammalian species, experimental studies involve carefully controlled exposures, typically to single compounds, whereas humans are exposed to a plethora of diverse mixtures with widely different endocrine-disrupting properties. There is also the possibility that the effects of POPs on T2D are not due to their endocrine-disrupting properties. A recent experimental study on POPs and insulin resistance suggested that xenosensor nuclear receptor-mediated mechanisms may be involved, not traditional hormonal receptor-mediated mechanisms (52); this is closely related to the second mechanism we discuss below.

B. Mitochondrial dysfunction-related mechanisms

Mitochondrial dysfunction has recently emerged as having a potentially pathogenic role in developing T2D (187, 188). Impaired mitochondrial oxidative activity may lead to ectopic fat accumulation in various organs including skeletal muscle, liver, and pancreas that can mediate insulin resistance and secretary dysfunction in pancreas β-cells (187, 188). At present, experimental studies have mainly focused on which molecular pathways explain the relationship between mitochondrial function and T2D; in contrast, few studies have examined the factors that can contribute to the development of mitochondrial dysfunction. Mutations in mitochondrial DNA, mutations in nuclear genes that code for a mitochondrial component, and aging are the most widely studied possi-

ble causes of mitochondrial dysfunction (189, 190). The traditional T2D risk factors (excess fat intake and/or physical inactivity) have also been reported to cause mitochondrial dysfunction (191, 192).

There is substantial evidence that a variety of environmental chemicals can damage mitochondria (193, 293). Many early toxicological studies demonstrated that DDT, DDT metabolites, PCBs, and TCDD all induced mitochondrial toxicity (194–196). One well-known and relevant example is the development of insulin-dependent diabetes after human intoxication with the rodenticide Vacor [3-(4-nitrophenyl)-1-(pyridin-3-ylmethyl)urea] which selectively destroys the insulin-producing β-cells in the pancreas (197). Vacor inhibits NADH:ubiquinone reductase activity of mitochondrial complex 1 in the pancreatic β-cells (198). It is therefore plausible that POPs could induce insulin resistance and T2D through mitochondrial toxicity. However, the doses of POPs in these early experimental studies were closer to the range of toxicity (194–196); thus, their findings might not be relevant to current POP exposure levels in humans. In addition, the inverted U-shaped association between POPs and T2D cannot be explained by this mechanism because there were clear monotonic dose-response relationships in the range of toxicity (194–196).

Therefore, a critical question is whether the current background levels of POPs can affect mitochondria. The recent animal study with subchronic exposure to a low-dose POP mixture similar to the background concentrations observed in many current human populations induced mitochondrial dysfunction (52). A comparison of gene expression profiles in the liver of rats fed the high-fat diet contaminated with POPs vs the high-fat diet without POPs demonstrated a significant reduction in the expression of several genes related to mitochondrial function such as PGC1α, citrate synthase, medium-chain acyl coenzyme A dehydrogenase, and succinate dehydrogenase. All of these findings suggest that chronic exposure to low-dose POP mixtures can gradually induce the impairment of mitochondrial function, finally leading to development of insulin resistance and T2D.

As we discussed in *Section IV.C*, chronic low-grade inflammation in adipose tissue is considered a key mechanism in the development of metabolic disorders like insulin resistance and T2D (199). In fact, mitochondrial dysfunction plays a fundamental role in chronic low-grade inflammation (200). In addition, recent studies have reported a diversity of adipose tissue macrophages depending on obesity status. Adipose tissue macrophages from obese animals with high-fat diets have a classically activated inflammatory phenotype, whereas adipose macrophages from healthy lean mice have alternatively activated macrophages that can protect adipocytes from inflammation (201). Mitochondrial dysfunction can inhibit the function of alternatively activated macrophages through the inhibition of IL-4 (202, 203). Therefore, if POPs can induce mitochondrial dysfunction, even without obesity, POP-induced phenotypic switch in adipose tissue macrophage polarization may be also possible, activating classic inflammatory responses.

The next critical question is how the inverted U-shaped association is possible if the mechanism linking POPs to T2D is mitochondrial dysfunction. Could the mitochondrial dysfunction caused by low-dose POPs be reversed by a somewhat increased dose of POPs? There is experimental evidence suggesting that, with increasing doses of chemicals, cells can increase their production of cytoprotective and restorative proteins including growth factors, phase II and antioxidant enzymes, and protein chaperones through the activation of enzymes such as kinases and deacetylases and transcription factors such as Nrf-2 and NF-κB (204). In particular, it is possible that an increasing dose of chemicals can improve mitochondrial function (205, 206). Furthermore, this mechanism can contribute to the protection against pancreatic β-cell death (207).

In one animal study, glutathione (GSH) content in various organs was measured in mice after treatment across a broad range of TCDD doses (0.15–150 ng/kg/d) (208). Increased GSH synthesis is one marker of cytoprotective and restorative responses (209, 210). Compared to control mice, very low-dose subchronic exposure to TCDD (0.15 ng/kg/d for 13 wk), which was estimated to be similar to current human background exposure, led to GSH depletion. However, increased doses of TCDD increased GSH levels. On the other hand, acute exposure did not show GSH depletion at low doses, but GSH levels increased with higher doses of TCDD. This finding suggests that only a chronic low-dose exposure to TCDD can lead to GSH depletion, but it can be reversed with increasing doses of TCDD. How then can intracellular GSH content be linked to mitochondrial dysfunction? Because mitochondria lack enzymes to synthesize GSH de novo, mitochondrial GSH originates from cytosolic GSH (211). Therefore, intracellular GSH depletion directly affects mitochondrial GSH content. Mitochondrial GSH is the main line of defense in the maintenance of the appropriate mitochondrial redox environment to avoid or repair oxidative modifications (212).

In the experimental study on TCDD (208), the authors did not further investigate the reason for GSH depletion with the very low-dose chronic exposure to TCDD. However, the depletion of GSH may not be specific to this POP. Chronic exposure to many chemicals can lead to intracellular GSH depletion because GSH is consumed through

phase II conjugation of chemicals during the process of metabolism (213). In fact, the link between low-dose environmental POPs and T2D in the general population was first hypothesized from epidemiological findings based on serum γ-glutamyltransferase, which has been deemed a biomarker of cumulative exposure to various environmental pollutants that are conjugated by GSH and the status of chronic intracellular GSH depletion (213, 294).

Taken together, experimental studies suggest that chronic exposure to low-dose POP mixtures, similar to current human exposures, may favor the development of mitochondrial dysfunction through GSH depletion and, finally, insulin resistance and T2D. However, these effects might not obey linear dose-responses, perhaps because the activation of cytoprotective and restorative responses including the increase of GSH synthesis can reverse such adverse effects. As discussed in the context of endocrine-disrupting properties, although the increased dose of POPs may improve mitochondrial function, these high doses should not be considered "safe" or beneficial because of the likelihood of other harmful effects on other aspects of human physiology.

Another important point here is that increasing the POP concentration is not the only way to improve mitochondrial function. Mitochondria can be activated with well-accepted health promotion behaviors like exercise, consumption of phytochemicals, or calorie restriction (204, 214). Interestingly, all of these factors are traditionally known to be beneficial to prevent and/or control T2D (215–217). A recent in vitro and in vivo experimental study reported the protective effects of resveratrol, a plant polyphenol, against PCB-mediated impairment of glucose homeostasis in adipocytes through enhanced Nrf2 signaling (218), the same pathway in which certain levels of chemicals can improve mitochondrial function, as we discussed above (204).

VII. Future Research Issues

We have summarized the main issues that should be included in future research programs in Table 6. Details are explained below.

A. Human studies

Although current human evidence linking POPs to T2D is substantial, more prospective studies are needed. Until now, most prospective studies were not specifically designed to test the hypothesis that POPs increase the risk of T2D. Because some studies used existing information on POPs that was collected for other reasons, a broad range of POPs was not considered. The common failure to measure the multiple POPs may lead to a serious underestimation of relative risks; this occurs despite the positive correlations among serum concentrations of some POPs, for reasons explained in *Section V.B*. Furthermore, POPs are likely to have additive and perhaps multiplicative interactions with other types of diabetogenic environmental pollutants. It is impressive that so little of this has been formally tested in humans and animals.

Table 6. Suggestions for Main Items to Be Included in Research Agendas

Human studies
More well-designed prospective studies on POPs and T2D
Focusing on the general population with low-dose exposure
Measurement of a broad range of POPs
Large sample size
Serial measurement of POPs, adiposity, and biomarkers
Disentangle the interrelations between obesity and POPs on T2D
Role of POPs on gut microbiota
Extended follow-up from early life (even in utero) exposure to adult exposure
Effects of gene-POP interactions on the risk of T2D
Known genetic factors of T2D
Xenobiotic-metabolizing genes
Comprehensive reevaluation of diet considering both nutrients and POPs
Role of POPs in the development of complications among patients with T2D
POPs and T1D
Develop methods to decrease body burden of POPs
Experimental studies
Use real-world scenarios in terms of dose, mixtures, duration of POPs
Consider using POP mixtures extracted from human adipose tissue
Continuous lifetime exposure starting from in utero exposure
Possible biological mechanisms underlying the inverted U-shaped associations
Effect of POP mixtures on pancreatic β-cells
Evaluation of mitochondrial dysfunction coupled with activation of cytoprotective and restorative responses
Evaluation of traditional endocrine-disrupting properties and related mechanisms
POPs and T1D

Future prospective studies should consider several methodological and scientific issues. First of all, studies should be performed in the general population with low concentrations of POPs because populations living in highly contaminated areas are not likely to have a valid reference group with close to null POP exposures. Second, a large sample size is recommended to ensure that the study includes a substantial number of subjects with very low levels of POPs who can act as an appropriate reference group. Third, although it is often assumed that one-time measurement of POPs appropriately reflects long-term exposure to POPs, serial measurements of POPs are recommended because serum concentrations of POPs are directly affected by weight changes, which are becoming more common in modern societies. Fourth, the interaction between POPs and obesity requires further investigation. Because there can be both pharmacodynamic and biolog-

ical interactions between POPs and obesity, serial measurements of adiposity and clinically relevant endocrine biomarkers are also necessary to disentangle the complicated interrelationships between obesity and POPs. Related to this issue, future studies should assess the importance of POP total body burden. Such burden is essentially determined by POP exposure and body fat mass; hence, it may help explain the interactions between POPs and obesity that have been observed in epidemiological studies (37, 40, 41). Finally, the possible effects of POPs on gut microbiota and on inflammatory disorders ought to be incorporated as well in prospective studies.

It is also important to acknowledge what the available human studies indicate about critical periods of exposure to POPs. As shown in *Section II*, current human evidence suggests that chronic exposure to POP mixtures during adulthood may be sufficient to induce T2D. Although the individuals assessed in adulthood likely had early-life exposures to POPs, animal studies also support that early-life exposure to POPs might not be a necessary condition for T2D development (52, 54).

However, the hypothesis on the developmental origins of health and disease remains relevant (219), and research integrating POPs into that hypothesis would be scientifically important. Epidemiological studies starting from in utero exposure (or even prenatally in the subject's parents), continuing to early fetal, childhood, adolescence, and adult periods would be helpful to determine how important early-life exposure to POPs is to the development of metabolic dysfunction and how changes in exposure patterns during the lifetime affect metabolic function.

Although genome-wide association studies have identified a number of loci associated with T2D (220), the role of genetic factors in the relationships between POPs and T2D has not been investigated yet. Gene-environment interactions between known T2D genes and POPs on the development of T2D are plausible. In addition, genetic polymorphisms in xenobiotic-metabolizing enzymes need to be evaluated because they have influence on clearance and internal dose of POPs (221). Several small-scale studies have reported that a polymorphism of GSH S-transferase, one of the phase II xenobiotic-metabolizing enzymes, is associated with the risk of T2D (222–224). Therefore, the interaction between GSH S-transferase variants and POPs on the risk of T2D is another plausible hypothesis.

Contamination of foods from POPs also requires further study. A healthy diet plays a very important role in the prevention of the development of T2D and is also critical in the management of T2D. At present, dietary issues that have been considered include excess calorie intake, glycemic index, saturated fat intake, and others (225). Because POP-contaminated food is the main source of external exposure to POPs in the general population, studies focusing only on nutritional values of food deal with just one aspect of diet. It remains unknown to what extent animal food consumption might be partly detrimental due to the POPs these items contain. A more comprehensive approach considering both nutrients and pollutants like POPs is necessary to validly evaluate the effects of diet on T2D.

It is also necessary to evaluate the influence of POPs in the development of complications among patients with T2D. Hyperglycemia itself not only defines T2D but also is a cause of long-term diabetic complications (226). In one cross-sectional study, serum concentrations of POPs were associated with poorer glycemic control and the risk of peripheral neuropathy among patients with T2D (227). Also, epidemiological studies have reported that serum concentrations of POPs are associated with self-reported cardiovascular diseases and predicted the future risk of stroke in the general population (228, 229). Because all these diseases are common long-term complications of T2D, it is highly plausible that POPs affect the development of various such complications.

Another largely unexplored area is the possible association between POPs and type 1 diabetes (T1D) (230), an autoimmune disease destroying the pancreatic β-cells (231). Although some cross-sectional studies have suggested a possible positive association between POPs and T1D (232, 233), a prospective study from Sweden reported a decreased risk of T1D among children with high in utero exposure to POPs compared to those with low-dose exposures (234). If the link between chemicals and autoimmunity can also be explained by the endocrine-disrupting properties of these chemicals (235), low doses could be more harmful than high doses, producing an inverted U-shaped association. Because the Swedish study used serum collected in the 1970s, the distribution of POPs would be in the higher dose range of the inverted U-shaped association, as in population D in Figure 4. Therefore, future studies on this topic should also be performed among populations with low-dose exposure.

Finally, research and pilot projects are needed to identify and evaluate policies and interventions to combat the adverse effects of POPs. First of all, there are ways to decrease human exposures to POPs; whereas plans to implement the Stockholm Convention of POPs have been developed in some countries, others are not fulfilling their obligations as signatories of the Convention. Studies on the levels of POPs in the global environment show that emission sources of POPs have shifted from industrialized countries of the Northern Hemisphere to less developed countries in tropical and subtropical regions (236). These

patterns may be due to late-implemented bans, the illegal use of restricted POPs, or the use of POPs in the control of malaria (237). In addition, many developing countries have large open dumping sites of municipal wastes with inappropriate control, which are a new source of POPs (238). Therefore, much more energetic public and private policies to combat the use and/or emission of POPs are needed.

However, in the past six decades, POPs have widely contaminated animal and human food webs across the planet. Under this situation, a plant-based diet is one option to prevent further exposure to POPs at the individual level because POP contamination is much lower in these diets compared to animal-based diets (239). There may also be ways to increase POP excretion from the body. Although POPs are excreted through feces, a substantial amount of POPs excreted through bile is reabsorbed through enterohepatic recirculation (184). Experimental animal studies suggest that dietary fiber may be efficient to absorb POPs in the gut and increase their excretion via feces (240, 241). Therefore, a plant-based diet with high dietary fiber may be helpful to decrease half-lives of POPs, hence decreasing body burden. These methods must be tested in well-designed large randomized clinical trials; if they were proven to be effective to prevent and/or manage T2D, they would hence provide further evidence on causal relations between POPs and T2D. It is interesting to note that a vegan diet was more effective than a conventional diet in the treatment of T2D, although this randomized, controlled clinical trial was performed without any consideration on POPs (242).

Importantly, under the assumption of an inverted U-shaped association, researchers should consider the possibility that some efforts to decrease POP body burden might lead to lower but more harmful concentrations for specific endpoints of concern. In this sense, the evaluation of benefits of decreasing body burden of POPs can be better tested in patients with T2D or prediabetic stages, focusing on improvement of glycemic control, because such patients can be regarded as already being in the range of harmful doses.

B. Experimental studies

Because most chlorinated POPs were banned several decades ago and evidence for a strong association between low-dose POP mixtures and T2D first emerged from human studies, laboratory research about chlorinated POPs does not seem to be as active as research on other environmental chemicals. Since human studies require large investments and long time commitments, more in vivo and in vitro experimental studies are needed. In particular, experimental studies with POP exposures that mimic real-world scenarios in terms of dose, mixtures, and duration are necessary to understand epidemiological findings observed in humans. The ultimate metabolic dysfunction phenotype (such as T2D) due to mixtures may differ considerably from studies of single chemicals in isolation. As a first step, researchers can evaluate whether similar or different biological effects are observed for specific POPs and how divergent the results are depending on the coexistence of other POPs with variable doses. If there are substantial differences in biological effects, laboratory researchers could consider using POP mixtures that are directly extracted from human adipose tissue in their experiments. Possible aging effects on the relations of POPs with the risk of T2D also require further experimental studies.

It is difficult to perform experimental studies of POP mixtures to explore underlying molecular mechanisms of the inverted U-shaped associations or the mixture effects that are observed in human studies. Therefore, experimental studies focusing on individual POPs over a broad range of doses and on mixtures of several POPs have clear merits. So far, many experimental studies on individual POPs have focused on POPs with dioxin activity, but more research on POPs without dioxin activity will also be helpful for understanding human findings on POPs.

In addition, in terms of exposure duration, animal studies only focusing on early-life exposures may not be relevant to humans because humans are continuously exposed to POPs before conception though death. It would be interesting to evaluate whether biological results of prenatal exposure to POPs without exposure after birth are different from those of prenatal exposure to POPs with continuous exposure after birth.

Additional studies are needed to examine whether chronic exposures to low-dose POPs affect pancreatic β-cells. When the pathogenesis of T2D is classified into two stages, insulin resistance and insulin secretory defects, the latter part is an important triggering factor for the progression of prediabetic states to full-blown T2D (243). A recent review article proposes possible mechanisms linking EDCs, including POPs, to the dysfunction of pancreatic β-cells (244); however, the exposure doses used in that study may not be relevant to current human exposure levels. More human relevant situation-based experimental studies are still needed.

VIII. Conclusion

The continuing worldwide increase in the occurrence of T2D is a great social, medical, and economic burden. Al-

though obesity is the most well-known risk factor for T2D, a growing body of evidence links T2D to background exposure to environmental chemicals, in particular chlorinated POPs. As typical chemicals contaminating adipose tissues as well as all lipid compartments in biological systems, the available epidemiological and experimental evidence largely shows that background contamination from POP mixtures including OC pesticides and PCBs is strongly associated with the development of T2D. Inconsistencies concerning findings for specific individual POPs may arise due to different patterns of POP mixtures between and within populations despite high correlations among serum concentrations of many individual POPs. Differences in the shape of the dose-response curves among human studies may reflect an inverted U-shaped association secondary to mitochondrial dysfunction or their endocrine-disrupting properties. The bottom line is that low-dose effects of POPs appear to be quite real in humans. However, at present human evidence on POPs and obesity remains insufficient. Besides promoting T2D,

Figure 5.

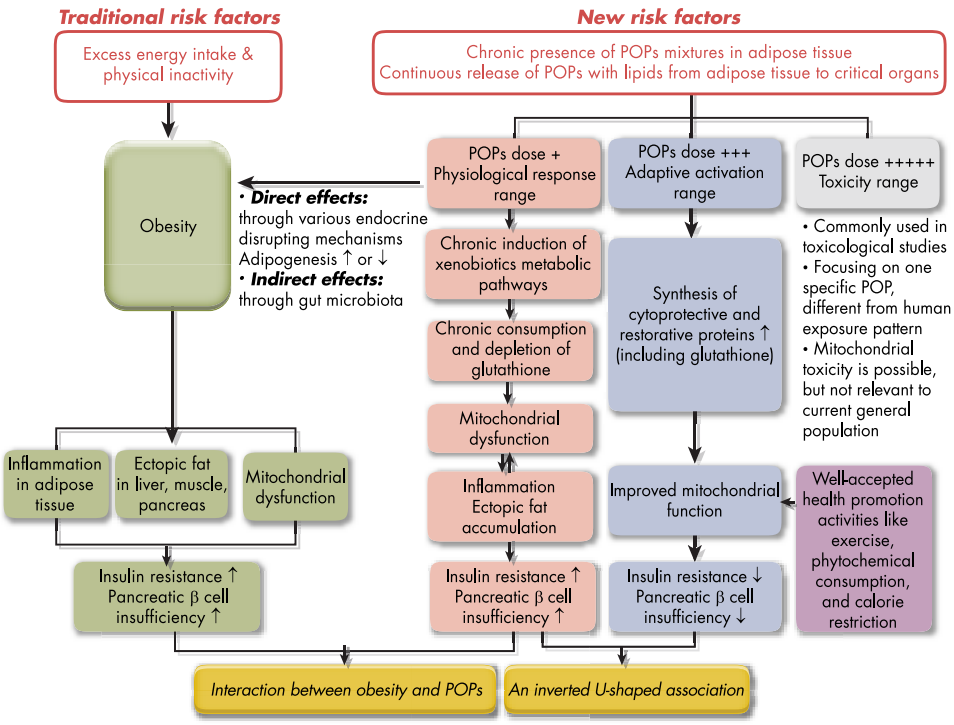


Figure 5. Summary of postulated POPs and T2D relationship with possible mechanisms. Under the current paradigm (labeled "Traditional risk factors"), lifestyle changes characterized by excess energy intake and a lack of physical activity have led to the obesity and T2D epidemic. Inflammation in adipose tissue, lipotoxicity in liver, muscle, and pancreas, and mitochondrial dysfunction are considered to be primary mechanisms. However, adipose tissue also contains POPs because of the contaminated environment and food web. As depicted under an expanded paradigm (labeled "New risk factors"), POP mixtures consisting of several hundred compounds are stored in adipose tissue, are continuously released to circulation, and reach critical organs along with serum lipids. Human responses to POP mixtures may differ depending on levels of POPs. There can be low-dose POP mixtures that are not high enough to induce any chemical-specific responses. However, even at low doses POPs at least induce physiological responses like phase I, phase II, and phase III xenobiotic metabolism pathways aimed to increase the excretion of POPs. In particular, phase II glutathione conjugation can lead to chronic consumption and depletion of intracellular glutathione. Intracellular glutathione depletion can cause mitochondrial dysfunction that is closely related to inflammation and ectopic fat accumulation; all of these mechanisms are also known to play important roles in the pathogenesis of traditional obesity-related T2D. However, a somewhat increased dose of POP mixtures can activate increased synthesis of cytoprotective and restorative proteins, including glutathione synthesis. This activation may improve mitochondrial function, which in theory might decrease the risk of T2D. Therefore, we can expect the inverted U-shaped associations between POPs and T2D. Importantly, mitochondria function can be improved with other well-accepted health promotion behaviors like exercise, phytochemical consumption, or calorie restriction; they are traditionally known to be beneficial to prevent and/or control T2D. In the range of high-dose POPs, we can expect traditional toxicity responses. Many toxicological studies of POPs deal with this high range of POPs and focus on one specific POP. However, exposure patterns used in experimental settings are very different from human exposure patterns in terms of doses, mixtures, and exposure duration of POPs. Therefore, the relevance of experimental findings to humans is unclear. On the other hand, POPs can increase or decrease adipose hyperplasia and/or hypertrophy depending on dose or kinds of POPs. Various endocrine-disrupting mechanisms may be involved in these relationships. POPs can indirectly induce obesity through the influence on gut microbiota. However, in the risk of T2D, the worst-case scenario could be the combination of antiadipogenic chemicals and excess energy intake. Also, it is important to note that adipose tissue can play dual roles: promoting T2D, and providing a relatively safe place to store POPs.

adipose tissue might play dual roles by providing a relatively safe place to store POPs.

The overview and summary of our hypotheses on the relationships between POPs and T2D, with emphasis on possible mechanisms, are presented in Figure 5. At present, inflammation, ectopic fat accumulation, and mitochondrial dysfunction are considered key mechanisms that link obesity and T2D—without any consideration for POPs (94, 199, 245). However, these mechanisms can also be linked to POP exposure, and there is neither adipose tissue nor lipid uncontaminated with POPs in our world. Therefore, the scientific community should recognize POPs when exploring the pathophysiological roles of obesity in the development of insulin resistance and T2D. However, this hypothesis requires more evidence from experimental studies because it is possible that other mechanisms operate.

The evidence about the potential influence of POPs in the pathogenesis of T2D can no longer be ignored. More prospective studies with serial measurement of a broad range of POPs and adiposity are needed to disentangle the interrelationships between obesity and POPs on the development of T2D. Also, we encourage laboratory researchers to design studies that resemble real-world scenarios as much as possible, in terms of dose, mixtures, and duration of POP exposure. However, experimental studies for the achievement of a better understanding of biological mechanisms behind the inverted U-shaped associations and mixture effects may require traditional approaches focusing on individual or sets of POPs. Experimental studies and studies in humans have long been known to complement each other. Researchers must continue to thoughtfully consider findings from other fields of study when they design research studies and interpret study findings.

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