POPs exposure and CVD prevalence are associated?

Research

Association between Serum Concentrations of Persistent Organic Pollutants and Self-Reported Cardiovascular Disease Prevalence: Results from the National Health and Nutrition Examination Survey, 1999–2002

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Background: There is now increasing evidence that exposure to persistent organic pollutants (POPs) can contribute to the development of inflammatory diseases such as atherosclerosis.

Objective: The objective of this study was to examine associations of serum concentrations of POPs with self-reported history of cardiovascular disease (CVD).

Design: Cross-sectional associations of serum POPs concentrations with the prevalence of self-reported CVD were investigated in 889 adults ≥ 40 years of age in the National Health and Nutrition Examination Survey, 1999–2002. We selected 21 POPs [3 polychlorinated dibenzo-*p*-dioxins (PCDDs), 3 polychlorinated dibenzofurans (PCDFs), 5 dioxin-like polychlorinated biphenyls (PCBs), 6 nondioxin-like PCBs, and 4 organochlorine (OC) pesticides] because they were detectable in ≥ 60% of participants.

Results: Dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides were positively associated with the prevalence of CVD only among females. Compared with those in the lowest quartile of serum concentration, the odds ratios for CVD across increasing quartiles were 0.9, 2.0, and 5.0 for dioxin-like PCBs (p for trend < 0.01), 1.2, 1.2, and 3.8 for nondioxin-like PCBs (p for trend < 0.01), and 1.9, 1.7, and 4.0 for OC pesticides (p for trend = 0.03). PCDDs showed positive trends with the prevalence of CVD in both males and females; adjusted odds ratios were 1.4, 1.7, and 1.9 (p for trend = 0.07, males and females combined).

Conclusions: Our findings need to be carefully interpreted because of the cross-sectional design and use of self-reported CVD. Prospective studies are needed to clarify these associations.

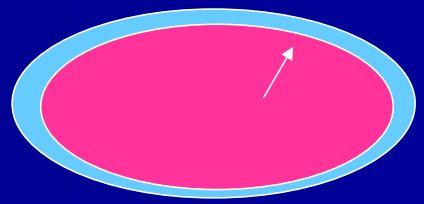
Key words: cardiovascular diseases, dioxin, persistent organic pollutants, pesticides, polychlorinated biphenyls. *Environ Health Perspect* 115:1204–1209 (2007). doi:10.1289/ehp.10184 available via *http://dx.doi.org/* [Online 25 May 2007]

Introduction-1

- POPs is a possible cause of CVD (cardio vascular disease) (Mastin, 2005)

POPs (persistent organic pollutants):
stable, accumulate in adipose tissue, lasting toxic body burden

- POPs → CVD: Biological pathways



1. PCBs or TCDD → atherogenic serum lipid levels ↑ in animals/humans (in guinea pig/rat: Bombick et al. 1984; Lovati et al. 1984; guinea pig: Swift et al.1981)

2. POPs cause direct damage to endothelial cell via oxidative stress (Hennig et al. 2002; Stegeman et al. 1995; Toberek et al. 1995)

Introduction-2

- POPs is a possible cause of CVD (cardio vascular disease) (Mastin, 2005)

Epidemiologic evidences

Occupational or accidental exposures to POPs (brief, high dos)
→ ischemic heat disease ↑
(Seveso chohort: Bertazzi yet al. 1998, 2001; US workers: Calvert et al. 1998; Swedish workers: Gustavsson and Hogstedt, 1997; others)

General population: (A) people in ZIP core areas contaminated with POPs vs (B) those in clean ZIP codes in US
→ Hospital discharge rate with CHD and myocardial infarction
= A > B (Sergeev and Carpenter, 2005: EHP,113: 756)

Introduction-3

- POPs is a possible cause of CVD (cardio vascular disease) (Mastin, 2005)

Evidences in general populations (low level but long term exposure) are needed.

Lee et al. (2006) Diebetes Care, 29: 1638.

Dose-response relation between serum POPs and diabetes prevalence (NHANES, 1999-2002 data)

Adj OR= 14.0, 14.7, 38.3, and 37.7 (P for trend < 0.001)

Serum POPs (0-25th,25-50th,50-75th, 75th-)
Ref=<LOD

Introduction-4

- POPs is a possible cause of CVD (cardio vascular disease) (Mastin, 2005)

NHANES (1999-2000, 2001-2002):
US nationally representative sample

Serum concentration of:

polychlorinated dibenzo-pdioxins (PCDDs)
Polychlorinated dibenzofurans (PCDFs)
PCBs
Hexachlorobenzene (HCB)
Organochlorines (OCs)

Self-reported
CVD prevalence

Methods-1

NHANES: National Health and Nutrition Examination survey, conducted by CDC

A complex, multistage probability sample (probability will be defined according to the population size and research interest) ; targets: 2 months-85 years of age

Home interview
Physical examination
Blood /urine collection

9965 persons in 1999-2000

11039 persons in 2001-2002

Methods-2

NHANES: National Health and Nutrition Examination survey, conducted by CDC

9965 persons in 1999-2000 → PCDDs, PCDFs, PCBs, OC pesticides → Random 1/3 of ≧12 years

11039 persons in 2001-2002 → PCDDs, PCDFs, PCBs, OC pesticides → Random 1/3 of ≧20 years

OC pesticides, PCBs (other than coplanar PCBs) → Random 1/3 of 12-19 years

PCDDs, PCDFs, PCBs, and OC pesticides were all measured as individual chemicals by high-resolution gas chromatography/high-resolution mass spectrometry using isotope dilution for quantification. All of these analytes were measured in approximately 5 mL serum using a modification of the method of Turner et al. (1997).

Methods-3

NHANES: National Health and Nutrition Examination survey, conducted by CDC

49 POPs → 21 POPs for which at least 60% of study subjects had concentrations > LOD:

3 PCDDs, 3 PCDFs, 5 dioxin-like PCBs, 6 nondioxinlike PCBs, and 4 OC pesticides (see Tables 3 and 4).

Subjects: 1,054 study participants ≥ 40 years of age with information on serum concentrations of the 21 selected POPs

– 165 diabetic participants = 889 participants

Methods-4

Cumulative measures POPs:

e.g., PCDDs:
A. 1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin
B. 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin
C. 1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin

<LOD = 0
0-25th = 1
25-50th = 2
50th-75th = 3
75th- = 4

X = A:3 + B:4 + C:2 = 9
Y = A:0 + B:1 + C:1 = 2
→ cumulative measure of PCDDs

CM_PCDDs: Σ rank of 3 PCDDs (0-12)
CM_PCDFs: Σ ranks of 3 PCDFs (0-12)
CM_dioxin-like CBs: Σ ranks of 5 dioxin-like PCBs (0-20)
CM_dioxin-like PCBs: Σ ranks of 6 nondioxinlike PCBs (0-24)
CM_OC pesticides: Σ ranks of 4 OC pesticides (0-16)

Methods-5

Self-reported prevalence of CVD

If they answered “yes” to any of the following questions: CVD = 1

- “Has a doctor or other health professional ever told you that you had CHD?”
- “Has a doctor or other health professional ever told you that you had angina/angina pectoris?”
- “Has a doctor or other health professional ever told you that you had heart attack/myocardial infarction?”
- “Has a doctor or other health professional ever told you that you had a stroke?”

Methods-6

Logistic regression models were used for the calculation of adjusted OR:

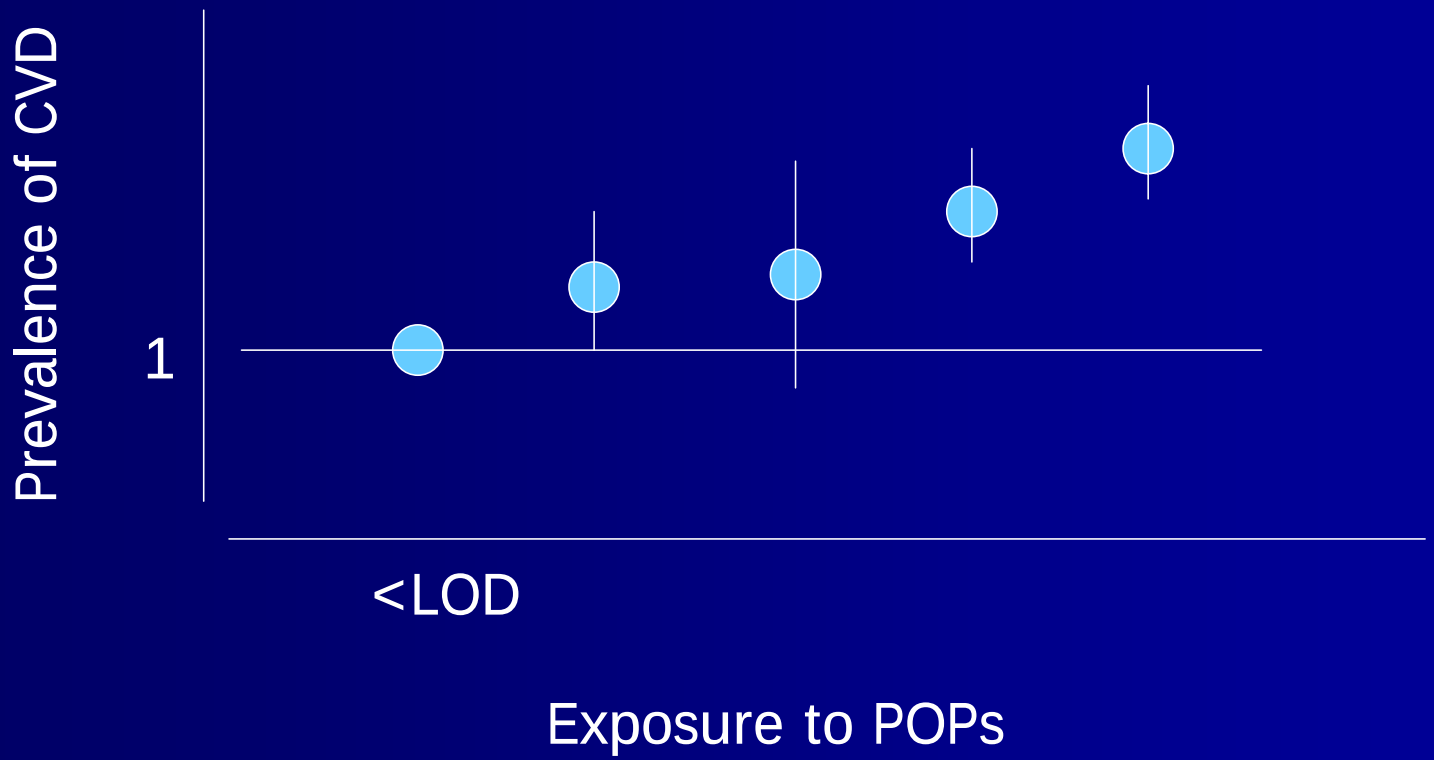
Adjusting CVD risk factors:

age (years), race/ethnicity, poverty income ratio (continuous), body mass index (BMI; continuous), cigarette smoking (never, former, or current), cotinine levels (nanograms per milligram), alcohol consumption (grams per day), leisure time physical activity (vigorous, moderate, or none), status of hypertension (yes/no), total cholesterol (continuous), HDL (high-density lipoprotein)-cholesterol (continuous), triglyceride (continuous), and C-reactive protein (continuous)

SAS 9.1

Results

1. Correlation between POPs and CVD risk factors (Table 1)
2. CVD prevalence by the POPs (cumulative) exposure levels (Table 2)
3. CVD prevalence by individual POPS (Tables 3 & 4)



1. Correlation between POPs and CVD risk factors (Table 1)

Table 1. Age-adjusted Spearman correlation coefficients[a] between five categories of lipid-adjusted POPs with demographic or cardiovascular risk factors by sex.

CVD risk factors	PCDDs	PCDFs	Dioxin-like PCBs	Nondioxin-like PCBs	OC pesticides
Males					
Age	0.39**	0.23**	0.48**	0.44**	0.47**
Race	NS	NS	NS	NS	–0.20**
Poverty income ratio	NS	NS	0.14**	NS	NS
BMI	0.21**	0.10*	0.10*	NS	0.20**
Current smoker	–0.16**	NS	–0.12*	NS	NS
Exercise	NS	NS	NS	NS	–0.11*
Alcohol consumption	NS	NS	0.11*	0.10*	NS
HDL cholesterol	NS	NS	NS	0.14**	NS
Total cholesterol	NS	NS	NS	NS	NS
Triglycerides	NS	NS	NS	NS	0.18**
C-reactive protein	NS	NS	NS	NS	0.11*
Females					

NS, not significant. For race, white = 1 and others = 0. For current smoker, current = 1 and others = 0. For exercise, yes = 1 and no = 0.

[a]Before calculating correlation coefficients, detectable values of each POP were individually ranked, and the rank order of the individual POPs in each subclass were summed to arrive at the subclass value; all nondetectable values were ranked as 0. *$p < 0.05$. **$p < 0.01$.

Lipid adjusted POPs: by total cholesterol and triglycerides

Five sub-classes of POPs were correlated(r=0.32-0.84 m, 0.28-0.86 f)

Table 1. Age-adjusted Spearman correlation coefficients[a] between five categories of lipid-adjusted POPs with demographic or cardiovascular risk factors by sex.

CVD risk factors	PCDDs	PCDFs	Dioxin-like PCBs	Nondioxin-like PCBs	OC pesticides
Females					
Age	0.42**	0.36**	0.62**	0.51**	0.57**
Race	NS	0.10*	0.10*	NS	–0.30**
Poverty income ratio	NS	NS	0.10*	0.10*	–0.18**
BMI	0.10*	NS	NS	–0.14**	0.19**
Current smoker	–0.25**	–0.10*	NS	NS	NS
Exercise	NS	NS	NS	NS	NS
Alcohol consumption	NS	NS	NS	NS	NS
HDL cholesterol	NS	NS	0.10*	0.12**	–0.17**
Total cholesterol	NS	–0.15**	–0.09*	NS	NS
Triglycerides	NS	–0.10*	NS	–0.13**	0.16**
C-reactive protein	NS	NS	NS	–0.10*	0.15**

NS, not significant. For race, white = 1 and others = 0. For current smoker, current = 1 and others = 0. For exercise, yes = 1 and no = 0.

[a]Before calculating correlation coefficients, detectable values of each POP were individually ranked, and the rank order of the individual POPs in each subclass were summed to arrive at the subclass value; all nondetectable values were ranked as 0. *$p < 0.05$. **$p < 0.01$.

2. CVD prevalence by the POPs (cumulative) exposure levels (Table 2)

Table 2. Number of cases/total number and adjusted OR (95% CI) for prevalence of cardiovascular diseases by quartiles of PCDDs, PCDFs, dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides in males and females.

Analyte	< 25th	25th to < 50th	50th to < 75th	≥ 75th	p_{trend}
Males					
PCDDs	7/106	12/107	19/107	23/107	
	Referent	1.7 (0.6–4.7)	2.1 (0.8–5.9)	2.2 (0.8–6.1)	0.14
PCDFs	13/106	12/107	17/107	19/107	
	Referent	0.7 (0.3–1.8)	0.9 (0.4–2.2)	0.7 (0.3–1.7)	0.60
Dioxin-like PCBs	6/106	16/107	17/107	22/107	
	Referent	2.2 (0.8–6.5)	1.8 (0.6–5.3)	1.7 (0.6–5.5)	0.64
Nondioxin-like PCBs	7/106	17/107	14/107	23/107	
	Referent	2.3 (0.8–6.4)	1.3 (0.5–3.9)	1.8 (0.6–5.0)	0.61
OC pesticides	10/106	12/107	18/108	21/106	
	Referent	0.7 (0.2–1.9)	0.9 (0.3–2.4)	0.9 (0.3–2.3)	0.96

ORs were adjusted for age, race, poverty income ratio, BMI, cigarette smoking, serum cotinine, alcohol consumption, exercise, HDL cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein. Detectable values of each POP were individually ranked, and the rank orders of the individual POPs in each subclass were summed to arrive at the subclass value. All not detectable values were ranked as 0. The summary values were categorized by cutoff points of 25th, 50th, and 75th values of the sum of ranks.

No association between POPs exposure and CVD in males

2. CVD prevalence by the POPs (cumulative) exposure levels (Table 2)

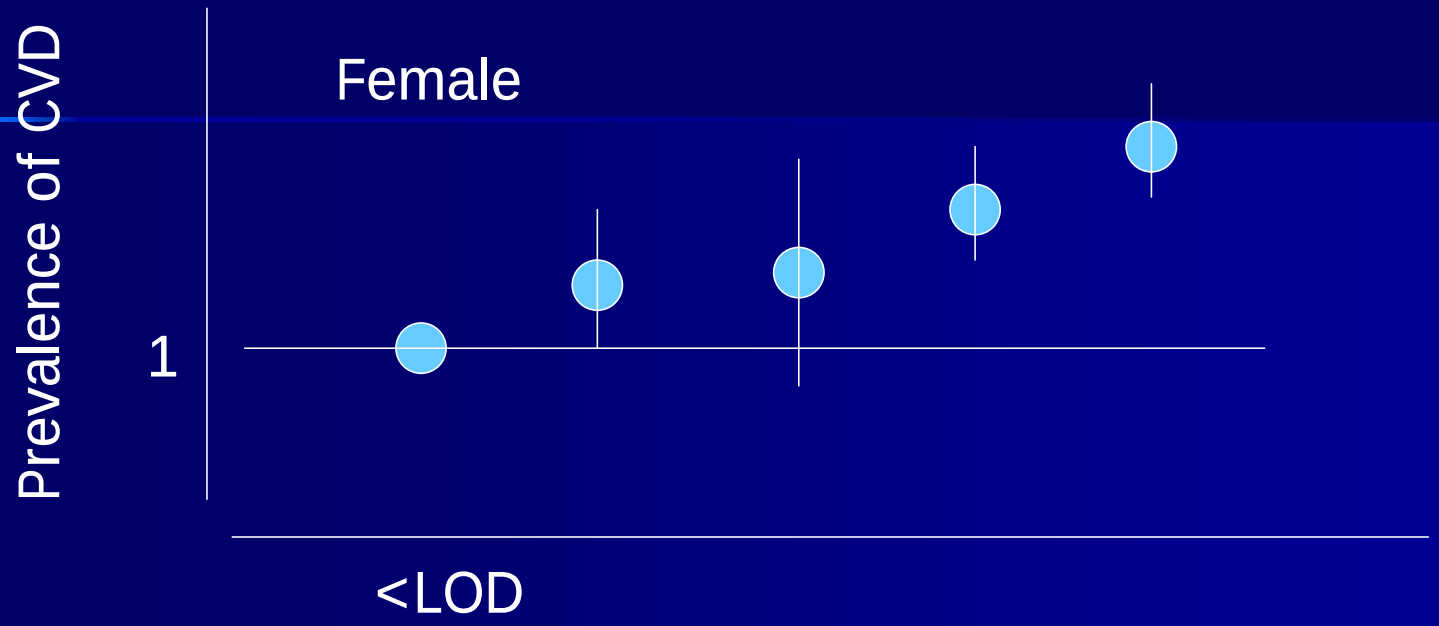
Table 2. Number of cases/total number and adjusted OR (95% CI) for prevalence of cardiovascular diseases by quartiles of PCDDs, PCDFs, dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides in males and females.

Analyte	< 25th	25th to < 50th	50th to < 75th	≥ 75th	p_{trend}
Females					
PCDDs	8/115	9/116	11/116	19/115	
	Referent	1.1 (0.3–3.3)	1.5 (0.5–4.3)	2.0 (0.7–6.4)	0.16
PCDFs	9/115	10/116	13/116	15/115	
	Referent	0.9 (0.3–2.5)	1.1 (0.4–3.0)	1.0 (0.3–2.8)	0.92
Dioxin-like PCBs	4/115	8/116	12/116	23/115	
	Referent	0.9 (0.2–3.5)	2.0 (0.5–7.6)	5.0 (1.2–20.4)	< 0.01
Nondioxin-like PCBs	5/115	9/115	9/117	24/115	
	Referent	1.2 (0.4–4.0)	1.2 (0.4–4.2)	3.8 (1.1–12.8)	0.02
OC pesticides	3/115	9/116	10/116	25/115	
	Referent	1.9 (0.5–7.7)	1.7 (0.4–7.1)	4.0 (1.0–17.1)	0.03

ORs were adjusted for age, race, poverty income ratio, BMI, cigarette smoking, serum cotinine, alcohol consumption, exercise, HDL cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein. Detectable values of each POP were individually ranked, and the rank orders of the individual POPs in each subclass were summed to arrive at the subclass value. All not detectable values were ranked as 0. The summary values were categorized by cutoff points of 25th, 50th, and 75th values of the sum of ranks.

Exposure levels to dioxin-like PCBs, nondioxin-like PCBs and OC pesticides were associated with CVD prevalence in females

Summary of Results in Table 2 (image)



Exposure to dioxin-like PCBs (p<0.01)
Exposure to nondioxin-like PCBs (p<0.02)
Exposure to OC pesticides (p<0.03)

PCDDs showed positive trends with the prevalence of CVD in both males and females; adjusted odds ratios were 1.4, 1.7, and 1.9 (*p* for trend = 0.07, males and females combined). ???

3. CVD prevalence by individual POPS : PCDDs

Table 3. Concentration (pg/g of lipid), number of cases/total number, and adjusted OR (95% CI) for prevalence of self-reported cardiovascular diseases by category of PCDDs in males and females.

Analyte	Detection rate (%)	Not detectable	Detectable				p_{trend}
			< 25th	25th to < 50th	50th to < 75th	≥ 75th	
Males							
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	82.2	—	26.6[a]	42.1	61.3	111	
		5/76	3/86	14/89	21/89	18/87	
		Referent	0.9 (0.2–4.0)	4.3 (1.3–14.2)	4.1 (1.3–12.6)	2.5 (0.8–7.7)	0.04
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	89.5	—	20.7	40.0	61.7	111	
		3/45	12/95	17/96	11/96	18/95	
		Referent	3.2 (0.8–13.3)	3.7 (0.9–15.4)	1.7 (0.4–7.6)	2.4 (0.5–10.3)	0.94
1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin	82.0	—	192	310	469	899	
		4/77	7/87	18/88	16/88	16/87	
		Referent	1.5 (0.4–6.0)	3.7 (1.1–12.6)	2.7 (0.8–9.6)	2.1 (0.6–7.7)	0.28
Females							
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	83.8	—	27.6	45.9	66.1	111	
		6/75	5/96	3/97	12/97	21/97	
		Referent	1.0 (0.3–3.7)	0.4 (0.1–1.9)	1.7 (0.5–5.2)	2.8 (0.9–8.6)	0.04
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	93.1	—	25.5	50.2	76.6	135	
		3/32	12/107	7/108	11/108	14/107	
		Referent	1.6 (0.3–7.9)	1.3 (0.2–7.7)	2.2 (0.4–12.0)	1.9 (0.3–10.8)	0.45
1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin	92.9	—	278	445	660	1,170	
		4/33	10/107	4/107	12/108	17/107	
		Referent	0.6 (0.1–2.4)	0.2 (0.1–1.1)	0.7 (0.2–2.7)	0.7 (0.2–2.8)	0.74

ORs were adjusted for age, race, poverty income ratio, BMI, cigarette smoking, serum cotinine, alcohol consumption, exercise, HDL cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein.

[a]Median concentrations are displayed in each category.

3. CVD prevalence by individual POPS : Dioxin-like PCBs, females

Table 4. Concentration (ng/g of lipid), number of cases/total number, and adjusted OR (95% CI) for prevalence of cardiovascular diseases by categories of specific POPs belonging to dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides in females.

Analyte	Detection rate (%)	Not detectable	Detectable				p_{trend}
			< 25th	25th to < 50th	50th to < 75th	≥ 75th	
Dioxin-like PCBs							
2,4,4′,5-Tetrachlorobiphenyl (PCB-74)	87.2	—	8.2[a]	13.9	20.5	36.1	
		2/59	6/100	8/101	8/101	23/101	
		Referent	1.1 (0.2–6.1)	1.2 (0.2–6.4)	1.3 (0.2–7.3)	4.5 (0.8–24.8)	0.01
2,3′,4,4′,5-Pentachlorobiphenyl (PCB-118)	87.7	—	8.6	15.2	26.4	49.3	
		2/57	9/98	5/105	8/101	23/101	
		Referent	1.8 (0.3–9.4)	0.6 (0.1–4.1)	1.3 (0.2–7.8)	4.5 (0.8–25.5)	0.02
3,3′,4,4′,5-Pentachlorobiphenyl (PCB-126)	88.1	—	18.3	31.6	51.0	95.4	
		3/55	9/101	7/102	11/102	17/102	
		Referent	1.3 (0.3–5.8)	1.4 (0.3–6.6)	1.6 (0.4–7.4)	2.6 (0.6–12.2)	0.17
2,3,3′,4,4′,5-Hexachlorobiphenyl (PCB-156)	71.4	—	5.9	9.0	12.1	20.9	
		3/132	5/83	7/83	15/81	17/83	
		Referent	2.0 (0.4–9.5)	2.6 (0.6–12.0)	9.2 (2.1–39.4)	10.4 (2.3–46.7)	< 0.01
3,3′,4,4′,5,5′-Hexachlorobiphenyl (PCB-169)	89.6	—	13.3	21.7	32.4	51.0	
		3/48	5/103	8/104	16/103	15/104	
		Referent	0.6 (0.1–2.7)	0.9 (0.2–3.9)	1.2 (0.3–5.3)	1.2 (0.3–5.1)	0.38
Nondioxin-like PCBs							

Table 4. Concentration (ng/g of lipid), number of cases/total number, and adjusted OR (95% CI) for prevalence of cardiovascular diseases by categories of specific POPs belonging to dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides in females.

Analyte	Detection rate (%)	Not detectable	Detectable				
			< 25th	25th to < 50th	50th to < 75th	≥ 75th	p_{trend}
Nondioxin-like PCBs							
2,2′,4,4′5-Pentachlorobiphenyl (PCB-99)	74.2	—	6.0	9.7	14.5	26.9	
		10/119	4/84	3/87	12/86	18/86	
		Referent	0.3 (0.1–1.1)	0.2 (0.1–1.0)	1.1 (0.4–3.0)	1.5 (0.5–3.9)	0.08
2,2′,3,4,4′,5-Hexachlorobiphenyl (PCB-138)	87.7	—	18.3	32.1	51.3	91.0	
		1/57	10/100	4/102	7/102	25/101	
		Referent	6.8 (0.8–58.9)	1.6 (0.2–15.9)	3.6 (0.4–32.8)	13.4 (1.6–115.0)	< 0.01
2,2′,4,4′,5,5′-Hexachlorobiphenyl (PCB-153)	90.3	—	27.3	48.5	71.8	127.0	
		1/45	7/104	8/105	9/103	22/105	
		Referent	3.7 (0.4–34.8)	3.0 (0.3–27.1)	3.6 (0.4–33.5)	10.4 (1.1–94.1)	< 0.01
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl (PCB-170)	88.3	—	9.2	15.2	21.9	36.4	
		1/54	5/102	11/101	10/103	20/102	
		Referent	2.5 (0.3–23.3)	3.8 (0.4–33.3)	3.5 (0.4–32.1)	9.2 (1.0–84.5)	0.01
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl (PCB-180)	92.2	—	18.9	34.6	51.3	86.4	
		1/36	6/107	10/106	10/107	20/106	
		Referent	1.8 (0.2–16.5)	2.0 (0.2–17.9)	2.0 (0.2–18.7)	4.5 (0.5–40.9)	0.07
2,2′,3,4′,5,5′,6-Heptachlorobiphenyl (PCB-187)	82.5	—	7.4	11.2	16.8	30.4	
		1/86	8/93	9/98	12/95	17/95	
		Referent	5.0 (0.6–43.5)	3.5 (0.4–30.2)	5.8 (0.7–50.1)	7.4 (0.9–63.6)	0.07

Table 4. Concentration (ng/g of lipid), number of cases/total number, and adjusted OR (95% CI) for prevalence of cardiovascular diseases by categories of specific POPs belonging to dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides in females.

Analyte	Detection rate (%)	Not detectable	Detectable				
			< 25th	25th to < 50th	50th to < 75th	≥ 75th	p_{trend}
OC pesticides							
p,p´-Dichlorodiphenyltrichloroethane	100	—	189	556	1,145	2,440	
		—	8/115	9/116	10/116	20/115	
			Referent	0.8 (0.3–2.9)	0.7 (0.2–2.1)	1.7 (0.6–4.9)	0.22
Oxychlordane	93.7	—	12.1	20.2	31.4	50.5	
		0/29	3/108	9/108	9/110	26/107	
			Referent	1.9 (0.4–7.7)	1.7 (0.4–7.6)	6.8 (1.6–29.3)	< 0.01
trans-Nonachlor	98.3	—	15.4	27.2	42.4	80.8	
		0/8	2/113	10/114	12/114	23/113	
			Referent	3.7 (0.7–18.6)	3.4 (0.7–17.1)	6.5 (1.3–33.6)	0.03
Heptachlor epoxide	68.2	—	5.9	9.2	13.1	23.9	
		9/147	1/78	8/80	13/79	16/78	
		Referent	0.1 (0.1–1.3)	1.1 (0.3–3.2)	2.0 (0.7–5.8)	1.9 (0.6–5.7)	0.05

ORs were adjusted for age, race, poverty income ratio, BMI, cigarette smoking, serum cotinine, alcohol consumption, exercise, HDL cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein.

[a]Median concentrations are displayed in each category.

Summary of Results: CVD prevalence were associated with followings:

Cumulative indicators for five sub-classes of POPs

Dioxin-like PCBs ($p<0.01$)
Nondioxin-like PCBs ($p<0.02$)
OC pesticides ($p<0.03$)

Individual POPs

Both sexes:
1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (male, female) (PCDDs)
Females only:
2,4,4´,5-Tetrachlorobiphenyl (PCB-74)
2,3´,4,4´,5-Pentachlorobiphenyl (PCB-118)
2,3,3´,4,4´,5-Hexachlorobiphenyl (PCB-156)
2,2´,3,4,4´,5-Hexachlorobiphenyl (PCB-138)
2,2´,4,4´,5,5´-Hexachlorobiphenyl (PCB-153)
2,2´,3,3´,4,4´,5-Heptachlorobiphenyl (PCB-170)
2,2´,3,4,4´,5,5´-Heptachlorobiphenyl (PCB-180)
Oxychlordane
trans-Nonachlor
Heptachlor epoxide

Discussion-1: The findings are in agreement with the previous cohort studies in occupational or accidental settings; the association was even stronger in the current study.

1. A puzzling finding because the exposure level was far lower in the current study.

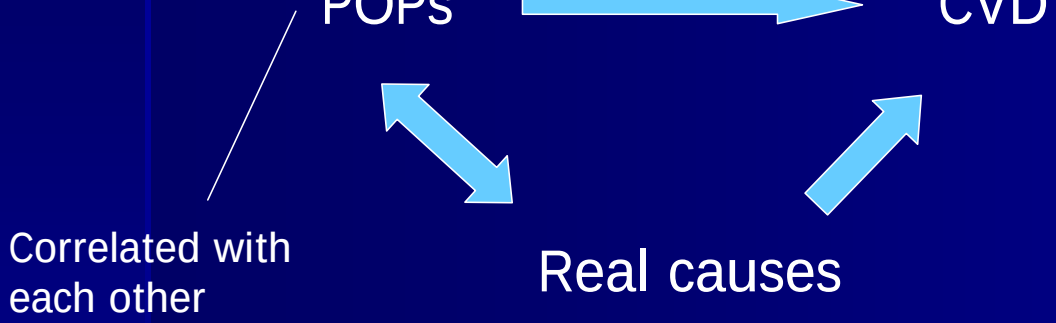
The possible explanations may be:

(a) the previous studies failed to select a true reference group

(b) the previous studies did not examine and additive or synergistic effect

Discussion-2: Observed association is causal?

CVD was associated with various POPs with different toxicologic profiles



2,3,7,8-tetrachlorodibenzo-p-dioxin (Bombick et al.1984; Lovati et al. 1984; Swift et al. 1981), coplanar PCBs (Henning et al. 2002) polychlorinated biphenyls (Toborek et al. 1995)

POPs ← CVD

The Findings need to be carefully interpreted.

Discussion-3: only females showed strong positive associations with dioxin-like or nondioxin-like PCBs or OC pesticides.

Differences between the sexes in the response of nonreproductive cells to TCDD or PCBs have been observed in several animal studies (Enan et al. 1996; Vega-Lopez et al. 2007; Wyde et al. 2001).

The previous studies in occupational settings have been performed among men; the sex difference reported in the present study is of importance.

Discussion-5: the strength of the association (CVD-exposure) and TEFs

TEFs = toxic equivalent factors, a measure of ability to bind to the AhR (aryl hydrogen receptor)

Affinity to AhR was important to induce atherosclerosis (Hennig et al. 2002; Stegeman et al. 1995; Toborek et al. 1995) → the POPs of higher TEFs are associated with the CVD prevalence?

The present study: No

POPs with lower TEFs (e.g., nondioxin-like PCBs, dioxin-like PCBs with lower TEFs) showed strong association.

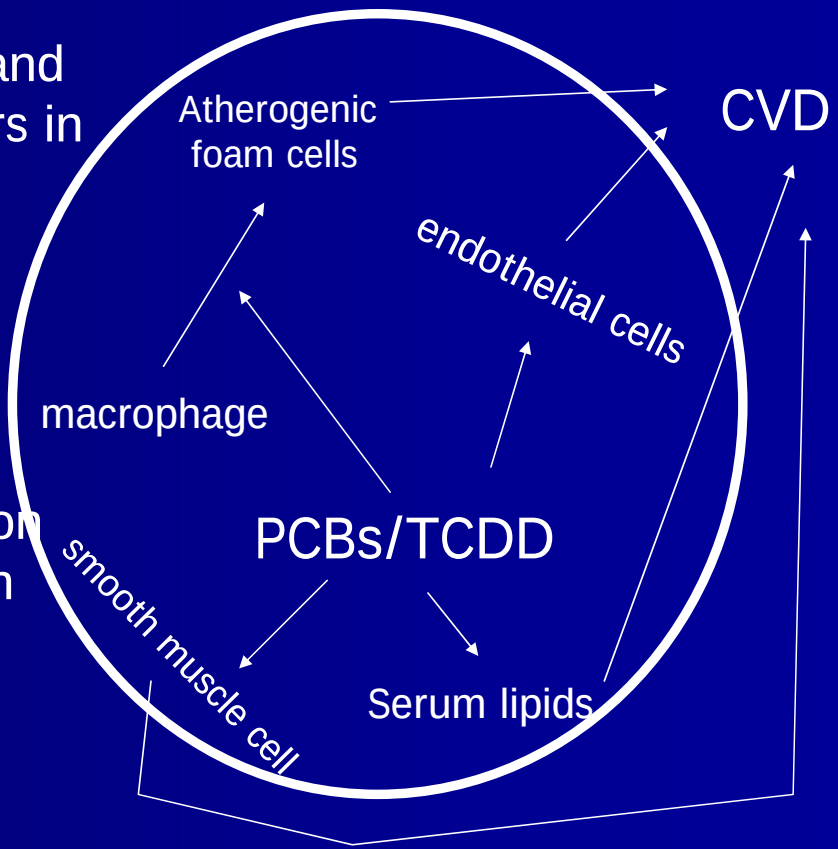
Affinity to AhR may not be a critical pathway of toxicity of POPs in humans for some oputcomes (cf. CVD prevalence), or the association of some POPs with CVD may not be direct.

Discussion-4: Experimental evidences that suported the current findings

1. PCBs or TCDD can compromise the normal function of vascular endothelial cells by activating oxidative stress–sensitive signaling pathways and subsequent proinflammatory events critical in the pathology of atherosclerosis and CVD (Hennig et al. 2002; Stegeman et al. 1995; Toborek et al. 1995).

2. Exposure to TCDD increased serum cholesterol, triglyceride, and phospholipids and suppressed low- density lipoprotein receptors in the liver (Bombick et al. 1984; Lovati et al. 1984; Swift et al. 1981).

3. TCDD promoted the differentiation of macrophages to atherogenic foam cells or deregulated several genes in cell proliferation and apoptosis in smooth muscle cell (Dalton et al. 2001; Vogel et al. 2004).



Discussion-5: Limitations and advantages

Limitation

1. Cross-sectional design
2. CVD self-reported
3. Fatal events not considered
4. LOD vary according to the volume of sample available

Advantages

1. Rare population study

Conclusion (as it is in the text, also see the abstract)

In summary, we found positive associations between serum concentrations of some POPs and the prevalence of CVD in this sample of the U.S. population. Thus, prospective study of the relation between background
dioxin exposure and validated CVD should be a priority in further study of these associations. Both the exposure and the disease have substantial prevalence, and the public health significance of a causal relation of POPs with CVD should be noted.