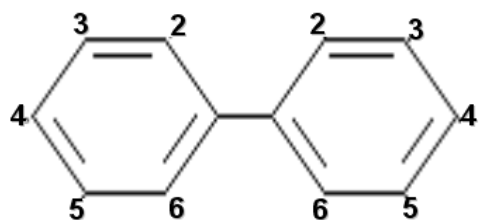
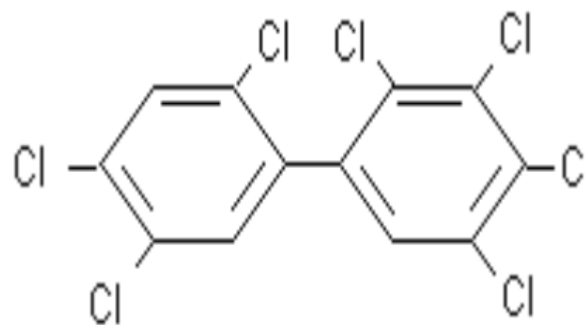


# PCB Exposure as a Risk Factor for Hypertension, Cardiovascular Disease and Diabetes

David O. Carpenter, MD  
Director  
Institute for Health and the Environment



**(a)**



**(b)**

**Figure 2-1** Polychlorinated biphenyl molecule.

(a) shows a biphenyl molecule showing the 10 possible locations where a chlorine atom may be attached to the molecule.

(b) shows a PCB molecule with chlorine substitution at the 245 locations on one phenyl ring, and at the 2345 locations on the second phenyl ring. This particular PCB congener is referred to as 245-2345 CB or alternatively, PCB 180 (IUPAC nomenclature).

# Anniston, Alabama

- Anniston is a city of about 24,000 people. It is the home of one of two US plants operated by the Monsanto Corporation for the manufacture of polychlorinated biphenyls, which were sold under the trade name, Aroclor, from 1929-1971.
- We have studied blood pressure in relation to serum PCB and pesticide levels in 772 residents, ages 18-93 years.
- PCB/pesticide analysis done by CDC



- 400,000 metric tons (MT) of PCB produced 1920s-1971 (estimated from Monsanto data)
- Over 4,550 MT of PCB dumped in Anniston landfills (from USEPA assessment 1979)
- A minimum of 20.4 MT emitted to the atmosphere from 1953 – 1970 (from Monsanto data)

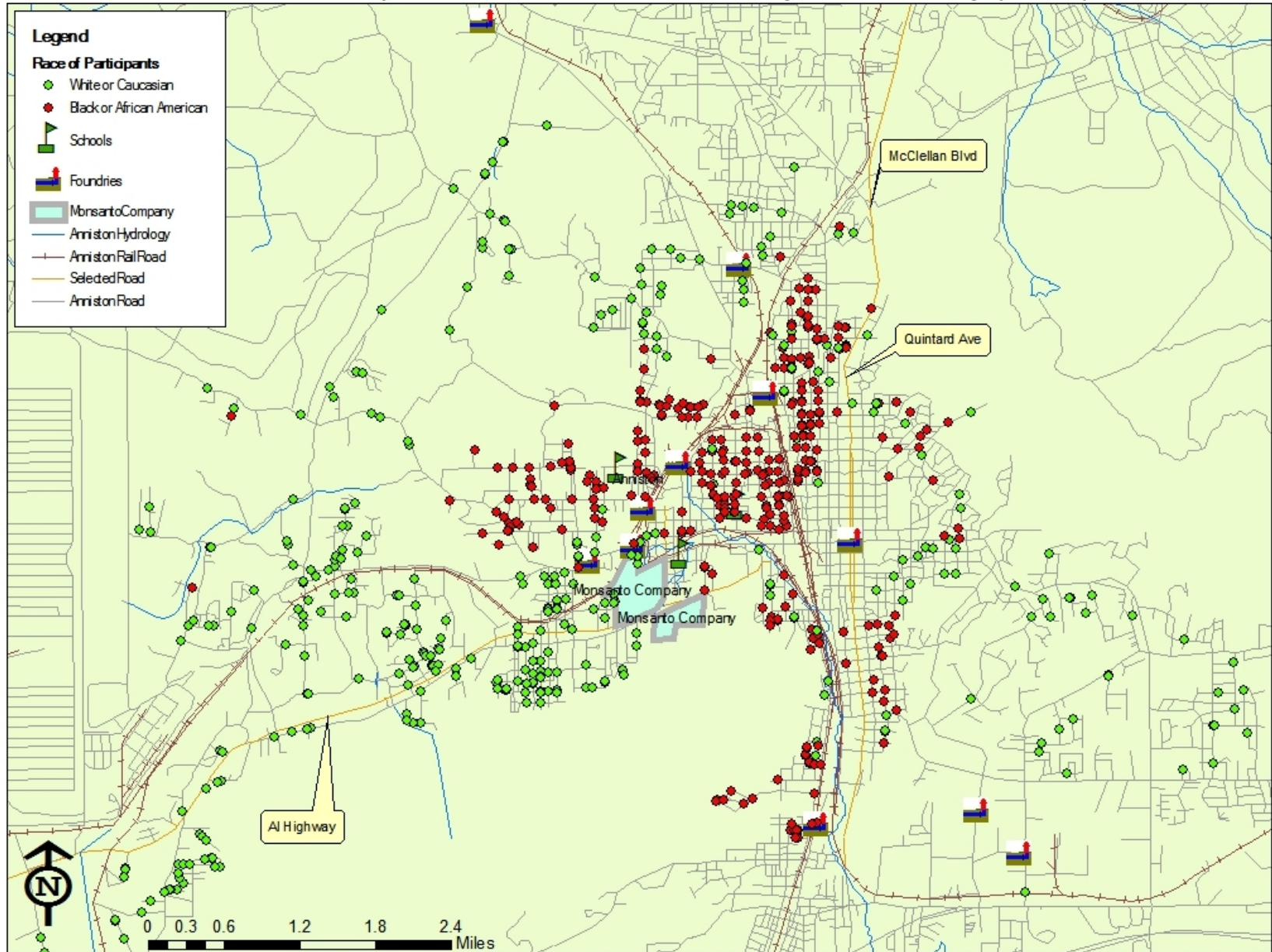


- 14,000 MT of PCB distillation waste (Montars) dumped in Anniston landfills (from Monsanto data)

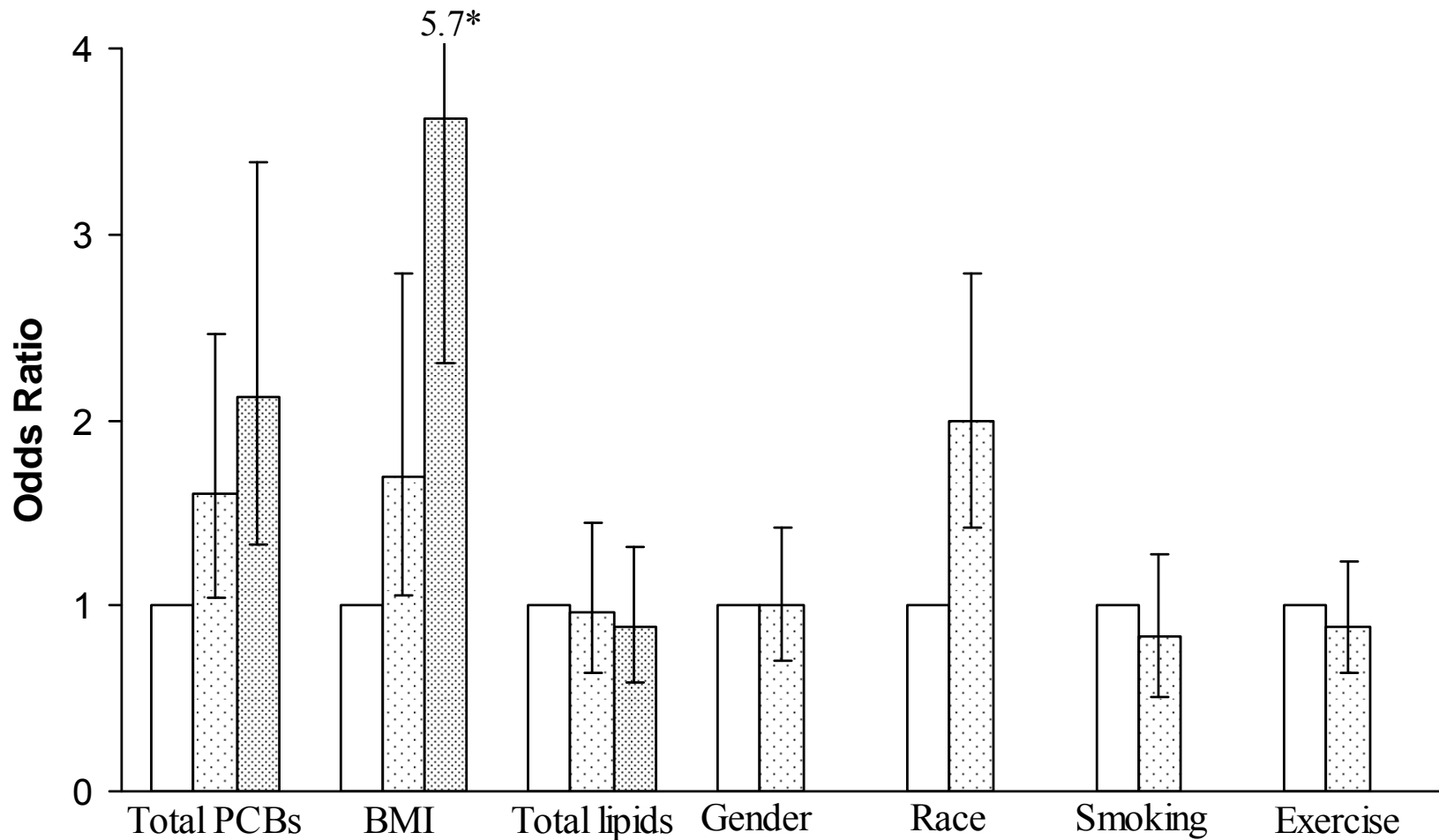
**Table 1.** Selected demographic characteristics of the study participants stratified by the use of anti-hypertensive medication.

Covariate	No Medication (n=394)	On Medication (n=365)
Age, years: Mean (SD)	47.6 (15.5)	62.8 (11.9)
Sum PCBs, ng/g whole weight: Mean (SD)	4.72 (11.1)	8.78 (12.6)
BMI	29.8 (7.2)	32.9 (7.9)
Gender, n (%): Male	126 (31.9)	104 (28.5)
Female	268 (68.1)	261 (71.5)
Race, n (%) Caucasian	223 (56.6)	184 (50.6)
African-American	171 (43.4)	180 (49.4)

# Race of Participants in the Anniston Community Health Survey (ACHS)



**Figure 1.** Odds ratios ( $\pm$  95% confidence intervals) for clinical hypertension in relation to increasing tertiles of total PCBs, serum lipids, BMI (normal, overweight, obese) as well as gender (male vs. female), race (Caucasian vs. African-American), smoking (more than 100 lifetime cigarettes) and exercise (10 min or more daily) adjusted for age.



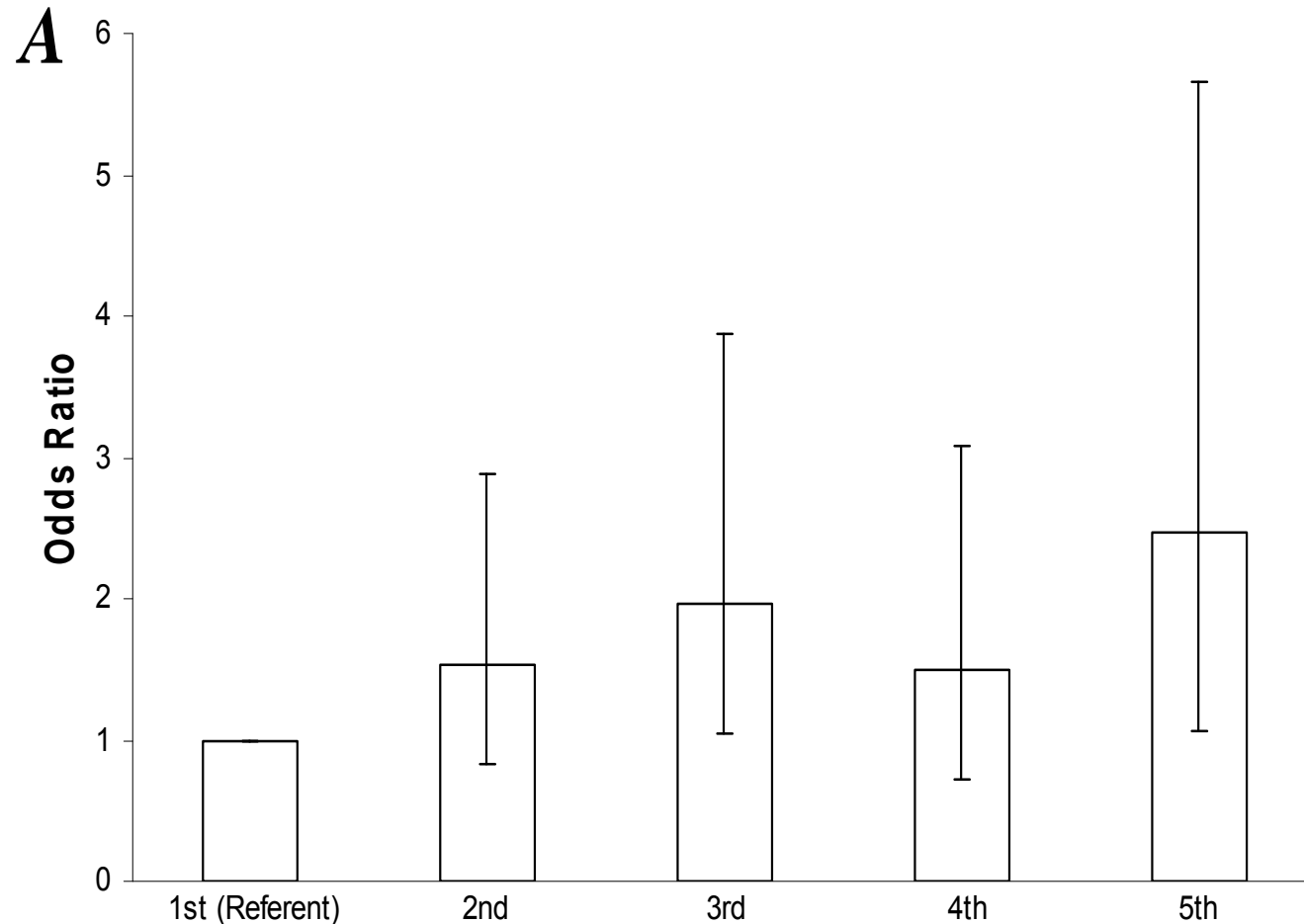
**Table 2.** Adjusted Odds Ratios <sup>a</sup> and 95% Confidence Intervals for systolic and diastolic hypertension in relation to total PCBs (ng/g whole weight) among study participants not taking anti-hypertensive medication (n=394).

PCBs Tertiles (ng/g whole weight)	Odds Ratios (95% Confidence Intervals) <sup>a</sup>	
	Systolic Hypertension (n=53)	Diastolic Hypertension (n=56)
1. (0.09-1.23)	1.00 (Referent)	1.00 (Referent)
2. (1.24-3.64)	3.05 (0.77-12.04)	4.27 (1.50-12.15)
3. (3.65-170.4)	3.87 (1.13-13.17)	4.49 (1.34-14.99)

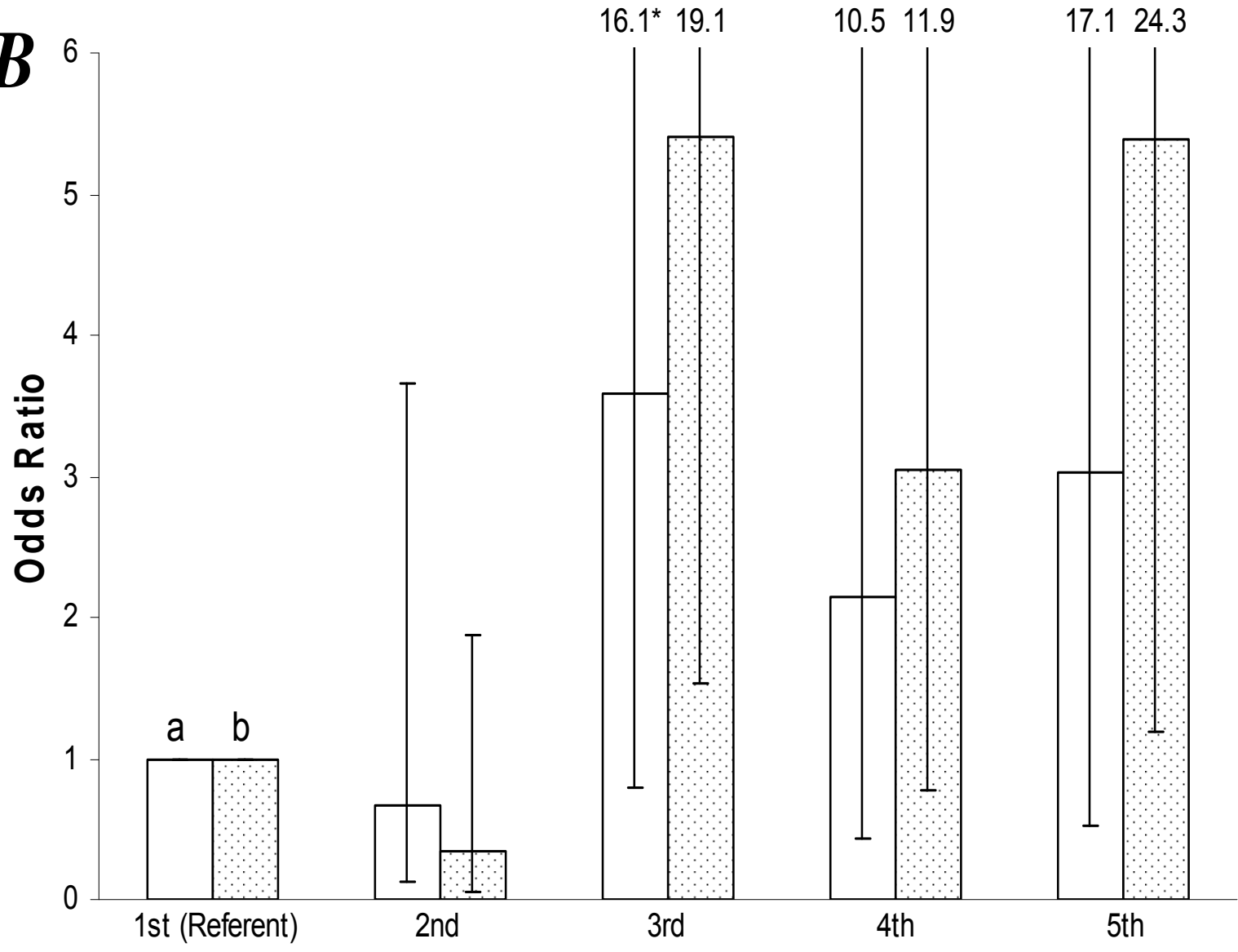
a. Adjusted for age, BMI, total serum lipids, gender, race, smoking status, and physical activity.

**Figure 2.** Odds Ratios and 95% confidence intervals for the quintiles of total PCBs in relation to (A) clinical hypertension for all 758 participants and (B) systolic (a) and diastolic (b) hypertension in those participants (n=365) not on antihypertensive medication. For part A the referent PCB concentration range was 0.1-1.1 ppb, and the ranges for the second to fifth quintiles were 1.2-2.4, 2.5-4.3, 4.4-9.3 and 9.4-170.4 ng/g. For part B the referent PCB concentration range was 0.1-0.5 ppb, and the ranges for the second to fifth quintiles were 0.6-1.5, 1.6-2.9, 3.0-5.7 and 5.8-170.4 ng/g.

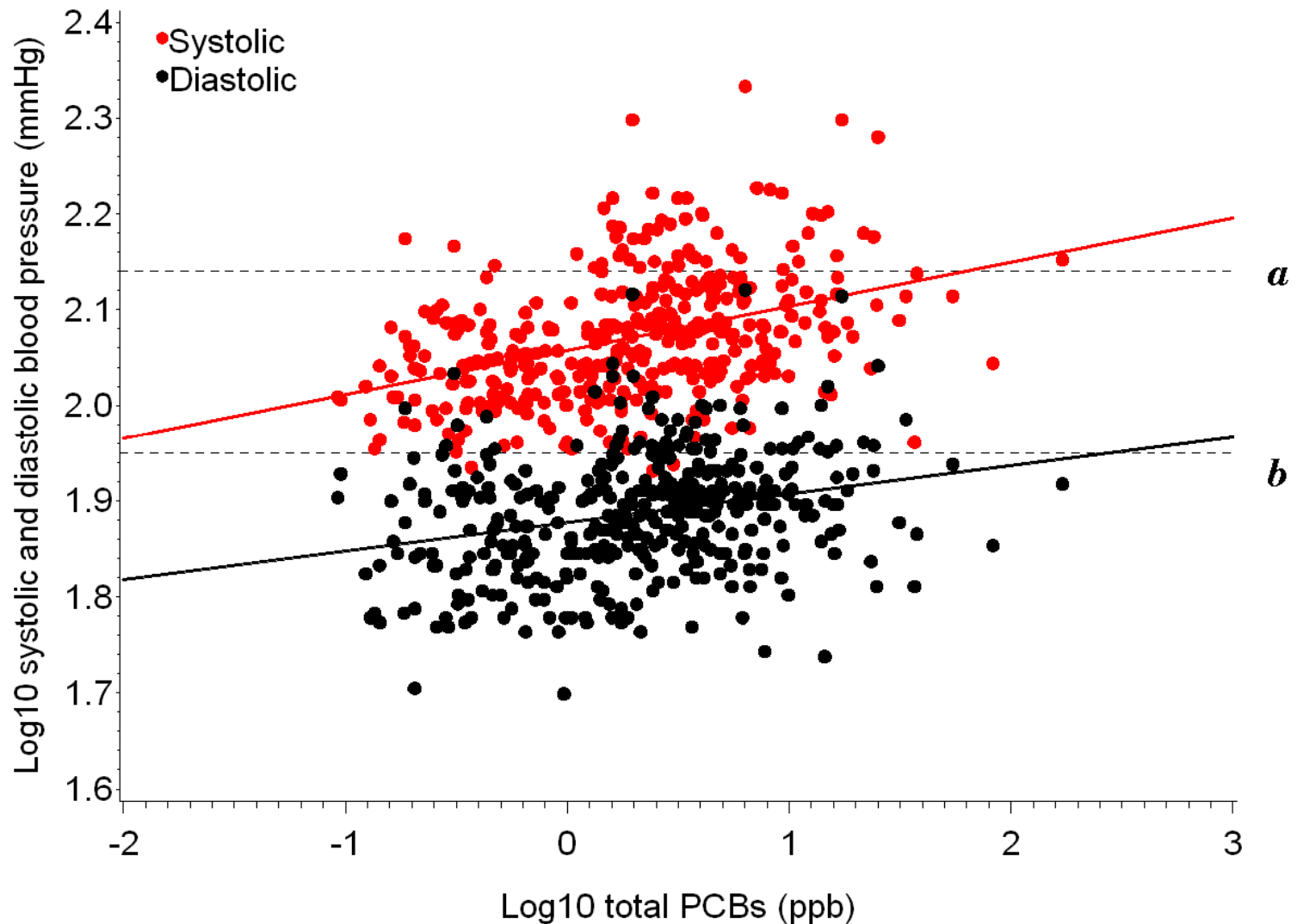
---



***B***



**Figure 2.** Linear regression of systolic and diastolic blood pressure on total PCBs concentration. The dashed lines show cut-off pressures for systolic (a) and diastolic (b) hypertension.



**Table 2.** Linear regression of total PCBs in relation to those individuals with full (n=394) and normotensive systolic (n=341) and diastolic (n=338) blood pressure ranges.

Full systolic blood pressure		Full diastolic blood pressure	
$\beta \pm SE^a$ 0.017 $\pm$ 0.008*		$\beta \pm SE^a$ 0.014 $\pm$ 0.009	
$\beta_1 \pm SE^{b,c}$ 0.023 $\pm$ 0.09*	$\beta_2 \pm SE^{b,d}$ 0.028 $\pm$ 0.10*	$\beta_1 \pm SE^{b,c}$ 0.034 $\pm$ 0.09*	$\beta_2 \pm SE^{b,d}$ 0.035 $\pm$ 0.10*
Normotensive systolic blood pressure		Normotensive diastolic blood pressure	
$\beta \pm SE^a$ 0.013 $\pm$ 0.006*		$\beta \pm SE^a$ 0.002 $\pm$ 0.007	
$\beta_1 \pm SE^{b,c}$ 0.007 $\pm$ 0.006	$\beta_2 \pm SE^{b,d}$ 0.020 $\pm$ 0.007*	$\beta_1 \pm SE^{b,c}$ 0.014 $\pm$ 0.007*	$\beta_2 \pm SE^{b,d}$ 0.020 $\pm$ 0.008*

<sup>a</sup>toxicant is presented in continuous scale.

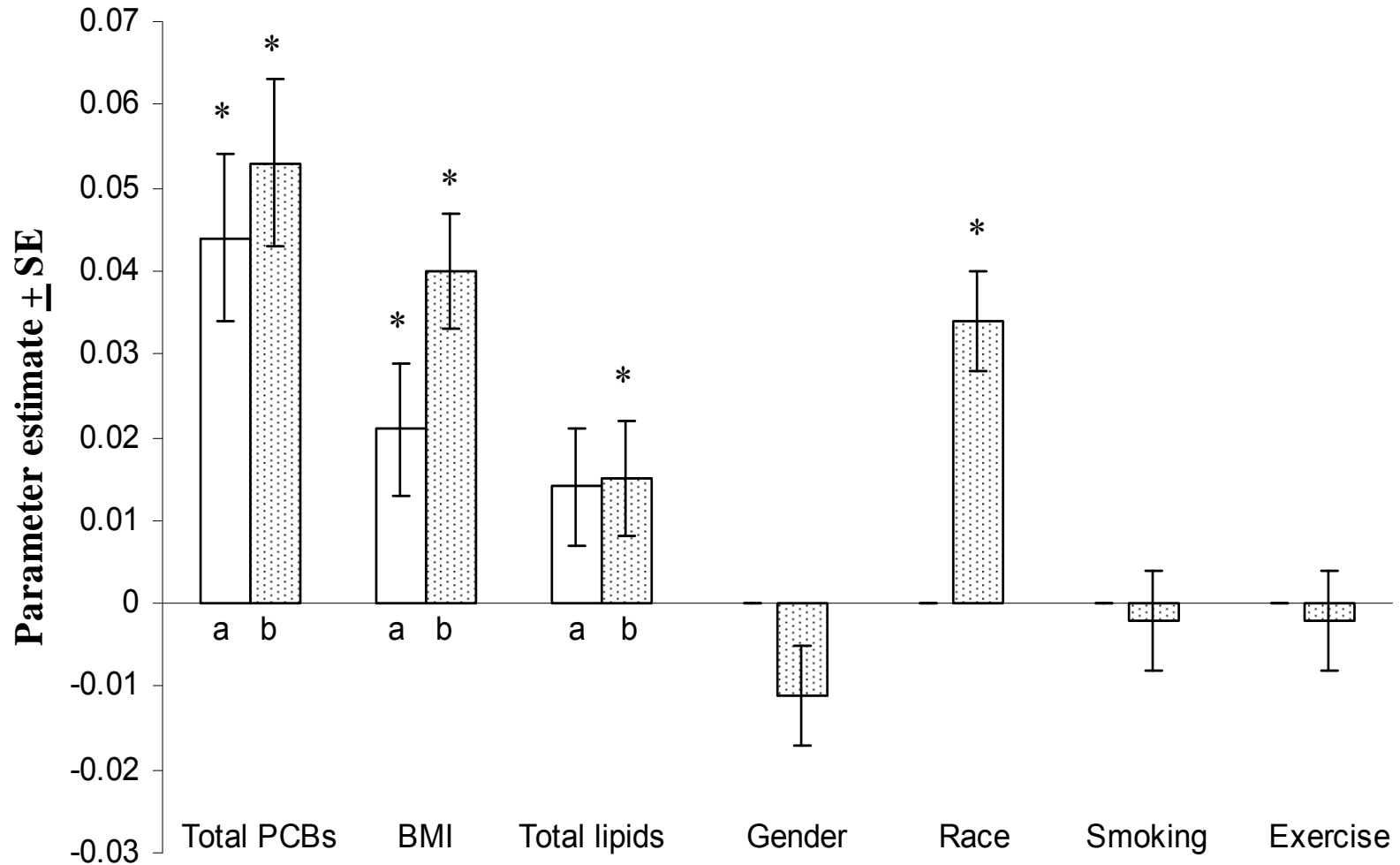
<sup>b</sup>toxicant is presented in tertiles.

<sup>c</sup>regression coefficient of toxicant's second tertile.

<sup>d</sup>regression coefficient of toxicant's third tertile.

\*p < 0.05.

# Parameter estimates ( $\beta$ coefficients) and ( $\pm$ SE) of mean diastolic blood pressure in relation to total PCBs and principal risk factors after adjustment for age



<sup>a</sup>second tertile PCB (1.23 – 3.65 ng/g), second tertile BMI (24.9 – 29.9 kg/m<sup>2</sup>), second tertile total lipids (553.1 – 665.5 mg/L).

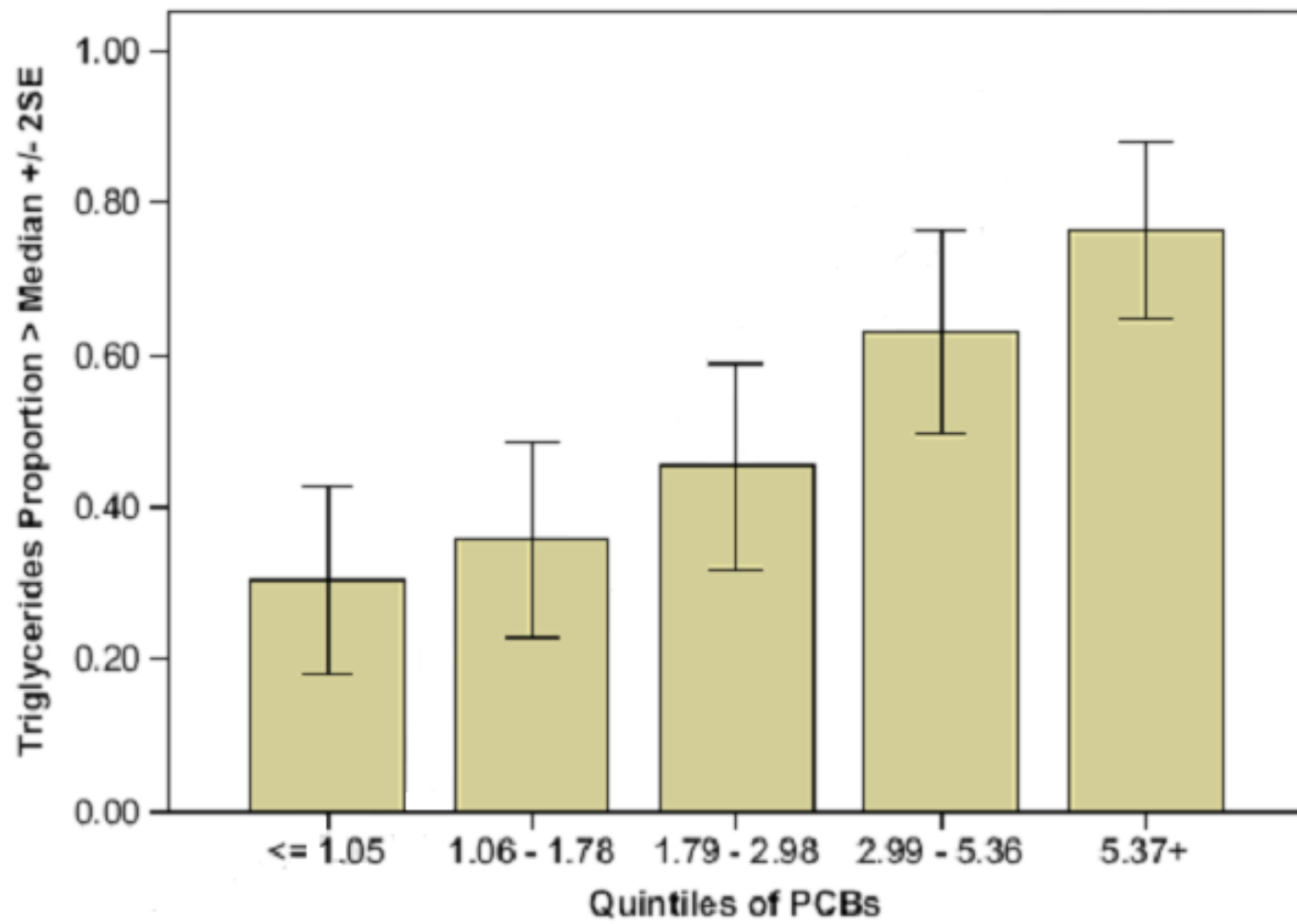
<sup>b</sup>third tertile PCB (3.66 – 170.4 ng/g), third tertile BMI (30.0 – 65.0 kg/m<sup>2</sup>), third tertile total lipids (665.6 – 1436.2 mg/L).

\* $p < 0.05$ .

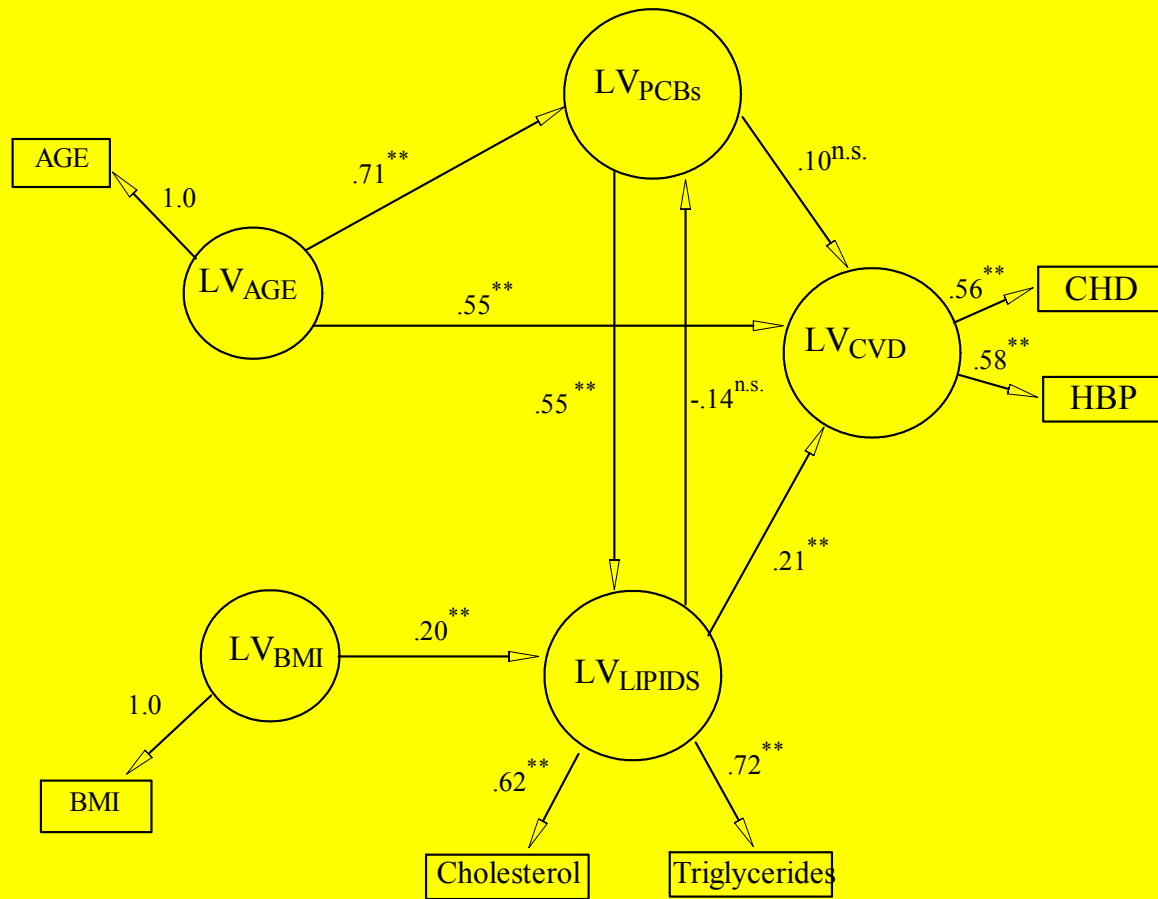
# POPs and Cardiovascular Disease

- There is some evidence that POPs-exposed persons have elevated rates of cardiovascular disease.
- We determined serum lipids, 101 PCB congeners, DDE, HCB and mirex in 335 adult Mohawks.
- We applied structural equation modeling with definition of latent variables and confirmatory factor analysis to study this relation.

**B**



- Nonrecursive Model with Feedback Loop



\* p < .05  
 \*\* p < .01

- These results indicate that PCBs increase the risk of cardiovascular disease indirectly through a stimulation of synthesis of lipids by the liver.
- We and others have also shown that PCBs can directly damage endothelial cells, which may promote atherosclerosis.

# 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

Myung-Hwa Ha,<sup>1,2</sup> Duk-Hee Lee,<sup>1</sup> and David R. Jacobs Jr.<sup>3,4</sup>

- **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  $\geq 40$  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  $\geq 60\%$  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.
- **Environ Health Perspect 115: 1204-1209: 2007**

# Diabetes and PCB Exposure

- Recent studies have demonstrated greater risk of developing diabetes among people with higher PCB levels in their blood.
- We have done a study of Native Americans and find that those with higher PCBs have an almost 4-fold increased risk of diabetes.

# Diabetes Mellitus to June 1995

		Ranch Hand		
	Comp (N=1276)	Bkg (N=422)	Low (N=284)	High (N=283)
N (%)	169 (13.2)	40 (9.5)	49 (17.2)	57 (20.1)
RR	1.0	0.7	1.3	1.5
95% CI		0.5, 1.0	1.0, 1.7	1.2, 2.0

*Henriksen et al, 1997*

**Table 3. Association between diabetes, wet-weight and lipid-adjusted total PCBs, mirex, HCB and DDE after adjustment for age, gender, body mass index and smoking status in Mohawk adults.**

	<b>Tertile</b>	<b>Odds Ratio (95% CI) Wet Weight</b>	<b>Odds Ratio (95% CI) Lipid Adjusted</b>
Total PCBs	Lowest	1	1
	Medium	2.15 (0.80 – 5.80)	1.87 (0.79 – 4.44)
	Highest	3.9 (1.46 – 10.43)	3.29 (1.42 – 7.64)
Mirex	Lowest	1	1
	Medium	1.21 (0.57 – 2.58)	0.82 (0.40 – 1.7)
	Highest	0.98 (0.45 – 2.12)	0.89 (0.43 – 1.82)
HCB	Lowest	1	1
	Medium	0.94 (0.33 – 2.67)	2.64 (1.01 – 6.87)
	Highest	6.22 (2.29 – 16.94)	6.79 (2.65 – 17.44)
DDE-85	Lowest	1	1
	Medium	1.83 (0.65 – 5.19)	2.44 (0.87 – 6.81)
	Highest	6.43 (2.25 – 18.37)	6.79 (2.65 – 17.44)

# NHANES, Lee et al.

- Data from 2 dioxins, one PCB and three pesticides. (Diabetes Care 29: 1638: 2006)
- When risk of diabetes was classified according to the sum of all six POPs, adjusted ORs were 1.0, 14.0, 14.7, and 38.3.
- Later (Diabetes Care 30: 1596: 2007) they conclude that the relation is strongest for dioxin-like PCBs and chlorinated pesticides, but weak for dioxins and non-dioxin-like PCBs.

# Obesity and Diabetes

- Lee et al. (2006) looked at obese persons (BMI > 30 kg/m<sup>3</sup>) in relation to sum of 6 POPs:

– <25 <sup>th</sup> %	1 of 129 people
– 25 <sup>th</sup> to 50 <sup>th</sup> %	14 of 153 people
– 50 <sup>th</sup> to 75 <sup>th</sup> %	29 of 176 people
– 75 <sup>th</sup> to 90 <sup>th</sup> %	32 of 87 people
– >90 <sup>th</sup> %	31 of 80 people

Conclusion: Obesity does not cause diabetes!

What are the mechanisms of these actions on hypertension, lipids and glucose regulation?

- Some effects are understood, such as binding to the Ah receptor, competition for binding proteins and altered rates of metabolism.
- Others are less clear, such as altered lipid synthesis and insulin receptor sensitivity.
- The most likely mechanism is probably gene induction.

# *Dioxin and PCBs alter gene regulation*

- Hokanson et al. (Human Exp Toxicol 23: 555: 2004) found that of 2,400 genes (MCF-7 cells) regulated by estrogen, 317 were upregulated and 488 were down regulated by TCDD.
- Johnson et al. (EHP 112: 403:2004) investigated 200 genes regulated by the Ah Receptor and their interactions.
- Vezina et al. (EHP 112: 1636: 2004) compared gene expression from TCDD, a furan, a dioxin-like PCB and a non-dioxin-like PCB, and found all different.

# Conclusions:

- Exposure to PCBs and other POPs is ubiquitous.
- These chemicals increase the risk of the major chronic diseases, hypertension, cardiovascular disease and diabetes.
- The concentrations that increase risk are common in the general population.
- It is very important to find ways to reduce the risk of exposure to these chemicals.