

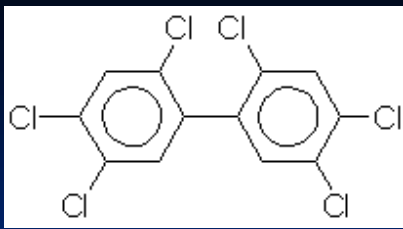
“Middle Age”: Examples Of High Exposures to Mixtures of Hormonally Active Chemicals And Health Effects [e.g. DDE, PCBs, PBDE, Phthalates]



Henry A. Anderson, MD
Wisconsin Division of Public Health
October 24, 2010
Ramazzini Days, Carpi, Italy

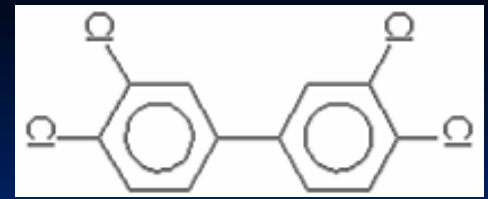


1992 - 2010



PCB 153

PCBs



PCB 77

- 2 million tons produced from 1920's to 1970's
 - Use banned in 1977
 - Cooling & insulating fluid for transformers & capacitors
 - Housing materials: caulk, paint, insulation, floor finish
- 209 Congeners
 - Toxicity related to structure
 - Many have biological half-life of 10 years or longer
- Exposure
 - Occupations with contact with in-place products, **recycling workers**
 - Consumption of contaminated food, Indoor air/dust?

PCBs are being Dumped in Developing Countries through E-wastes

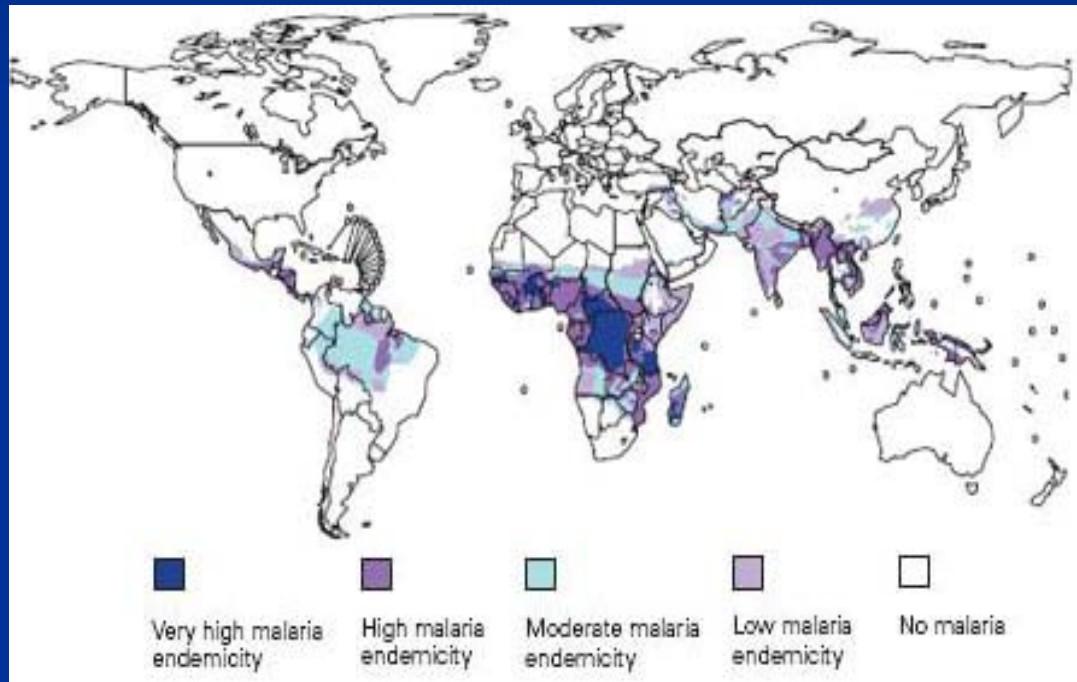
Known and Suspected Routes of e-waste Dumping



There is currently no system for tracking legal or illegal (under international law) shipments of electronic waste therefore, there is no quantitative data on volumes or even all of the true destinations. Some electronic waste is shipped as "working equipment" only to end-up as waste upon arrival. This map indicates information collected through investigations by organizations such as the Basel Action Network, Silicon Valley Toxics Coalition, Toxics Link India, SCO (Pakistan), Greenpeace and others.



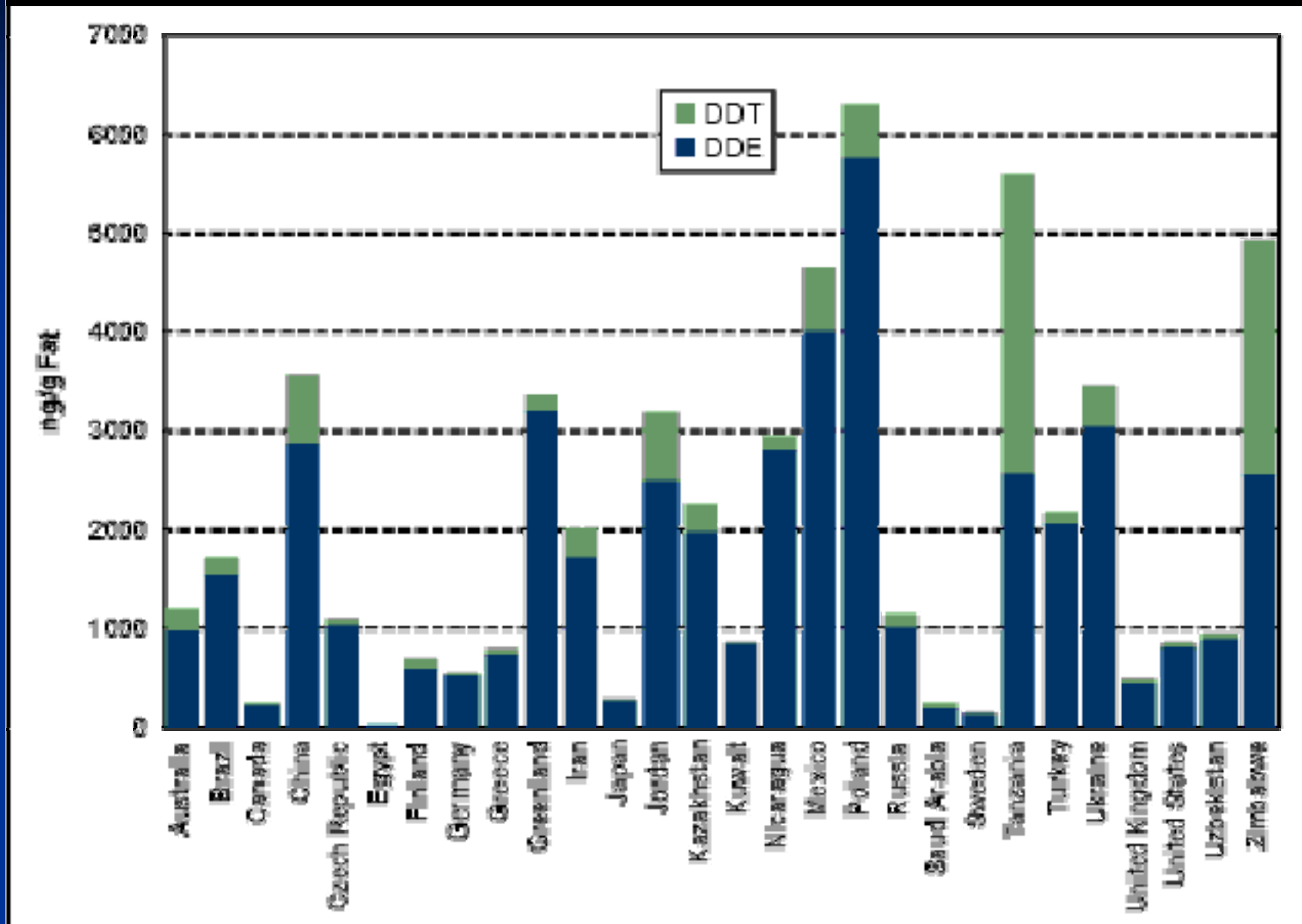
Current Status of Malaria Activity Around the World





DDT spraying – vegetable market

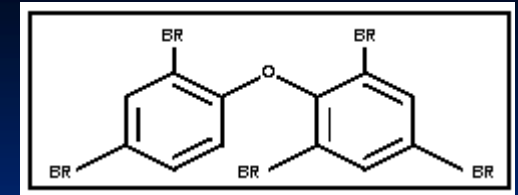
DDT and DDE in Breast Milk and Adipose Tissue Around the World (1990s–2000s)



Source: NRDC



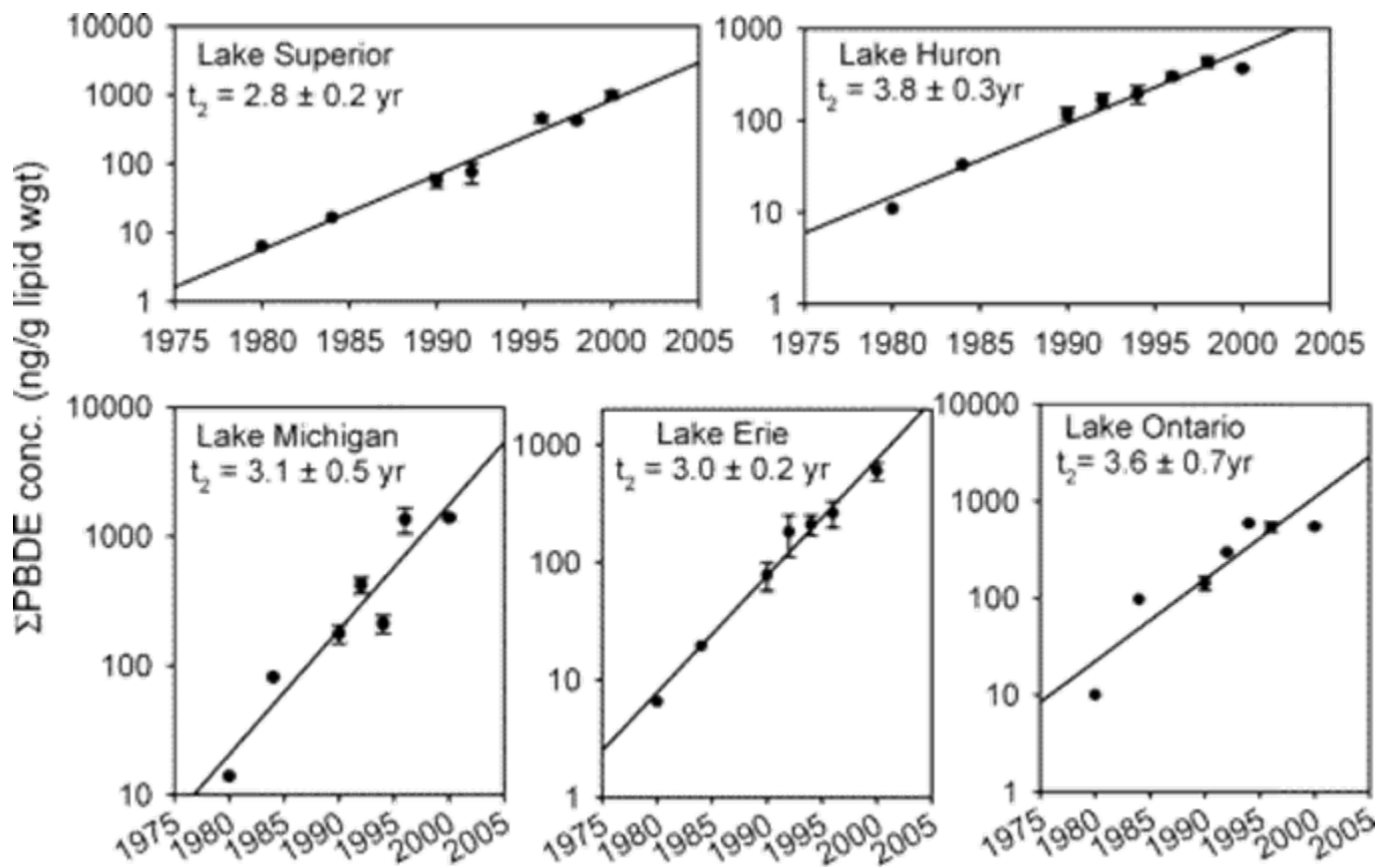
PBDEs



PBDE 100

- **Flame retardants for consumer goods, including cars**
 - Use began in 1980
 - PentaBDE used in foam and fabrics (phased out 2004)
 - Highest use in North America, particularly in CA
 - DecaBDE used in electronics (phase out in next 3 yrs)
- **209 congeners**
 - Half lives vary: BDE 209 - weeks, BDE 47 and BDE 153 - years
- **Exposure**
 - Manufacturing workers, **recycling**
 - Can migrate out of products into environment, house dust
 - Contaminate foods

PBDEs in Great Lakes Fish



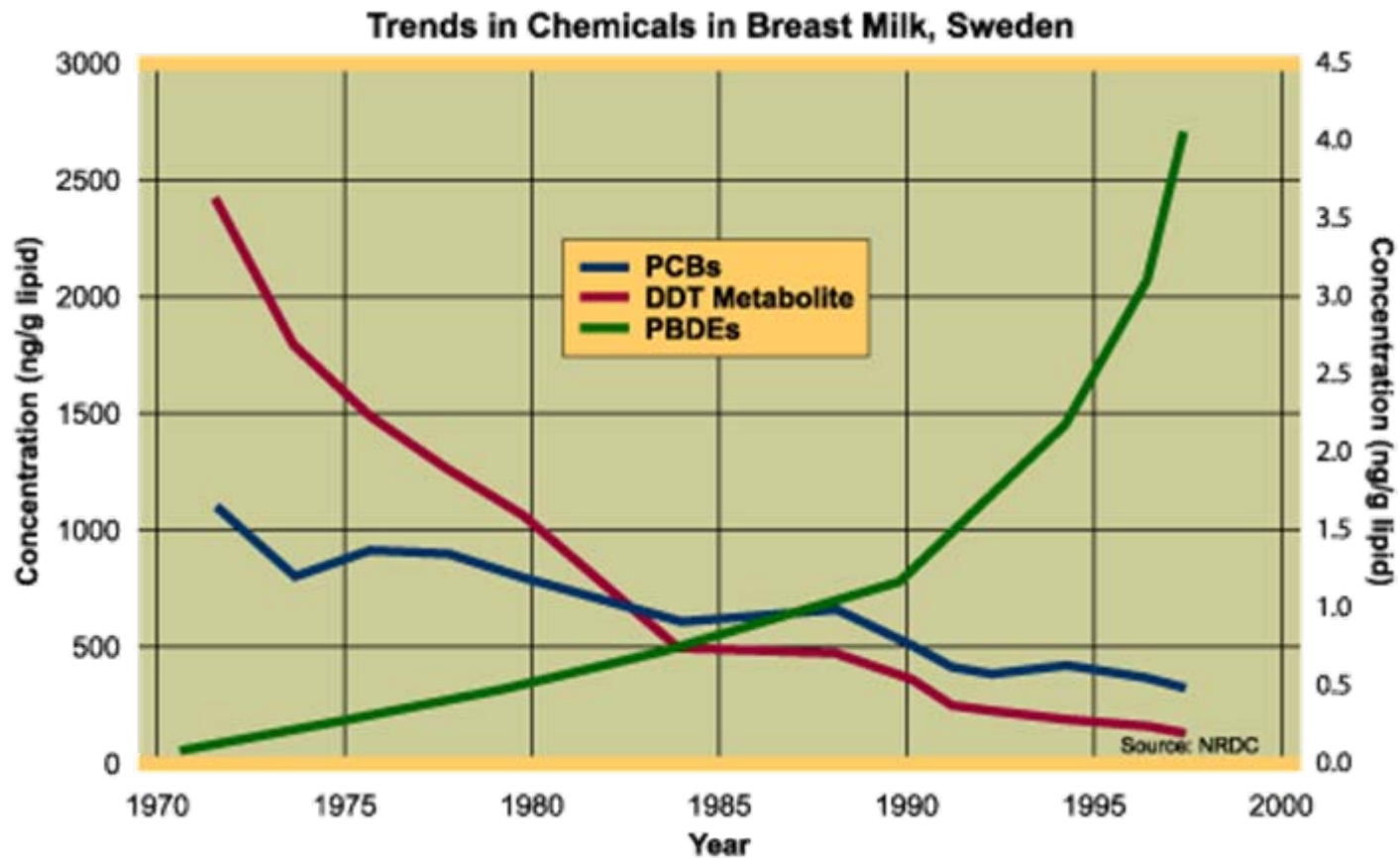
Zhu and Hites, Environ Sci Technol 38:2779, 2004

Home Exposures & Serum PBDEs in GL Cohort

Exposure Factor	Correlation Coefficient
Family room television bromine reading	0.48 *
Hours watching TV	-0.13
Computer bromine reading	-0.07
Foam Pillow bromine reading	0.38 *
Top layer of mattress or pad bromine reading	0.22
Primary car seat bromine reading	0.35 *
Hours in primary car	0.03
Nona- and deca-BDE in dust	0.21
Penta-BDE in dust	0.42 *
PBDE in PUF air sampler	0.28
Sport-caught fish past month	0.07

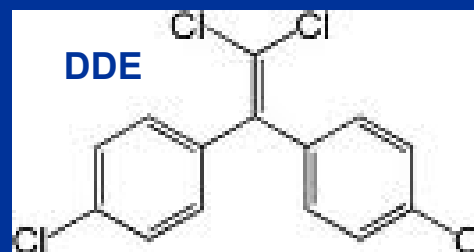
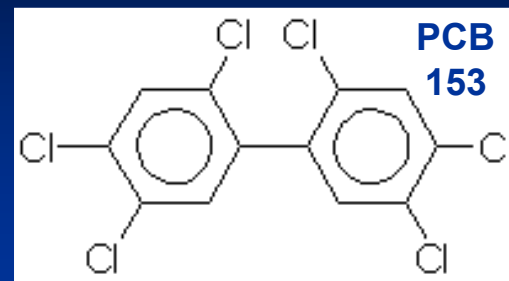
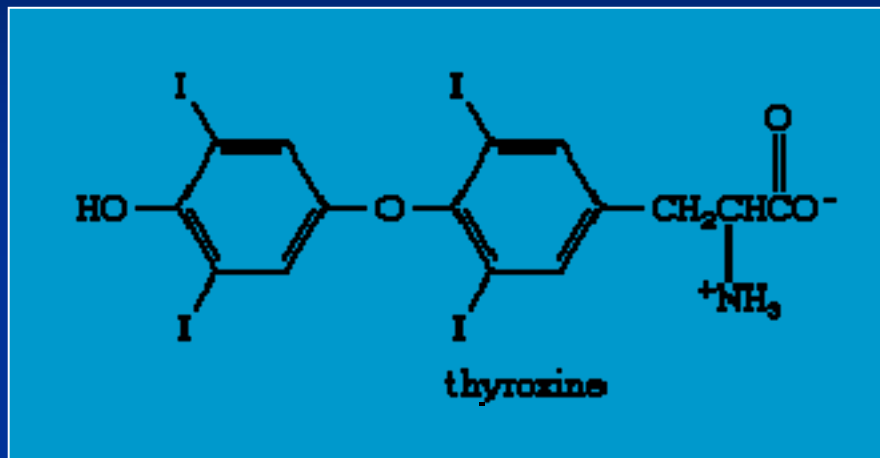
N= 44, bromine quantified with X-ray fluorescence, R-square=0.63 for model with all 4 significant factors. Imm et al., Environ Sci Technol, in press

Time Trends for Contaminants in Human Breast Milk - Sweden

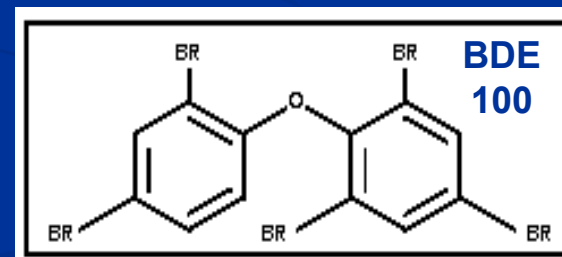
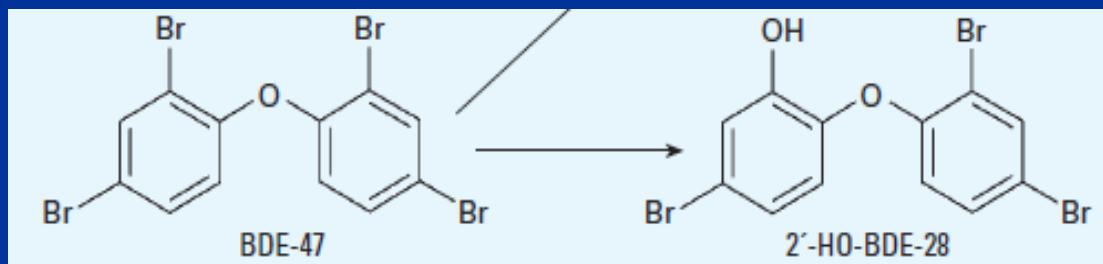


National Resource Defense Council

Persistent Organic Pollutants (POPs) and Thyroxine (T₄)

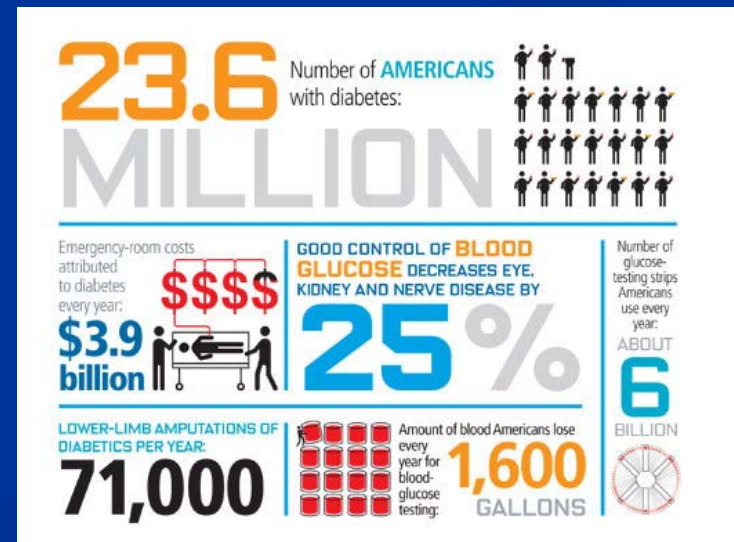
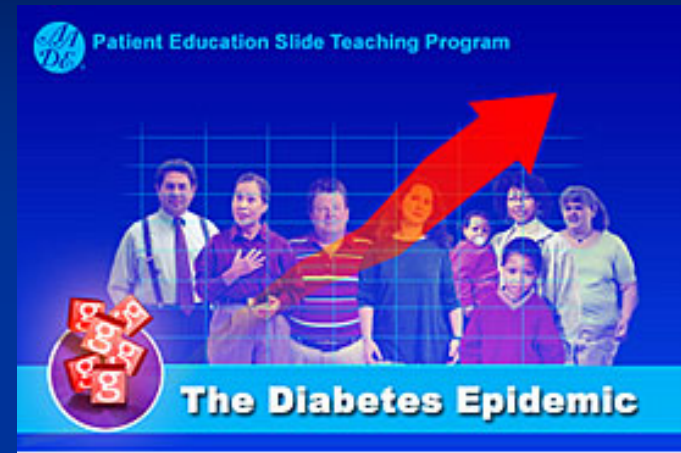
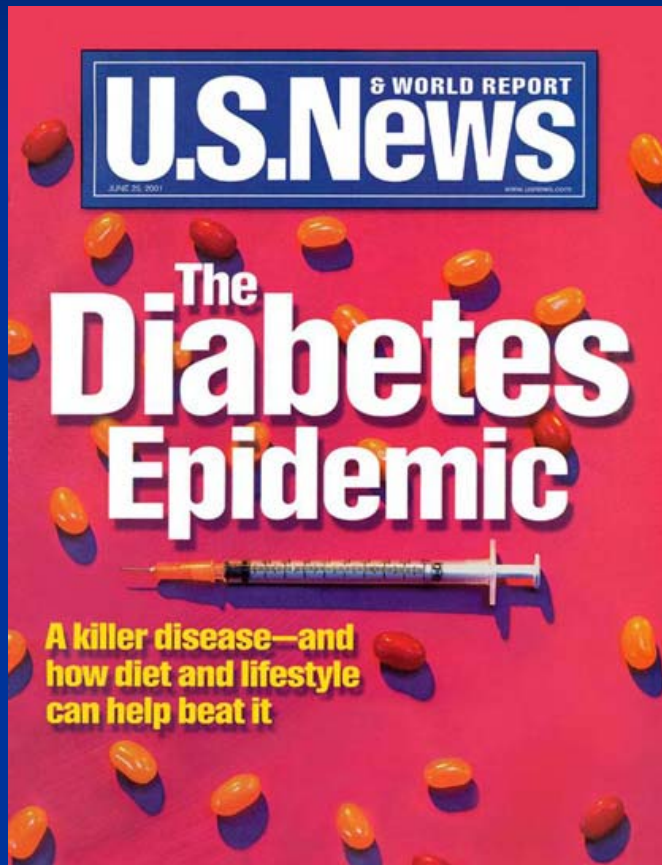


Metabolism increases structural similarity to thyroxine

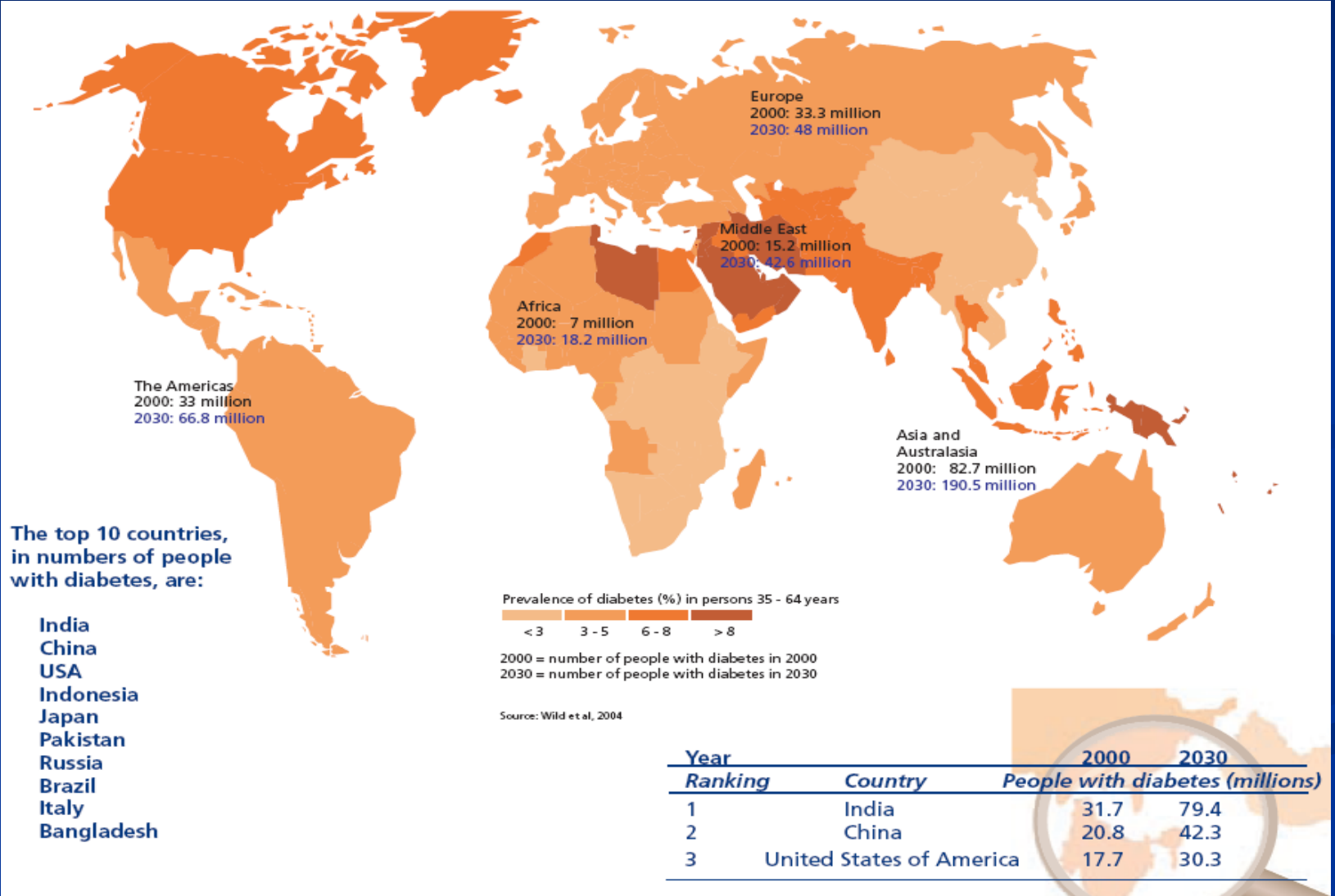


A World-wide Epidemic of Type 2 Diabetes

A role for Endocrine Disruptors?



Estimates of Diabetes Prevalence around the World



Comparison of Prevalence of Type 2 Diabetes

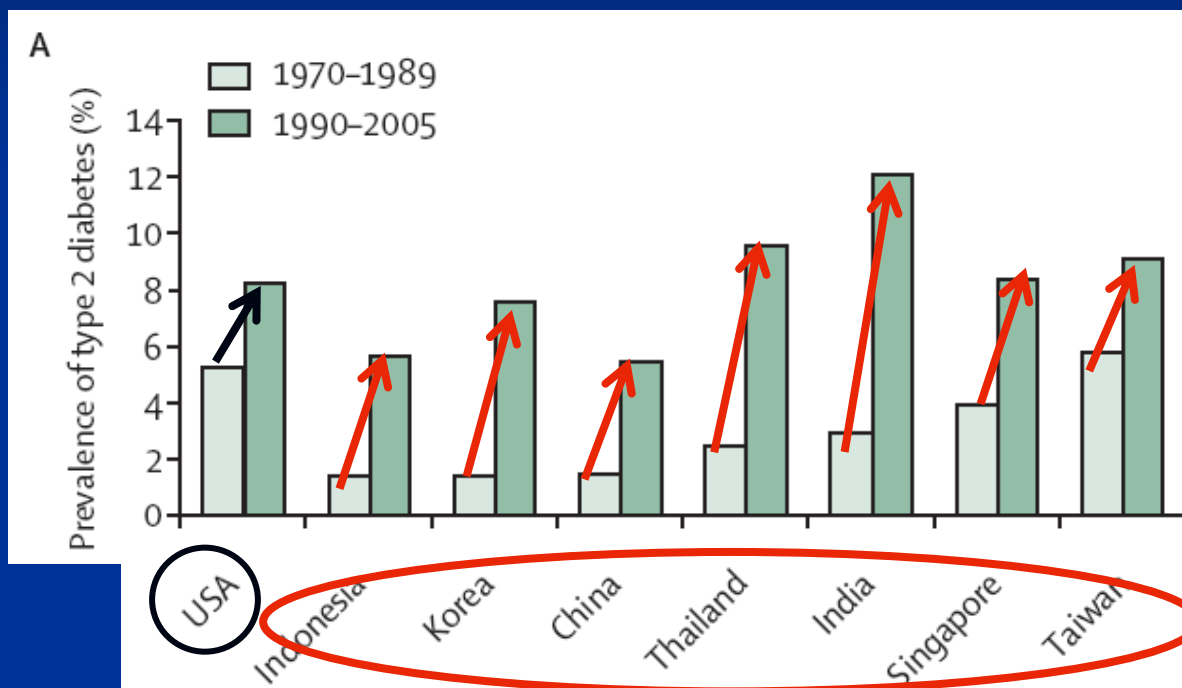


Figure 1: Comparison of prevalence rates of diabetes in selected countries between 1970-1989 and 1990-2005

Great Lakes Cohort Study



1. 1992-5: Fish Consumption Survey

2542 Habitual GL Fish Consumers

-Charter Boat Captains & Spouses
-WI Anglers

1664 Referents

-regionally matched to anglers
-eating <12 GL fish meals/year

PCBs, DDE, Dioxins on subgroup

520 donated blood sample

99 donated blood sample

Hormones and health survey on 255 participants with left over serum

2. 2001-3 Repeat Biomarker Study

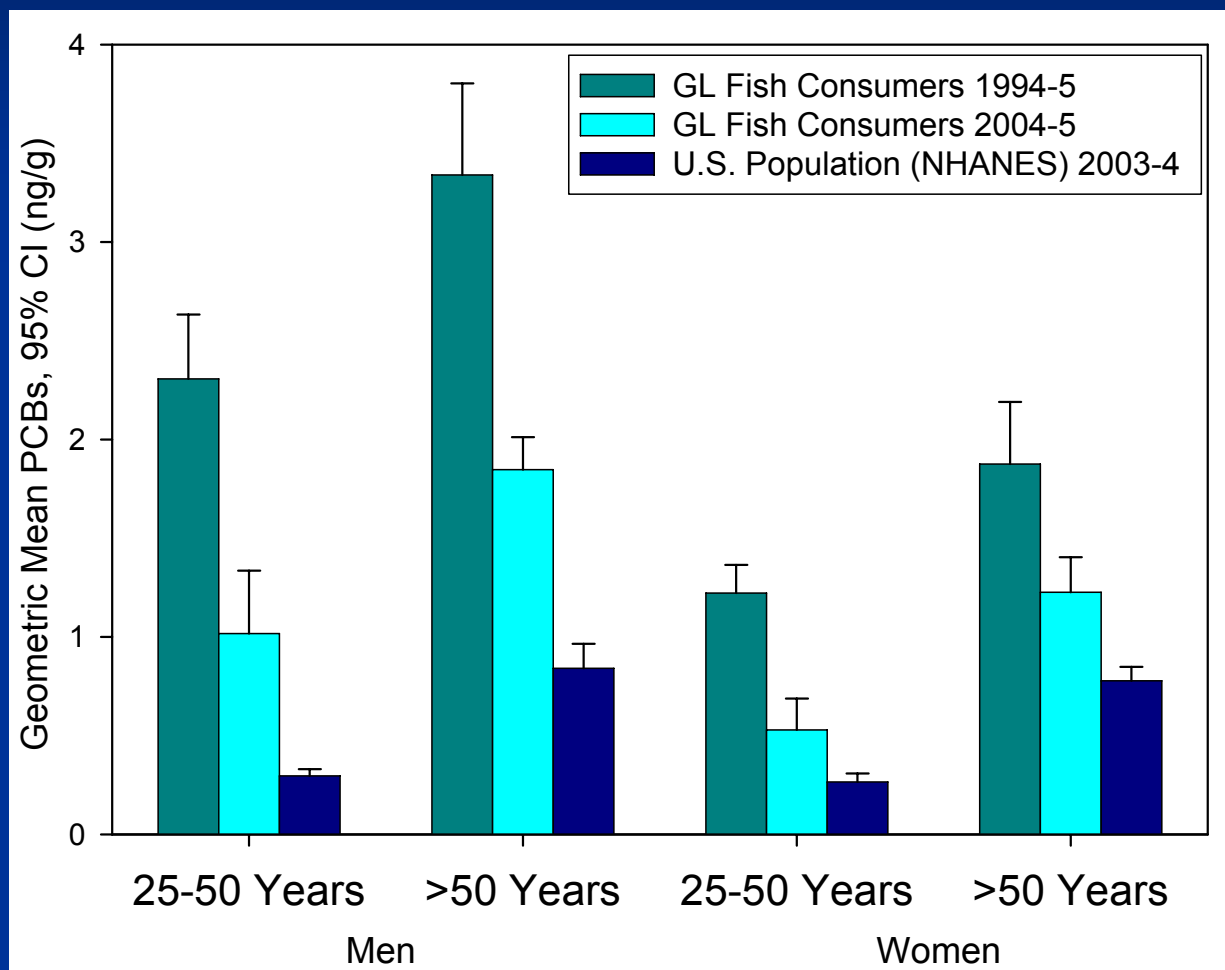
212 bloods and surveys: PCBs, DDE, PBDEs, health, fish consumption

3. 2004-5 Endocrine Disruptors Study

1788 surveys: health and fish consumption

526 bloods: PCBs, DDE, PBDEs, Hemoglobin A_{1c}, hormones

Cross Sectional PCB Exposures in Great Lakes Residents



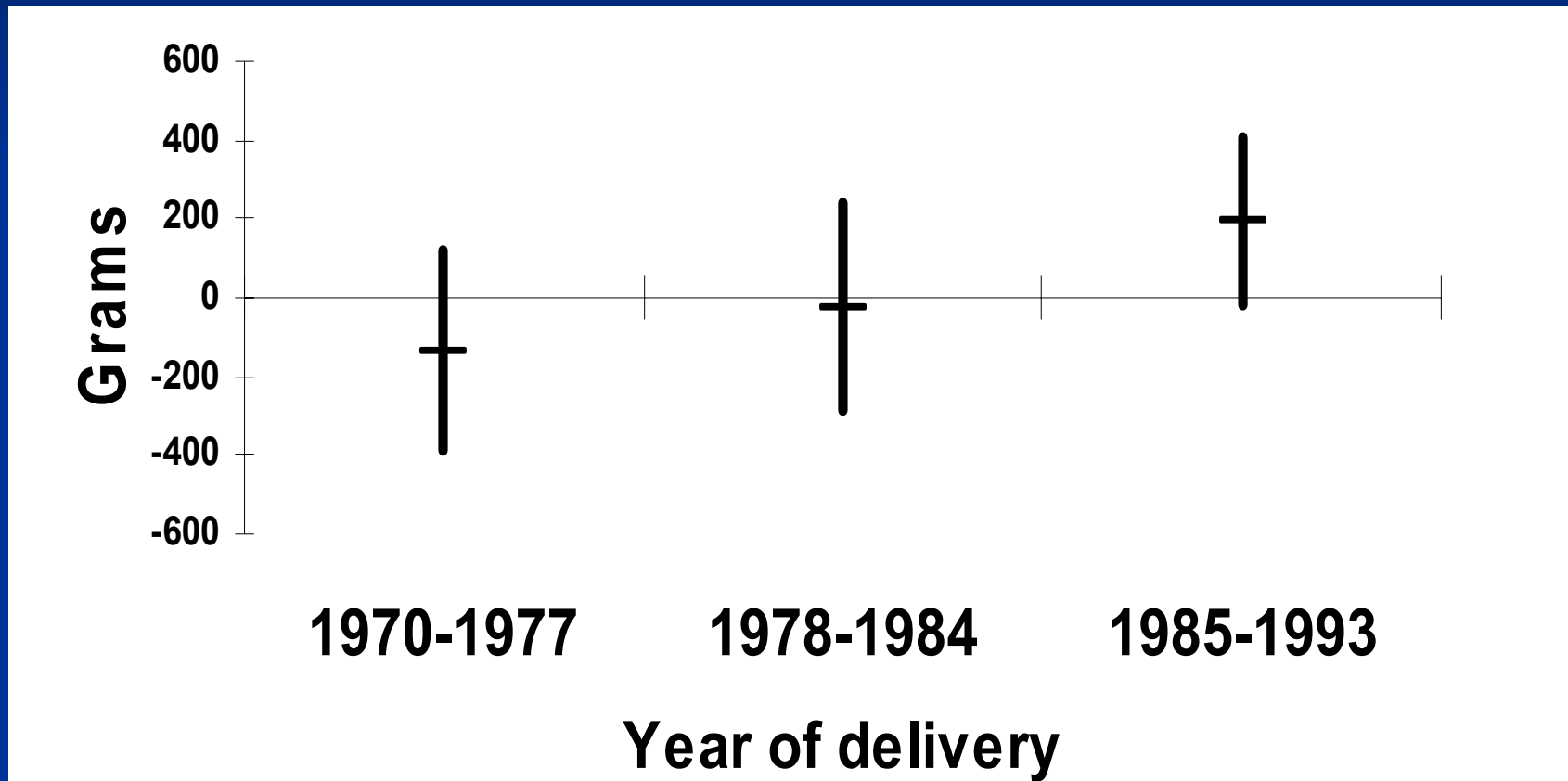
N=248 men and 189 women in 1994-1995 and 262 men and 107 women in 2004-2005
NHANES N=331 men and 330 women. Turyk et al, 2010

GL Cohort Health Outcomes



- Lower birth weights were associated with Great Lakes fish intake and higher DDE levels before pregnancy.
 - Weisskopf et al., Environ Res 97:149, 2005
- Steroid hormone alterations
 - PCBs associated with decreased sex-hormone binding globulin (SHBG)-bound testosterone in men
 - Persky et al., EHP 109:1275, 2001
 - PCBs and PBDE associated with decreased follicle stimulating hormone (FSH) in postmenopausal women
 - Anissa Lambertino, unpublished data
- Thyroid dysregulation
- Diabetes

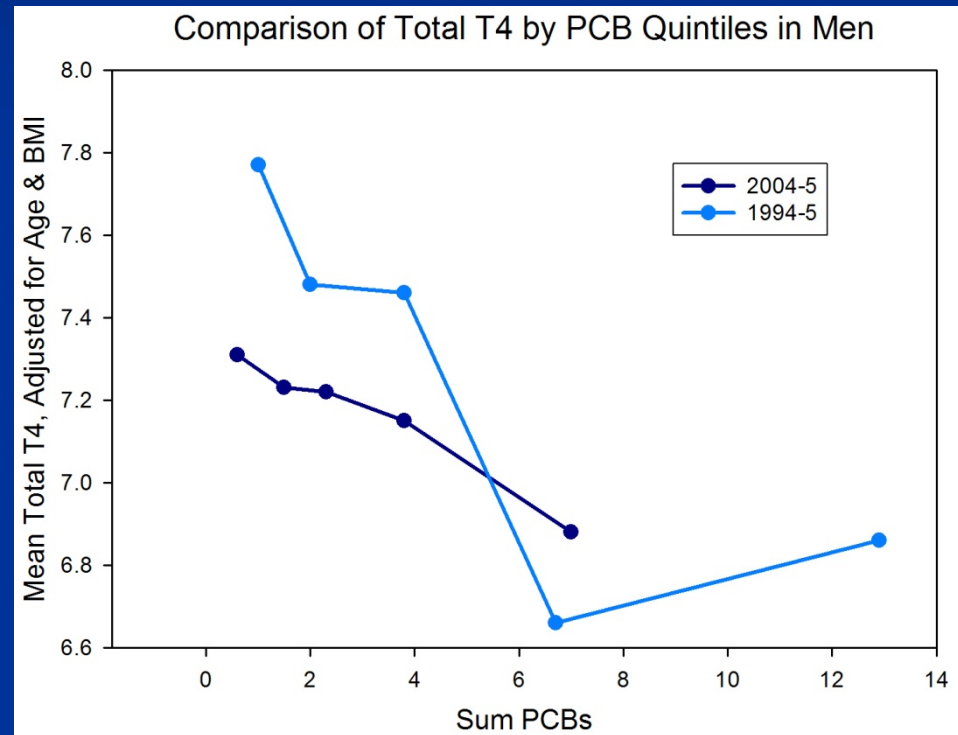
Adjusted Mean Differences in Birthweight High” vs None GLSCF Consumption, by Delivery Years



Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. Weisskopf MG, Anderson HA, Hanrahan LP, Kanarek M, Falk CM, Steenport DM, Draheim L and the Great Lakes Consortium

Cross Sectional Associations of PCBs and Thyroid Hormones in Males at Times 1 and 2

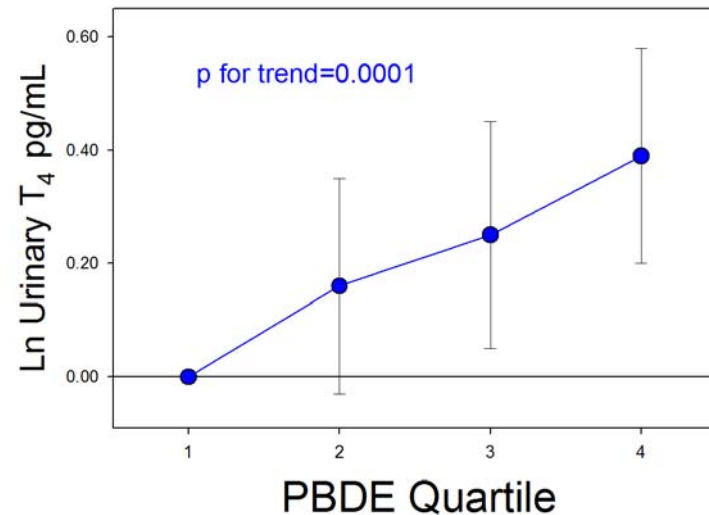
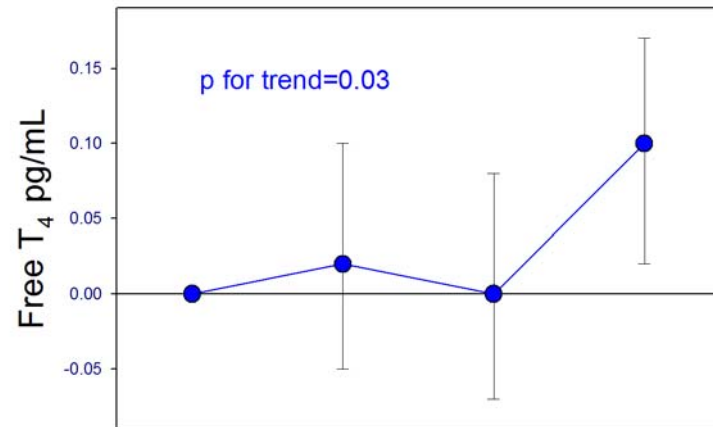
Hormone	Time 1	Time 2
N	178	304
Total T4	↓	↓ (BL)
Free T4	NS	↓
Total T3	NS	NS
TSH	NS	NS



**Different methodology: Free thyroxine index in 1994 and free T4 in 2004
 No significant associations of DDE with hormones at time 1 or 2

PBDEs and Thyroid Hormones in Men

- PBDEs were associated with higher levels of thyroxine (T_4), free T_4 , and urinary T_4 in 308 male fish consumers without thyroid disease



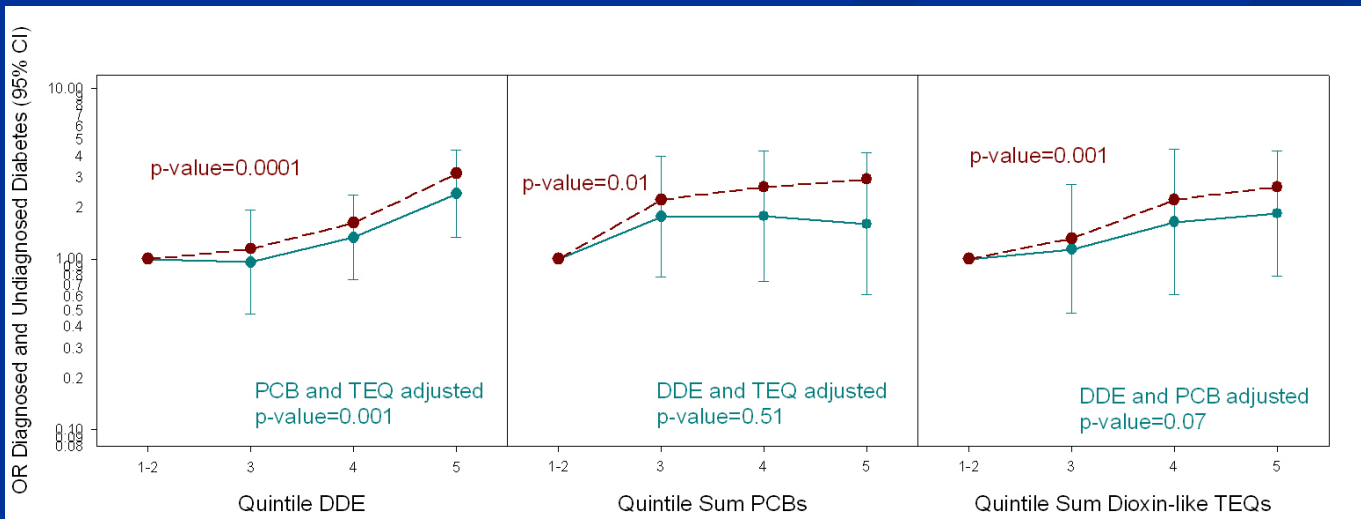
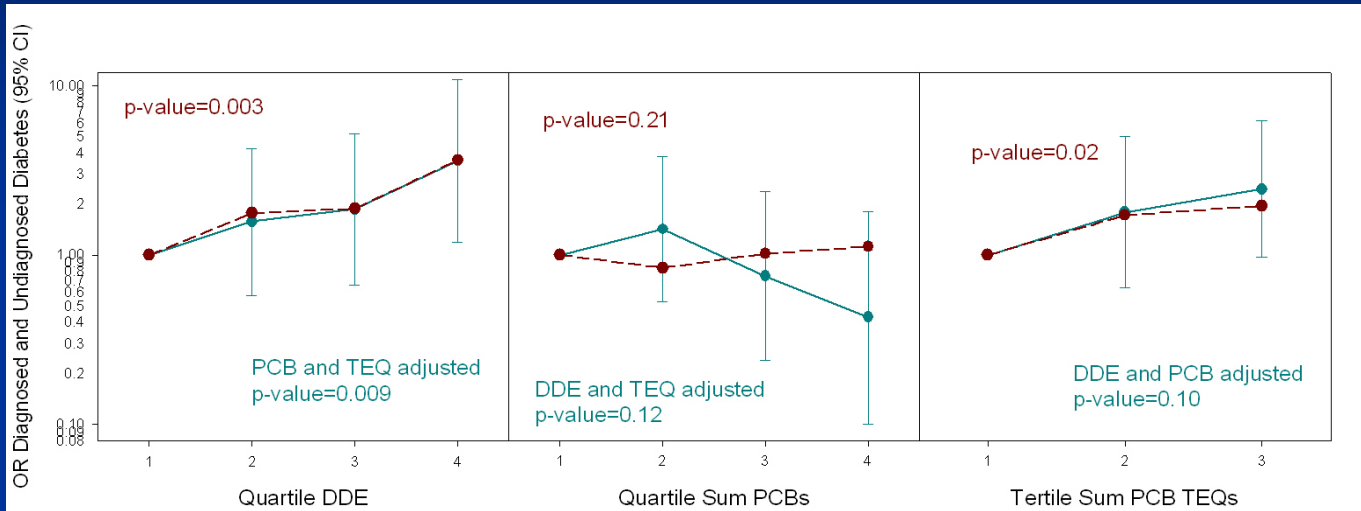
Type 2 Diabetes Risk Factors

- Age
- Gender
- Race/ethnicity (African American, Hispanic, Native American, Asian, Pacific Islander)
- Overweight, BMI ≥ 25 kg/m²
- Central adiposity
- Habitual physical inactivity
- Stress
- Family history/genetic markers

Past Studies of OCs and Diabetes

- Dioxin – high exposure -- mixed results
 - Occupational exposures—herbicides—only TCDD measured
 - Seveso, Italy
- Dioxin – low/moderate exposure – positive associations
 - Vietnam veterans – Operation Ranch Hand
- PCBs/DDE -- high exposure -- mixed results
 - Capacitor/electrical utility workers
 - Persky—LaSalle plant
 - Slovakia—environmental - ↑FG high pollution area, DDE, HCB
 - Pesticide applicators -- sum DDE+DDT
- PCBs/DDE/dioxin - low exposures - positive associations
 - Associations often found with more than one OC
 - Colinearity of measured exposures with real risk?

Diabetes in GL Cohort (top) and NHANES 1999-2003 (bottom)



Diabetes Incidence and DDE Exposure

DDE Tertile	Tertile Range (ng/g)	New cases	Person years	Incidence/ 1000 person years	Incidence Rate Ratio*		
					IRR	95% CI	P-value
1	<1.0-2.2	2	1325	1.5	1		
2	2.2-5.3	12	1336	9.0	5.4	1.2, 25.3	0.03
3	5.4-49.2	22	1286	17.1	8.8	1.8, 43.2	0.008
Linear trend over tertiles							0.006

*Adjusted for age, BMI, gender, PCBs and yr sport caught fish consumption

Remained significant with further adjustment for smoking and lipids assessed during follow up.

Similar trends for males and females. No interactions by exposure or BMI.

PBDEs and Diabetes in GL Cohort

- No association with PBDE exposure overall
- Having hypothyroid disease affected the association of PBDEs with diabetes
 - With hypothyroid disease, PBDEs associated with diabetes
 - OR=13.5 (95% CI=0.7, 251, p=0.08)
- DDE was significantly associated with diabetes in the cohort
 - PBDE exposure modified the association of DDE with diabetes
 - The strongest risk of diabetes was in fish consumers with higher levels of both PBDEs and DDE

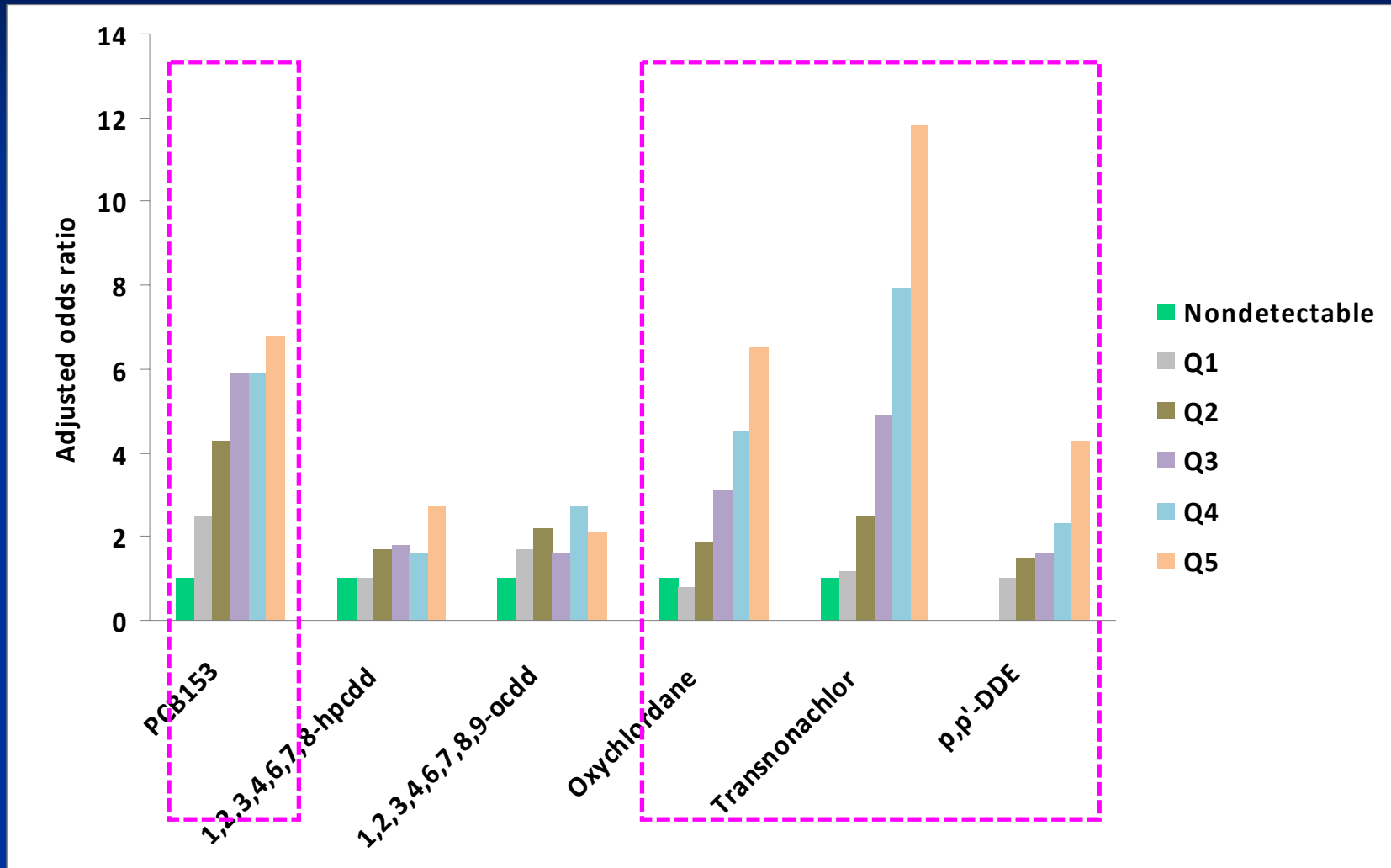
NHANES 1999-2002: Measurement of 50 POPs in the U.S. General Population

- Polychlorinated Dibenzo-p-dioxins (PCDDs)
- Polychlorinated Dibenzofurans (PCDFs)
- Dioxin-like PCBs
- Non-dioxin-like PCBs
- Organochlorine Pesticides

6 POPs were detected among $\geq 80\%$ of subjects

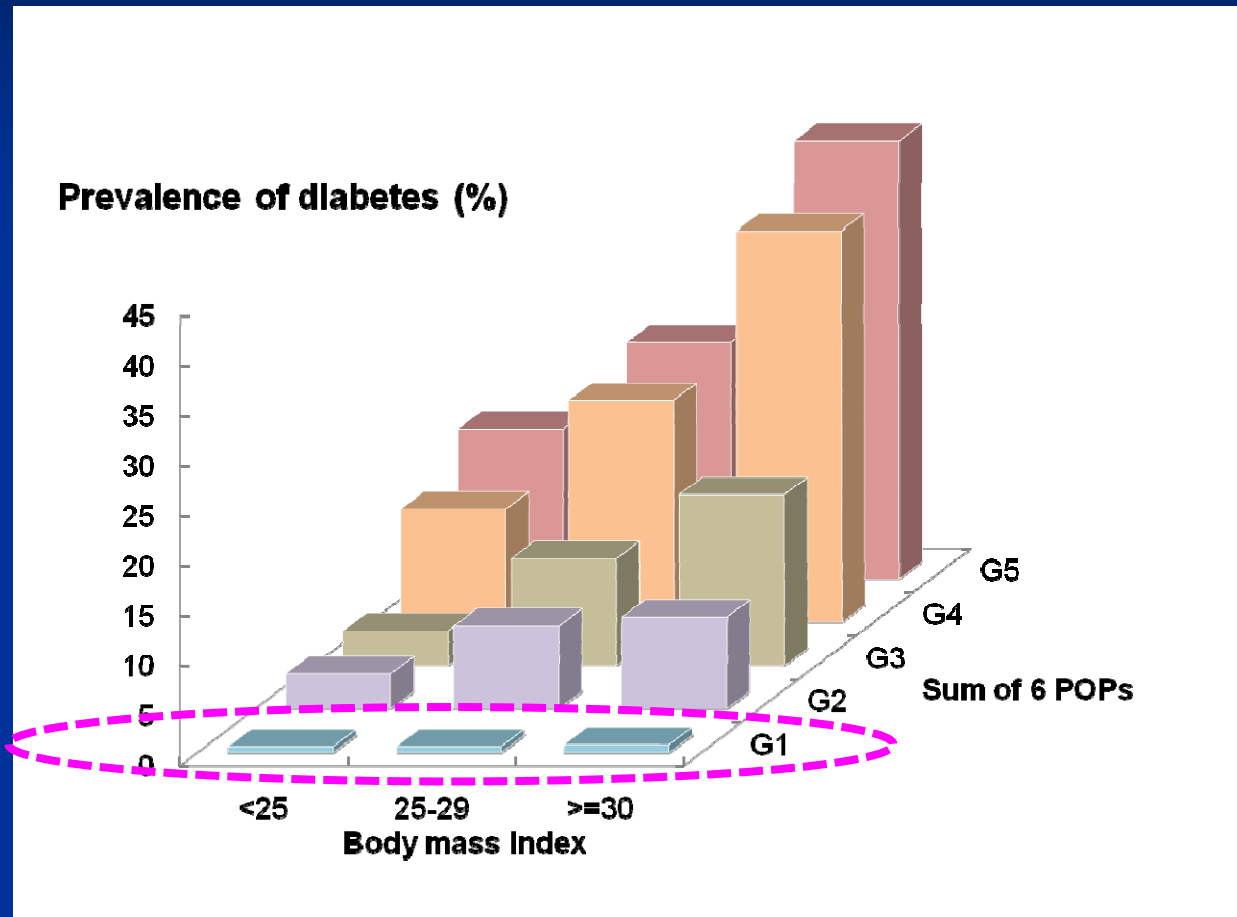
- 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153)
- 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin
- 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin
- oxychlordan
- p,p'-DDE
- trans-nonachlor

NHANES Associations Between POPs and Diabetes



† Adjusted for age, race, sex, poverty income ratio, body mass index, and waist circumference

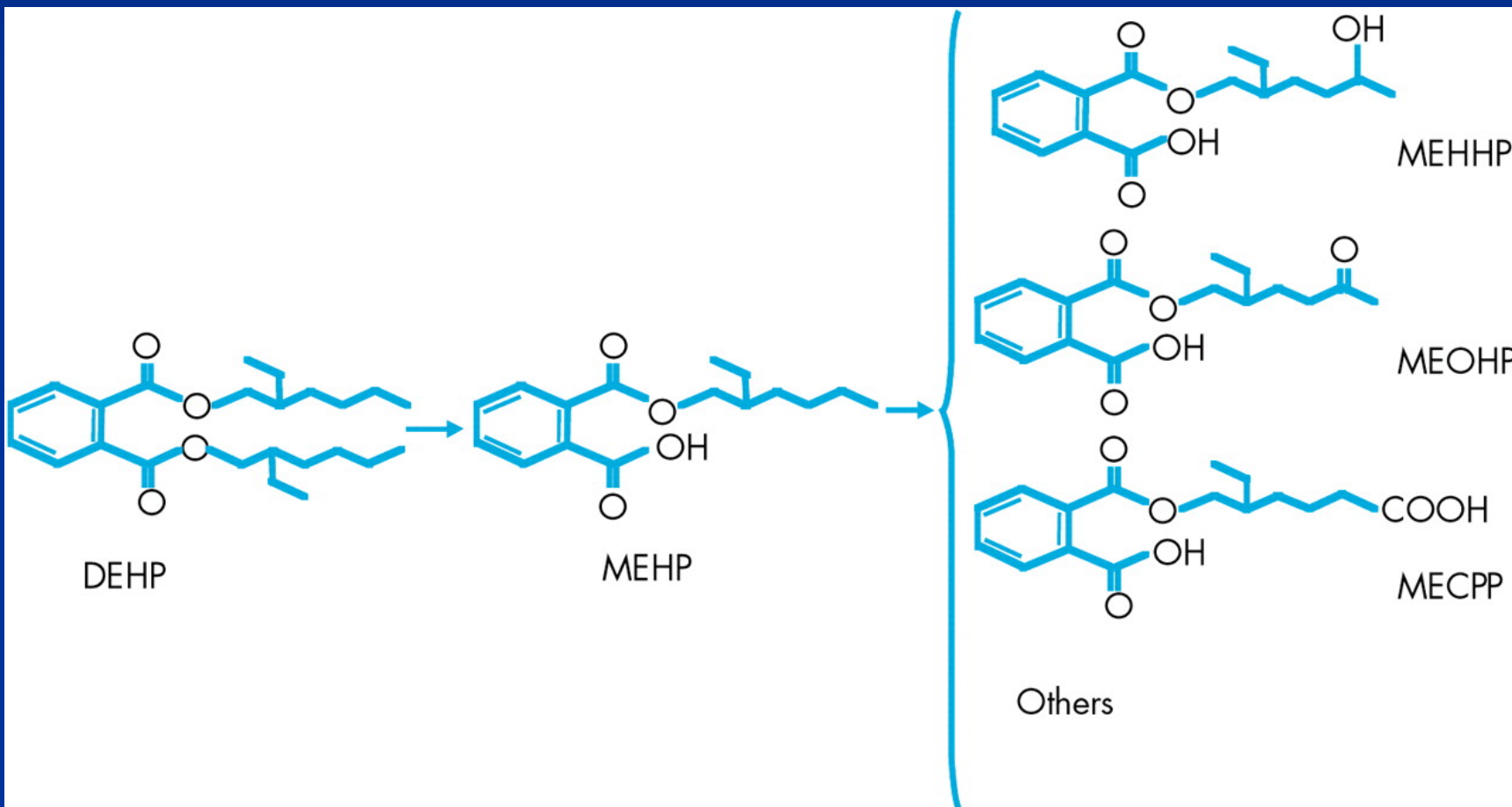
Interaction Between POPs and Obesity on the Risk of Diabetes



† Adjusted for age, race, sex, poverty income ratio, body mass index, and waist circumference



Phthalate esters



NHANES Biomonitoring Results for Phthalate Metabolites 1999 - 2002

Phthalate Metabolites tested

MBP - mono-butyl phthalates

MEP - mono-ethyl phthalate

MEHP - mono-(2-ethyl) -hexyl phthalate

MBzP - mono-benzyl phthalate

MEHHP - mono-(2-ethyl-5-hydroxyhexyl) phthalate

MEOHP - mono-(2-ethyl-5-oxohexyl) phthalate

For all phthalate metabolites except MEHP > 95% of subjects were at \geq LOD for MEHP, 80% of subjects were \geq LOD

NHANES Urinary Phthalate Metabolites: Obesity and Insulin Resistance

Medscape®

www.medscape.com

Outcome	Crude analysis		Adjusted model 1 ^a		Adjusted model 2 ^b	
	β (SE)	p-Value	β (SE)	p-Value	β (SE)	p-Value
Waist circumference						
1999–2002 (n = 1,451 crude, 1,292 adjusted)						
MBP	1.39 (0.51)	0.011	0.98 (0.50)	0.059	0.79 (0.47)	0.106
MBzP	1.18 (0.47)	0.017	1.29 (0.34)	0.001	1.09 (0.36)	0.005
MEHP	0.24 (0.40)	0.550	0.62 (0.44)	0.170	0.53 (0.42)	0.217
MEP	0.95 (0.32)	0.005	0.77 (0.29)	0.013	0.66 (0.31)	0.041
2001–2002 (n = 781 crude, 696 adjusted)						
MEHHP	1.82 (0.58)	0.007	1.71 (0.56)	0.008	1.65 (0.50)	0.005
MEOHP	2.00 (0.63)	0.006	1.81 (0.60)	0.009	1.79 (0.55)	0.005
HOMA (ln)						
1999–2002 (n = 651 crude, 622 adjusted)						
MBP	0.061 (0.024)	0.016	0.064 (0.024)	0.011	0.043 (0.023)	0.081
MBzP	0.059 (0.027)	0.037	0.079 (0.023)	0.002	0.061 (0.022)	0.009
MEHP	0.035 (0.023)	0.143	0.031 (0.025)	0.225	0.016 (0.024)	0.526
MEP	0.067 (0.021)	0.004	0.056 (0.020)	0.008	0.044 (0.021)	0.045
2001–2002 (n = 344 crude, 327 adjusted)						
MEHHP	0.054 (0.029)	0.078	0.055 (0.028)	0.064	0.038 (0.023)	0.126
MEOHP	0.066 (0.031)	0.052	0.060 (0.032)	0.076	0.044 (0.027)	0.125

^aAdjusted for age, age², race/ethnicity, total fat and calorie intake, physical activity level, smoking exposure, and urine creatinine. ^bAdjusted for model 1 covariates plus GFR, ALT, and GGT.

Workers are exposed to industrial chemicals as well as being simultaneously exposed to a mixture of various low dose POPs and other chemicals from diet and the environment.

Study of interactive effects a priority

Study Partners/Funding

- **Henry A. Anderson, Pamela Imm and Lynda Knobeloch**
 - Wisconsin Department of Health and Family Services
- **Victoria Persky, Sally Freels, Anissa Lambertino, and Yi Li**
 - University of Illinois-Chicago
- **Robert Chatterton, Jr.**
 - Northwestern University
- Wisconsin State Laboratory of Hygiene
- Michigan Department of Community Health
- University of Wisconsin-Madison, Survey Research Center
- The Great Lakes Consortium
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**Thank
you!**

