Persistent Organic Pollutants: Metabolic Effects and Interventions to Reduce Body Burdens

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Aims

1. Overview of metabolic disturbances associated with POPs exposures

2. Overview of existing interventions aimed at enhancing the excretion of POPs

Discussion

- Continuation of POPs biomonitoring
- Beyond regulation: Public health messages to reduce body burdens of POPs

Persistent Organic Pollutants (POPs)

Organochlorine pesticides
PBDEs (flame retardants)
PCBs

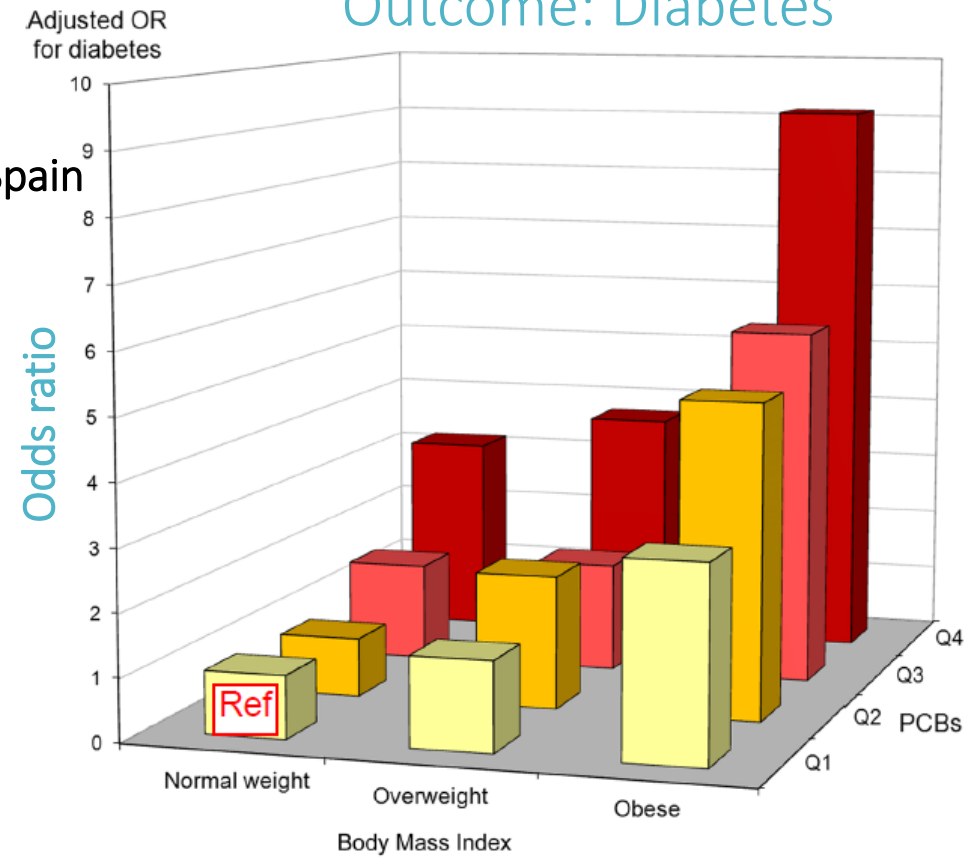
Chemicals resistant to environmental degradation

Half-lives in human tissues
- PCB-52: 2.6y
- PCB-153: 14.4y
- PCB-170: 15.5y

POPs and Diabetes

Outcome: Diabetes

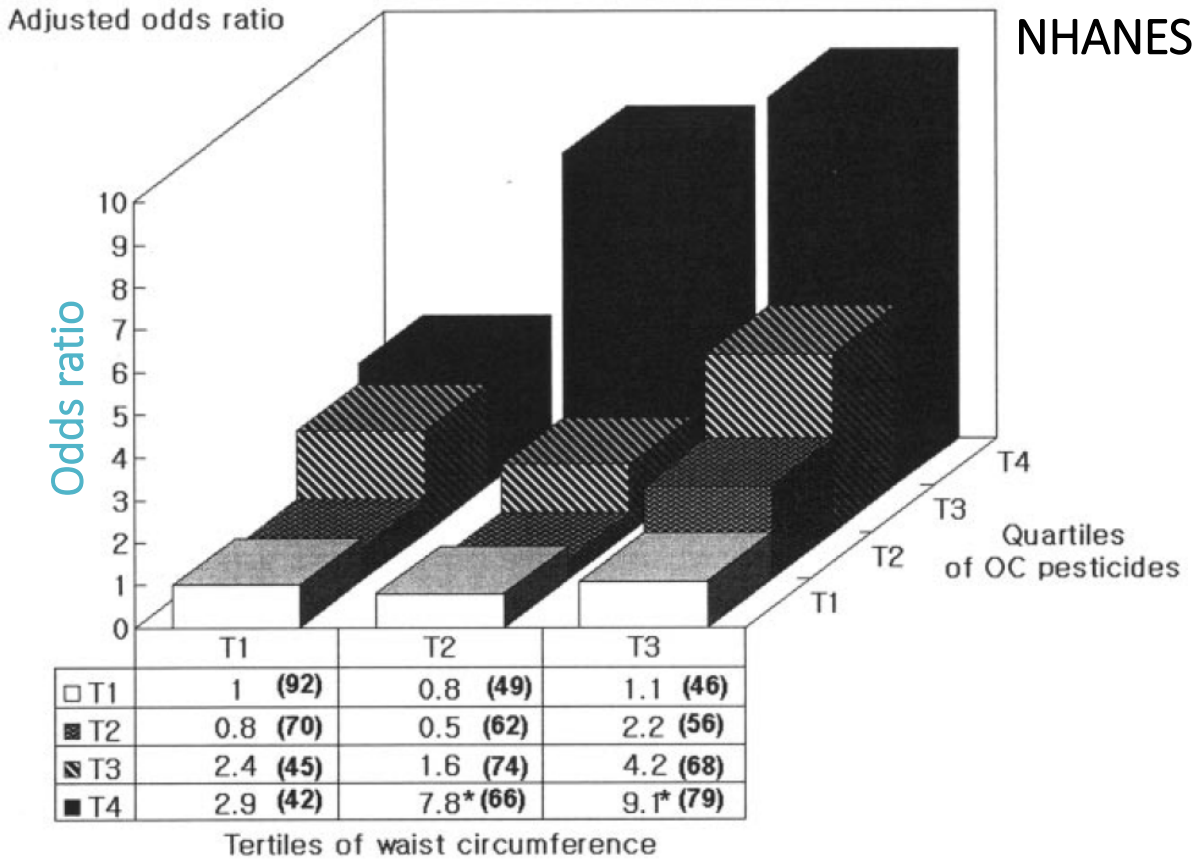
Catalunya, Spain
N=866



Gasul, Env Sci & Tech 2012

Outcome: Insulin Resistance

NHANES



	T1	T2	T3
□ T1	1 (92)	0.8 (49)	1.1 (46)
▩ T2	0.8 (70)	0.5 (62)	2.2 (56)
▨ T3	2.4 (45)	1.6 (74)	4.2 (68)
■ T4	2.9 (42)	7.8* (66)	9.1* (79)

Tertiles of waist circumference

Lee, 2010

POPs are endocrine disruptors associated with Type 2 diabetes, hypertension, cardiovascular disease, thyroid hormone alterations

PIVUS study: 70-year-olds in Sweden. 5-year follow-up, n=725

- Participants with the highest levels of POPs at 70y (upper 60th percentile) had 7-8x the risk of developing diabetes by 75y
- PCBs and organochlorine pesticides:
  - Positive associations with
    - Total cholesterol
    - LDL-c
  - Weak or no associations with HDL-c

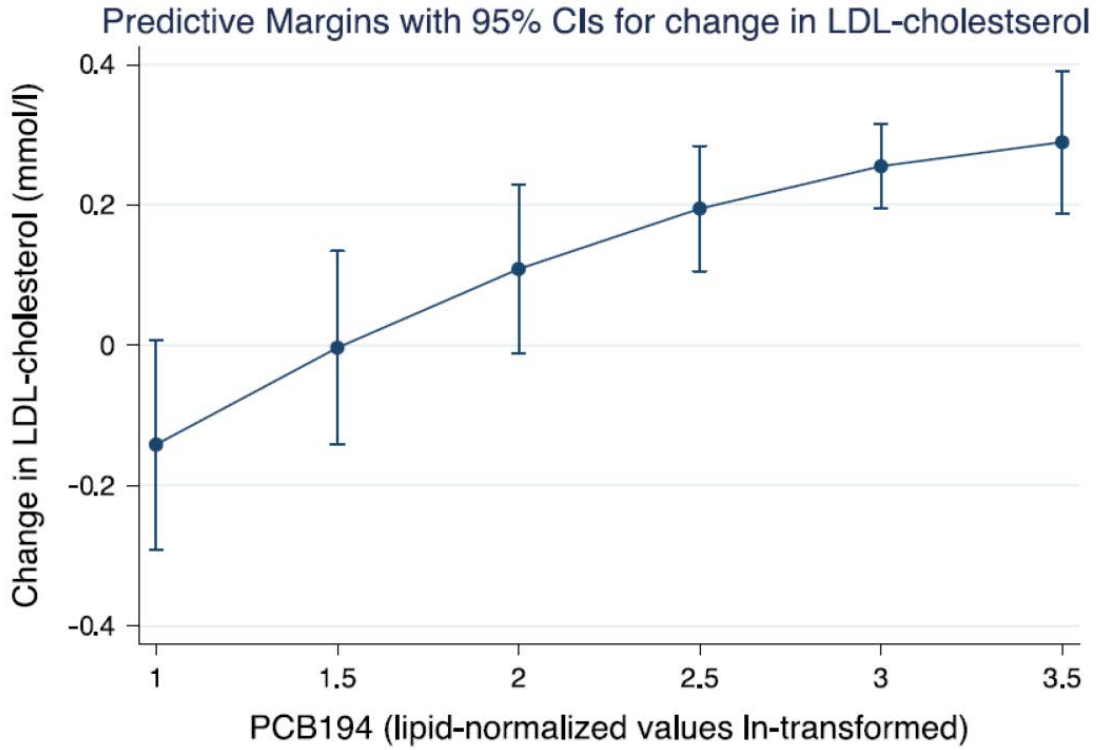


Fig. 1. Relationship between PCB 194 levels (lipid-normalized (ng/g lipid) and ln-transformed) and the change in LDL-cholesterol between age 70 and 75 years using predictive margins with 95% CI intervals ($p=8.1 \times 10^{-10}$).

Sources: Lee, Diabetes Care 2011

Penell, Environmental Research 2014

Nested Case-Control study within the CARDIA study

Participant ages: 18-30 years of age in 1985–1986 (year 0) - 50% black, 50% white

Locations: Minneapolis, Oakland, Chicago, Birmingham (USA)

90 CASES: diabetic by Year 20

Type-2 diabetes: glucose lowering medication use or fasting glucose ≥126mg/dl at ≥2 exams

90 CONTROLS: non-diabetics at Year 20

Fasting glucose <100mg/dl during all follow-up exams

Frequency matched to controls on BMI at Y0

Follow-up years: 2, 5, 7, 10, 15, 20 and 25

CARDIA

Coronary Artery Risk Development in Young Adults

Exposure and outcome measures

Exposure: POPs in serum obtained in 1987-88 (CARDIA Year 2)

- 55 POPs measured: 9 organochlorine pesticides, 35 PCBs, 10 PBDEs, and 1 PBB
  (Measured at the CDC Laboratories using GC/MS)
- Included in study: POPs with >75% detectability (32 POPs)
  8 organochlorine pesticides, 23 PCBs, and 1 PBB
- Concentrations of POPs in CARDIA (1987-88) were 3-5x higher than similar aged people in NHANES (2003-04)

Outcomes: Glucose and lipid metabolism markers (years 2, 7, 10, 15, 20, 25)

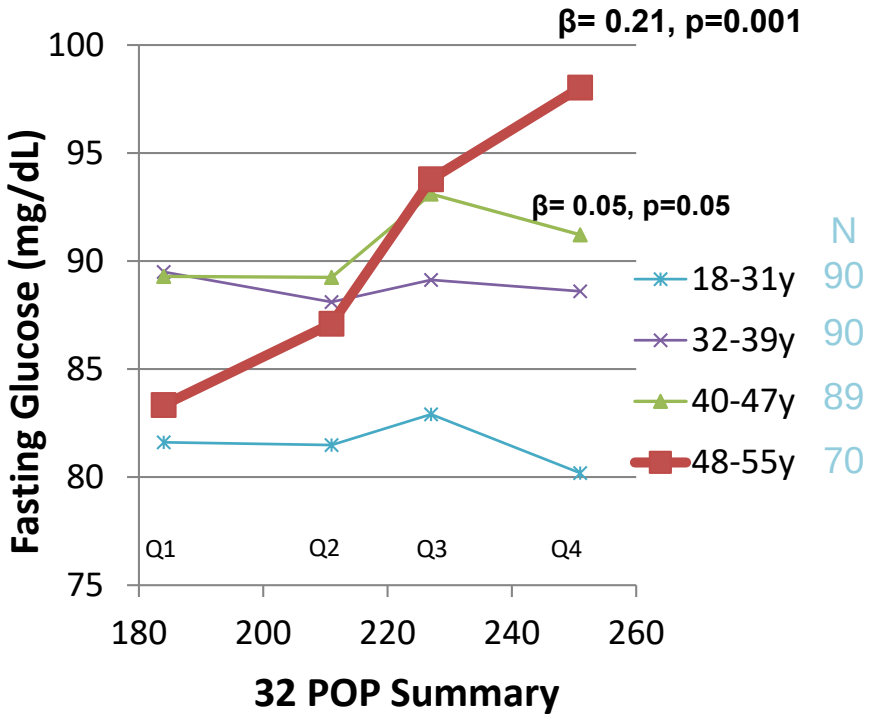
POPs and glucose regulation

23-year follow-up

32 POP Summary and Fasting Glucose (mg/dl)

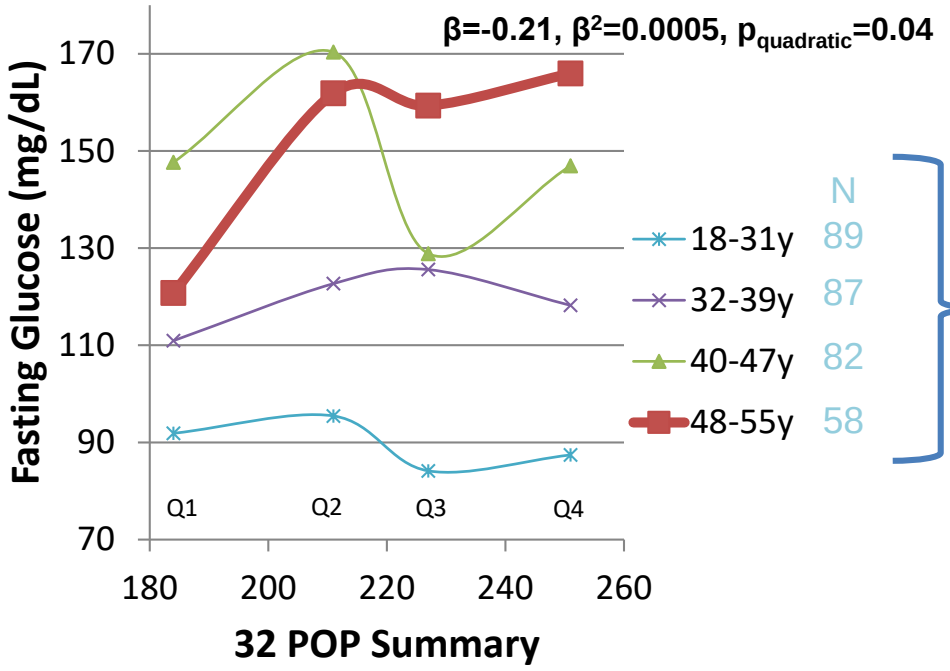
Summary score: Σ ($logPOP_{individual}$ / $logPOP$ std. $deviation_{group}$)

No Diabetes



Age Interaction: p= 0.001

Diabetes



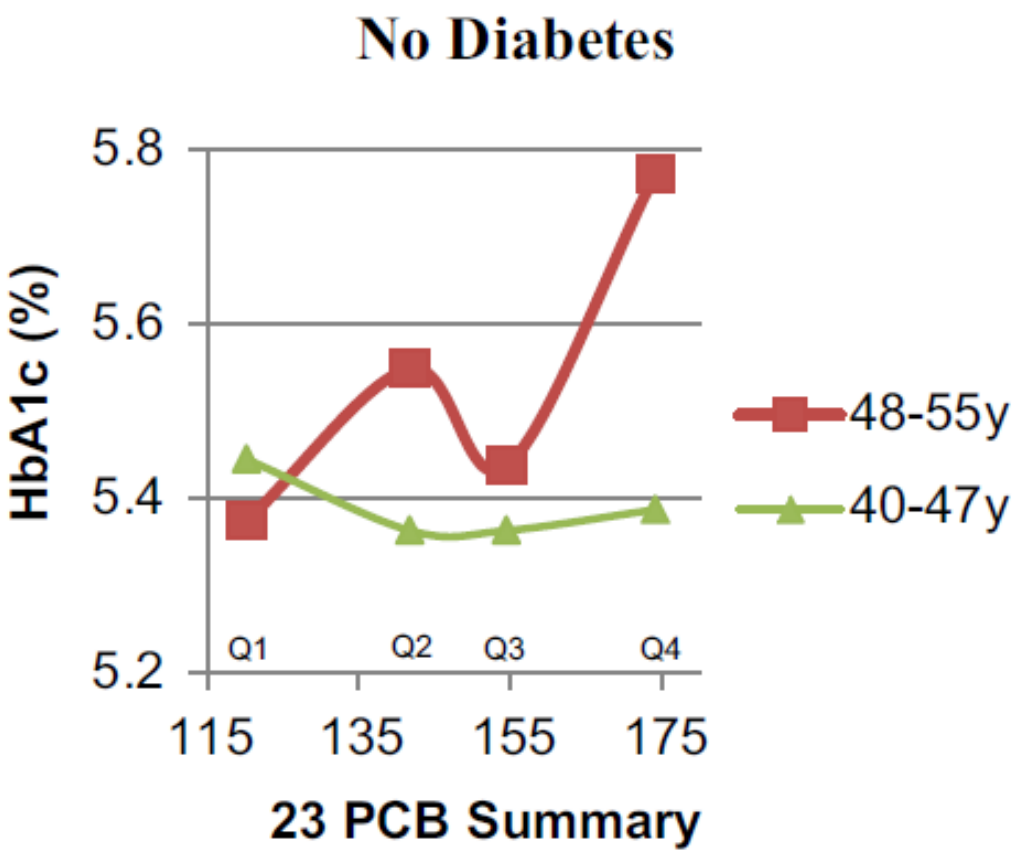
Same participants at different ages

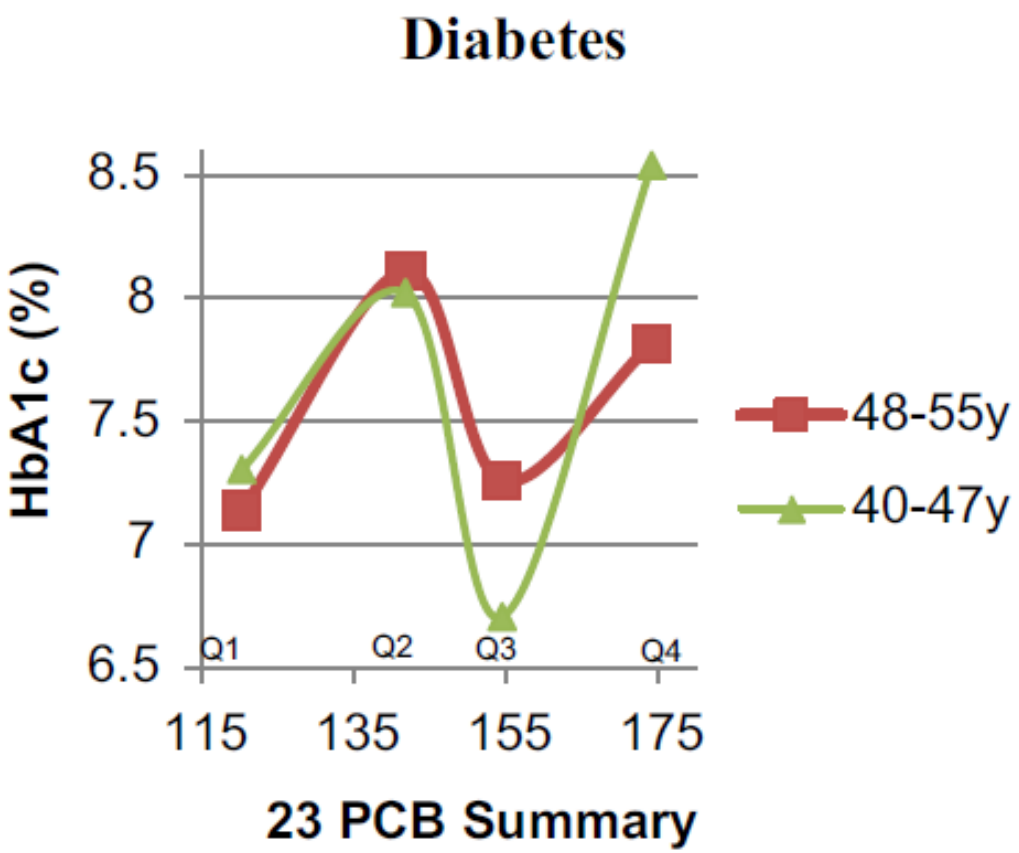
Age Interaction: p= 0.004

Adjustments: race, sex, exam center, exam period and concurrent BMI

Suarez-Lopez JR, Environmental Research 2015

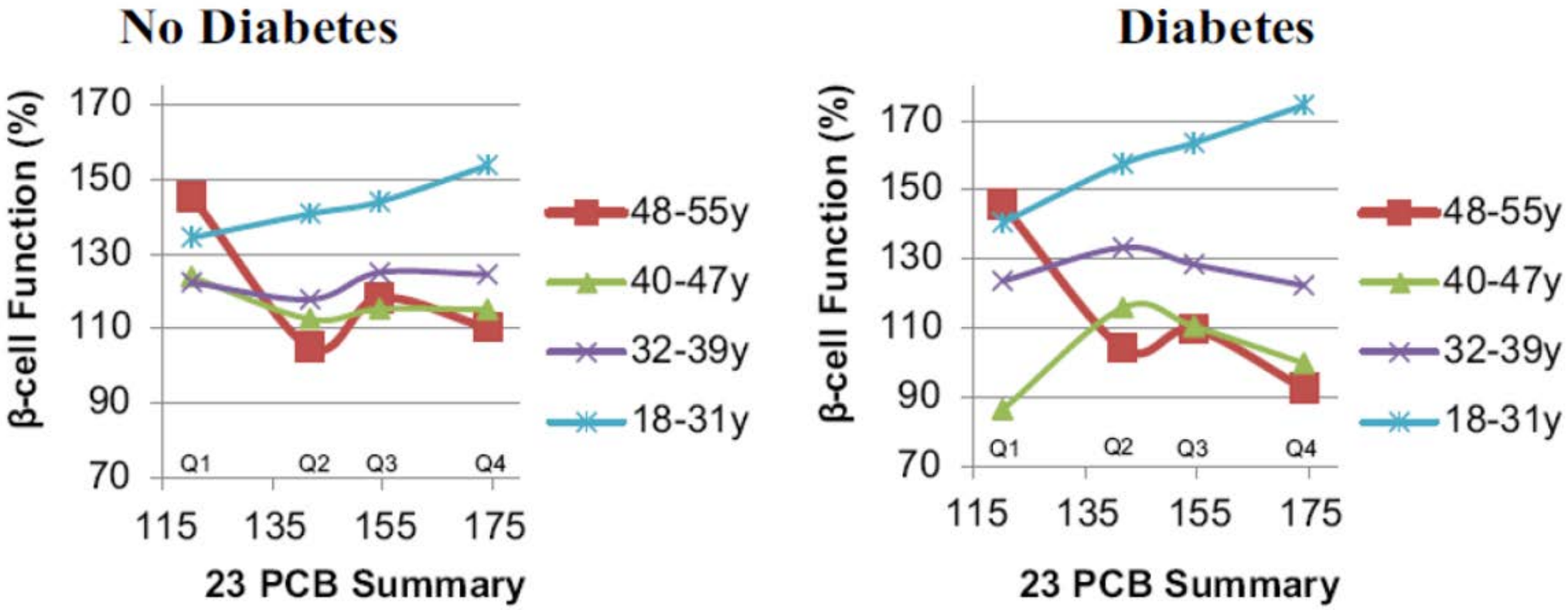
PCBs and hemoglobin A1c%





Suarez-Lopez JR, Environmental Research 2015

PCBs and β-cell function



Suarez-Lopez JR, Environmental Research 2015

POPs in young adulthood

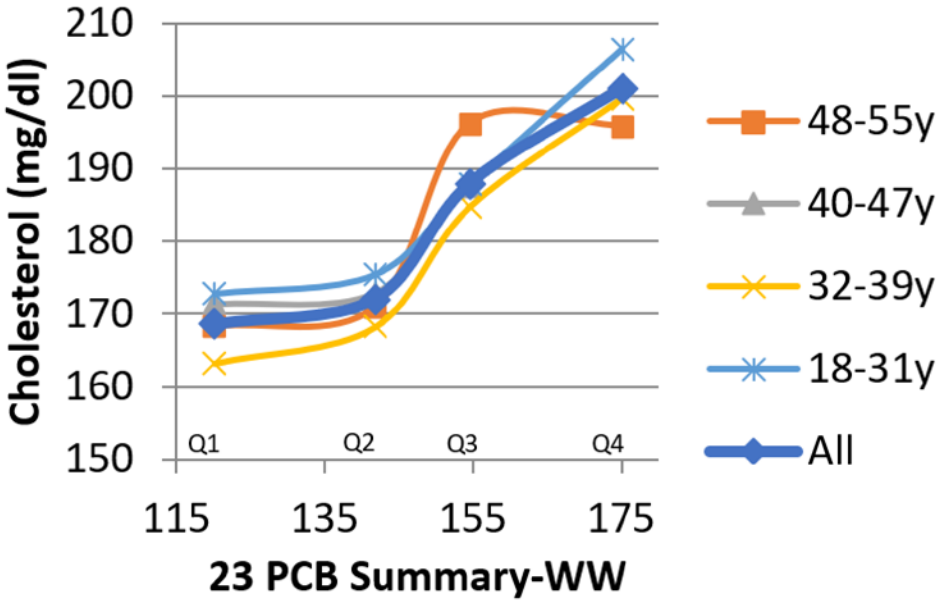
Associated with alterations in glucose metabolism when participants reached the 5th decade of life

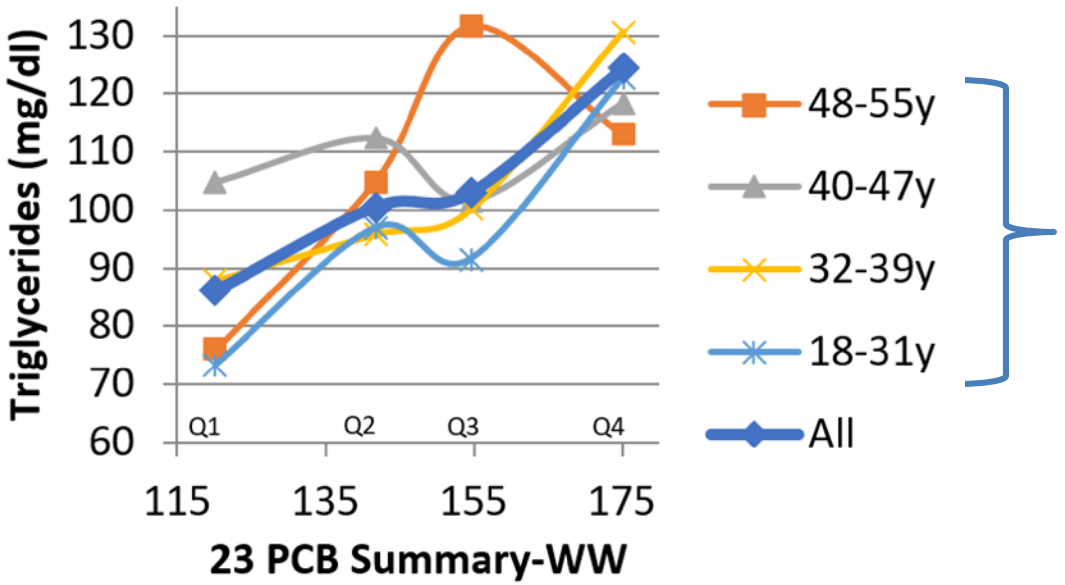
- Positive associations: fasting glucose, HbA1c% levels
- Inverse associations: β-cell function and insulin sensitivity (HOMA-2)
- No associations with BMI

POPs and blood lipids

23-year follow-up

Figure. Longitudinal associations of PCB summary scores (year 2) and blood lipids (years 2 - 25). Excludes participants using lipid-lowering medication at blood draw.





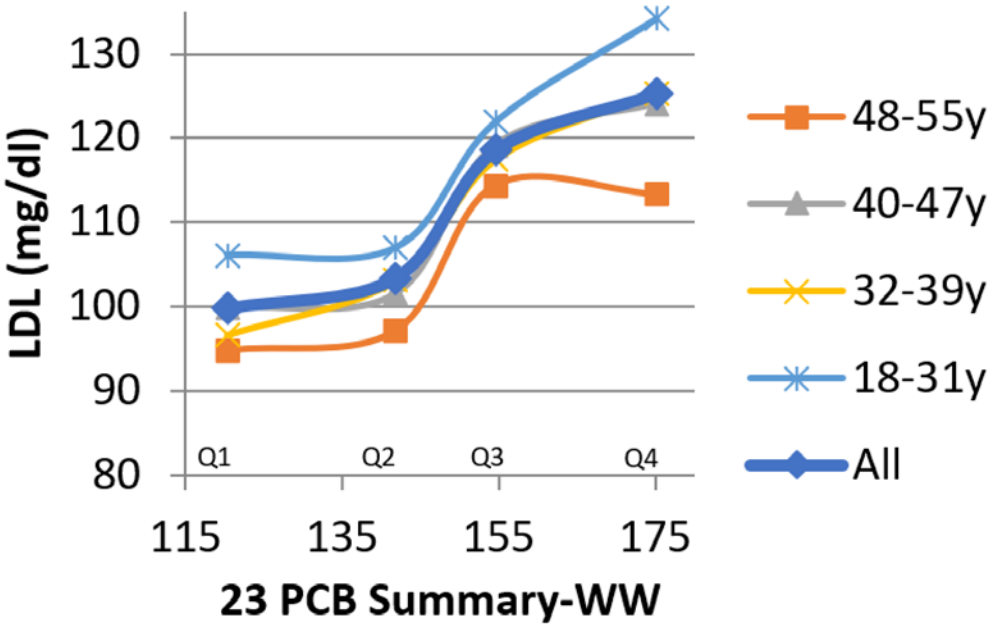
Same participants at different ages

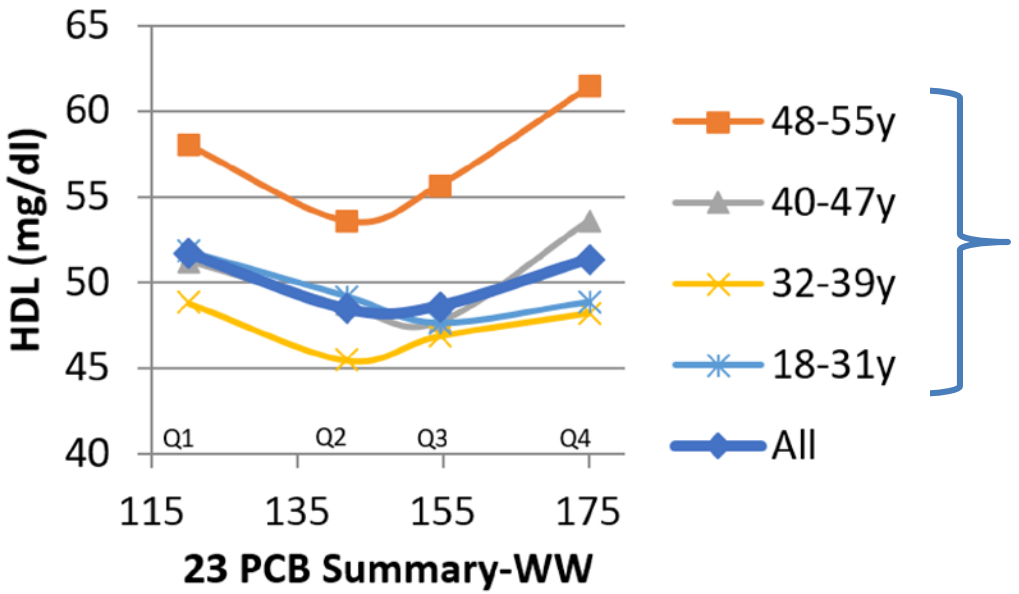
No interaction by age at blood draw or diabetes status

Adjusted for age, race, gender, concurrent BMI, exam center, exam year, diabetes and smoking status.

Suarez-Lopez JR, Environmental Toxicology and Pharmacology, 2019

Figure. Longitudinal associations of PCB summary scores (year 2) and blood lipids (years 2 - 25). Excludes participants using lipid-lowering medication at blood draw.





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Suarez-Lopez JR, Environmental Toxicology and Pharmacology, 2019

POPs in young adulthood

- PCBs were positively associated with alterations in blood lipids up to 23 years later, using both wet-weight and lipid-standardized concentrations
    - *total cholesterol, triglycerides, LDLs, oxidized LDLs and cholesterol-HDL ratio*
- Associations stronger among participants with higher BMI
- Associations did not vary as participants aged
- Organochlorine pesticides (OCPs) probably not associated with lipid changes
    - *Associations were only observed using the wet-weight score*

Interventions to Reduce Body Burdens of POPs

Currently there is no standard regime to eliminate POPs from the body

Pilot studies: Bile acid resins and POPs

- Cholestyramine treatment for 48-72hrs
  - Increase fecal excretion of chlordecone (organochlorine pesticide) by 7x
  - Output of chlordecone was 10-20x greater in bile than in feces
    - Suggests that chlordecone is reabsorbed in intestine

Source: Cohn, NEJM 1978

Before and after 6m treatment with colestimide on serum Dioxins and PCBs

Table 1 Blood level of dioxins before and after the treatment in nine subjects

Dioxins (pg-TEQ/g-fat)			
	Before Treatment	6month Treatment	Reducation Raete
1	50	40	20%
2	19	21	−11%
3	43	36	16%
4	57	35	39%
5	20	17	15%
6	40	31	23%
7	100	74	26%
8	40	32	20%
9	27	26	4%
mean	44	35	17%
SD	25	16	14%

Table 2 Blood level of PCBs before and after the treatment in nine subjects

PCBs (ng/g-fat)			
	Before Treatment	6month Treatment	Reducation Raete
1	240	190	21%
2	110	130	−18%
3	190	190	0%
4	360	200	44%
5	73	63	14%
6	260	230	12%
7	580	430	26%
8	360	280	22%
9	130	120	8%
mean	256	204	14%
SD	159	106	18%

Mochida, Fukuoka Acta Med., 2007 (review)
Sakurai, Internal Medicine 2004 and 2006

Total PCB reduction between Standard Pringles vs Olestra Pringles for 1 year

- Location: Anniston, AL - PCB manufacturing for 40 years
- Mean age: 60y
- 62% female
- BMI: 33
- Anniston, AL: >50th %tile of PCBs of NHANES 2005-2007

➨ **Intervention**

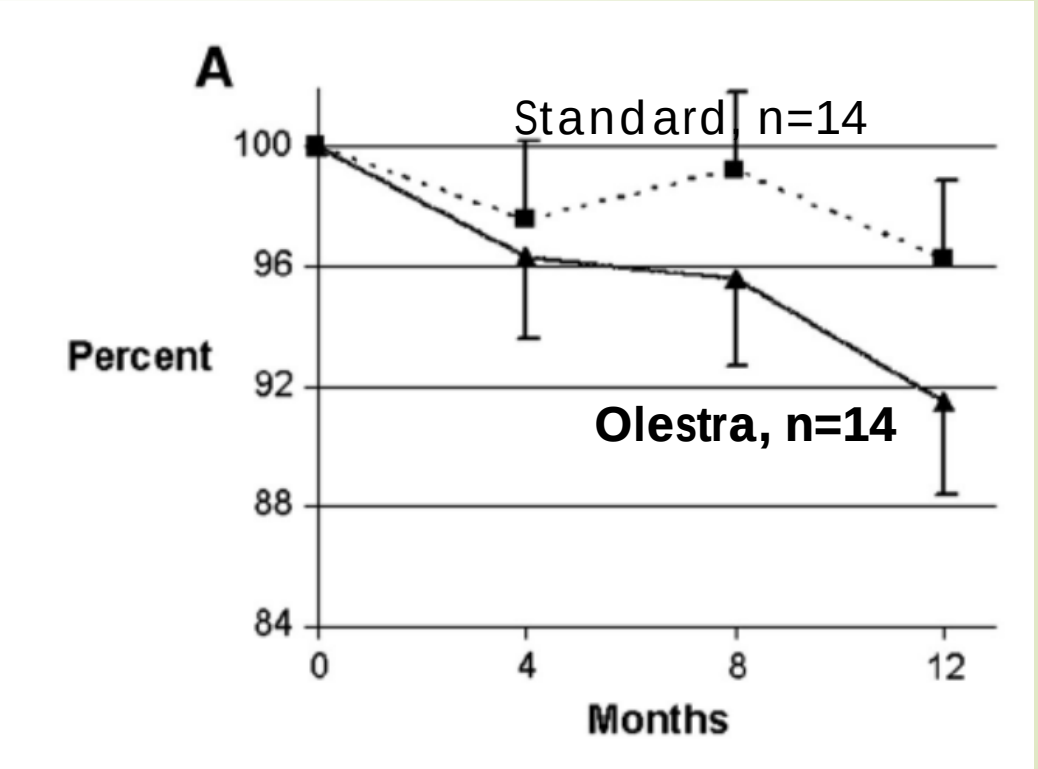
- 15g of Olestra: (≈12 pringles) x 1 year

Source: Jandacek, J Nutr Biochem 2014

Serum PCB reduction between Standard Pringles vs Olestra Pringles for 1 year

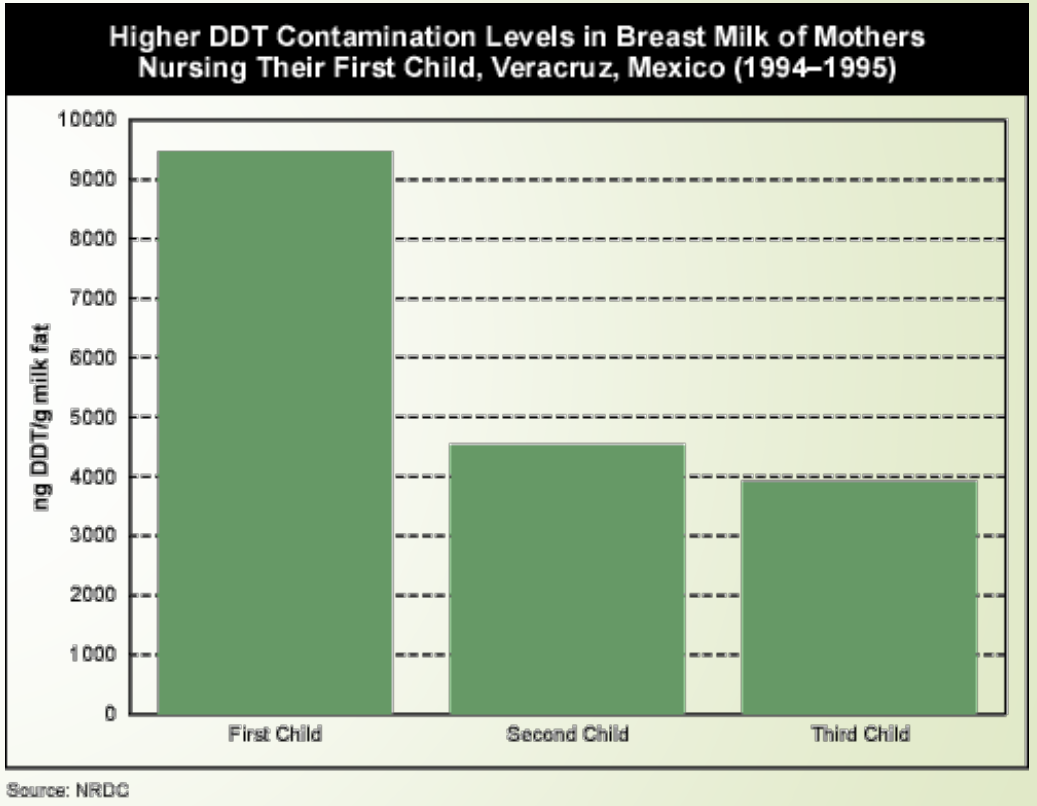
Results: Olestra (vs standard) resulted in:

- 2x the decrease in PCBs
  - 8% vs 4% decrease
- 3x the decrease in DDE
  - 16% vs 5% decrease



Source: Jandacek, J Nutr Biochem 2014

Breastfeeding can reduce body burdens of POPs (POPs go to the child!)



NO-POPs Trial

Nuts and Olestra for Persistent Organic Pollutant Reduction Trial

Research Team

- **Jose Ricardo Suarez, MD, PhD,** Principal Investigator
- **Cheryl Rock, PhD**
- **Andrea LaCroix, PhD**
- **Elizabeth Quintana, MS RDN,** Research Coordinator and Dietitian
- **Eunha Hoh, PhD,** POPs measurement
- **Bilge Pakis, EdD,** Project Manager

Students:

- Brianna Thrift
- Anita Dev
- Susan Saleh
- Jia Li Chen
- Dana Datuin

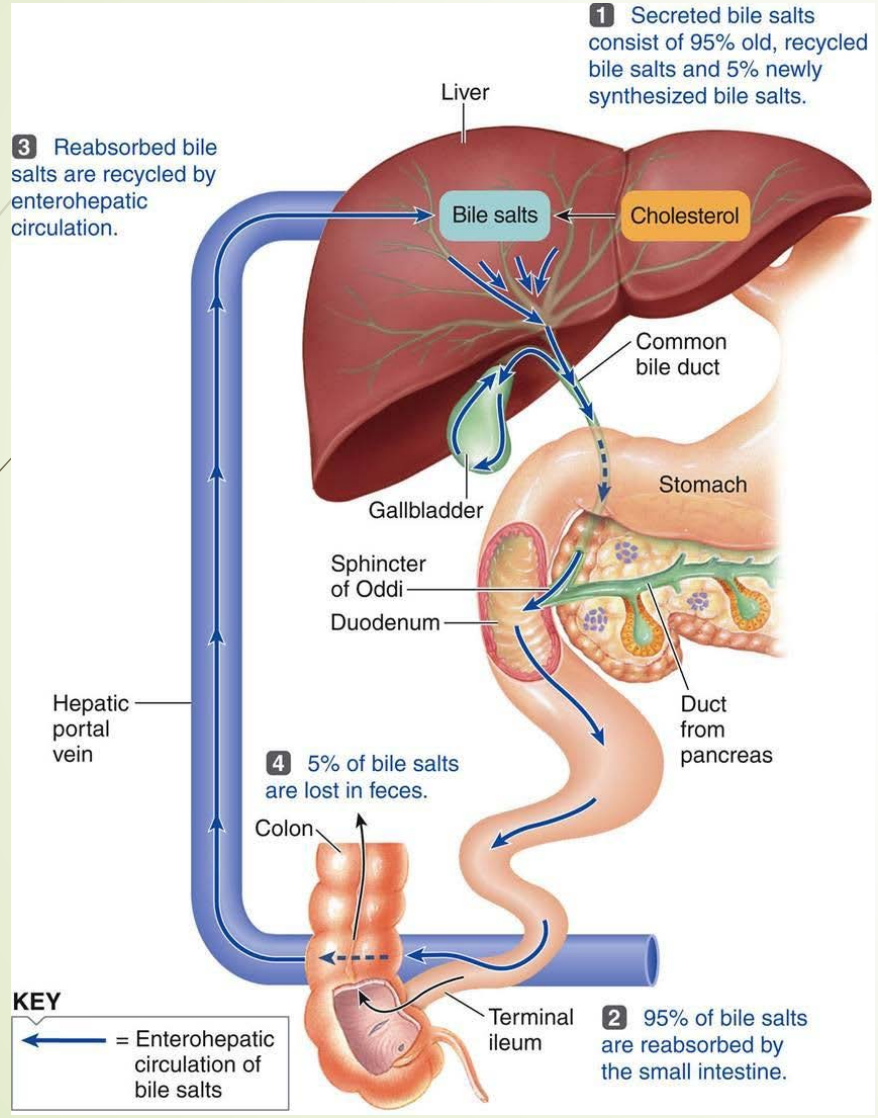
Funding: JPB Foundation: JPB Environmental Health Program, Harvard University

Objectives: Randomized controlled trial

- To assess if daily supplementation with A) nuts or B) olestra vs Placebo
  - Increases the fecal excretion of POPs
    - Measured at baseline and 4-5 days after treatment start
  - Decreases the levels of POPs in plasma
    - Measured at baseline and after 6 months

- Participants: 46 Healthy adults (50-70y) in San Diego, CA

Mechanism of action



Chlordecone levels in bile are 10-20x greater in bile than feces

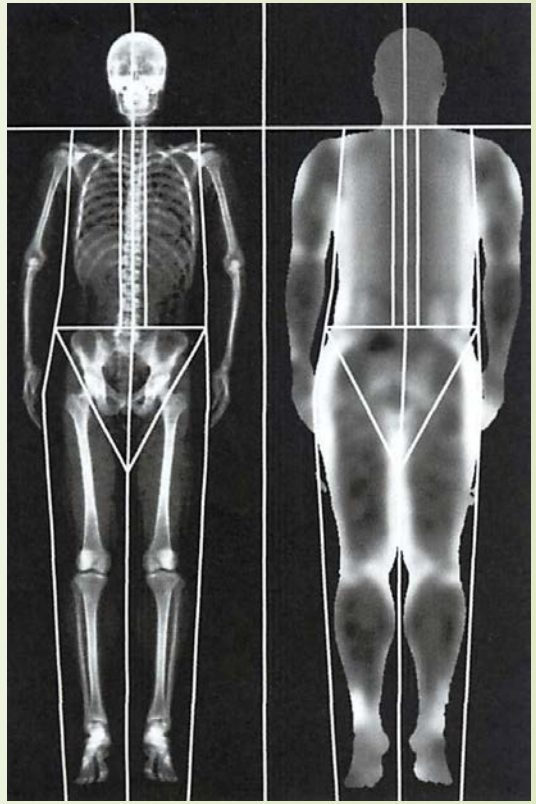
Cohn, NEJM 1978

Specimens

- Plasma
- Serum
- Whole blood
- Stool

Measures

- Height/Weight
- HbA1c
- Serum Lipids (HDL, LDL, Triglycerides, Total Cholesterol)
- DEXA – Body Fat%



POPs Measurement

Hoh Laboratory at San Diego State U.

- 6 Organochlorine pesticides
- 4 PCB congeners
- 5 PBDEs

Conclusions/Discussion

- Experimental and epidemiological evidence indicate that POPs can alter glucose and lipid metabolism in adults
  - Strong associations with diabetes and pre-diabetes
- There is still rationale for biomonitoring for POPs
  - Present in food webs (fish, meat, dairy primarily)
  - Concentrations in people are declining (NHANES)
    - Higher concentrations in older populations
- Important to continue regulation of persistent compounds
- Expand research on identifying methods to enhance the excretion of persistent pollutants

Acknowledgements

- NO-POPs trial:
  The JPB Foundation - The JPB Environmental Health Program managed by the Harvard T. H. Chan School of Public Health.
- CARDIA:

  The Young Adult Longitudinal Trends in Atherosclerosis (YALTA) study is supported by R01HL53560.

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  Dr. David Jacobs Jr., University of Minnesota

  Dr. Duk-Hee Lee, Kyungpook National University

Acronyms

- BMI: Body mass index
- CARDIA: Coronary Artery Risk Development in Young Adults
- DEXA: Dual-energy X-ray absorptiometry
- HbA1c%: Hemoglobin A1c %
- HDL: High-density lipoprotein cholesterol
- HOMA-2: Homeostasis model assessment-2
- LDL: Low-density lipoprotein cholesterol
- NHANES: National Health and Nutrition Examination Survey
- OCPs: Organochlorine pesticides
- PBB: Polybrominated biphenyl
- PBDEs: Polybrominated diphenyl ethers
- PCBs: Polychlorinated biphenyls
- PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors
- POPs: Persistent organic pollutants
- WW: Wet weight