Diabetes and Persistent Organic Pollutants

Mary Turyk, PhD
University of Illinois at Chicago, School of Public Health
POPs

- Halogenated → stability, inflammability
- PCBs, dioxins, OC pesticides (DDT, HCB, chlordane), PBDEs
- Long half-lives, reflects long-term exposure
- Stored in adipose tissues
- Predominant exposure from food: fish, meat, dairy
- Some environmental exposure: consumer products, building materials (PBDEs)
- All human exposures are mixtures
- No humans are unexposed to POPs mixtures
- Multiple health impacts including endocrine disruption
Type 2 Diabetes

• **Risk factors**
  - Age
  - Ethnicity
  - Family history
  - Adiposity (unhealthy diet and physical inactivity)
  - Inflammation
  - Hormones
  - Environmental Chemicals

• **Clinical diagnosis:**
  - Prediabetes: FPG 100-125 mg/dL or HA1c 5.7-6.4%
  - Diabetes: FPG ≥ 126 mg/dL or HA1c ≥ 6.5%

• **Insulin sensitivity:**
  - HOMA-IR: calculated from fasting insulin & glucose

• **Diabetes transition:**
  - Early stage development of insulin resistance
  - Late stage development of insulin secretory defects (β cells)
# Prevalent Diabetes and POPs Exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Exposure, ng/g</th>
<th>OR Diagnosed &amp; Undiagnosed (HA1c &gt;6.4)</th>
<th>OR Diagnosed, Undiagnosed &amp; Prediabetes (HA1c &gt;5.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DDE</strong></td>
<td>&lt;LOD-1.2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.3-2.0</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>2.1-4.0</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>4.1-24.0</td>
<td>4.1</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td><strong>P trend</strong></td>
<td>0.003</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Dioxin-like PCBs</strong></td>
<td>&lt;LOD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.2-0.3</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>0.3-1.6</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td><strong>P trend</strong></td>
<td>0.11</td>
<td>0.06</td>
</tr>
</tbody>
</table>

- N=503, diabetes prevalence =11%, Age mean=59 years, range=30-80 years, 71% males
- Adjusted for age, BMI, gender, triglycerides and cholesterol
- Diabetes was not associated with total PCBs or PBDEs, but was associated with PBDEs in persons with hypothyroidism
- Associations with dioxin-like PCBs were not independent of DDE
- Turyk et al, Chemosphere 75;674, 2009
Limitations of Diabetes Prevalence Study

- Lack of data on temporality
  - Reverse causality
  - Does diabetes result in changes in POP metabolism?
### Diabetes Incidence and DDE Exposure

<table>
<thead>
<tr>
<th>DDE Tertile</th>
<th>Tertile Range (ng/g)</th>
<th>New cases</th>
<th>Person years</th>
<th>Incidence/1000 person years</th>
<th>Incidence Rate Ratio</th>
<th>IRR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;lod-2.2</td>
<td>2</td>
<td>1325</td>
<td>1.5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.2-5.3</td>
<td>12</td>
<td>1336</td>
<td>9.0</td>
<td>5.5</td>
<td>1.2</td>
<td>25.1</td>
<td>0.03</td>
</tr>
<tr>
<td>3</td>
<td>5.4-49.2</td>
<td>22</td>
<td>1286</td>
<td>17.1</td>
<td>7.1</td>
<td>1.6</td>
<td>31.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*P trend* 0.008

- N=471
- Adjusted for age, BMI, gender
- Association remained significant with further adjustment for smoking, alcohol use and lipids assessed during follow up.
- Total PCBs and individual congeners were not associated with diabetes incidence
- Turyk et al Environmental Health Perspectives 117;1076, 2009
Meta-Analysis Diabetes and POPs

- **Heterogeneity:**
  - PCBs: stronger associations cross-sectional, females and non-white
  - DDE: stronger associations non-white
- **Song et al., J Diabetes 8:516, 2016**
LaSalle, IL Cross Sectional Study: Diabetes and PCBs

<table>
<thead>
<tr>
<th>PCB Exposure</th>
<th>Females: OR (p-value)</th>
<th>Males: OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum 38 congeners</td>
<td>4.4 (0.02)</td>
<td>3.0 (1.3, 7.0)</td>
</tr>
<tr>
<td>Dioxin-like (105, 118, 156, 157, 167, 189)</td>
<td>10.0 (0.004)</td>
<td>2.7 (1.3, 5.8)</td>
</tr>
<tr>
<td>Non-dioxin like (total - dioxin-like)</td>
<td>4.0 (0.03)</td>
<td>3.0 (1.3, 7.2)</td>
</tr>
<tr>
<td>Estrogenic (52, 99, 101, 110, 153)</td>
<td>3.4 (0.01)</td>
<td>3.0 (1.2, 7.5)</td>
</tr>
<tr>
<td>Anti-Estrogenic (105, 156)</td>
<td>12.3 (0.004)</td>
<td>2.4 (1.2, 4.9)</td>
</tr>
</tbody>
</table>

- Capacitor manufacturing plant employees
- **Females**: adjusted for age, BMI, triglycerides, cholesterol, DHEA, FSH, T3-uptake, n=93, diabetes prevalence =16%
- Persky et al., Environmental Research 111:817, 2011

- **Males**: adjusted for age, BMI, lipids, n=63, diabetes prevalence =11%
- Persky et al, Environmental Health 11:57, 2012
LaSalle, IL Cross Sectional Study: HOMA-IR and PCBs

<table>
<thead>
<tr>
<th>PCB Exposure</th>
<th>Females: Beta (p-value)</th>
<th>Males: Beta (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum 38 congeners</td>
<td>-0.16 (0.08)</td>
<td>-0.02 (-0.13, 0.10)</td>
</tr>
<tr>
<td>Dioxin-like (105, 118, 156, 157, 167, 189)</td>
<td>-0.08 (0.24)</td>
<td>-0.02 (-0.11, 0.07)</td>
</tr>
<tr>
<td>Non-dioxin like (total - dioxin-like)</td>
<td>-0.17 (0.07)</td>
<td>-0.02 (-0.14, 0.10)</td>
</tr>
<tr>
<td>Estrogenic (52, 99, 101, 110, 153)</td>
<td>-0.19 (0.04)</td>
<td>-0.03 (-0.14, 0.09)</td>
</tr>
<tr>
<td>Anti-Estrogenic (105, 156)</td>
<td>-0.07 (0.04)</td>
<td>-0.03 (-0.11, 0.06)</td>
</tr>
</tbody>
</table>

- Capacitor manufacturing plant employees

- **Females**: adjusted for age, BMI, triglycerides, cholesterol, SHBG, CRP, T3-uptake, n=72, only participants without diabetes
- Persky et al., Environmental Research 111:817, 2011

- **Males**: adjusted for age, BMI, lipids, n=52, only participants without diabetes
- Persky et al, Environmental Health 11:57, 2012
# Meta-Analysis Fasting Glucose and HOMA-IR with POPs

- Random-effect pooled mean differences of metabolic traits comparing the highest with the lowest chemical concentration categories

- Song et al., J Diabetes 8:516, 2016

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Fasting Glucose (mg/dL)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Subjects (No. Studies)</td>
<td>Mean Difference (95% CI)</td>
</tr>
<tr>
<td><strong>Dioxin</strong></td>
<td>4075 (5)</td>
<td>3.96 (1.23, 6.70)</td>
</tr>
<tr>
<td><strong>PCB</strong></td>
<td>2882 (3)</td>
<td>3.27 (1.87, 4.67)</td>
</tr>
<tr>
<td><strong>Chlorinated pesticides</strong></td>
<td>836 (2)</td>
<td>0.81 (-3.31, 4.93)</td>
</tr>
</tbody>
</table>
Hypothesized mechanisms through which POPs could impact diabetes development

- Adiposity
- Dyslipidemia
- Inflammation
- Oxidative stress
- Perturbation of endogenous hormones (steroid or thyroid)
Biomarkers of Diabetes Risk and POPs

- Are POPs associated with biomarkers of diabetes risk?

- Do biomarkers of diabetes risk mediate associations of POPs with diabetes?

- Do biomarkers of diabetes risk modify associations of POPs with diabetes?

Diabetes Risk Biomarkers

• **C reactive protein (CRP)**
  o Marker of systemic inflammation
  o ↑ diabetes risk

• **Adiponectin**
  o Adipocyte cytokine with anti-inflammatory properties
  o ↓ diabetes risk, ↑ insulin sensitivity

• **Gamma-glutamyl transferase (GGT)**
  o Liver enzyme induced by oxidative stress and involved in the metabolism of xenobiotics, such as POPs
  o ↑ diabetes risk
### Adjusted Associations of Diabetes Risk Biomarkers with HA1c, Incident Diabetes, and POPs

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HA1c % (β, p-value)</th>
<th>Incident Diabetes (OR, p-value)</th>
<th>DDE</th>
<th>Sum PCBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>-0.16, 0.0004</td>
<td>0.20, 0.002</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>CRP</td>
<td>0.01, 0.70</td>
<td>3.22, 0.02</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>GGT</td>
<td>0.08, 0.15</td>
<td>1.70, 0.08</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

- n=413, females and males for HA1c
- n=287, females and males for incident diabetes (16 cases)
- Biomarkers did not mediate associations of POPs with HA1c or incident diabetes
- DDE and PCB-118 were associated with HA1c
- DDE and PCB congeners were associated with incident diabetes
Modification of associations of LnDDE with HA1C by level of BMI, CRP, GGT and adiponectin (n=413 males and females)
## Associations of Hormones with HA1c & POPs

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HA1c % (β, p-value)</th>
<th>DDE</th>
<th>Sum PCBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG</td>
<td>-0.13, 0.007</td>
<td>-0.05, 0.28</td>
<td>-0.05, 0.46</td>
</tr>
<tr>
<td>Testosterone</td>
<td>-0.04, 0.03</td>
<td>0.05, 0.56</td>
<td>0.14, 0.15</td>
</tr>
</tbody>
</table>

- n=313 males
- Hormones did not mediate associations of POPs with HA1c
- Turyk et al, unpublished

![Graph showing beta estimates for LnDDE at 25th, 50th, and 75th percentiles of SHBG and Testosterone.]

- SHBG
- Testosterone

**Percentile of SHBG or Testosterone**
Joint Association of DDE Exposure and Great Lakes Fish Meals on HA1c Levels

Adjusted for age centered, BMI centered, sex, diabetes medication use and serum lipids, n=413
Key Points

• POPs have been associated with type 2 diabetes in many epidemiological studies.

• Our studies suggest that POPs may have a stronger impact on the later rather than earlier stages of diabetes development.

• Adiponectin, CRP, GGT, and steroid hormones were not associated with POPs and did not mediate associations of POPs with HA1c.

• Adiponectin, CRP, GGT, BMI, and steroid hormones modified the associations of POPs with HA1c, with stronger associations in persons with higher levels of the diabetes risk factor.
Current Work

- **Hispanic Community Health Study/Study of Latinos (HCHS/SOL)**
  - Cohort of multiethnic Hispanics from Chicago, San Diego, New York and Miami
  - Men and postmenopausal women ages 45-74 years
  - 1,175 prediabetes and 1,175 normal glucose at baseline
  - Measure POPs and sex steroid and thyroid hormones at baseline
  - Measure development of metabolic dysfunction at six year follow up
    - diabetes, prediabetes, insulin resistance and β cell dysfunction
Current Work

- Examine the relationships of POPs and endogenous hormones with the subsequent development of diabetes, prediabetes, insulin resistance and β cell dysfunction.

- Explore effects of POPs at early (insulin resistance) and late (insulin secretory defects) stages of diabetes transition.

- Explore effect modification and mediation by obesity, inflammation and hormonal status on associations of POPs with metabolic dysfunction.
Study Partners/Funding

- UIC: Victoria Persky, Sally Freels, Giamila Fantuzzi
- Wisconsin Department of Health and Family Services: Henry A. Anderson, Lynda Knobeloch & Pamela Imm
- Northwestern University: Robert Chatterton, Jr.
- ATSDR 75/ATH598322, US EPA STAR Program Grant RD-83025401-1 & NIEHS 1R21ES017121-01A1

LaSalle Study funded by Illinois Department of Public Health under cooperative agreement U50/ATU502923 from the ATSDR
  - Victoria Persky, Julie Piorkowski, Sally Freels, John Dimos, Lin Kaatz Chary, Terry Unterman (UIC), Robert Chatterton, Jr (Northwestern), H. Leon Bradlow, Daniel W. Sepkovic (Hackensack University Medical Center), Virlyn Burse (Battelle Memorial Institute), Kenneth McCann (Illinois Department of Public Health)

Persistent Organic Pollutants, Endogenous Hormones and Diabetes in Latinos, NIEHS R01 ES025159-01A1
  - Victoria Persky, Martha Daviglus, Sally Freels, Noel Chavez, Terry Unterman, Robert Sargis (UIC), Jianwen Cai, (University of North Carolina at Chapel Hill), Robert Kaplan (Einstein College of Medicine), Neil Schneiderman (University of Miami), Gregory Talavera (San Diego State University), Andreas Sjodin (CDC),

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) was carried out as a collaborative study supported by contracts from the National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute to the University of North Carolina (N01- HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01- HC65236), and San Diego State University (N01-HC65237). The following institutes/centers/offices contribute to the HCHS/SOL through a transfer of funds to the National Heart, Lung, and Blood Institute: National Institute on Minority Health and Health Disparities, National Institute on Deafness and Other Communication Disorders, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Neurological Disorders and Stroke, and NIH Institution-Office of Dietary Supplements.