Perinatal DDT Exposure Impairs Energy Expenditure and Metabolism in Adult Female Mice

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Average Body Weight & Obesity Has Been Rising in Animals Over Time
# DDTs and Risk of Diabetes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Description (n)</th>
<th>Chemical</th>
<th>Diagnostic</th>
<th>Risk Estimate adjOR (95% CI)</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 2010</td>
<td>US (multi-site) CARDIA nested CC, ≥16y (180)</td>
<td>DDT, p,p′</td>
<td>FBG, meds</td>
<td>0.9 (0.3, 2.6)</td>
<td>Q4 vs Q1 pg/g (serum) ≥2 vs &lt;20 ng/g (serum)</td>
</tr>
<tr>
<td>Cox et al. 2007</td>
<td>US (NHANES 1988-89) CS, 220y (1,303)</td>
<td>DDT, p,p′</td>
<td>SR</td>
<td>1.9 (1, 3.7)</td>
<td>≥20.8-26.6 vs ≤20.7 ng/g lipid (serum) ≥20.7 vs &lt;20.7 ng/g lipid (serum)</td>
</tr>
<tr>
<td>Everett et al. 2007</td>
<td>US (NHANES 1999-2004) CS, 320y (1,830)</td>
<td>DDT, p,p′</td>
<td>SR, Hba1c</td>
<td>1.17 (0.95, 1.45)</td>
<td>&gt;57,315 (Q1) vs ≤215 (Q1) pg/g (serum)</td>
</tr>
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<td>Everett et al. 2010</td>
<td>US (NHANES 1999-2004) CS, 320y (1,049)</td>
<td>DDT, p,p′</td>
<td>SR, Hba1c</td>
<td>1.96 (1.29, 2.98)</td>
<td>&gt;4,600 vs 44,600 pg/ml (serum)</td>
</tr>
<tr>
<td>Son et al. 2010</td>
<td>US (multi-site) CARDIA nested CC, ≥16y (80)</td>
<td>DDT, p,p′</td>
<td>FBG, meds</td>
<td>10.6 (1.3, 84.9)</td>
<td>&gt;58.6 (&gt;75th) vs &lt;22.81 (&lt;25th) ng/g (serum) ≥168.6 vs &lt;168 ng/g lipid (serum)</td>
</tr>
<tr>
<td>Ukopec et al. 2010</td>
<td>Slovakia (eastern, polluted) CS, 221y (2,047)</td>
<td>DDT, p,p′</td>
<td>FBG, 2hr glucose</td>
<td>1.84 (1.03, 2.27)</td>
<td>1,560 (75 to &lt;90th) vs ND ng/g lipid (serum)</td>
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<tr>
<td>Son et al. 2010</td>
<td>US (multi-site) CARDIA nested CC, ≥16y (80)</td>
<td>DDT, p,p′</td>
<td>FBG, meds</td>
<td>12.3 (1,3, 113.2)</td>
<td>[110 (56,250[med]=95th, cases)] ng/g lipid (serum)</td>
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<tr>
<td>Lee et al. 2010</td>
<td>US (NHANES 1999-2004) CS, 320y (1,303)</td>
<td>DDE, p,p′</td>
<td>self report</td>
<td>0.7 (0.2, 1.9)</td>
<td>990 (300-5,300][med]=95th, cases] ng/g lipid (serum)</td>
</tr>
<tr>
<td>Rignell-Hydbom et al. 2009</td>
<td>Sweden (Lund) WHLA nested CC, ≥742</td>
<td>DDE, p,p′</td>
<td>OGTT</td>
<td>5.5 (1.2, 25)</td>
<td>1100 (390-2,490)[med]=95th, cases] ng/g lipid (serum)</td>
</tr>
<tr>
<td>Cox et al. 2007</td>
<td>US (NHANES 1988-89) CS, 220y (1,303)</td>
<td>DDE, p,p′</td>
<td>self report</td>
<td>2.63 (1.2, 5.8)</td>
<td>667.4 (med, T3) vs 162.2 (med, T1) ng/g lipid (serum)</td>
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<td>Everett et al. 2010</td>
<td>US (NHANES 1999-2004) CS, 320y (3,049)</td>
<td>DDE, p,p′</td>
<td>self report, Hba1c</td>
<td>1.9 (1,3, 3.18)</td>
<td>3,605-22,328 (Q3) vs 54-621 (Q1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Lee et al. 2006</td>
<td>US (NHANES 1999-2004) CS, 320y (2,106)</td>
<td>DDE, p,p′</td>
<td>self report</td>
<td>2.3 (1,5)</td>
<td>&gt;1,617 (&gt;75th) vs ≤1,617 (75th) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Rignell-Hydbom et al. 2007</td>
<td>Sweden (east/west-coast), fisherman’s wives ≥543</td>
<td>DDE, p,p′</td>
<td>self report</td>
<td>1.3 (1.1, 1.5)</td>
<td>23.3-5.3 (T2) vs &lt;2.2 (T1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Rylander et al. 2005</td>
<td>Sweden (nat’l registry), fisherman’s wives ≥184</td>
<td>DDE, p,p′</td>
<td>self report</td>
<td>1.05 (1.01, 1.10)</td>
<td>544.6 (T3) vs 246.1 (T1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Rylander et al. 2005</td>
<td>Sweden (nat’l registry), fisherman ≥171</td>
<td>DDE, p,p′</td>
<td>self report</td>
<td>1.05 (0.98, 1.1)</td>
<td>4.1-24.0 (Q4) vs ≤1.2 (Q1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Son et al. 2010</td>
<td>S. Korea (Uijin) CS, 340y (60)</td>
<td>DDE, p,p′</td>
<td>FBG, medication</td>
<td>12.7 (1,9, 83.7)</td>
<td>8.4 (med, T3) vs 2.7 (med, T1) ng/g lipid (serum)</td>
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<tr>
<td>Ukopec et al. 2010</td>
<td>Slovakia (eastern, polluted) CS, 221y (2,047)</td>
<td>DDE, p,p′</td>
<td>FBG, 2hr glucose</td>
<td>1.94 (1.11, 3.78)</td>
<td>23.3-5.3 (T2) vs &lt;2.2 (T1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Philibert et al. 2009</td>
<td>Canada (Northern Ontario) First Nation, ≥101</td>
<td>DDE, p,p′</td>
<td>SR</td>
<td>3.56 (0.91, 13.08)</td>
<td>≥23.3-5.3 (T2) vs &lt;2.2 (T1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Turyk et al. 2009a</td>
<td>US (Great Lakes), prospective fish eaters, ≥50</td>
<td>DDE</td>
<td>self report</td>
<td>5.5 (1.2, 25.1) IRR</td>
<td>544.6 (T3) vs 246.1 (T1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Codru et al. 2007</td>
<td>US (Akwasasne) Mohawks CS, ≥352</td>
<td>DDE</td>
<td>FBG, medication</td>
<td>6.2 (1.8, 21.9)</td>
<td>4.1-24.0 (Q4) vs ≤1.2 (Q1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Turyk et al. 2009b</td>
<td>US (Great Lakes) fish eaters CS, ≥503</td>
<td>DDE</td>
<td>self report</td>
<td>3.6 (1,4, 9.4)</td>
<td>8.4 (med, T3) vs 2.7 (med, T1) ng/g lipid (serum)</td>
</tr>
<tr>
<td>Son et al. 2010</td>
<td>S. Korea (Uijin) CS, 340y (60)</td>
<td>DDD, p,p′</td>
<td>FBG, meds</td>
<td>3.6 (0.8, 16.3)</td>
<td><strong>lower 95% confidence interval</strong> <strong>upper 95% confidence interval</strong> <strong>risk estimate</strong></td>
</tr>
</tbody>
</table>

Dr. Kris Thayer
Developmental Origins of Metabolic Disease

La Merrill & Birnbaum 2011
Could Developmental Exposure to DDT Increase Adult Risk of Obesity and Diabetes?
Internal Dose in Range of Human Exposure

- CA (CHDS) pregnancies
- MHANES Cox 2007
- Norwegian adults Rylander 2009
- Downstream plant Kreiss 1981
- S. African children Bouwman 1992
- S. African infants Bouwman 1992
- Mexican children Herrera Portugal 2005

ng DDE/ml

- CA (CHDS) pregnancies
- MHANES Cox 2007
- Norwegian adults Rylander 2009
- S. African infants Bouwman 1992
- Mexican children Herrera Portugal 2005
- Montreal adults Gautier 2014

ng DDT/ml
Perinatal DDT Increases Early Adult Adiposity

A) Body Mass (g) over Age (months)
B) Fat Mass (%) over Age (months)
C) Fat mass (g) over Age (months)
D) Lean Mass (g) over Age (months)
What Causes Excess Body Mass?

• The 1st Law of Thermodynamics!
  Excess Mass = Energy Intake > Energy Expenditure

• Energy Intake
  Food calories

• Energy Expenditure
  10-30% physical activity
  60-80% resting metabolic rate (homeothermy)
  10% adaptive thermogenesis (response to cold and diet)

Landsberg 2012
Perinatal DDT Decreases Thermogenesis

Food Intake (g/day)

Core Temperature (°C)

Age (months)

$P < 0.1$
Perinatal DDT Decreases Energy Expenditure

**EE (kcal/kg/hr)**

- VEH
- DDT

**VO₂ (ml/kg/hr)**

~70% EE

**Movement (Counts)**

~20% EE

**Temperature (°C)**

10% EE

**Time at 4C (min)**

- **VEH**
- **DDT**

**~70% EE**

**~20% EE**

**10% EE**
Mammalian body temperature maintenance is essential. Therefore when thermogenic capacity is reduced, metabolic compensation occurs. Does this metabolic compensation increase susceptibility to diet induced- metabolic disruption?
HFD Increases Susceptibility to Adult Insulin Resistance Induced by Perinatal DDT

**Insulin (µg/l)**
- VEH
- LFD
- DDT
- HFD

**Glucose (mg/dl)**
- VEH
- LFD
- DDT
- HFD

**AUC**
- VEH
- LFD
- DDT
- HFD

$P_i=0.08$
Perinatal DDT Reduces Hepatic Proteins Downstream of Insulin in HFD-fed Mice

Normal Insulin Signaling

- Insulin
- Insulin Receptor
- ERK1/2
- AKT
- GSK3
- Proliferation
- Glucose Uptake
- Glycogen Synthesis

Fold Change

<table>
<thead>
<tr>
<th>IR b tot</th>
<th>AKT 473</th>
<th>AKT 308</th>
<th>AKT tot</th>
<th>GSK3 phos</th>
<th>GSK3 tot</th>
<th>ERK phos</th>
<th>ERK tot</th>
<th>Hsc 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEH</td>
<td></td>
<td></td>
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<tr>
<td>DDT</td>
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</table>
HFD Attenuates the Depressive Effect of Perinatal DDT on Thermogenesis

**A**

- Age (wks)
- Body Mass (g)

**B**

- Fat Mass (%)

**C**

- Cumulative Caloric Intake (kcal)

**D**

- Temperature (°C)

- VEH
- LFD
- DDT
- HFD

- P = 0.01

HFD attenuates the depressive effect of perinatal DDT on thermogenesis.
Brown Adipose Tissue: A Primer

• BURNS energy to make heat
• Neonatal response to ambient temperature
• Recently discovered to be present and active in adult humans
  – Presence of BAT in adult humans associated with lower diabetes risk (A1C)
  – Activation of adult human BAT may contribute to loss of over 4 kg body fat annually
Pathway to Thermogenesis: Respiration and its Uncoupling in Brown Adipose
HFD Attenuates the Depressive Effect of Perinatal DDT on BAT Thermogenesis & Substrate Utilization

A) $P_{<0.01}$

B) $P_{<0.01}$

C) $P_{<0.05}$

D) $P_{<0.05}$

E) $P_{<0.05}$

F) $P_{<0.05}$

G) $P_{<0.05}$

H) $P_{<0.05}$
Working Model: Perinatal DDT Exposure Impairs Respiration and its Uncoupling in Brown Adipose

- **DDT** affects various metabolic pathways:
  - **FA Oxidation**
  - **FA Transporter**
  - **LPL**
  - **Lipogenesis**
  - **Lipoprotein Particles**
  - **Glycerol**
  - **Twist1**
  - **Pgc1a**
  - **Twist1**
  - **Dio2**
  - **Cpt**
  - **Ucp1**
  - **ETC**
  - **ATP**
  - **NADH**
  - **FADH2**
  - **Glycolysis**
  - **Gluconeogenesis**
  - **Pgc1a**
  - **FA-CoA**

**Key Metabolic Processes**:
- **Lipid Metabolism**
- **Carbohydrate Metabolism**
- **Aerobic Oxidation**
- **Anaerobic Glycolysis**
- **Insulin Resistance**
Results Summary

• Perinatal DDT exposure leads to...
  – Increased adipose in early adulthood
  – Decreased energy expenditure
    • Decreased thermogenesis
  – Susceptibility to HFD
    • Insulin resistance
    • Decreased thermogenesis
      – Defects in brown adipose substrate utilization implicated
Malaria & Climate Change

• Predictions about mosquitoes carrying malaria
  – Larger numbers in existing range
  – Expanse of distribution

Melting glaciers are a source of marine DDTs:
≥ 60% to subalpine lakes
46% DDTs in Canadian Archipelago

Macdonald 2005
Thank you for your attention!

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Dr. Kristina Thayer
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