Using the key characteristics of endocrine disruptors to organize mechanistic support of the developmental basis of endocrine disruption

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What are Endocrine Disrupting Chemicals?

Endocrine Disrupting Chemicals (EDCs) are defined by the Endocrine Society as:
“an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”

Endocrinology, September 2012, 153(9):4097–4110

Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

Overweight and obesity are on the rise worldwide

WHY IS THE PREVALENCE INCREASING?

It is changing faster than a lone genetic cause would predict.
Average body weight & obesity have been rising in animals over time.

P < 1.2 x 10^{-7}
>20,000 animals
24 populations
8 species

Klimentidis et al. PRSB 2010
Let us learn history lessons

• Who decides if a chemical is a carcinogen?
  – Many groups (GHS, EU, USEPA, USNTP, CalEPA Prop 65) decide from Monographs of the International Agency for Research on Cancer IARC, part of the World Health Organization

• How does IARC identify carcinogens?
  ↓ Epidemiology, rodent assays
  ↑ Mechanistic, in vitro assays

• Key Characteristics of Carcinogens
  – A framework for organizing data related to the intrinsic properties of carcinogens
  – Incomplete ‘mechanistic pathway’ ≠ decision-making inaction
  – Help identify data gaps
Expert Meeting on Advancing the Key Characteristics Framework to Reproductive Toxicants and EDCs

- March 7-8\textsuperscript{th}, 2018 in Berkeley CA
- Sponsored by: CalEPA
- Zoeller and La Merrill invited to lead the evaluation of whether developing KCs of EDCs was feasible

https://doi.org/10.1038/s41574-019-0273-8

\textbf{NATURE REVIEWS | ENDOCRINOLOGY}

\textbf{OPEN}

Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification

\textit{Michele A. La Merrill\textsuperscript{1,1}, Laura N. Vandenberg\textsuperscript{2}, Martyn T. Smith\textsuperscript{3}, William Goodson\textsuperscript{4}, Patience Browne\textsuperscript{5}, Heather B. Patinsal\textsuperscript{6}, Kathryn Z. Guyton\textsuperscript{7}, Andreas Kortenkamp\textsuperscript{8}, Vincent J. Cogliano\textsuperscript{9}, Tracey J. Woodruff\textsuperscript{10}, Linda Rieswijk\textsuperscript{11}, Hideko Sone\textsuperscript{12}, Kenneth S. Korach\textsuperscript{13}, Andrea C. Gore\textsuperscript{14}, Lauren Zeise\textsuperscript{15} and R. Thomas Zoeller\textsuperscript{16}}
Universal EDC Characteristics Are
The pesticide DDT and its metabolite DDE: model chemicals to reveal the mechanisms of obesogens
What does “yesterday’s chemical” have to do with today’s diseases?

Developmental Origins of Adult Disease
Chronic adult disease: let’s consider developmental origins

Childhood Obesity and Environmental Chemicals

Michele La Merrill, PhD, MPH, and Linda S. Birnbaum, PhD, DABT

KCs in Data integration: 
DDT/E phenotype in humans

• More than 100 epidemiology studies
  – Numerous are longitudinal
  – Numerous assess exposure prenatally
  – Associations between DDT and DDE and adverse outcomes such as
    • obesity,
    • diabetes mellitus,
    • infertility,
    • and cancers
Meta-analyses & systematic reviews of DDE exposure support association with obesity

Etiology and Pathophysiology

Endocrine-disrupting chemicals and obesity development in humans: A review

J. L. Tang-Péronard1,2, H. R. Andersen3, T. K. Jensen3 and B. L. Heitmann1,3

Etiology and Pathophysiology

Do environmental pollutants increase obesity risk in humans?

Y. Wang,1,2 K. Hollis-Hansen,1,2 X. Ren,1 Y. Qiu1,3 and W. Qu4,5

Environmental Health Perspectives

Association between Exposure to p,p′-DDT and Its Metabolite p,p′-DDE with Obesity: Integrated Systematic Review and Meta-Analysis

German Cano-Sancho,1 Andrew G. Salmon,2 and Michele A. La Merrill1

1Department of Environmental Toxicology, University of California, Davis, Davis, California, USA
2Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, USA

Published 18 September 2017.

Conclusions: We classified p,p′-DDT and p,p′-DDE as “presumed” to be obesogenic for humans, based on a moderate level of primary human evidence, a moderate level of primary in vivo evidence, and a moderate level of supporting evidence from in vivo and in vitro studies. https://doi.org/10.1289/EHP527
Child Health and Development Studies: prospective birth cohort

~15,000 pregnant women in the Kaiser Permanente Health Plan joined the CHDS in 1960s.
> 500 maternal serum samples from 1960 subjected to GC/MS for analysis of a mixture of 20 POPs.
> 50 year health follow-up in >500 adult daughters.
Prenatal DDT exposure positively associated with adiposity of women in their fifties

β = 2.62 (p < 0.05)

β = 1.24 (p < 0.05)

Only association in a mixture of 2 dozen POPs

La Merrill et al.  
Intl J of Obesity 2020
DDT and DDE are associated with diabetes in humans.
Human studies indicate obesity increases risk of association between DDE and diabetes

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Country</th>
<th>Design</th>
<th>Exposure</th>
<th>Units</th>
<th>Outcome</th>
<th>Statistic</th>
<th>Meta-RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Weight</strong></td>
<td></td>
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</tr>
<tr>
<td>CHS</td>
<td>Spain</td>
<td>CS</td>
<td>Serum p.p'DDE WW</td>
<td>SR-T2D/MED/FBG</td>
<td>OR (Q2)</td>
<td>1.20 (0.37, 3.90)</td>
<td></td>
</tr>
<tr>
<td>HELSINKI-BCS Finland</td>
<td>CS</td>
<td></td>
<td>Serum p.p'DDE LW</td>
<td>OGTT</td>
<td>OR (p50&lt;p90)</td>
<td>1.33 (0.41, 4.26)</td>
<td></td>
</tr>
<tr>
<td>SPORT-FISH-CONS US</td>
<td>P</td>
<td></td>
<td>Serum p.p'DDE WW</td>
<td>SR-T2D</td>
<td>IRR Tertile increase</td>
<td>3.00 (0.34, 26.20)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
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<tr>
<td><strong>Overweight</strong></td>
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<td></td>
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</tr>
<tr>
<td>CHS</td>
<td>Spain</td>
<td>CS</td>
<td>Serum p.p'DDE WW</td>
<td>SR-T2D/MED/FBG</td>
<td>OR (Q3)</td>
<td>1.30 (0.40, 4.20)</td>
<td></td>
</tr>
<tr>
<td>SPORT-FISH-CONS US</td>
<td>P</td>
<td></td>
<td>Serum p.p'DDE WW</td>
<td>SR-T2D</td>
<td>Adjusted IRR Tertile increase</td>
<td>1.70 (0.59, 4.90)</td>
<td></td>
</tr>
<tr>
<td>HELSINKI-BCS Finland</td>
<td>CS</td>
<td></td>
<td>Serum p.p'DDE LW</td>
<td>OGTT</td>
<td>OR (p50&lt;p90)</td>
<td>2.60 (1.14, 5.92)</td>
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<td>Subtotal</td>
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<tr>
<td><strong>Obese</strong></td>
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</tr>
<tr>
<td>CHS</td>
<td>Spain</td>
<td>CS</td>
<td>Serum p.p'DDE WW</td>
<td>SR-T2D/MED/FBG</td>
<td>OR (Q4)</td>
<td>1.70 (0.30, 9.60)</td>
<td></td>
</tr>
<tr>
<td>HELSINKI-BCS Finland</td>
<td>CS</td>
<td></td>
<td>Serum p.p'DDE LW</td>
<td>OGTT</td>
<td>OR (&gt;p90)</td>
<td>1.82 (0.71, 4.65)</td>
<td></td>
</tr>
<tr>
<td>SPORT-FISH-CONS US</td>
<td>P</td>
<td></td>
<td>Serum p.p'DDE WW</td>
<td>SR-T2D</td>
<td>IRR Tertile increase</td>
<td>2.20 (1.13, 4.30)</td>
<td></td>
</tr>
<tr>
<td>OBE-Anhrepol Belgium</td>
<td>CS</td>
<td></td>
<td>Serum p.p'DDE LW</td>
<td>OGTT/HbA1c/HOMA-IR NS</td>
<td></td>
<td>3.47 (1.08, 11.15)</td>
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</tr>
<tr>
<td>Subtotal</td>
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</tr>
<tr>
<td>Overall</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>1.96 (1.41, 2.72)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
KC in Data integration: DDT/E phenotype in animals

- Two rodent species
  - Developmental exposure to DDT and DDE
    - Leads to increased body and fat mass in subsequent generations

- Three rodent species
  - Exposure to DDT and/or DDE
    - Causes disruption of energy expenditure
Perinatal DDT increase adiposity in adult mice

La Merrill et al. PLOS ONE 2014
Cano-Sancho et al. EHP 2017
Perinatal DDT decreases Energy Expenditure (EE) and metabolism in adult mice

Resting metabolic rate $\approx 70\%$ EE

Activity $\approx 20\%$ EE

Adaptive thermo $\approx 10\%$ EE

La Merrill et al PLOS ONE 2014
Is reduced adaptive thermogenesis in adult mice initiated in early life?

Perinatal DDT & DDE impair response to cold in neonatal mice

Postnatal day 5

Dr. Sarah Elmore

Postnatal day 12
**DDT and DDE Key Characteristics**

<table>
<thead>
<tr>
<th>EDC Characteristic</th>
<th>Mechanistic evidence for BPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Interacts with or activates hormone receptors</strong></td>
<td>DDT, and to a lesser extent DDE, activates nuclear ERs in a variety of species and tissues. DDT binds to the transmembrane domain of FSHR.</td>
</tr>
<tr>
<td><strong>2. Antagonizes hormone receptors</strong></td>
<td>DDE competitively antagonizes androgen receptor.</td>
</tr>
<tr>
<td><strong>3. Alters hormone receptor expression</strong></td>
<td>DDT prevents the internalization of TSHR.</td>
</tr>
<tr>
<td><strong>4. Alters signal transduction in hormone responsive cells</strong></td>
<td>DDT and DDE reduce insulin signaling in mouse liver and adipocytes. DDT enhances cAMP production through FSHR.</td>
</tr>
<tr>
<td><strong>5. Induces epigenetic modifications in hormone producing or responsive cells</strong></td>
<td>DDT and DDE modify DNA methylation of mice and humans in the insulin signaling, insulin resistance, type 2 diabetes mellitus, and thermogenesis KEGG pathways. DDT and DDE alter hypothalamic Dnmt1 expression in rats.</td>
</tr>
</tbody>
</table>

**Bold**, supports human and other animal diabesogen phenotypes
KC4. Impaired insulin signaling by DDT

Normal Insulin Signaling

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

**La Merrill et al. 2014**

Teal = VEH
Red = DDT
KC5. Insulin signaling enriched with DMR in blood from humans and mice

Left half of gene boxes = DMR in infant mouse blood
Right half of gene boxes = DMR in adult human blood
Increased (blue) or decreased (yellow) DNA-CH₃ in exposed mammal
KC4. DDTs decrease insulin stimulated glucose uptake by adipocytes
## DDT and DDE Key Characteristics

<table>
<thead>
<tr>
<th>EDC Characteristic</th>
<th>Mechanistic evidence for BPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. <em>Alters hormone synthesis</em></td>
<td>DDT and DDE increase hepatic PC, PEPCK, FDPase, G6Pase in rats. DDT and DDE decrease Dio2 expression in mouse brown fat.</td>
</tr>
<tr>
<td>7. <em>Alters hormone transport across cell membranes</em></td>
<td>DDT and DDE reduce glucose stimulated insulin secretion. Passive secretion of corticosterone from rodent adrenal glands is reduced by low dose DDE.</td>
</tr>
<tr>
<td>8. <em>Alters hormone distribution or circulating hormone levels</em></td>
<td>DDT and DDE increase circulating insulin levels in mice. DDE increases serum LH and FSH in mice.</td>
</tr>
<tr>
<td>9. <em>Alters hormone metabolism or clearance</em></td>
<td>DDT and DDE increase hepatic E2 hydroxylation and methylation, as well as o-methylase activity, in rats. DDT and DDE increase testosterone metabolism in rats.</td>
</tr>
<tr>
<td>10. <em>Alters fate of hormone producing or responsive cells</em></td>
<td>DDT and DDE increase liver fat and total mass in rodents and non-human primates.</td>
</tr>
</tbody>
</table>

**Bold**, supports human and other animal diabesogen phenotypes
KC8. Mice with DDT and DDE exposure have increased levels of circulating insulin

La Merrill et al PLOS ONE 2014; unrestrained excursion also seen in Yau & Mennear, Toxicol & App Pharm 1977
KCs in data integration: DDT & DDE mechanistic data

• There are 10,000s of mechanistic scientific papers on DDT and DDE that provide substantial evidence for all of the 10 KCs.
• DDT and/or DDE
  – Prevent the internalization of TSHR and reduces the expression of Dio2 in brown adipose tissue
  – Alter DNA methylation in the insulin signaling and T2D pathways
  – Increase circulating insulin levels
  – DDT impairs insulin signaling
• These mechanistic studies identified by the KCs approach are consistent with obesity, reduced energy expenditure, and T2D
Impaired thermogenesis is a common theme among diabesogens

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Effect on obesity risk</th>
<th>Effect on T2D risk</th>
<th>Thermogenesis Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERINATAL DDT OR DDE</td>
<td>Positive effect</td>
<td>Positive effect</td>
<td>Impaired</td>
</tr>
<tr>
<td>CLOZAPINE AND SIMILAR DRUGS</td>
<td>Positive effect</td>
<td>Positive effect</td>
<td>Impaired</td>
</tr>
<tr>
<td>A GENE CALLED FTO (Intronic SNP)</td>
<td>Positive effect</td>
<td>Positive effect</td>
<td>Impaired</td>
</tr>
<tr>
<td>PRENATAL TOBACCO</td>
<td>Positive effect</td>
<td>Positive effect</td>
<td>Impaired</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

EDC group participants:
Patience Brown (OECD)
Vincent Cogliano (US EPA)
Bill Goodson (SF, USA)
Kate Guyton (IARC)
Ken Korach (NIEHS, USA)
Andreas Kortenkamp (Brunel, UK)
Linda Rieswijk (UCB, USA)
Martyn Smith (UCB, USA)
Hideko Sone (NIES, Japan)
Laura Vandenberg (UMass, USA)
Tracey Woodruff (UCSF, USA)
Lauren Zeise (CalEPA)
Tom Zoeller (UMass, USA)

Past Trainees:
INSERM
Dr. German Cano-Sancho
CalEPA
Dr. Sarah Elmore

MY RESEARCH FUNDING
CalEPA OEHHA
13-E0014-1

NIEHS
ONES R01 ES024946
P30 ES023513

Rachel Carson; Photographer: Alfred Eisenstaedt; National Portrait Gallery, Smithsonian Institution
Widespread Insulin Resistance

Age-adjusted Percent of Obese Adults

1994

2009

<14.0%  14.0-17.9%  18.0-21.9%  
22.0-25.9%  >26.0%

Age-adjusted Percent of Diabetic Adults

1994

2009

<4.5%  4.5-5.9%  6.0-7.4%  
7.5-8.9%  >9.0%

Lifetime risk of developing diabetes for individuals born in the US in 2000

Ogden 2010 & 2012, CDC’s Division of Diabetes Translation. National Diabetes Surveillance System
How you can be involved

• Educate your local organizations and policy-makers about the importance of EDCs
  – Intro to EDC Guide is available in six languages
    • English, Spanish, French, Russian, Arabic and Portuguese
    • [https://www.endocrine.org/topics/edc/introduction-to-edcs](https://www.endocrine.org/topics/edc/introduction-to-edcs)
  – Need to take action
    • Guideline assays (OECD, USEPA) only cover KCs 1, 2, and 6

INTRODUCTION TO ENDOCRINE DISRUPTING CHEMICALS (EDCs)
A GUIDE FOR PUBLIC INTEREST ORGANIZATIONS AND POLICY-MAKERS
Strategic Approach to International Chemicals Management (SAICM)

- **SAICM** is a policy framework to promote chemical safety around the world
- hosted by the United Nations Environment Programme
- Endocrine Society collaborated with non-profit organization IPEN to
  - educate conference attendees about EDCs,
    - Give out copies of the **Guide** to educate representatives about the importance of EDCs and the need to take action
  - draft and revise the text, and
  - build support for the resolution.
    - Over 120 governments

https://endocrinewhites.gr/endocrine-society-influences-edc-policy-around-the-world/
**Considering Cause: DDT and DDE as presumed obesogens**

**Conclusions:** We classified \textit{p,p'-DDT} and \textit{p,p'-DDE} as “presumed” to be obesogenic for humans, based on a moderate level of primary human evidence, a moderate level of primary \textit{in vivo} evidence, and a moderate level of supporting evidence from \textit{in vivo} and \textit{in vitro} studies. [https://doi.org/10.1289/EHP527](https://doi.org/10.1289/EHP527)

<table>
<thead>
<tr>
<th>Hill’s Causal Considerations</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength:</td>
<td>Effect size modest</td>
</tr>
<tr>
<td>Consistency &amp; Coherence:</td>
<td>Obesity consistent across at least 3 mammalian species</td>
</tr>
<tr>
<td>Specificity:</td>
<td>DDT and DDE have been isolated in affirmative cell culture and in rodent experiments</td>
</tr>
<tr>
<td>Temporality:</td>
<td>DDT/E -&gt; impaired thermogenesis -&gt; obesity</td>
</tr>
<tr>
<td>Biological Gradient:</td>
<td>DDT dose dep. decrease in bAR response and expression; DDE dose dep. decrease in uncoupled respiration</td>
</tr>
<tr>
<td>Experimental Reversibility</td>
<td>Extensive: thermogenesis-EE-obesity experimentally; Some: DDE-thermogenesis with CL316,243; Non-existent: DDT/E-thermogenesis-EE-obesity experimentally</td>
</tr>
<tr>
<td>Analogy</td>
<td>Extensive: genetic/pharmaceutical/developmental exposure-SNS-thermogenesis-EE-obesity links</td>
</tr>
</tbody>
</table>
Melting Glaciers are a Source of DDTs

- Semi-volatile
  - Long range atmospheric transport
  - Accumulate in cold regions
  - 46% of DDTs Canadian Archipelago from melting glaciers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (pg/L)</th>
<th>Total glacial input (kg)</th>
<th>Glacial input for 1993 (kg/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-HCH</td>
<td>256</td>
<td>205</td>
<td>39</td>
</tr>
<tr>
<td>γ-HCH</td>
<td>115</td>
<td>92</td>
<td>18</td>
</tr>
<tr>
<td>ΣDDT</td>
<td>480</td>
<td>384</td>
<td>74</td>
</tr>
<tr>
<td>CHLOR</td>
<td>35</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>HCB</td>
<td>65</td>
<td>52</td>
<td>10</td>
</tr>
<tr>
<td>PCB</td>
<td>3.5</td>
<td>2.8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Polar bear
Water

Macdonald 2005, Blais 2001
Glucose metabolism is associated with DDT in mouse serum and mammary tumors as well.

(pink solid is from sera, outlined pink is from tumor)
HFD Attenuates the Depressive Effect of Perinatal DDT on BAT Thermogenesis & Substrate Utilization in 9 mo old mice

La Merrill et al 2014
High Fat Diet Increases Susceptibility to the Effects of Perinatal DDT on Thermogenesis

Size of perinatal DDT effect

In 9 month old mice:

- Low fat diet fed mice: 0.56°C lower with DDT
- High fat diet fed mice: 1.19°C lower with DDT

La Merrill et al 2014
Perinatal DDT Increases Lipid Utilization

Lipid Synthesis & Utilization

- Acetyl CoA
- ACC
- Malonyl CoA
- ATPCL
- FAS
- Citrate
- Fatty Acids
- β Oxidation
- Acetyl CoA

Krebs Cycle

La Merrill et al 2014
Lipid utilization a common theme in human sera metabolome too

<table>
<thead>
<tr>
<th>Metabolic pathways</th>
<th>opDDT pval</th>
<th>ppDDT pval</th>
<th>ppDDE pval</th>
<th>ppDDT:ppDDE pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnitine shuttle</td>
<td>0.0006</td>
<td>0.3832</td>
<td>0.0306</td>
<td>0.0729</td>
</tr>
<tr>
<td><strong>Linoleate metabolism</strong></td>
<td>0.0006</td>
<td>0.0191</td>
<td>0.0004</td>
<td>0.0003</td>
</tr>
<tr>
<td>Drug metabolism - other enzymes</td>
<td>0.0015</td>
<td>0.1978</td>
<td>0.0009</td>
<td>0.0166</td>
</tr>
<tr>
<td>Arginine and Proline Metabolism</td>
<td>0.0020</td>
<td>0.0221</td>
<td>0.0621</td>
<td>0.2129</td>
</tr>
<tr>
<td><strong>Glycosphingolipid metabolism</strong></td>
<td>0.0024</td>
<td>0.0431</td>
<td>0.0113</td>
<td>0.0003</td>
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<tr>
<td>Lysine metabolism</td>
<td>0.0075</td>
<td>0.0072</td>
<td>0.0039</td>
<td>0.0065</td>
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<tr>
<td>Omega-3 fatty acid metabolism</td>
<td>0.0124</td>
<td>1.0000</td>
<td>0.0029</td>
<td>0.0077</td>
</tr>
<tr>
<td>Fatty Acid Metabolism</td>
<td>0.0131</td>
<td>0.1107</td>
<td>0.0005</td>
<td>0.0026</td>
</tr>
<tr>
<td><strong>Fatty acid activation</strong></td>
<td>0.0253</td>
<td>0.0257</td>
<td>0.0007</td>
<td>0.0021</td>
</tr>
<tr>
<td>Aspartate and asparagine metabolism</td>
<td>0.0306</td>
<td>0.0020</td>
<td>0.2304</td>
<td>0.0286</td>
</tr>
<tr>
<td>Saturated fatty acids beta-oxidation</td>
<td>0.0321</td>
<td>1.0000</td>
<td>0.1387</td>
<td>0.0438</td>
</tr>
<tr>
<td>Urea cycle/amino group metabolism</td>
<td>0.0325</td>
<td>0.0006</td>
<td>0.2550</td>
<td>0.2104</td>
</tr>
</tbody>
</table>
Do any of these metabolic effects actually matter in terms of chronic diseases that kill people?
In PIVUS people and our mouse model, we have confirmed DDT and DDE increase LV cardiac mass in mice and people - mostly mediated by obesity.

Prenatal DDT increases LV cardiac mass in adult mice.
La Merrill et al. EHP 2016

DDE exposure increase LV mass mostly mediated by obesity.
La Merrill et al. (PIVUS) Env Res 2017
In CHDS daughters and our mouse model, we have confirmed DDT increase breast cancer risk.

Perhaps this is also mediated by obesity?

Reduced oxygen consumption could lead to Warburg-like glycolysis in adipose aka ‘stroma’

(KC#10: Nutrient Supply; Hallmark: Deregulating cellular energetics)

Unpublished mouse model
Ishikawa & La Merrill

Unpublished mouse model
Ishikawa & La Merrill
B-AR canonical pathway from PIVUS and mouse blood DNA methylation
Supporting *in vivo* evidence: developmental low doses within the human DDE exposure range are also associated with obesity.