Transgenerational Inheritance of Prenatal Obesogen Exposure

Bruce Blumberg, Ph.D.
Department of Developmental and Cell Biology
Department of Pharmaceutical Sciences
Developmental Biology Center
University of California, Irvine
Main Points

- Obesogens exist and contribute to obesity epidemic
- Obesogen action may involve reprogramming of stem cells
- Are the effects of obesogen exposure permanent?
The Worldwide Obesity Epidemic

- 34% of the US population are clinically obese (BMI > 30)
  - Double worldwide average (CDC statistics)

- 68% are overweight (BMI > 25) - 86% estimated by 2020
The Worldwide Obesity Epidemic

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The Worldwide Obesity Epidemic

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  - Double worldwide average (CDC statistics)

• 68% are overweight (BMI > 25) - 86% estimated by 2020

• Obesity accounts for a huge fraction of healthcare costs
  - $85.7 billion annually in US (2005), $147 billion (2009)
  - New model (J. Health Economics, 2012) - $209.7 billion in 2008
    • 20.6% of US healthcare costs.

• Obesity is associated with increases in
  • Metabolic syndrome -> type 2 diabetes
  • cardiovascular disease
  • hypertension
  • stroke
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

Sources: CDC (map), U.S. Census bureau (numbers)
How does obesity occur?

- **Prevailing wisdom** – “couch potato syndrome”
  - Positive energy balance, i.e., too much food, too little exercise

- **Are there other factors in obesity?**
  - Stress (elevated glucocorticoids)
  - Inadequate sleep (stress?)
  - “Thrifty” genes which evolved to make the most of scarce calories
  - Viruses, gut microbes, SNPs

- **What about role of prenatal nutrition or in utero experience?**
  - Southampton studies
  - Maternal smoking decreases birth weight and increases obesity

- **Is there a role for industrial chemicals in rise of obesity?**
  - Baillie-Hamilton (2002) postulated a role for chemical toxins
  - Obesity epidemic roughly correlates with a marked increase in the use of chemicals (plastics, pesticides, etc.)

- **Many chemicals have effects on the endocrine system**
Hormonal control of weight

- Hormonal control of appetite and metabolism
  - Leptin, adiponectin, ghrelin are key players
  - Leptin, adiponectin - adipocytes
  - Grehlin - stomach
  - Thyroid hormone/receptor
    - Sets basal metabolic rate

- Hormonal control of fat cell development and lipid balance
  - Regulated through nuclear hormone receptors RXR, PPARγ
  - PPARγ - master regulator of fat cell development
    - increased fat cell differentiation
    - increased storage in existing cells
    - Increased insulin sensitivity

Endocrine Disrupting Chemicals (EDCs) affect many organ systems

- “Endocrine Disruptor - an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.” - The Endocrine Society, 2012
  - Wrong signal, loss of signal, wrong place at wrong time
  - Hormones work at low concentrations and so do EDCs

- How are we exposed to EDCs?
  - persistent pollutants (POPs)
  - dietary components (pesticides)
  - personal care products
  - cleaning materials
  - food packaging
Evidence for adverse reproductive outcomes from EDC exposure is very strong
- mounting evidence for effects on ... thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis

11/10/2009 - AMA Adopts Endocrine Society Resolution
- Need new policies to decrease EDC exposure

EU parliament (3/15/2013) directed the European Commission to present bans or restrictions of the use of EDCs by June 2015
- (489 for, 102 against)
# Endocrine Disrupting Chemicals (EDCs)

**HERBICIDES**
- 2,4,-D
- 2,4,5,-T
- Alachlor
- Amitro
- Atrazine
- Linuron
- Metribuzin
- Nitrofen
- Trifluralin

**FUNGICIDES**
- Benomyl
- Ethylene thiourea
- Fenarimol
- Hexachlorobenzene
- Mancozeb
- Maneb
- Metiram - complex
- Tributyltin
- Vinclozolin
- Zineb

**INSECTICIDES**
- Aldicarb
- beta-HCH
- Carbaryl
- Chlordane
- Chlordecone
- DBCP
- Dicofol
- Dieldrin
- DDT and metabolites
- Endosulfan
- Heptachlor / H-epoxide
- Lindane (gamma-HCH)
- Malathion
- Methomyl
- Methoxychlor
- Oxychlordane
- Parathion
- Synthetic pyrethroids
- Transnonachlor
- Toxaphene

**INDUSTRIAL CHEMICALS**
- Bisphenol - A
- Polycarbonates
- Butylhydroxyanisole
- Cadmium
- Chloro- & Bromo-diphenyl
- Dioxins
- Furans
- Lead
- Manganese
- Methyl mercury
- Nonylphenol
- Octylphenol
- PBDEs
- PCBs
- Pentachlorophenol
- Penta- to Nonylphenols
- Perchlorate
- PFOA
- p-tert-Pentylphenol
- Phthalates
- Styrene

**TESTOSTERONE SYNTHESIS INHIBITOR**
- Estrogen receptor agonist
**THYROID HORMONE DISRUPTOR**
- Androgen receptor antagonist

**METALS**

- Cadmium
- Chloro- & Bromo-diphenyl
- Dioxins
- Furans
- Lead
- Manganese
- Methyl mercury
- Nonylphenol
- Octylphenol
- PBDEs
- PCBs
- Pentachlorophenol
- Penta- to Nonylphenols
- Perchlorate
- PFOA
- p-tert-Pentylphenol
- Phthalates
- Styrene
Endocrine Disrupting Chemicals (EDCs)

Pesticides
- Alachlor
- Amitrole
- Atrazine
- Linuron
- Metribuzin
- Nitrofen
- Trifluralin

Herbicides
- Nitrofen
- Trifluralin

Fungicides
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- Ethylene thiourea
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- Mancozeb
- Maneb
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Insecticides
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- Chlordane
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- Malathion
- Methomyl
- Methoxychlor
- Oxychlordane
- Parathion
- Synthetic pyrethroids
- Transnonachlor
- Toxaphene

Flame Retardants
- Carbaryl
- Chlordane
- Dieldrin
- DDT and metabolites
- Endosulfan

Industrial byproducts
- Dieldrin
- DDT and metabolites
- Endosulfan

Surface protectors
- Methomyl
- Methoxychlor

Sunscreens
- Transnonachlor
- Toxaphene

Plastics
- Butylhydroxyanisole
- Cadmium
- Chlorophenyl dichloride

Plasticizers
- Lead
- Manganese
- Methyl mercury

Cosmetics
- PBDEs
- PCBs
- Pentachlorophenol

Over 1,000 EDCs
- p-tert-Pentylphenol
- Phthalates
- Styrene

Testosterone synthesis inhibitor
Thyroid hormone disruptor
Estrogen receptor agonist
Androgen receptor antagonist

METALS

INDUSTRIAL CHEMICALS
- Bisphenol - A
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- Cadmium
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- Perchlorate
- PFOA
- p-tert-Pentylphenol
- Phthalates
- Styrene
EDCs are in many personal care products

- **Shampoo**: Average number of chemicals: 15. Most worrying: Sodium Lauryl Sulphate; Tetrasodium and Propylene Glycol. Possible side-effects: Irritation; possible eye damage.

- **Hairspray**: Average number of chemicals: 11. Most worrying: Octinoxate, isopropylparaben. Possible side-effects: Allergies; irritation to eyes, nose and throat; hormone disruption, linked to changes in cell structure.

- **Eye Shadow**: Chemicals: 26. Most worrying: Polyoxyethylene terephthalate. Possible side-effects: Linked to cancer; infertility; hormonal disruptions and damage to the body's organs.


- **Foundation**: Chemicals: 24. Most worrying: Polymethyl methacrylate. Possible side-effects: Allergies; disrupts immune system; links to cancer.

- **Lipstick**: Chemicals: 33. Most worrying: Polymethyl methacrylate. Possible side-effects: Allergies; links to cancer.


- **Perfume**: Chemicals: 250. Most worrying: Benzaldehyde. Possible side-effects: Irritation to mouth, throat and eyes; nausea; linked to kidney damage.

- **Fake Tan**: Chemicals: 22. Most worrying: Ethyiparabens, Methylparabens, Propylparabens. Possible side-effects: Rashes; irritation; hormonal disruption.

- **Body Lotion**: Chemicals: 32. Most worrying: Methylparabens, Propylparabens, Polyoxyethylene Glycol, which is also found in oven cleaners. Possible side-effects: Rashes; irritation; hormonal disruption.
EDCs are in many personal care products...
Not everyone agrees about the hazards of EDCs (e.g., industry stakeholders)

NEWS ITEM: Estrogen-imitating chemicals in the environment suspected of wide-ranging biological anomalies...

(including hermaphroditism in animals and lower sperm counts in human beings)

We in the business community prefer a cautious 'wait-and-see' approach over needless media scare-mongering...
# Recent trends in select reproductive disease, disorders and function

<table>
<thead>
<tr>
<th>Reproductive Diseases/Disorders</th>
<th>Increase</th>
<th>Period</th>
<th>Location</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular cancer</td>
<td>1–6%</td>
<td>1953 - 1999</td>
<td>Europe</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>1973 - 2003</td>
<td>USA</td>
<td>[21]</td>
</tr>
<tr>
<td>Certain childhood cancers</td>
<td>20 – 24%</td>
<td>1976 - 2005</td>
<td>USA</td>
<td>[22]</td>
</tr>
<tr>
<td>Autism</td>
<td>700–800%</td>
<td>1990 - 2006</td>
<td>California</td>
<td>[23]</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>3% per year</td>
<td>1997 - 2006</td>
<td>USA</td>
<td>[24]</td>
</tr>
<tr>
<td>Birth defects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Gastroschisis</em></td>
<td>300%</td>
<td>1978 - 2005</td>
<td>California</td>
<td>[26]</td>
</tr>
<tr>
<td><em>Congenital hypothyroidism</em></td>
<td>138%</td>
<td>1987 - 2003</td>
<td>New York</td>
<td>[27]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive Function</th>
<th>Time</th>
<th>Location</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported difficulty conceiving and maintaining pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>All ages</em></td>
<td>60% more women</td>
<td>1982; 2002</td>
<td>USA</td>
</tr>
<tr>
<td><em>&lt;25 years old</em></td>
<td>200% more women</td>
<td>1982; 2002</td>
<td>USA</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2.9% shorter gestation</td>
<td>1992 - 2002</td>
<td>USA</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>19-36%</td>
<td>1968-2002</td>
<td>Norway</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>122%</td>
<td>1989-2004</td>
<td>USA</td>
</tr>
<tr>
<td>Premature puberty:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Age at onset of breast development</em></td>
<td>1 – 2 years younger</td>
<td>1940 - 1994</td>
<td>USA, Denmark</td>
</tr>
<tr>
<td><em>Age at onset of menstruation</em></td>
<td>2.5 – 4 months younger</td>
<td>1940 - 1994</td>
<td>USA</td>
</tr>
<tr>
<td>Sperm count</td>
<td>~1% decline per year</td>
<td>1931 - 1994</td>
<td>Western countries</td>
</tr>
<tr>
<td>Serum testosterone</td>
<td>1% decline per year</td>
<td>1987 - 2004</td>
<td>Boston, USA</td>
</tr>
</tbody>
</table>
Endocrine Disrupting Chemicals (EDCs)

- Are EDC-mediated disturbances in endocrine signaling pathways involved in adipogenesis and obesity
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Endocrine Disrupting Chemicals (EDCs)

- Are EDC-mediated disturbances in endocrine signaling pathways involved in adipogenesis and obesity
The Nuclear Hormone Receptor Superfamily

### Known Receptors

#### Classical receptors (from biochemistry)
- **GR**: cortisol
- **MR**: aldosterone
- **AR**: testosterone
- **PR**: progesterone
- **ER**: estradiol
- **VDR**: 1,25-(OH)₂ vit D₃
- **TR**: triiodothyronine
- **EcR**: 20-OH ecdysone

#### Orphan Receptors
- **Vertebrate**
  - TR-2 α,β
  - NGFI-B α,β,γ
  - ROR α,β,γ
  - Rev-erb α,β
  - SF-1 α,β
  - COUP α,β,γ
  - HNF-4 α, β
  - Tlx α,β
- **Drosophila**
  - DHR78
  - DHR38
  - DHR3
  - E75, E78
  - FTZ-F1 α,β
  - svp
  - HNF-4
  - till

#### Adopted (EX) Orphans
- **RAR**: all-trans retinoic acid
- **RXR**: 9-cis retinoic acid
- **PPAR**: fatty acids, eicosanoids
- **LXR**: oxy-sterols
- **FXR**: bile acids
- **BXR**: benzoates

#### Nearly adopted orphans (natural ligands?)
- **CAR**: androstanes, xenobiotics
- **SXR/PXR**: steroids, xenobiotics

### Orphan Receptors

#### Vertebrate
- **No known homologs**
  - ERR α,β,γ
  - DAX-1
  - SHP
  - GCNF

#### C. elegans
- ~250 nuclear receptors

#### D. melanogaster
- ~20 nuclear receptors

#### H. sapiens
- ~48 genes

#### Arabidopsis
- no family members
EDCs and the obesogen hypothesis

- **Obesogens** - chemicals that inappropriately stimulate adipogenesis and fat storage, disturb adipose tissue homeostasis, or alter control of appetite/satiety to lead to weight gain and obesity

- Pre- and postnatal exposure to EDCs such as environmental estrogens (ER) increases weight
  - DES, genistein, bisphenol A

- Thiazolidinedione anti-diabetic drugs (PPARγ)
  - Increase fat storage and fat cell number at all ages in humans

- Urinary phthalates correlate with waist diameter and insulin resistance in humans
  - Many chemicals linked with obesity in epidemiological studies

- Several compounds cause adipocyte differentiation in vitro (PPARγ)
  - Phthalates, BPA, alkylphenols, PFOA, organotins

- Existence of obesogens is plausible
Endocrine disruption by organotins

- Organotins -> imposex in mollusks
- Sex reverses genetically female flounder and zebrafish -> males
- Which hormone receptors might be organotin targets?
- We found that tributyltin (TBT)
  - Binds and activates at ppb (low nM) two nuclear receptors, RXR and PPARγ critical for adipogenesis
  - TBT induced adipogenesis in cell culture models (nM)
  - Prenatal TBT exposure led to weight gain in mice, in vivo

Grun et al., Molec Endocrinol, 2006
TBT increases testis fat pad weight at 10 weeks

16% increase
$p = 0.037$

Fat depot size increases at the expense of overall body mass

Grun et al., Molec Endocrinol, 2006
How does TBT exposure cause weight gain?

- Changes in the hormonal control of appetite and satiety?

- Altered ability of adipocytes to process and store lipids?

- Increased number of adipocytes or pre-adipocytes?

- Mesenchymal stem cells (MSCs) (now called multipotent stromal cells) precursors to many lineages including bone, cartilage, and adipose.
  - MSCs differentiate into adipocytes following rosiglitazone exposure
  - MSCs may (or may not) home to adipose depots after induction

- **Hypothesis**: TBT induces adipogenesis in MSCs
MSCs can give rise to many cell types in vivo

- PPARγ controls choice between fat and bone pathways
- Expression and activation of PPARγ favors the fat and inhibits bone formation.

Prenatal Exposure

- CMC
- ROSI
- TBT

- C57Bl6/J Pregnant Dam
- In utero exposed offspring
- MSC isolation and culture

Takada et al., 2009 Nature Reviews Immunology 5, 442-447

Kirchner et al, 2010 Molecular Endocrinology 24, 526-539
Prenatal TBT exposure reprograms MSCs to become fat cells instead of bone cells

- TBT exposure increases fat depot size in 4 month old males and females
- TBT only decreases BMD in females (like ROSI in humans)
How does prenatal TBT exposure promote adipocyte differentiation?

Effects of in utero TBT exposure on adipogenic pathway genes

<table>
<thead>
<tr>
<th>uninduced</th>
<th>+ TBT 14D</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARγ2+/−</td>
<td>PPARγ2+</td>
</tr>
<tr>
<td>Fabp4+</td>
<td>Fabp4+</td>
</tr>
<tr>
<td>LEP+</td>
<td>LEP+</td>
</tr>
<tr>
<td>Pref1−</td>
<td>Pref1−</td>
</tr>
<tr>
<td>GyK+</td>
<td>GyK+</td>
</tr>
<tr>
<td>PEPCK+</td>
<td>PEPCK+</td>
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<td>/</td>
<td>/</td>
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<tr>
<td>/</td>
<td>LPL+</td>
</tr>
<tr>
<td>/</td>
<td>ADIPOQ+</td>
</tr>
</tbody>
</table>

TBT has epigenetic effects on PPARγ target genes

Kirchner et al., 2010 Molec Endocrinol, 24, 526-539
Are effects of TBT exposure transgenerational? (i.e., permanent)

**TREATMENTS**
- DMSO
- ROSI 0.5 μM
- TBT 5.42 nM (50x < NOAEL)
- TBT 54.2 nM (5x < NOAEL)
- TBT 542 nM

**MULTI-GENERATIONAL EFFECT**
- FEMALE PRE-TREATMENT
- P0 MATING
- F1 BIRTH

F1→ MATE→ F2
- Sacrificed
- Mating

F2→ MATE→ F3
- Sacrificed

8 weeks old
- Body weight
- Adipose tissue weight
- Adipocyte size
- MSC gene expression profile
- Liver adiposity
- Hepatic gene expression

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

*Heavier fat depots*

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

*Larger fat cells*

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

*Increased expression of fat-specific genes in MSCs*

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

*Non-alcoholic fatty liver disease*

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

Non-alcoholic fatty liver disease

Chamorro-Garcia et al., Environ Health Perspect, 2013
TBT exposure has transgenerational effects

Increased hepatic gene expression

Chamorro-Garcia et al., Environ Health Perspect, 2013
Obesogen exposure and development

- Organotins are exceptionally potent agonists of RXR and PPARγ at environmentally-relevant levels (ppb)
  - ~5 nM EC₅₀, 12.5 nM Kᵥ on RXRα
  - ~20 nM EC₅₀ and Kᵥ on PPARγ

- TBT drives adipocyte differentiation in cell culture models

- TBT exposure during development induces adipogenesis in two vertebrate species: mouse and Xenopus
  - Inhibits bone formation in culture and in females

- The effects of maternal TBT exposure are transgenerational
  - Fat depot size, adipocyte size, MSC gene expression - males
  - Adipocyte size, MSC gene expression - females
  - Little overall effect on total weight at 8 weeks

- Multiple potential modes of action
  - PPARγ-RXR
  - Aromatase expression/function - estradiol levels
  - Glucocorticoid levels
  - Other stressors?
Conclusions - organotins and obesity

• Is organotin exposure a contributing factor for obesity?
  - Adult exposure rapidly induces adipogenic genes
    • Drugs that activate PPARγ increase obesity
  - Prenatal TBT exposure permanently alters adult phenotype
  - Prenatal TBT exposure recruits MSCs to adipocyte lineage and diverts them from bone lineage

• Are humans exposed to sufficient levels of TBT for concern?
  - PVC is up to 3% w/w (0.1 M) organotins
  - Prevalent contaminants in dietary sources
  - Fungicide on high value crops, used in water systems
  - Average blood level of 27 nM in 32 random people tested
  - TPT levels from ~0.5–2 nM in Finnish fishermen

• Human exposure to organotins may reach levels sufficient to activate high affinity receptors
  - 1000 x lower dose than natural dietary RXR and PPARγ ligands

Is the environment making us fat?
Obesogens - Just the Tip of the Iceberg?

<table>
<thead>
<tr>
<th>Obesogens</th>
<th>TBT/TPT</th>
<th>DES</th>
<th>Nicotine</th>
<th>fructose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phthalates</td>
<td>Bisphenol A</td>
<td>Air pollution</td>
<td>COX2 inhibitors</td>
<td></td>
</tr>
<tr>
<td>PFOA</td>
<td>Genistein</td>
<td>BaP</td>
<td>PCBs ?, PBDEs ?</td>
<td></td>
</tr>
</tbody>
</table>

- Organophosphate pesticides
- Imidazole fungicides

- What don't we know yet?
  - How many obesogens are out there
  - Body burdens in population
  - Molecular targets of action beyond RXR-PPAR
  - Critical windows of exposure
  - How does prenatal exposure alter adult phenotype?
  - Is the prenatal reprogramming epigenetic?
Implications For Human Health

- Diet and exercise are insufficient to explain obesity epidemic particularly in the very young

- Obesogens inappropriately stimulate adipogenesis and fat storage
  - Prescription drugs
    - Thiazolidinedione anti-diabetic drugs (Actos, Avandia)
    - Atypical antipsychotics, anti-depressants
  - Environmental contaminants
    - organotins, estrogens (BPA, DEHP), PFOA/S, DDE, POPs
    - triflumizole, zoxamide

- Prenatal obesogen exposure reprograms exposed animals to be fat
  - Epigenetic changes alter fate of stem cell compartment -> more preadipocytes and more adipocyte progenitors

- Obesogens shift paradigm from treatment to prevention during pregnancy, childhood and puberty
  - Reduced exposure to obesogens, optimized nutrition
Chemicals with Transgenerational Effects

- Tributyl tin (RXR, PPARγ, estrogen) plastic, industrial use, water pipes) - increased fat mass, reprogram stem cells to produce more fat cells over time, fatty liver disease (Chamorro-cia et al, 2013)

- Vinclozolin (anti-androgen) - fungicide, impairs male reproductive function (Anway and Skinner, 2005)

- Plastics derived mixture, BPA, DEHP, DBP, (estrogen, anti-androgen) obesity, reproductive diseases, sperm epimutations (Manikkam et al, 2013)

- Hydrocarbons, JP-8 jet fuel (?) obesity, reproductive diseases, sperm epimutations (Tracey et al, 2013)

- BPA, estrogen (plastics, thermal paper, recycled paper, food packaging), altered social interactions, modified gene expression (Wolstenholme et al, 2012)
EDCs and Human Health

- Endocrine disruptors act at low, environmentally-relevant doses to adversely affect a variety of organ systems.

- Endocrine disruptors are widespread in diet, personal care products and environmental contaminants.

- Prenatal or early life exposures to endocrine disruptors can have permanent effects on the health and susceptibility to disease of exposed individuals.

- Effects of prenatal exposures can be transmitted to subsequent generations, i.e., your descendents.

- Existence of chemicals with transgenerational effects raises the stakes for the consequences of our failure to reduce exposure to these chemicals.
• UCI - Blumberg Lab
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