Obesity: Role of Environmental Chemicals

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Overview

- History
- Background information on obesity: setting the stage
- Examples of environmental chemicals and obesity
- Data gaps and needs
A Little History...

2002-2003
Ballei-Hamilton, Chemical toxins: a hypothesis to explain the global obesity epidemic, J Alt and Comp Med, 2002
Heindel: Endocrine Disruptors and the Obesity Epidemic, Commentary, Tox Sci, 2003

2002-2004
NIEHS PAR: The fetal basis of adult disease: role of the environment
Levin and Heindel, Obesity: fetal origins and environmental influences, Duke Integrated Toxicology Program and NIEHS sponsored symposium, 2004

2006
Bruce Blumberg coined “Obesogen”

2011-2015
NIEHS PAR: Role of environmental chemical exposures in the development of obesity, type 2 diabetes, and metabolic syndrome (R21 and R01)

2012 - Obesity grantee meeting
2014 - Metabolic disruptor meeting, Parma
Chemical Toxins: A Hypothesis to Explain The Global Obesity Epidemic

![Graph showing synthetic chemical production and percent overweight adults over years](image)

Baillie-Hamilton 2002
### Numerous Chemicals Produce Weight Gain

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pesticides</strong></td>
<td>(Chadwick et al., 1988; Deichmann et al., 1972; Deichmann et al., 1975; Dorgan et al., 1999; Hovinga et al., 1993; Stellman et al., 1997; Takahama et al., 1972; Villeneuve et al., 1977)</td>
</tr>
<tr>
<td><strong>Organophosphates</strong></td>
<td>(Breslin et al., 1996; Cranmer et al., 1978; Nicolau, 1983; Tran-kina et al., 1985)</td>
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<tr>
<td><strong>Carbamates</strong></td>
<td>(Walker et al., 1994; Yen et al., 1984)</td>
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<tr>
<td><strong>Polychlorinated biphenyls</strong></td>
<td>(Clark, 1981; Dar et al., 1992; Hovinga et al., 1993)</td>
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<tr>
<td><strong>Polybrominated biphenyls, fire retardants</strong></td>
<td>(Gupta et al., 1983)</td>
</tr>
<tr>
<td><strong>Plastics, phthalates, and bisphenol A</strong></td>
<td>(Ema et al., 1990; Howdeshell et. al., 1999; Rubin et al., 2001)</td>
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<tr>
<td><strong>Heavy metals, such as cadmium and lead</strong></td>
<td>(Antonio et al., 1999; Hovinga et al., 1993)</td>
</tr>
<tr>
<td><strong>Solvents</strong></td>
<td>(Chu et al., 1986; Gaworski et al., 1985; Hardin et al., 1987; Moser et al., 1995; Wahlberg, 1979)</td>
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## Causes of Weight Gain (Multifactorial)

<table>
<thead>
<tr>
<th>Genetic background</th>
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<tbody>
<tr>
<td><strong>Congenital Illness</strong></td>
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<tr>
<td>(Hypothyroidism, Cushing’s Syndrome)</td>
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<tr>
<td><strong>Drug use</strong></td>
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<tr>
<td>(Thiazolinedione antidiabetics; Tricyclic antidepressants; Selective serotonin uptake inhibitors; Atypical anti-psychotic drugs)</td>
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<tr>
<td><strong>Viruses</strong></td>
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<tr>
<td>(Adenovirus 36)</td>
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<tr>
<td><strong>Antibiotics</strong></td>
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<tr>
<td><strong>Environment</strong></td>
</tr>
<tr>
<td>(Lack of exercise; Lack of sleep; Microbiome; Stress (increased glucocorticoids); Nutrition (sugar, fats, additives); Environmental chemicals)</td>
</tr>
</tbody>
</table>
Control of Weight: An Endocrine Issue

Weight gain is controlled by the endocrine system. Thus it is sensitive to disruption by endocrine disrupting chemicals.
Endocrine Disruptors Defined

An **exogenous chemical**, or mixture of chemicals, that **interferes with** any aspect of **hormone action**

Endocrine Disrupting Chemicals

- Current use Pesticides
- Flame Retardants
- Plastics
- Herbicides
- Industrial byproducts
- Plasticizers
- Personal Care Products
- Surfactants
- Cosmetics
- Solvents
- Sunscreens
- Antioxidants
- Heavy Metals
- Persistant Organic Pollutants
- Polycyclic aromatic Compounds
We All Carry a Chemical Body Burden

- 287 chemicals in cord blood
- 47 chemicals in every pregnant woman tested
- In breast milk (PCBs, dioxins, pesticides, flame retardants)
- Of people tested by CDC:
  - BPA in 93%
  - Phthalates 50-97%
  - PFCs in 91-99%
  - PBDEs in 100%
  - Triclosan in 80%
  - PCBs in 100%

The presence of chemicals in the womb does not mean that they are causing harm.

However, it does mean that we have accepted a strategy whereby every pregnant woman is contaminated with chemicals, without her knowledge...with the potential for harm.
Developmental Origins of Disease

• It is clear that developmental exposures to environmental chemicals can lead to a variety of diseases/dysfunctions later in life.

• Sensitivity to develop obesity also has its origins during development (in utero and early childhood) with some effects during adulthood.

• What is the role of environmental chemical exposures?
Developmental Basis of Obesity: Obesogen Hypothesis

• An emerging **hypothesis** that the obesity epidemic is due, in part, to environmental exposures during development

• We hypothesize that there is a subset of endocrine disruptors, obesogens, that can act during development to

  Food intake and exercise are important but environmental chemicals can alter the “set-point” for gaining weight – how much food it takes to put on weight – and also how much exercise is needed to reduce weight via alterations in developmental programming.

thereby altering the programming of the “setpoint” or sensitivity for developing obesity later in life.
Proof of Principle: Effect of Maternal Smoking during Pregnancy on Childhood Weight at School Entry

Risk Estimate

- never smoked (n = 3,847)
- < 10 cigarettes per day (n = 638)
- ≥ 10 cigarettes per day (n = 110)

Overweight

Obese

von Kries et al., 2002
Proof of Principle: Developmental Exposure to DES

- Exposure of CD-1 mice to DES for 5 days at birth resulted in increased weight gain starting at puberty in female mice.
- No change in food intake or exercise.
- Non-monotonic dose response.

Newbold et al.
Developmental BPA Exposure and Weight Gain

Animal Studies
- Multiple labs
- Multiple species
- Sex differences
- Dose range (10ug/kg-70ug/kg)

Human Studies
- Cross sectional: adults and children
- Prospective

- N=12-14/gp
- GD18-Lactational day 16
- CD-1 Males

Greenberg and Rubin (unpublished data)
Developmental Exposure to BPA Affects Brain Satiety Centers

Fetal BPA exposure

Appetite (NPY) neurons

Increased Food Intake

Weight Gain

Satiety (POMC) neurons

Ross and Desai, unpub
Developmental DEHP Exposure Increases Visceral Fat Tissue and Adipocyte Number

Schmidt et al., EHP, 2012
Examples of Published Human Studies

- Gladen et al, Prenatal & early life exposures to low levels of PCBs and DDE are associated with increased weight in boys and girls at puberty, J. Pediatr., 2000.

- Smink et al, Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years, Acta Paediatrica, 2008

- Verhulst et al, Intrauterine exposure to environmental pollutants (POPs) and body mass during the first 3 years of life, EHP, 2009

- Syme et al, Prenatal exposure to maternal cigarette smoking and accumulation of intra-abdominal fat during adolescence, Obesity, 2010

- Halldorsson et al, Prenatal exposure to perfluooctanoate and the risk of overweight at 20 years of age: a prospective cohort study, EHP, 2012

- Runde et al, Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy AJ, 2012

- Cupul-Uicab et al, Prenatal exposure to persistent organochlorines and childhood obesity in the US collaborative perinatal project, EHP, 2013

- Harley KG et al, Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the SHAMACOS cohort, EHP, 2013

- Valvi et al, Prenatal bisphenol A urine concentration and early rapid growth and overweight risk in the offspring, Epidemiology, 2013

- Warner et al, Prenatal exposure to dichlorodiphenyltrichloroethane and obesity at 9 years of age in the CHAMACOS study cohort, AJM, 2014
Prenatal PAH Exposure is Associated with BMI Z-score at Age 5 & 7

Adjusted Mean BMI Z-score

BMI Z-score at age 5
P for trend = 0.01, n=422

BMI Z-score at age 7
P for trend = 0.04, n=341

Prenatal Ambient Air PAH Exposure (Ng/M$^3$)

Adjusted for age, gender, ethnicity, birth weight, maternal obesity and maternal receipt of public assistance [Rundle et al., AJE, 2012]
Epigenetic Transgenerational Inheritance of Obesity

• Positive results
  - Tributyl tin (M and F)
  - DDT (M and F)
  - Hydrocarbon mixture (jet fuel) (M and F)
  - BPA DEHP, DBP (M and F)

• Negative results
  - Permethrin/DEET mixture
  - Vinclozolin
  - Dioxin
Obesogens – Just the Tip of the Iceberg?

- PFOA
- Estradiol
- Genistein
- Lead
- PCBs
- Phthalates
- DES
- Nicotine
- Air Pollution
- Tributyltin
- PBDEs
- Bisphenol A
- Monosodium Glutamate
- Artificial Sweeteners
- Benzo[a]pyrene (PAH)
- Fructose?
- Some Drugs
- Organophosphate Pesticides (Parathion, Diazinon, Chlorpyrifos)
- Organochlorine Pesticides (DDT/DDE, HCB)
- Triflumizole (fungicide)
Current NIEHS Obesity/Diabetes Funding

- **57 total grants** (P01, R01, R03, R21, U01) currently funded to address obesity and diabetes

- Of funded obesity and diabetes grants:
  - **20** work with animal models
  - **5** are basic cellular/molecular studies
  - **32** work with human cohorts, and exposures studied are different for **adult** versus **birth** cohorts

### Exposures Studied: Adult Cohorts

<table>
<thead>
<tr>
<th>Air Pollutants</th>
<th>Particulates</th>
<th>Traffic Pollutants</th>
<th>NO / NO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorinated Compounds</td>
<td>PCBs</td>
<td>Dioxins</td>
<td>Hexachlorobenzene</td>
</tr>
<tr>
<td>Fluorinated Compounds</td>
<td>PFCs</td>
<td>PFOAs</td>
<td>PFOSs</td>
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<tr>
<td>Metals</td>
<td>Arsenic</td>
<td></td>
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<tr>
<td>Nutrition / Diet</td>
<td>High fat diet</td>
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<tr>
<td>Pesticides</td>
<td>Chlorinated Pesticides</td>
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</table>

### Exposures Studied: Birth Cohorts

<table>
<thead>
<tr>
<th>Hormonal Mimics</th>
<th>BPA</th>
<th>Phthalates</th>
<th>Other EDCs</th>
<th>DES</th>
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<tbody>
<tr>
<td>Air Pollutants</td>
<td>Particulates</td>
<td>Traffic Pollutants</td>
<td>PAHs</td>
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<tr>
<td>Metals</td>
<td>Arsenic</td>
<td>Lead</td>
<td>Cadmium</td>
<td>Copper</td>
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<tr>
<td>Nutrition / Diet</td>
<td>High fat diet</td>
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<tr>
<td>Pesticides</td>
<td>Chlorinated pesticides</td>
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<tr>
<td>Psychosocial Stress</td>
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Data Gaps and Needs...

This “obesogen” field is less than 10 years old thus there is a long list of data needs/questions to be answered.

• Determine which chemicals have ability to cause weight gain (characteristics)?
  – Screens to detect and prioritize
• Define dose responses (internal doses), timing, sites and mechanism(s).
• Assess multiple chemicals and integrate with other stressors.
• Measure multiple overlapping endpoints: diabetes, liver function, muscle metabolism, brain satiety, GI effects, inflammation.
• Coordinate animal studies and endpoints with human cohort studies….improved interactions between epidemiologists and animal researchers.
• Improve exposure assessments in human studies...integrate genetics and environmental exposures to disease onset and severity.
• Prove altered “setpoint” or susceptibility hypothesis.
• Hold Grantee meetings...
• Integrate into field of obesity research and prevention.
We hold our future in our hands and it is our children

The End....but just the beginning