Establishing Causal Links Between Obesogens and Obesity

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What is Causing the Obesity Pandemic?

Key Question: What has changed in last 50-70 years?

**NOT Major Players**
- Genetics
- Lack of Exercise

**Nutrition (diet)**
- AND Obesogens

- **Timeline**
- **Epidemic of obese 6-month-old babies**
  
  Kim et al Obesity, 2005

- **Obesity increasing in primates, feral rodents and domestic pets**
  
Current Focus

• The current focus of the clinical community is on overeating as the cause of obesity epidemic thus their focus is on diets, drugs and surgery

• And if that was working there should be a decline in the rates of obesity

• BUT the rates of global obesity rates are increasing especially in infants and children

• THEREFORE, something is missing... a focus on what are the causes of the overeating?

• WE PROPOSE that obesogens are the key...

• Obesogens modify eating behaviors AND

• Obesogens provide a focus on prevention
Endocrine Control of Metabolism

All hormones and hormonal pathways are potential targets for obesogens
Endocrine Control of Metabolism

All hormones and hormonal pathways are potential targets for obesogens
An endocrine disruptor is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.

Zoeller et al., Endocrinology, 2012

A chemical designed for specific purpose…but with side effect…mimic or antagonize hormone action. (~1000)

>100,000 chemicals in commerce

Some % are toxic because they interfere with some aspect of the endocrine system

Endocrine Disruptors

Some endocrine disruptors stimulate weigh gain

Obesogens
Principles of Obesogen Action (same as principles of hormone action)

- Obesogens act via **hormone receptors** (agonist, or antagonist).
- Obesogens responses are **tissue specific**.
- Obesogen effects are **sexually dimorphic**.
- Obesogens can act at **low doses**.
- Obesogens can have **non-monotonic dose responses** (non-linear).
- Obesogen effects are **life-stage specific**: effects in adults but **development is most sensitive life-stage**.
- There may be a **lag time between exposure and weight gain**.
Obesogen Paradigm: Obesity Starts *in Utero*

• The obesity pandemic is due, in part, to exposures to endocrine disrupting chemicals during development.

• These chemicals, called **obesogens**, act during development to
  
  • *Interfere with adipose tissue development*
    • Via an increase in the number or size of fat cells
  
  • *Interfere with the control food intake and metabolism*
    • Via effects on the development of the pancreas, liver, GI tract, brain and/or muscle

thereby altering the programming of the obesity set-point or sensitivity for developing obesity later in life.
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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.
General Scheme of Obesogen Action

Obesogen

Interference with hormone and signaling pathways

Adipocyte differentiation, number and size

Increase food intake

Altered microbiome

Obesogen
Obesogens Can Alter Many Metabolic Endpoints
Exposures to Obesogens Are Ubiquitous (Air, Dust, Food, Water, Skin)

We all carry a burden of many obesogens
We are born pre-polluted!

- Bisphenols
- Pthalates
- Parabens
- Non-steroid estrogens
- Pharmaceutical drugs
- Personal care products
- Food preservatives
- Vinyl flooring
- Resins, Can linings, Thermal paper
- Hard/Soft plastic
- Anti-fouling paints Disinfectants
- Solvents
- Pesticides
- Polychlorinated biphenyls
- Organotins
- Electronics
- Electricals
- Brominated Flame retardants
- Clothing
- Furniture
Clinicians are Already Familiar with Obesogens

Antidepressant Medications and Body Weight

Diabetes Medications and Body Weight

\( \uparrow: \text{thiazolidinediones, sulfonylureas, insulin} \)

\( \downarrow: \text{GLP-1RA, SGLT-2i, metformin} \)

Diethylstilbestrol (DES)

Enzymatic activity inhibited by tributyl tin

Environmental tributyl tin

PMID: 32067051

PMID: 41669880

PMID: 30465123
Proof of Principle: Effect of Maternal Smoking during Pregnancy on Childhood Weight at School Entry

von Kries et al., 2002

Strong human and animal data
Obesogens with the Most Supporting Data

- Maternal Smoking (nicotine)
- Air Pollution (PAH, PM$_{2.5}$)
- DDT
- Bisphenols (A, S, F, AF...)
- Phthalates (DEHP, DBP, DisBP)
- Tributyl tin

By definition, *in vivo* data needed!
Potential obesogen: only *in vitro* data.

Red indicates a replacement chemical
Additional Obesogens*

- Perfluorinated compounds (PFAS)
- Flame retardants (PBDE, OPFR)
- Dioxin and polychlorinated biphenyls (PCBs)
- Fructose
- Non-nutritive sweeteners
  - Aspartame
  - Sucralose
  - Saccharin
- Agricultural chemicals
  - Chlorpyrifos
  - Diazinon
  - Neonicotinoids
  - Permethrin
  - Tolyfluanid
- Food preservatives/additives/emulsifiers
  - Methyl and butyl paraben
  - Tween 80/carboxymethylcellulose
  - 3-tert-butyl-4-hydroxyanisole (3-BHA)
  - Dioctyl sodium sulfoisuccinate (DOSS)
- Monosodium Glutamate
- Cadmium
- Arsenic
- Dibutyltin

RED indicates a replacement chemical

*An obesogen does not have to act via an endocrine mechanism
The Western Diet is Obesogenic

- High fat
- High sugar
- High salt
- Low fiber
- High in processed food
- Inadequate fresh fruit and vegetables

Contains obesogens

- Bisphenol A
- Phthalates
- PFAS
- Fructose
- Methyl and butyl parabens
- Tween80/carboxy cellulose
- 3-tert-butyl-4-hydroxyanisole (3-BHA)
- MSG
- Pesticides
The Western Diet is prevalent among low-income and minority populations.

Because of what they eat and where they live, these populations have the highest levels of obesogens …double whammy!!!
Potential Obesogens*

• Glyphosate
• Diazinon
• Eldrin
• Strobilurin pesticides
• Triclosan
• Triflumizole
• BADGE (bisphenol A diglycidal ether)
• Atrazine
• House dust extracts
• Alkylphenols and alcohols
• DINCH

• * Only in vitro data or one animal study

Red indicates replacement chemical
TBT, BPA and DEHP Program a Dysfunctional Adipocyte

Which chemicals will cause dysfunctional adipocytes?

BPA results in dysfunctional fat cells
Ariemma, D Esposito 2016

DEHP programs a dysfunctional adipocyte
Prenatal PAH and PM$_{2.5}$ Exposure (Air Pollution) Increases Weight Gain and Fat Mass

- Greater prenatal PAH exposure associated with:
  - Increased weight
  - Larger fat cells
  - Increased PPARγ expression

- Similar effects observed in F2 generation

PM$_{2.5}$ Inflammation
Gut microbiome
Impairs glucose tolerance
Insulin resistance
Increased adipose tissue

Some in vitro data
Strong animal data
Some human data

Yan Z et al. PLOS One 2015
Rundle et al., Am J Epidemiol, 2012)
Some Phthalates are Obesogens

Butyl benzyl phthalate, di isobutyl phthalate, di ethyl hexyl phthalate (DEHP)

- Strong *in vitro* and animal data
- Some human data

3T3-L1 cells

Developmental exposure and overweight at age 12 yrs

Harley et al 2018

Schmidt et al., EHP, 2012

Ho et al Biosci Rep 2012

8 weeks exposure C57/B6 mice
Bisphenol A is an Obesogen

Females (Mice)  
Prenatal + Postpartum

Developmental Exposure  
Rat model  
Increased weight  
Increased food intake

Lipid accumulation in HepG2 cell

Appetite (NPY) neurons

3T3-L1 cells

Satiety (POMC) neurons

Strong in vitro and animal data  
Inconsistent human data

Age

Beverly Rubin  
Rep Tox 2017

Ross and Desai, 2018
Organotins are Obesogens

**Tributyl Tin**

- PVC is up to 3% w/w (0.1 M) organotins
- TPT used as fungicide on high value crops
- Binds and activates at ppb (low nM) two nuclear receptors, RXR and PPARγ critical for adipogenesis

![Graph showing gonadal fat pad weight comparison between control and TBT treated groups](image)

![Bar graph showing lipid staining % surface for hMSC with CMC, ROSI, and TBT](image)

![Bar graph showing calcium staining % surface for hMSC with MDII and TBT](image)

**Strong in vitro and animal data**
**Minimal human data**
**Transgenerational Inheritance**

Grun et al., Molec Endocrinol, 2006
Obesogens Stimulate Food Intake

Obesogens answer the question: What causes increased food intake?

- BADGE.2H2O is positively associated with binge eating disorder
- BPA can influence dopaminergic system that controls reward eating

Hedonic Pathway; Reward; Craving; Addiction

Stimulate Food intake

Stimulate Satiety

Homeostatic Pathway: Appetite and satiety
Obesogens and High Fat Diet Interactions

Butyl benzyl phthalate

HFD=Increase adipose tissue and liver fat

Imidacloprid

Larger effect with HFD

- BPA
- Butyl benzyl phthalate
- DEHP
- TBT
- Nicotine
- Chlorpyrifos
- Imidacloprid
- DDT
- Permethrin
- Atrazine

Prenatal Exposure to Tributyl Tin: Sensitizes males to Weight Gain on a Higher Fat Diet (F4 Males)

Humans:
- Easy to gain weight
- Harder to lose weight

Resistant to fat loss!

Gain weight more easily and harder to lose weight!

Chamorro-Garcia et al., Nature Comm 2017
Obesogens Alter the Microbiome (which plays important role in obesity)

10-hydroxy-cis-12-ocadecenoic acid (HYA) from high fat diets (role in obesity and adipocyte size)

- BPA, BPS
- Phthalates
- PFAS
- PBDE
- TCDD
- PCBs
- PAH (Air pollution)
- Methyl paraben
- Triclosan

<a href='https://www.freepik.com/vectors/bacteria'>Bacteria vector created by pch.vector - www.freepik.com</a>
Some Obesogens Cause Weight Gain Without an Increase in Food Intake

- DES
- Chlorpyrifos
**Transgenerational Epigenetic Inheritance of Obesity**
(Real and Potentially VERY Important)

- **Positive results**
  - Tributyltin (M and F)
  - DDT (M and F)
  - Hydrocarbon mixture (jet fuel) (M and F)
  - BPA, DEHP, DBP (M and F)
  - BPA

- **Negative results**
  - Permethrin/DEET mixture
  - Vinclozolin
  - Dioxin

Perinatal serum levels of DDT in normal weight human grandmothers was associated with increased odds for obesity in their granddaughters at age 26 (OR=3.6, p=0.009).

Multigenerational Obesity (F2)

PMID: 33853850
The Perfect Storm for Obesity

**Development:** Obesogens & Nutrition, Stress...

- Altered “homeostatic” programming
- Hedonic, reward pathway
- Number of Fat cells, Fat cell function
- Energy expenditure, metabolic rate
- Inflammation
- Emotional and/or stress responses

**Throughout Life:** Stress on Abnormal Metabolic System (second hit!)

- Increased consumption of fat and sugar leading to “food addiction”
- Reduced Exercise, Altered Microbiome

**Continued exposure to Obesogens, leading to more fat cells, inflammation, altered homeostatic and reward pathways**

Epidemic of Obesity and Metabolic Diseases
Prevention of Obesity

**Development:** Reduce Exposures to obesogens, improve nutrition...

- Reduce developmental programming of altered metabolism and set point
- Improved energy expenditure, metabolic rate

**Throughout Life:** Improve nutrition (second hit!)

- Decrease consumption of fat and sugar leading to “food addiction”
- Increase exercise, Improve microbiome

**Reduce exposure to obesogens, leading improved metabolism homeostatic and reward pathways**

Prevention of Obesity and Metabolic Diseases
Causal Link: Where are we?

Difficult to prove...but we know:
• Obesogens
• Causal link, in vitro and animal studies, collaborating associations in human studies
• Exposure
• When they act
• Mechanisms/Pathways
• Interact with diet
• Interventions (diet, drugs, surgery)...still obesity pandemic

Precautionary Principle...Assume causal link and ADD a focus on PREVENTION

Focus on improving nutrition and reducing obesogen exposures (pre-conception, pregnancy, early childhood and across lifespan).
We hold our future in our hands and it is our children... and their health

The End....but just the beginning