

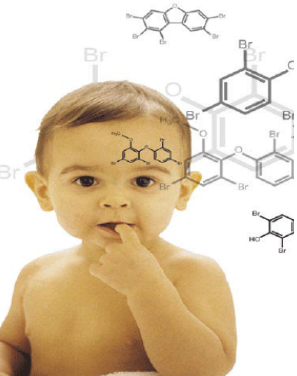
Establishing Causal Links Between Obesogens and Obesity

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Director

Healthy Environment and Endocrine Disruptor Strategies

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www.heeds.org



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

Kim et al Obesity, 2005

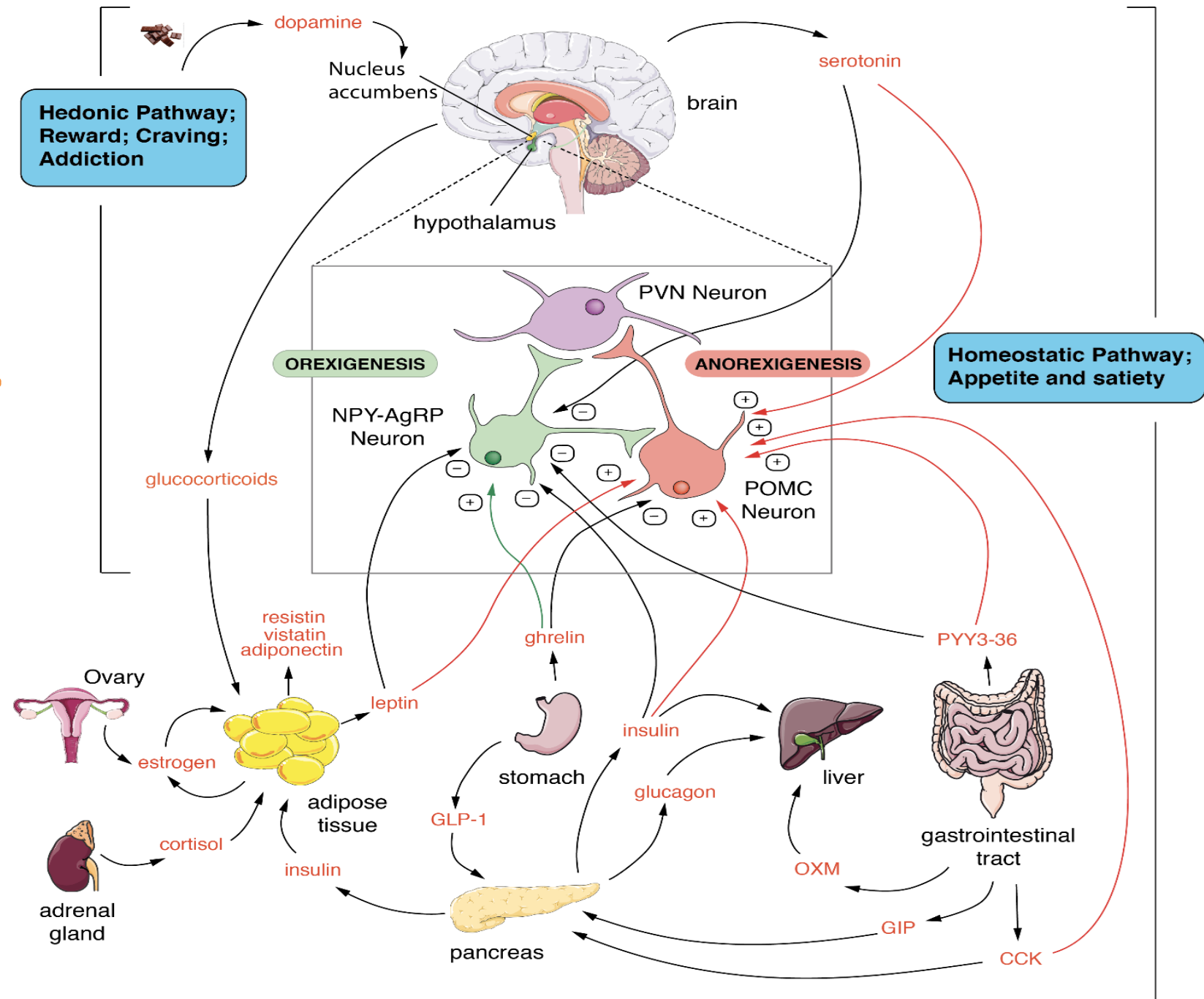
Klimentidis et al Proc Biol Sci 2011

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

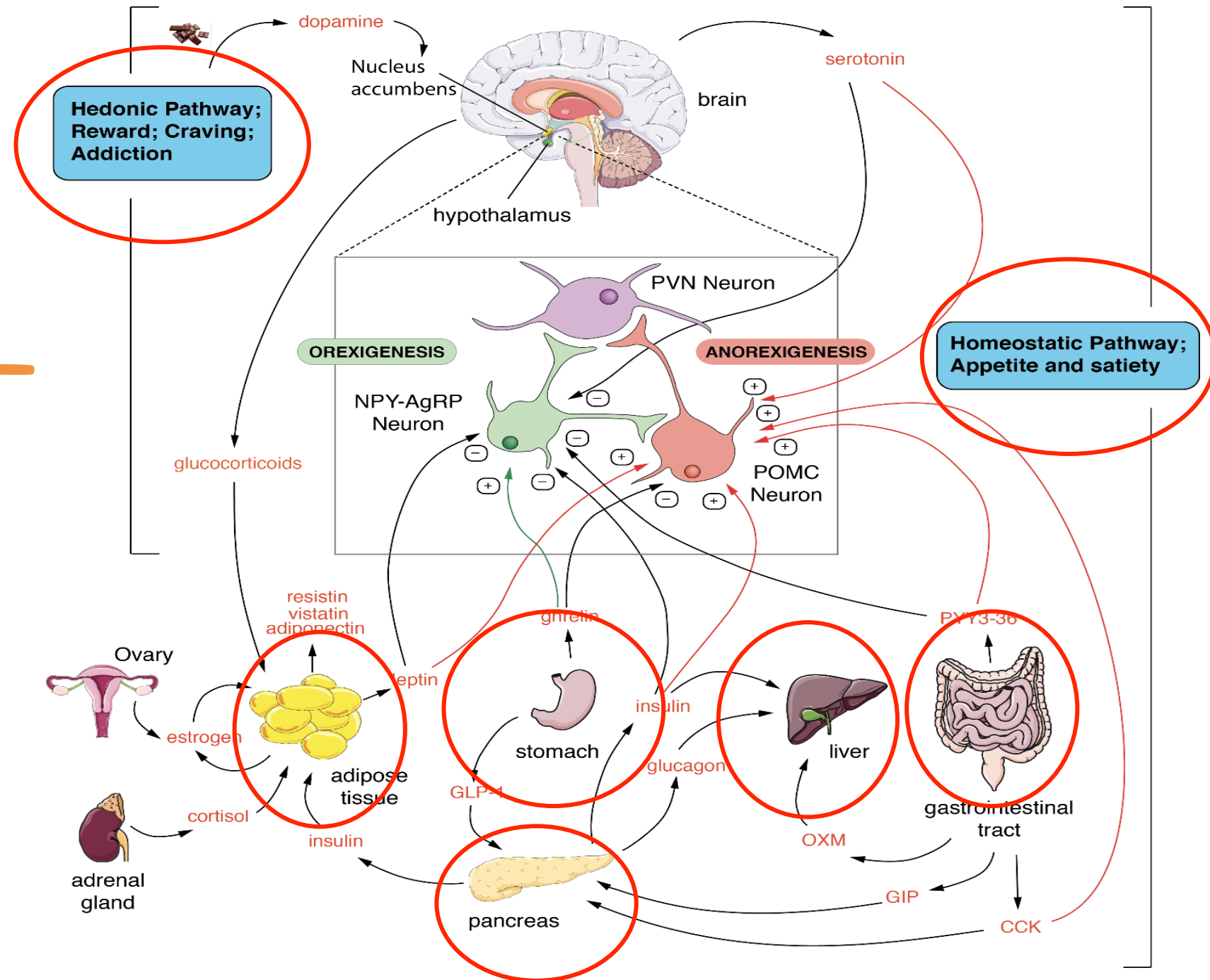
Endocrine Control of Metabolism

All hormones and hormonal pathways are potential targets for obesogens



Endocrine Control of Metabolism

All hormones and hormonal pathways are potential targets for obesogens



Environmental Chemicals: Endocrine Disruptors

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)

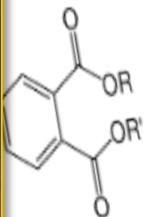
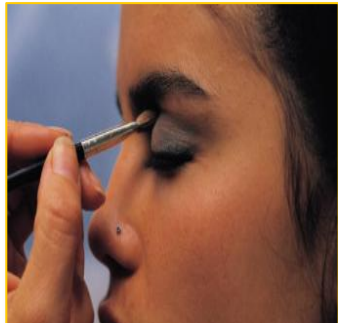
>100,000 chemicals in commerce

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.

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**

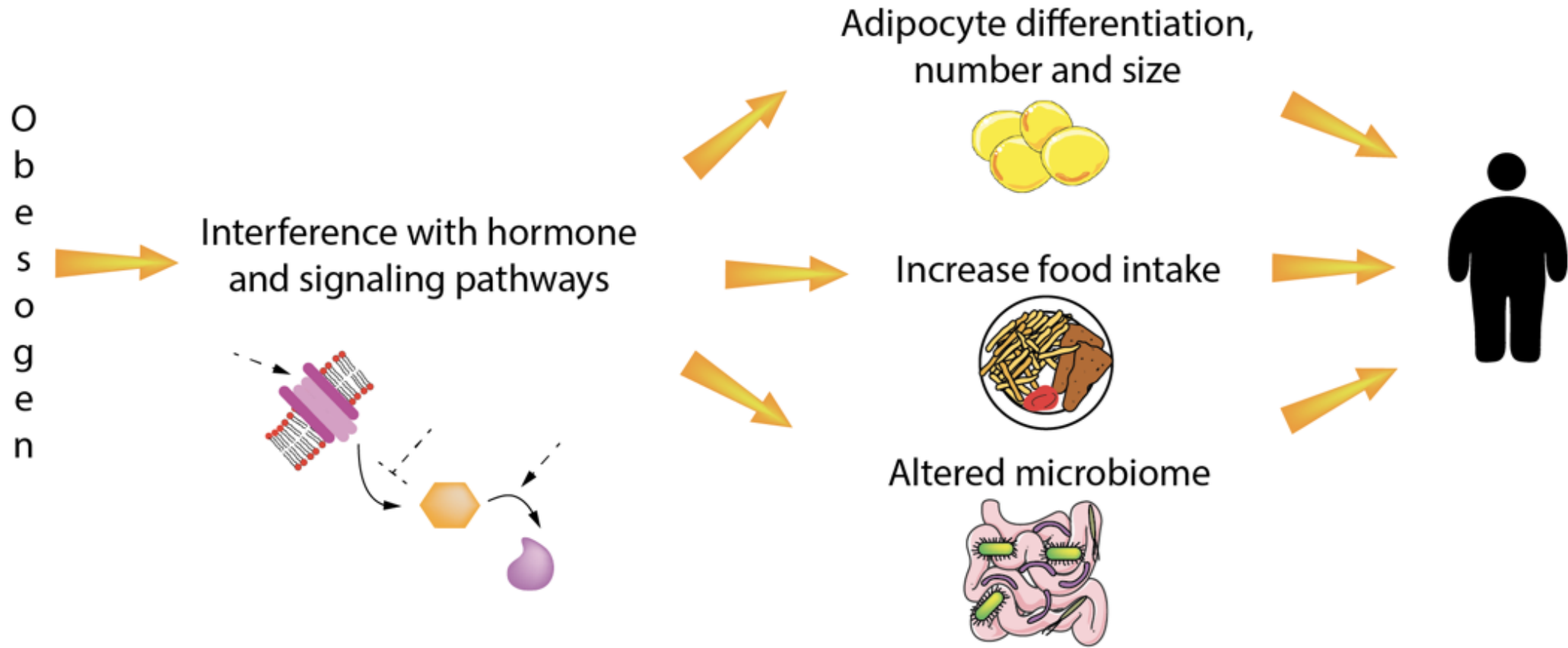
Food intake and exercise are important but environmental chemicals can alter the set-point for gaining weight – how much food it takes to put on weight – and also how much exercise is needed to reduce weight via alterations in developmental programming.

then

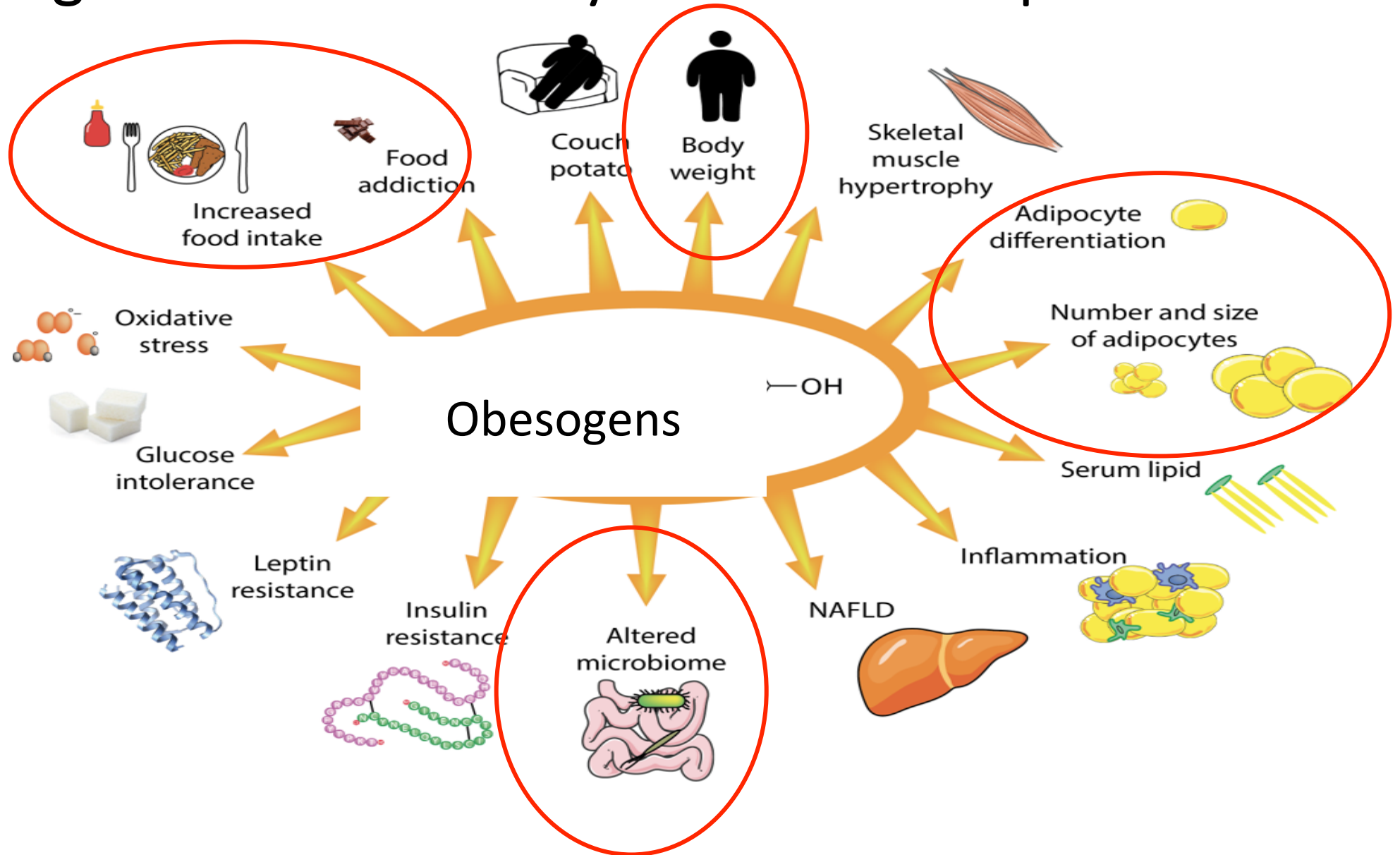
set point or sensitivity for developing obesity later in life.

, brain

General Scheme of Obesogen Action



Obesogens Can Alter Many Metabolic Endpoints

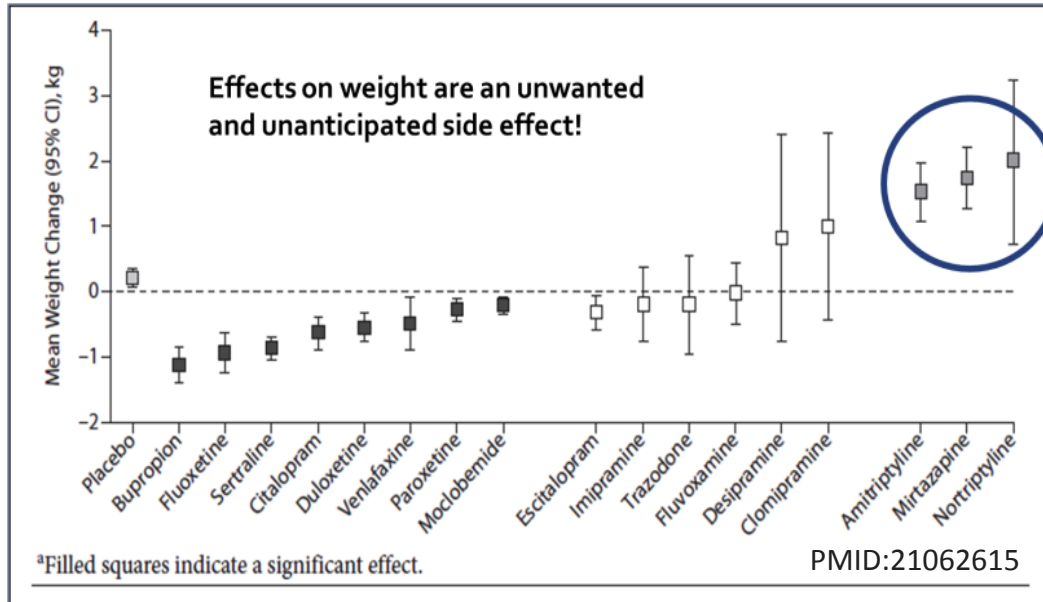


Exposures to Obesogens Are Ubiquitous (Air, Dust, Food, Water, Skin)



Clinicians are Already Familiar with Obesogens

Antidepressant Medications and Body Weight

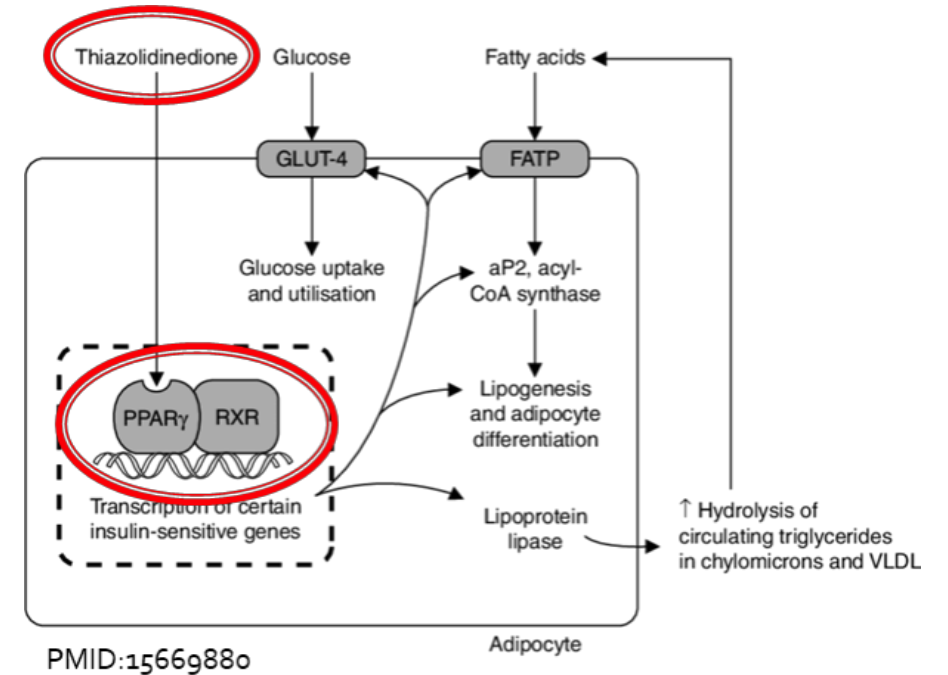
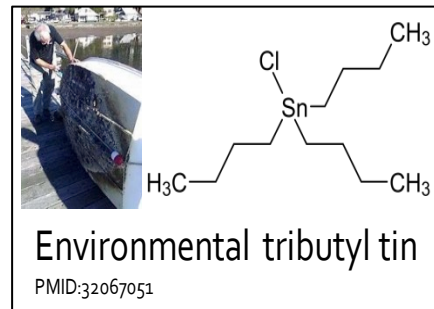
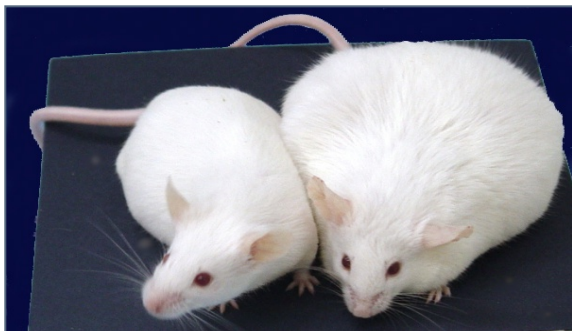


Diabetes Medications and Body Weight

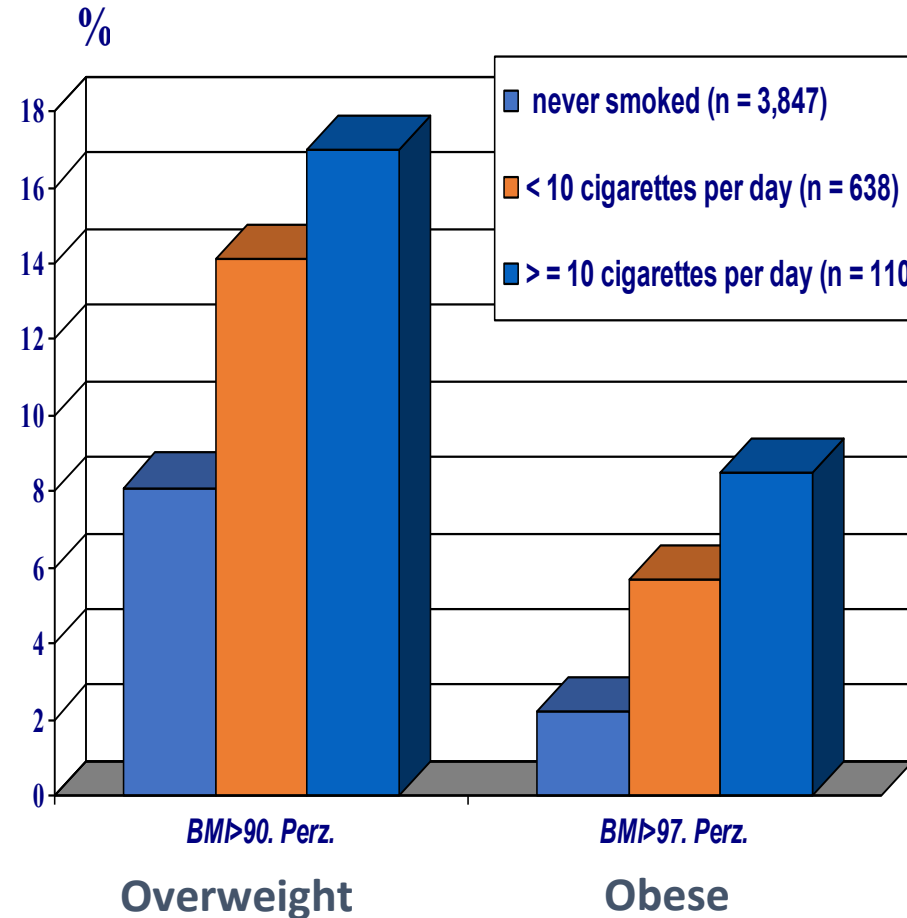
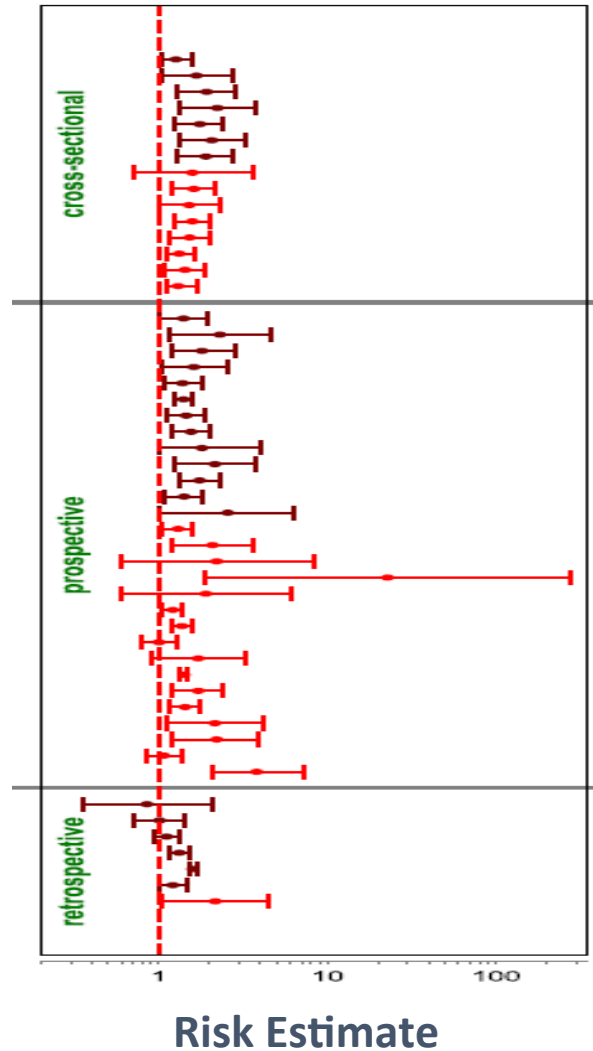
↑: **thiazolidinediones**, sulfonylureas, insulin
 ↓: GLP-1RA, SGLT-2i, metformin

PMID: 30465123

Diethylstilbestrol (DES)



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



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

In vitro
Zebrafish
Rodents
Human

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 sulfosuccinate (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

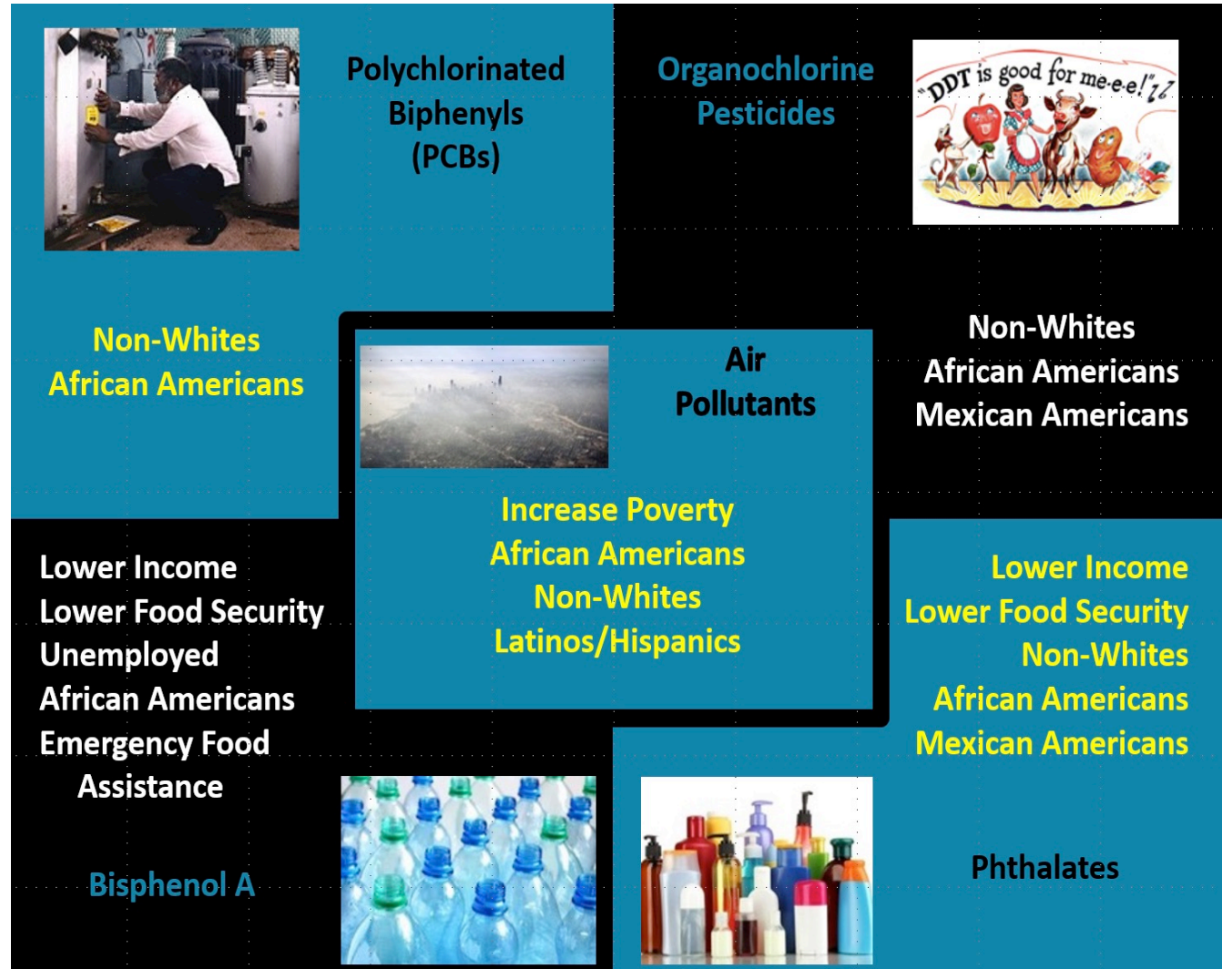
Contains obesogens

- Bisphenol A
- Phthalates
- PFAS
- Fructose
- Methyl and butyl parabens
- Tween80/carboxycellulose
- 3-tert-butyl-4-hydroxyanisole (3-BHA)
- MSG
- Pesticides

Differences in Environmental Pollutant Exposures Contribute to Health Disparities in Obesity

The Western Diet is prevalent among low-income and minority populations.

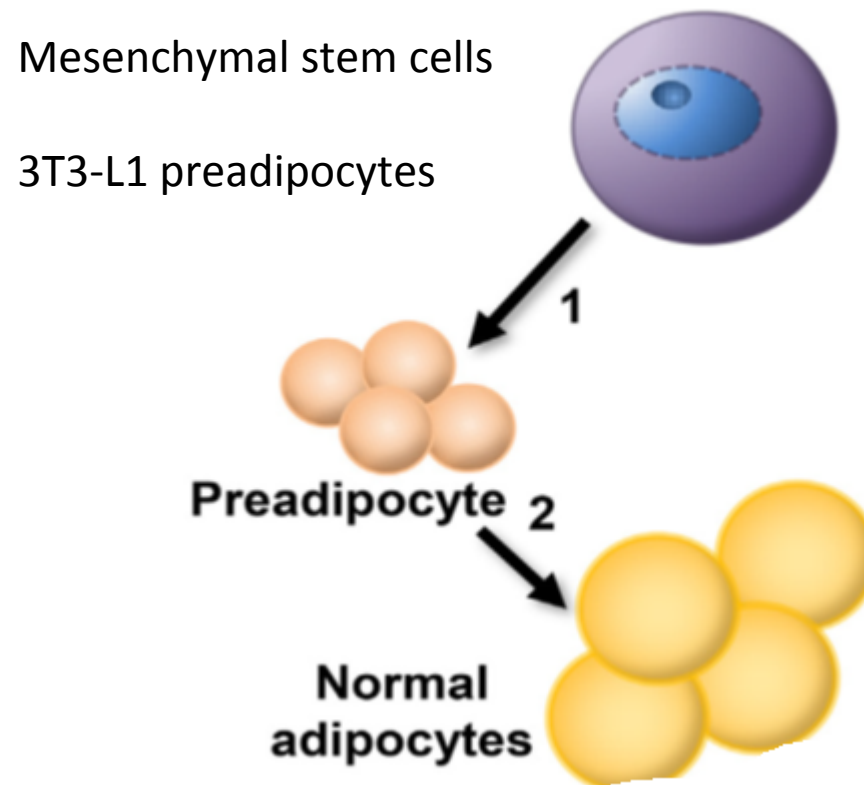
Because of what they eat and where they live, these populations have the highest levels of obesogens ...double whammy!!!



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

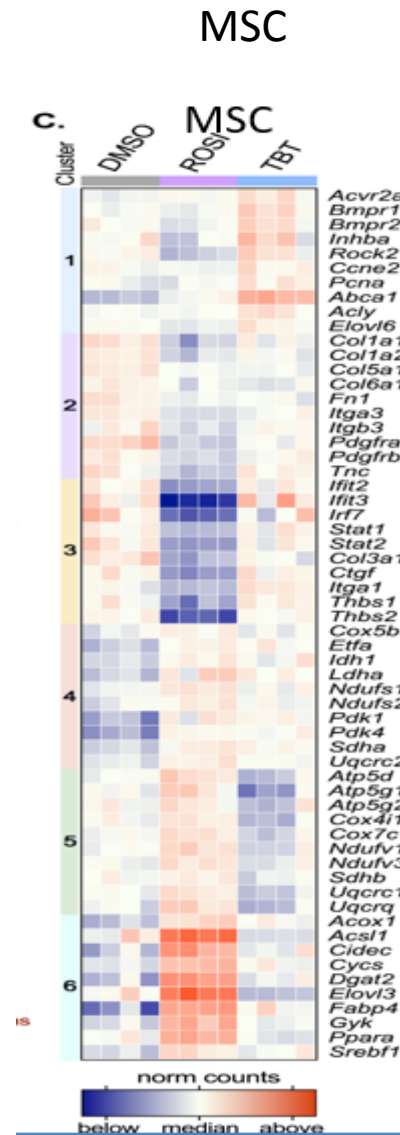
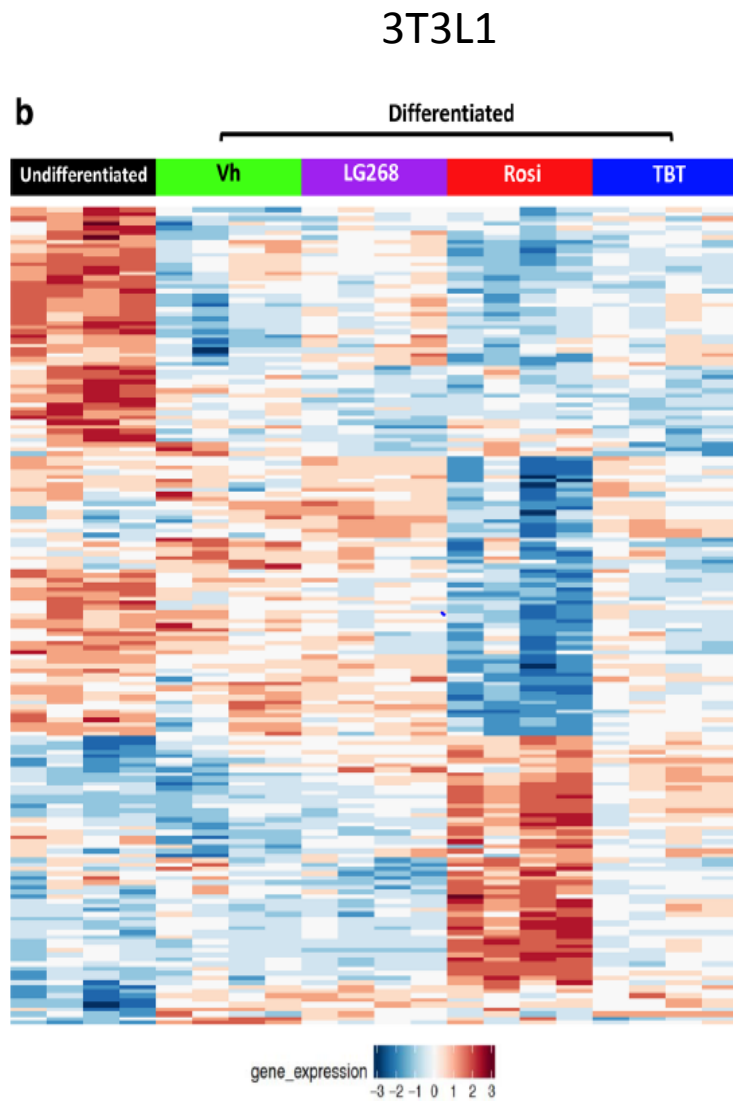


TBT , BPA and DEHP Program a Dysfunctional Adipocyte

SM Regnier et al, Obesity, 2015

S Kim et al Arch Tox, 2018

Endocrinology. 2018;159(8):2863-2883. BM Shoucri et al



TBT Adipocyte: (immature or incompletely differentiated)

- Store fat
- Decreased glucose uptake
- Lower adiponectin
- Lack of downregulation of Proinflammatory and Profibrotic transcripts
- No induction of browning transcripts



Which chemicals will cause dysfunctional adipocytes ?

BPA results in dysfunctional fat cells

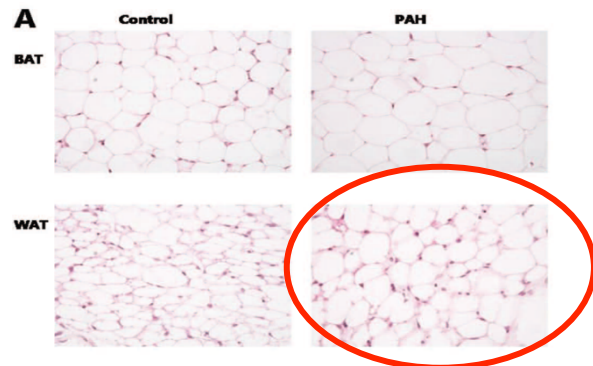
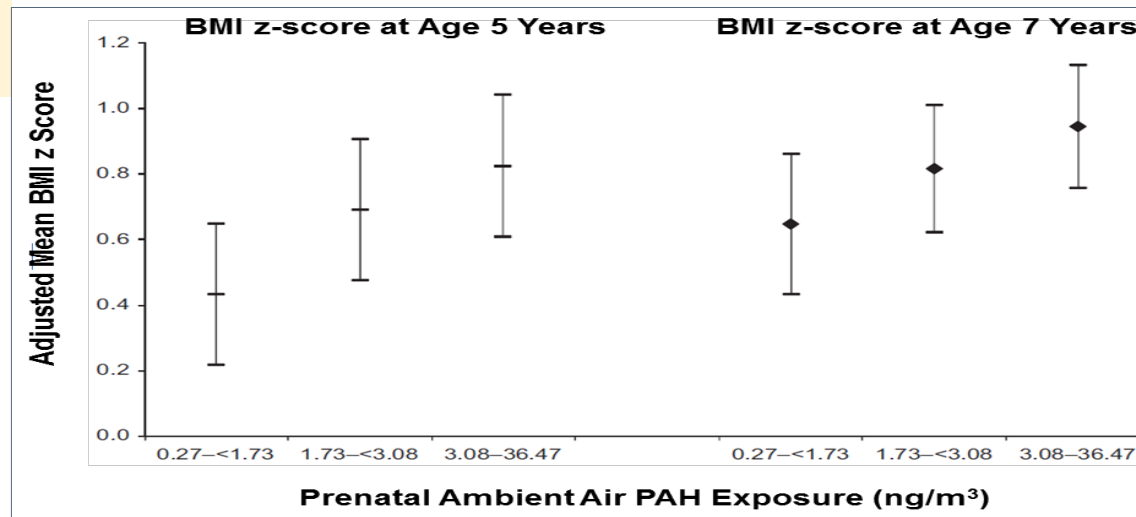
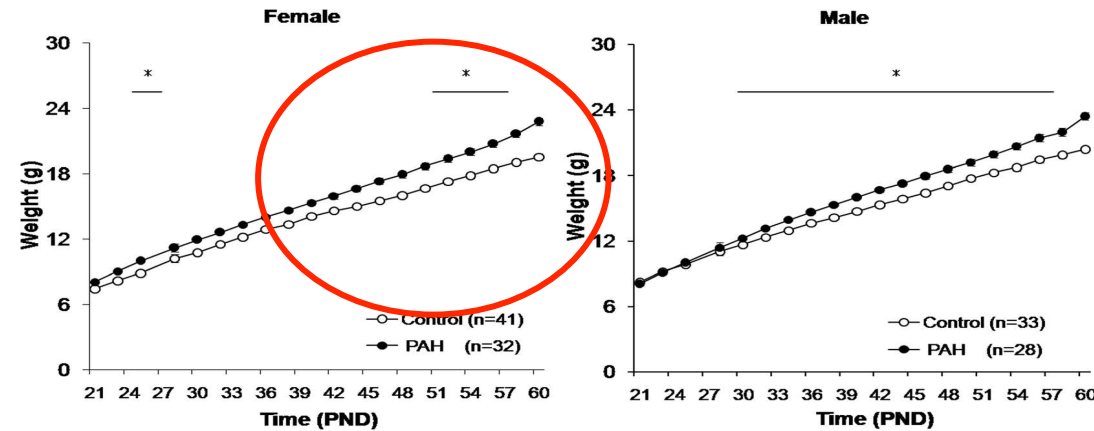
Ariemma, D Esposito 2016

DEHP programs a dysfunctional adipocyte

Prenatal PAH and PM_{2.5} Exposure (Air Pollution) Increases Weight Gain and Fat Mass



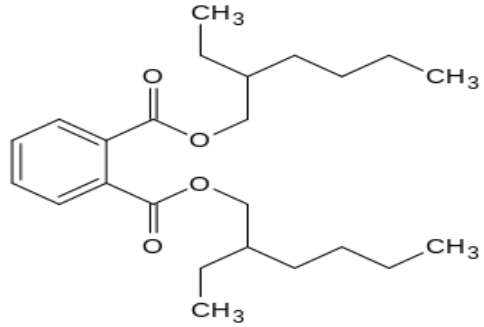
- Greater prenatal PAH exposure associated with:
 - Increased weight
 - Larger fat cells
 - Increased PPAR γ expression
- Similar effects observed in F2 generation



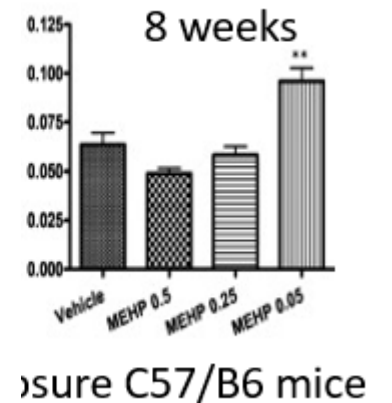
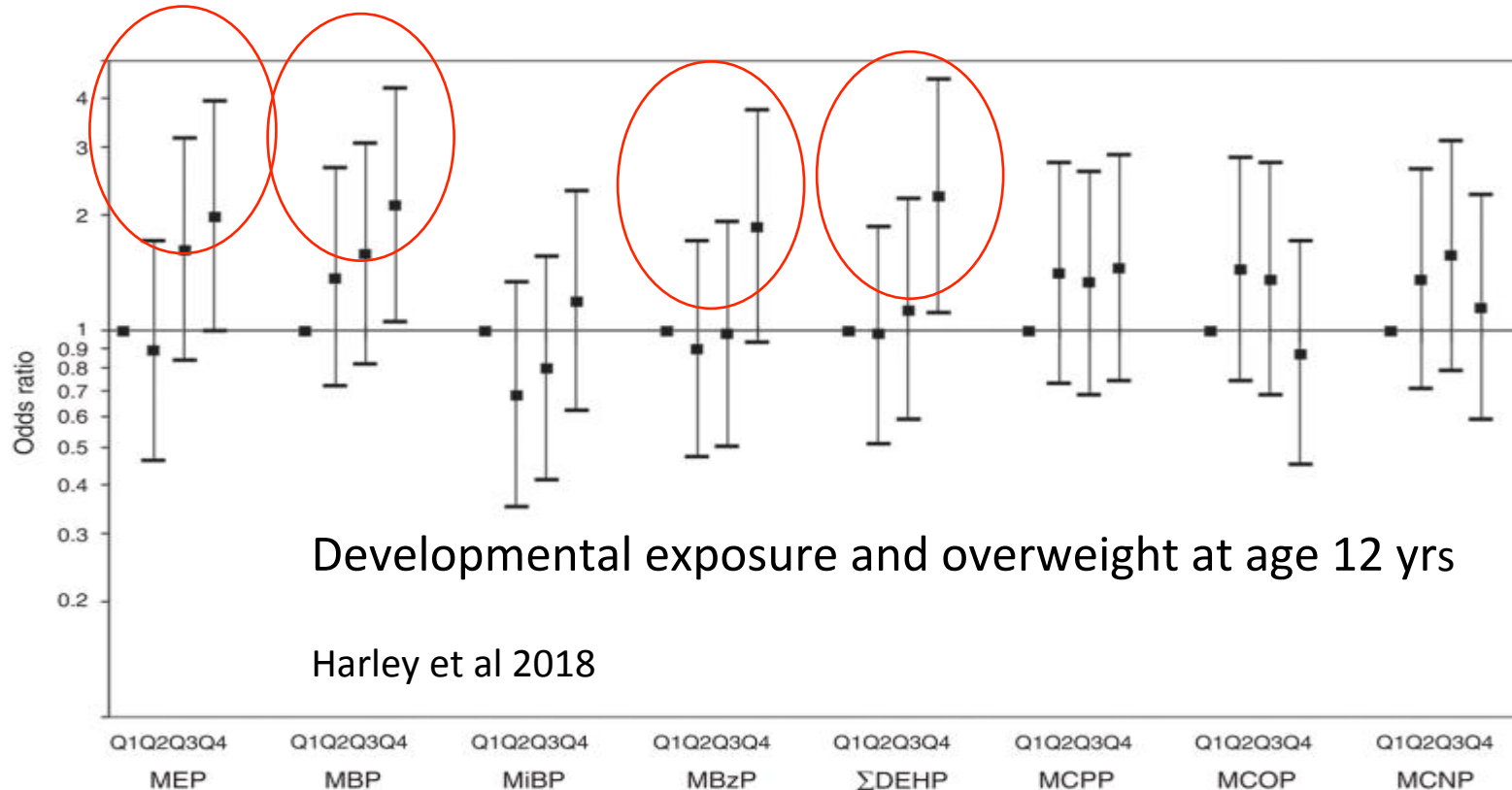
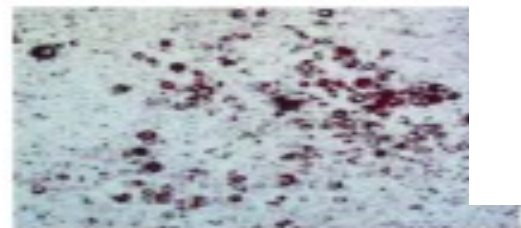
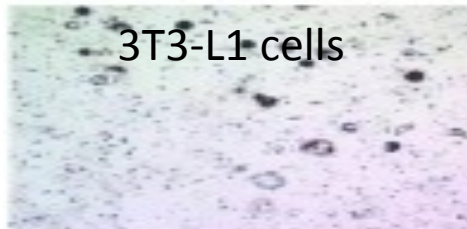
PM_{2.5}
 Inflammation
 Gut microbiome
 Impairs glucose tolerance
 Insulin resistance
 Increased adipose tissue

Some in vitro data
Strong animal data
Some human data

Some Phthalates are Obesogens



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

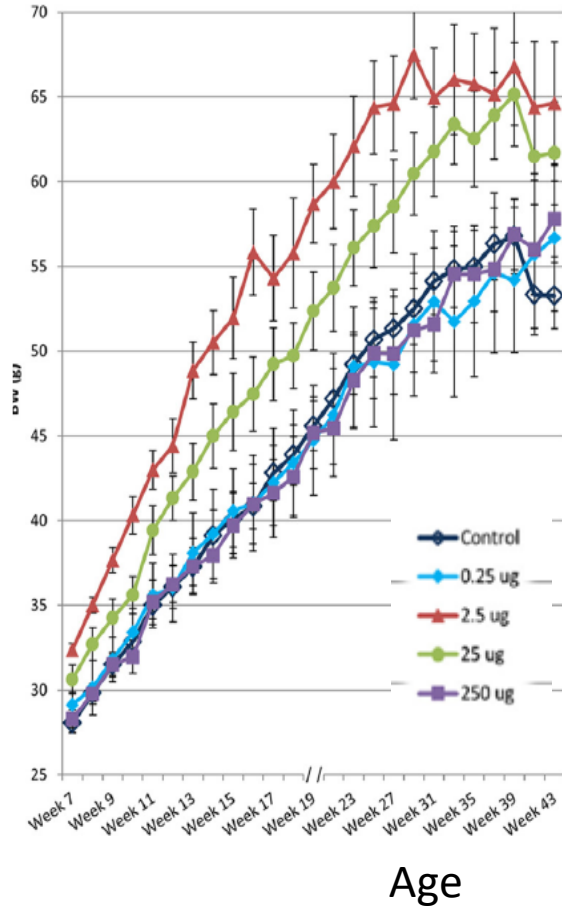


- Strong *in vitro* and animal data
- Some human data

Bisphenol A is an Obesogen



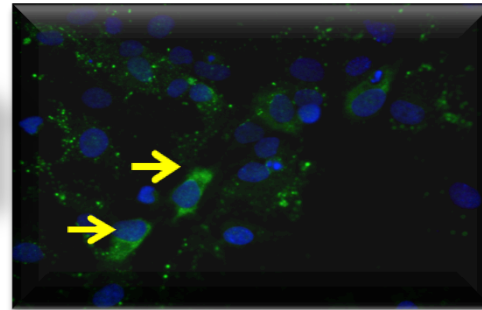
Females (Mice)
Prenatal + Postpartum



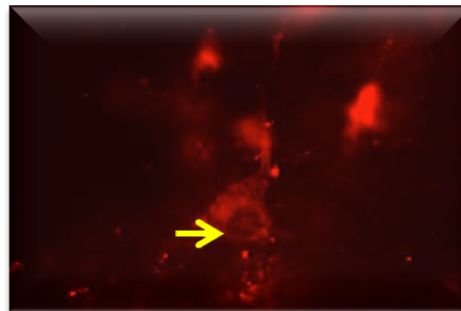
Beverly Rubin
Rep Tox 2017

Developmental Exposure
Rat model

Increased weight
Increased food intake



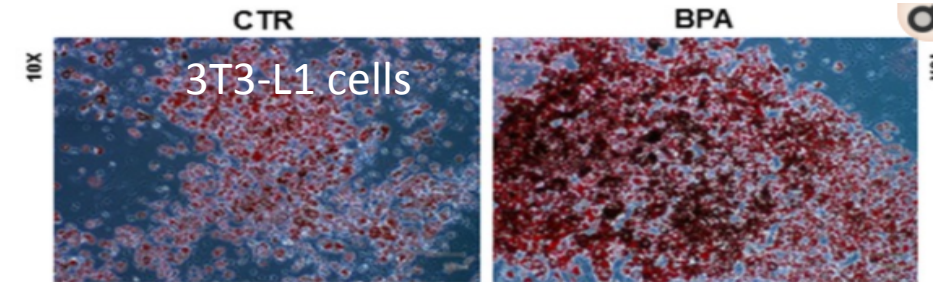
Appetite (NPY) neurons



Satiety (POMC) neurons

Ross and Desai, 2018

Lipid accumulation
in HepG2 cell

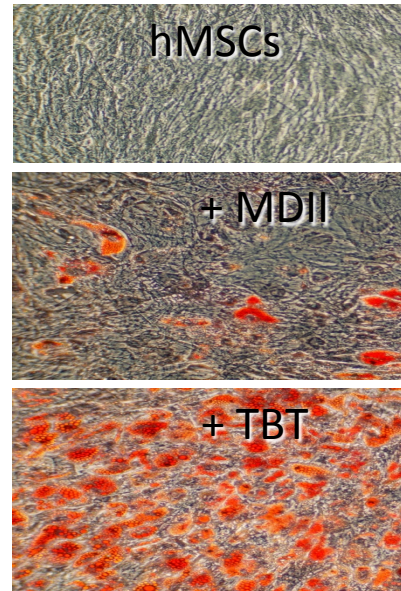
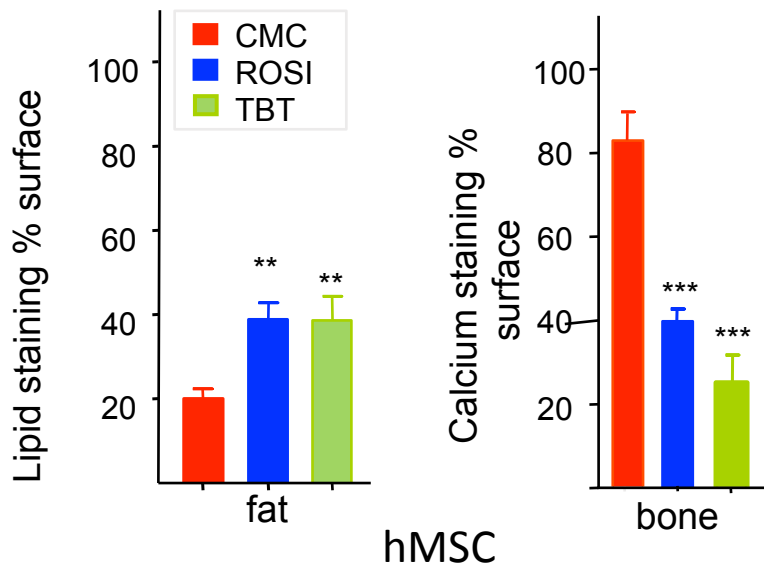
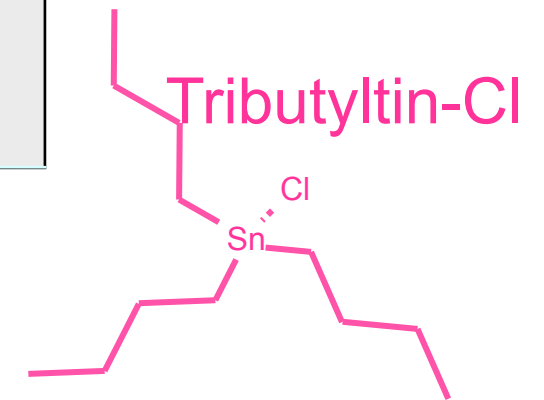
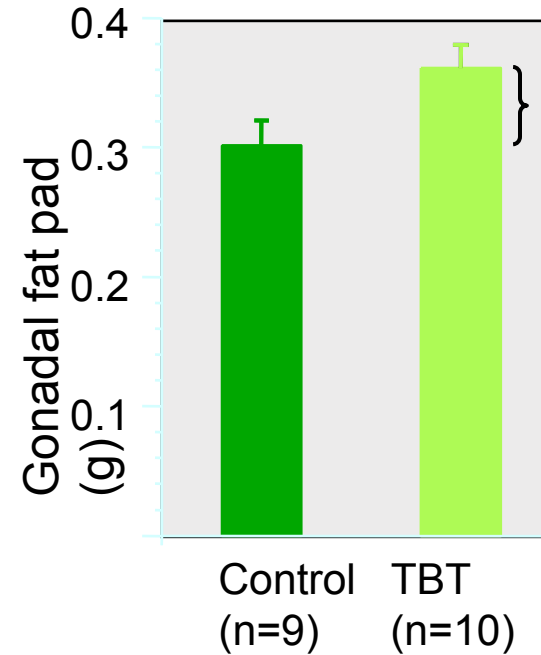


Strong *in vitro* and animal data
Inconsistent human data

Organotins are Obesogens

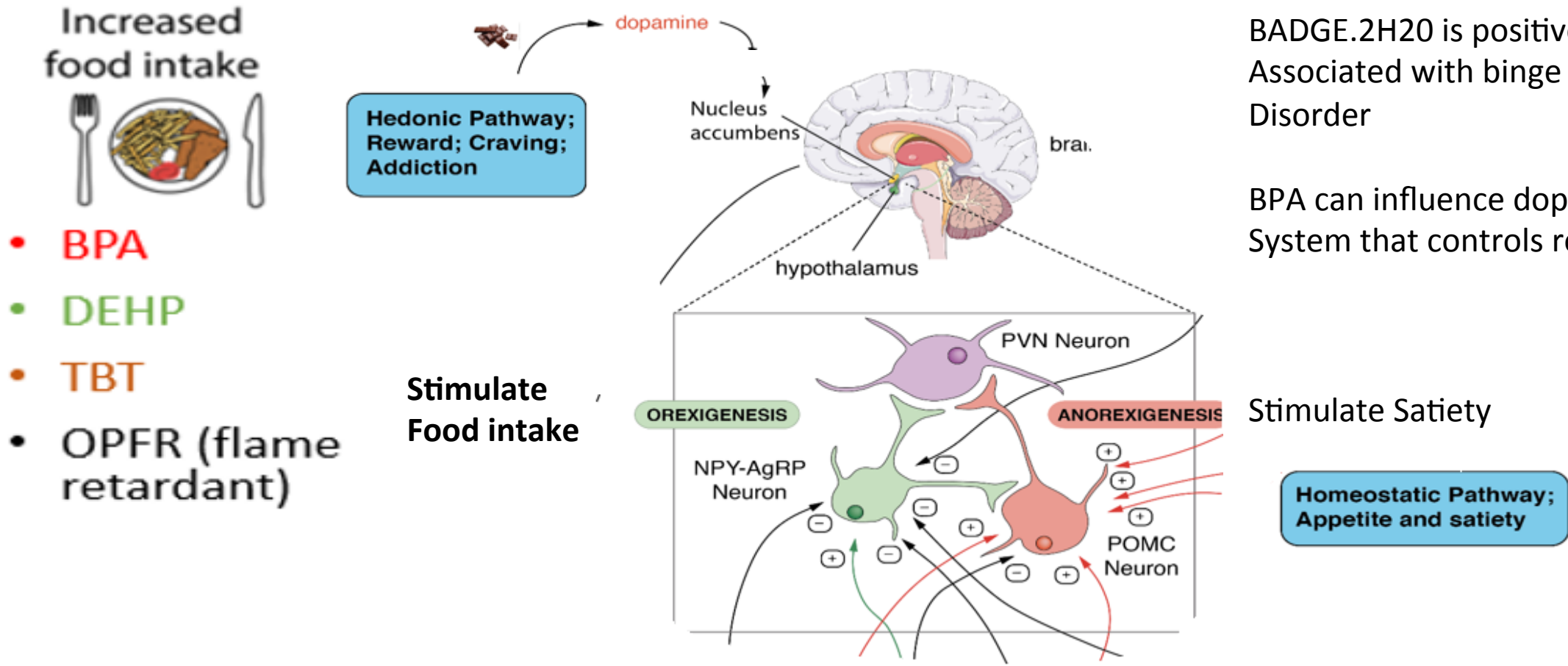
Tributyl Tin

- 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 PPAR γ critical for adipogenesis



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

Obesogens Stimulate Food Intake



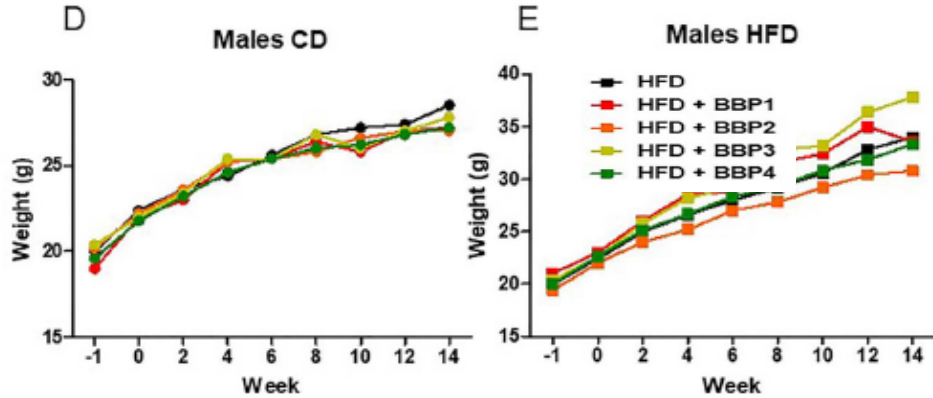
BADGE.2H2O is positively Associated with binge eating Disorder

BPA can influence dopaminergic System that controls reward eating

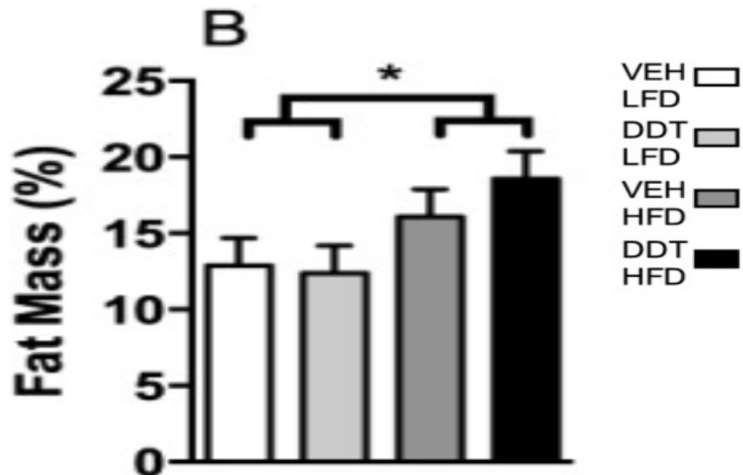
Obesogens answer the question: What causes increased food intake?

Obesogens and High Fat Diet Interactions

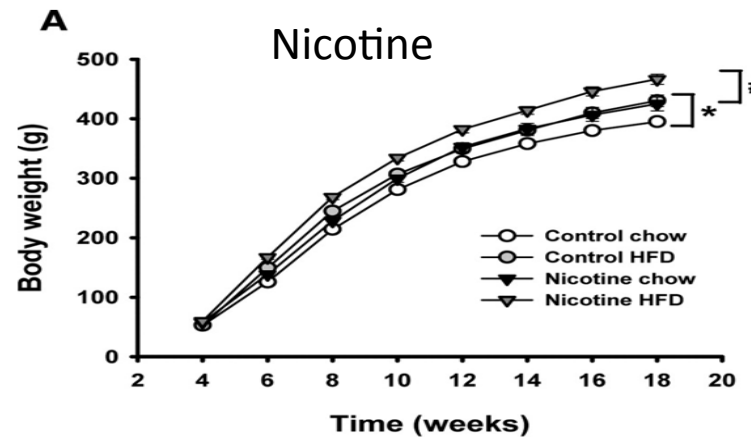
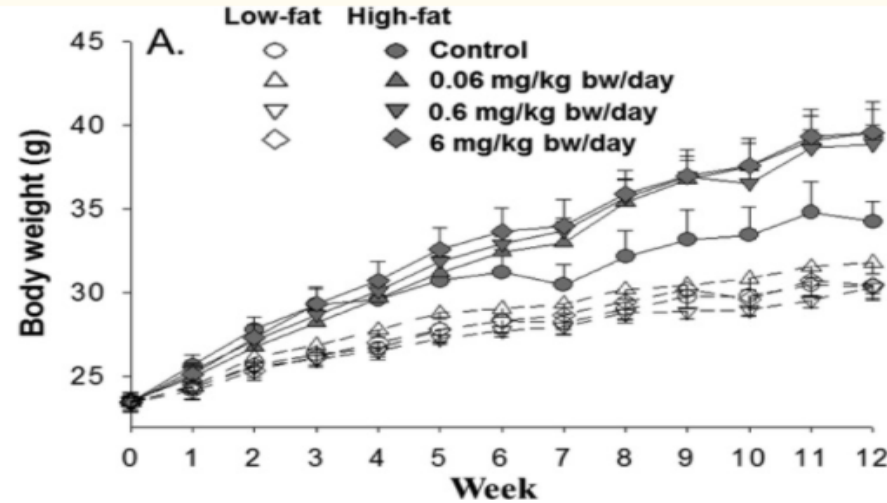
Butyl benzyl phthalate



HFD=Increase adipose tissue and liver fat



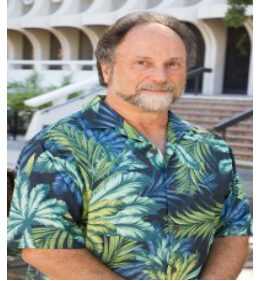
Imidacloprid



Larger effect with HFD

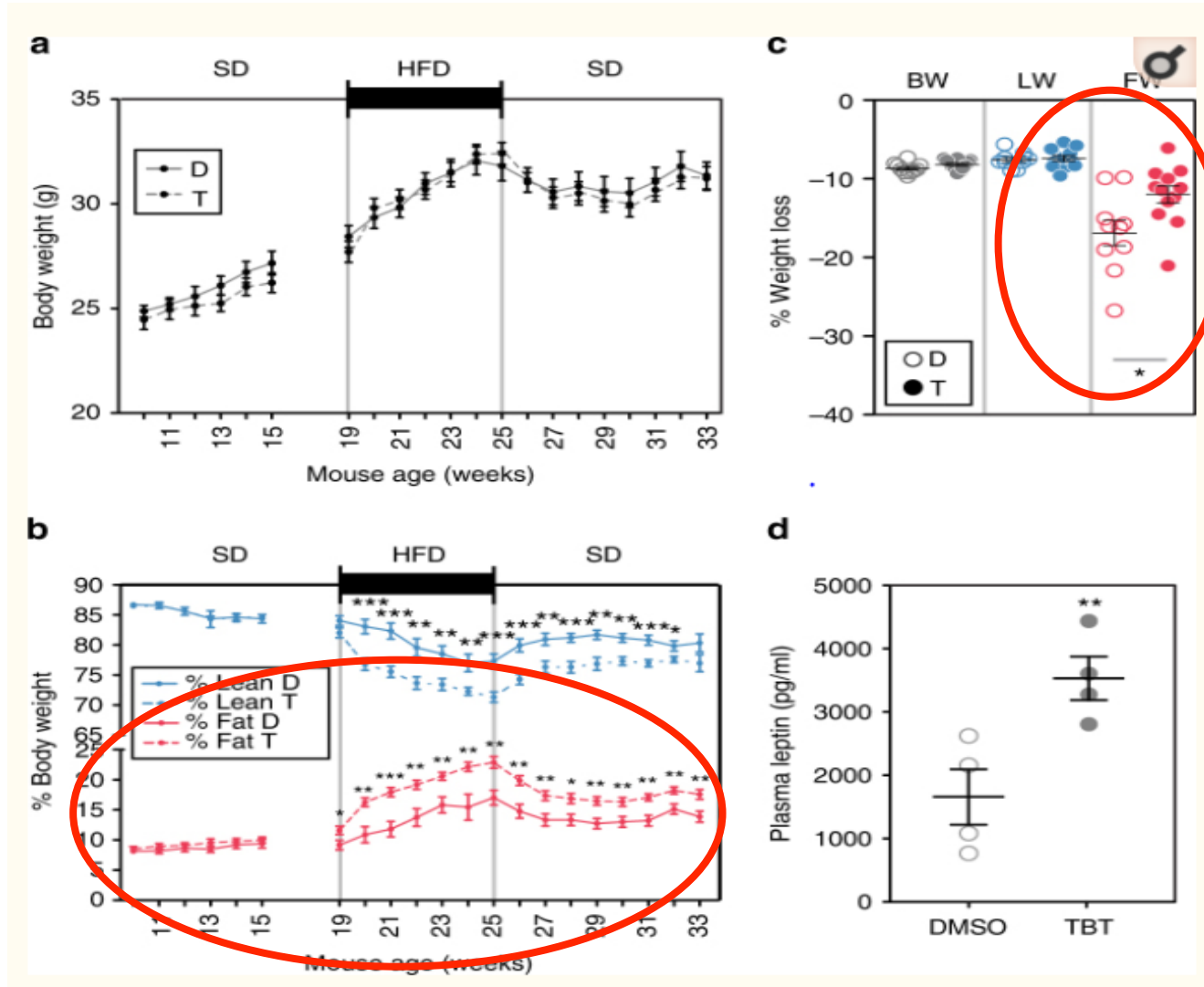
- BPA
- Butyl benzyl phthalate
- DEHP
- TBT
- Nicotine
- Chlorpyrifos
- Imidacloprid
- DDT
- Permethrin
- Atrazine

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!

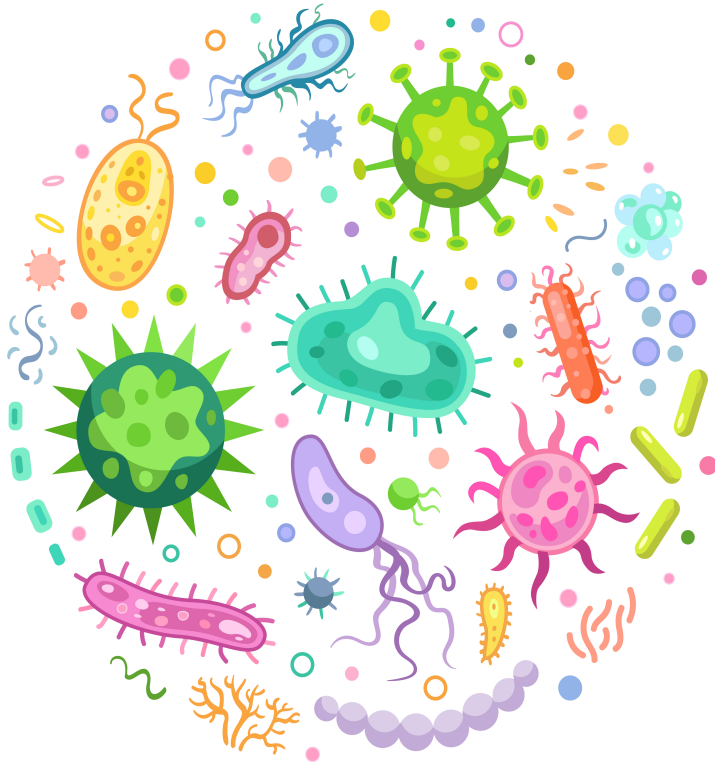
Obesogens Alter the Microbiome (which plays important role in obesity)

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

Altered
microbiome



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



Some Obesogens Cause Weight Gain Without an Increase in Food Intake

- DES
- Chlorpyrifos

IMPORTANT!

Transgenerational Epigenetic Inheritance of Obesity (Real and Potentially VERY Important)

- **Positive results**

- Tributyltin
- DDT
- ...
- BPA

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

- **Negative results**

- Permethrin/DEET mixture
- Vinclozolin
- Dioxin

Gestating mother exposed to an endocrine

Exposure (F0)

F₃



Assess
Weight
Gain (F4)

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



Poster Contest by HRIDAY with support from WHO SEARO

The End....but just the beginning