

Metabolism Disruptors

Obesity and Diabetes

Jerry Heindel, PhD

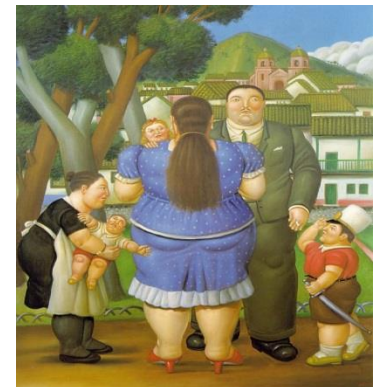
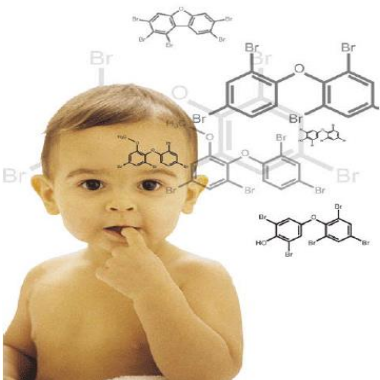
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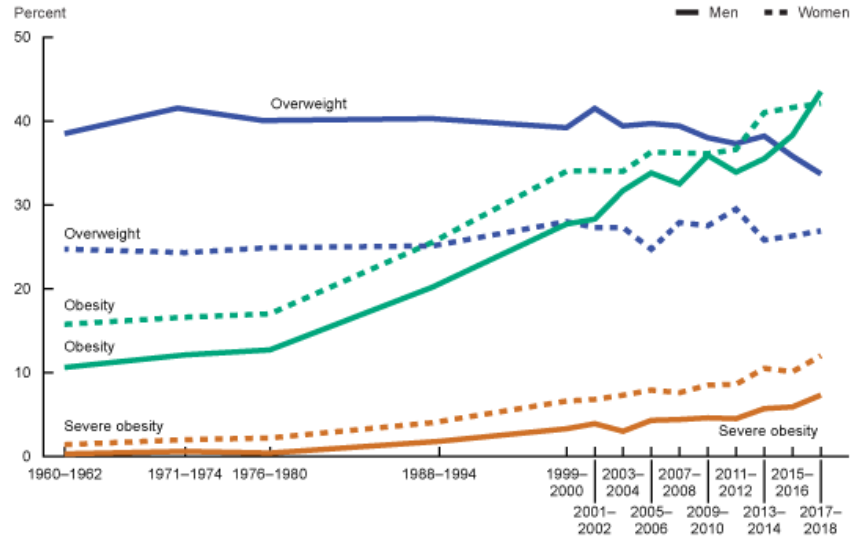
nadal@umh.es



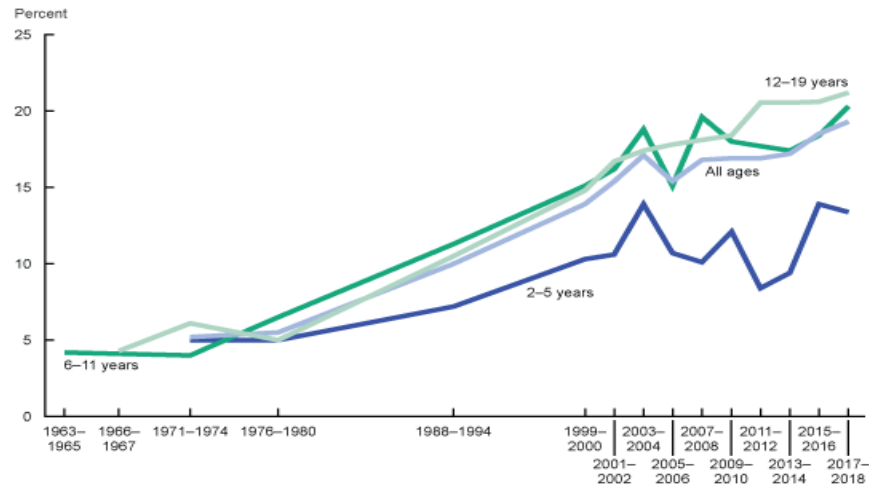
Setting the Stage...

- 1991, Wingspread, Endocrine Disruptor
- Focus on estrogen, androgen, thyroid
- 2003, Developmental Origins of Health and Disease
- 1997, Paula Baillie-Hamilton, made the connection between toxins and obesity
- 2002, Baillie-Hamilton, Chemical Toxins: a hypothesis to explain the global obesity epidemic (J Alt and Comp Med)
- 2006, Bruce Blumberg coined the term Obesogen
- 2006, Diabetogen hypothesis (Paloma Alonso-Magdalena and Angel Nadal)
- 2011,2013 Obesity/obesogen workshops
- 2014, Metabolic disruptor meeting Parma, Italy
- 2017, Metabolism Disruptors,(Heindel et al)
- 2024, Consensus on the Key Characteristics of Metabolism Disruptors (La Merrill et al)

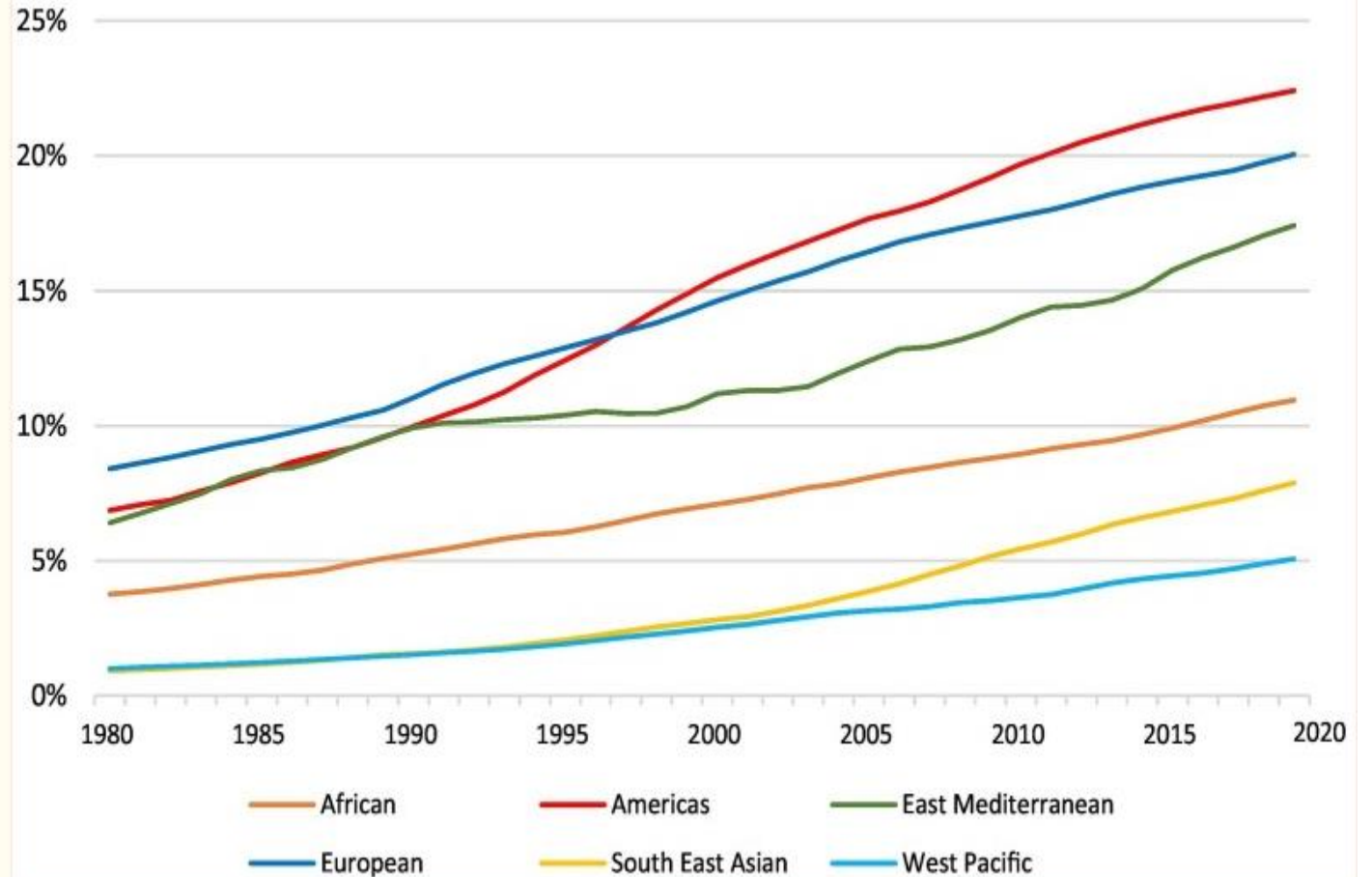
Trends in Obesity among Adults in US



Trends in Obesity among Children and Adolescents (Age 2-19) in US



Global Trends in Obesity



OBESITY - A COMPLEX PROBLEM



Metabolism Disruptors

- Metabolism Disruptors are environmental agents that alter energy metabolism.
- They disrupt **signaling pathways** (e.g., hormone receptors and transcription factors) in various cell types and tissues that regulate energy intake and expenditure, nutrient handling, adiposity, and insulin resistance, leading to **obesity and type 2 diabetes**.
- Metabolism Disruptors can be:
 - natural (e.g., metals, viruses),
 - anthropogenic (prescription drugs),
 - environmental (insecticides, plastics, household chemicals, particulate matter),
 - food components (fructose, *trans*-fats, preservatives, emulsifiers).
- **The majority of metabolism disruptors are endocrine disruptors.**

Endocrine Disruptors

An **endocrine disruptor** is an exogenous chemical, or a mixture of chemicals, that **interferes with any aspect of hormone action** (Zoeller et al. Endocrinology, 2012).

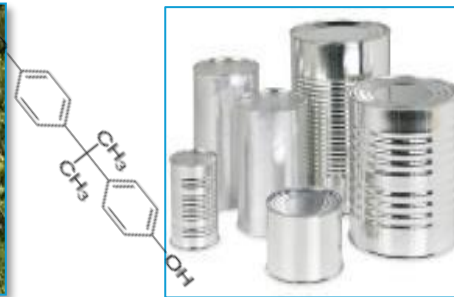
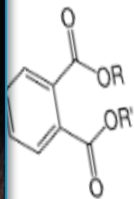
A chemical designed for a specific purpose but with a side effect of mimicking or antagonizing hormone action.

>300,000 chemicals in commerce

Some % are toxic, via
**Alterations of DNA
mutagens
or general toxicity**

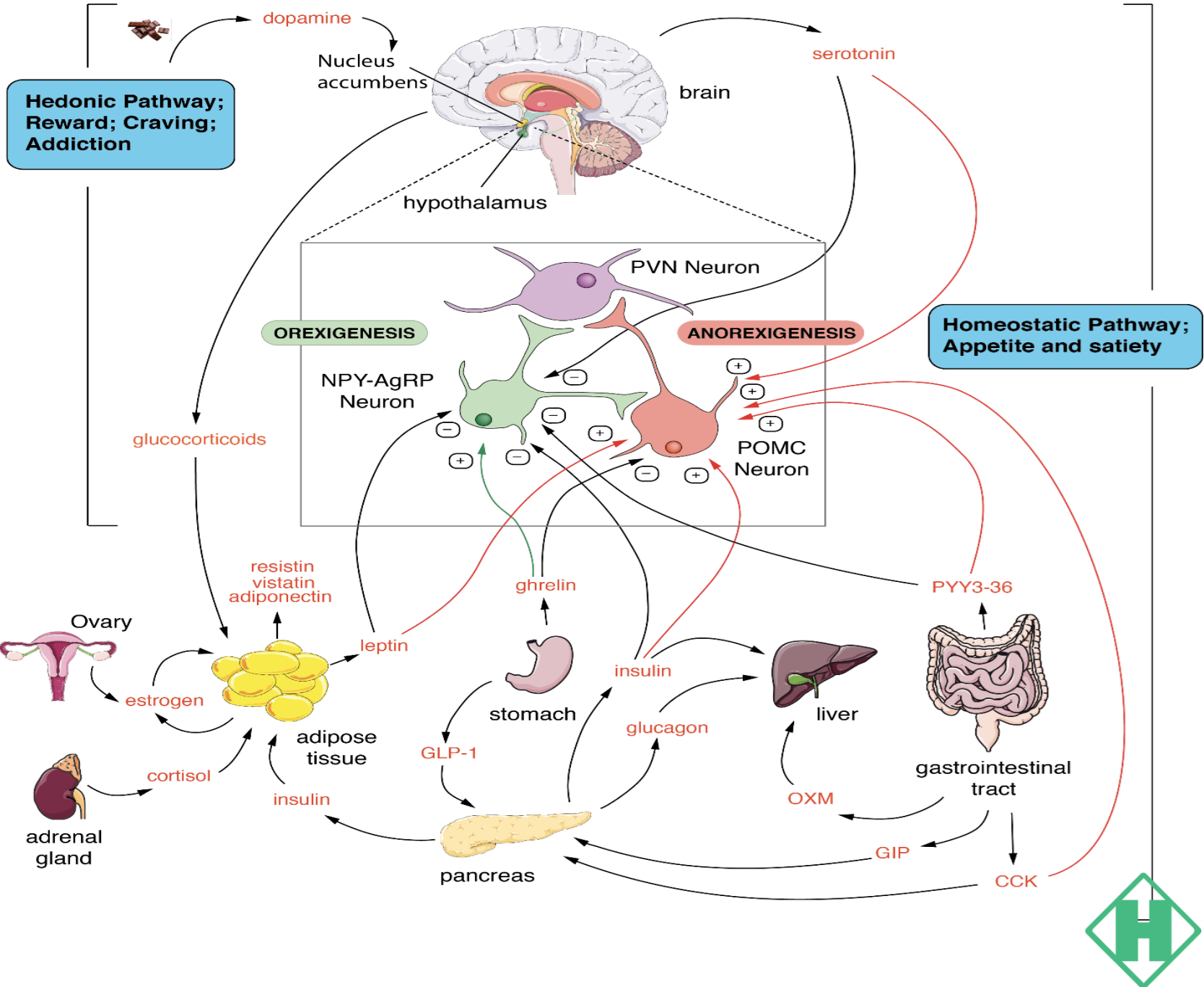
Some % are toxic because
they interfere with some
aspect of the endocrine
system
Endocrine Disruptors

Some are toxic because
they cause an increase in
fat or alter insulin secretion
Metabolism Disruptors



Hormonal Control of Metabolism

All hormones and hormonal pathways are potential targets For Metabolism Disruptors.



We all carry a Chemical Body Burden



287 chemicals in
cord blood

In **breast milk** (BPA, PCBs,
dioxins, pesticides,
mercury, flame retardants)

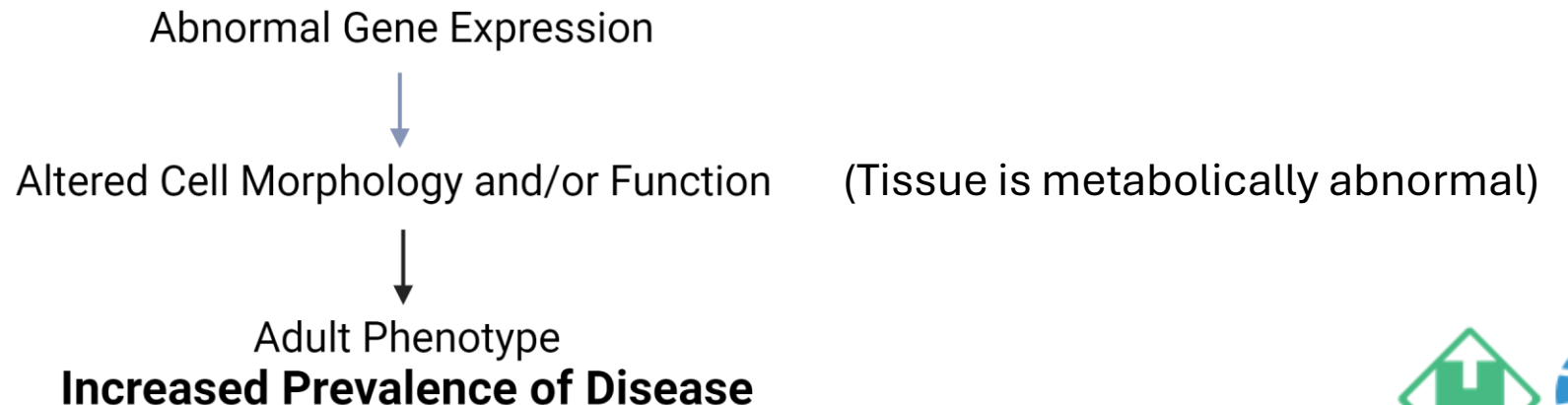
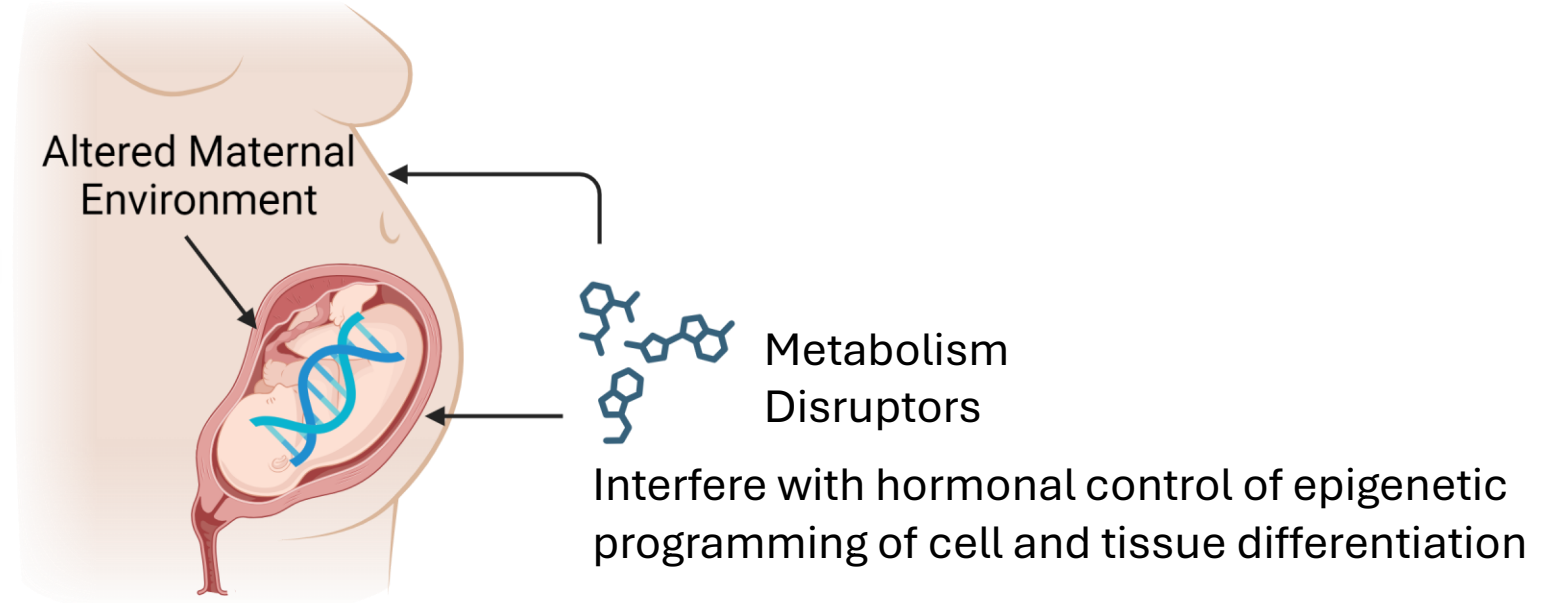


47
chemicals in every **pregnant**
woman tested



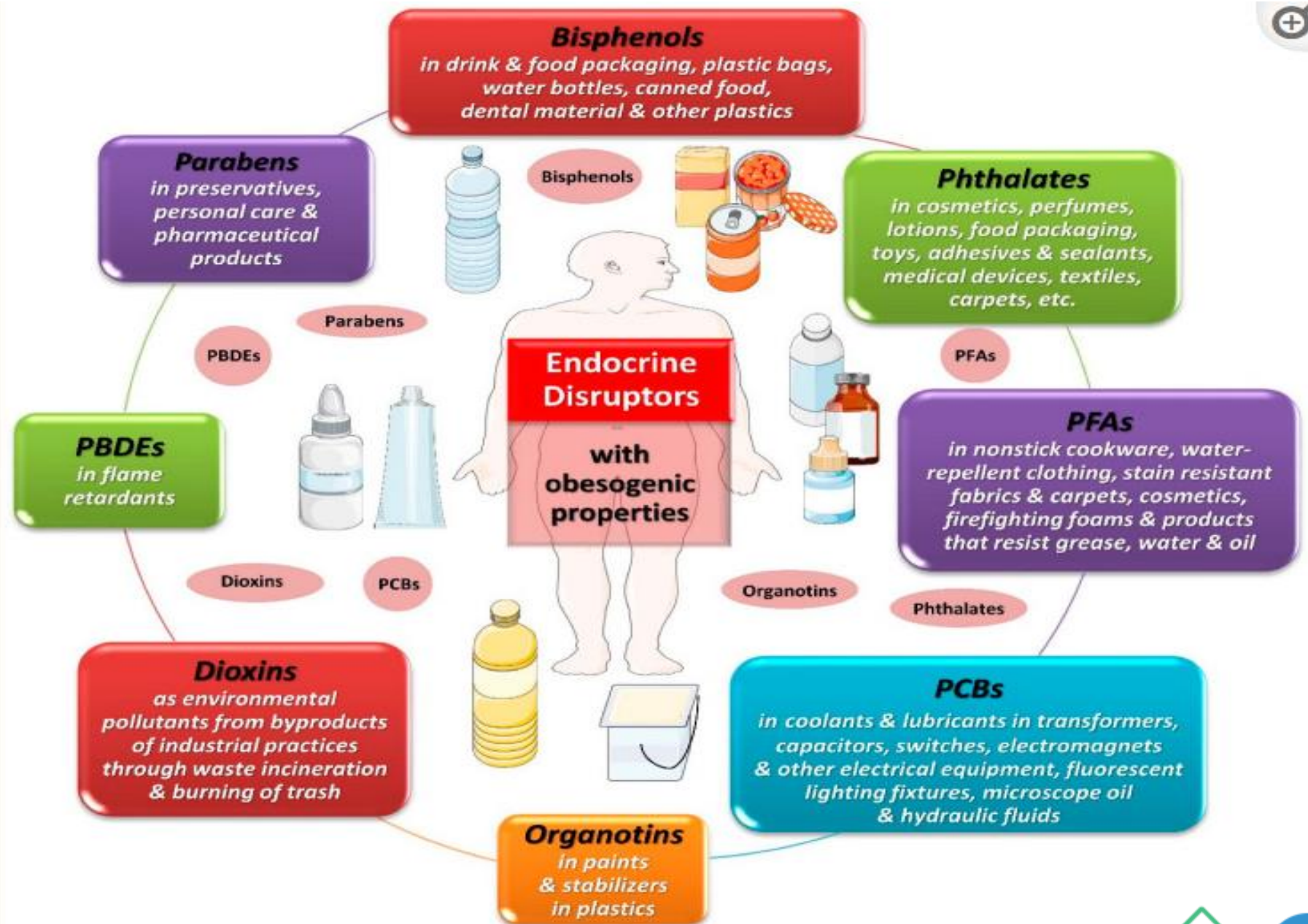
Development: Most Sensitive Time for Exposure to Metabolism Disruptors

**A bad start...
lasts a lifetime!**



Metabolism Disrupting Chemicals

We are born pre-polluted!



M. Dalamaga et al Int J Mol Sci 2023

The Western Diet (Ultra-processed) is Obesogenic

Western Diet

- High fat
- High sugar
- High salt
- Low fiber
- Inadequate fresh fruit and vegetables
- Micronutrient deficient
- **High in ultra-processed food**
- **Addictive**
- **Advanced glycation products**

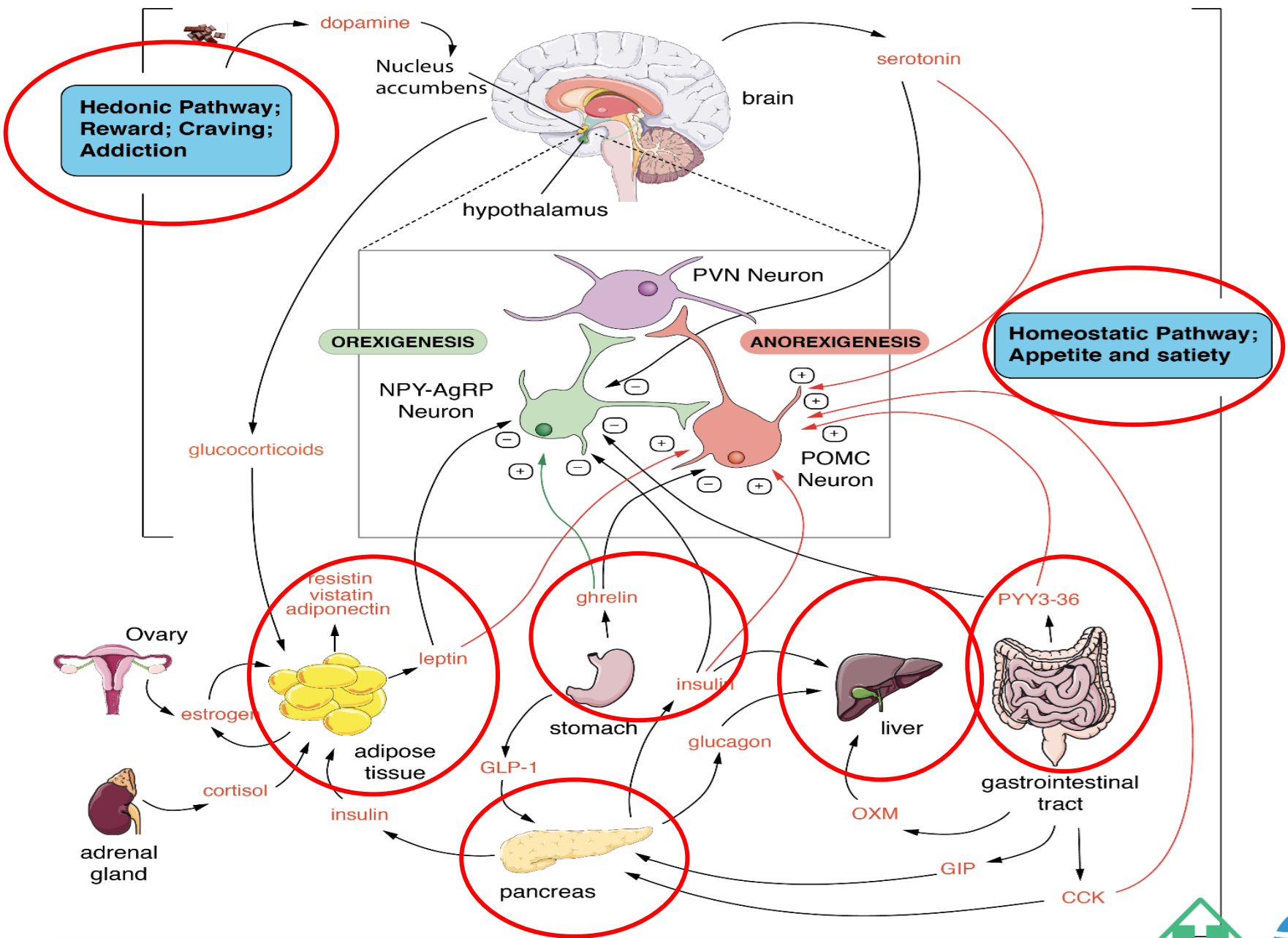
Contains metabolic disruptors

- Bisphenol A
- Phthalates
- PFAS
- Fructose
- Non-nutritive sweeteners
- Methyl and butyl parabens
- Tween80/carboxy cellulose
- 3-tert-butyl-4-hydroxyanisole (3-BHA)
- Monosodium glutamate (MSG)
- Red coloring 40*
- Yellow coloring 5 and 6*
- Pesticides (PFAS)

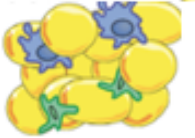
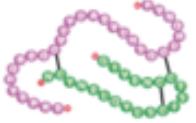
* Potential obesogens



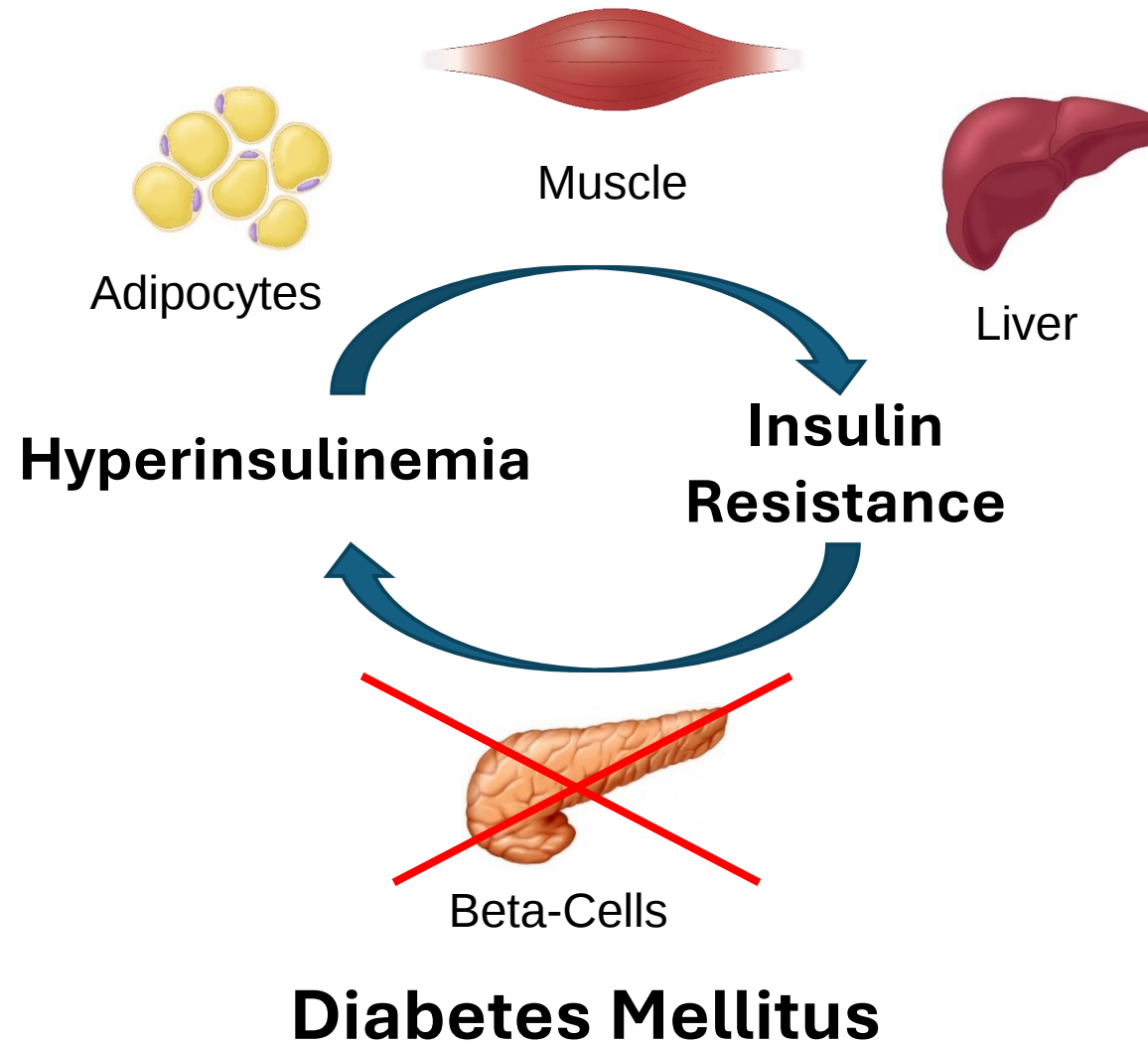
Sites of Action of Obesogens



Obesogens Affect Multiple Endpoints

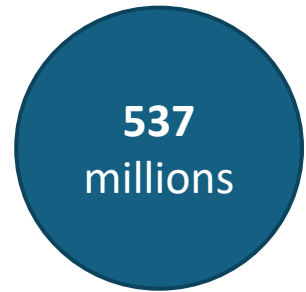
Altered microbiome 	Increased food intake 	Larger effect with HFD	Inflammation 	NAFLD 	Dysfunctional Adipocyte 	Insulin resistance 	Increase ROS
• BPA, BPS • Phthalates • PFAS • PBDE • TCDD • PCBs • PAH (Air pollution) • Methyl paraben • Triclosan	• BPA • DEHP • TBT • OPFR (flame retardant)	• BPA • Butyl benzyl phthalate • DEHP • TBT • Nicotine • Chlorpyrifos • Imidacloprid • DDT • Permethrin • Atrazine	• BPA • TBT • DEHP • PBDEs • Triclosan • CMC • PM_{2.5} • Western diet	• BPA • DEHP • TBT • DDT • PCBs • BaP • Triclosan	• BPA • DEHP • TBT • TCP	• BPA • DEHP • PM_{2.5} • PFOS • Atrazine • Cadmium • Permethrin • Western diet • OPFRs • Chlorpyrifos	• BPA • TBT • BBP • DEHP • PFAS • Atrazine • Cadmium • Chlorpyrifos • {CBs • PBDE • Air pollution

Obesity

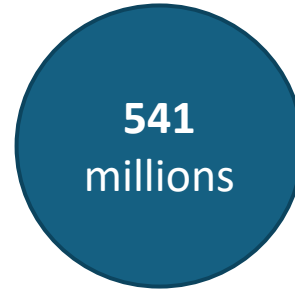


Worldwide Epidemic of Diabetes

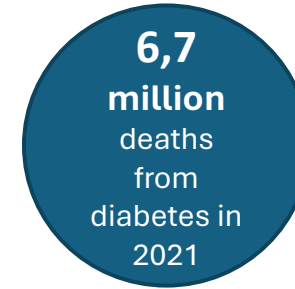
IDF Diabetes Atlas 2021



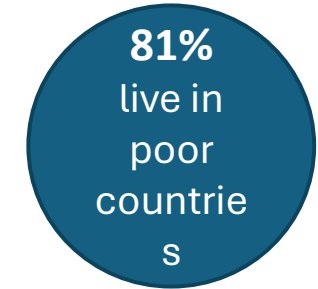
**1 in 10 adults
suffer diabetes**



**541 million adults
have glucose
intolerance**



**1 person dies
every 5 seconds**

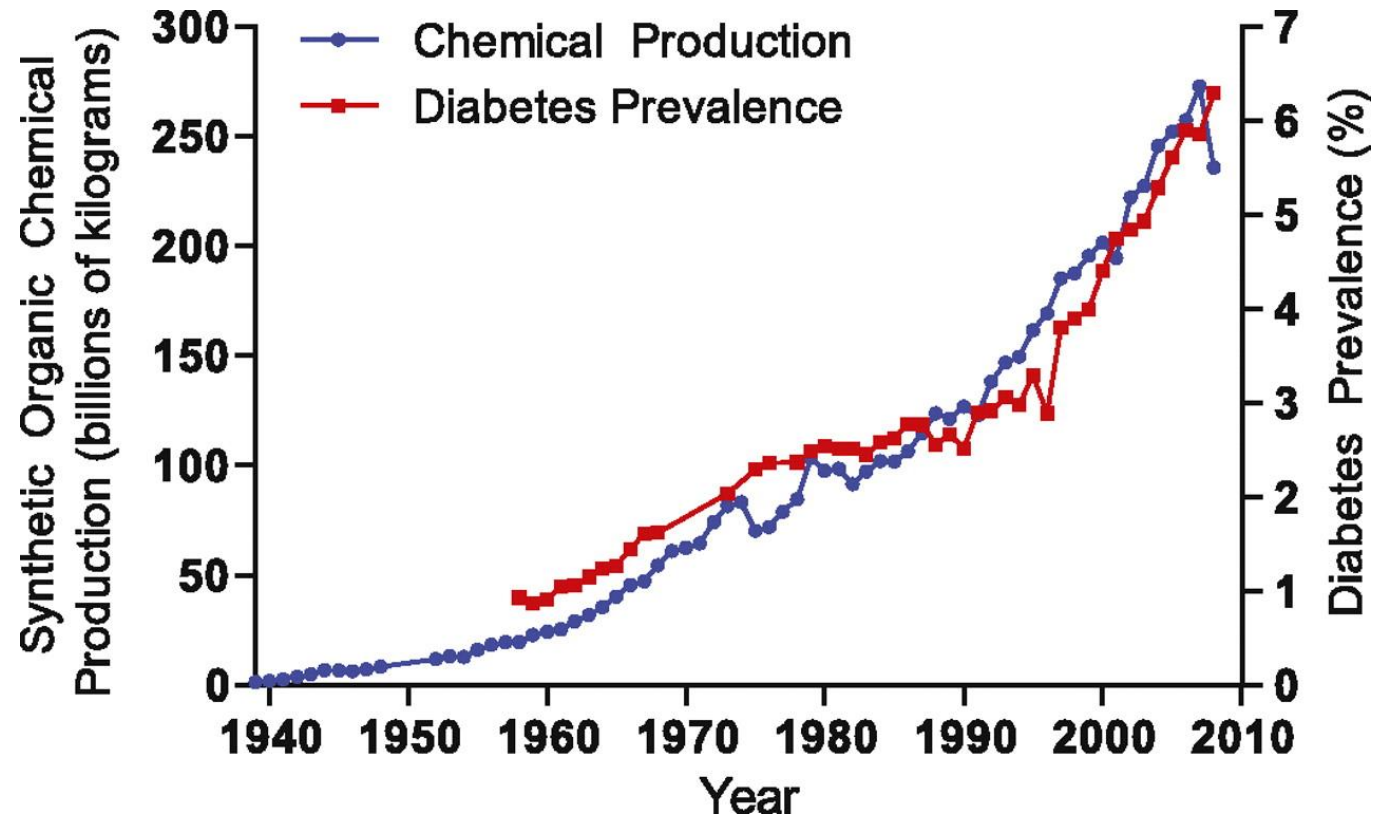


**4 out of 5 live in
low- and middle-
income countries**

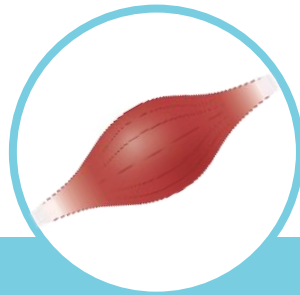
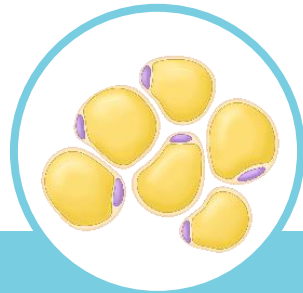
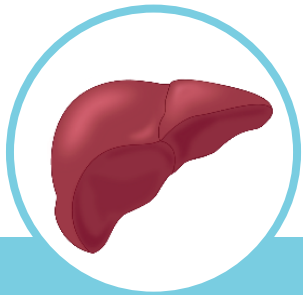


**835,000 million € in healthcare spending.
An increase of 316% in the last 15 years.**

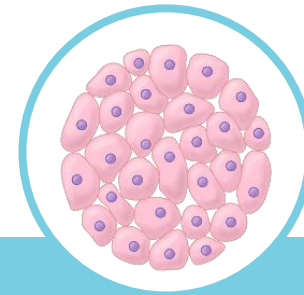
U.S. synthetic chemical production and diabetes prevalence



The **etiology** of type 2 diabetes is based on



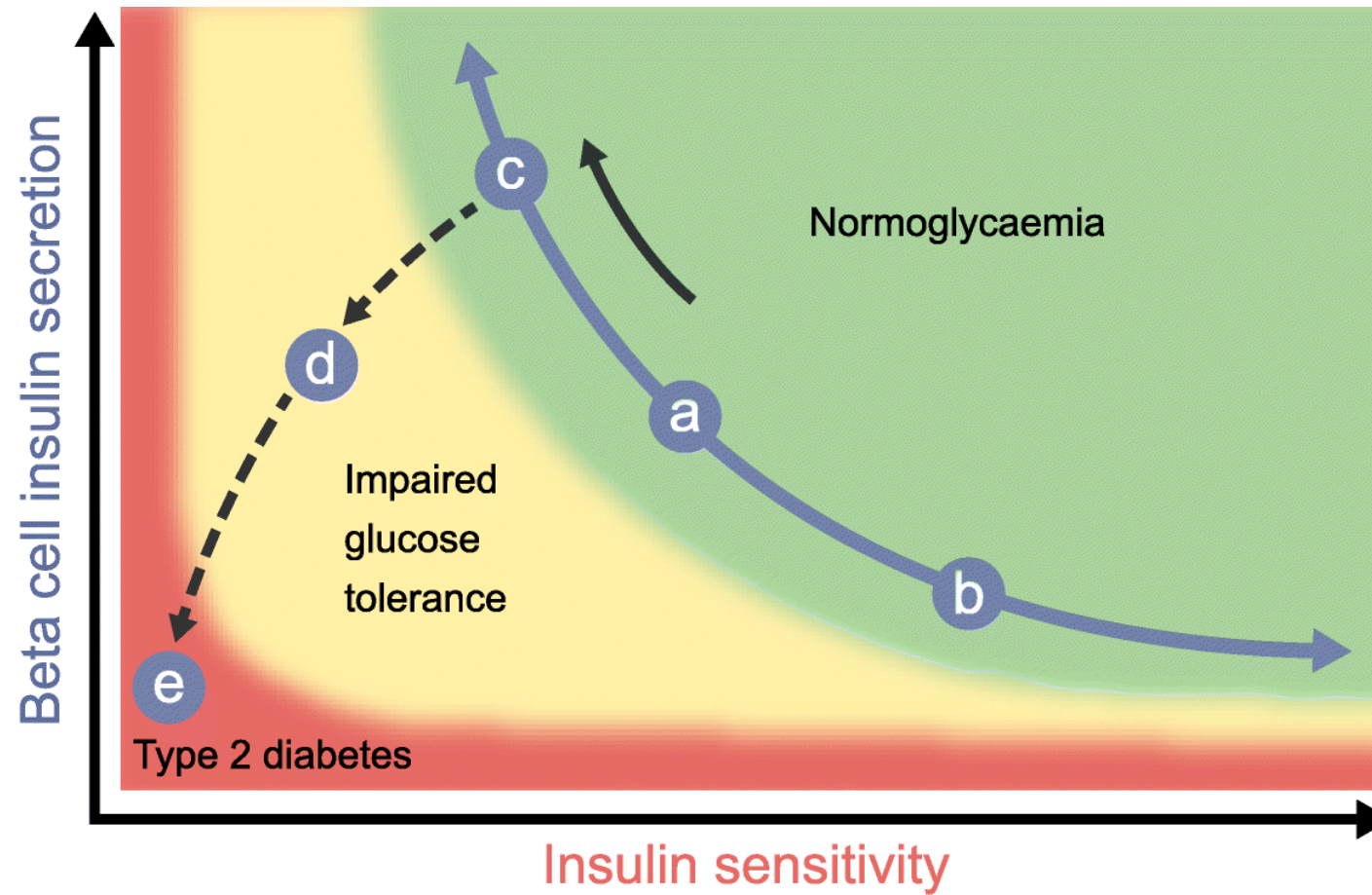
The induction of
insulin resistance



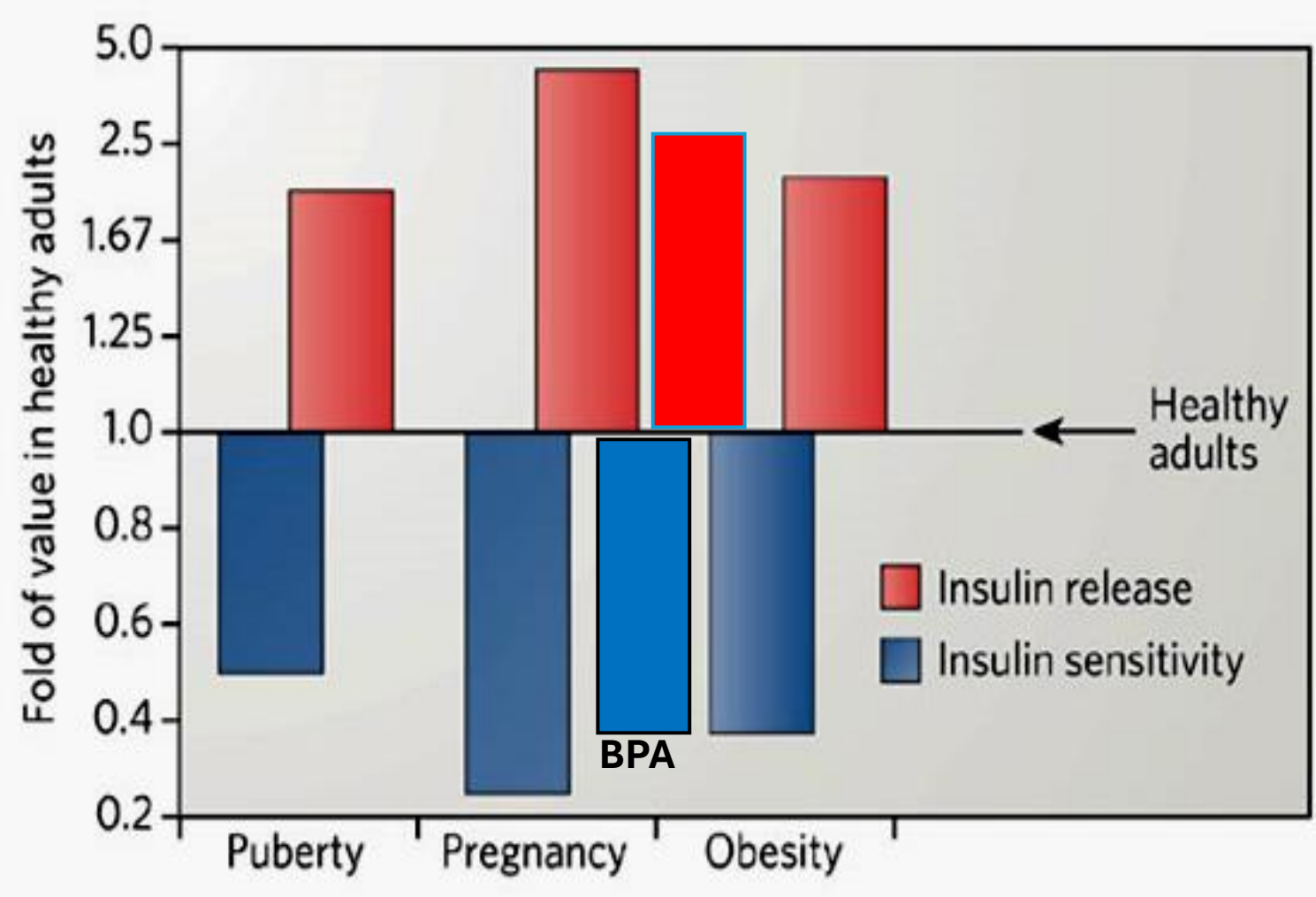
Decreased β -cell
function
and/or β -cell mass

Genetic predisposition and **environmental factors** play key roles

Relationship between Insulin sensitivity and insulin release



Insulin sensitivity and insulin responses during puberty, during pregnancy and in obesity relative to that in healthy adults



β-cell Dysfunction

Arsenic ^{1, 2, 3}	Incretin signalling disruption
TCDD ¹	Altered Ca ²⁺ flux
Cadmium ^{1, 2}	Reduced beta cell ATP production
Mercury ^{1, 2}	Reduced insulin gene expression
PCBs ^{1, 2, 3}	Insulin granule exocytosis disruption
Vacor ^{2, 3}	Altered oestrogen signalling
BPA ^{1, 2, 3}	Oxidative and ER stress
Other phenols ¹	Mitochondrial dysfunction
Triphenyltin ¹	DNA damage
Phthalates ¹	Serotonin depletion
DDT/DDE ^{1, 2}	Apoptosis and necrosis
PBDEs ¹	Decreased proliferation
OC pesticides ^{1, 3}	Inflammation/insulinitis
Alloxan ^{1, 2}	Altered epigenetics
	Cytoskeletal disruption

¹Cell, islet and tissue assays

²Animal models

³Epidemiological and clinical studies

Insulin Resistance

Altered expression of insulin signalling intermediates
PPAR and GR signalling disruption
Disruption of glucose transport and utilisation
Disrupted gluconeogenesis and glycogen handling
Increased cellular senescence

Inflammatory cytokines
Altered lipid metabolism
Adipose and adipokine disruption
Impaired mitochondrial function
Oxidative stress

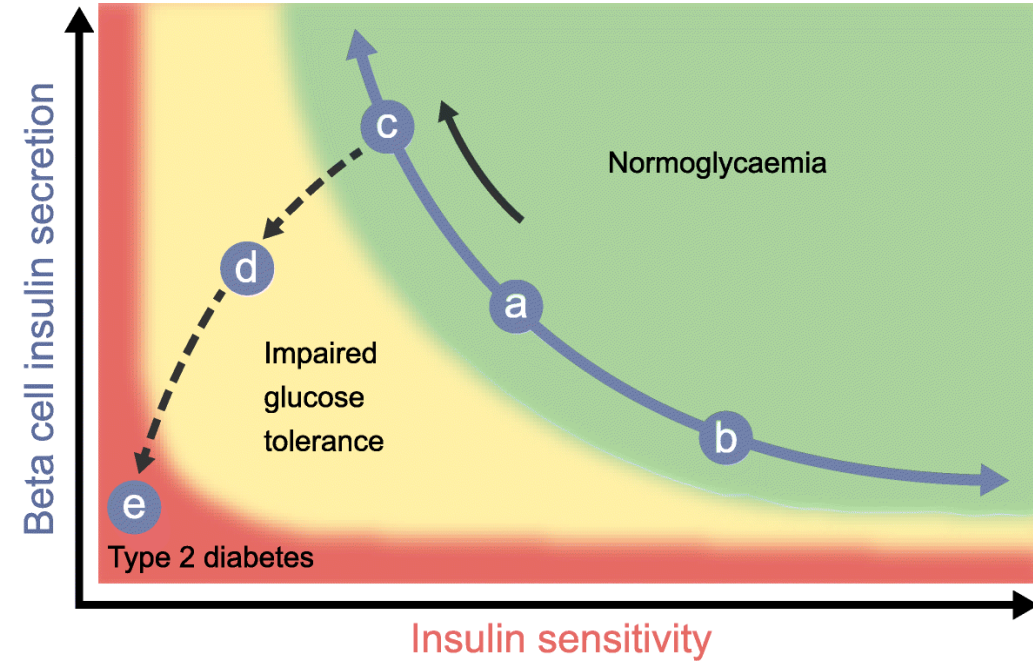
Tolylfluorid^{1, 2}
TCDD^{1, 2, 3}
BPA^{1, 2, 3}
Phthalates^{1, 2, 3}

PM^{2, 3}
Arsenic^{1, 2, 3}
PCBs^{1, 2, 3}
Cadmium^{1, 2, 3}

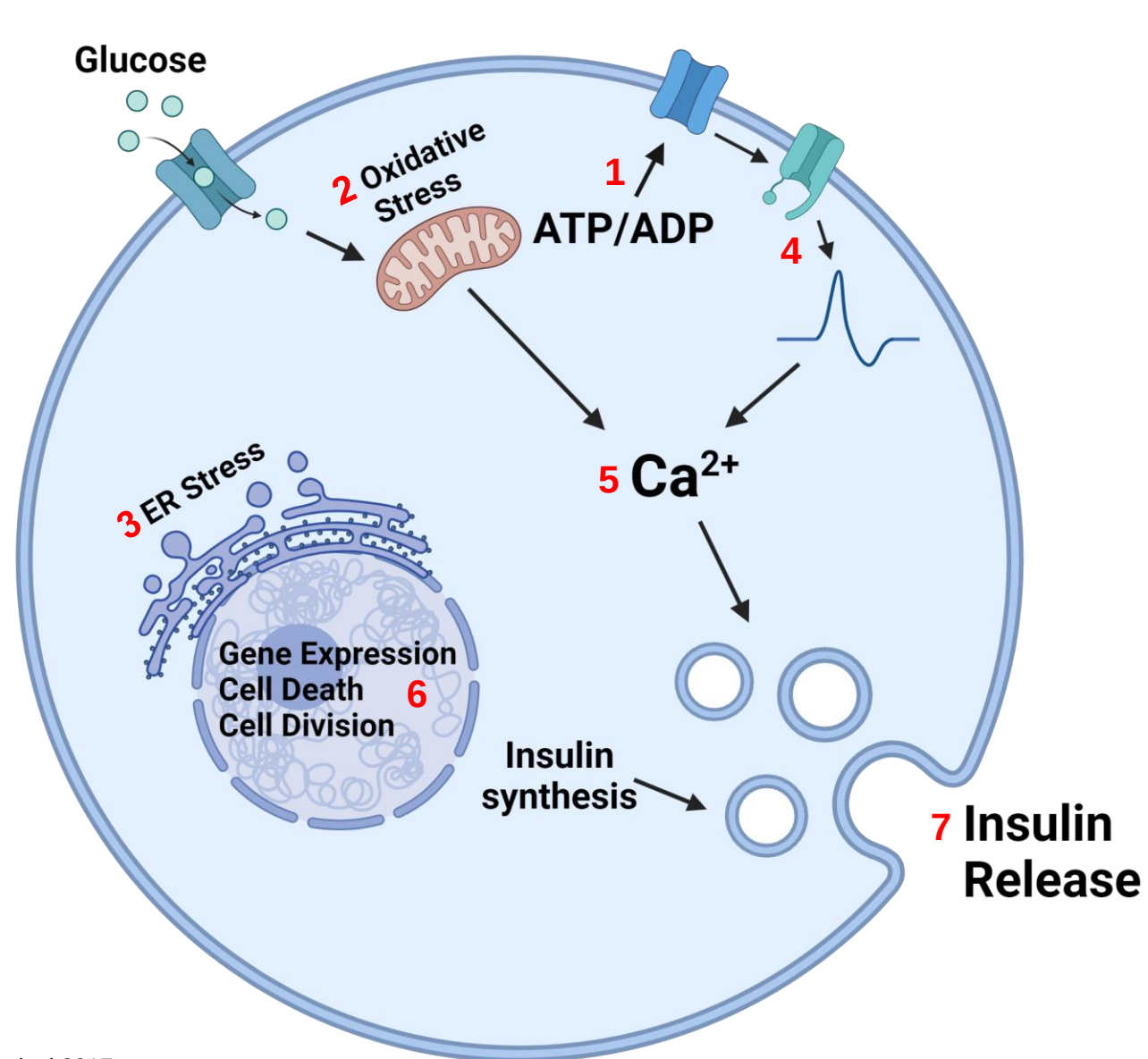
POPs^{2, 3}
PFASs^{1, 2, 3}
Malathion^{2, 3}
Atrazine²

PBDEs^{2, 3}
PCDD/Fs³
DDT/DDE^{2, 3}

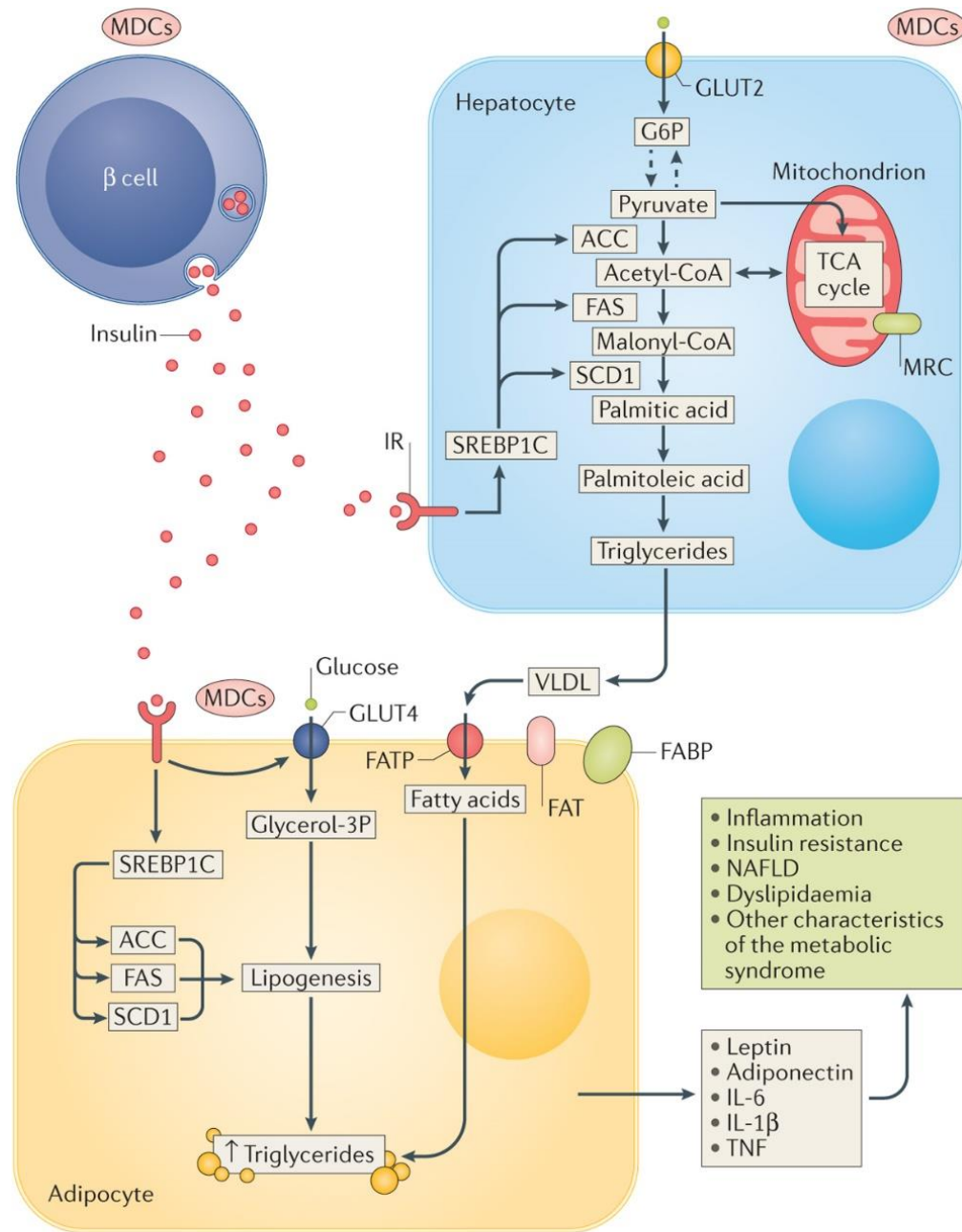
Mercury^{2, 3}
OC pesticides^{2, 3}



Metabolic Disruption of β -cells



- 1** Bisphenol-A
Nonylphenol
Octylphenol
Triphenyltin
- 2** Bisphenol-A
Phthalates
Mercury
Cadmium
- 3** Bisphenol-A
Phthalates
- 4** Bisphenol-A
- 5** Bisphenol-A
Arsenic
PCBs
Triphenyltin
- 6** Bisphenol-A
Phthalates
Cadmium
- 7** Bisphenol-A
Phthalates
Dioxins
PCBs
PFAS



Summary

- The prevalence of obesity and type 2 diabetes continues to increase.
- Obesity is a major risk factor for type 2 diabetes
- Exposure to MDCs during development and adulthood increased the susceptibility to develop obesity and/or type 2 diabetes.
- Many of the same chemicals can lead to obesity and diabetes: including plastics (bisphenols, phthalates, PFAS) from food packaging.
- The key to improving health is to reduce exposure to MDCs. This will require changes to regulations and policies.

Good News: MDCs offer the Opportunity to Prevent Obesity and Type 2 Diabetes Prevention!

- Reduce **exposure to environmental chemicals** before and during **pregnancy**
 - Eliminate plastics/canned food
 - Filtered drinking water
 - Organic cleaners, organic food
 - Careful with cosmetics/sunscreens
- Breastfeed and reduce environmental exposures during **infancy and toddler stages**.
- Watch nutrition, exercise and chemical exposures **throughout life**.
- The ultimate solution to this health crisis requires **new legislation** to stop the production of MDCs.