

Environmental Chemicals and their Impact on Child Health: A Focus on Endocrine Disrupting Chemicals.

Jon B Tinglestad Conference
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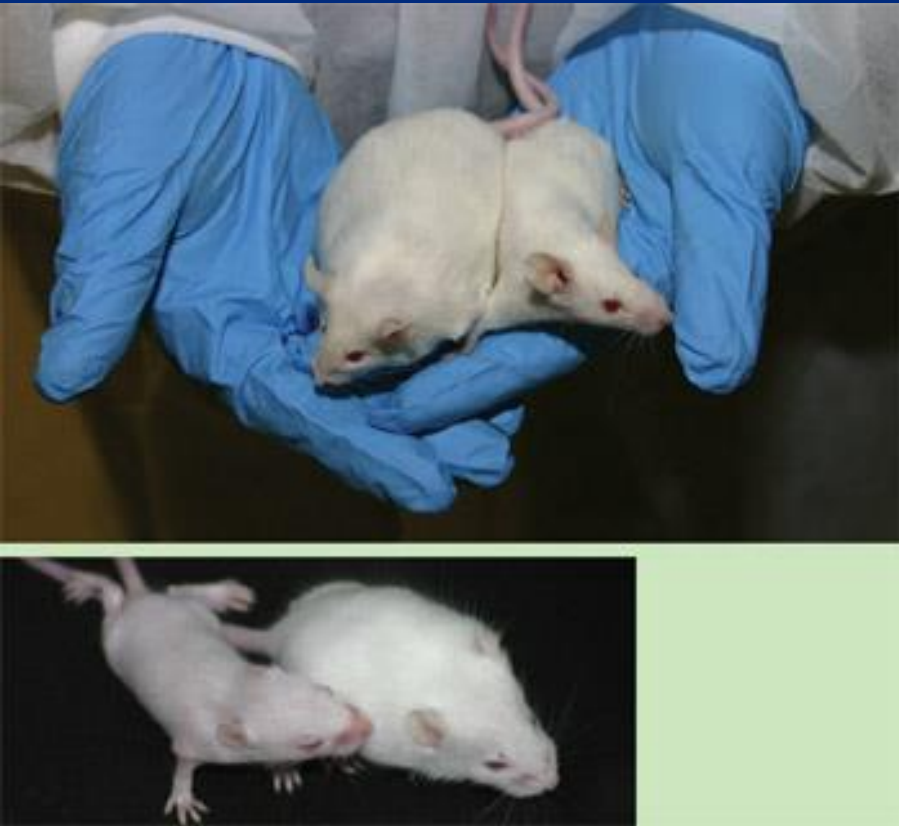
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Objectives



- Define ‘endocrine disrupting chemicals’ (EDCs) and their properties.
- Identify the most common and/or problematic EDCs.
- Appreciate that EDC exposure can generate phenotypes that persist ≥ 3 generations
- Employ strategies to minimize exposure and risk .

Perfluorooctane sulfonate (PFOS) exposure

Environmental Health Perspectives May 2007 115:A251-256

Conflicts/Disclosures

- I have no financial conflicts or disclosures
- I will not discuss use of unapproved/experimental devices

Endocrine Disrupting Chemicals (EDCs): Definitions

- US EPA: “An exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes”
- WHO/UNEP: “An exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in intact organisms, or its progeny or (sub) population”
- EU: “Exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function”
- Endocrine Society (2015): “An exogenous chemical, or mixture of chemicals, that interfere with any aspect of hormone action”

Four lines of EDC research:

(Gore et. al. *Endocrine Reviews* 2015;36:E1-E150)

- Animal studies:
 - Consequences of EDC exposure on development and physiology in animal models.
- Mechanistic studies
 - Effects in cells or tissues from exposed animals looking at gene expression, epigenetic changes, molecular events etc
- Epidemiological studies in humans:
 - Comparing body burden of EDCs and disease propensity in humans.
 - Prospective studies
- Occupational/Acute exposure in humans
 - Investigation of humans with know occupational or acute exposure.

Strong evidence for role of EDCs in:

(Gore et. al. *Endocrine Reviews* 2015;36:E1-E150)

- Obesity and diabetes
- Female reproductive system
- Male reproductive system
- Hormone-sensitive cancers in females
- Prostate gland
- Thyroid gland function
- Neurodevelopment and neuroendocrine system

EDCs are highly heterogeneous:

- >85,000 registered chemicals in use
 - >1,000 of those tested act as EDCs
- Synthetic chemicals
 - Solvents/lubricants and byproducts
 - Polychlorinated biphenyls (PCBs), dioxins
 - Fuels/explosives
 - Perchlorate, Jet fuel8
 - Flame retardants
 - Polybrominated diphenyl ethers (PBDEs)
 - Plastics and plasticizers
 - Bisphenol A (BPA), BPS, phthalates
 - Pesticides/insecticides
 - Methoxychlor, chlorpyrifos, parathion, dichlorodiphenyltrichloroethane (DDT)
 - Fungicides
 - Vinclozalin, organotins (tributyltin), maneb

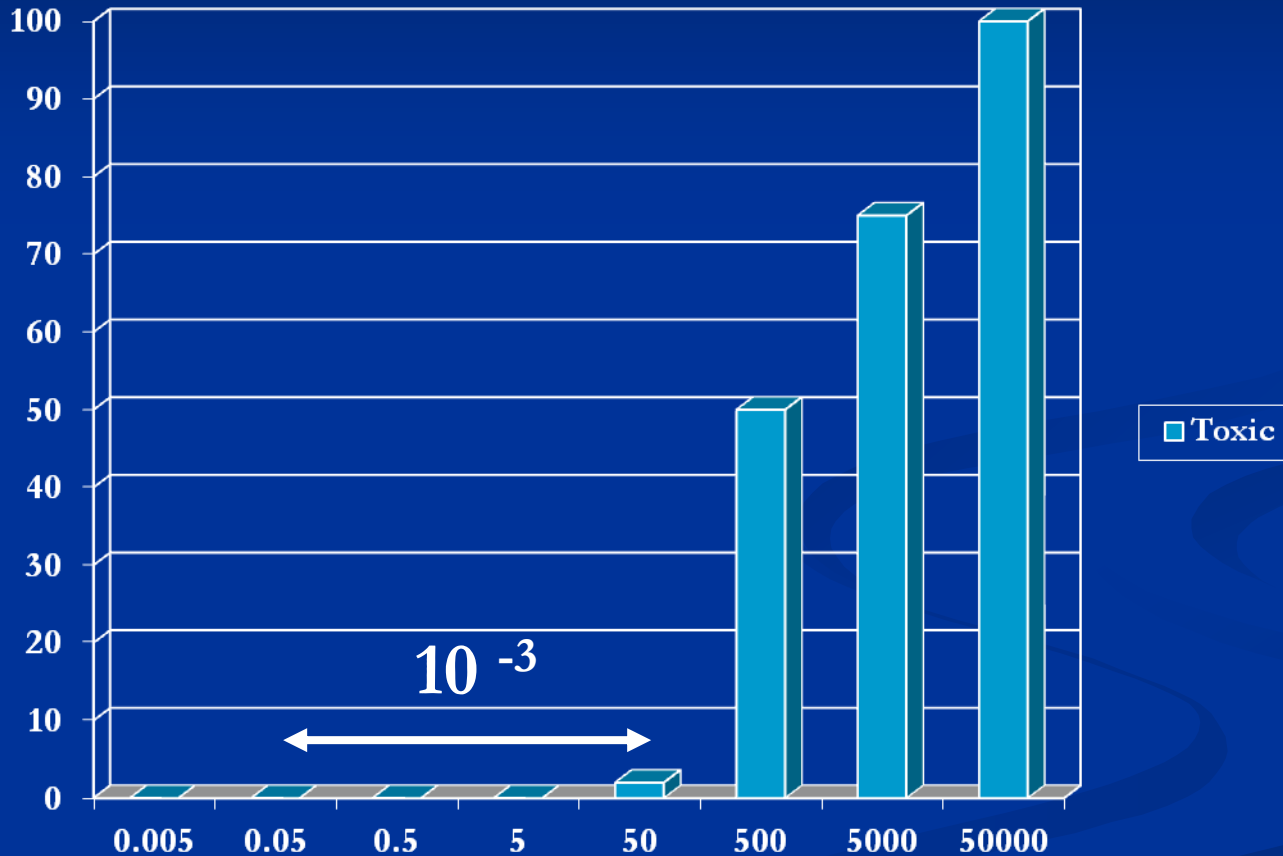
EDCs are highly heterogeneous:

- Natural compounds, drugs, personal care products
 - Phytoestrogens (especially soy and soy products)
 - Genestein, Coumestrol
 - Nicotine
 - Pharmaceuticals
 - Diethylstilbestrol (DES), phthalates
 - Personal care products
 - Detergents: nonylphenol
 - UV screens: 4-methylbenzylidene camphor
 - Lotions/fragrances: phthalates
 - Antibacterial sanitizer: **triclosan**

EDCs have special characteristics...

- May be toxic at high levels but at low levels behave more like a drug or a hormone
 - Complex dose-response curves
 - Active at very low concentrations
- May have long latency period between exposure and effect
 - In utero exposure can lead to adult disease
- May act synergistically at low level
 - xenoestrogens
- Multiple windows of susceptibility
 - Fetal, early childhood, adolescence, post menopausal
- Gender, genetics, nutrition, stress etc. modulate effects
- Effects of some EDCs can be transmitted to further generations via germ-line epigenetic modifications
 - ≠ DNA mutation

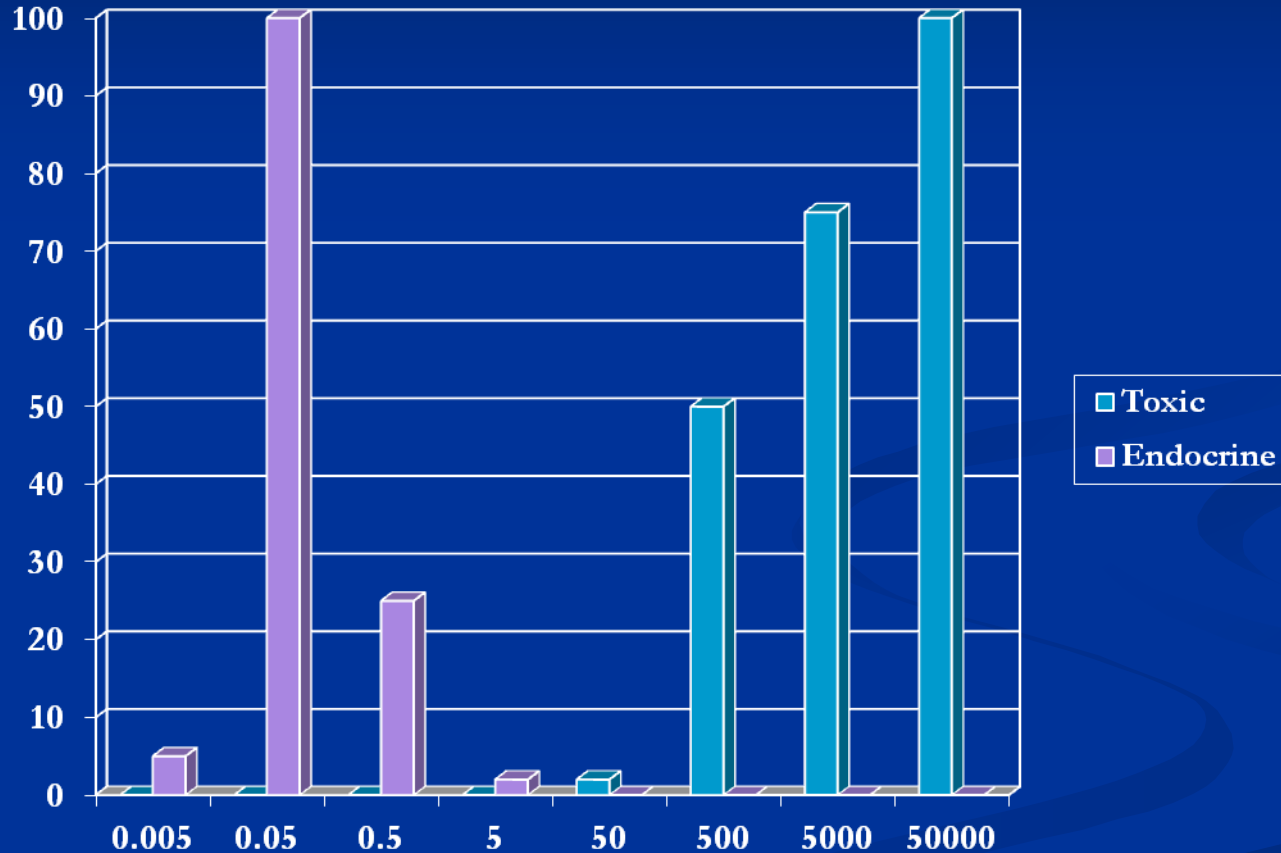
How regulatory agencies determine reference (safe) dose (amount/kg day⁻¹)



↑
Reference Dose (\approx safe)

↑
Lowest Observed Adverse Effect Level (LOAEL)

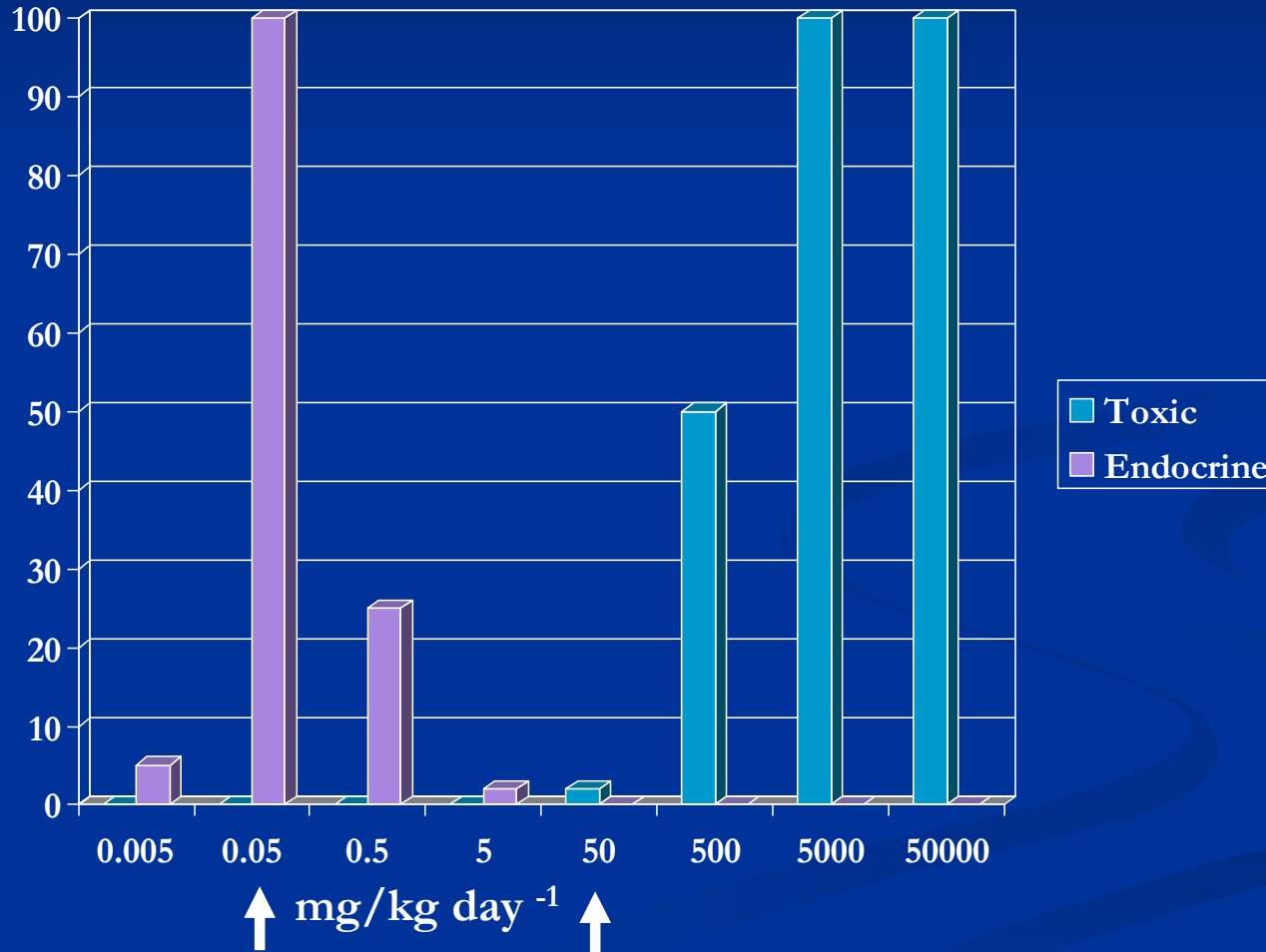
How EDCs behave: non-monotonic and non-predictable dose response curves



Reference Dose (\approx safe)

Lowest Observable Adverse Effect Level (LOAEL)

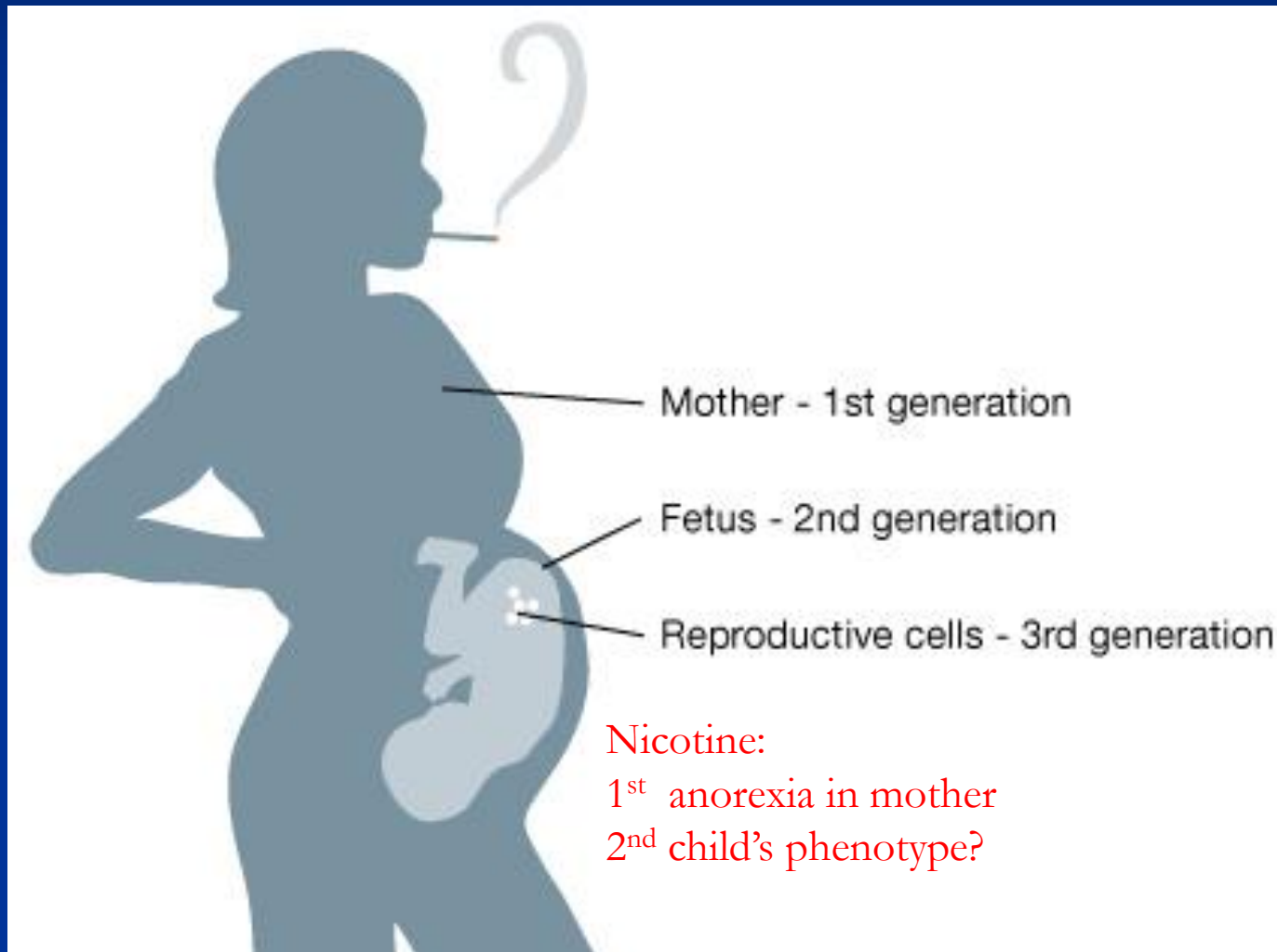
Toxic and endocrine disruption dose response curves for BPA are distinct



Reference Dose (\approx safe)

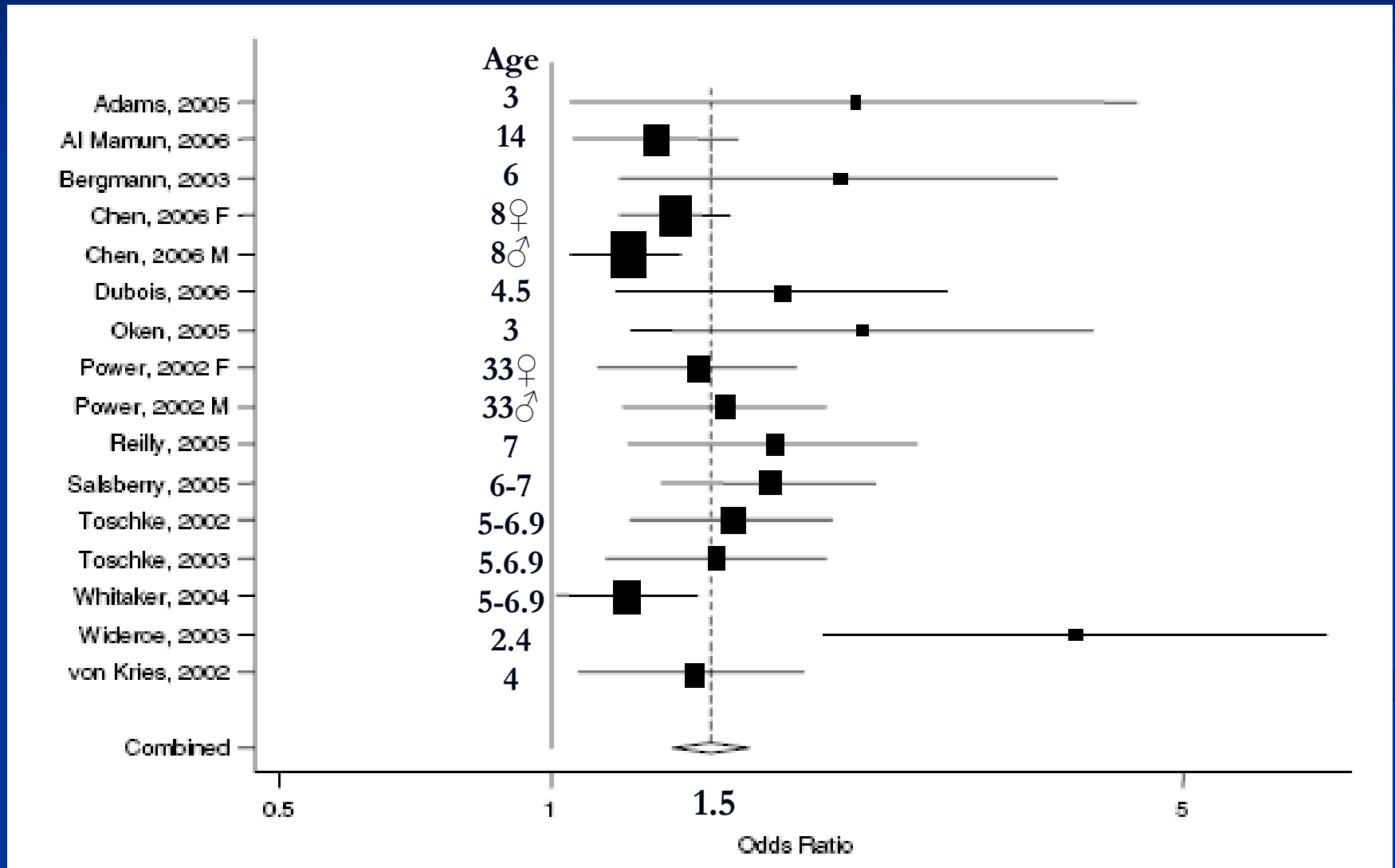
Lowest Observable Adverse Effect Level (LOAEL)

Gestational exposure to EDCs potentially directly exposes 3 generations

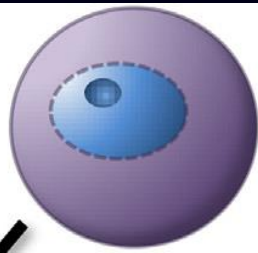


Effect of maternal smoking during pregnancy on offspring overweight (n= 84,563, @ 3-33 years of age)

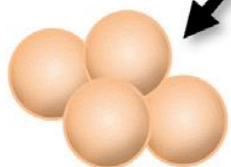
Oken E, Levitan EB, Gillman MW Int J Obesity 2008;32:201-210



Mesenchymal Stem Cell (MSC)

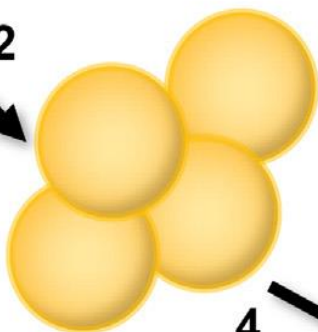


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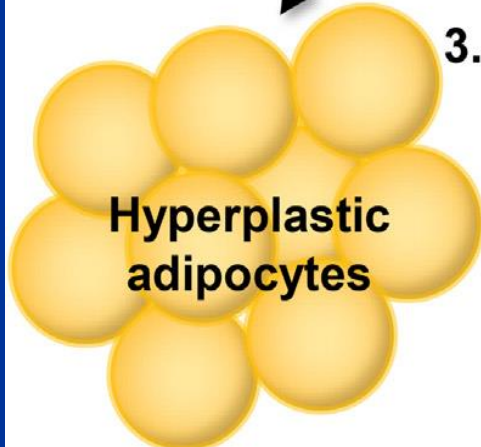
Preadipocyte

2



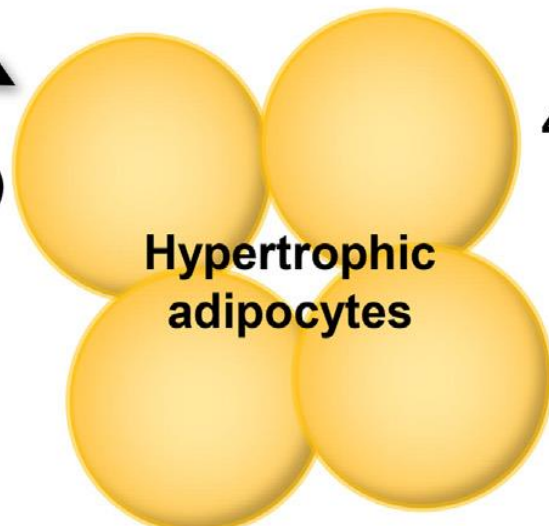
Normal adipocytes

3



Hyperplastic adipocytes

4



Hypertrophic adipocytes

1. Increased adipogenic commitment

- | | |
|----------------|--------------|
| BADGE | Quinoxyfen |
| Firemaster 550 | Tributyltin |
| Fludioxonil | Triflumizole |

2. Increased adipocyte differentiation

- | | | |
|----------------|-----------------|--------------|
| Acetamiprid | Flusilazole | Triphenyltin |
| BADGE | Forchlorfenuron | Triflumizole |
| BDE-47 | PCB-77 | |
| BPA | Pymetrozine | |
| DES | Quinoxyfen | |
| Dioxin | Spirodiclofen | |
| Firemaster 550 | Tebupirimfos | |
| Fludioxonil | Tributyltin | |

3. Increased adipocyte proliferation (in vivo)

- BPA
- DES
- Nicotine
- PCB-77
- Tributyltin

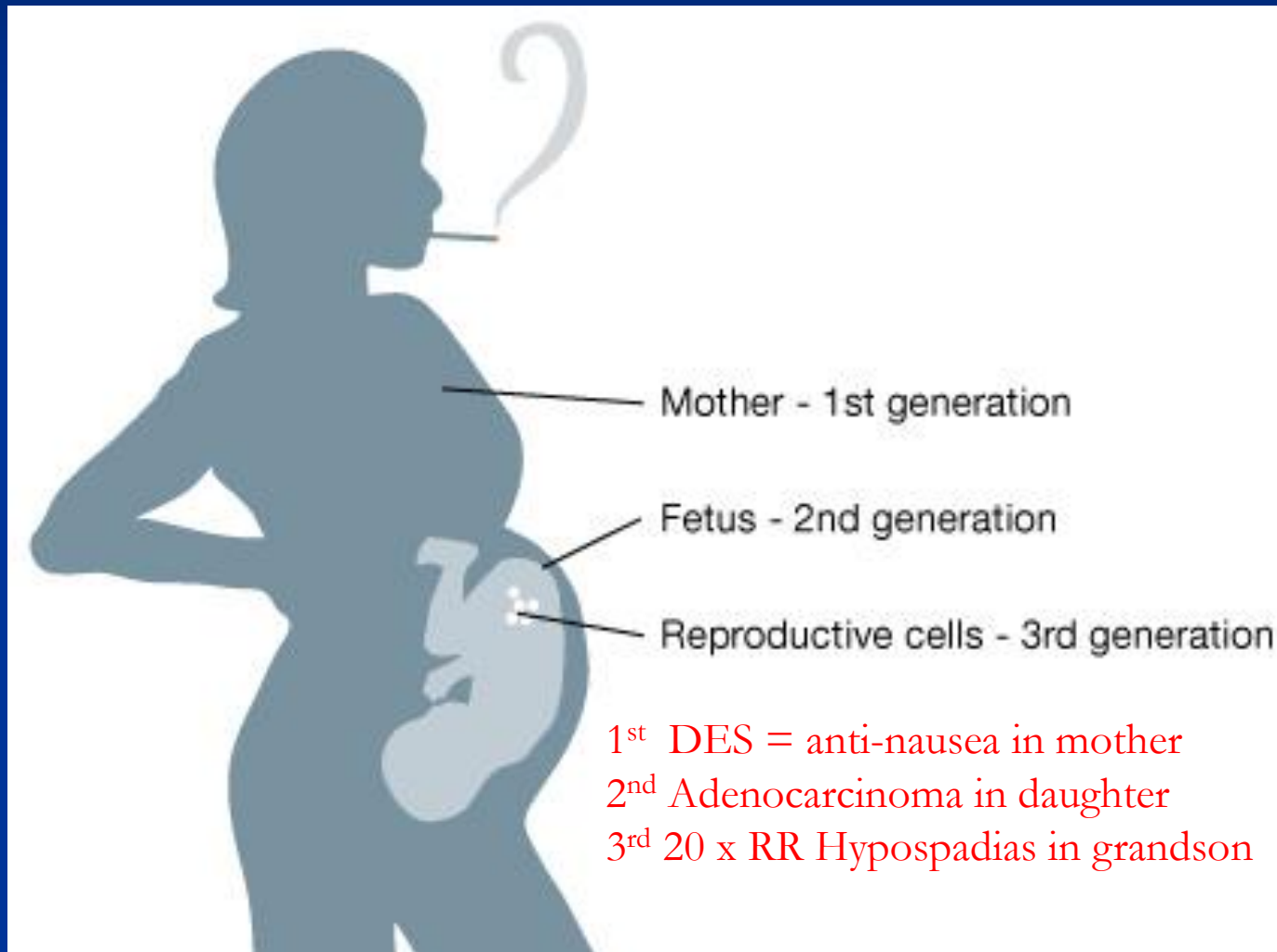
4. Increased lipid uptake (in vivo)

- BPA
- Nicotine
- PCB-77
- Tributyltin

Metabolism Disruptors and Metabolic Disruption (Heindel 2016)

	Obesity	Diabetes	Fatty Liver
Bisphenol A (BPA)	+++	+++	+++
Phthalates (DEHP)	+++	+++	+++
Tributyl Tin (TBT)	+++	+++	+++
Nicotine/smoking	+++	++	+++
Air Pollution (PAH)	++	+++	+++
PCBs	+	+++	+++
Arsenic	++	+++	+++
DDT/DDE	+++	++	+
PFOA	++		+++
PFOS		+	+++
Dioxin (TCDD)		++	+++
Others			

Gestational exposure to EDCs potentially directly exposes 3 generations

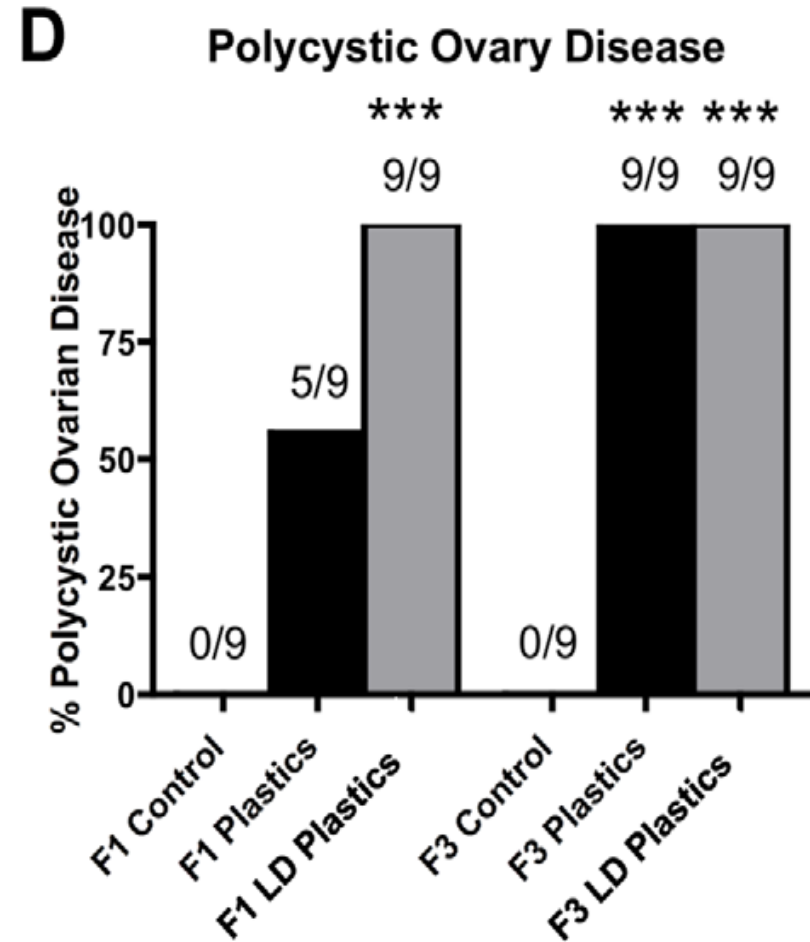
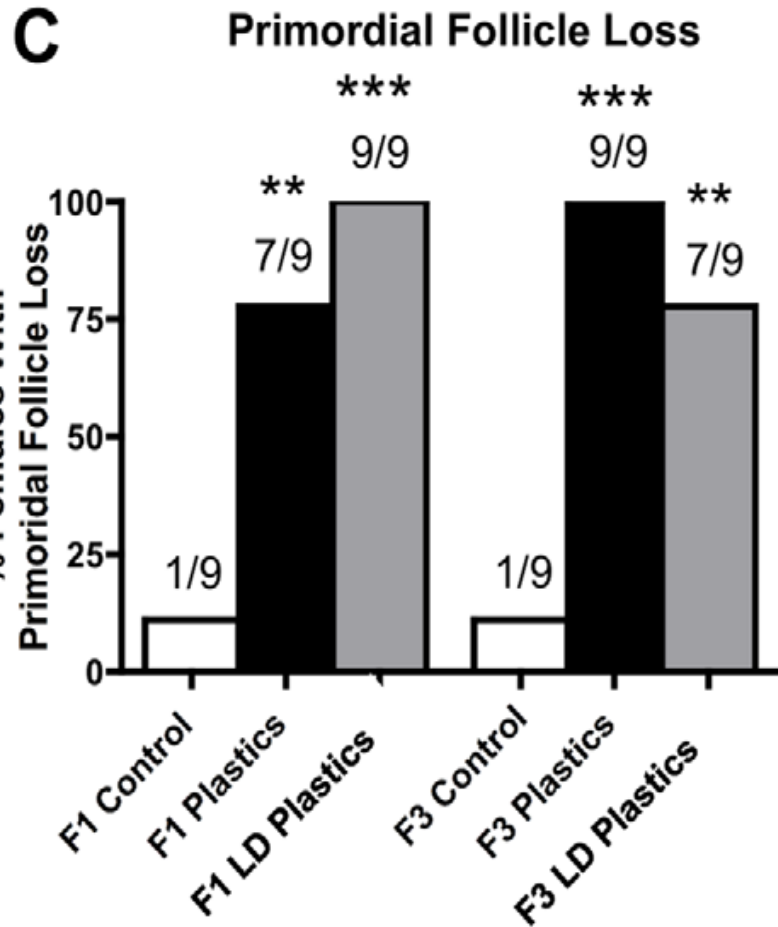


Transient gestational exposure to EDCs causes trans-generational inheritance of reproductive disease

Manikkah M et al 2012 PLoS ONE 7(2)e31901.

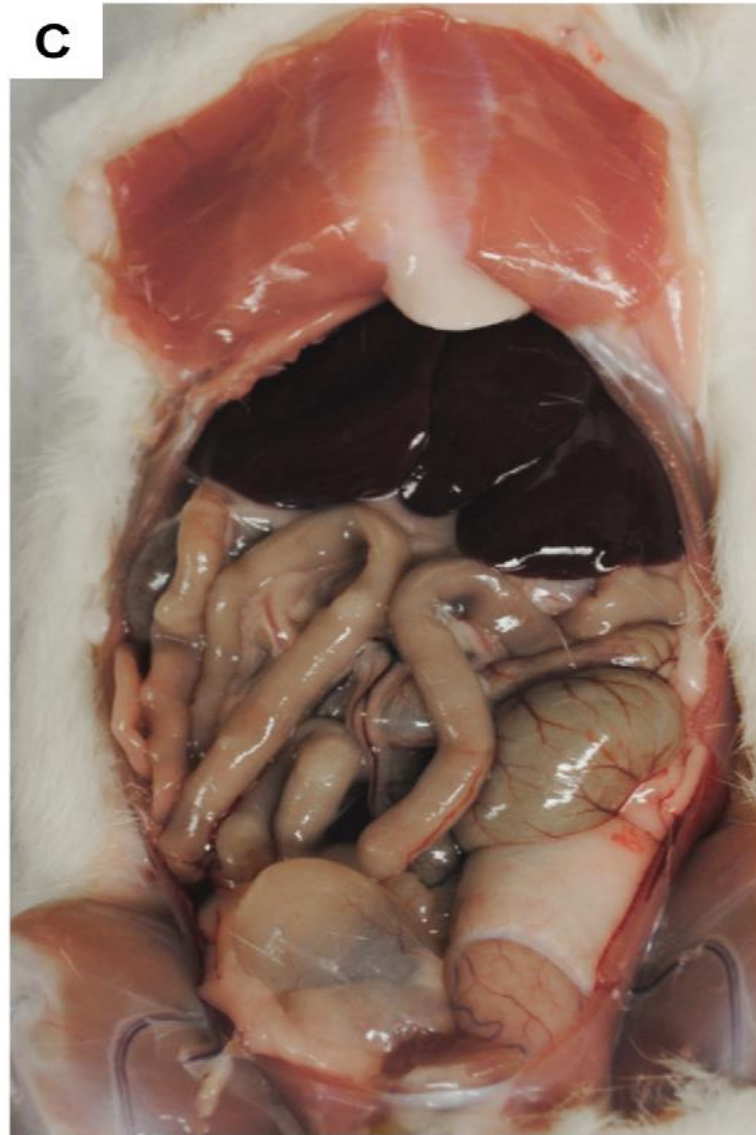
Generation	Pesticides Permethrin and DEET	Plastics BPA and Phthalate mix	Dioxin	Hydrocarbons jet fuel/JP8
gen 1 or F ₀ “Great GM”	Transient exposure to EDC during early embryonic gonadal sex determination			
gen 2 or F ₁ “Grandmother”	Reproduce with no EDC exposure			
gen 3 or F ₂ “Mother”	Reproduce with no EDC exposure			
gen 4 or F ₃ “Child”	Normal puberty ↓ pool of primordial follicles	Early puberty ♀ ↓ pool of primordial follicles PCOS	Early puberty ♀ ↓ pool of primordial follicles	Early puberty ♀ ↓ pool of primordial follicles ↑ Sperm apoptosis

Female reproductive disease in 3rd generation removed from exposure to low dose plastic mix (BPA, DEHP, DBP –Skinner)

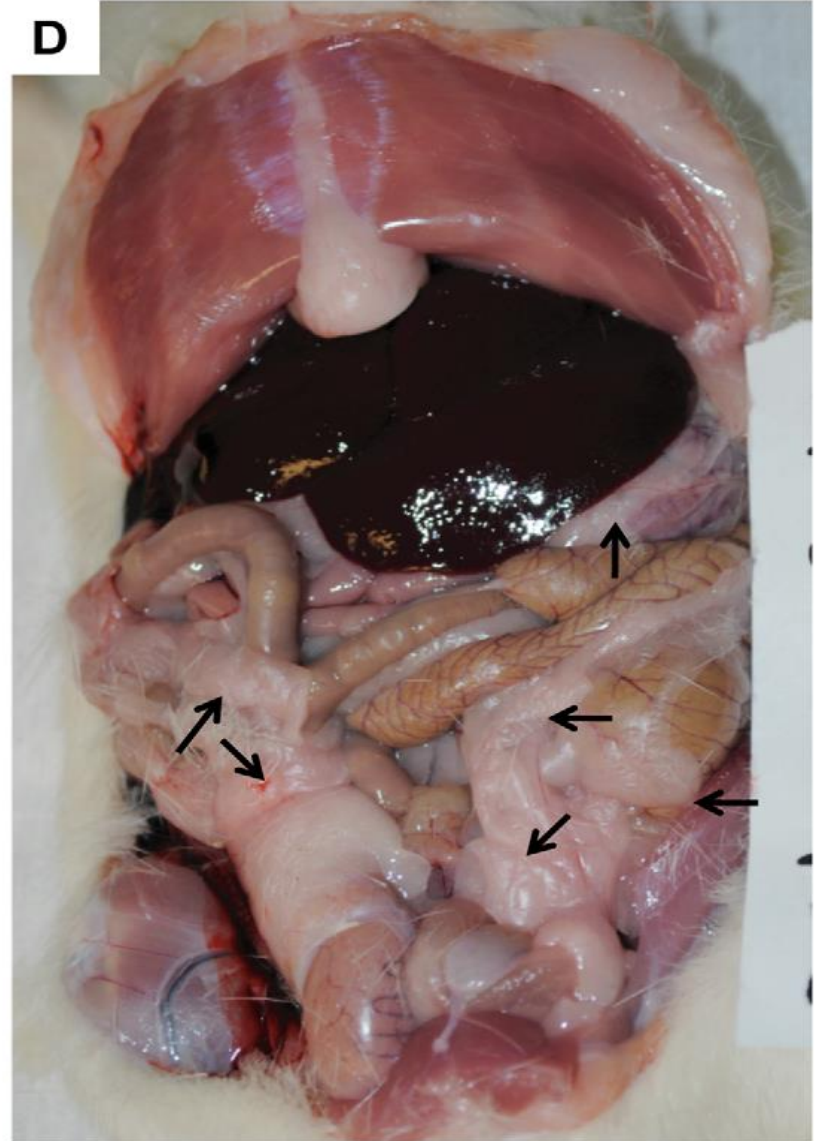


Visceral fat in 3rd generation removed from exposure to low dose plastic mix (BPA, DEHP, DBP – Skinner et al)

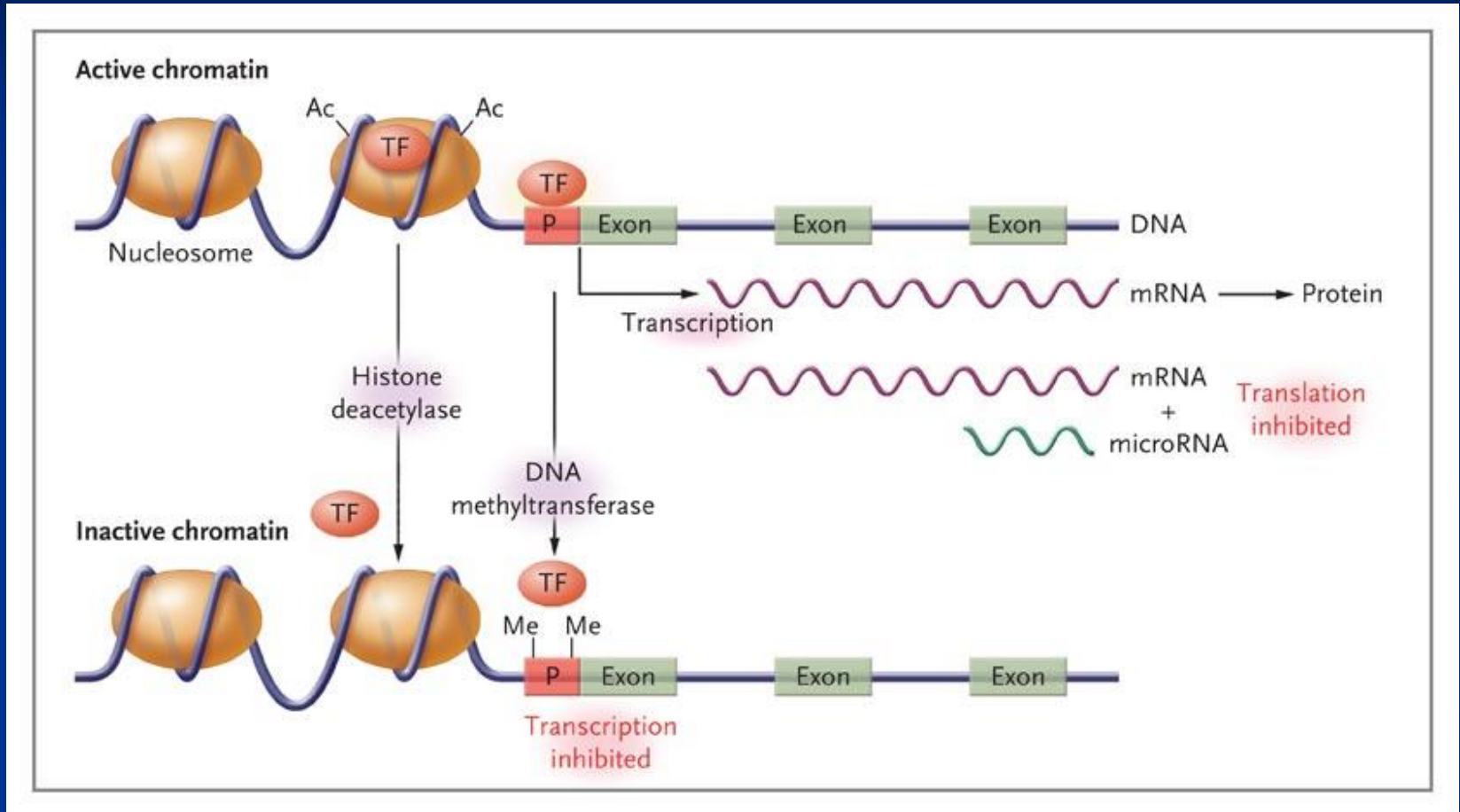
Non-Obese Rat Abdominal Fat Deposition



Obese Rat Abdominal Fat Deposition



Regulation of Gene Expression through Epigenetic Processes

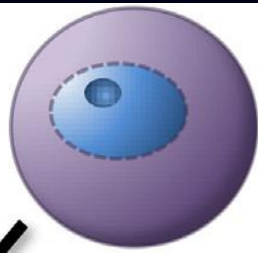


Gluckman P et al. N Engl J Med
2008;359:61-73

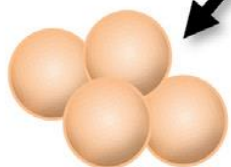


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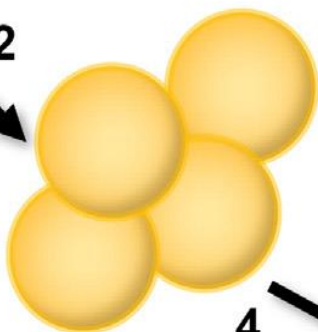


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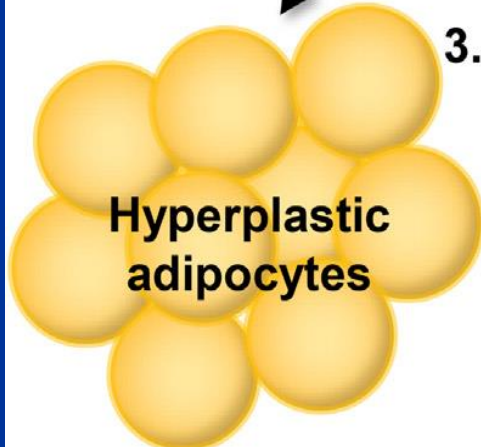
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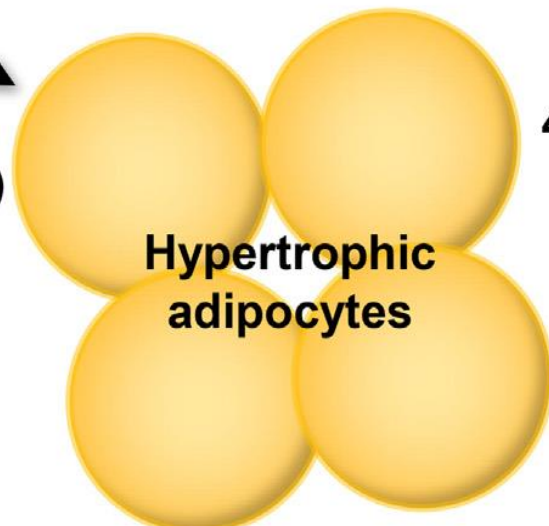
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Bisphenol A

vom Saal and Hughes EHP 2005;113:926-33

- Building block of polycarbonate
 - Bottles, can liners, carbonless receipts, dental resins
 - 6.4 billion pounds/year
- Readily leaches
 - Extremes of pH, temperature and age, detergents
- Potent “endocrine disruptor”
 - Gestational exposure (maternal consumption of ppb):
 - permanent androgen mediated prostate hypertrophy in rodents
 - Decreased sperm count
 - aneuploidy
 - Intraductal hyperplasia and carcinoma in situ in rats
- Other effects
 - Cognitive-behavioral
 - Excessive aggression in males
 - Hyperactive/inattentive

Bisphenol A

vom Saal and Hughes EHP 2005;113:926-33

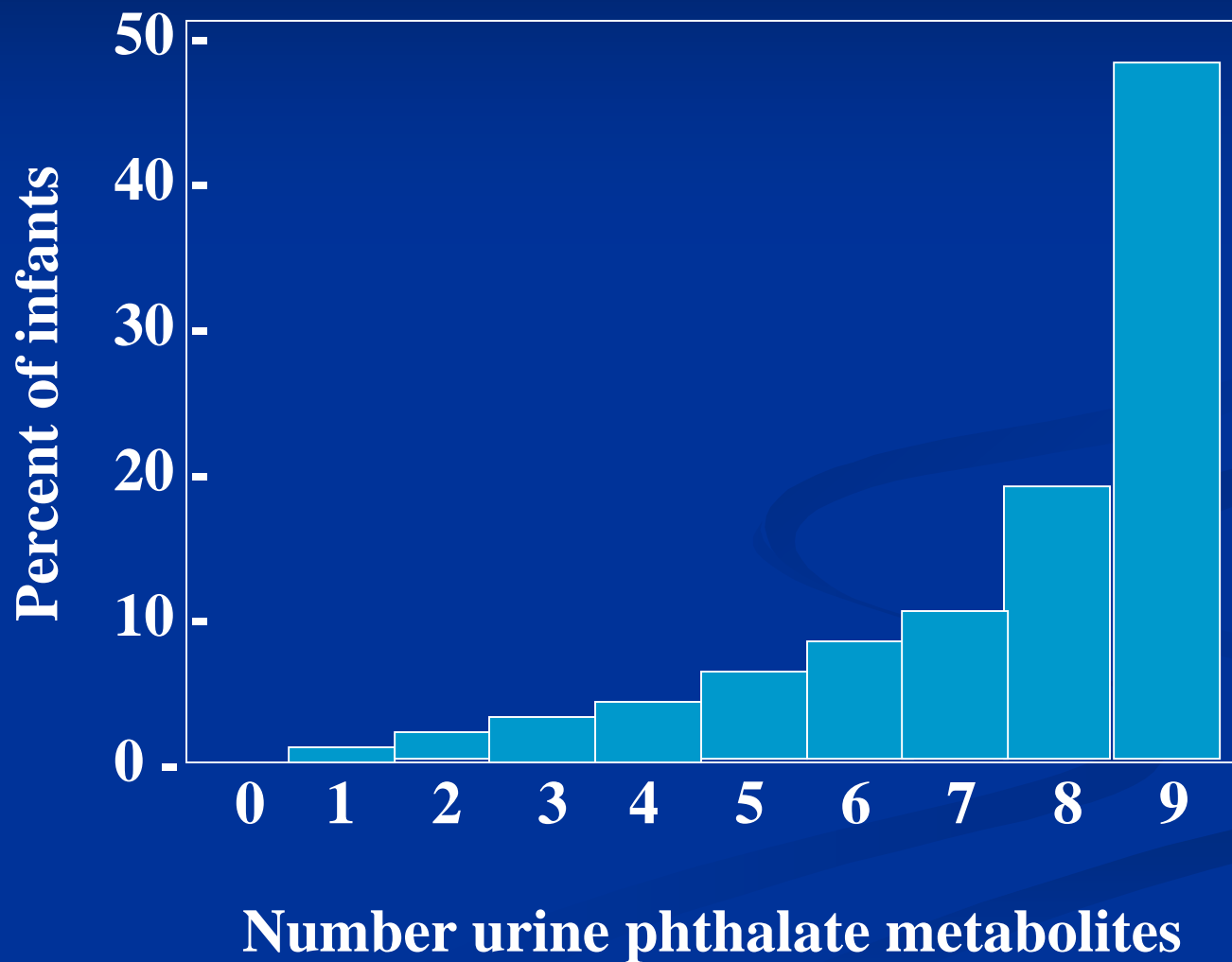
- Common in humans
 - 95% of urine samples +
 - Maternal/fetal plasma, placenta, breast milk
 - Amniotic fluid levels 5X maternal plasma
 - Median BPA levels in humans exceed levels required to cause adverse effects in mice
 - 94/115 published in vivo studies demonstrate biological effects at low levels (below the LOAEL of 50 mg/kg/day)
 - 40/115 show effects below reference value (50 ug/kg/d)
- Evidence supports effects in humans:
 - Obesity, in adults and children
 - PCOS, ASD, ADD and other externalizing behaviors

Phthalates

- Commonly used
 - Plasticizers that are non covalently bound to substrates
 - Plastics, cosmetics, shampoos, toys, pacifiers, meds, blood bags
 - Common in people
 - 75% US adults \geq 5 urinary metabolites
 - Present in breast milk, formula
 - NICU infants – from medical equipment
- Known endocrine disruptors
 - Anti-androgenic in fetus
 - Levels in cord blood and breast milk positively associated with:
 - cryptorchidism and hypospadias
 - reduced sperm count and testosterone levels are correlated
- Low testosterone in men associated with:
 - Obesity
 - Insulin resistance
 - Diabetes

Number of phthalate metabolites in infant urine

Sathyannarayana S. *Pediatrics* 2008;121:e261-268



Perfluoroalkyl Acids (PFAAs)

Environmental Health Perspectives May 2007 115:A251-256

■ PFAAs

- Surfactants/components in > 200 applications
 - Water/stain repellents

■ Perfluorooctanoic acid (PFOA)

- Teflon etc

■ Perfluorooctanoyl sulfonate (PFOS)

- Scotchguard, Stainmaster
- Long $t_{1/2}$ in humans (4-7 yrs!)

■ Sources

- Food
 - Wrappers – eg. Microwave popcorn!
- Cook-ware
- Soil/dust
 - DuPont sites in NC
- Water
 - Cape Fear River (GenX c-6 version)
- Breast milk



Chris Reuther and Joseph TarDEHP

Gestational Exposure to PFOA and Body Composition at 80 Weeks

Environmental Health Perspectives May 2007 115:A251-256



A Role for Perfluorinated Chemicals (PCAs) in Human Obesity and Metabolic Disease?



Ubiquitous

- > 90% adults have PCAs
 - PFOS @ 30.4 ppb
 - PFOA @ 5.2 ppb
- Cord blood
 - ≈ 10% maternal serum levels
 - 100% with PFOS
 - 99% with PFOA
- Breast milk
 - ≈ 1% maternal serum levels
 - 200 ngm/day to infant

Correlations

- Decrease in infant birth weight
 - - 69 gms for PFOS
 - - 104 gms for PFOA
- **Obesity at age 20 in women exposed in utero**
 - **Prospective study**

PBDE and OP Associated IQ Loss, Intellectual Disability and Costs of European Children Born in 2010

Polybrominated Diphenyl Ether (PBDE) flame retardants

Strong Toxicological Evidence

Organophosphate (OP) Pesticides

70-100% probability:

0.3 – 1.9 loss IQ points

€ 1.4 – 19.4 x 10⁹ per yr.

544 – 8,080 attributable cases intellectual disability

€ 0.1 – 1.2 x 10⁹ per yr.

Moderate/High Epi Evidence

70-100% probability:

1.7 – 7.0 loss IQ points

€ 40.8 – 164 x 10⁹ per yr.

16,500 – 84,400 attributable cases intellectual disability

€ 5.9 – 30.5 x 10⁹ per yr.

Attributable Cases and Cost of EDC-Associated Neurodevelopment Disorders

	Toxicological Evidence	Epidemiologic Evidence	Probability	Attributable Cases Cost per yr.
Autism	Moderate	Low	20-39%	126 – 631 € 79 – 399 mil
ADHD OP	Strong	Low-Moderate	20-69%	19,388 – 31,154 € 1.2 – 2.9 bil
PBDE				22,600 € 1.4 – 2.1 bil

Attributable Cases and Cost of EDC-Associated Obesity and Diabetes

Exposure/ Outcome	Toxicological Evidence	Epidemiologic Evidence	Probability of causation	Attributable Cases Cost per year
Prenatal BPA Obesity at 10 yr.	Strong	Low	20-69%	42,200 € 1.5 bil
Prenatal DDE Obesity at 10 yr.	Moderate	Moderate	40-69%	1,555 € 24.6 mil
Adult Phthalate Adult Obesity	Strong	Low	40-69%	53,900 € 12.6 bil
Adult DDE Adult diabetes	Moderate	Low	20-39%	28,200 € 835 mil
Adult Phthalate Adult diabetes	Strong	Low	40-69%	20,500 € mil

Conclusions

- “The evidence for adverse reproductive outcomes from EDCs is strong, and there is mounting evidence for effects on other endocrine systems including thyroid, neuroendocrine, obesity and metabolism”
- Key issues are age at exposure, latency from exposure, mix of EDCs and other factors, dose response dynamics and the ability to transmit effects to future generations via germline epigenetic modifications

Pediatrics 2012;130:e1757;

AAP COUNCIL ON ENVIRONMENTAL HEALTH

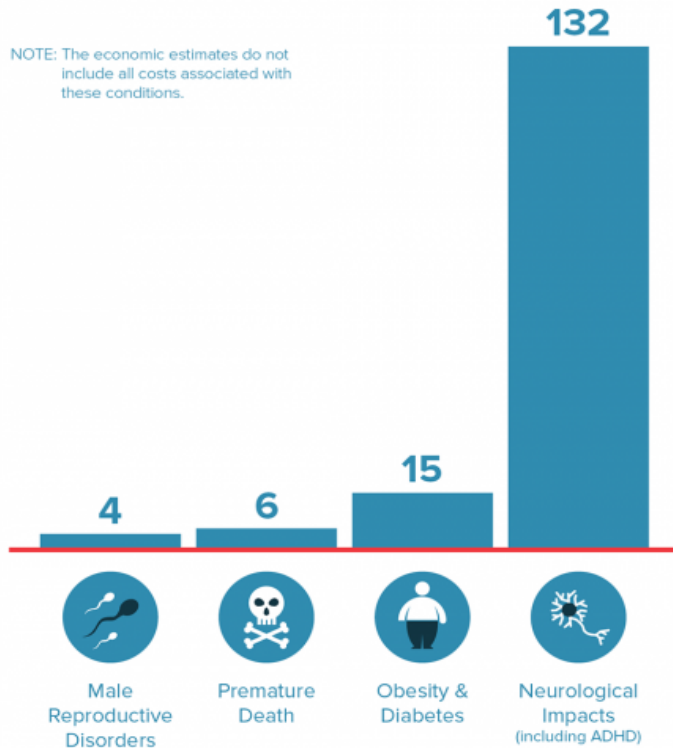
- Epidemiologic evidence demonstrates associations between early life exposure to pesticides and pediatric cancers, decreased cognitive function, and behavioral problems. Related animal toxicology studies provide supportive biological plausibility for these findings.
- Prospective contemporary birth cohort studies in the United States link early-life exposure to organophosphate insecticides with reductions in IQ and abnormal behaviors associated with attention-deficit/hyperactivity disorder and autism.
- Strong evidence documenting a role in human disease for many EDC is still lacking and may be difficult to generate as is a complete scientific consensus.

HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR.

This is the tip of the iceberg: Costs may be as high as €270B.

€157B Cost by Health Effect

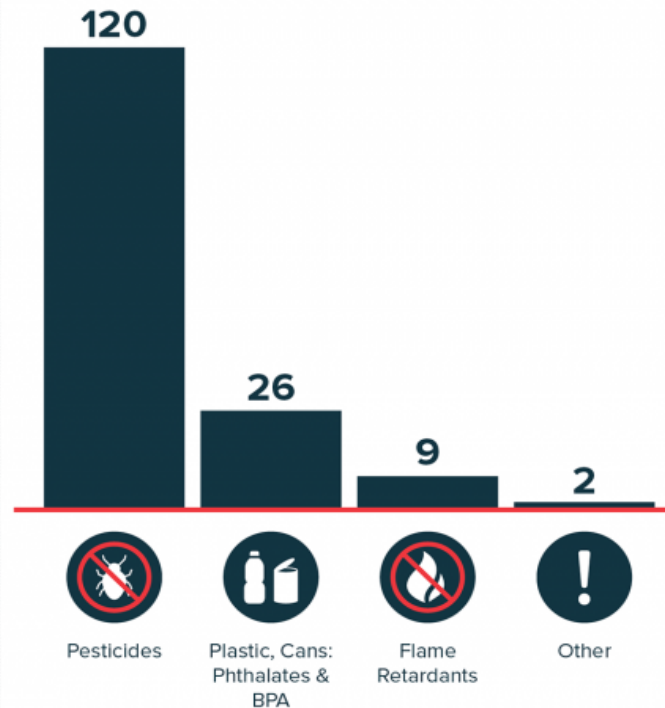
NOTE: The economic estimates do not include all costs associated with these conditions.



SOME EDC-RELATED HEALTH OUTCOMES NOT INCLUDED:

- Breast Cancer
- Prostate Cancer
- Immune Disorders
- Female Reproductive Disorders
- Liver Cancer
- Parkinson's Disease
- Osteoporosis
- Endometriosis
- Thyroid Disorders

€157B Cost by EDC Type



SOME EDCs NOT INCLUDED:

- Atrazine
- 2, 4-D
- Styrene
- Triclosan
- Nonylphenol
- Polycyclic Aromatic Hydrocarbons
- Bisphenol S
- Cadmium
- Arsenic
- Ethylene glycol

Endocrine Disrupting Chemicals (EDCs) interfere with hormone action to cause adverse health effects in people.

“THE TIP OF THE ICEBERG”

The data shown to the left are based on fewer than 5% of likely EDCs. Many EDC health conditions were not included in this study because key data are lacking. Other health outcomes will be the focus of future research.

Minimize Risk: Pesticides

■ Diet

- Scrub and wash produce with water
- Throw away outer leaves
- Trim and discard skin and fat from meats
- Eat lower fat foods and lower on the food chain
- Purchase organic
- Follow “Dirty Dozen and Clean 15” approach
 - <http://www.ewg.org/foodnews>

■ Home, School, Day Care

- Use non/least toxic pest-control methods
 - <http://www.epa.gov/safepestcontrol/citizens-guide>
 - Traps > baits > spray > fogger/bombs
- Vacuum regularly to reduce dust/dirt
- Wash child's hands

Minimize Risk: BPA/Phthalates

- Avoid plastics marked:
 - 3 = PVC (phthalates and organotin)
 - 6 = Polystyrene
 - 7 = Other (polycarbonate can contain BPA)
 - Select glass or polypropylene (#5 softer more opaque)
 - Polycarbonate baby bottles eliminated in US July 2012
 - If polycarbonate is used:
 - Avoid high temperature and harsh detergents
 - Leaching accelerates after 50-100 washes
- Choose BPA free containers
 - Stainless or glass vs. “BPA-free” plastic
 - BPS – a regrettable substitution?
- Wash hands after handling receipts (BPA)
- Avoid recycled paper products for food (BPA)

Minimize Risk: BPA/Phthalates

- Look for PVC-free products
 - Consider high quality wooden toys
 - Look for approval by EU on label
- Limit infant care products and unless medically necessary avoid lotions and powders (phthalates)
 - Look for “phthalate free” products
- Avoid scented personal care products and cosmetics
 - Cologne, lotion, personal care products (phthalates)
 - Cosmetic safety www.ewg.org/skindeep
- Avoid scented household products (phthalates)
 - Glade plugins , car air fresheners etc.
- Minimize inhalation and hand-mouth ingestion
 - Vacuuming with HEPA filter, frequent wet (not dry) dusting
 - Especially important for flame retardants PBDE/Organohalogens
 - Routine house-hold filter maintenance

Minimize Risk: BPA/Phthalates

- Minimize inhalation and hand-mouth ingestion
 - Vacuuming with HEPA filter, not sweeping or dry dusting
 - Routine filter maintenance
- Never heat food in plastic containers
 - Microwave in ceramic or glass containers
 - Don't let cling wrap touch food – use paper towel
- Avoid micro waving in grease or water resistant paper packaging (perfluoroalkyl acids)
 - Microwave popcorn, pot pies etc.
- Avoid food in plastic wrap
 - Pliable cling wrap contains phthalates as plasticizer
 - Especially avoid meats and cheeses in cling wrap
 - Buy @ deli and have wrapped in paper (PFAAs??)
 - Cut away portion in contact with wrap

Minimize risk: BPA/other

- Avoid canned foods (BPA from lining)
 - Single soda per day ↑ odds of obesity
 - Glass, frozen or fresh
 - Do not store at high temperatures or for long times
 - Do not heat food in the can
- Avoid ready to feed and concentrated formula in cans (BPA)
- Avoid smoking and ETS exposures
 - Nicotine replacement contraindicated in pregnancy
- Use filtered tap water
 - Reverse osmosis > activated carbon filter
 - Don't reuse bottled water bottles

Major References and Resources

- Gore AC et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews* 2015;36:E1-E150.
- Heindel JJ et al. Metabolism Disrupting Chemicals and Metabolic Disorders. *Repro Toxic* 2016;68:3-33.
- American Academy of Pediatrics (AAP)
 - Pediatrics 2012 130;e1757

Major References and Resources

- Collaborative on Health and the Environment
 - A reputable group of scientists, organizations with a concern for the environmental influences on health (ECU's PHWRTC is a member of the diabetes-obesity working group)
 - Lots of reasonable handouts and information for the layperson
 - www.healthandtheenvironment.org

Major References and Resources

- Pediatric Environmental Health Specialty Units
 - Coordinated by Association of Occupational and Environmental Clinics to provide free academically based consultation for health care providers
 - Anticipatory guidance by age
 - Lots of good links
 - Endorsed by AAP
 - <http://peht.ucsf.edu/index.php>