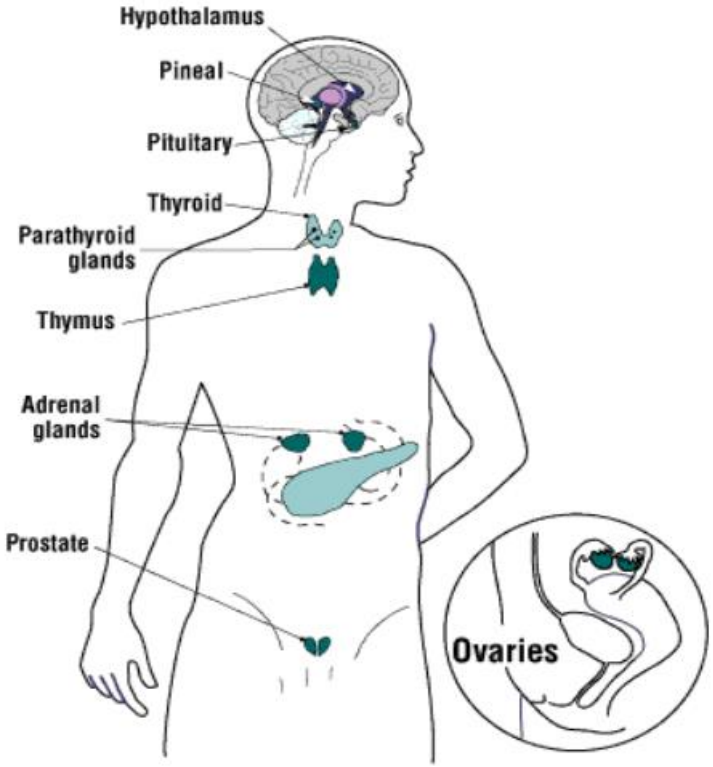
EFFECTS of ENDOCRIN DISTRUPTING CHEMICALS

ANKARA-2020

ENDOCRINE DISTRUPTING CHEMICALS

- The endocrine system is a network of glands and organs that produce, store, and secrete hormones. When functioning normally, the endocrine system works with other systems to regulate your body's healthy development and function throughout life.



The endocrine system is important because it coordinates and regulates many essential body functions such as:

- Growth and maturation.
- Behaviour.
- Reproduction and embryo development.
- Production, use and storage of energy.
- Balance and maintenance of water and salt (electrolytes) in the body.
- Reaction to stimuli (e.g., fright, excitement).

- The hormones released by the endocrine system act as chemical “messengers” that signal when and how to carry out certain physiological processes.
- In humans for example, at the onset of puberty, the testes release male sex hormones (androgens) in boys, and
- the ovaries release female sex hormones (estrogens) in girls.

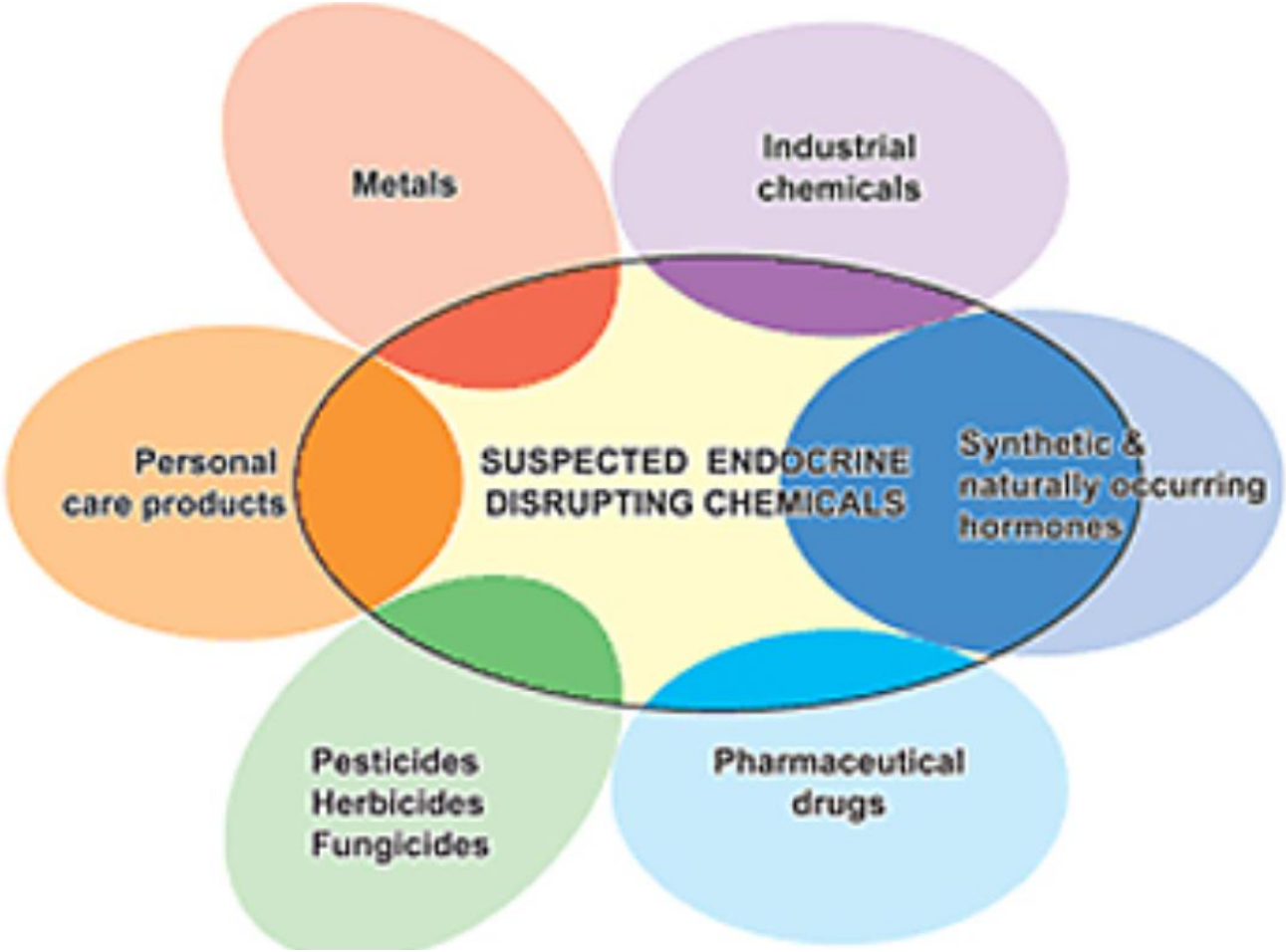
  These hormones prepare the body for reproductive functions and prompt the development of secondary sexual characteristics in young women and men.
- Too much or too little thyroid activity affects how the brain, heart, muscles, liver and other parts of the body work. It can affect how hot or cold someone usually feels, and whether they gain or lose weight easily.

- Hormones act on certain proteins in the body called receptors, which bind to specific hormones. This is often referred to as a lock-and-key mechanism the hormone is the “key” that “unlocks” the hormone receptor to do what is needed.
- An example of this activity is when the pancreas releases insulin into the bloodstream as blood sugar rises after a meal. The insulin unlocks cells to allow sugar to be used for energy. It also helps the body to store surplus blood sugar in the liver, to be released as needed.
- Insulin resistance and Type 2 diabetes occur when this lock-and-key mechanism is damaged and the body becomes unable to use insulin properly.

ENDOCRINE DISTRUPTING CHEMICALS

- Endocrine-disrupting chemicals (EDCs) are substances in the environment (air, soil, or water supply), food sources, personal care products, and manufactured products that interfere with the normal function of your body's endocrine hormone system
- Some EDCs act like "hormone mimics" and trick our body into thinking that they are hormones, while other EDCs block natural hormones from doing their job.

ENDOCRINE DISTRUPTING CHEMICALS



- People are exposed to EDCs and potential EDCs in daily life in four main ways:
- Crops we grow: Farm workers as well as consumers are vulnerable to the impacts of many different kinds of pesticides, some of which are EDCs

- Things we make: Manufacturing and recycling of electrical and electronic equipment can increase exposure to PCBs, lead and brominated flame retardants

- Places we work and live: Our homes, factories and offices expose workers to EDCs in electronic and electrical equipment, building materials and textiles. Construction materials such as treated wood, flooring, sealants, lacquers and paints may contain or be treated with potential EDCs, including phthalates and pentachlorophenol. Office supplies, floors, and furniture could contain brominated flame retardants

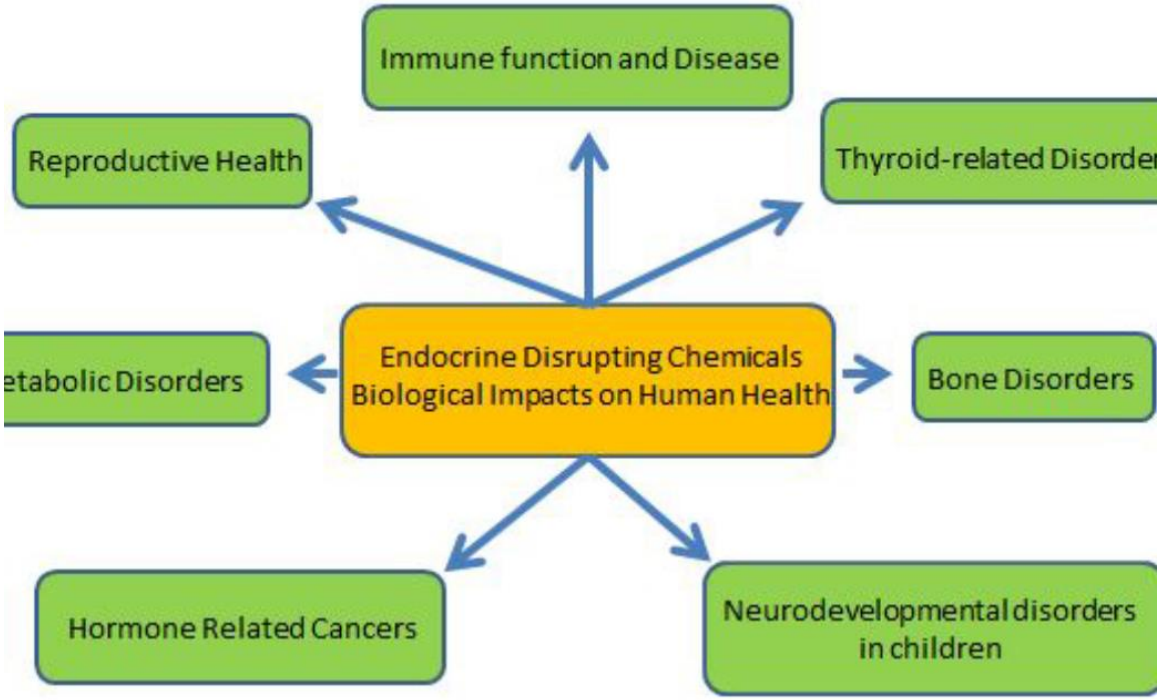
- Things we buy: Many household items, including clothing, bedding, personal care products and plastic containers contain potential EDCs such as phthalates, perfluorochemicals and phenols

- Other sources of exposure to EDCs or potential EDCs are from thermal paper used for cash register receipts and the lining of some food containers, both of which contain bisphenol A (BPA). Contact with chemicals used in cosmetics and personal care products also result in exposure to EDCs or potential EDCs.

ENDOCRINE DISTRUPTING CHEMICALS

Effect of EDCs

- adverse developmental effect
- reproductive system,
- neurological, and
- Immunological effects
- some cancers and
- obesity in mammals.



Source: State of the Science of Endocrine Disrupting Chemicals – 2012
Inter-Organization Programme for the Sound Management of Chemicals

- The ability of both natural and synthetic chemicals to mimic the effects of hormones in humans and other vertebrates has been recognised for decades.
- Synthetic steroids were used as ingredients in pharmaceuticals to deliberately alter reproductive cycles of livestock animals beginning around 1940.

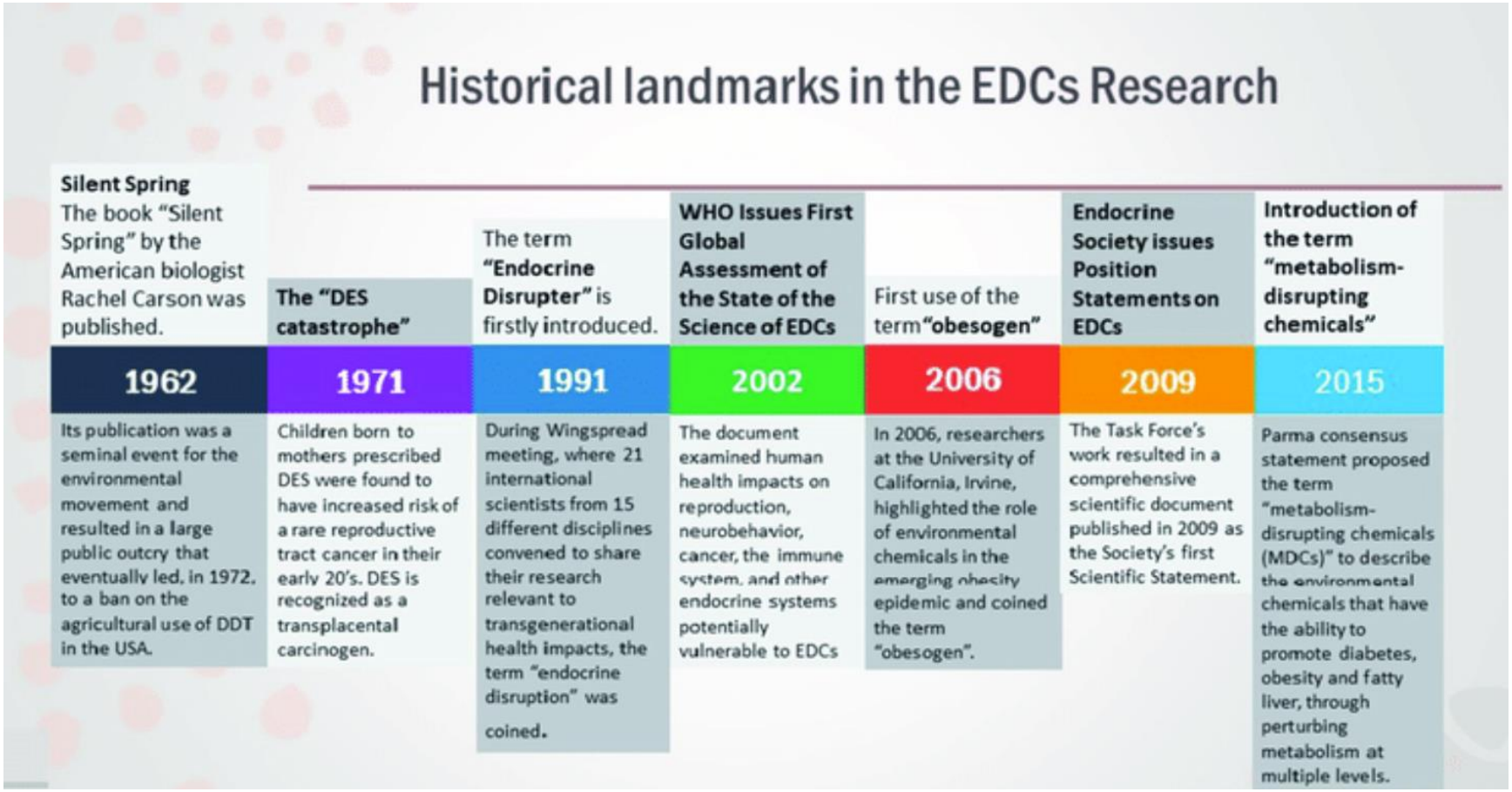
- In the 1950s, endocrinologists began to measure the levels of hormones in human blood samples. Unusually high or low levels of these hormones were associated with altered endocrine function.
- In the 1962 book, Silent Spring, Rachel Carson examined the effect of chemical pesticide spraying on wildlife. We now know that Dichlorodiphenyltrichloroethane (DDT), chemical discussed in the book, is an endocrine disrupter.

- Furthermore, decreased sperm quality and increasing trends of endocrine related cancers in some industrialized countries in the last few decades have raised concerns that there may be links between environmental chemicals to which humans are exposed and such diseases.

- In the 1990s, new attention was focused on endocrine disruption.
- The Wingspread Conference held in 1991 brought together experts from a variety of disciplines such as toxicology, ecology, immunology, psychiatry, and law to discuss the evidence on endocrine disrupters available at that time.
- The outcome of this conference was a consensus statement hypothesizing that environmental chemicals could be potentially detrimental to wildlife and humans by acting on endocrine systems

- Books, such as Our Stolen Future (Theo Colborn, Dianne Dumanoski and John Peterson Myers, 1996) by raised public and government awareness.
- Around the same time, reproductive failure in fish downstream from water treatment plants leading to population declines, and species of mollusks affected in coastal areas due to a particular chemical (i.e. tributyltin) contained in anti-fouling paints on boats were reported. In response, countries began to develop

Historical landmarks in the EDCs Research



Persistent Organic Pollutants(POPs)

Endocrine disrupters (EDCs)	Description and characteristics
PERSISTENT ORGANIC POLLUTANTS (POPS)	
Dichlorodiphenyltrichloroethane (DDT)	A synthetic insecticide with a long half-life, extensive use, and lipophilic nature. The United States banned DDT in 1972 due to its effects on the environment and human health. DDT and its metabolites seem to contribute to the manifestation of endocrine-related diseases, including diabetes mellitus.
Dioxins	Dioxins are mainly by-products of industrial processes but can also result from natural processes, such as volcanic eruptions and forest fires. Their half-life in the body is estimated to be 7 to 11 years. They accumulate in food chain and in the adipose tissue of human body. The most harmful dioxin is 2,3,7,8-tetrachlorodibenzo -p-dioxin (TCDD).
Polychlorinated biphenyls (PCBs)	Man-made synthetic chemical mixtures, widely used in electrical equipment, ink solvents and especially plasticizers until the late 1970s, after which time they were banned. Their use has been associated with the obesity epidemic.
Perfluorinated compounds (PFCs)	PFCs have been detected in food packaging, furniture, clothes, cookware, and non-stick surfaces in order to repel grease and oil. They have been linked with obesity and adipose tissue dysfunction.
Polybrominated flame retardants	They have been used in a variety of materials, such as furniture, electronics, and construction materials, as flame retardants. Via accumulating in the environment and human fat tissue, these man-made chemicals have been linked with adverse health outcomes, including obesity.

NON PERSISTENT EDCS

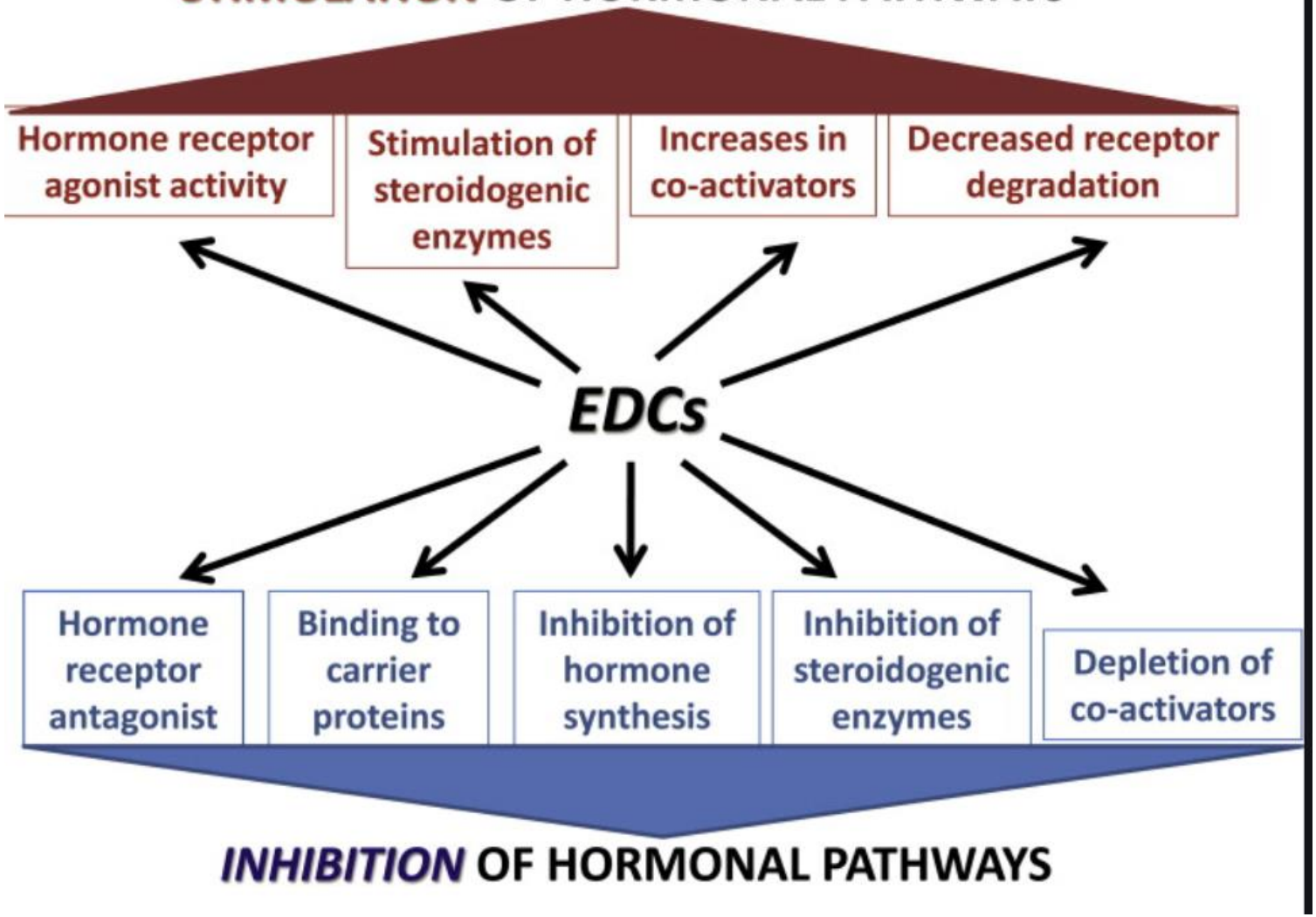
NON-PERSISTENT EDCS	
Bishenol A (BPA)	A synthetic organic compound, mainly used as plasticizer, is commonly detected in water bottles, food containers, and metal-based cans. The magnitude of human exposure to this EDC is depicted to the observation that ~93% of Americans have measurable urine levels of BPA. It is characterized by a rapid metabolization to its non-bioactive forms and a short half-life (4–5 h in adult humans).
Phthalates	Pthalates have been widely used in the manufacture of polyvinyl chloride plastics and vinyl products. As a result, they have been detected in multiple household products, including pacifiers, children's toys, food packaging, medical devices, and furnishings. Animal models have displayed a close interrelationship between phthalates and metabolic disease.
Tributyltin	An organotin commonly used as a heat stabilizer and as fungicide. It can also be found in house dust. Although data on human exposures are scarce, it has been detected in human liver and blood.

SOURCE OF EDCs

Common EDCs	Used In
DDT, Chlorpyrifos, Atrazine, 2, 4-D, Glyphosate	Pesticides
Lead, Phthalates, Cadmium	Children's Products
Polychlorinated biphenyls (PCBs) and Dioxins	Industrial Solvents or Lubricants and their Byproducts
Bisphenol A (BPA), Phthalates, Phenol	Plastics and Food Storage Materials
Brominated Flame Retardants, PCBs	Electronics and Building Materials
Phthalates, Parabeans, UV Filters	Personal Care Products, Medical Tubing, Suncreen
Triclosan	Anti-Bacterial Soaps, Colgate Total
Perfluorochemicals	Textiles, Clothing, Non-Stick Food Wrappers, Mircowave Popcorn Bags, Old Teflon Cookware

- Disruptors may act **directly or indirectly.**
- **Direct acting disruptors are usually hormone agonists or antagonists that interfere with hormone actions on target cells.**
- **May alter hormone synthesis and secretion**
- **May alter conjugation and binding to carrier proteins**
- **Indirect acting disruptors alter hormone dynamics in circulation, change hormone metabolism, or interfere with hormone regulation**

Mechanisms of Endocrine Disruption



- Endocrine disruptors are known to cause harmful effects to human through various exposure routes.
- These chemicals mainly appear to interfere with the endocrine or hormone systems.
- As importantly, numerous studies have demonstrated that the accumulation of endocrine disruptors can induce fatal disorders including obesity and cancer.

Although limited scientific information is available on the potential adverse human health effects, concern arises because endocrine disrupting chemicals presenting in the environment at very low levels have been shown to have adverse effects.

Even though exposure to specific EDCs may be low, there can be a “cocktail effect” as various EDCs combine or interact to affect the way our bodies work.

People are exposed to low levels of many different potential EDCs over long periods. They warn that the cocktail effect could be responsible for exacerbating the adverse effects of certain chemicals

- Some research shows that these substances are also adversely affecting human health in similar ways;
- resulting in reduced fertility ,
- alterations in sperm quality and
- abnormalities in sex organs, endometriosis,
- early puberty,
- altered nervous system abd immune function,
- certain cancers,
- respiratory problems,
- metabolic issues; diabetes, obesity, cardiovascular problems, growth,
- neurological and learning disabilities, and more.

- High EDC exposures during fetal development and childhood can have long-lasting health effects since there are periods where hormones regulate the formation and maturation of organs.
- Early-life exposures have been linked to developmental abnormalities and may increase the risk for a variety of diseases later-in-life.
- Importantly, various EDCs have been found to cross the placenta and become concentrated in the fetus' circulation. Other EDCs can be transferred from mother to infant through breast milk.

- A widely diverse range of chemicals has been reported to possess endocrine-disrupting activity, including both naturally occurring chemicals (e.g., cadmium, arsenic, mercury, lead), phytochemicals (e.g., genistein) and synthetic by-products of industrial (e.g., nonylphenol), chemical (e.g., phthlates), manufacturing (e.g., polybrominated biphenyls (PBBs), and agricultural (e.g., atrazine) practices.

- Approximately 870 chemicals were reported in the literature to possess endocrine disruptive activity .
- However, some EDCs such as dioxins, PCBs and the heavy metals are among the most extensively studied environmental pollutants known.
- Furthermore, in cases where newly recognized EDCs are thought to be toxic at very low doses and/or have a potentially widespread human exposure, they can become a research priority among funding agencies and new, risk-relevant information is obtained
- Examples of EDCs that have been designated as research priorities and given priority consideration in recent years are bisphenol A (BPA), the phthalates, and flame retardant compounds.

Endocrine Distrupters include

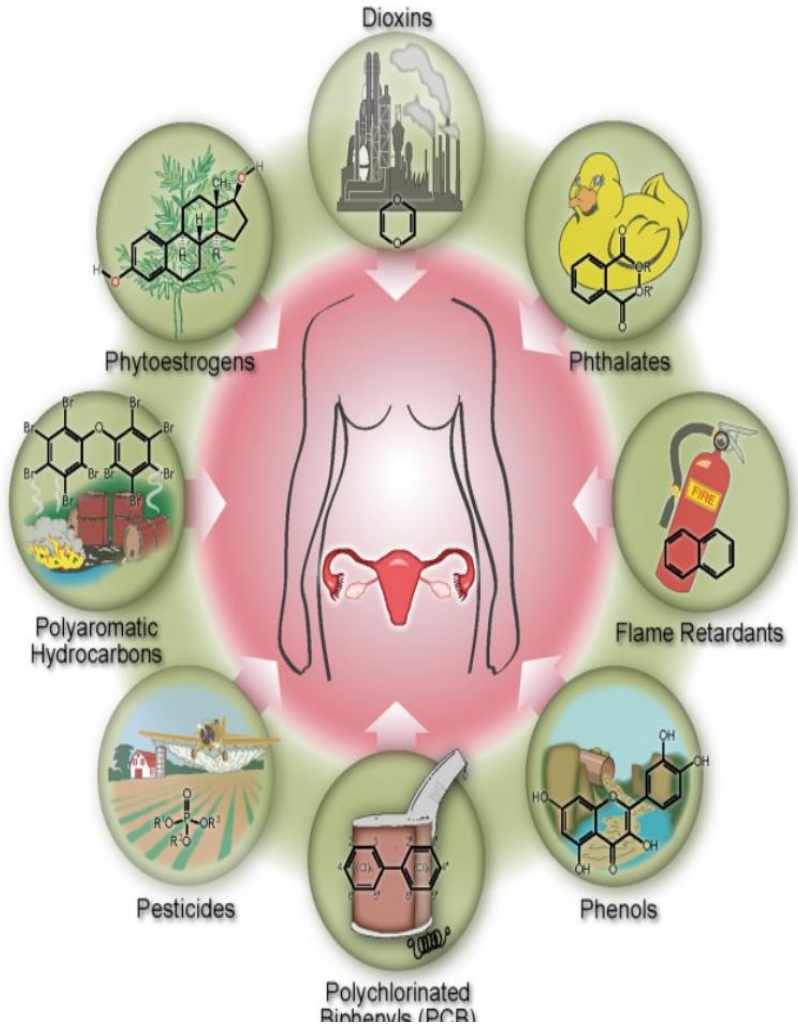
- **Pesticides**

-herbicides, insecticides, …

- **Plasticizers**
- **Natural plant metabolites**
- **Pharmaceuticals**

-contraceptives, drugs,…

- **Detergents**
- **Chemicals from cooking & burning**
- **Antibiotics**
- **Metals**



What are some sources of endocrine disruptors?

- plastic bottles,
- metal food cans,
- detergents,
- flame retardants,
- food, toys,
- cosmetics, and
- pesticides

How are We Exposed?

- Since EDCs come from many different sources, people are exposed in several ways, including the air we breathe, the food we eat, and the water we drink. EDCs can also enter the body through the skin.

EXPOSURE AND REGULATION OF ENDOCRINE DISRUPTORS

- Food is the major route of exposure to endocrine disruptors .
- According to an article reported by Schecter et al., a total of 32 food samples from three major supermarket chains in Dallas were contaminated with polybrominated diphenyl esters (PBDEs).
- In this study, PBDEs are detected mainly in fish, meat, and dairy products. BPA exposure also occurs through diet, including contaminated food and water.

- Some endocrine-disrupting chemicals are slow to break-down in the environment. That characteristic makes them potentially hazardous over time.
- Endocrine disrupting chemicals cause adverse effects in animals.
- But limited scientific information exists on potential health problems in humans. Because people are typically exposed to multiple endocrine disruptors at the same time, assessing public health effects is difficult.

What are some common endocrine disruptors?

- **Bisphenol A (BPA)** — used to make polycarbonate plastics and epoxy resins, which are found in many plastic products including food storage containers
- **Dioxins** — produced as a byproduct in herbicide production and paper bleaching, they are also released into the environment during waste burning and wildfires
- **Perchlorate** — a by-product of aerospace, weapon, and pharmaceutical industries found in drinking water and fireworks

- **Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)** — used widely in industrial applications, such as firefighting foams and non-stick pan, paper, and textile coatings
- **Phthalates** — used to make plastics more flexible, they are also found in some food packaging, cosmetics, children's toys, and medical devices
- **Phytoestrogens** — naturally occurring substances in plants that have hormone-like activity, such as genistein and daidzein that are in soy products, like tofu or soy milk

- **Polybrominated diphenyl ethers (PBDE)** — used to make flame retardants for household products such as furniture foam and carpets
- **Polychlorinated biphenyls (PCB)** — used to make electrical equipment like transformers, and in hydraulic fluids, heat transfer fluids, lubricants, and plasticizers
- **Triclosan** — may be found in some anti-microbial and personal care products, like liquid body wash

How do people encounter endocrine-disrupting chemicals?

- People may be exposed to endocrine disruptors through food and beverages consumed, pesticides applied, and cosmetics used. In essence, your contact with these chemicals may occur through diet, air, skin, and water.
- Even low doses of endocrine-disrupting chemicals may be unsafe. The body's normal endocrine functioning involves very small changes in hormone levels, yet we know even these small changes can cause significant developmental and biological effects.
- This observation leads scientists to think that endocrine-disrupting chemical exposures, even at low amounts, can alter the body's sensitive systems and lead to health problems.

- NIEHS-supported research has discovered links between endocrine-disrupting chemicals and the ways in which wellbeing may be harmed, as shown by the following examples:

- **Immunity**

Children exposed to high levels of PFAS had a diminished immune response to vaccines.

- They can affect immune function directly, via action on immune cell surface receptors, or indirectly, through other physiological mediators. Because prolonged immune dysfunction elevates the risk of a myriad of communicable and noncommunicable diseases, EDC-mediated immunotoxicity is a significant human health concern.
- Age and sex are significant factors in the susceptibility to EDC-induced immunotoxicity

- **Metabolism** Long-term exposure to arsenic can disrupt metabolism, increasing the risk of diabetes and other metabolic disorders.

Puberty

Chemicals in lavender oil and tea tree oil are potential endocrine disruptors. Researchers found that persistent exposure to lavender oil products is associated with premature breast development in girls, and abnormal breast development in boys.

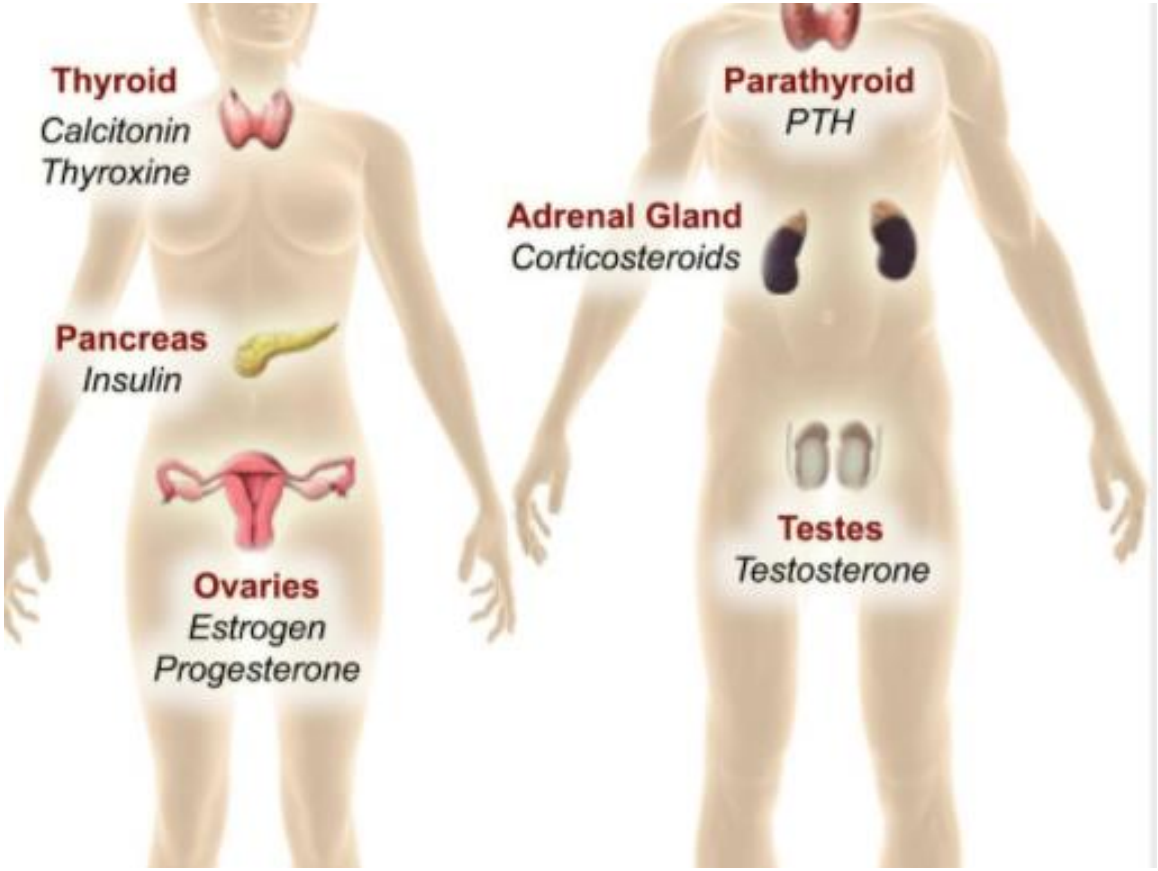
Reproduction

DES can cause epigenetic changes, altering the way genes are turned on and off, in reproductive organs of mice.

The findings provide a possible explanation for how endocrine disruptors affect fertility and reproduction

Some classes of EDCs (DDT, BPA, phthalates, PCBs, others) can affect reproductive health by mimicking or blocking the effects of male and female sex hormones.

Critical reproductive hormones, such as progestins, androgens, and estrogens, are the primary targets of many EDCs.



This figure illustrates that all major endocrine organs are vulnerable to endocrine disruption, including the HPA axis, reproductive organs, the pancreas, and the thyroid gland.

Examples of these EDCs are pesticides (e.g., dichlorodiphenyltrichloroethane(DDT), methoxychlor(MXC), vinclozolin, and atrazine),

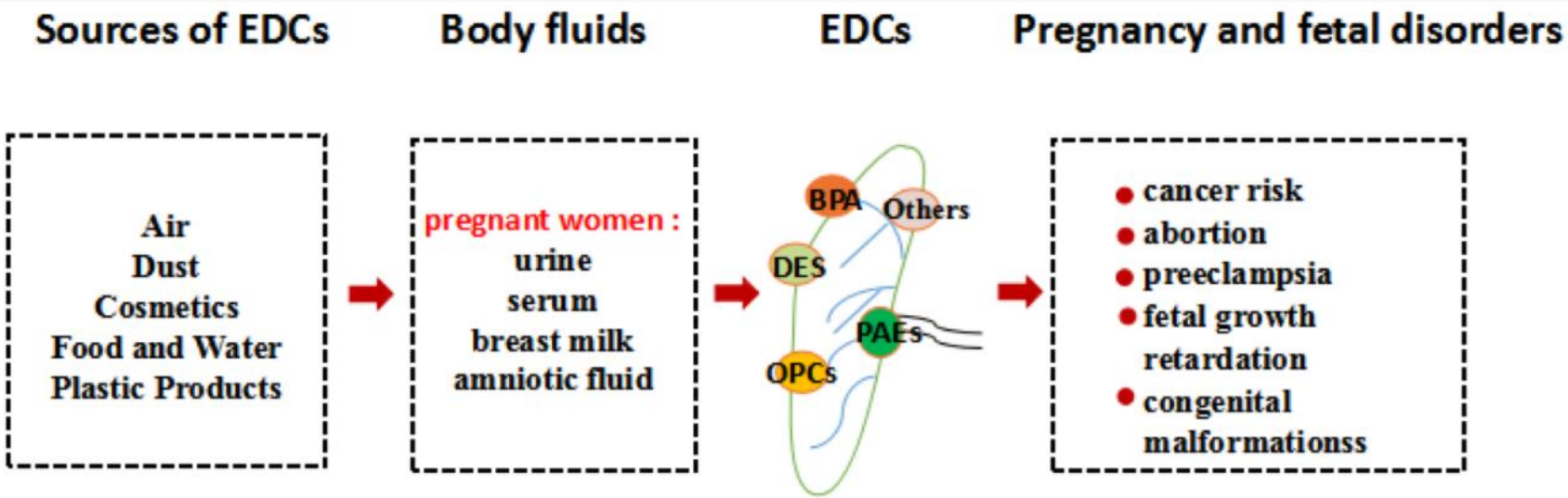
detergents and surfactants (e.g., octyphenol, nonylphenol and bisphenol-A(BPA), plasticizers(e.g., phthalates),

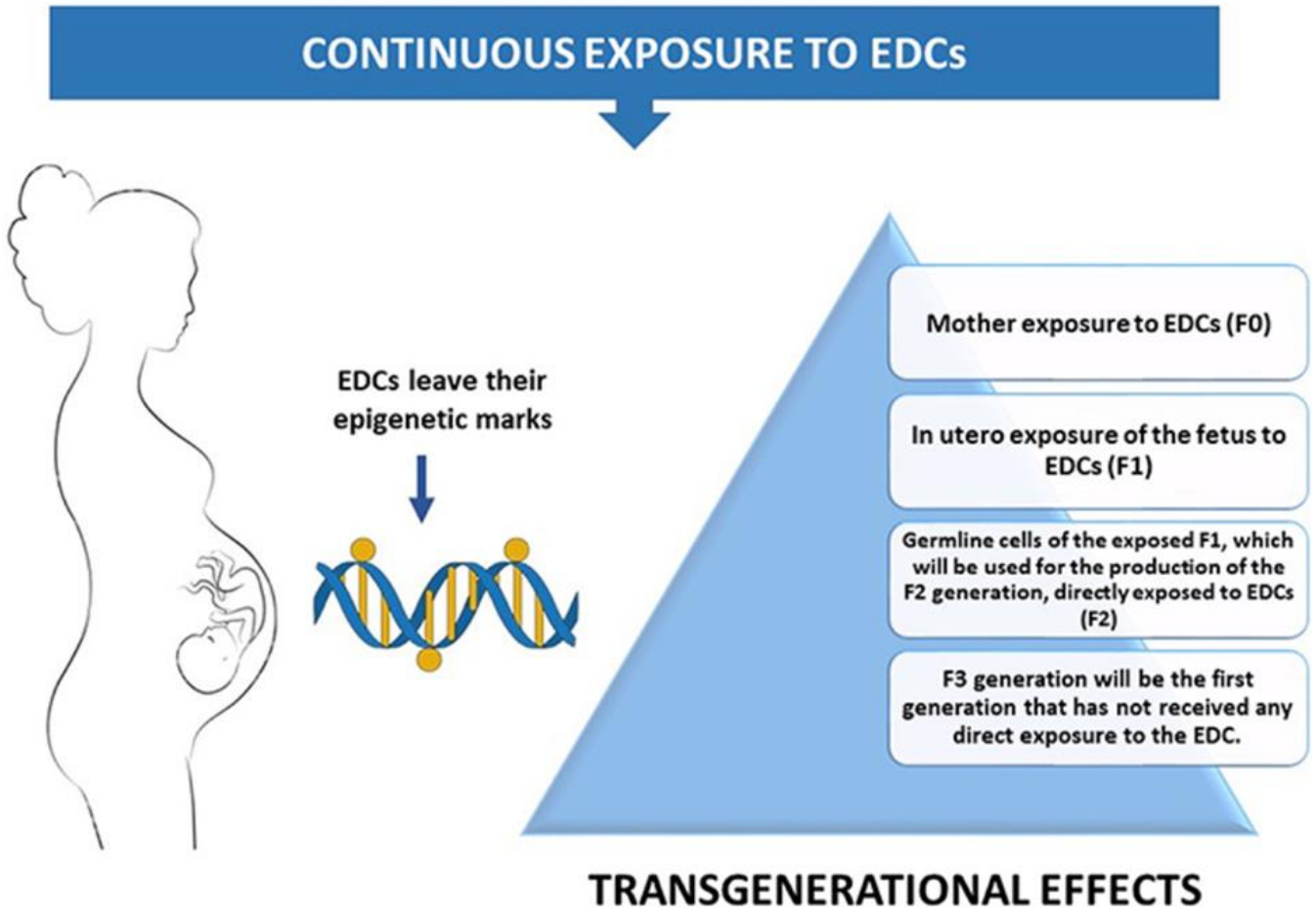
industrial compounds (e.g., polychlorinated biphenyls (PCBs) and 2,3,7,8- tetrachlorodibenzo-*p*-dioxin (TCDD), and

natural plant derivatives (e.g., genistein and coumesterol).

- Many studies indicate that exposure to these EDCs leads to reproductive defects such as reduced fertility and abnormal sexual development in both humans and wildlife.

, The transfer routes of several endocrine disrupting chemicals (EDCs) and the damages to pregnant women and fetuses. Pregnant women are exposed to EDCs from the air, food, and products which damage the placenta through body fluids, thereby causing health problems.

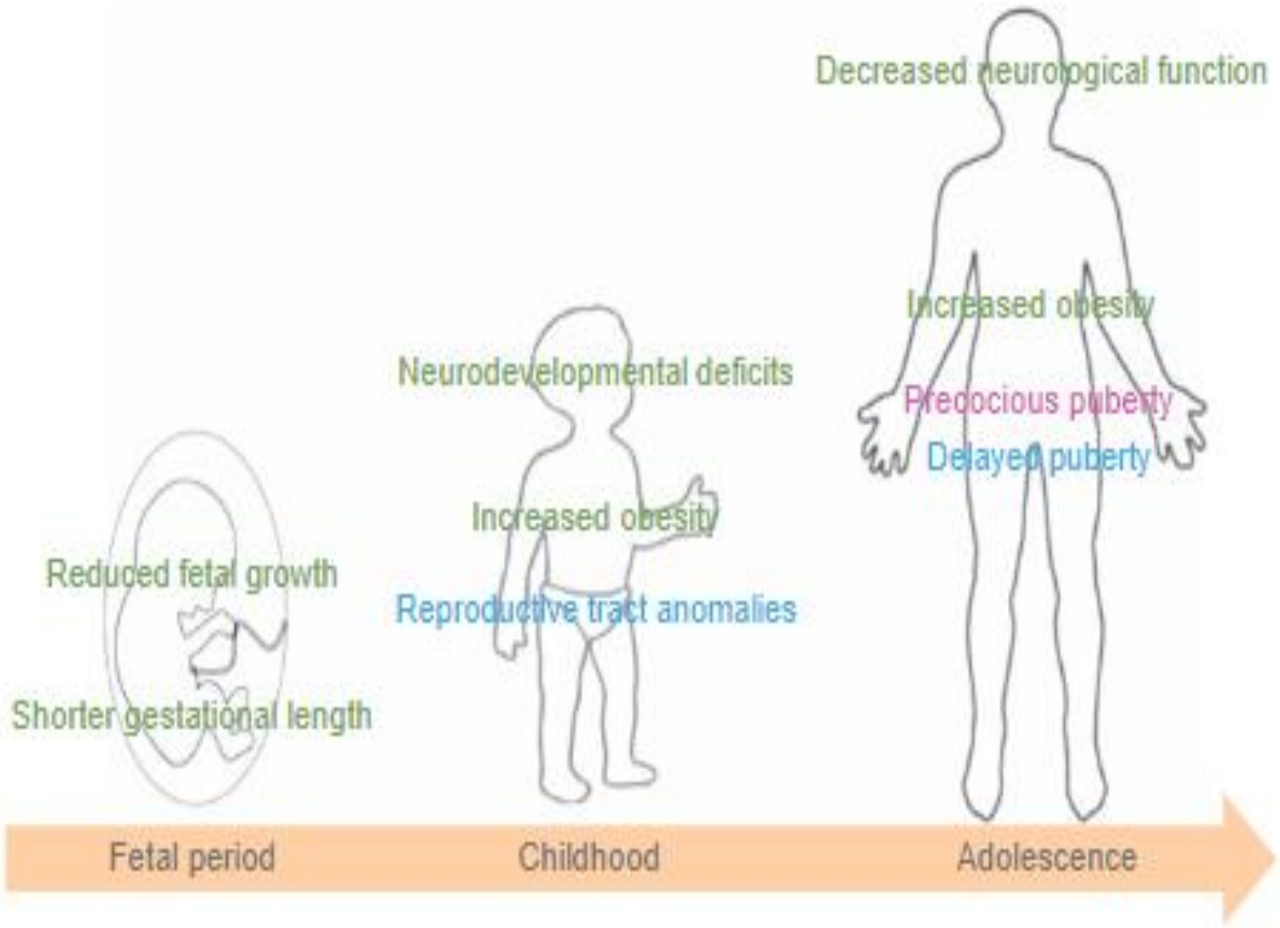



CONTINUOUS EXPOSURE TO EDCs
EDCs leave their epigenetic marks
Mother exposure to EDCs (F0)
In utero exposure of the fetus to EDCs (F1)
Germline cells of the exposed F1, which will be used for the production of the F2 generation, directly exposed to EDCs (F2)
F3 generation will be the first generation that has not received any direct exposure to the EDC.
TRANSGENERATIONAL EFFECTS

Neurodevelopmental effects

- EDCs may have particularly significant effects on neurodevelopmental processes.
- EDCs accumulate in fatty tissues of exposed individuals, are readily transferred across the placenta prenatally, and are expressed in breast milk.
- This perinatal exposure may have particularly deleterious effects on development.
- Indeed, there is growing recognition of the increased incidence of behavioral, cognitive, and/or emotional disturbances in children in the past 30 years, which has been proposed to be related to increased exposure to EDCs (Safer, Zito, & Fine, 1996).
- Exposure to EDCs during development may result in permanent, lifelong differences in sexual function and reproductive ability, as well as cognitive function and/or emotional reactivity/arousal.

- **Attention-deficit/hyperactivity disorder** (ADHD) is one of the most common childhood disorders, which can continue through adolescence and into adulthood. ADHD symptoms include difficulty staying focused, paying attention, and controlling behavior. Researchers reported in JAMA that ordinary exposure to **certain phthalates**, as found in urine samples, was associated with ADHD-related behaviors in adolescence. The **drug DES** may be linked to an increased chance of developing ADHD in the grandchildren of women who used it during pregnancy.

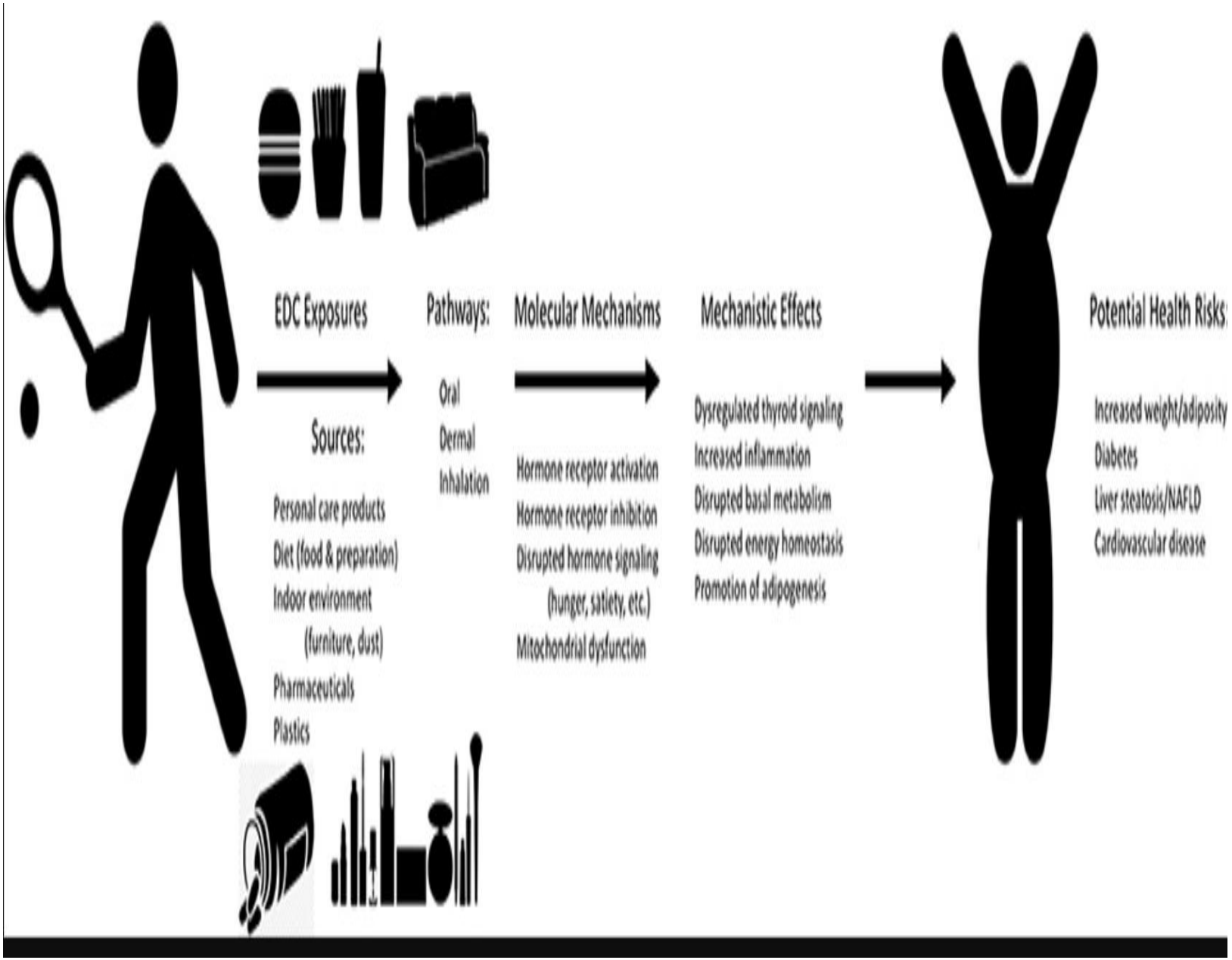


Child health effects observed following prenatal or childhood EDC exposures. Green signifies effects reported in both boys and girls; blue, effects reported in boys; and pink, effects reported in girls.

Obesity

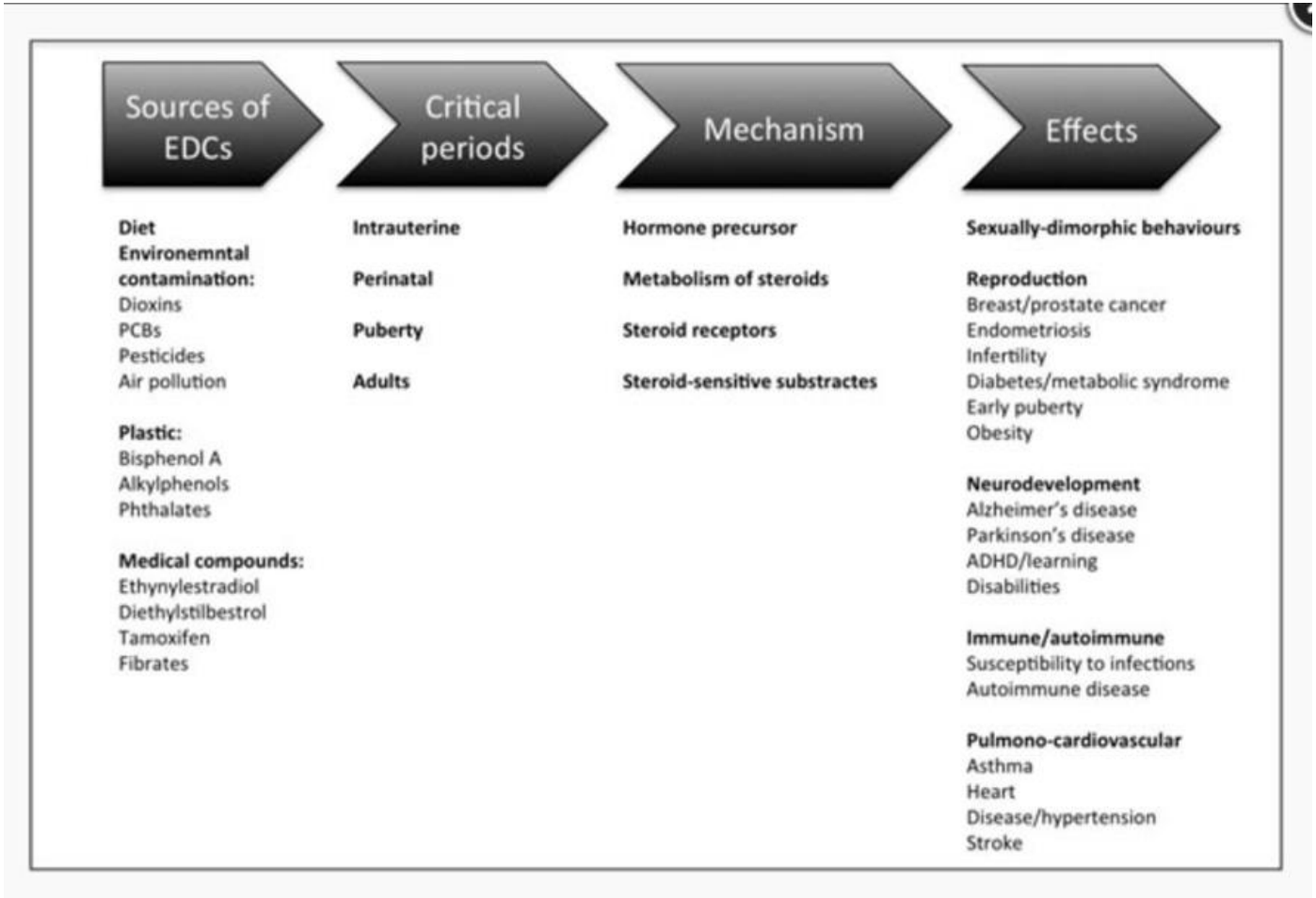
- The prevalence of overweight and obesity is rapidly increasing in the United States and worldwide . In addition to diet, physical activity, and genetics, environmental obesogens may play a role in these trends.
- Obesogens are defined as chemicals that inappropriately alter lipid homeostasis to promote adipogenesis and lipid accumulation. Experimental evidence showing that numerous chemicals may impart these effects is growing
- Recently, there have been a large number of studies investigating the relationships of EDCs with obesity, BMI, and a number of other related outcomes in young children and adolescents.
- Some EDCs have been linked to obesity and type 2 diabetes
- These chemicals are DDT, DDE, PCBs some industrial chemicals, BPA Some EDCs have been linked to obesity and type 2 diabetes
- Recently, studies have shifted to ubiquitous, non-persistent EDCs and their effects on childhood obesity.

- Certain phthalates in childhood may increase the risk of obesity in children.
- Some industrial chemicals and flame retardants can interfere with thyroid function


EDC Exposures
Sources:
Personal care products
Diet (food & preparation)
Indoor environment
(furniture, dust)
Pharmaceuticals
Plastics
Pathways:
Oral
Dermal
Inhalation
Molecular Mechanisms
Hormone receptor activation
Hormone receptor inhibition
Disrupted hormone signaling
(hunger, satiety, etc.)
Mitochondrial dysfunction
Mechanistic Effects
Dysregulated thyroid signaling
Increased inflammation
Disrupted basal metabolism
Disrupted energy homeostasis
Promotion of adipogenesis
Potential Health Risks:
Increased weight/adiposity
Diabetes
Liver steatosis/NAFLD
Cardiovascular disease

Cancer

- Exposure to estrogen or androgen mimicking EDCs can promote breast and prostate cancer growth and/or interfere with hormonal cancer therapy
- Prenatal exposure to some EDCs may after mammary gland development and increase breast cancer risk later-in-life


Sources of EDCs
Critical periods
Mechanism
Effects
Diet
Environemntal contamination:
Dioxins
PCBs
Pesticides
Air pollution
Plastic:
Bisphenol A
Alkylphenols
Phthalates
Medical compounds:
Ethynylestradiol
Diethylstilbestrol
Tamoxifen
Fibrates
Intrauterine
Perinatal
Puberty
Adults
Hormone precursor
Metabolism of steroids
Steroid receptors
Steroid-sensitive substractes
Sexually-dimorphic behaviours
Reproduction
Breast/prostate cancer
Endometriosis
Infertility
Diabetes/metabolic syndrome
Early puberty
Obesity
Neurodevelopment
Alzheimer's disease
Parkinson's disease
ADHD/learning
Disabilities
Immune/autoimmune
Susceptibility to infections
Autoimmune disease
Pulmono-cardiovascular
Asthma
Heart
Disease/hypertension
Stroke

Results of Disruptions

Inability to maintain homeostasis

Altered growth & development

Altered responses to external stimuli

Altered behavior

Suppressed gametogenesis

Elevated gestational losses

Embryonic malformation

Induced neoplasia or carcinogenesis