

Endocrine Disruptors

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disclosures

Contracted Research (Principal Investigators must provide information, even if received by the institution)

Abbvie, Organon

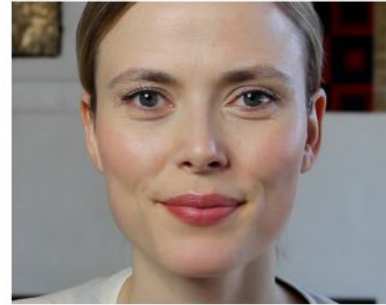
Stock Option Holder (Individual stocks/Stock options; diversified mutual funds do not need to be disclosed):

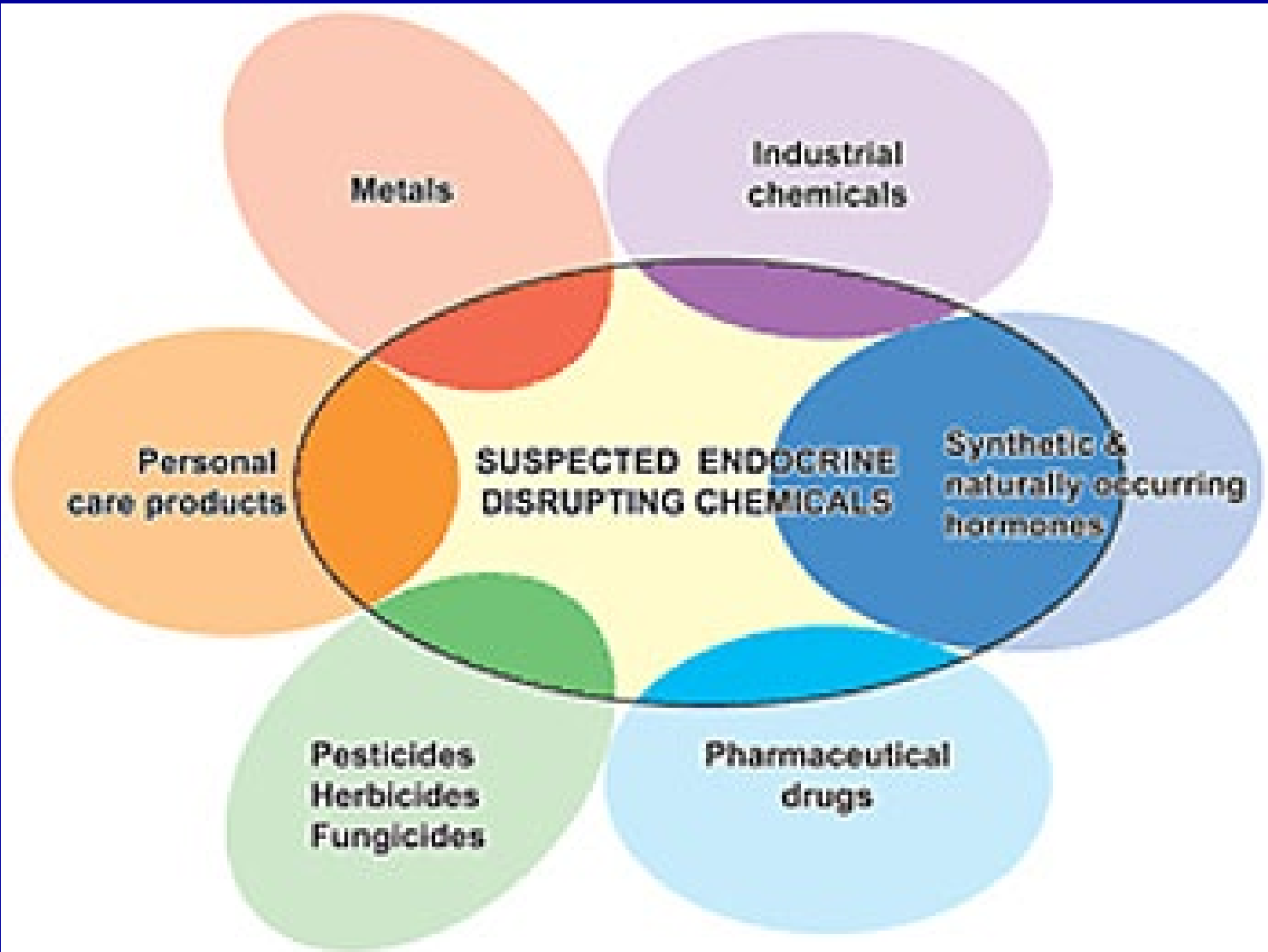
Dot lab

Learning Objectives

- Describe how endocrine disruption alters the developmental programming of the female reproductive tract through lasting epigenetic alterations
- Define how Xenoestrogens interfere with E3 action
- Identify the normal role of E3 in pregnancy

What are
**ENDOCRINE
DISRUPTING
CHEMICALS ?**





Some chemicals from the "families" above are potentially endocrine disruptors

Molecular Mechanisms of Endocrine Disruption

- Mimic or block hormone action
- Alter production, metabolism or secretion
- Alter transport/ carrier protein binding or levels
- Alter receptor levels
- Alter receptor DNA binding or transcriptional activation
- Epigenetic alterations

WHERE YOU CAN FIND EDCs



PESTICIDES



CHILDREN'S PRODUCTS



FOOD CONTACT MATERIALS



ELECTRONICS AND BUILDING MATERIALS

Category/Use

Example EDCs

Pesticides

DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate

Children's products

Lead, phthalates, cadmium

Food contact materials

BPA, phthalates, phenol

Electronics and Building materials

Brominated flame retardants, PCBs

Personal care products, medical tubing

Phthalates

Antibacterials

Triclosan

Textiles, clothing

Perfluorochemicals

Abbreviations: BPA: bisphenol A; 2,4-D: 2,4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls

How we are exposed to EDCs	Where the EDCs come from	EDC example(s)
Oral consumption of contaminated food or water	Industrial waste or pesticides contaminating soil or ground-water	PCBs, dioxins, perfluorinated compounds, DDT
Oral consumption of contaminated food or water	Leaching of chemicals from food or beverage containers; pesticide residues in food or beverage	BPA, phthalates, chlorpyrifos, DDT
Contact with skin and/or inhalation	Household furniture treated with flame retardants	BFRs
Contact with skin and/or inhalation	Pesticides used in agriculture, homes, or for public disease vector control	DDT, chlorpyrifos, vinclozolin, pyrethroids
Intravenous	Intravenous tubing	Phthalates
Application to skin	Some cosmetics, personal care products, anti-bacterials, sunscreens, medications	Phthalates, triclosan, Parabens, insect repellants
Biological transfer from placenta	Maternal body burden due to prior/current exposures	Numerous EDCs can cross the placenta
Biological transfer from mother's milk	Maternal body burden due to prior/current exposures	Numerous EDCs are detected in milk

Abbreviations: BFR: brominated flame retardant; BPA: bisphenol A; PCBs: polychlorinated biphenyls

Environmental Endocrine Disruptors: Reproductive Health



Alligators in Lake Apopka, FL

- Lake contaminated with dicofol, DDT, other industrial chemicals
- Reduced survival rates and egg hatching
- Many alligators have combinations of male and female reproductive organs
- Abnormal ovaries and testes, small penises
- Males with elevated estrogen and females with elevated testosterone levels (Guillette)

Effects of Endocrine Disruption

- Interference with reproduction
- Developmental malformations
- Increased cancer risk
- Disturbances in the immune and nervous system function

OCTOBER 4, 2010

Environment Special:
The oceans—why 70%
of our planet is in danger

The Facebook Movie:
The secret history of
social networking

TIME



**How the
first nine
months
shape
the rest
of your life**

The new science
of fetal origins

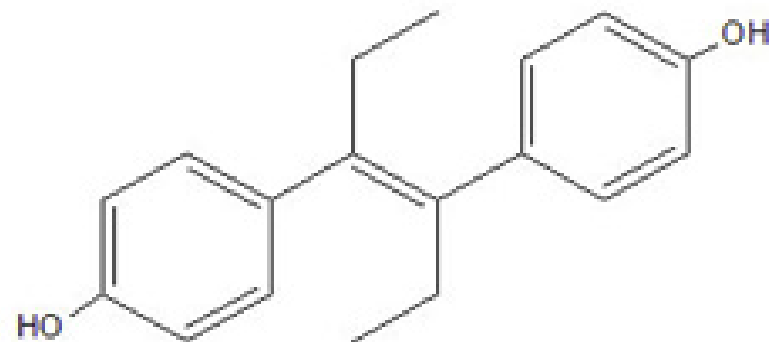
BY ANNIE MURPHY PAUL

WWW.TIME.COM

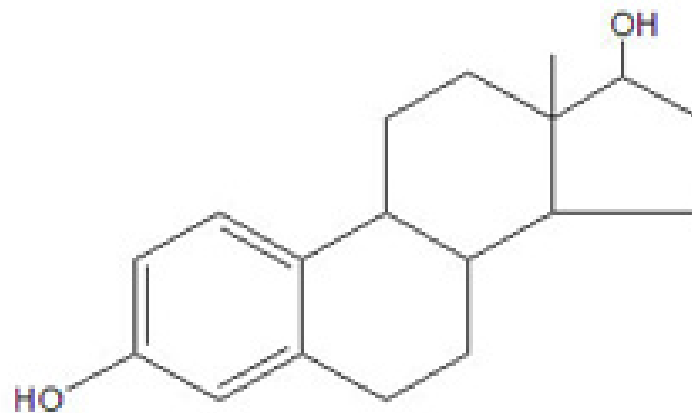
Does Endocrine Disruption
Affect Humans ?

Diethylstilbestrol
(DES)

DES



Diethylstilbestrol (DES)



17-β-Estradiol

Introduction – DES

- Between the 1940s and 1960s, millions of women were treated with DES.
- Correlation between DES exposure in mothers and the occurrence of adenocarcinoma of the vagina reported in 1971.
- High incidence of anatomic abnormalities of the genital tract that adversely affected their reproductive capacity

"Really?"

Yes...
desPLEX
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies...*

96 per cent live delivery with **desPLEX**
in one series of 1200 patients¹—
— bigger and stronger babies, too.²

No gastric or other side effects with **desPLEX**
— in either high or low dosage^{3,4,5}

(Each **desPLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating to assure prompt help in emergencies. **desPLEX** tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

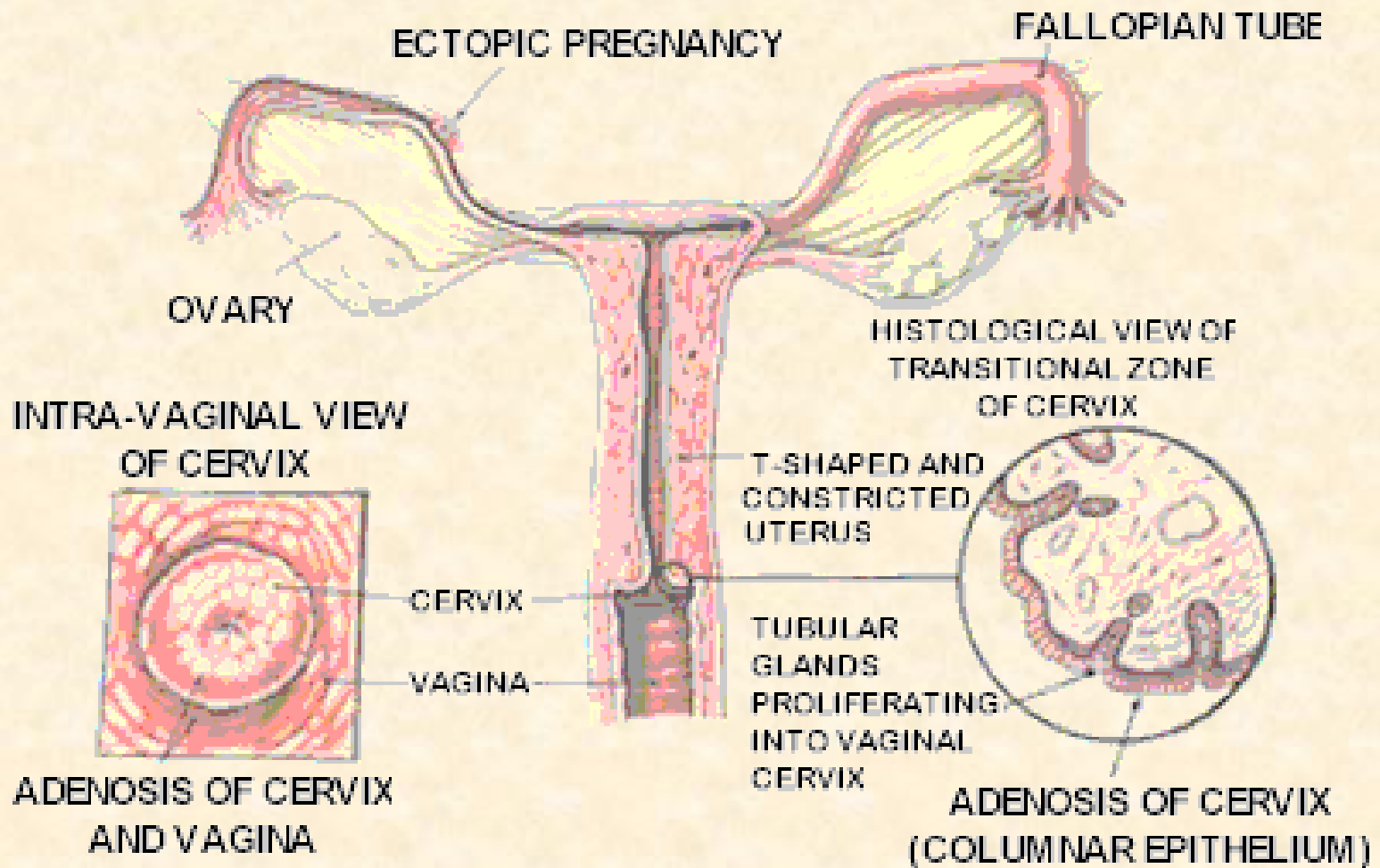
For further data and a generous trial supply of **desPLEX**, write to:
Medical Director

REFERENCES

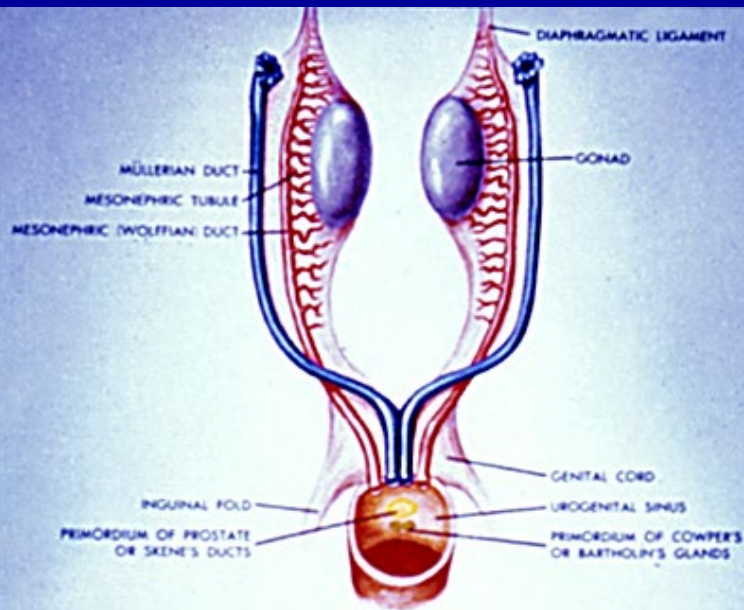
1. Conner, E. M., et al.: *Am. J. Obst. & Gynec.* 83:1298, 1952.
2. Gilman, L., and Kaplan, A.: *N. Y. St. J. Med.* 30:2812, 1950.
3. Kammer, K. J., South, M. J.: *Obst. Gynec.* 1952.
4. Fahn, S. F.: *Med. Times* 82:921, 1954; *Am. J. Surg.* 87:45, 1954.
5. Ross, J. W.: *J. Natl. M. A.* 42:70, 1951; 43:222, 1952.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

ABNORMALITIES DUE TO DES EXPOSURE

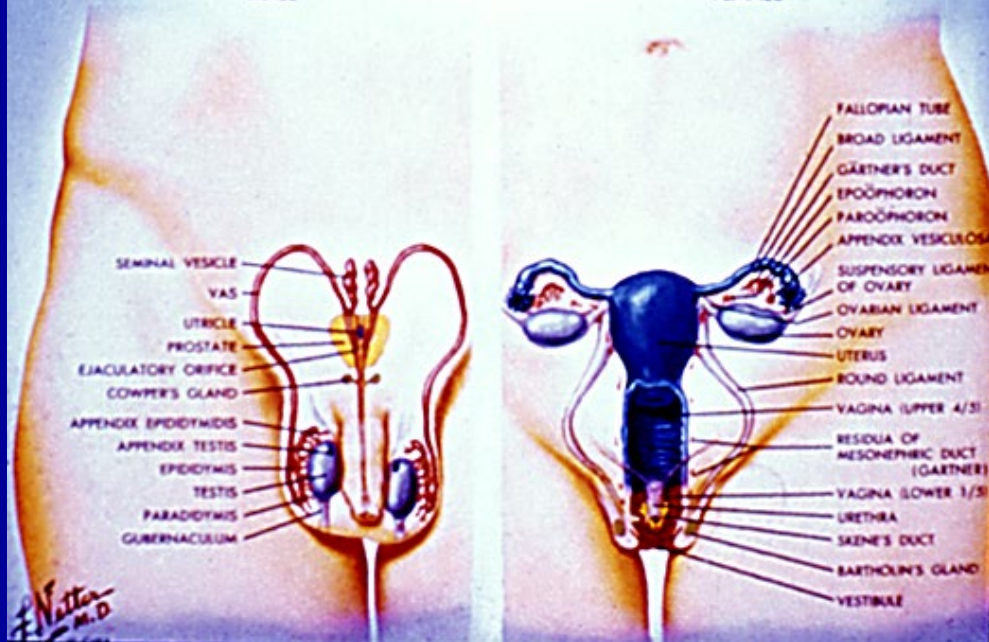


How Does DES Affect Müllerian Development ?

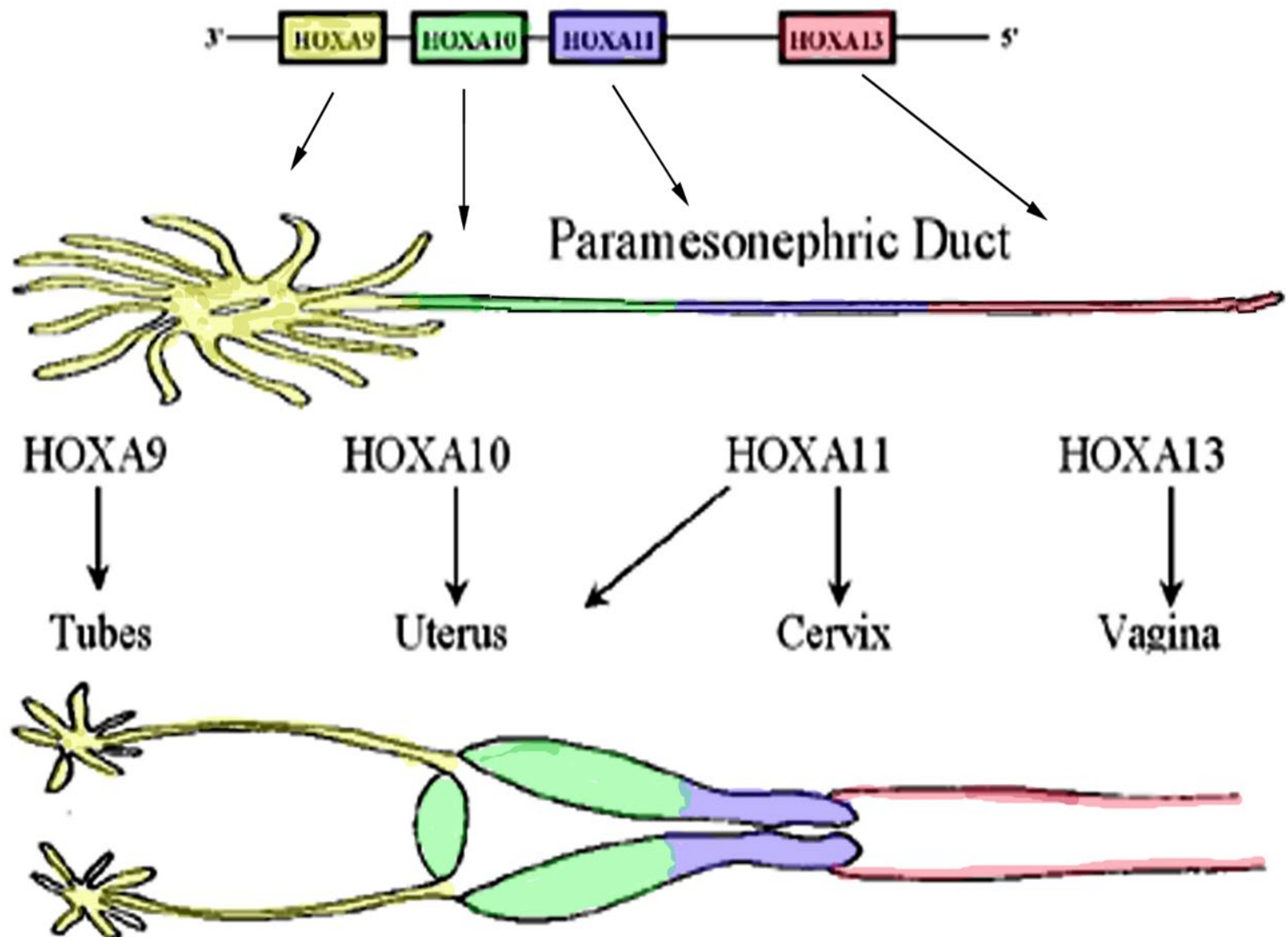


UNDIFFERENTIATED

← MALE
FEMALE →



HOX code of the Developing Müllerian System

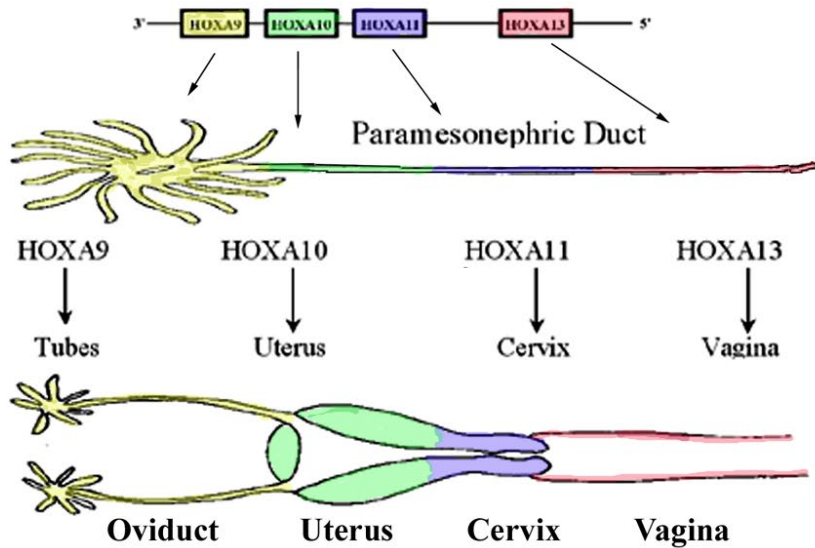


Effect of DES on HOX Gene Expression

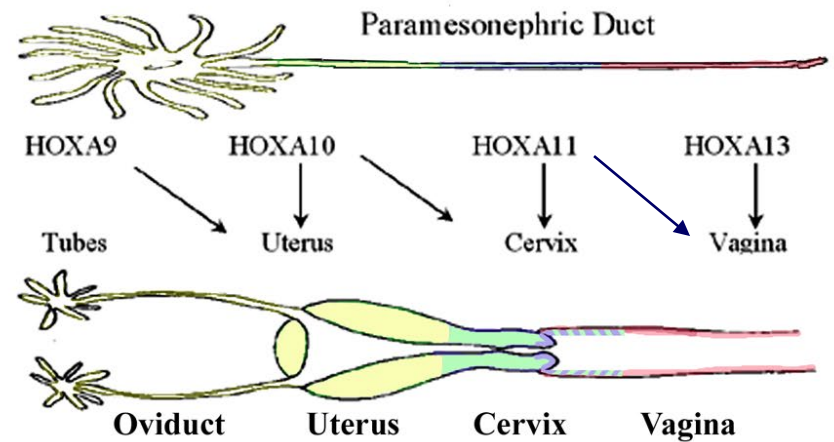
In adults DES is simply a “strong” estrogen.

DES Alters HOX Axis

HOX Code of the Developing Mullerian System



Alteration of the HOX Code by DES





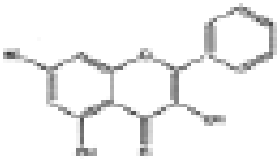

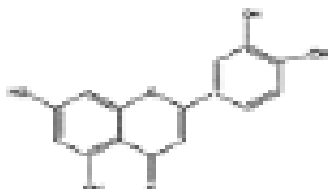








T-Shaped Uterus:

Uterus → Tube

Vaginal Adenosis:

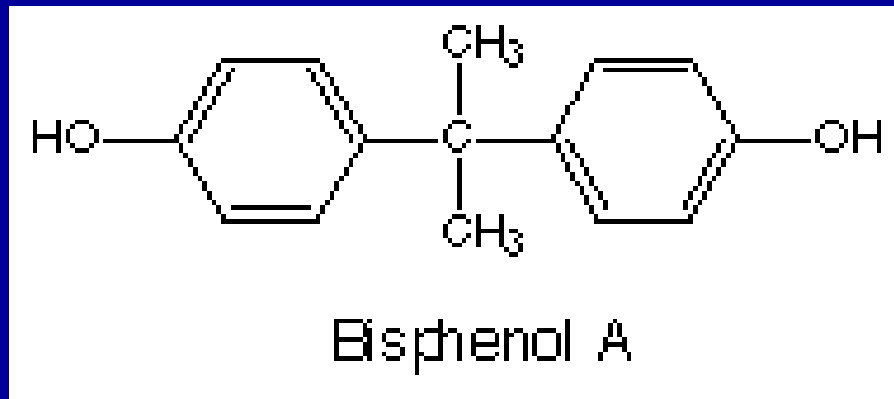
Vagina → Uterus or cervix

Estrogens

Steroids	Pollutants	Plant Products
 <p>17β-Estradiol</p>	 <p>DDT</p>	 <p>Genistein (isoflavone)</p>
<p>Pharmaceuticals</p>	 <p>PCB</p>	 <p>Luteolin (flavone)</p>
 <p>Diethylstilbestrol</p>  <p>Ethynyl Estradiol</p>	 <p>Bisphenol A</p>  <p>Nonylphenol</p>	 <p>Resveratrol (stilbene)</p>
<p>Fungal Products</p>	 <p>Kepone</p>	 <p>Coumestrol (coumarin)</p>
 <p>Zearalenone</p>		

Bisphenol A

A “weak” estrogen in adults

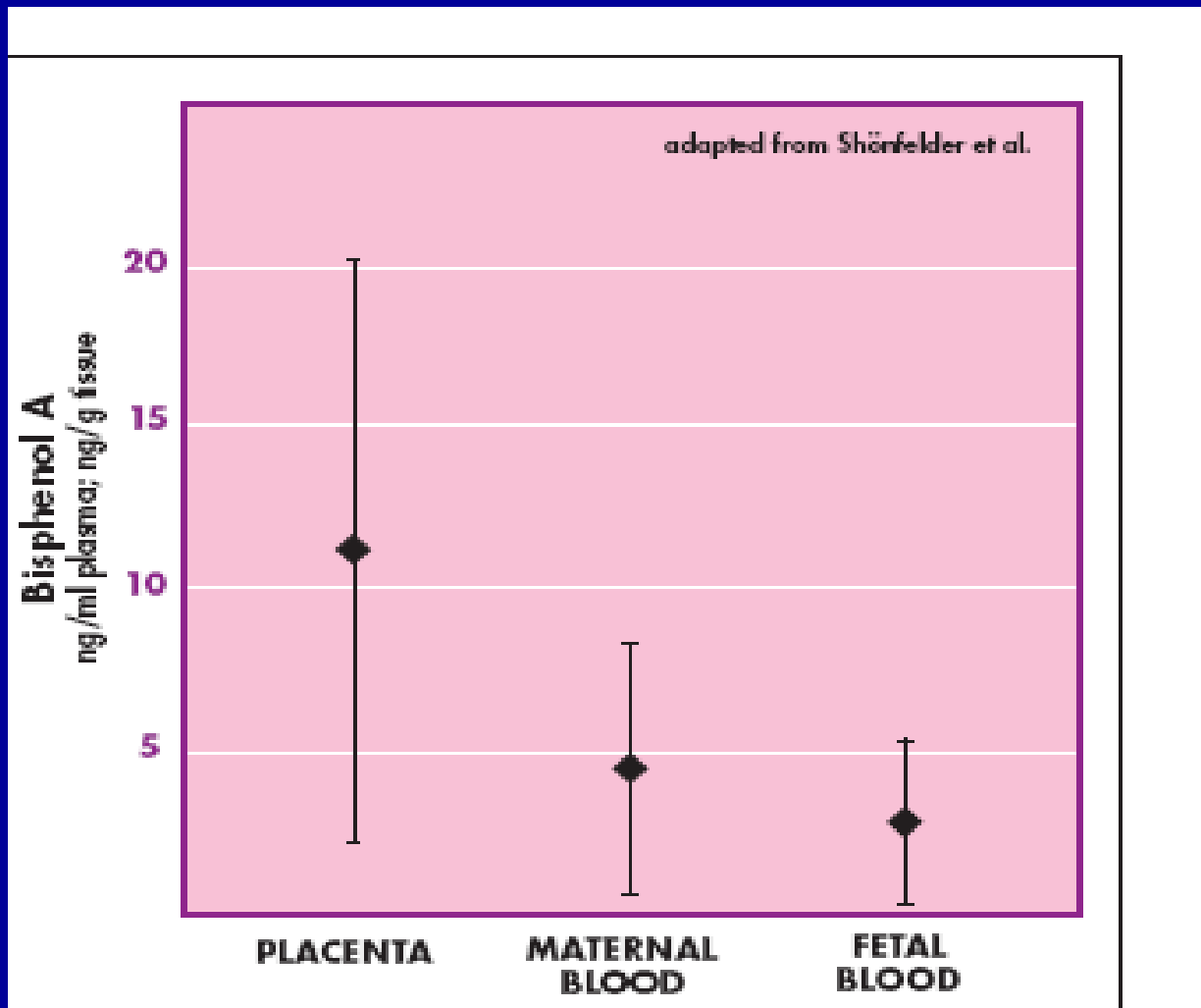


- Endocrine disruptor
- Stimulates uterine growth approximately 10^{-4} that of estradiol in adult animals.

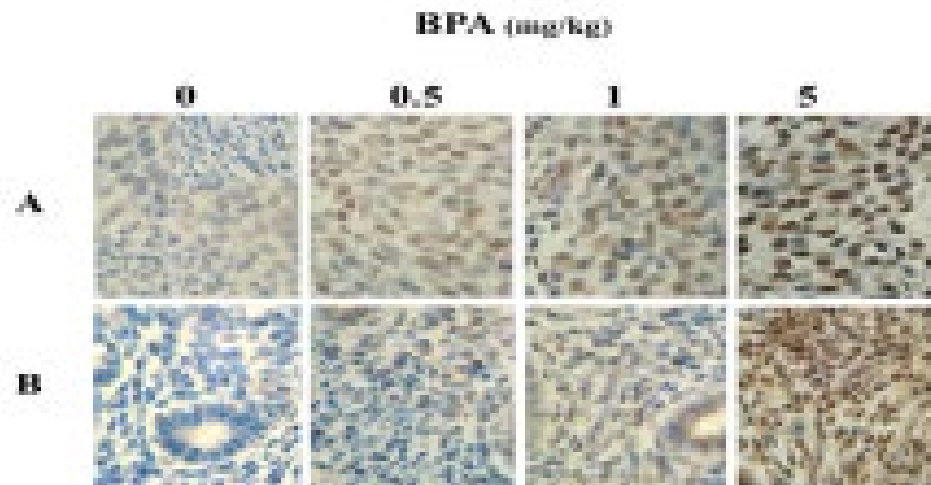
Sources of Exposure



Humans are widely exposed

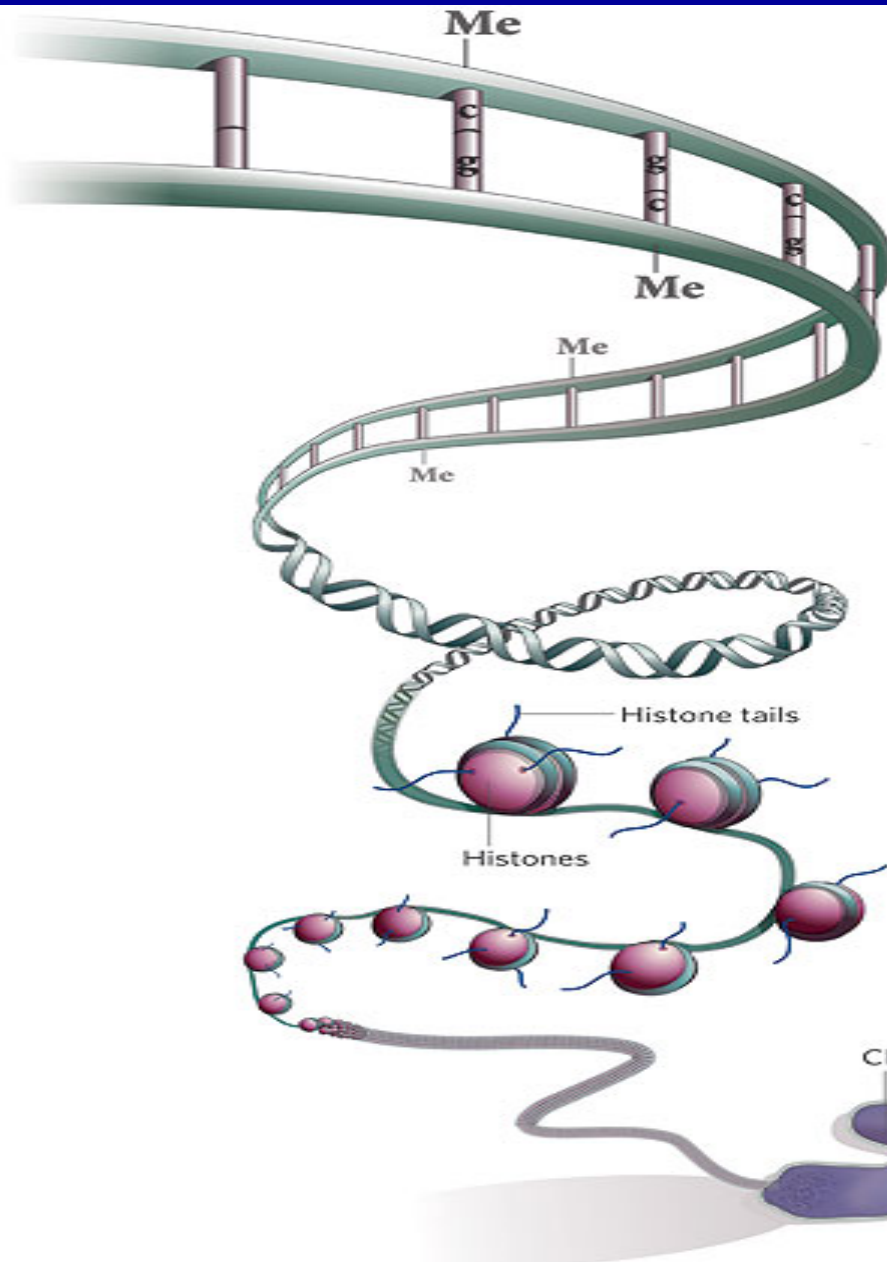


In Fetal Development BPA, distinct and opposite from DES, increases uterine HOXA10 expression



- While many xenoestrogens appear to be weak estrogens and vary only in potency, their effects are paradoxical when exposure occurs *in utero*.
- Persistent effects long after exposure.
- Not simply an estrogen agonist/antagonist effect.

Epigenetic Alterations



The two main components of the epigenetic code

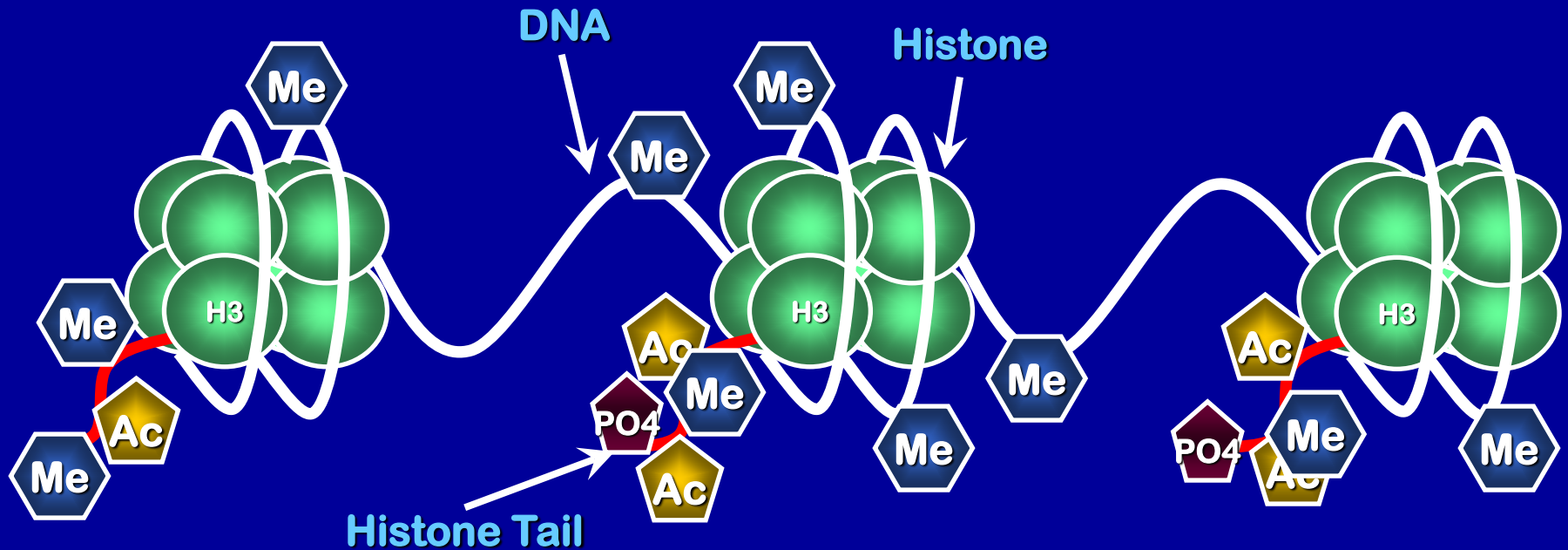
DNA methylation

Methyl marks added to certain DNA bases repress gene activity.

Histone modification

A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.

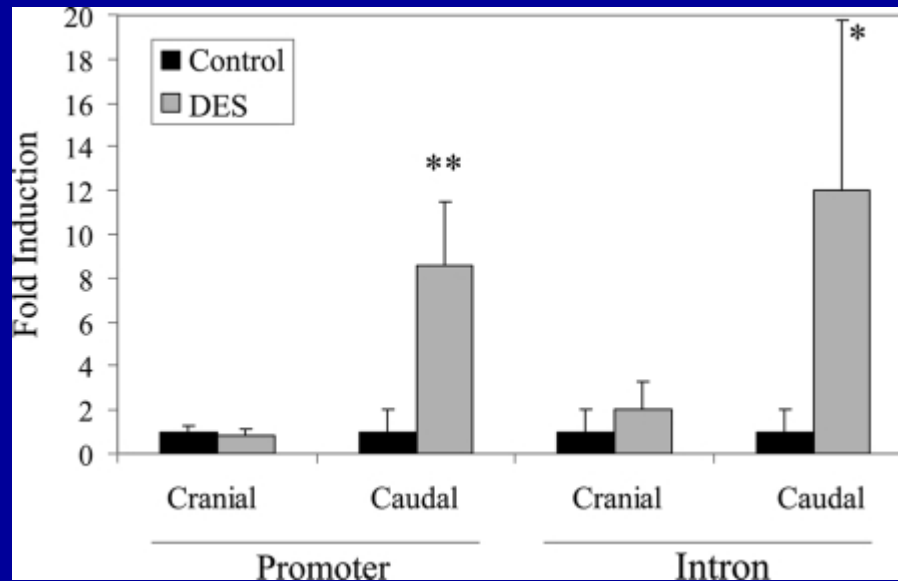
Chromatin Modifications



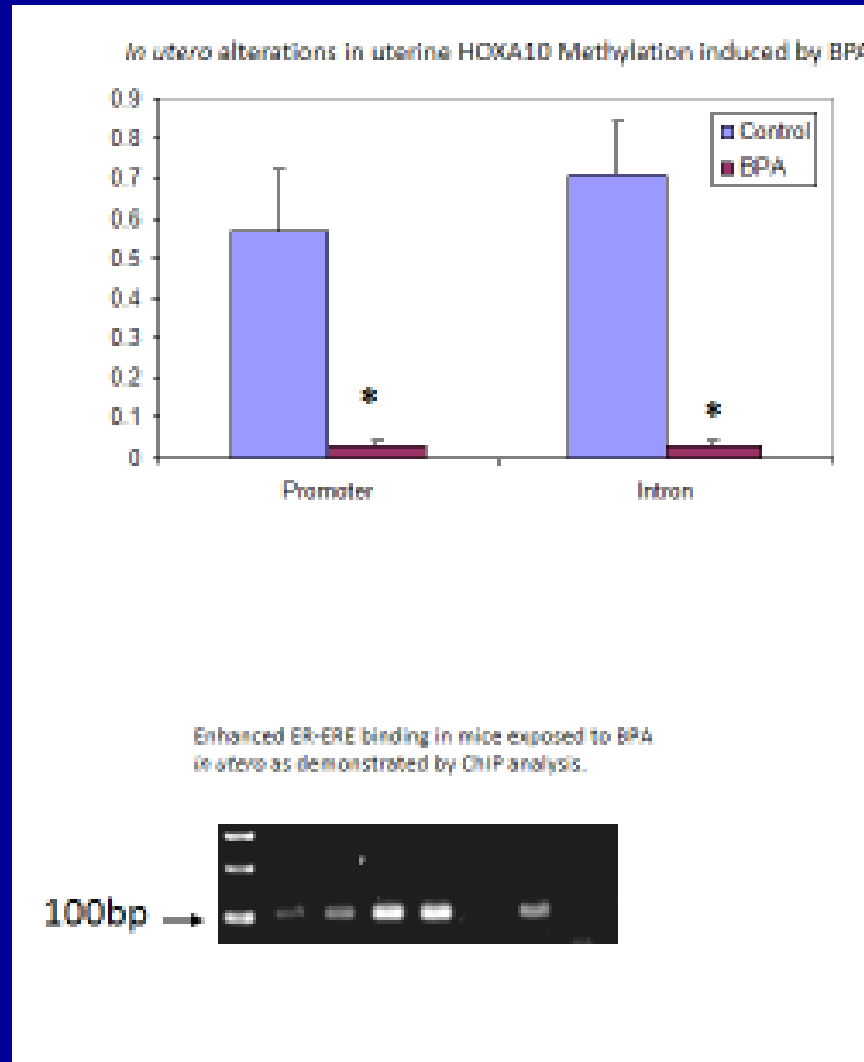
Euchromatin: Gene Activation

Heterochromatin: Gene Silencing

Hoxa10 methylation by DES



Methylation by BPA

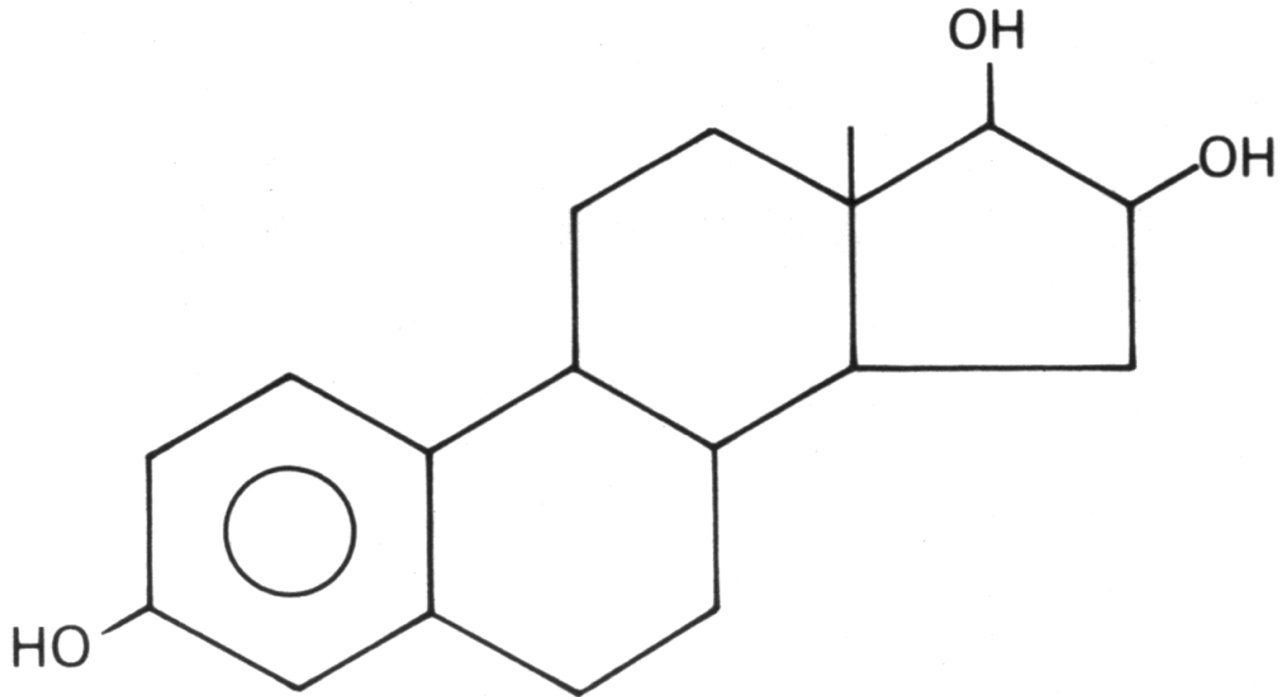


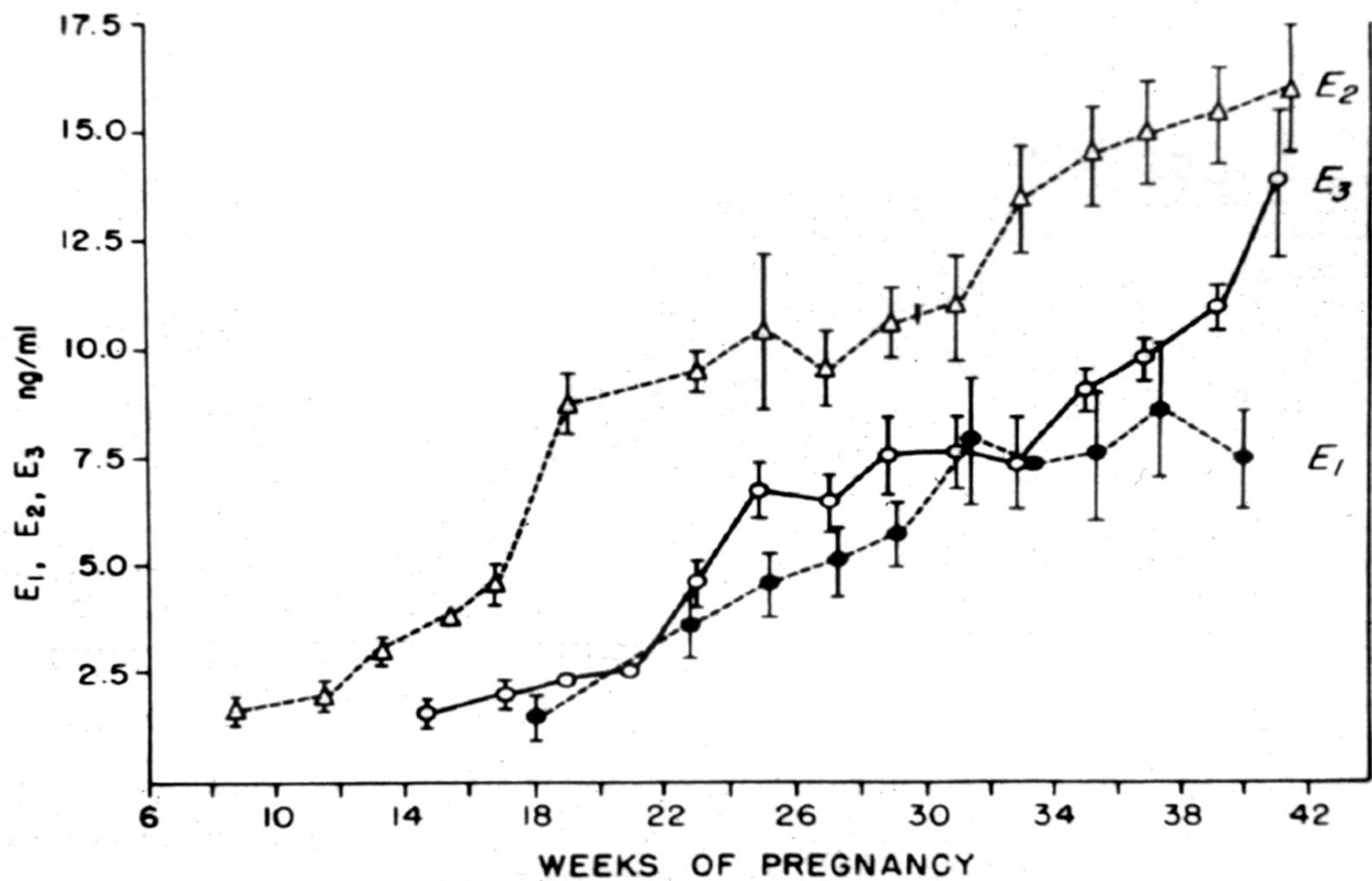
Are there naturally occurring estrogens that play a role in epigenetic programming?

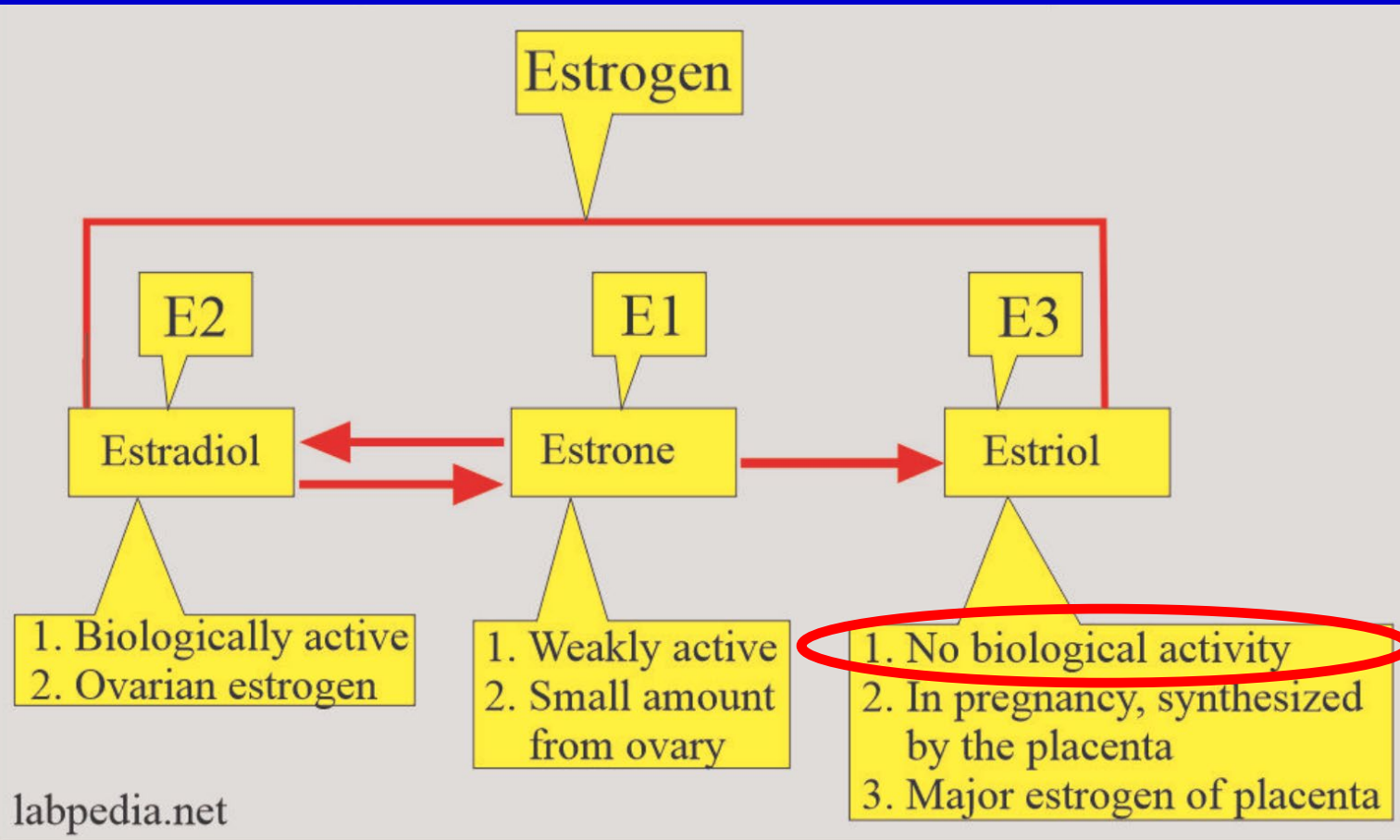
What do fetal estrogens tell us about endocrine disruption?

E₃

ESTRIOL







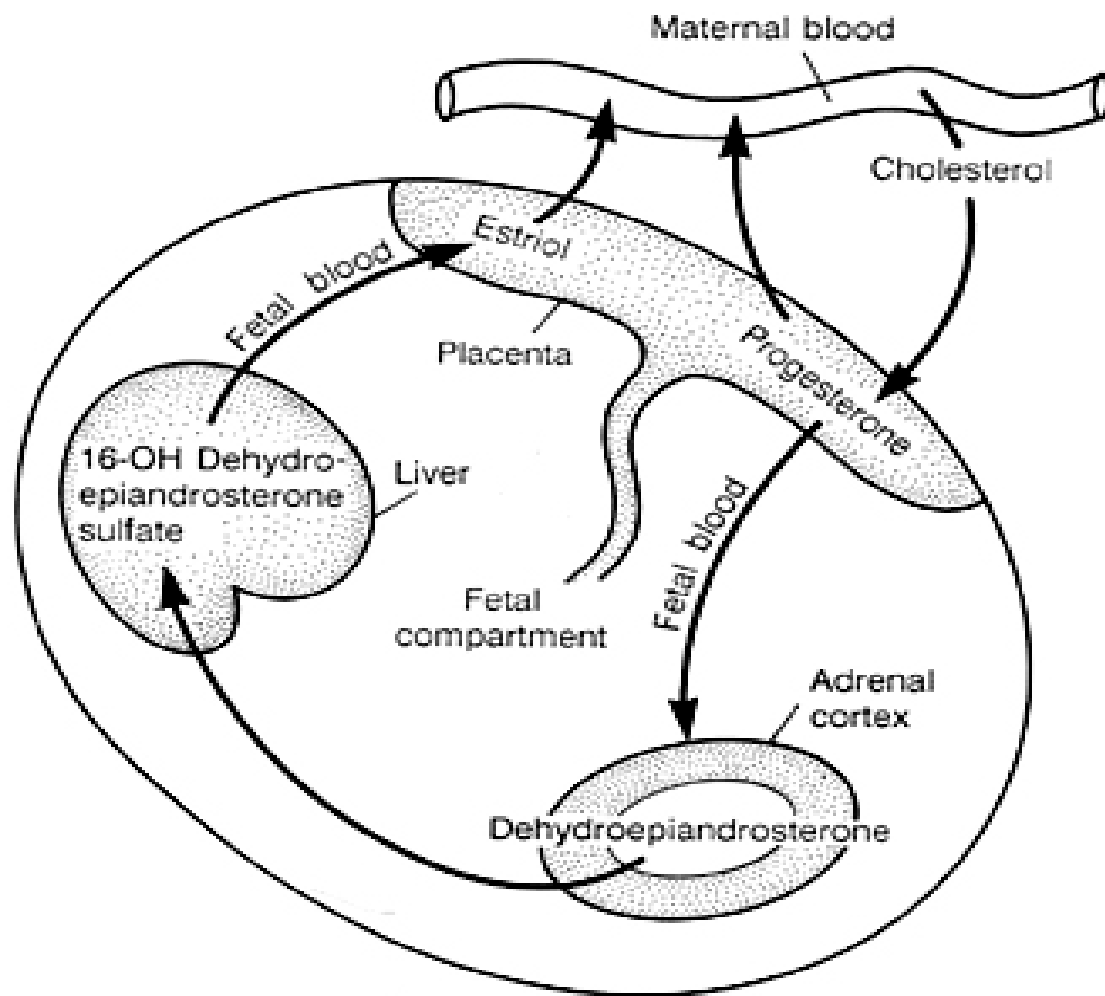
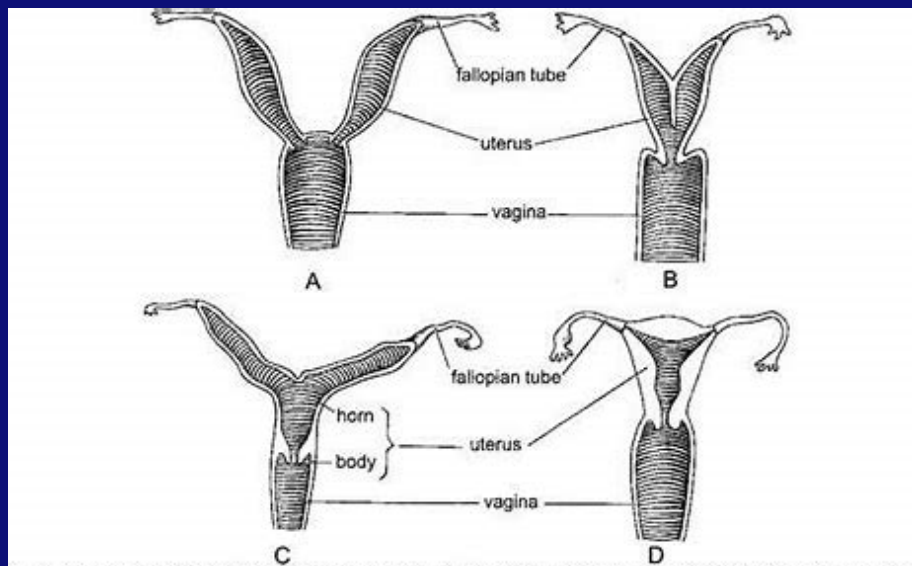
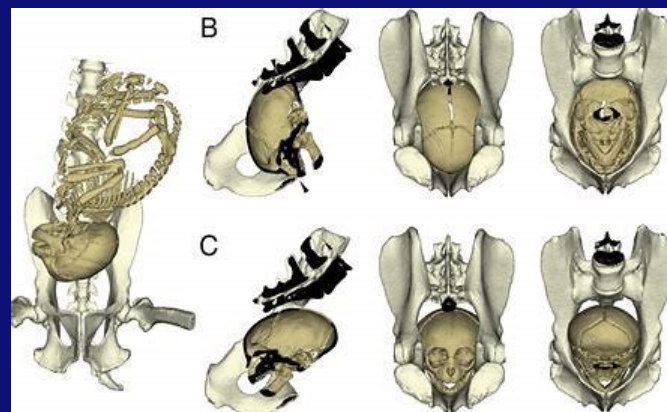
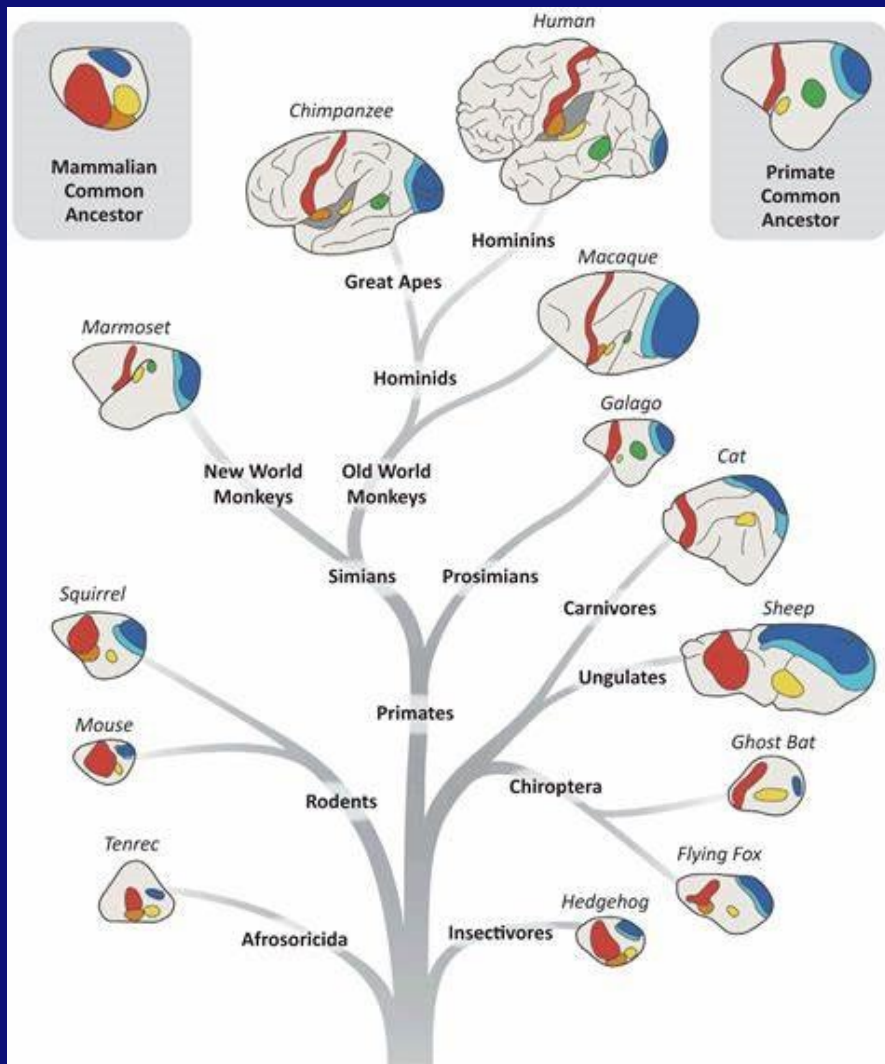
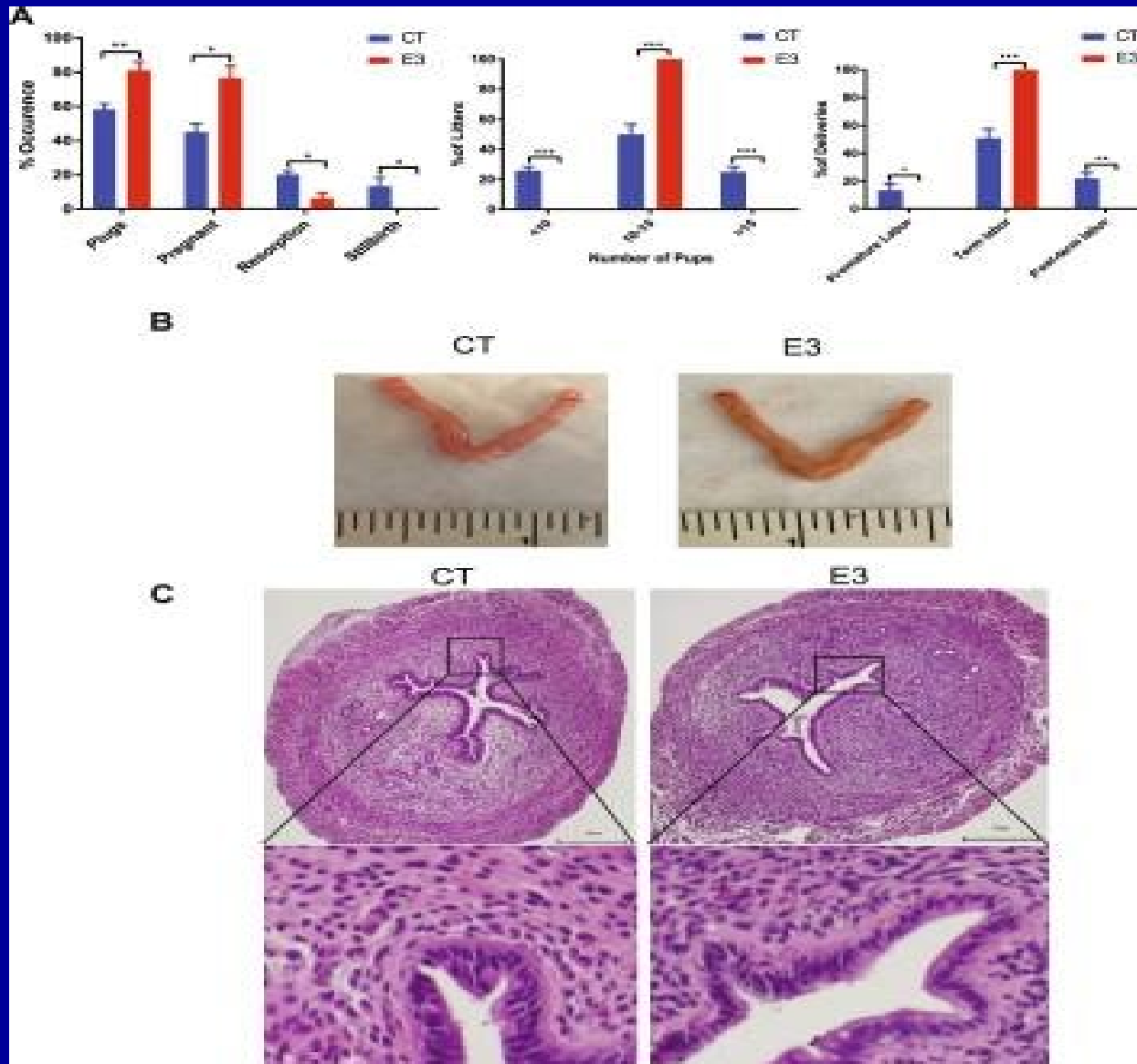


Figure 8-17 The human feto-placental unit, showing how the mother provides cholesterol to the placenta, which converts it to progesterone for release into the maternal and fetal circulations. In the fetus, progesterone is converted to dehydroepiandrosterone (DHEA) by the fetal zone of the adrenal glands. DHEA is then converted to 16-OH DHEA sulfate in the fetal liver. This steroid then goes to the placenta and is converted to estriol, the major estrogen secreted by the placenta.

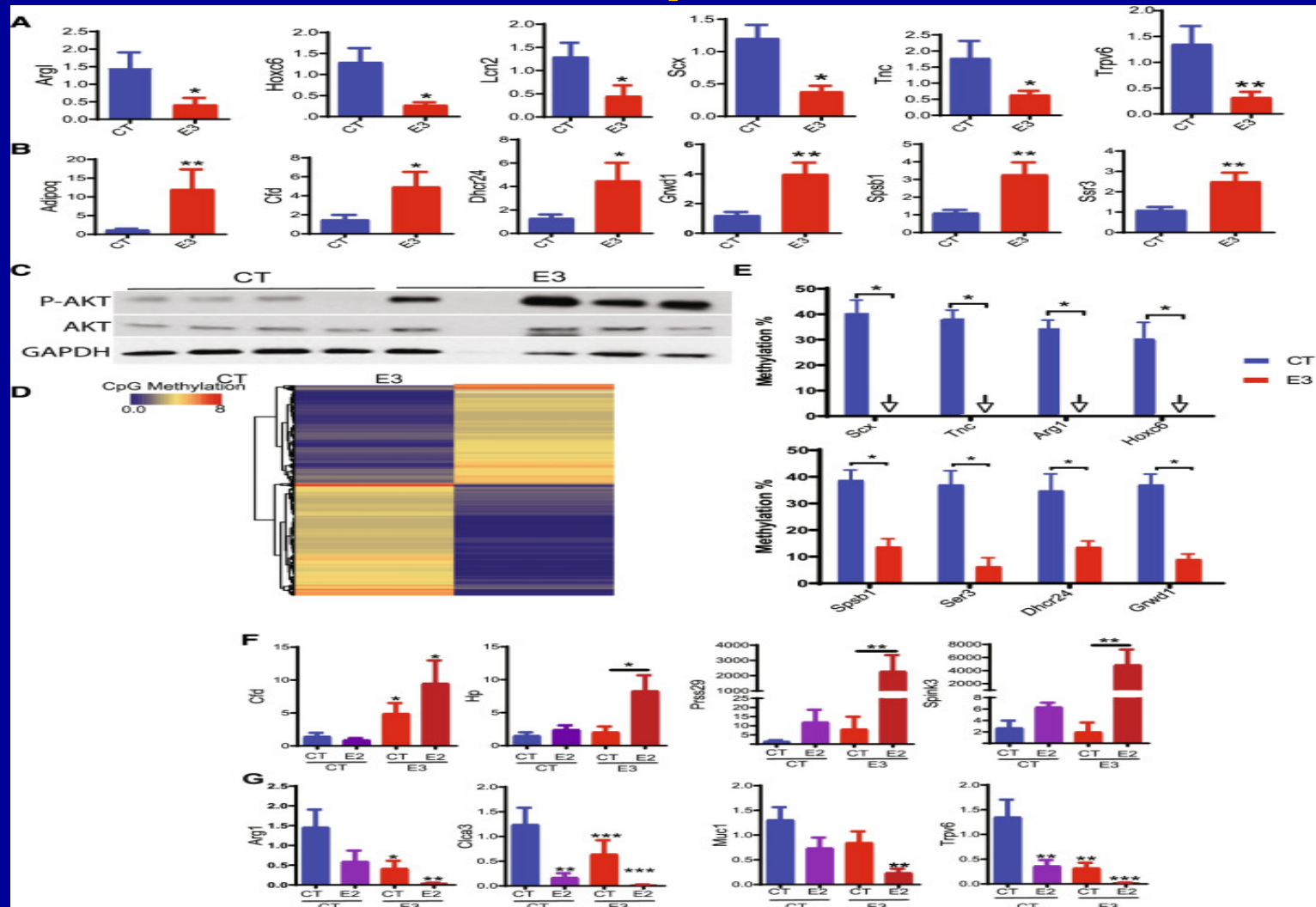


Developmental programming by fetal estrogens

E3 Effect on Reproduction

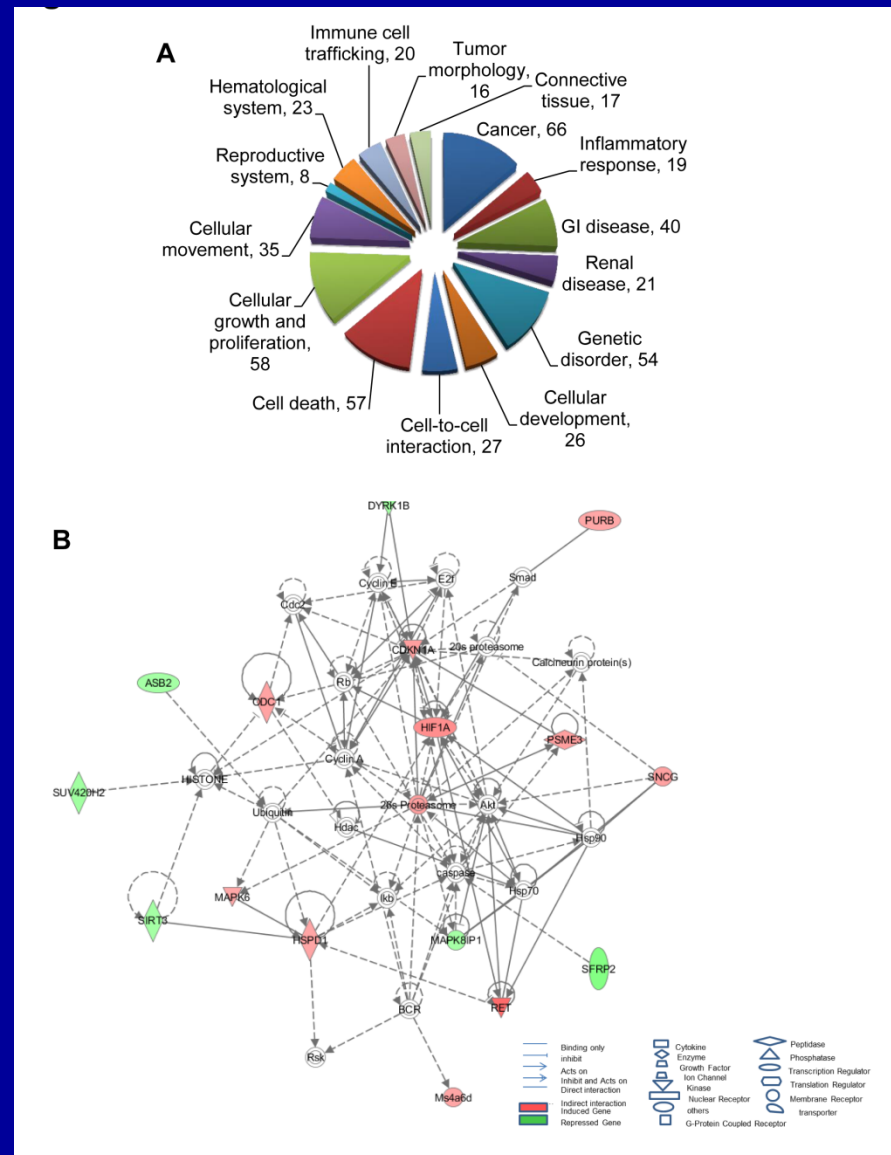


E3 Programming of Uterine Gene Expression

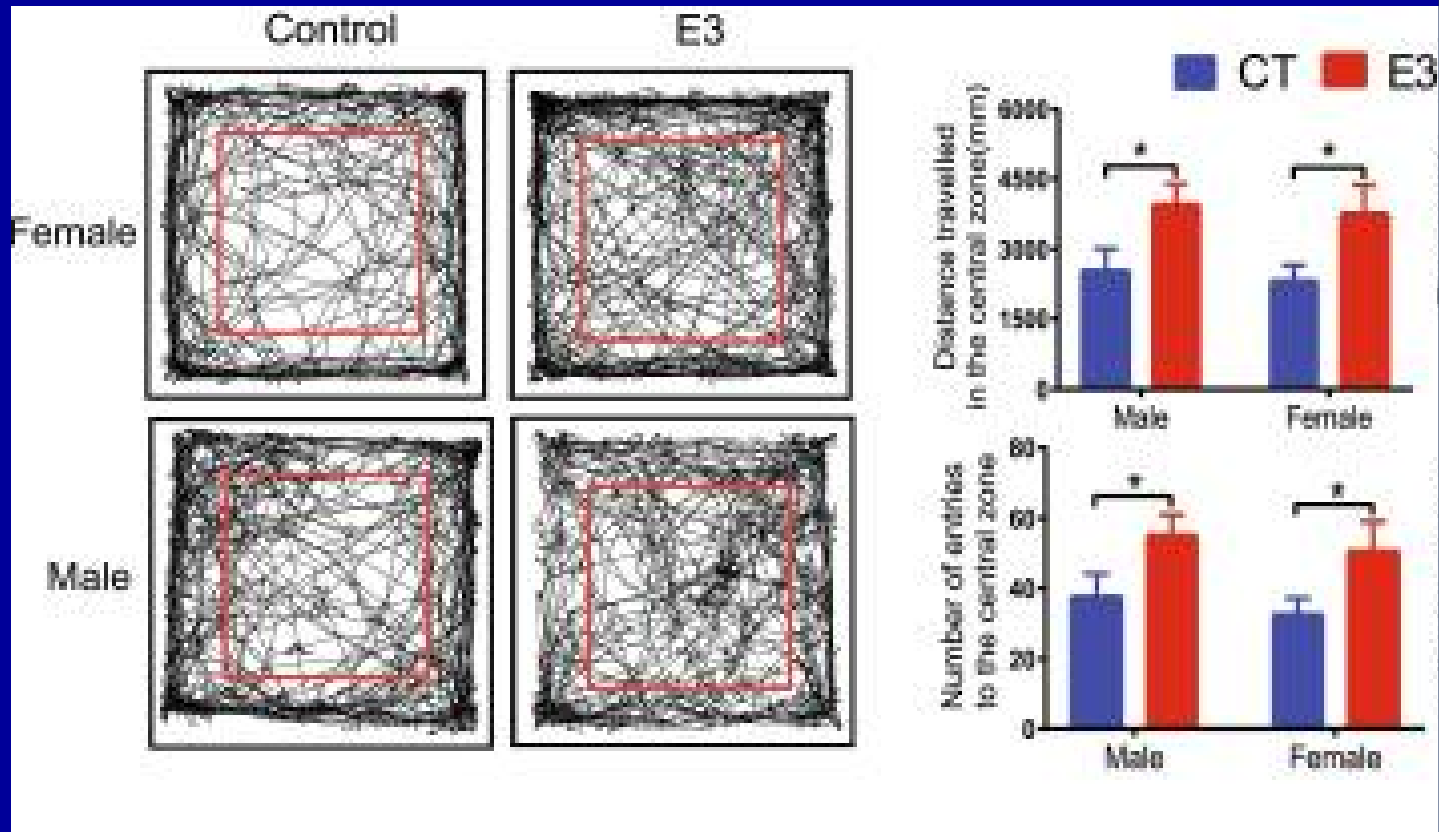


Epigenetic Programming by E₃

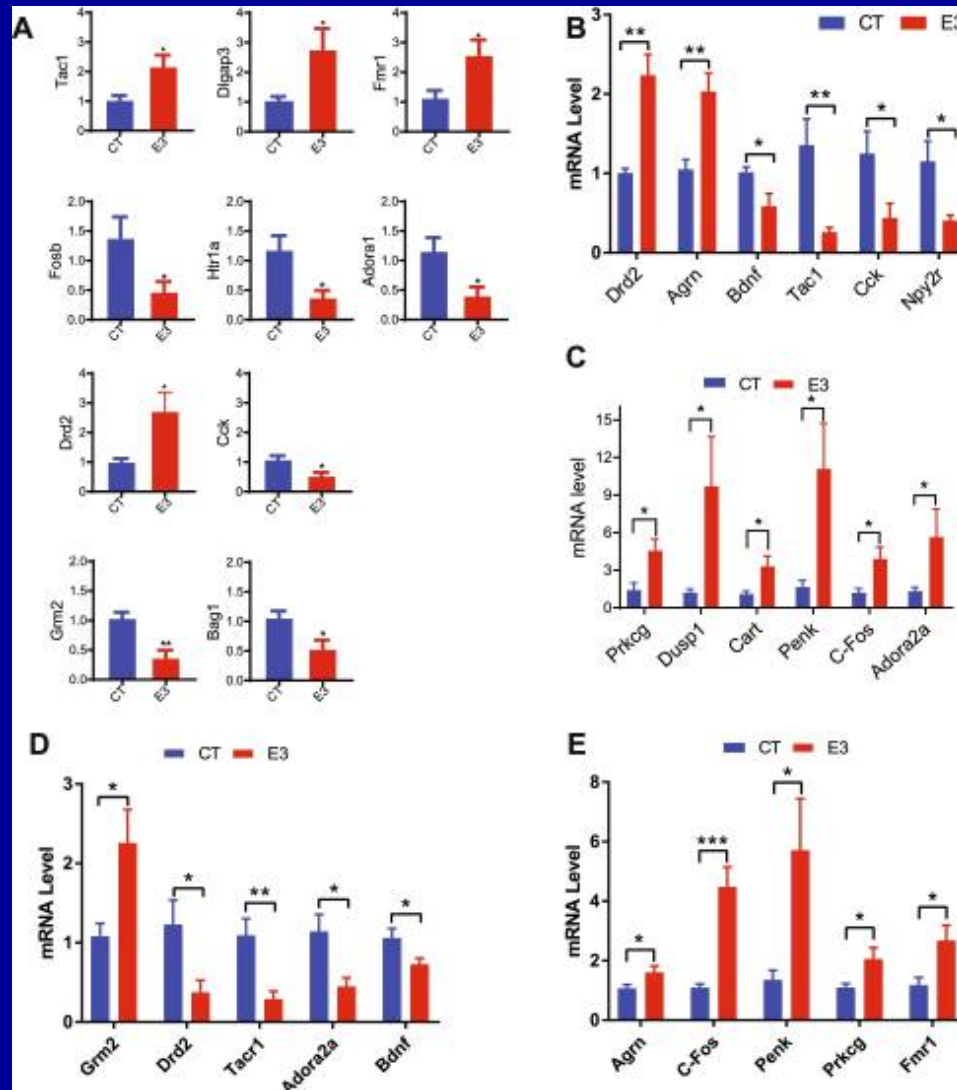
We identified 2252 genes that were significantly hypo-methylated and 2620 genes were hypermethylated in the E3-treated group



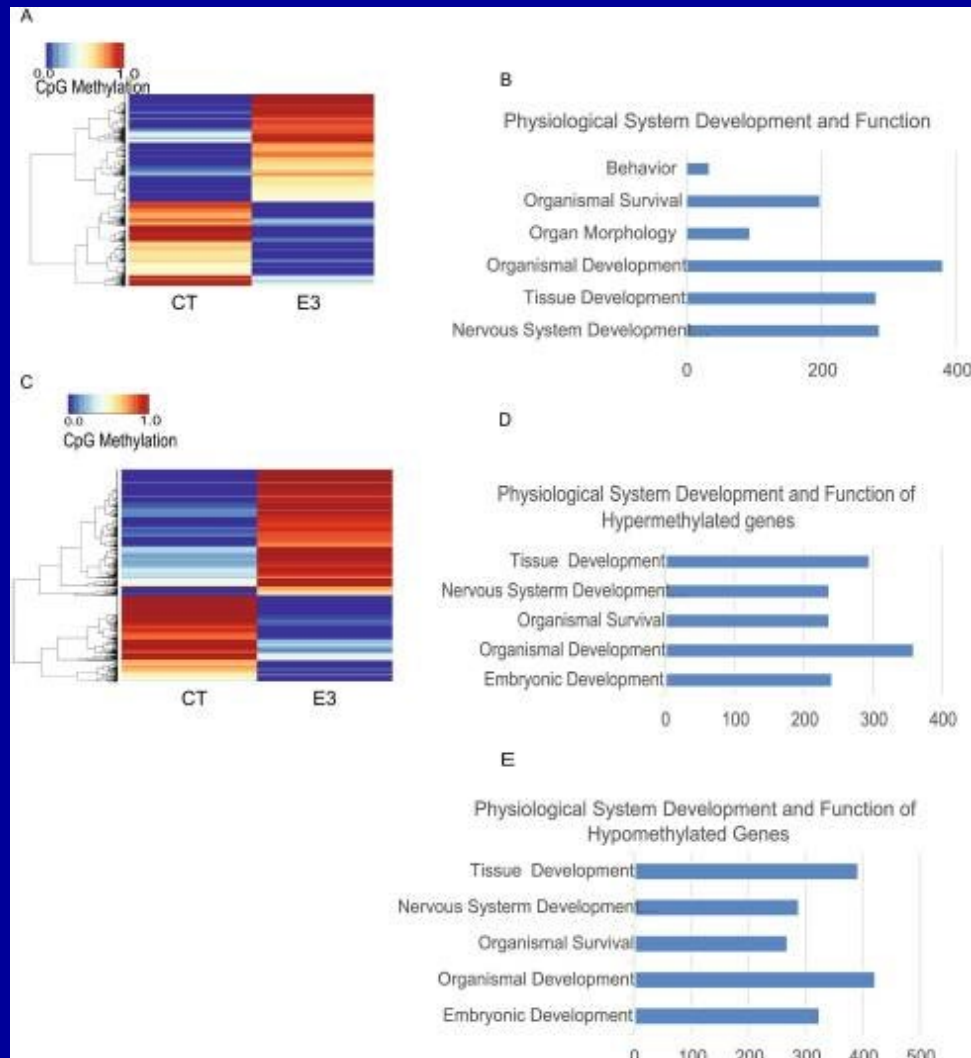
E3 Effect on Behavior



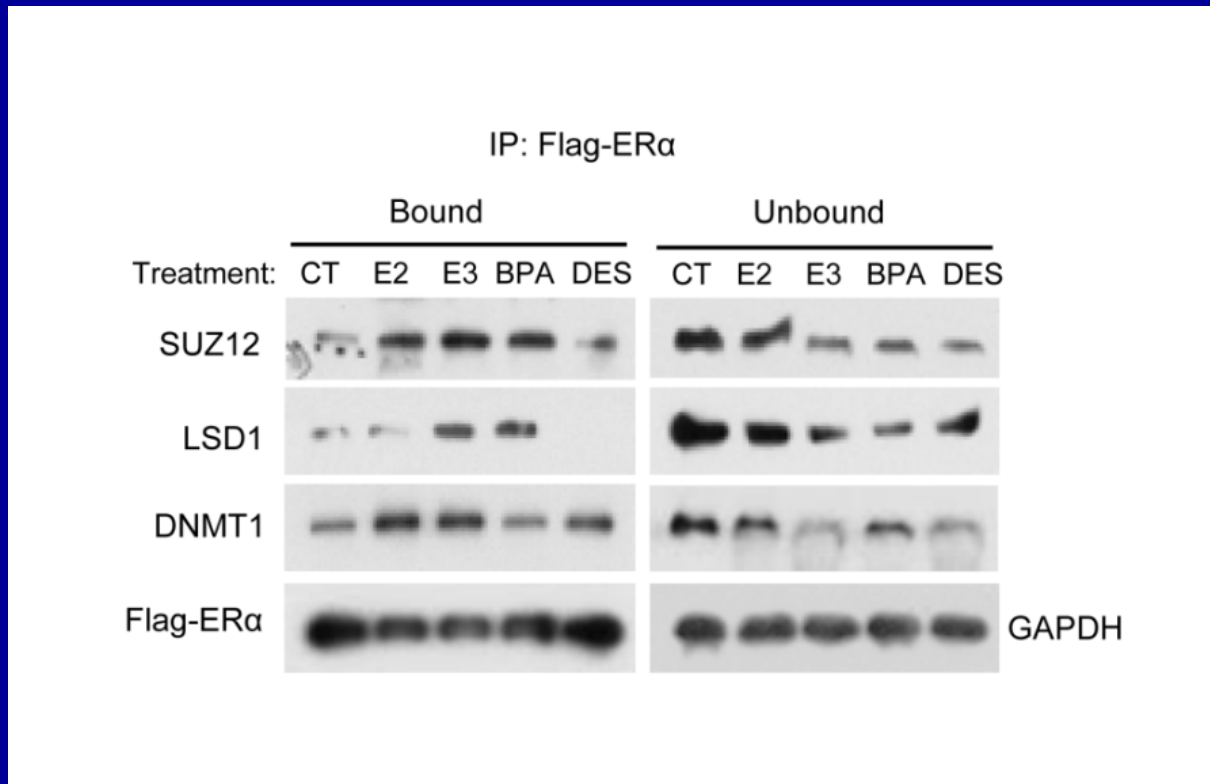
E3 Effect on Gene Expression in the Brain



Brain Methylation



Epigenetic modifiers bind directly to ER in a ligand dependant fashion.



Nuclear Receptor Signaling

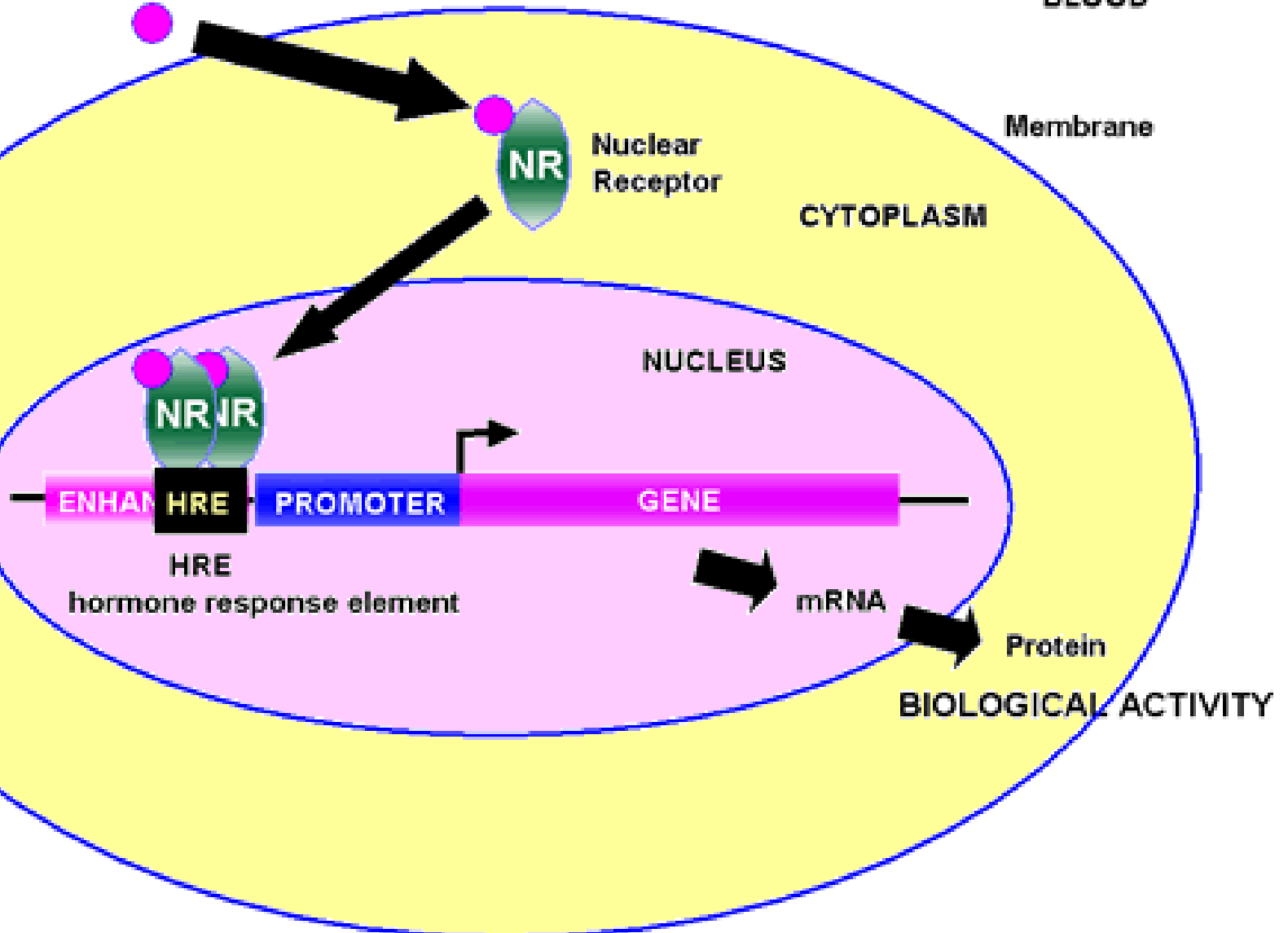
Hormone, e.g. a steroid

BLOOD

Membrane

CYTOPLASM

NUCLEUS



ENHANCER

NR NR

HRE

PROMOTER

GENE

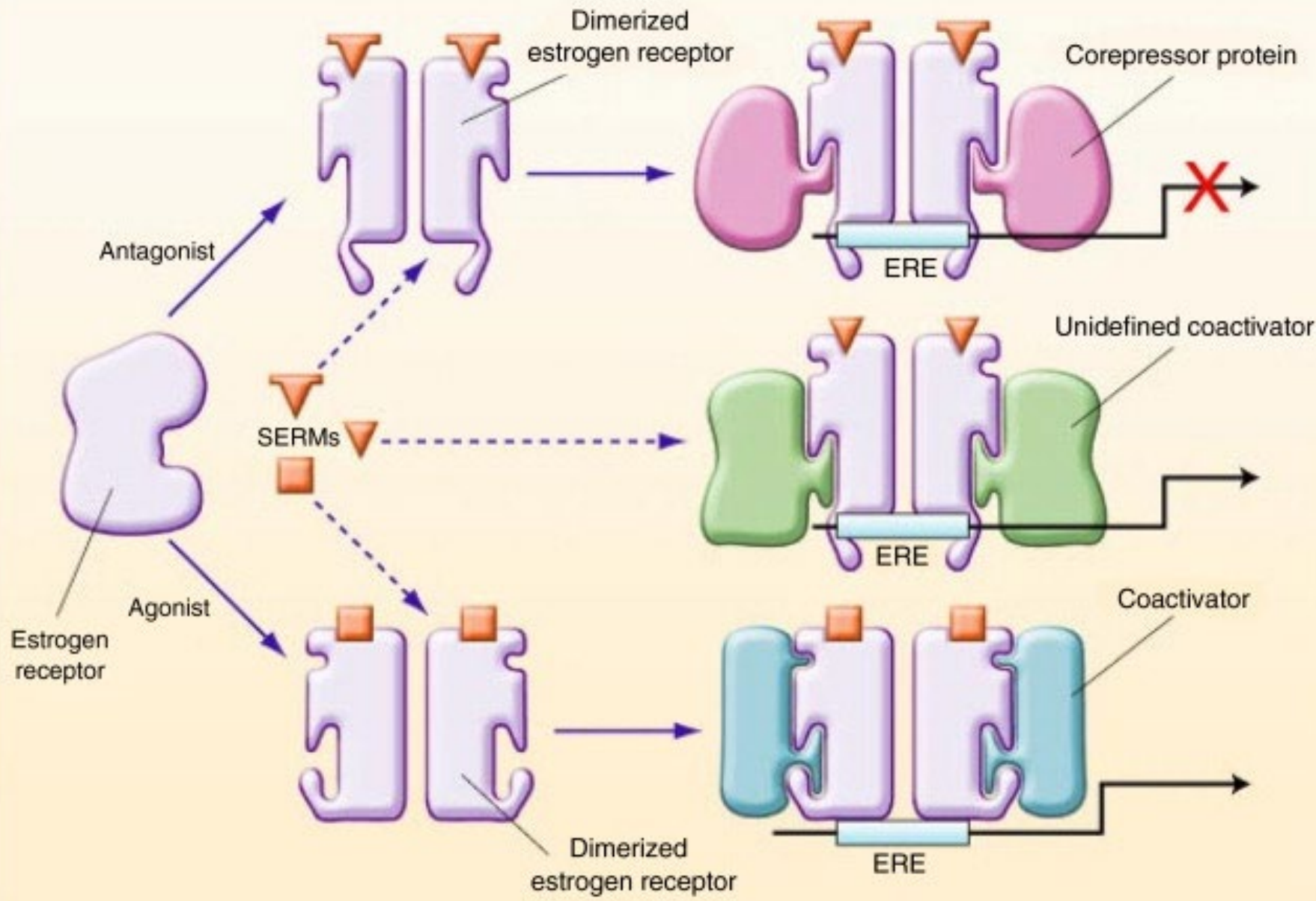
HRE

hormone response element

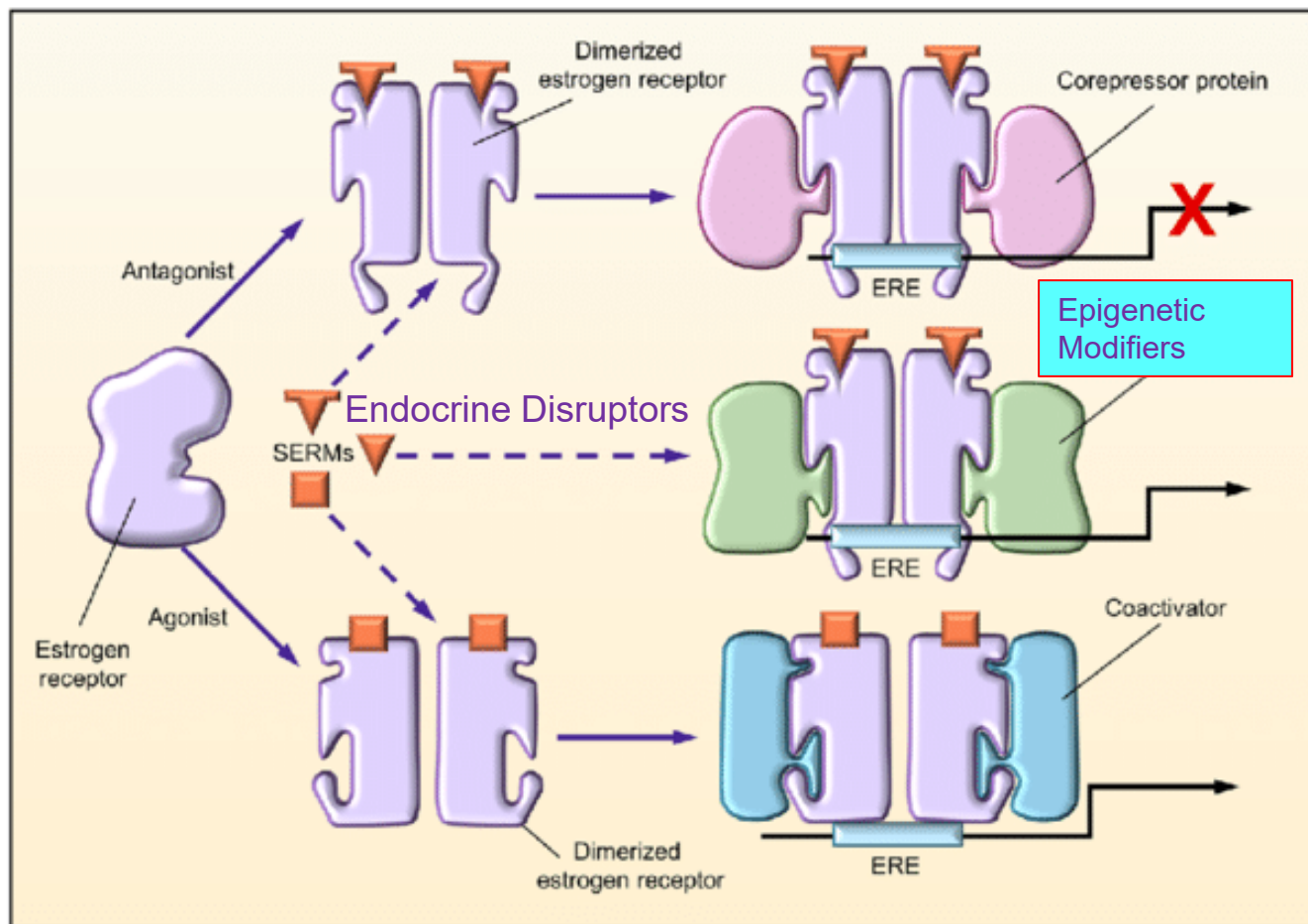
mRNA

Protein

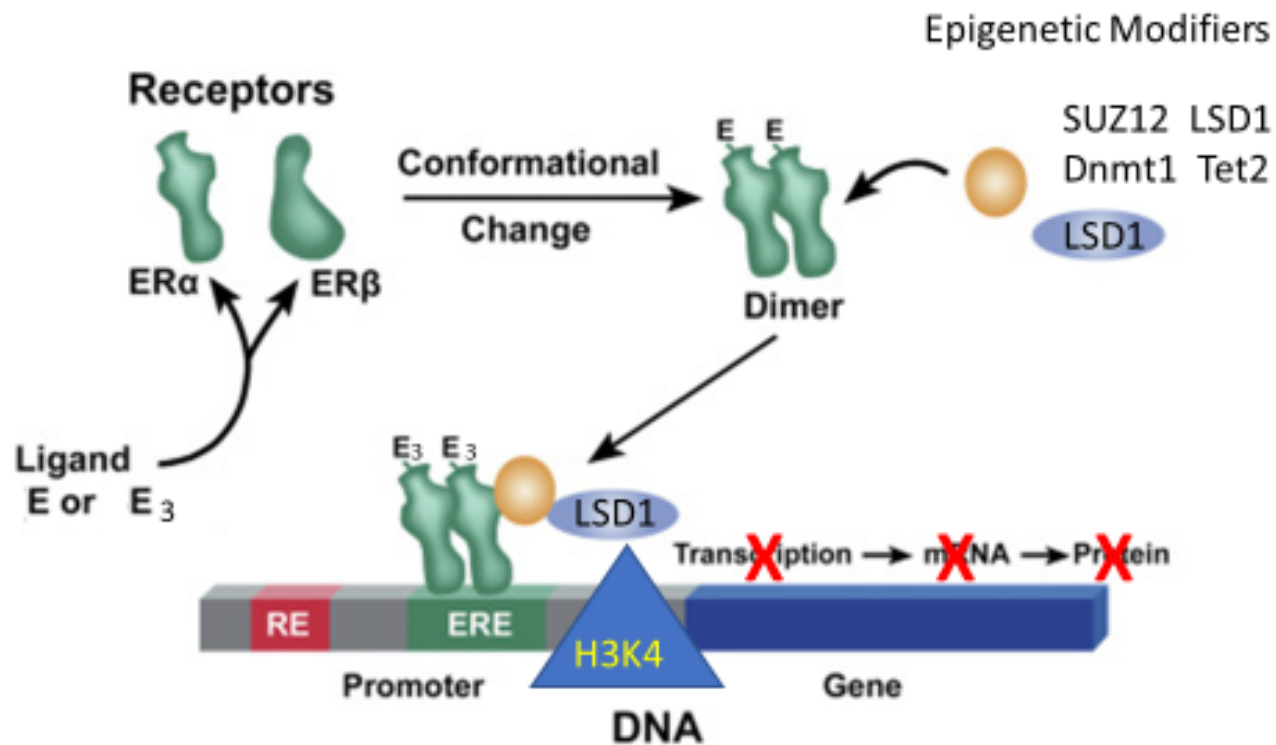
BIOLOGICAL ACTIVITY



Fetal Estrogens are SERMs that activate Epigenetic Programming



Model of E₃ Action:



Rather than a weak estrogen as defined by its function as a canonical transcriptional activator, E₃ could be a potent epigenetic modulator and influence developmental programming of the fetus.



Broader Issue:

- What role do the *in utero* environmental exposures play in the health of the next generation?



- Buy organic food products
- Avoid canned goods and BPA containing plastics
- Buy safe skincare products
- Use air and water filters



Endocrine Disruptor #1

BPA



EVERYDAY PRODUCTS WHERE BPA IS LURKING

Linked to:
Infertility
Breast cancer
Obesity
Heart disease
Early puberty
Behavioral



6

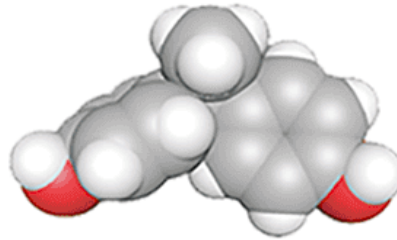


Prefer fresh, organic produce



1

Look for BPA-free signs



TIPS TO AVOID BPA IN FOOD AND WATER



2

Prefer glass or stainless steel over plastic

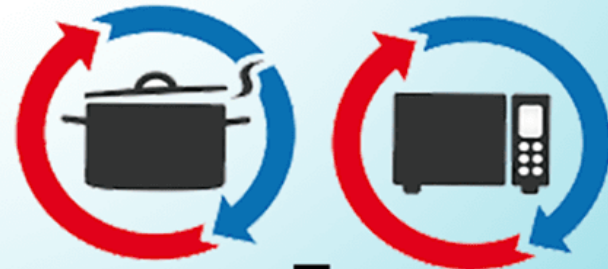


5

Avoid canned foods

4

Discard damaged plastic containers



3

Do not heat or microwave plastic containers

Endocrine Disruptor #2

Phthalates



Potential Health Effects From Phthalate Exposure

- Reduced testosterone levels
- Reduced fertility in women and men
- May lead to babies with cognitive or behavioral problems
- Changes with the endocrine function and thyroid hormones
- Liver and kidney toxicity
- Associated with some types of cancer
- Adverse outcomes for type 2 diabetes, insulin resistance, allergies, and asthma





How to Avoid Phthalates

- Look for products labeled, "Phthalate-Free."
- Use unscented products, or products scented with only essential oil/oils.
- Use clean beauty products
- Make your own cleaning products
- Use products packaged in glass when available

Endocrine Disruptor #3

Atrazine



- Atrazine is a chlorinated triazine systemic herbicide that is used to selectively control annual grasses and broadleaf weeds before they emerge. Pesticide products containing atrazine are registered for use on several agricultural crops, with the highest use on field corn, sweet corn, sorghum, and sugarcane.

Atrazine



WHAT:

Atrazine is a herbicide used on commercial crops and included in commonly used lawn-care products. It is the second most commonly used pesticide or herbicide in the U.S.

FOUND:

60 to 80 million pounds of atrazine are applied per year in the U.S. Once applied to crops, it contaminates groundwater and drinking water, with the highest concentrations in drinking water found in the Midwest.

SCIENCE:

Atrazine increases the conversion of testosterone into estrogens, especially estradiol. Higher concentrations of estradiol in the body can increase the risk of breast cancer. Studies link atrazine in drinking water to breast cancer.

TOP TIP:

Avoid using lawn chemicals and other pesticides that may contain atrazine. When possible, buy organic and pesticide-free produce. Avoid areas where atrazine is being applied.



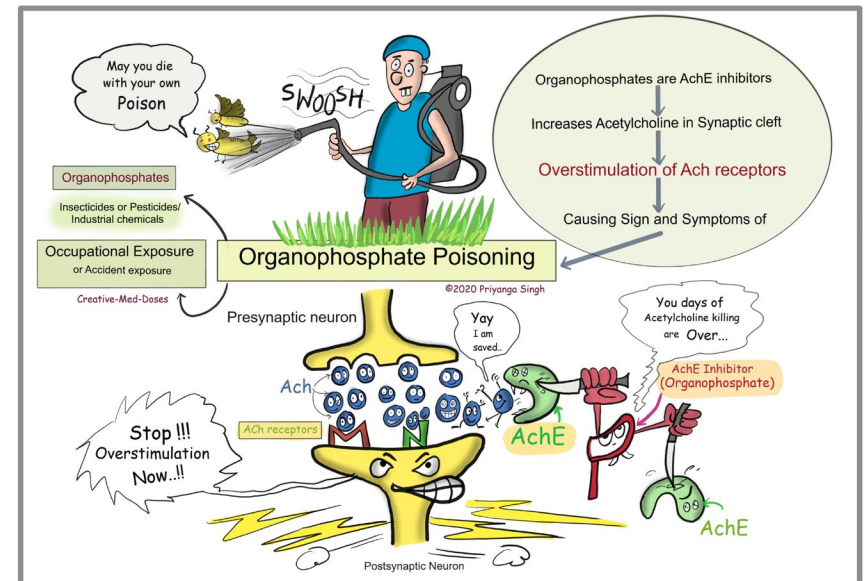
Endocrine Disruptor #4 Organophosphate



- Organophosphates are pesticides that target the CNS of insects
- Linked to brain development and reproductive defects
- Can alter testosterone and thyroid signaling

Ways to avoid:

- Limit your exposure to all pesticides
- Buy organic foods



Endocrine Disruptor #5

Perfluorinated Chemicals



Perfluorinated chemicals (PFCs) include a variety of man-made chemicals used across many industries since the 1940s. They're used to make non-stick cookware and are also found in certain textiles, leather, water-resistant apparel, rubber, and plastics.

People can be exposed to these chemicals through food, which is contaminated through soil, water, food packing, and processing equipment. PFCs are notorious for being resistant to biodegradation, meaning they easily build up in

humans and the environment.

Researchers are still hard at work determining the widespread biological effects of PFCs, but it is thought that they namely affect thyroid and sex hormone levels in the body. PFOA in particular has been linked to decreased sperm quality, low birth weight, kidney disease, thyroid disease, and cancers.^[10]

How to avoid PFCs: Opt for pans without the non-stick coating. A well-seasoned cast iron pot is a wonderful

ENDOCRINE DISRUPTORS

REDUCE EXPOSURES,
ESPECIALLY DURING
PREGNANCY



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