

# Endocrine disruptors: Science for science's sake, science for health protection



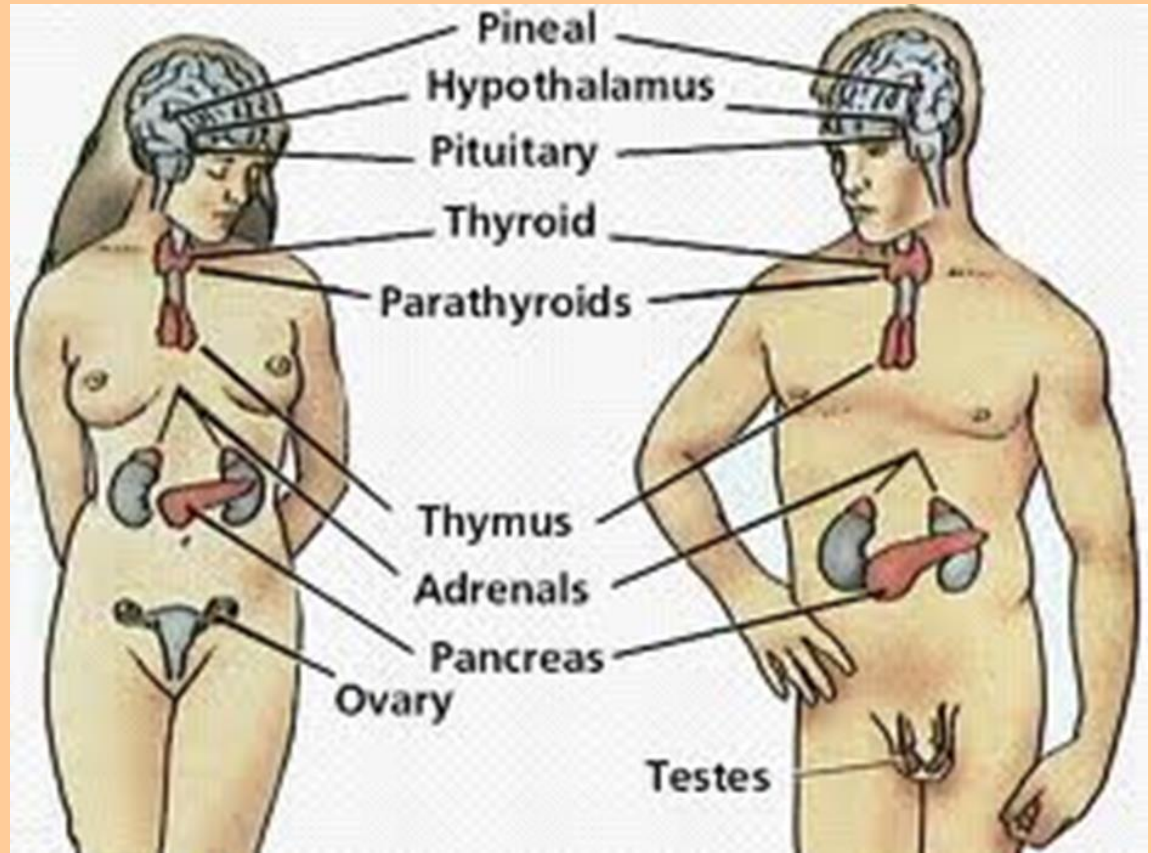
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Tufts University School of Medicine (Boston)  
Ecole Normale Supérieure (Paris)

# Endocrine System

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- The set of cells and organs that produce chemical “signals” called hormones.
- Hormones travel in the bloodstream in order to reach their respective target cells.

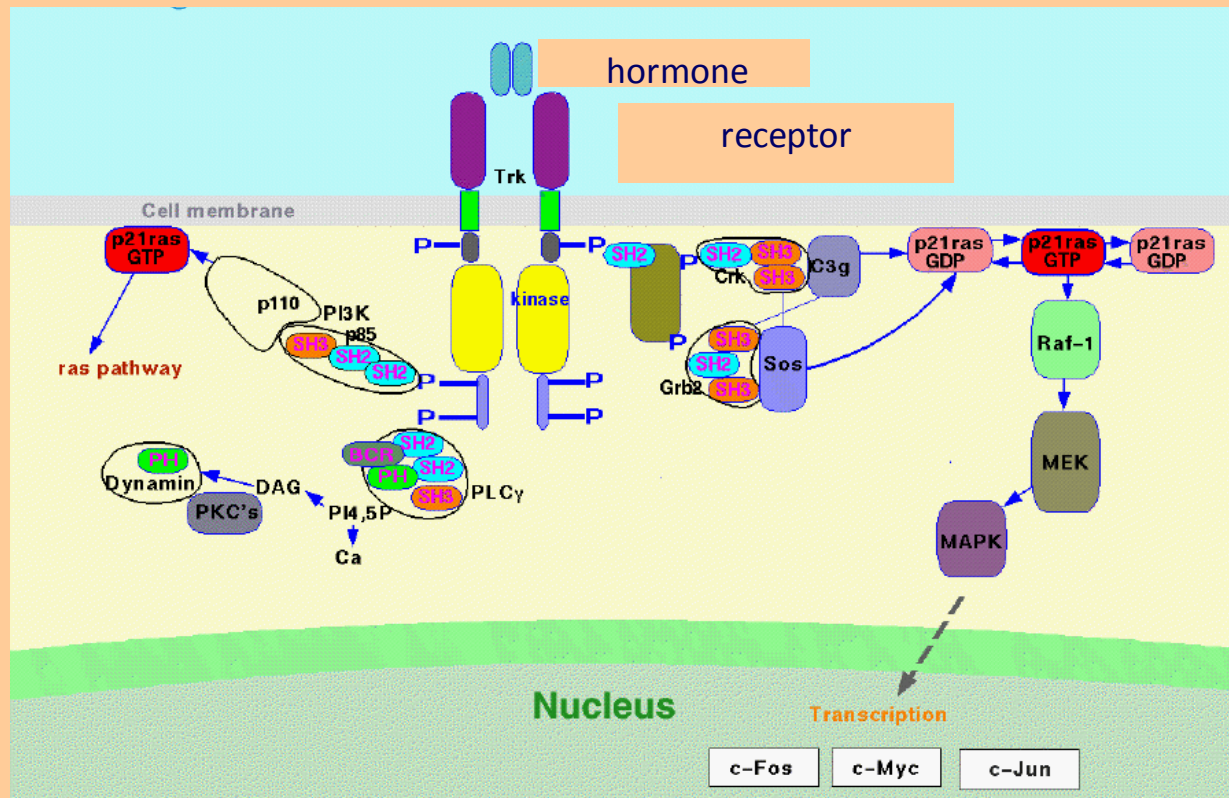


# Hormones: endocrine messengers

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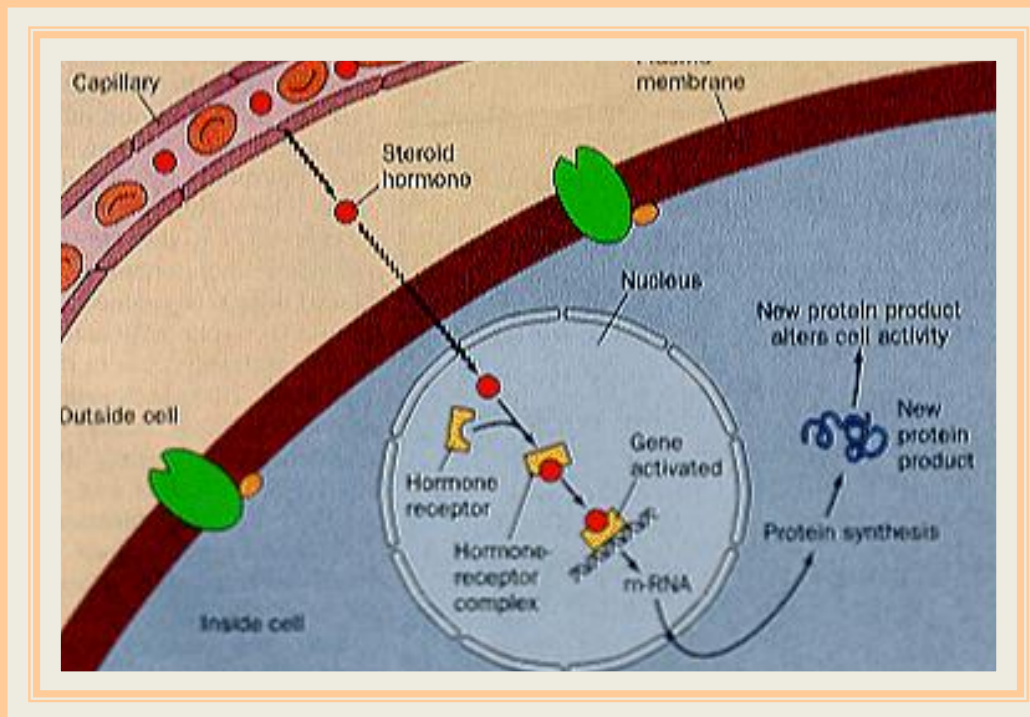
- Hormones travel in the bloodstream and thus reaching all the cells of the body.
- Hormones act exclusively upon their target cells.
- Target cells contain receptors that specifically recognize a particular hormone.

# Membrane receptor



# Intracellular (nuclear) hormone receptors

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The interactions between hormone receptor and DNA involve a network of cofactors.

# Endocrine System Functions

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- To maintain the constancy of the extracellular fluids (homeostasis).
- To regulate the nutrient supply to all cells of the body.
- To regulate development, growth and reproduction.

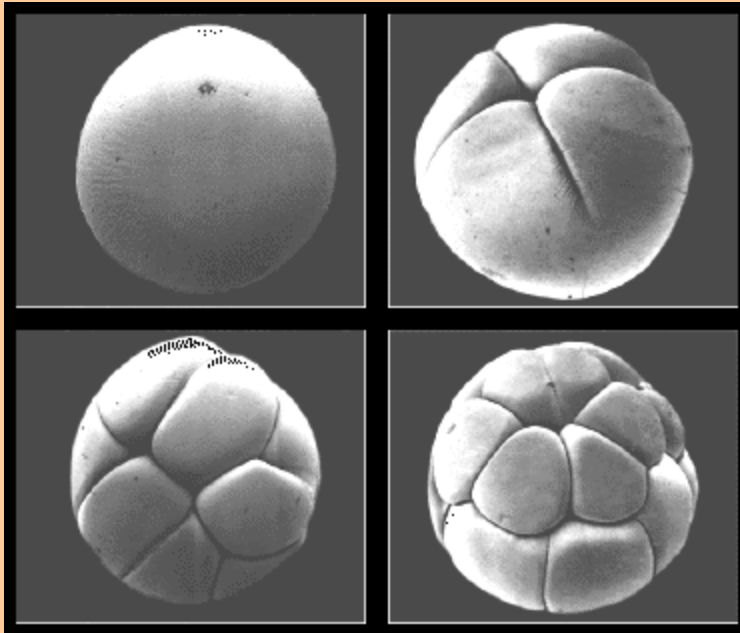


# Endocrine System Functions

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- **Organizational effects** are for the most part irreversible: for example, effect of thyroid hormone on fetal and newborn brain development.
- **Activational effects** are reversible upon removal of ligand/hormone: for example, the lining of the uterus thickens after exposure to estrogens and atrophies when estrogens are removed.

# The fragile fetus





# Congenital thyroid deficit

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Decreased levels of thyroid hormone

Mental retardation  
Increased fat production

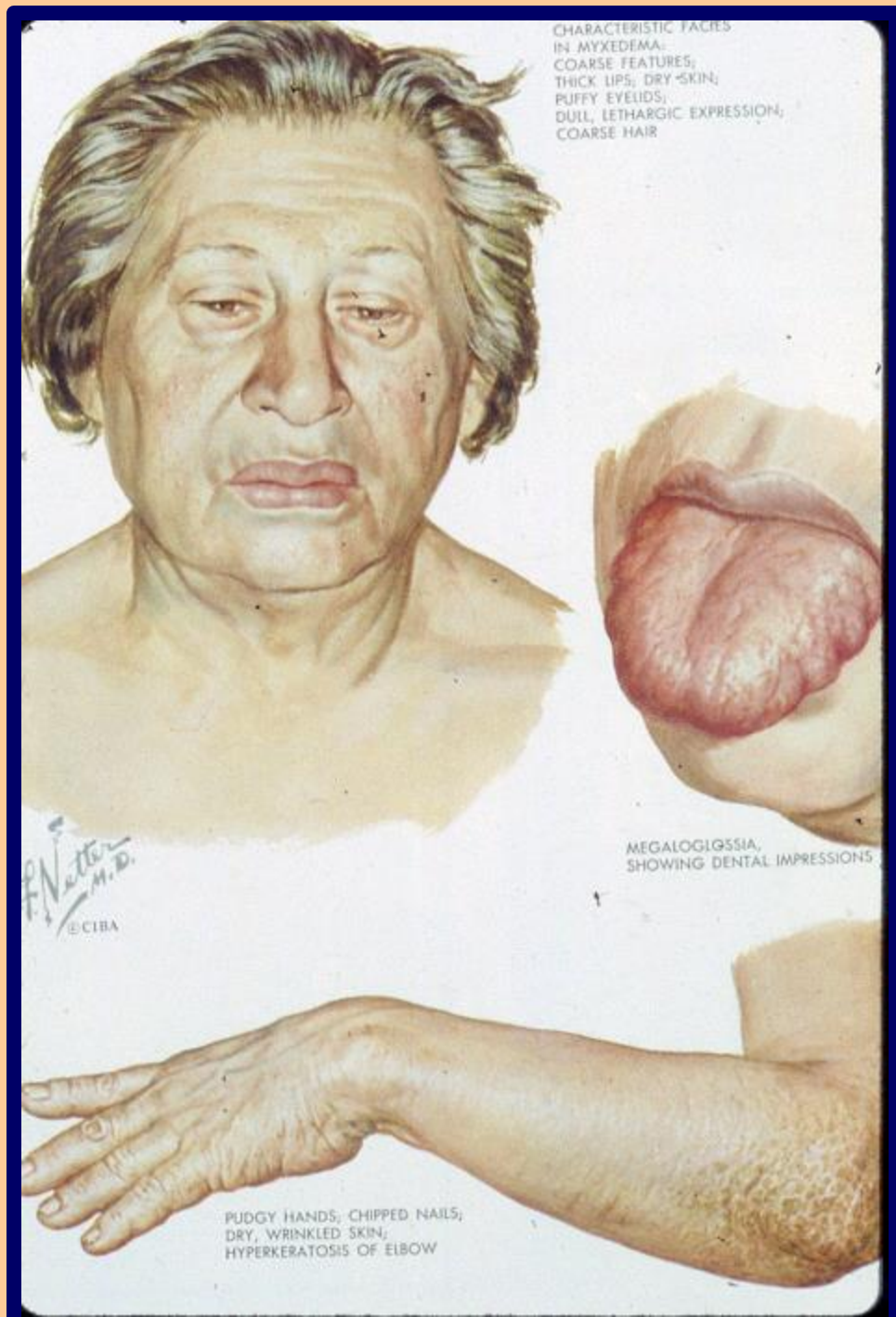
Can be corrected by thyroid treatment early in life



Age- 22 years  
Height –105 cm

# Myxedema (hypothyroidism)

Low levels of thyroid hormone



# Endocrine Disruptors

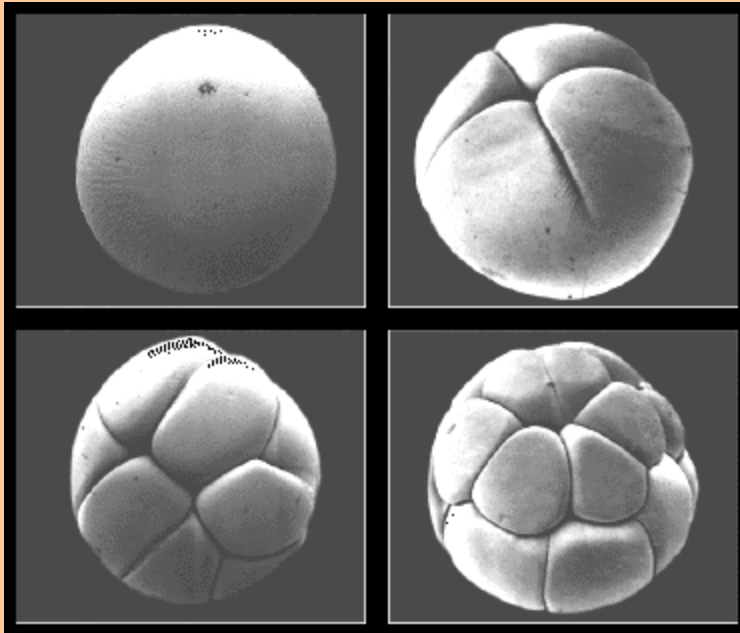
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Endocrine Disruptors are exogenous chemicals, or mixture of chemicals, that interfere with any aspect of hormone action.

Zoeller et al, Endocrinology, 153: June 25, 2012




# The fragile fetus





# Diethylstilbestrol (DES): a synthetic estrogen

Medscape® www.medscape.com



*"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 patients\*—  
— bigger and stronger babies, too."<sup>1</sup>

No gastric or other side effects with **desPLEX**  
— in either high or low dosage<sup>2,4,5</sup>

Source: J Midwifery Womens Health © 2003 Elsevier Science, Inc.

DES was given to millions of pregnant women in the US between the years of 1948 and 1971 with the purpose of preventing miscarriage.

DES treatment was banned in 1971 in the US when it was found to cause clear cell carcinoma of the vagina in young women exposed during fetal development.



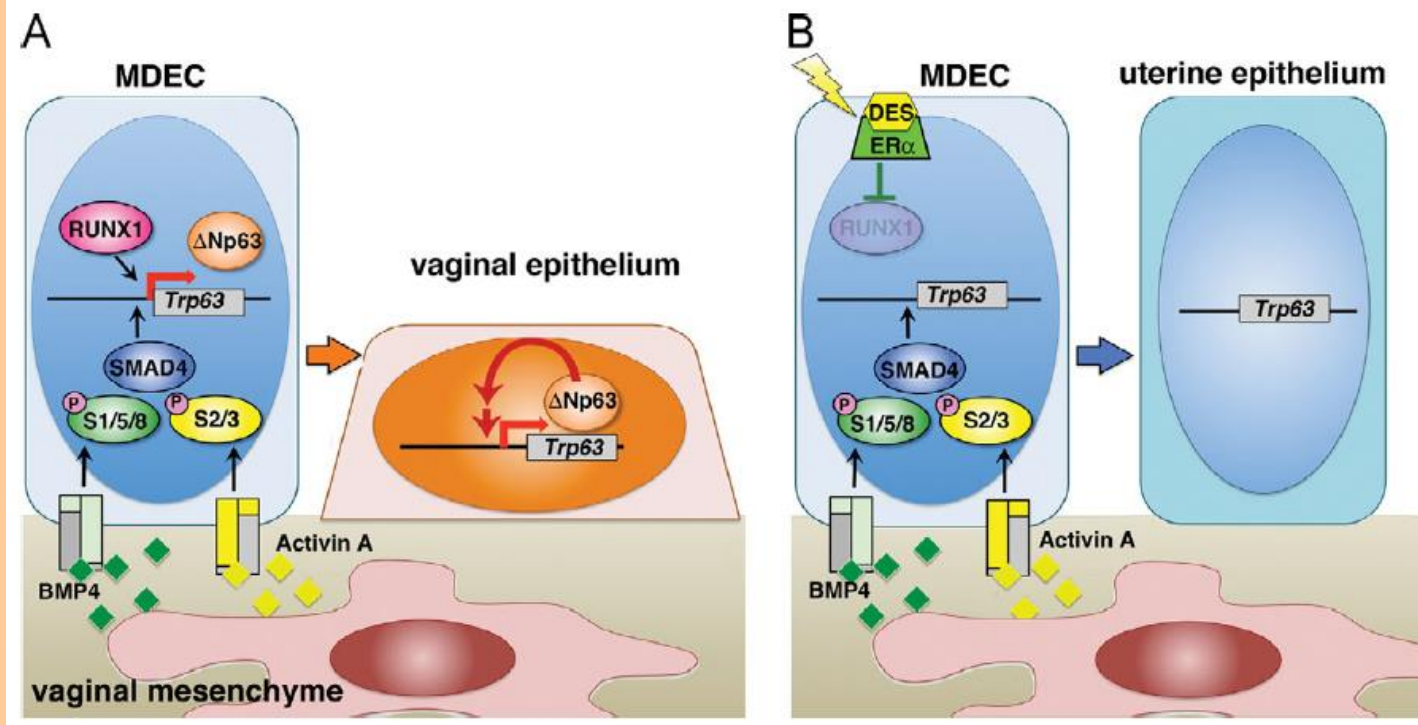
# Fetal xenoestrogen syndrome

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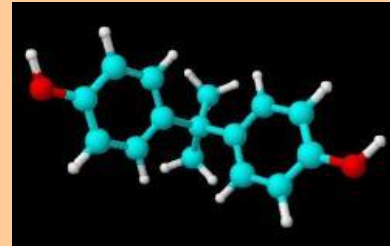
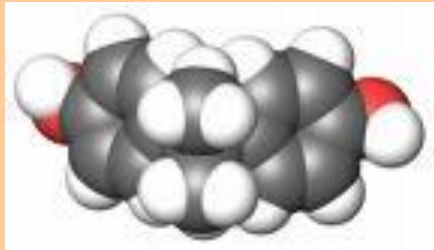
- This syndrome was observed in humans exposed during fetal development to the synthetic estrogen diethylstilbestrol (DES).
- DES was given to their mothers because it was (erroneously) believed to prevent miscarriage.
- Women exposed before the 13<sup>th</sup> week of gestation developed clear cell carcinoma of the vagina (1/1000), a cancer that manifested after puberty/during early adulthood.
- Additional anomalies: malformations of the oviduct and uterus, decreased reproductive success.
- Increased risk of breast cancer at the age of prevalence

# DES, vaginal adenosis and clear cell carcinoma: down-regulation of RUNX 1 by DES

M.M. Laronda et al. / *Developmental Biology* 381 (2013) 5–16



**Fig. 7.** Models: Epithelial cell fate decision in developing vagina. (A) Normal development. Mesenchymal BMP4 and ActA instruct undifferentiated MDECs to become vaginal epithelium by activating transcription of  $\Delta$ Np63 locus via SMAD/RUNX1-dependent mechanism. The BMP4/ActA action presumably induces chromatin remodeling to make the  $\Delta$ Np63 locus accessible to transcriptional machineries. The transcriptional activity of  $\Delta$ Np63 locus is then maintained/stabilized by a BMP/Actin-SMAD/RUNX-independent,  $\Delta$ Np63-dependent mechanism (red arrow). (B) DES-associated vaginal adenosis. DES/ER $\alpha$  (Kurita et al., 2004) downregulates RUNX1, and inhibits activation of  $\Delta$ Np63 locus and subsequent vaginal epithelial program. The  $\Delta$ Np63-negative MDECs differentiate into columnar uterine epithelium within the vagina, forming vaginal adenosis.



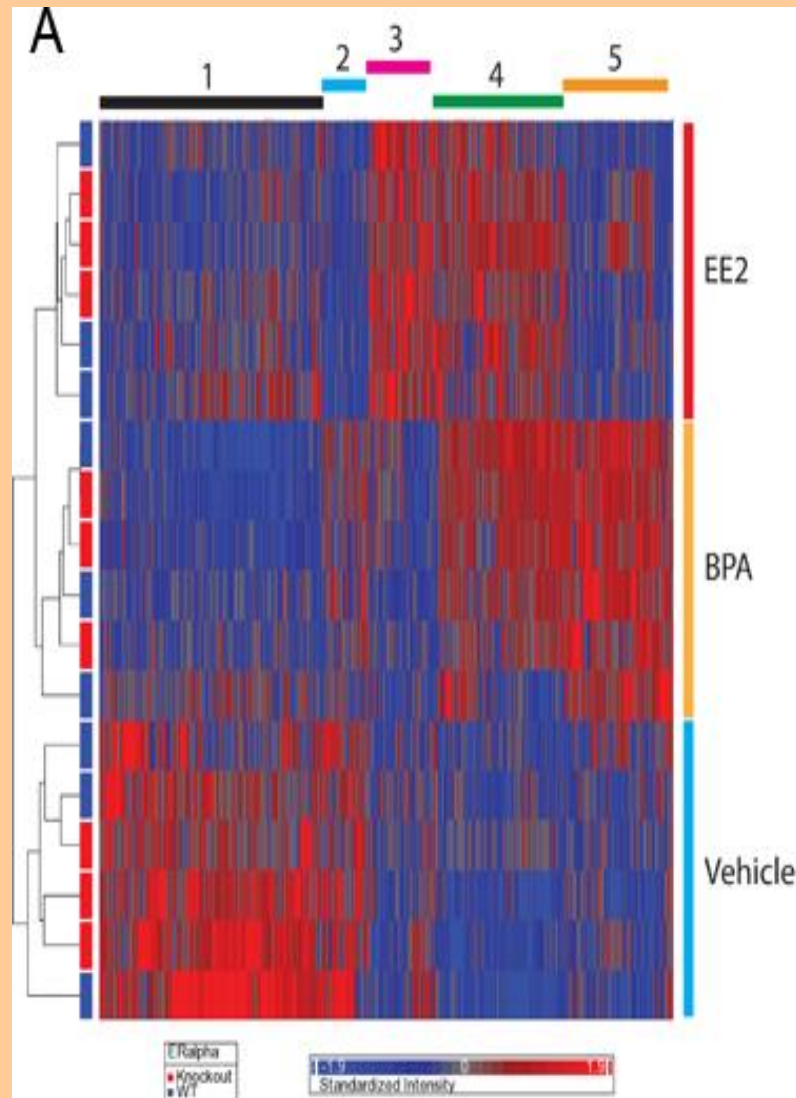
Bisphenol-A (BPA) is the building block of polycarbonate plastic, a component of other plastics and epoxy resins and as such is prevalent in our daily lives.

BPA is one of the highest volume chemicals produced worldwide. Over 8 billion pounds produced annually; 100 tons released into the atmosphere/year.

# REPORTED EFFECTS OF FETAL/NEONATAL EXPOSURE TO “SAFE” LEVELS OF BPA INCLUDE:

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- Early puberty (menarchy)
- Prostate changes
- Altered mammary gland development
- Changes in the uterus and ovary
- Decreased fecundity/fertility
- Changes in brain steroid receptor levels
- Changes in behavior (hyperactivity, increased aggressiveness, altered sexual behavior, increased susceptibility to drugs of addiction).
- Predisposition to cancer
- Obesity

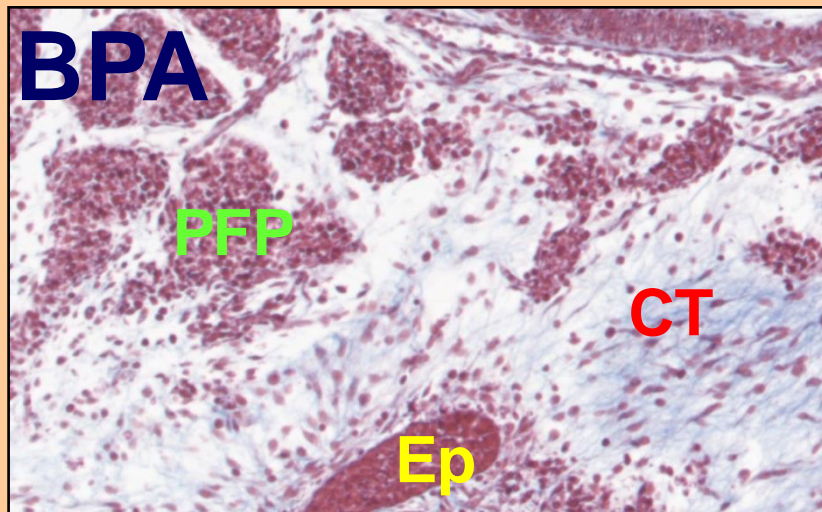
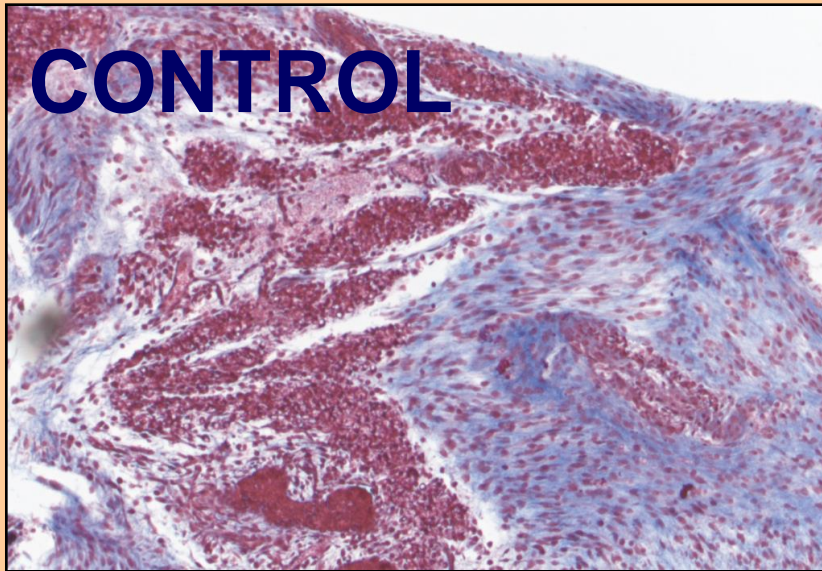


Heat Map: Clustering analysis of E19 mammary gland stroma.

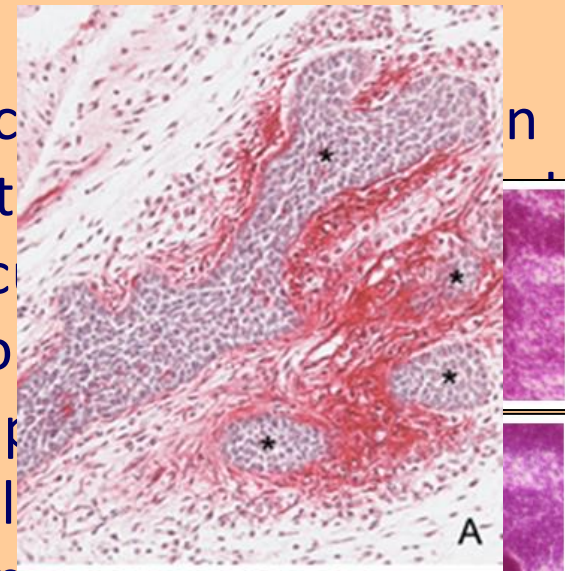
Stroma and Epithelium were separated by LCM. On the left axis, Red (KO animals) blue (WT)



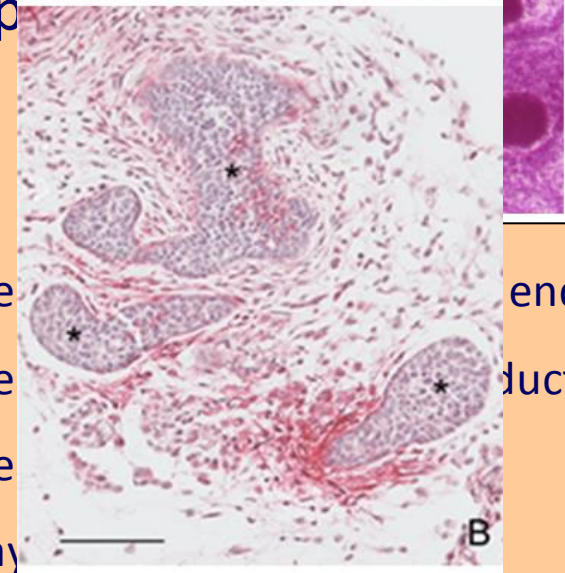
# Exposure to 250 ng BPA/kg BW/day alters overall organization of the fetal MG



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Delay



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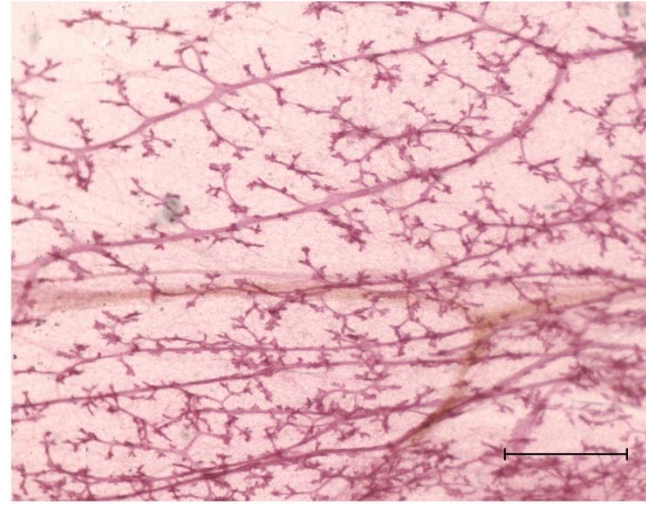
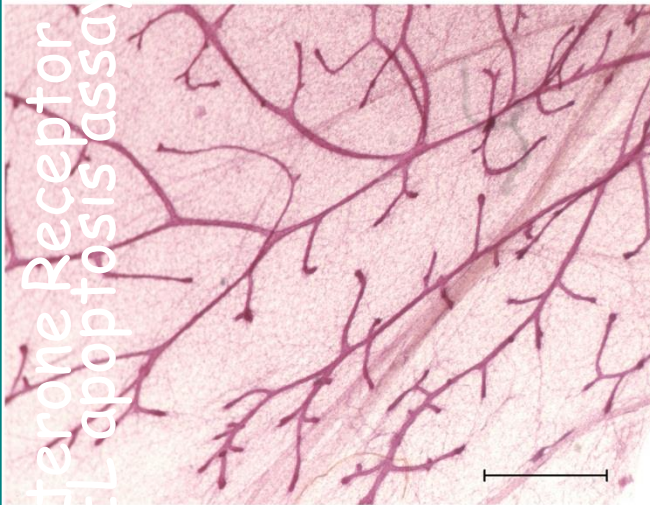


# Mammary gland development:

4 months

wholemout

Progesterone Receptor  
TUNEL apoptosis assay

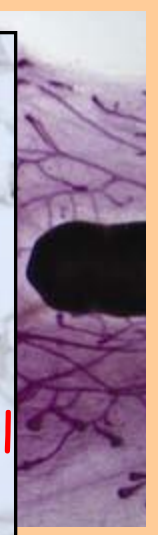


branching

Control

BPA

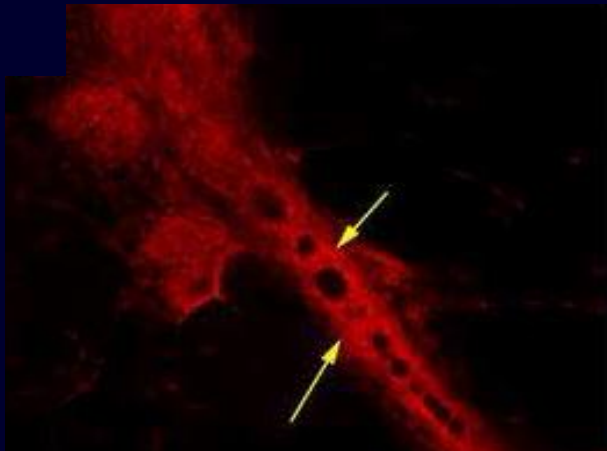
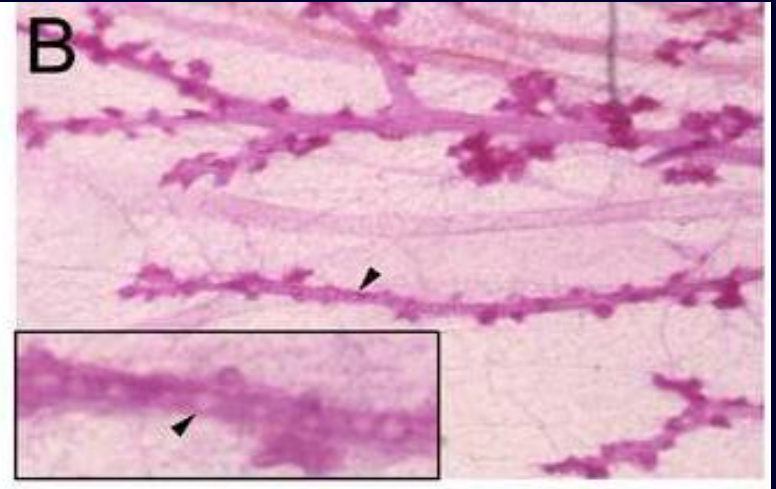
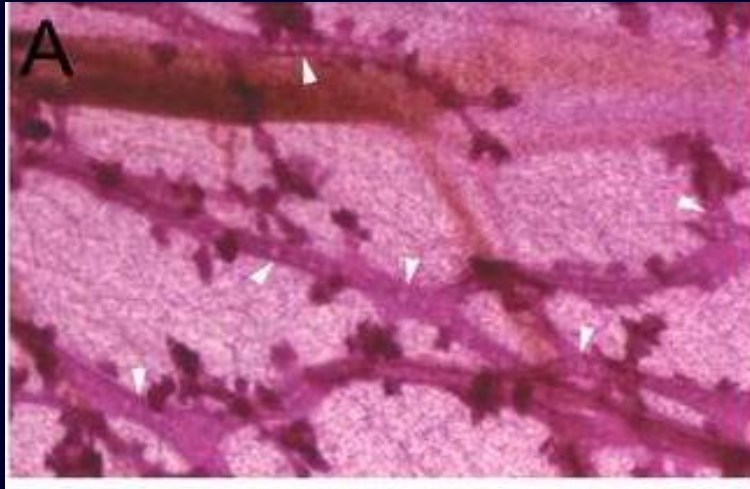
Control branching BPA



250 ng/kg BPA

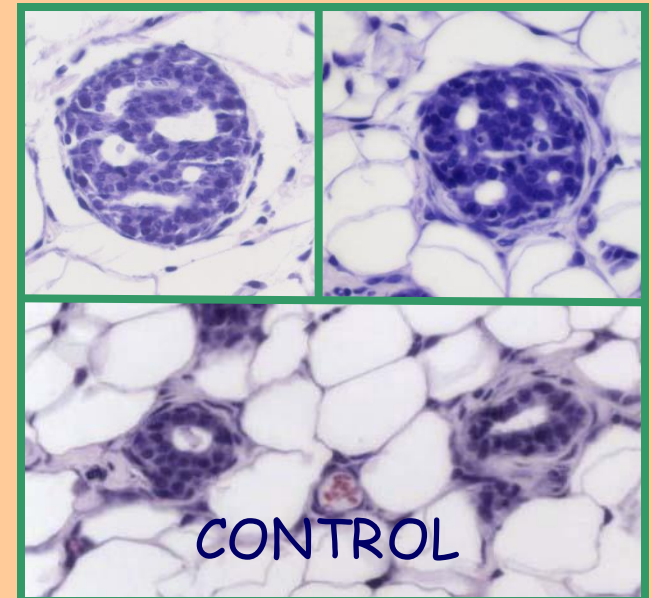
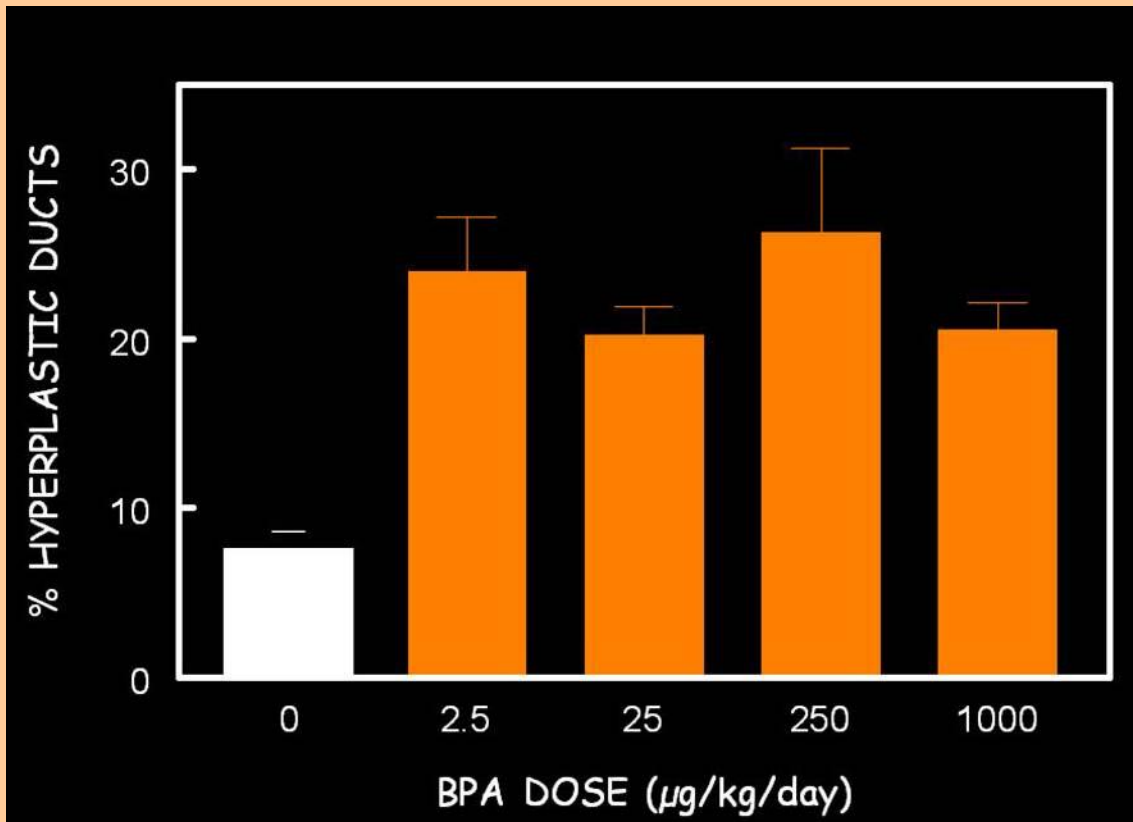
# "Beaded" ducts: intraductal hyperplasias

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# BPA induces ductal hyperplastic lesions and CIS in WF rats

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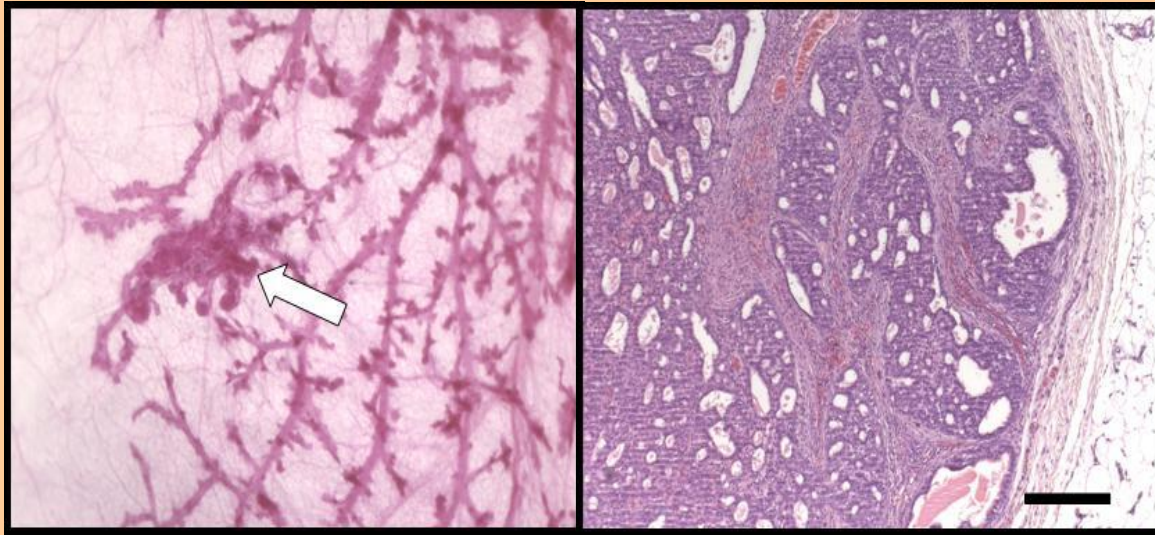
Unconjugated serum BPA was detected only in the 250 µg/kg dose:  $1.68 \pm 0.74$  ng/ml

# BPA increased the incidence of palpable mammary tumors in SD rats

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whole mount

H&E section





# Science and applied science

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- **Basic science (science for its own sake):** Living with uncertainty; there is always a new experiment to be done, a *t* to cross, an *i* to dot...100years from Galileo to Newton...time *is not* of the essence.
- **Medical Practice:** Time *is* of the essence, physicians have to reach conclusions and act *now* to prevent/cure/or save a life.
- **Medical epidemiology:** When testing a pharmacological agent the *null hypothesis* is chosen (no effect expected). Best to err on the side of a false-negative.
- **Public health epidemiology:** When studying exposures to potentially harmful agents choosing the *alternative hypothesis* (a deleterious effect expected) is a sound practice. Best to err on the side of a false-positive.

# Grant support

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- NIEHS-ES08314: Mechanisms of developmental toxicity of bisphenol A
- NIEHS-ES012301: Prenatal xenoestrogen exposure and mammary cancer
- NIEHS-ES015182 : Perinatal xenoestrogen exposure: epigenesis and neoplasia
- NIEHS-RC2ES018822: Does breast cancer start in the womb? BPA, mammatogenesis and neoplasia



