

# HEALTH EFFECTS OF PERINATAL EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS:

## STATE OF THE SCIENCE

Nicole Acevedo, Ph.D.

Tufts University School of Medicine, Boston, MA

Collaborative on Health and the Environment (CHE)-Alaska

December 10, 2014

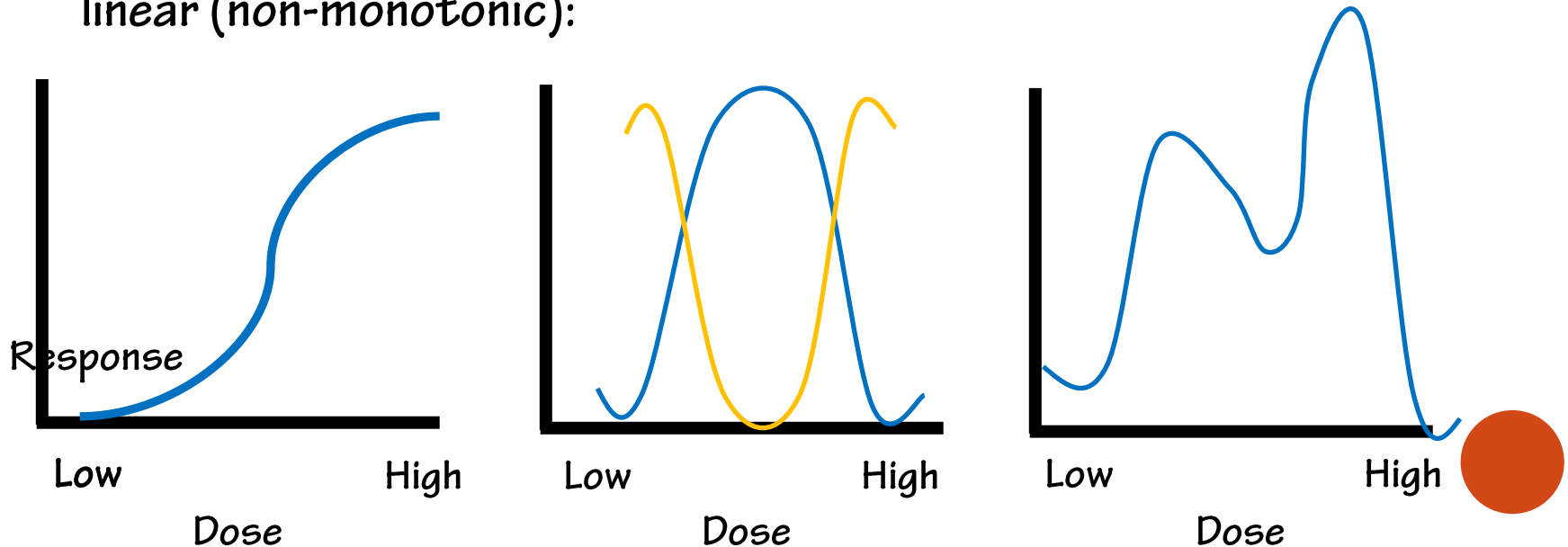
# THE ENDOCRINE SYSTEM

- Endocrine glands secrete molecules (hormones) directly into bloodstream to produce effects on distant target cells/tissues.
- Major hormone organs/systems include:
  - Hypothalamus
  - Pituitary
  - Stomach
  - Pancreas
  - Adipose Tissue
  - Adrenals
  - Cardiovascular
  - Thyroid/Parathyroid
  - Liver
  - Stomach
  - Mammary gland
  - Ovary/Uterus (female)
  - Testis/Prostate (male)
  - Placenta (female)

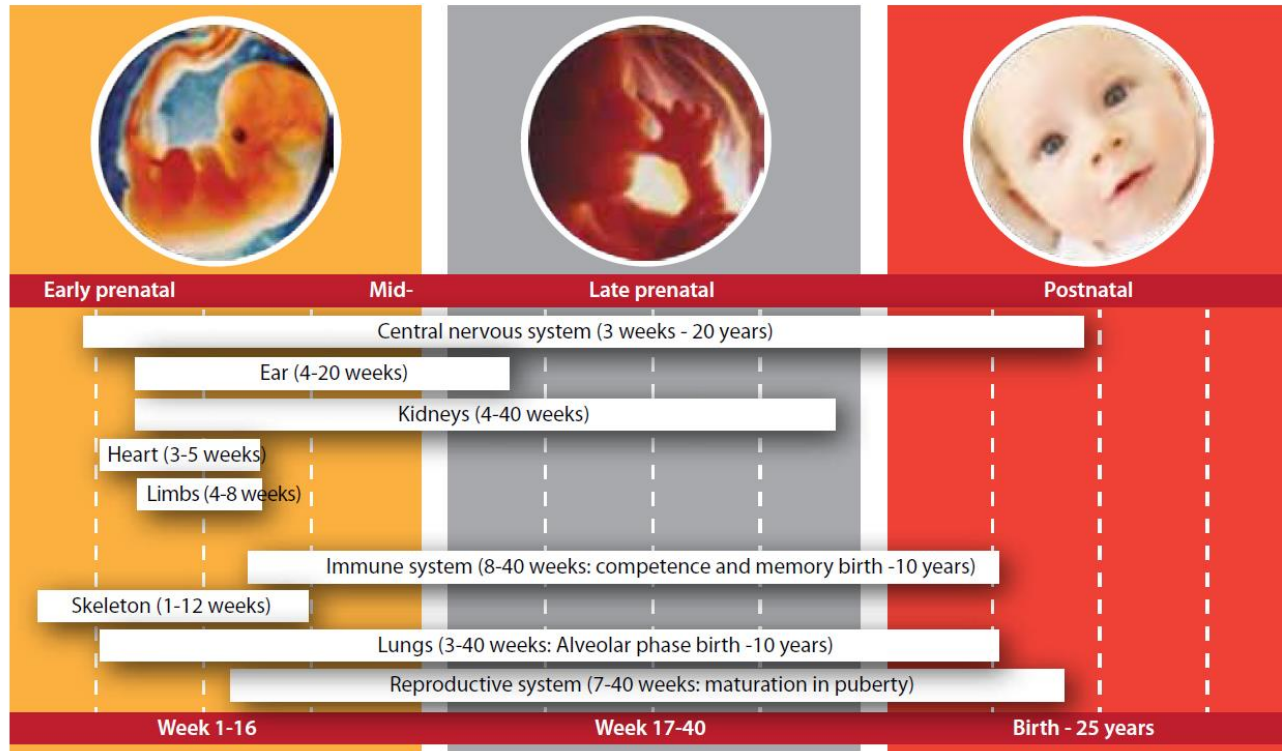


# HORMONE ACTION ON TARGET TISSUES

- Hormones exert effects via binding to high affinity receptors in target tissues.
- In adults, hormones have *transient* effects on target tissues.
- Low concentrations sufficient to initiate large biological effects.
- Dose-responses to naturally circulating hormones are non-linear (non-monotonic):



# CRITICAL WINDOWS OF HUMAN DEVELOPMENT



(WHO-UNEP State of the Science of Endocrine Disrupting Chemical (2013))

- **Hormone actions during development program postnatal function of target tissues.**
  - Estrogen/androgen and reproductive axis
  - Thyroid hormone and brain development
- **Impairment of proper hormone action during development can lead to irreversible health outcomes later in life.**



# LESSONS ON DEVELOPMENTAL EXPOSURE TO SYNTHETIC HORMONES: THE DES STORY



Yes...

**desPLEX**<sup>®</sup>

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<sup>4</sup>—  
— bigger and stronger babies, too.<sup>4, 5</sup>

No gastric or other side effects with **desPLEX**  
— in either high or low dosage<sup>3, 4, 5</sup>

(Each **desPLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicrotonized to smooth and accelerate absorption and activity. A portion of this ultramicrotonized 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. Canario, E. M., et al.: *Am. J. Obst. & Gynec.* 65:1298, 1953.
2. Gilman, L., and Koplowitz, A.: *N. Y. St. J. Med.* 50:2823, 1950.
3. Karnaky, K. J.: *South. M. J.* 45:1166, 1952.
4. Peña, E. F.: *Med. Times* 82:931, 1954; *Am. J. Surg.* 87:95, 1954.
5. Ross, J. W.: *J. Nat. M. A.* 43:20, 1951; 45:223, 1953.

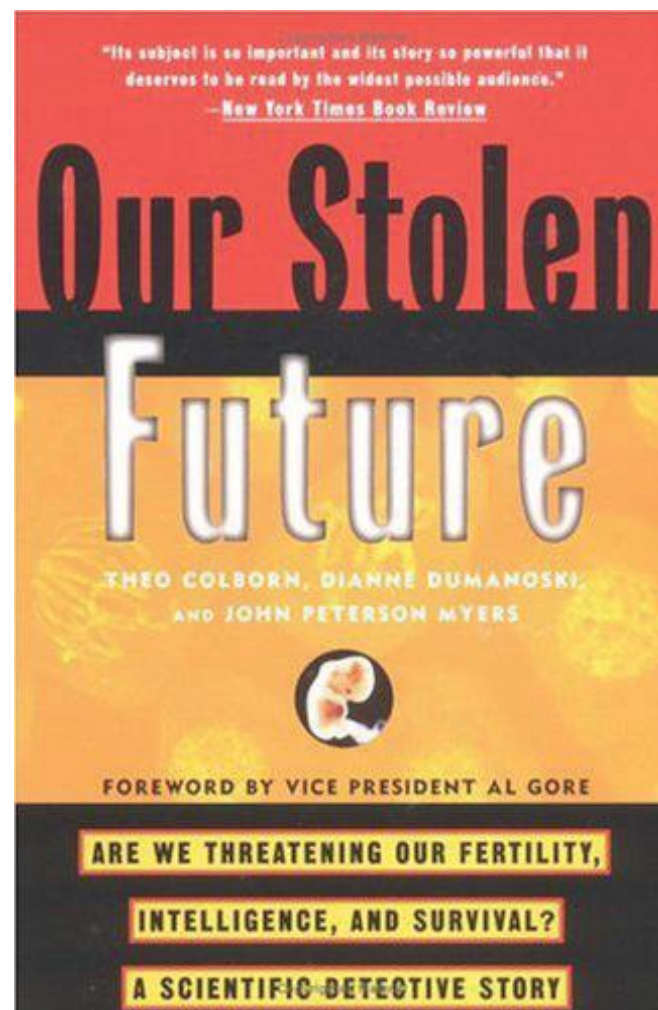
GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

- DES (diethylstilbestrol): synthetic estrogen prescribed worldwide between 1940-1971.
- Young women exposed *in utero* to DES have been diagnosed with reproductive tract malformations, infertility, and rare vaginal cancers.
- Recent studies show that as these exposed women reach the age where breast cancer is likely to manifest ( $\geq 40$  years of age), they experience a 2.5-fold greater risk of developing cancer compared to age-matched women not exposed fetally to DES.



# WHAT ARE ENDOCRINE DISRUPTING CHEMICALS (EDCs)?

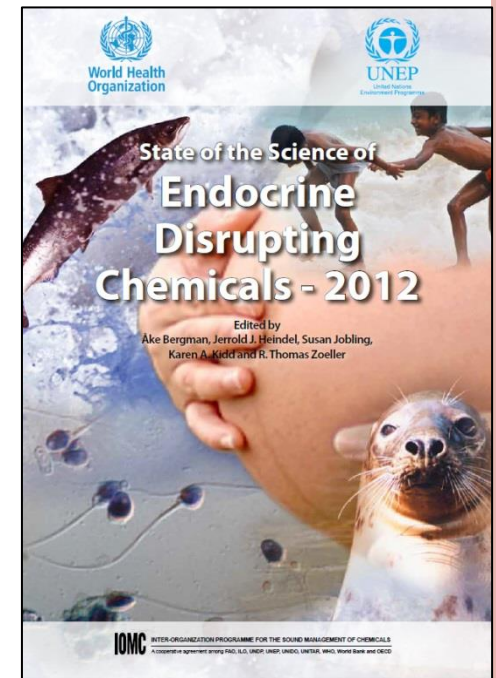
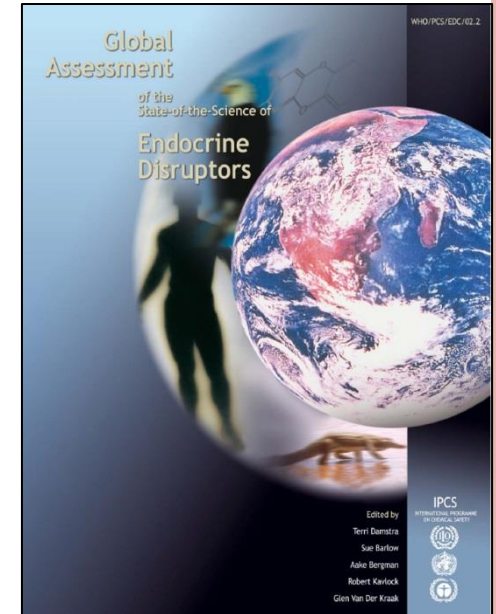
- (1991) Wingspread Conference convened to review evidence for endocrine disruption in developing organisms via exposure to synthetic chemicals introduced into the environment by human activity since the mid-1950s.
  - Hypothesis: fetal exposure to hormonally-active chemicals may be contributing to increasing epidemiological trends in altered metabolism, reproduction, behavior, immune, cardiopulmonary, and brain function, as well as in rates of cancer.
- (1996) Executive order for the US EPA to develop the Endocrine Disruptor Screening Program (EDSP):
  - Test chemical substances for ability to produce effects similar to those produced by estrogen, androgen and thyroid systems.






# WHAT ARE ENDOCRINE DISRUPTING CHEMICALS (EDCs)?

- (2002): World Health Organization (WHO)-International Programme on Chemical Safety :
  - Defined an endocrine disruptor as *“an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.”*
  - Determined need for “broad, collaborative, and international research initiatives” to provide evidence for adverse human health effects following exposure to chemicals that can affect the endocrine system.
- (2012): State of the Science of EDCs published by the WHO-United Nations Environment Programme.

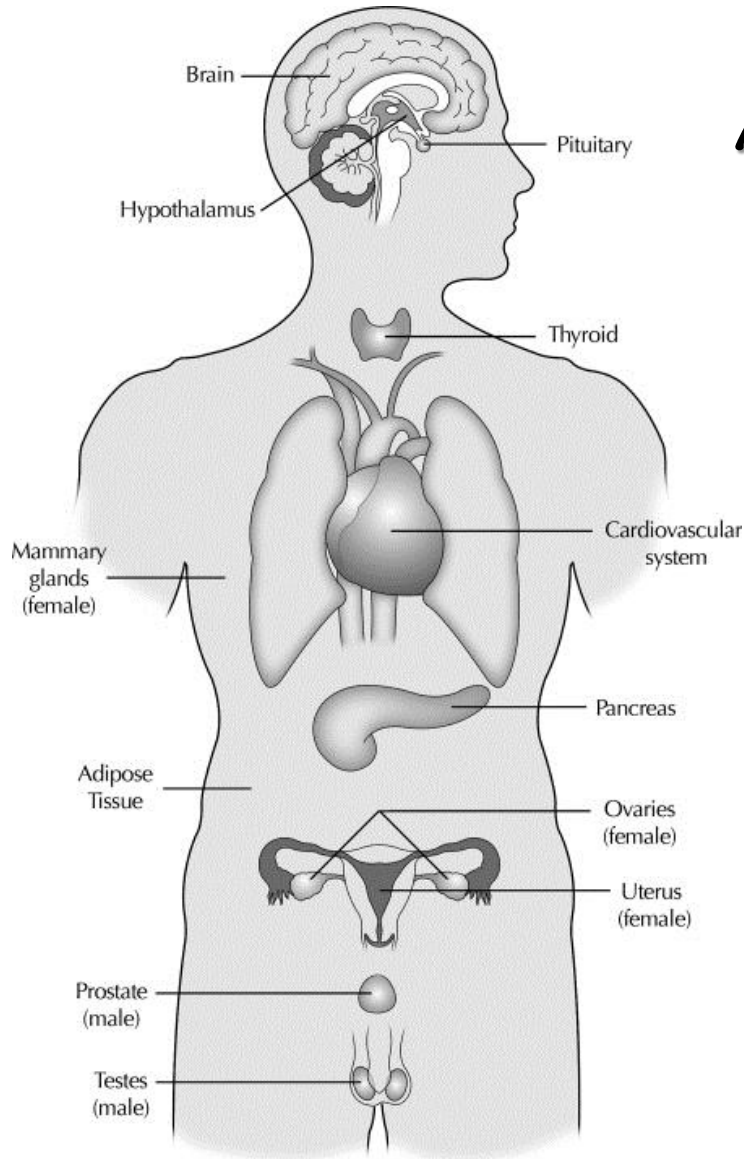


# CATEGORIES OF SOME KNOWN ENDOCRINE DISRUPTORS

- **Pharmaceutical estrogens:** diethylstilbestrol (DES).
  - **Phytoestrogens:** plant-derived estrogens: genistein
  - **Persistent Organic Pollutants (POPs):** by-products of burning process, chlorine bleaching, or manufacture of pesticides/herbicides or industrial chemicals.
    - Dioxins: classified human carcinogen.
    - Polychlorinated biphenyls (PCBs): U.S. production banned in 1977.
    - Pesticides/Herbicides/Fungicides: i.e. DDT/DDE, atrazine, vinclozolin.
    - Organotins: Tributyltin (TBT)
    - Polybrominated diphenyl ethers (PBDEs): flame-retardant chemicals; used in many consumer products.
    - Perchlorate: additive for many industrial products; rocket fuel.
    - Perfluorinated chemicals (PFCs): non-stick cookware; completely resistant to biodegradation!
  - **Plasticizers:** polyvinyl chloride (PVC) and polycarbonate plastics used for many consumer and medical device products.
    - Phthalates
    - Bisphenol A (BPA)
  - **Heavy Metals:**
    - lead, cadmium, mercury, arsenic
- 



# SENSITIVITY OF ENDOCRINE TISSUES TO EDCs



## Areas of potential disruption:

- Hormone synthesis.
- Receptor function (affinity vs potency).
  - Simultaneous interaction with multiple hormone receptors.
- Interference with developmental programming of tissues/organs.
  - Prenatal exposure may alter response of a tissue to hormone exposures in adulthood.
- Epigenetic processes that produce heritable transgenerational effects.
- Effects of mixtures with endogenous hormones and/or other EDCs.



# EDCS AND REPRODUCTIVE HEALTH

Documented endocrine disruption in human, primate, or rodent models

## Female

- Onset of puberty (dioxins)
- Altered endogenous estradiol (phytoestrogens, phthalates, chlorinated pesticides)
- Reduced fertility/fecundity (DES, TBT, phthalates, dioxins, BPA)
- Adverse pregnancy outcomes (TBT)
- Ovarian abnormalities (DES, chlorinated pesticides, phytoestrogens, BPA)
- Uterine abnormalities (DES, phytoestrogens, phthalates, dioxins, BPA)
- Endometriosis (phthalates)

## Male

- Reduced semen quality (phthalates, dioxins, PCBs)
- Altered endogenous testosterone (DES, dioxins)
- Cryptorchidism (DES, phthalates, dicarboximide fungicides)
- Hypospadias (phthalates, chlorinated pesticides, dicarboximide fungicides)
- Reduced anogenital distance (phthalates, chlorinated pesticides, dioxins, PCBs, dicarboximide fungicides)
- Altered sexual behavior (PCBs)
- Erectile dysfunction (BPA, phytoestrogens)
- Accessory sex organ abnormalities (dicarboximide fungicides)



# IMPLICATIONS OF EDCs ON OTHER DEVELOPMENTAL ENDPOINTS

## Impaired Neurodevelopment

- General cognitive deficits (PCBs, PBDEs, perchlorate)
  - Thyroid hormone insufficiency (PCBs)
- Attention deficit disorders (PCBs, BPA, PBDEs, phthalates)
- Altered organization of sexually dimorphic regions in the brain (BPA, phthalates)

## Metabolic Dysregulation

- Obesity (TBT, phytoestrogens, PFCs, PBDEs, BPA, PCBs, DES)
- Type 2 diabetes (PCBs, DDE, dioxin, pesticides, arsenic, flame-retardants)

## Impaired Immune Function

- Allergies (triclosan)
- Endometriosis (phthalates, possibly PCBs and dioxins)
- Auto-immune thyroid disease (PCBs)
- Asthma (phthalates)
- Inflammation (BPA)



# EDCs AND HORMONE-RELATED CANCERS

- **Breast Cancer:** DES, BPA
- **Endometrial Cancer:** DES
- **Prostate Cancer:** pesticides, arsenic
- **Testicular Cancer:** POPs

**Major challenges regarding determination of carcinogenic potential of EDCs:**

- Human epidemiological studies cannot easily examine effects of single chemicals.
- Valid animal models are not currently available for investigation of most endocrine-mediated cancers in humans.



# MAJOR CHALLENGES REGARDING IDENTIFICATION OF EDCs AND DETERMINATION OF ADVERSE HEALTH EFFECTS

- Inherent limitations of current testing methods for identification of EDCs.
  - Process further complicated by the ideological conflict between toxicologists and endocrinologists regarding possible low-dose effects and non-monotonic responses of EDCs.
- Incomplete assessment of all windows of susceptibility and routes of exposure for known and possible EDCs.
- Very little data is available on the health impacts of chemical mixtures.
- Need for widely-accepted system to evaluate the strength of evidence of exposures to possible EDCs and adverse health outcomes.
- Lack of consistent international regulatory standards for the manufacture and regulation of chemicals leads to exponential increases in the global burden of chemicals.





# RESOURCES

- State of the Science of Endocrine Disrupting Chemicals (2002,2012): reports by the World Health Organization and the United Nations Environment Programme.  
<http://www.unep.org/chemicalsandwaste/UNEPsWork/EndocrineDisruptingChemicals/GeneralReports/tabid/130228/Default.aspx>
- The Endocrine Disruption Exchange (TEDX) website: excellent resource for up-to-date information on the state of endocrine disruptor research.  
<http://endocrinedisruption.org/>
- US EPA Endocrine Disruptor Screening Program (EDSP) homepage:  
<http://www.epa.gov/endo/>

