

# Endocrine Disruption: Background and Overview

Mary L. Hixon, PhD

Department of Pathology and Laboratory  
Medicine

Brown University

January 24, 2011

# Background and Overview

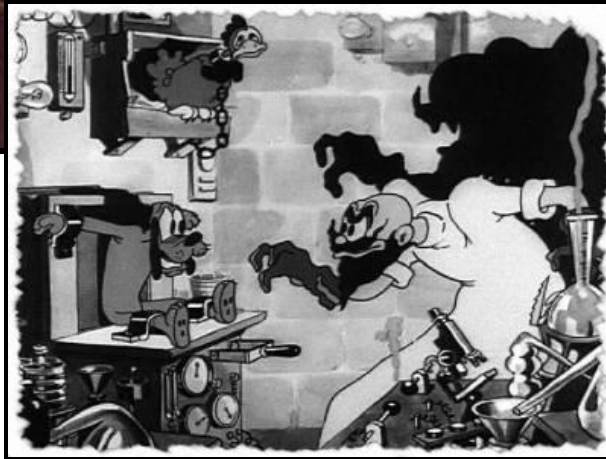
1. Basics of the endocrine system
2. What is endocrine disruption?
3. Methods of study, monitoring and evaluation  
Standards of evidence
4. Challenges/synergies presented by the presence of single versus multiple endocrine disruptors
5. Other current challenges

# Assessing risk: CNN Warns, "Don't Eat Your iPhone."



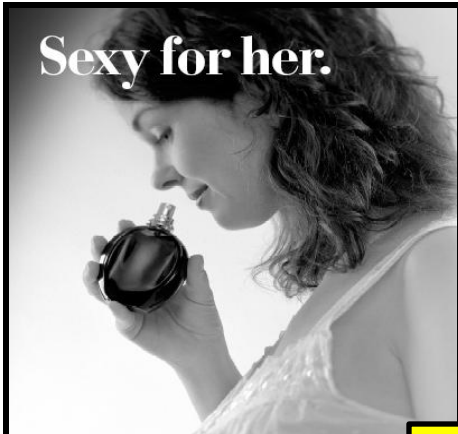
"Plastics make it possible."

## The Scientist



Sexy for her.

## The Media



For baby, it could really be poison.

## Toxic America

Toxic chemicals linked to birth defects are being found at alarming levels in women of childbearing age. And according to new laboratory tests (see chart at right), these same chemicals are being added to popular cosmetics and beauty aids, from Poison perfume to Afta Extra Extra Dry deodorant. Manufacturers use these chemicals, known as phthalates (thal-lates), to add flexibility and help dissolve other ingredients. They're also used in industrial adhesives, and in medical and consumer goods made with polyvinyl chloride plastic (PVC). But phthalates have been shown to damage the lungs, liver and kidneys, and to harm the developing testes of offspring. These results come from animal tests which, according to government scientists, are relevant to predicting health impacts in humans.

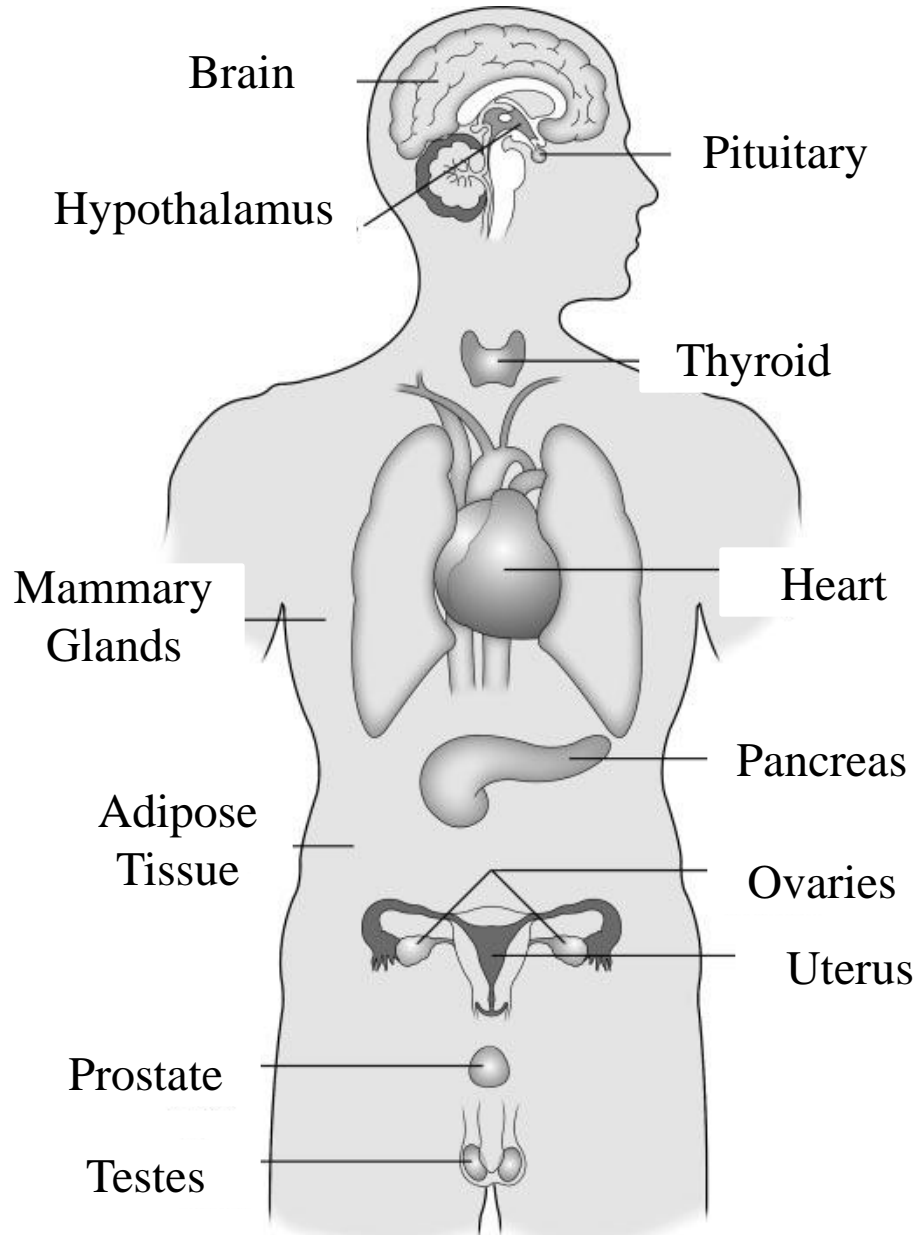
Despite this, the Food and Drug Administration doesn't regulate phthalates in cosmetics. In some cases, phthalates aren't even listed on the label. The FDA must act now. All cosmetics — as well as food-related and medical products containing phthalates — must be labeled. And manufacturers should publicly pledge to voluntarily remove phthalates as quickly as possible. Phthalate-free alternatives are available in every product category. And some companies have already announced phase-out policies. In the meantime, we believe that every consumer — indeed, anyone who cares about the health of future generations — should demand action from companies and the FDA. Learn more at [www.NoToxInYour.org](http://www.NoToxInYour.org). After all, Eternity is a long time.



# The Basics:

- Hormone
  - A molecule that functions as a message within an organism; its function is to convey information.
- Maintain Internal Homeostasis
- Support Cell Growth
- Coordinate Development
- Coordinate Reproduction
- Facilitate Responses to External Stimuli

# Major Endocrine Organs in Humans: Targets for EDCs

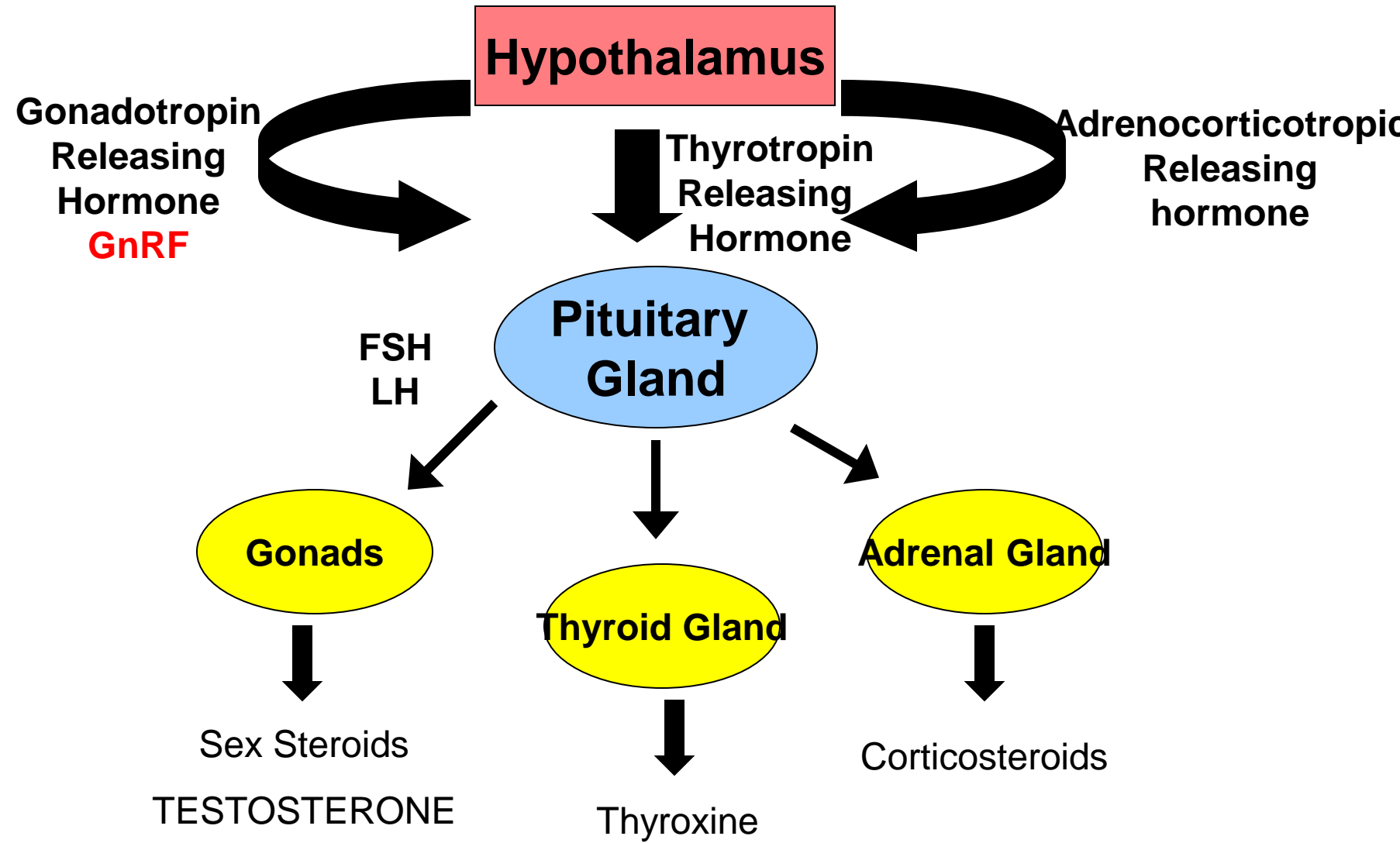


# Forms of Intercellular Communication

- **Endocrine**: secretion of a hormone by one cell with transmission via the blood, lymph, or intercellular fluid to a second, target, cell.
- **Paracrine**: secretion of a hormone by one cell with transmission via intercellular fluid to a second, nearby cell.
- **Autocrine**: secretion of a hormone by one cell with reception and response by the same cell.
- **Pheromonal**: secretion by one organism and sensation and response by a second.

# Physiology of the Reproductive System

## Hypothalamic-Pituitary-Gonadal Axis



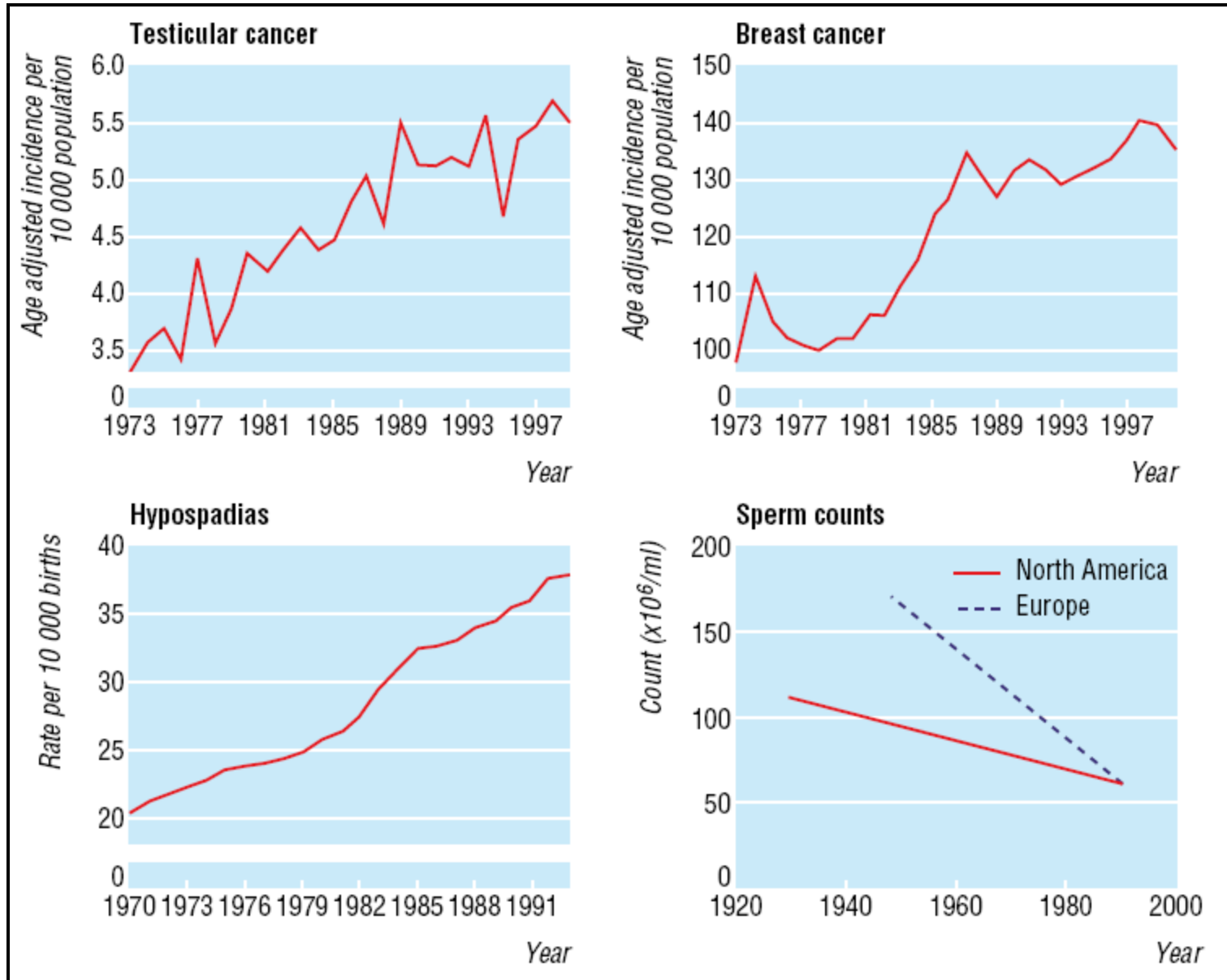
# Major Hormones Secreted by Anterior Pituitary

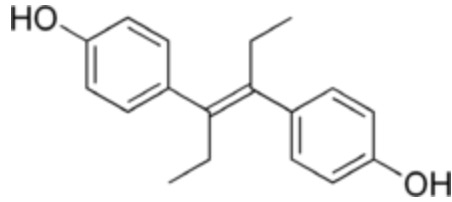
<b>Hormone</b>	<b>Target</b>	<b>Effect</b>
<b>ACTH</b>	Adrenal Gland	Secretion of Glucocorticoids
<b>FSH (Male)</b>	Testes	Growth of Reproductive System
<b>FSH (Female)</b>	Ovaries	Growth of Reproductive System
<b>GH</b>	Liver, Adipose Tissue	Lipid and Carbohydrate Metabolism
<b>LH (Male)</b>	Testes	Sex Hormone Production
<b>LH (Female)</b>	Ovaries	Sex Hormone Production
<b>Prolactin</b>	Ovaries, Mammary Glands	Secretion of Estrogen /Progesterone; lactation
<b>TSH</b>	Thyroid Gland	Thyroid Hormone Secretion

# What is Endocrine Disruption?

- History
  - Wingspread Conference
    - Evaluate the adverse effects observed in wildlife in the Great Lakes Region and other regions in the northern hemisphere. Wingspread, Racine, Wisconsin, 26–28 July 1991 .
  - The aims of the meeting were:
    - To integrate and evaluate findings from the diverse research disciplines concerning the magnitude of the problem of endocrine disruptors in the environment;
    - To identify the conclusions that can be drawn with confidence from existing data; and
    - To establish a research agenda that would clarify uncertainties remaining in the field.

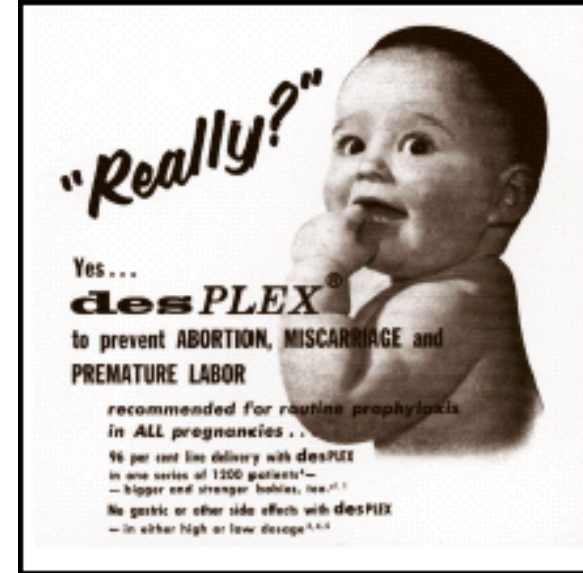
# Can exposure to EDCs explain the Trends in Reproductive Health in the US ?





# Diethylstilbestrol

- It was first prescribed by physicians to prevent miscarriages (in women who had had previous miscarriages) in the 1940s as an off-label use.
- an estimated 5-10 million persons were exposed to DES during 1941-1971
- 1950s through the beginning of the 1970s, DES was prescribed to prepubescent girls to begin puberty and thus stop growth by closing growth plates in the bones. Despite its clear link to cancer, doctors continued to recommend the hormone for "excess height."



**BISPHENOL A**

**PHYTOESTROGENS**

**PERCHLORATE**

# **Wingspread Conference Consensus Statement**

The developmental alterations that were observed in wildlife and humans were due to multiple chemicals that disrupted the endocrine system of developing organisms through different modes of action.

# The term Endocrine Disruptor was Coined

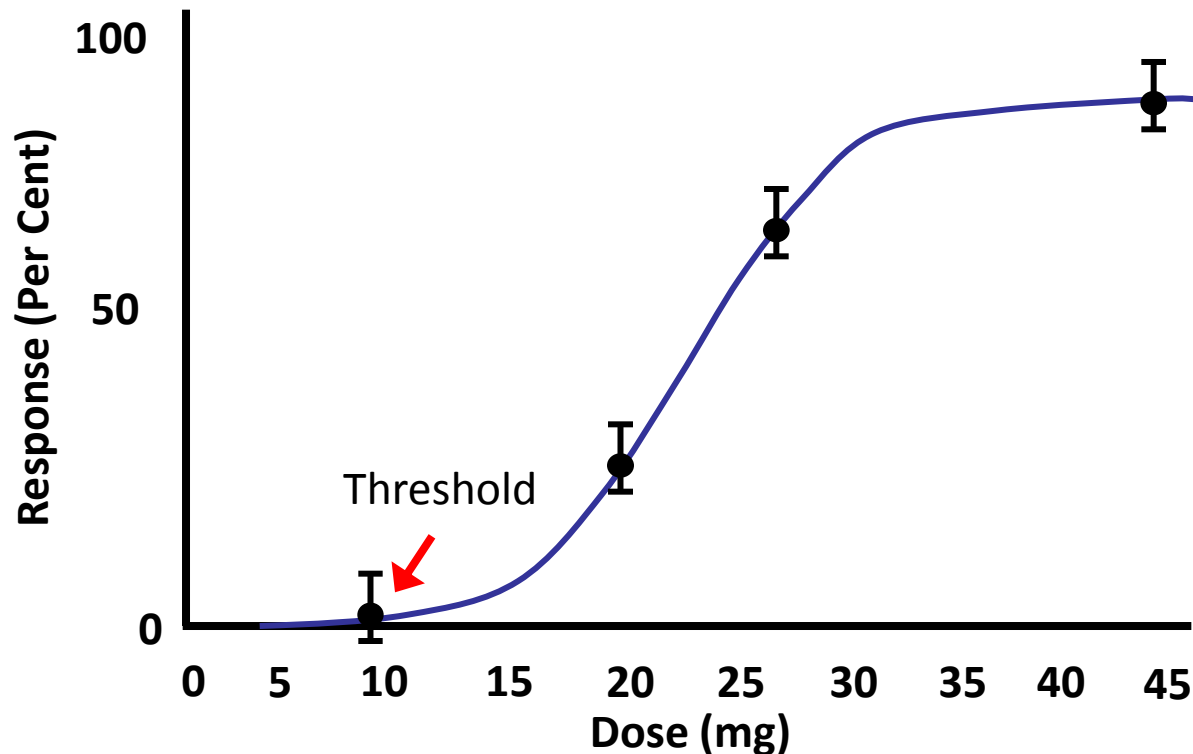
An exogenous agent which interferes with the **synthesis, secretion, transport, binding action, or elimination** of natural hormones in the body which are responsible for the maintenance of **homeostasis, reproduction, development, or behavior**.

From a physiological perspective, an endocrine-disrupting substance is a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment.

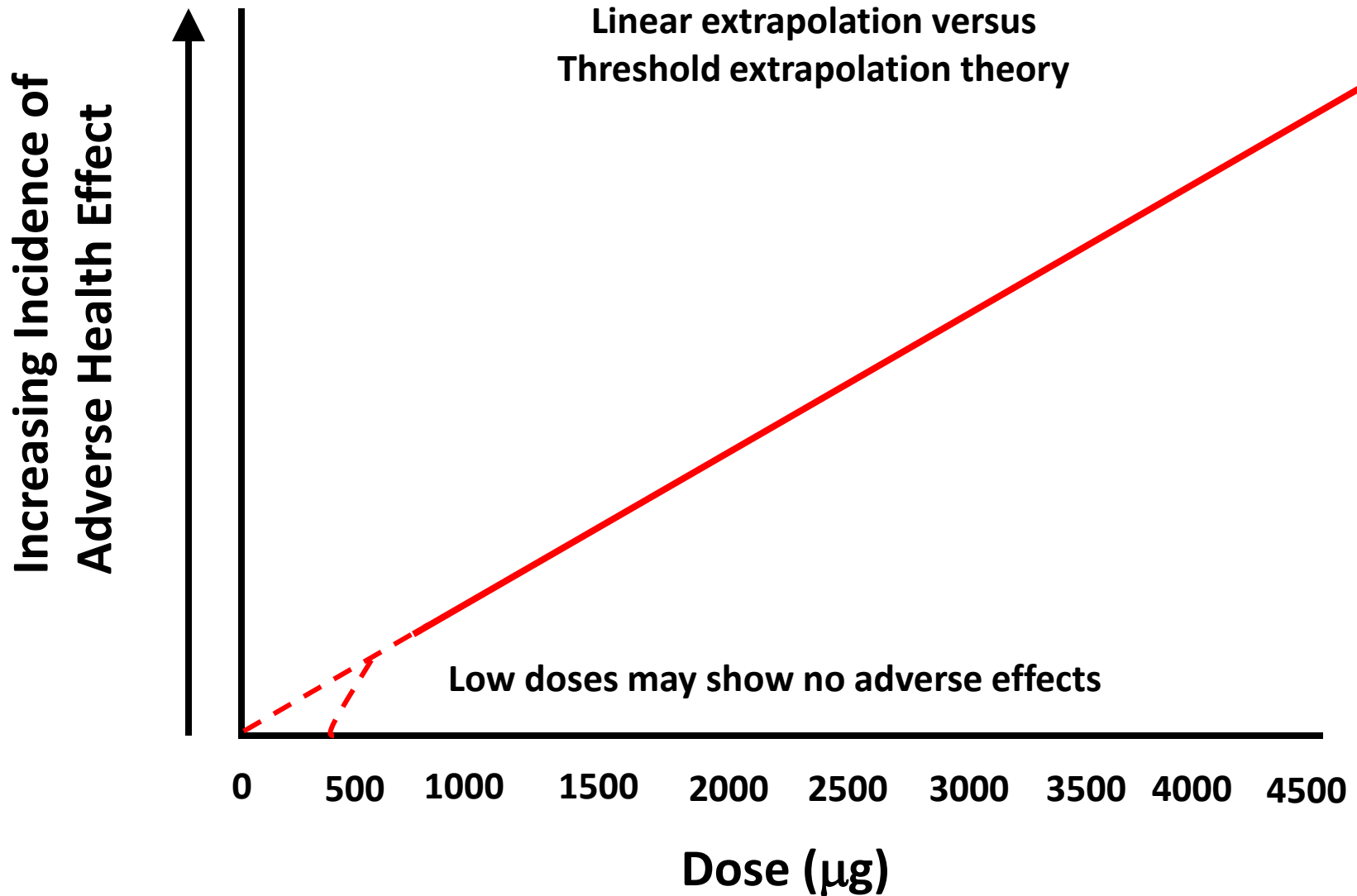
# Tox 101

# What is a sigmoidal dose response ?

- There is a threshold dose below which no one will be affected.
- There is a range of doses in which increasing numbers of individuals will be affected.
- There is a level at which everyone will be affected.

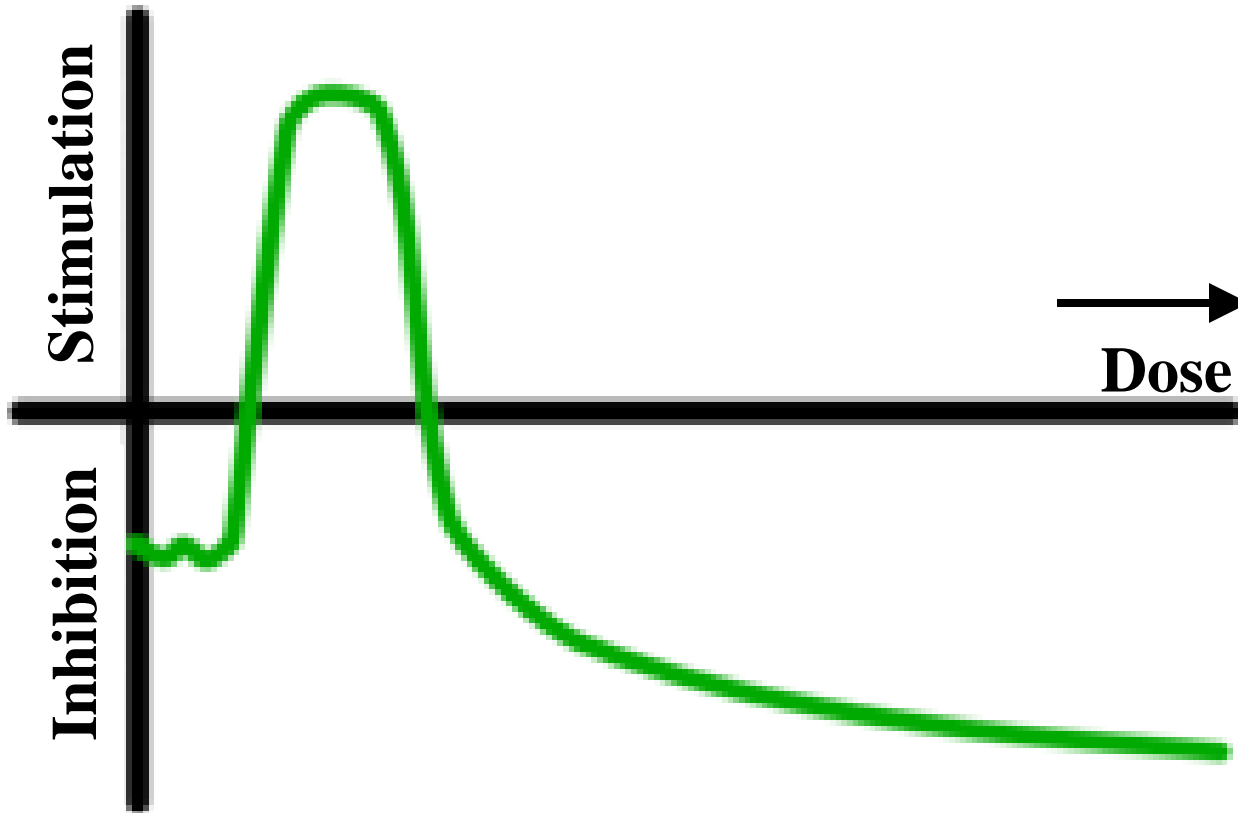


# High Dose to Low Dose Extrapolation



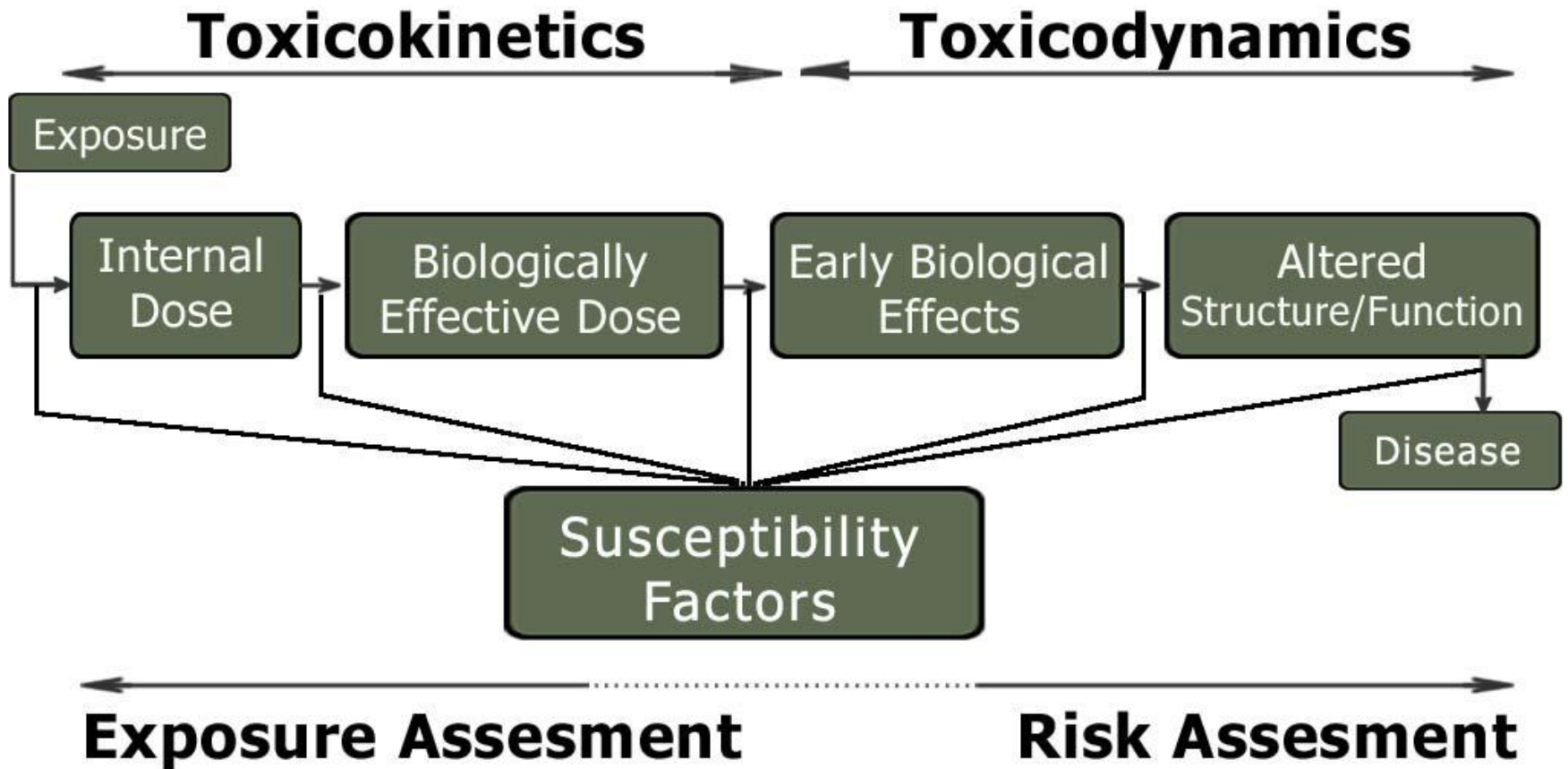
# Hormesis (to excite)

- A dose response phenomenon termed by Southam and Ehrlich in 1943.
- Low doses stimulate, high doses inhibit



The quantitation of the time course of toxicants in the body during the processes of **absorption, distribution, biotransformation, and excretion or clearance** of toxicants

The molecular, biochemical, and physiological effects of toxicants or their metabolites in biological systems. These effects are result of the interaction of the biologically effective dose of the ultimate (active) form of the toxicant with a molecular target



# Exposure to a Toxicant



Once a living organism has been exposed to a toxicant, the compound must get into the body and to its target site in an active form in order to cause an adverse effect !!!!!

ADME:

Absorption, Distribution, Metabolism, and Excretion



**Response**

**No Response**

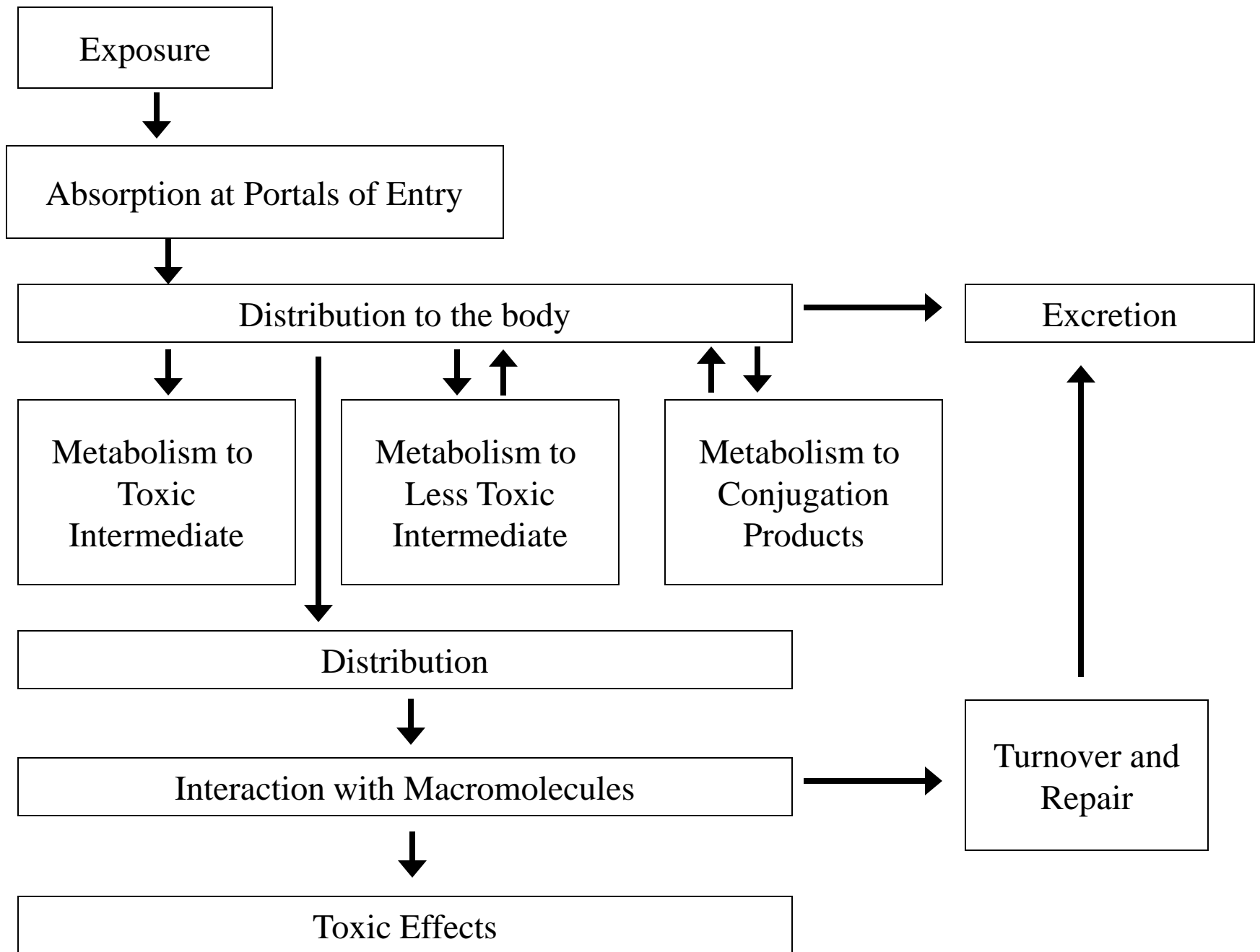
**Stored or  
eliminated**

# **What is Xenobiotic Metabolism ?**

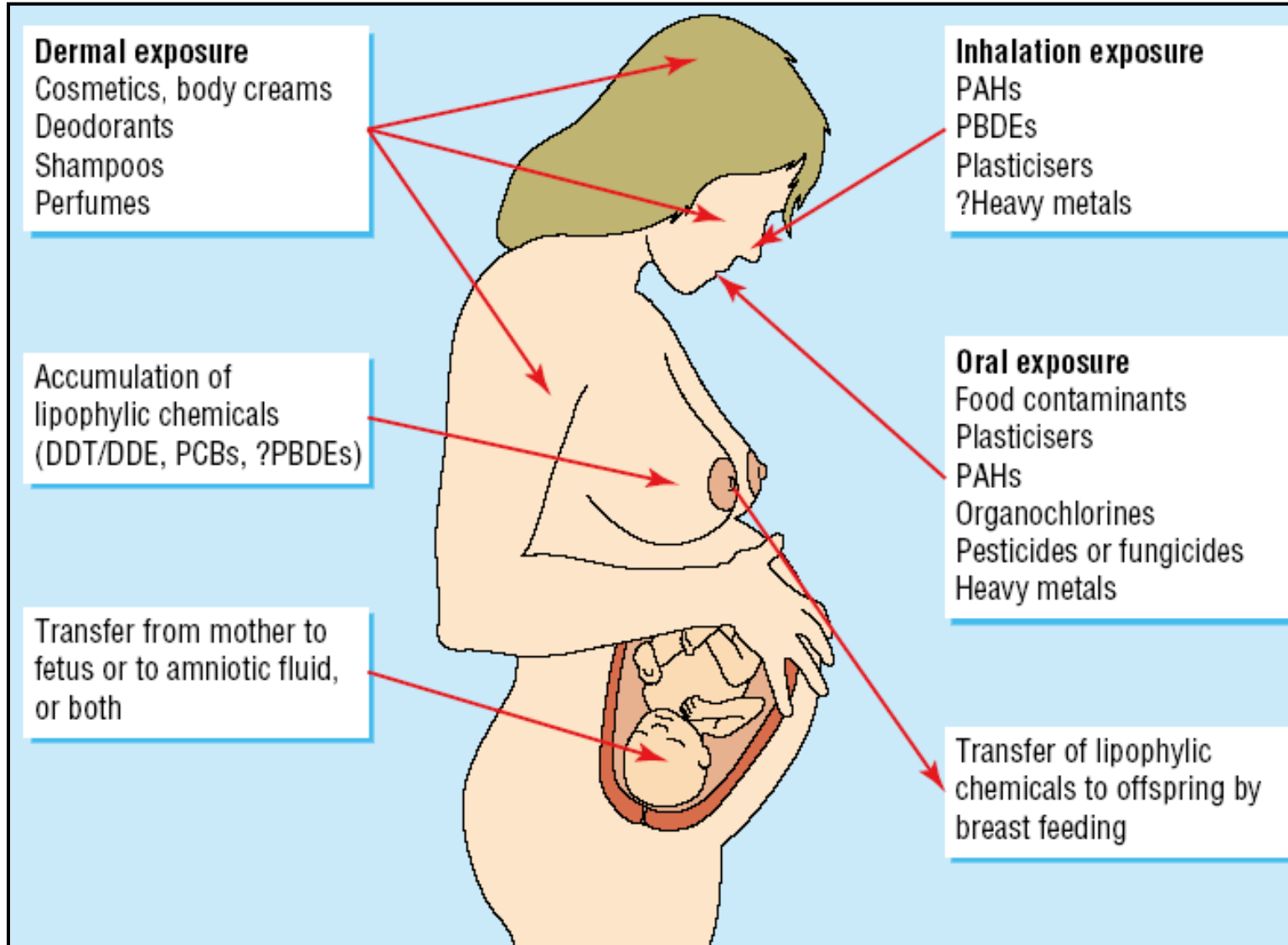
Xenobiotic metabolism is the sum of the physical and chemical changes that affect foreign substances in living organisms from uptake to excretion.

# **What is Toxication ?**

A term which implies activation of a chemical to a toxic metabolite.



# Routes of Human Exposure to Some Common Environmental Chemicals



# **Methods of study, monitoring and evaluation**

Basic Research Studies

versus

Large-Scale, Guideline-Compliant Studies

Standards of evidence

# **EDSTAC**

**Endocrine Disruptor Screening and  
Testing Advisory Committee**

# EDSTAC: Conceptual Framework

- General Considerations

- Want minimal number of screens and tests necessary to make sound decisions.
- Provide data that can be used for a wide variety of uses.
- Make best use of information generated in other screening and testing programs (particularly data on physiological changes in low dose groups)
- Adaptive to new science

- Specific Considerations

- Well defined endpoints
- Use minimal number of animals needed for scientifically valid results.
- Results should support further research
- Weight of evidence approach
- Reporting in format that facilitates database development and ease of information sharing.
- Clearly defined statistical and biological decision criteria.

# EDSTAC: Conceptual Framework

- **SCOPE**
  - Relevant for human health and ecological effects
  - Screening and testing will initially emphasize identification and characterization of effects that enhance, mimic, or inhibit **estrogen, androgen, and thyroid-related processes**.
    - More screens to be developed as the science evolves.
  - Should be capable of evaluating individual chemicals and mixtures.
  - EPA has already developed screening and testing protocols for carcinogenicity, developmental and reproductive toxicity, and neurotoxicity.
- **Priority setting:** sorting and prioritization of chemical substances and mixtures for evaluation in screening and testing batteries.
- **Tier 1 Screening:** to detect chemical substances and mixtures capable of acting on endocrine systems.
- **Tier 2 Testing:** to determine, characterize, and quantify the nature of the endocrine disrupting properties by prior information and/or tier 1 screening.

# EDSTAC: Tier 1 Screening

- Purpose: obtain a minimum, yet sufficient, set of valid, reliable data to detect whether a chemical substance or mixture may interact with the endocrine system.
- Characteristics
  - Inexpensive, quick and easy to perform
  - Validated and standardized ASAP
  - Sensitivity given priority over specificity (err on the side of false positive [Type I] errors rather than false negative [Type II] errors)
  - Capture multiple endpoints reflecting multiple modes of endocrine action.
  - Broadly predictive across species, gender, age, etc.
  - Yield a definite + or – for determining how or whether to proceed to tier 2.

# EDSTAC: High Throughput Pre-screening

- Subset of *in vitro* tier 1 assays that could be conducted with the assistance of automated technology
- Primary purpose is to provide preliminary biological activity information for a large number of chemicals in a relatively short period of time
- Transcriptional activation assays
  - AR
  - ER
  - THR
- Recommended for all high production volume chemicals (> 10,000 lbs per year) and all pesticides

Challenges presented by the  
presence of single versus  
multiple endocrine disruptors

# Mixtures

- Defined as a combination of two or more chemicals
  - contaminants in human breast milk
  - phytoestrogens in soy-based infant formula
  - mixtures of chemicals commonly found at hazardous waste sites
  - pesticide/fertilizers mixtures
  - disinfection byproducts
  - gasoline.

# Mixtures of Chemicals

- **Simple mixtures** generally contains 10 or less chemicals, the composition of which is qualitatively and quantitatively known.
  - Chemical composition Known
    - A cocktail of pesticides
    - A combination of medicines
- **Complex mixture** of tens, 100s or 1000s of chemicals, the composition of which is qualitatively and quantitatively not fully known.
  - Chemical composition is not well known
    - Workplace atmosphere
    - Diesel smoke
    - Crude oil
    - Drinking water

# Type of Changes in Dose Response Curves

- Additive
- Synergism
- Potentiation
- Antagonism

# Additive Multiple Chemical Interactions

- The described effect is equal to the sum of the effects
- **Most Common interaction**
- Test by selecting doses of each chemical that give equivalent responses; i.e., equivalent potencies
- Organophosphate pesticides  $2+2=4$

# Synergistic

It is not uncommon for the effect of two chemicals on an organism to be greater than the effect of each chemical individually, or the sum of the individual effects. **The presence of one chemical enhances the effects of the second.** This is called a synergistic effect or synergy, and the chemicals are sometimes described as showing synergism.

$$2+2 = 10$$



# Potentialiation

Increased effect of a toxic substance when exposure is in combination with another substance that is at exposure concentrations below the NOAEL.

$$2 + 0 = 8$$

Isopropanol + CCl<sub>4</sub>,  
Tumor promoters

# Estimating Safety for Potentiation

When potentiation is expected or suspected, an uncertainty factor of 100 to 1000 should be used in the risk model

# Antagonism

Two chemicals when administered together interfere with each others actions to produce a less toxic effect.

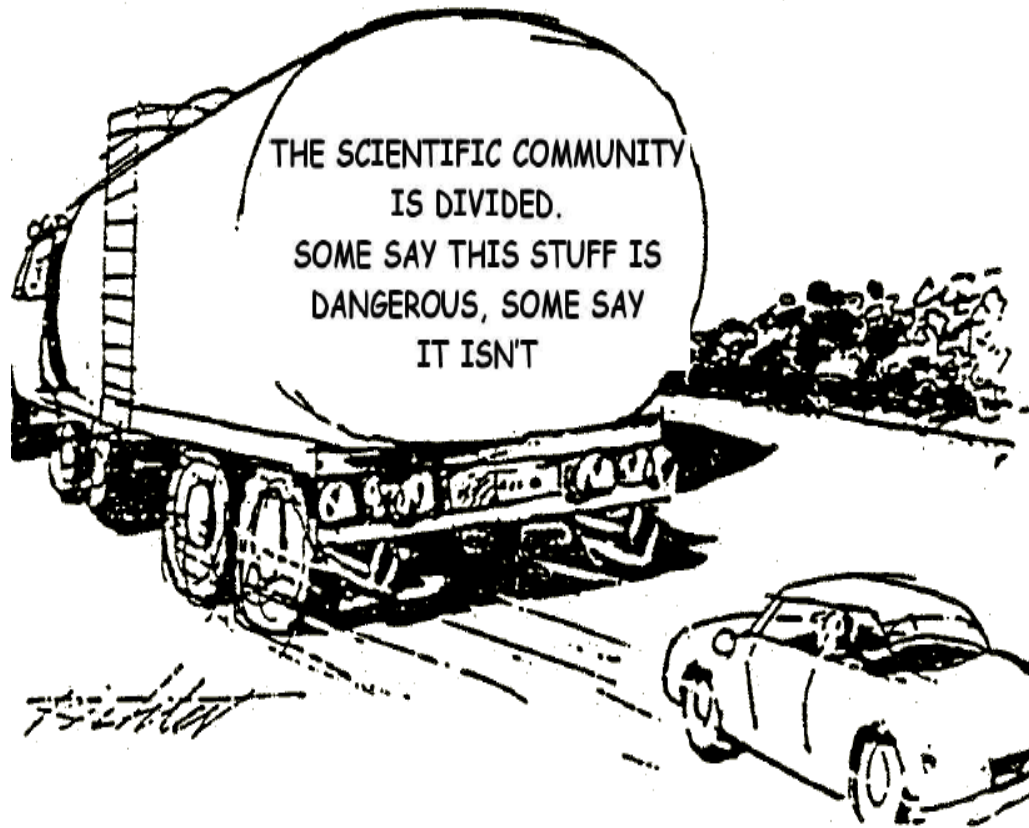
$$1+1=0.5$$

Dimercapol (chelating agent) + mercury, arsenic, or lead

# Important Issues in Endocrine Disruption

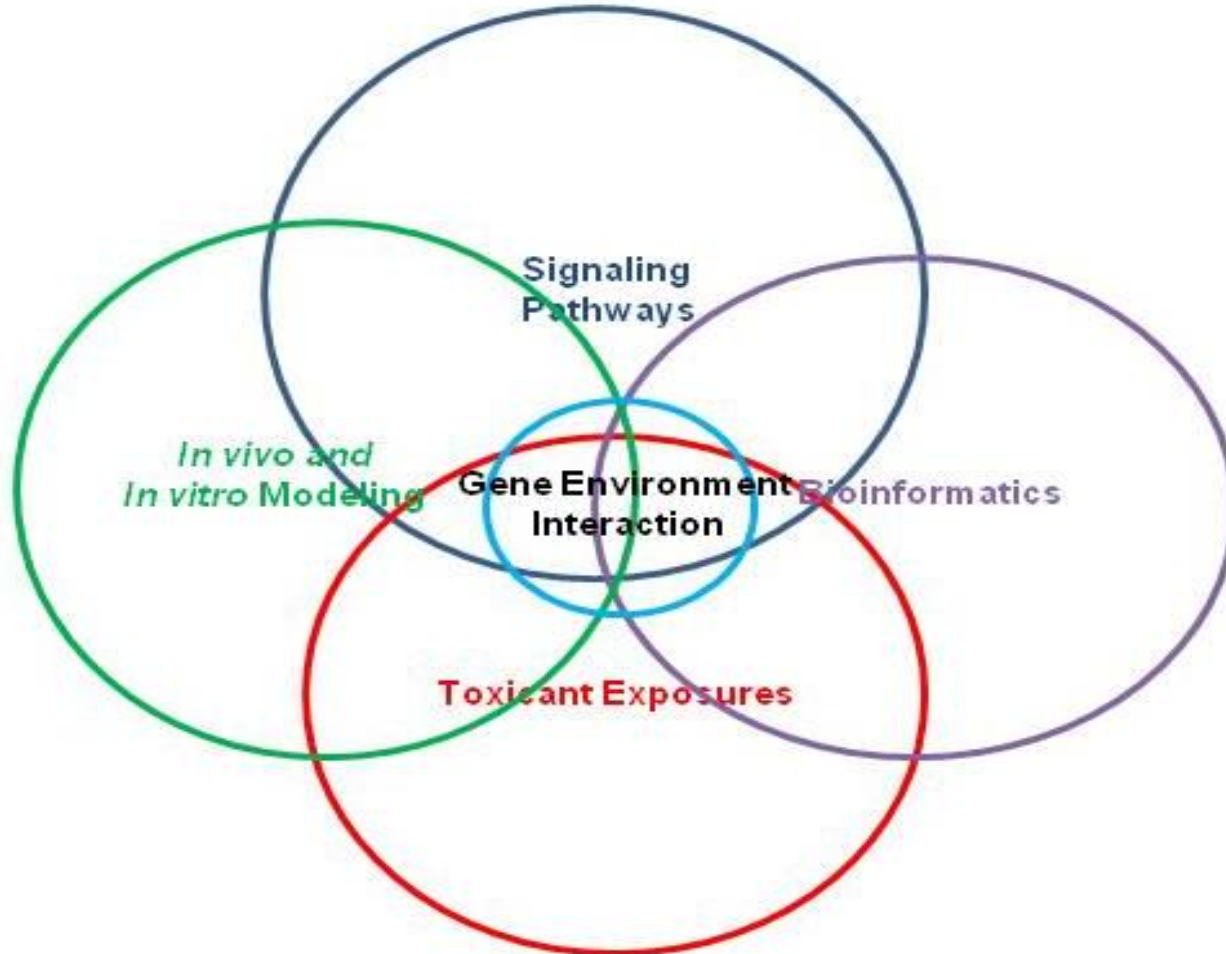
- Age at Exposure
  - Fetal Basis of Adult Disease
- Latency from Exposure
  - Reproductive effects may take years to observe
- Low Dose Exposures
  - Studies have primarily been high dose studies
- Importance of Mixtures
  - Studies have primarily been single exposures
- Nontraditional Dose-Response Dynamics
  - Effects at low physiologically relevant exposures
- Transgenerational Effects
  - You are what your great grandparents ate and were exposed to ?

# Challenges



# The Future

## Tox in the 21<sup>st</sup> Century: Measuring Toxicity, **Understanding The Biology**, and Assessing the Risk



Education, Education, Education