Course: *Toxicology, Path-438*

Applications of Pharmacology & Toxicology

Xenobiotics, Personal Care Products, Phthalates, Interactions Between Drugs, Herbs, and Diet, Endocrine Disruptors

Learning Objectives:

- Define "Xenobiotics" and explain how the body prevents their actions.
- Describe the disruption of normal cell functions by Xenobiotics and list the possible toxic effects of xenobiotics and examples of the target organs.
- List few examples of serious risks associated with the usage of certain personal care products.
- List examples of chemicals of concern in cosmetics / personal care products.
- Define" Phthalates", and describe its uses, its possible harmful effects on males and females and mention the possible routes of exposure.
- List the different mechanisms of drugs interaction. Give examples of some drugs interactions and mention their impact.
- Describe the health concerns of using herbal supplements and mention some example of their interactions with drugs and their possible harmful effects.
- Describe the categories of diet-drug interaction and mention the possible adverse effects of these interactions.
- Define "Endocrine disruptors", give examples and describe their different mechanisms of action on the endocrine system and mention their adverse effects on males and females.

Xenobiotics:

- A **xenobiotic** is a chemical which is found in an organism but is not normally produced or expected to be present in it.

- It can also cover substances which are present in much higher concentrations than are usual. Specifically, drugs such as antibiotics are xenobiotics in humans because the human body does not produce them itself, nor are they part of a normal diet.

- Natural compounds can also become xenobiotics if they are taken up by another organism, such as the uptake of natural human hormones by fish found downstream of sewage treatment plant outfalls, or the chemical defenses produced by some organisms as protection against predators.

Xenobiotics:

❖ How Does the Body Prevent the Actions of Xenobiotics ?

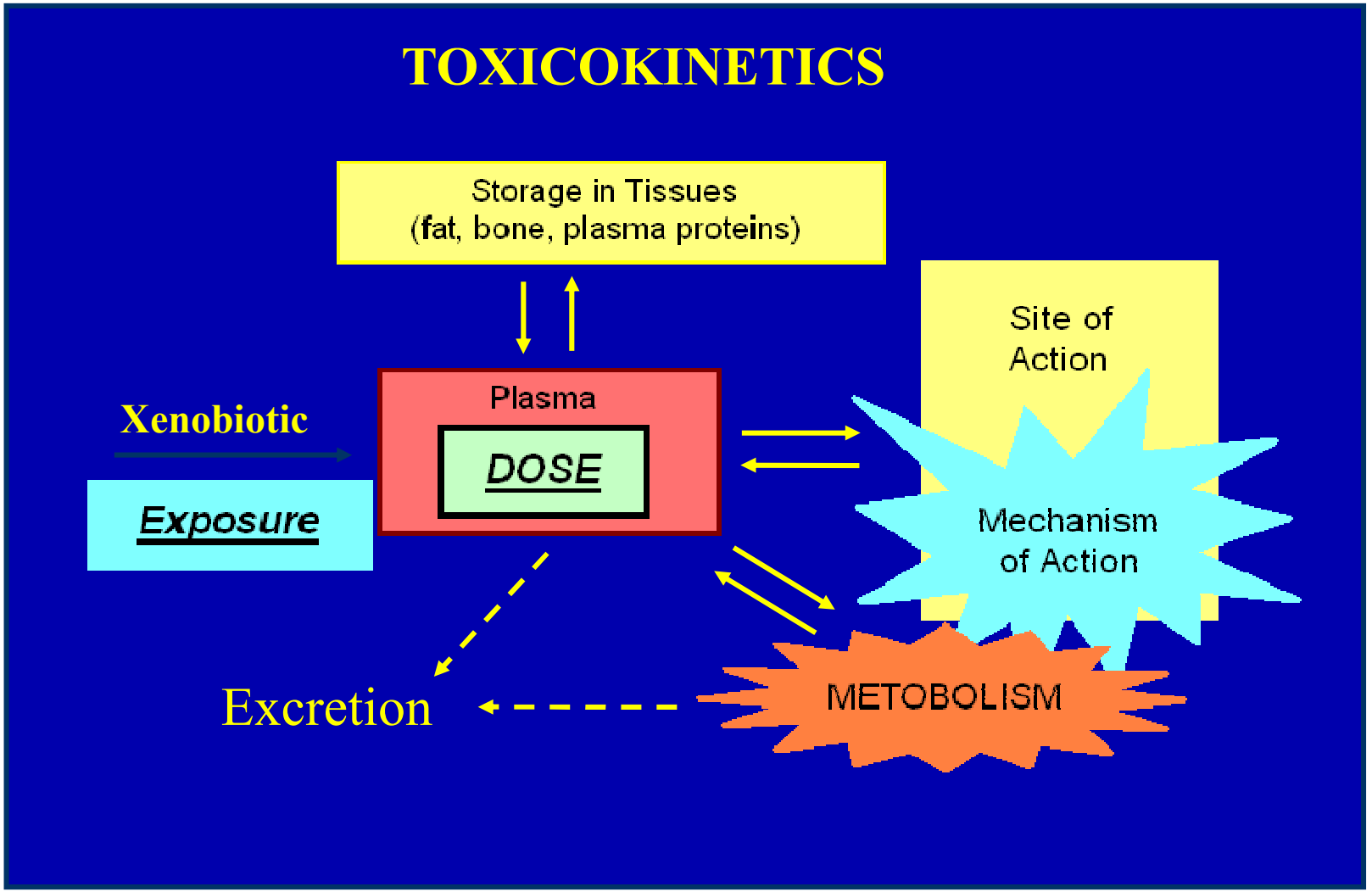
1) **Redistribution.**

2) **Excretion** – (primarily water soluble compounds):
   - kidney and liver.

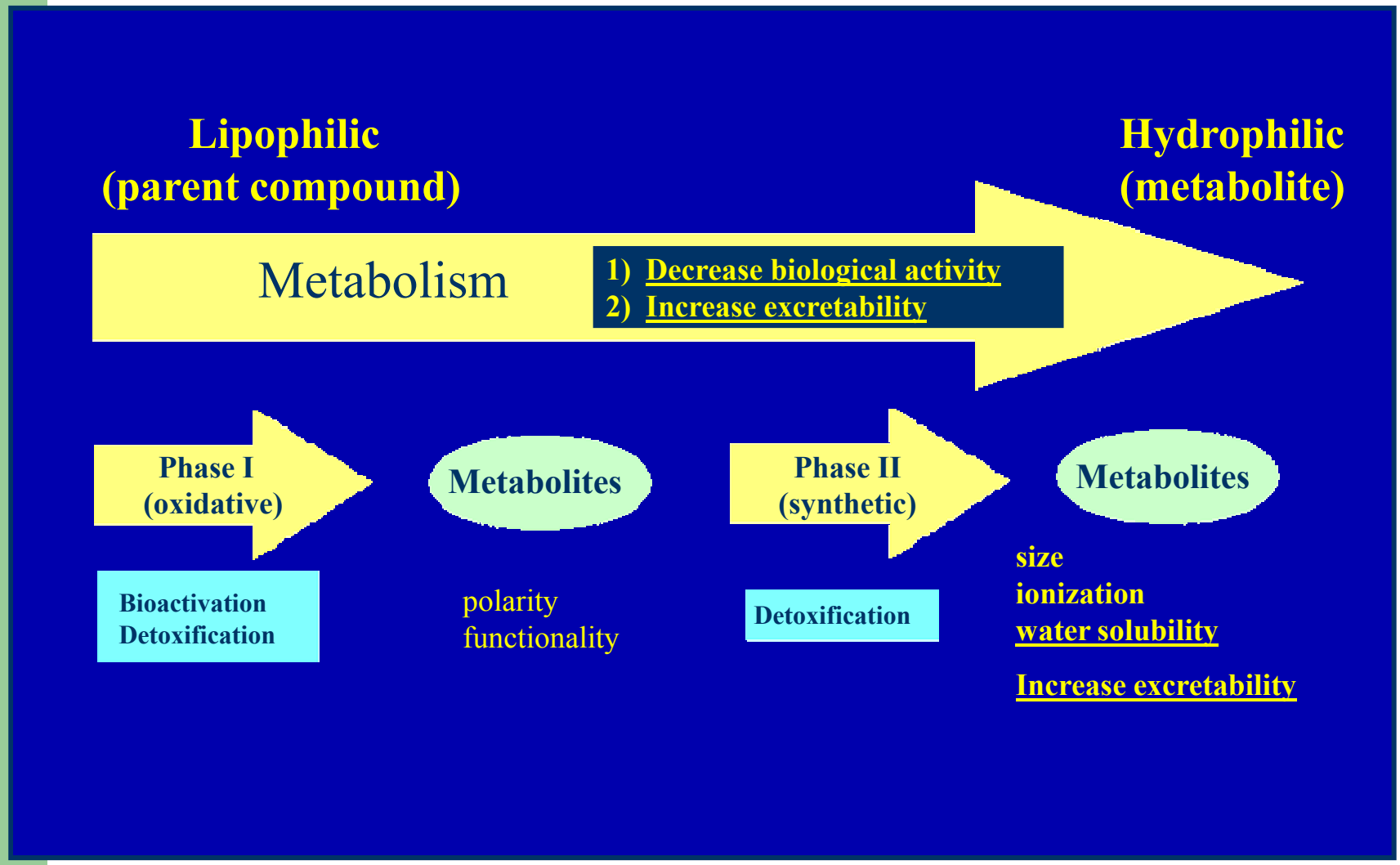
3) **Metabolism** – the major mechanism for terminating xenobiotic activity, and is frequently the single most important determinant of the duration and intensity of toxic responses to a xenobiotic.
   - **LIVER**, kidney, lung, GI, and others.

Note: 1) & 2) are highly dependant on 3).

Xenobiotics at Work:



General Scheme of Xenobiotic Metabolism



Xenobiotics – *Toxicity:*

- Some xenobiotics cause toxicity by disrupting normal cell functions:
  - Bind and damage proteins (structural proteins, enzymes).
  - Bind and damage DNA (mutations).
  - Bind and damage lipids.
  - React in the cell with oxygen to form "free radicals" which damage lipid, protein, and DNA.

Xenobiotics – *Toxicity:*

- Types of toxic effects:
  - Death - arsenic, cyanide.
  - Organ Damage - ozone, lead.
  - Mutagenesis - UV light.
  - Carcinogenesis - benzene, asbestos.
  - Teratogenesis – thalidomide.

- Target organ toxicity:
  - **Central Nervous System** – lead.
  - **Immune System** – isocyanates.
  - **Liver** - ethanol, acetaminophen.
  - **Respiratory Tract** - tobacco smoke, asbestos, ozone.
  - **Eye** - UV light (sunlight).
  - **Kidney** - metals **.**
  - **Skin** - UV light, gold, nickel.
  - **Reproductive System** – dibromochloropropane.

Personal Care Products:

❖ **Why are Personal Care Products Potentially Harmful:**

- Many formulations contain harmful ingredients that have extremely small molecules. These molecules penetrate the skin and the blood system and quickly build up in the organs and tissues.

❖ **Is the cosmetic counter really a dangerous place?**

- **Serious risks** may include: Irritation or allergic reaction, swelling and lesions, contact dermatitis, flushing, headaches, dizziness, nausea, diarrhea, hair loss, and vomiting.

- **More serious risks**: Hyper/hypo-pigmentation, violent coughing, labored breathing, eye "problems" and damage, disruption of cell development, destruction of proteins and cellular structure, premature aging, mental depression.

- **Even more serious:** Depletion of Oxygen, damage to the immune system, respiratory damage, reproductive damage, brain, liver, and kidney, abnormalities, corrosion, narcosis.

Personal Care Products:

- According to industry estimates, on any given day a consumer may use as many as ***25 cosmetic products containing more than 200 different chemical compounds.***

- 89% of the ingredients used personal care products have not been screened for safety by FDA or anyone else.

- Examples of chemicals of concern in cosmetics / personal care products:
  - **Carcinogens:** Acrylamide, Formaldehyde, Petroleum distillates– Diethanolamine, 1,4-dioxane.
  - **Endocrine disruptors/reproductive toxins:** Phthalates, Parabens, Toluene.
  - **Neurotoxins:** Lead acetate, Mercury.

Personal Care Products:

❖ Nail Salon Workers at Risk:

- 96% women.
- More than 380,000 workers nationwide.
- Exposed to acetone, toluene, formaldehyde, phthalates, methylacrylates, toluene sulfonamide formaldehyde (TSF) resin, and other volatile organics.
- Occupational Safety & Health Administration (OSHA) exposure standards ***do not address low-dose, long-term exposure.***
- ***Some safer products are available -but workers may not be aware of them.***

Phthalates:

- **Phthalates** are a class of widely used industrial compounds used as plasticizers especially in PVC (polyvinyl chloride). *It is colorless liquid with almost no odor, insoluble in water, and soluble in most organic solvents.*

- Various types of phthalates: Range from ***1-17 carbons and PVC plasticizers generally range from 4-13 carbons***.

- **Examples:**

  - **DINP** (di-isononyl phthalate): Superior anti-heat, anti-cold, and anti-volatile properties.

  - **DIDP** (di-isodecyl phthalate): Low volatile properties, anti-heat and anti-aging properties, and electricity insulation properties .

  - **DBP** (di-butyl phthalate)-***common ingredient in nail polish.***

  - **DEHP** (di-2-ethylhexyl phthalate)-used to make PVC.

Phthalates – *Uses & Exposure:*

- Accounts for 80–90 % of the world plasticizer consumption.
- Used primarily as plasticizers in polyvinyl chloride (PVC) products.
- Child's toys, kitchen floor, building materials.
- Medical devices: Plastic in IV, blood bags, etc.
- **Fixatives for perfume**, slowing down evaporation and making the scent linger longer.
- **Other uses:** *polish from chipping, hair sprays, new car smell (Partly the pungent odor of phthalates volatilizing from a hot plastic dashboard), nail extenders, bath soaps, detergents, aftershave lotions .*
- ***Highest level of exposure was women of child-bearing age:*** *High levels of DEP, DBP, BBP.* ***Likely sources of these exposures are through cosmetics***, including ***hair sprays, nail polishes and perfumes, which are common applications of DBP.***

Phthalates - *Harmful Effects:*

- At high doses of phthalates do constitute risks in the sense of traditional toxicology, these low doses change the stakes dramatically.

- ***Male reproductive development is acutely sensitive to some phthalates***. ***DBP & DEHP produced dramatic changes in male sexual characteristics*** when exposure took place *in utero*, at levels far beneath those of previous toxicological concern.

- **Males:**
  - Hypospadias (anomaly of the urethra).
  - Damage of Sertoli cells caused by a metabolite of DEHP, monoethylhexyl phthalate (MEHP).
  - Low sperm count.
  - Reductions in semen quality.
  - DNA damage to sperm.
- **Females:**
  - Premature breast development.
  - Premature birth.
- **Carcinogenic.**
- Damaged the liver of rats and mice at high doses.
  - Relevant to humans: unknown.

Drug Interactions;

- Drug interaction can be ***unidirectional or bidirectional.***

- **Classification of mechanism of interaction:**

  - **Alteration in absorption:**

    - ✓ **Complexation/Chelation** e.g. antacids + tetracycline and this causes tetracycline complexes with divalent cations forming an insoluble complex.
    - ✓ **Altered GI Transit**: e.g. anticholinergics + acetaminophen and this causes delay in absorption of acetaminophen.
    - ✓ **Altered Gastric pH** e.g. H-2 blockers + ketoconazole: dissolution of ketoconazole is decreased, resulting in reduced absorption.

  - **Alteration in hepatic metabolism:**

    - ✓ **Induction of Metabolism** e.g. phenobarbital + warfarin: phenobarbital increases the metabolism of warfarin, resulting in reduced anticoagulation
    - ✓ **Inhibition of Metabolism** e.g. cimetidine + theophylline: cimetidine reduces the clearance of theophylline causing an increase in adverse effects.

Drug Interactions;

❖ Classification of mechanism of interaction "***continued":***

➢ **Alteration in renal clearance:**

✓ **Increase in Renal Blood Flow** e.g. hydralazine + digoxin: hydralazine increases the renal clearance of digoxin.

✓ **Inhibition of Active Tubular Secretion** e.g. probenecid + penicillin: probenecid prolongs the half-life of penicillin, allowing single dose therapy.

✓ **Alterations in Tubular Reabsorption** e.g. antacids + aspirin: antacids reduce the tubular reabsorption of salicylate via an increase in urine pH.

➢ **Alteration in plasma protein binding:** e.g. phenytoin + valproic acid: protein binding of valproic acid is reduced.

Herbs Supplements & Drug Interaction:

- Widely used by consumers to improve general health & prevent or treat specific illnesses, do not require FDA approval before marketing, FDA must show that herbal supplement is unsafe before it can be removed from marketplace (e.g. ephedrine).

- ***Benefits of use of herbal products is unclear***, many herbal "remedies" of dubious effectiveness.

- **Efficacy:** limited number of studies to support traditional uses & benefits.

- **Consistency in ingredients:** variations occur in composition of herb & in preparation; may contain harmful components.

- **Safety issues:** ***products often considered "natural," therefore safe; may have toxic effects, however, some serious, even dangerous.***

- **Interactions:** may potentiate or interfere with actions of other herbs or drugs.

- **Contamination:** some products found to contain lead & other toxic metals; other contaminants include molds, bacteria, pesticides.

- **Adulteration of imported products**, including addition of synthetic drugs not identified on labels.

Herbs Supplements & Drug Interaction:

Examples of Herb-Drug Interactions

Herb	Drug	Interaction
American ginseng	Estrogens, corticosteroids	Enhances hormonal response
American ginseng	Breast cancer therapeutic agent	Synergistically inhibits cancer cell growth
American ginseng, karela	Blood glucose regulators	Affect blood glucose levels
Echinacea (possible immunostimulant)	Cyclosporine and corticosteroids (immunosuppressants)	May reduce drug effectiveness
Evening primrose oil, borage	Anticonvulsants	Lower seizure threshold
Feverfew	Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs	Negates the effect of the herb in treating migraine headaches
Feverfew, garlic, ginkgo, ginger, and Asian ginseng	Warfarin, coumarin (anticlotting drugs, "blood thinners")	Prolong bleeding time; increase likelihood of hemorrhage
Garlic	Protease inhibitor (HIV drug)	May reduce drug effectiveness
Kava, valerian	Anesthetics	May enhance drug action
Kelp (iodine source)	Synthroid or other thyroid hormone replacers	Interferes with drug action
Kyushin, licorice, plantain, uzara root, hawthorn, Asian ginseng	Digoxin (cardiac antiarrhythmic drug derived from the herb foxglove)	Interfere with drug action and monitoring
St. John's wort, saw palmetto, black tea	Iron	Tannins in herbs inhibit iron absorption
Valerian	Barbiturates	Causes excessive sedation

Drug –Diet Interaction:

- Diet-drug interactions fall into the following categories:
  - Medications can alter food intake by ***suppressing appetite*** or ***causing complications that interfere with food intake***.
  - Medications ***can alter absorption, metabolism & excretion of nutrients.***
  - Nutrients & other food components ***can alter absorption, metabolism & excretion of medications***.
  - Some interactions between food components & medications can be ***toxic.***

Drug –Diet Interaction:

- **Drug effects on food intake:** Reduce food intake through nausea & vomiting, alteration of taste sensations, suppression of appetite, drying mouth, inflammation or lesions in mouth or GI tract, side effects, including abdominal discomfort, constipation, diarrhea, drowsiness.

- **Drug effects on nutrient absorption:**

  - **Damage of intestinal mucosa:** Most widespread cause of problems with nutrient absorption; especially ***antineoplastic & antiretroviral medications***.

  - **Drug-nutrient binding:** binding of nutrients & drugs in GI tract, preventing absorption (ex. ***Ciprofloxacin***).

  - **Altered stomach acidity:** resulting in impaired absorption of vitamin B_{12}, folate & iron (ex. ***Antacids***).

  - **Direct inhibition:** drugs that impede nutrient absorption by interfering with intestinal metabolism or transport.

Drug –Diet Interaction:

- **Drug effects on nutrient metabolism:**
  - ***Enhancement or inhibition of activities of enzymes*** needed for nutrient metabolism (ex. Methotrexate with folate).

- **Drug effects on nutrient excretion:**
  - **Alteration in mineral reabsorption.**
  - **Increased excretion of vitamins & minerals (e.g. INH and vit. B6).**

Drug –Diet Interaction:

❖ Dietary effects on drug absorption:

- ***Stomach emptying rate:*** taking medications on empty stomach tends to increase absorption rate; taking medications on full stomach may delay its absorption rate (ex. Aspirin).

- ***Stomach acidity****:* absorption rates affected by acid or alkaline medium.

- ***Interactions with food components:*** may bind with drugs & inhibit absorption.

❖ Dietary effects on drug metabolism:

- **Alteration in activities of enzymes that metabolize drugs**:

  - ✓ Increased blood concentration of drug (stronger physiological effects): e.g. Grapefruit and statins (lipid lowering drugs).
  - ✓ Decreased effectiveness of drug (e.g. Warfarin and Vit. K).

- **Counteraction of drug effects in other ways.**

Drug –Diet Interaction:

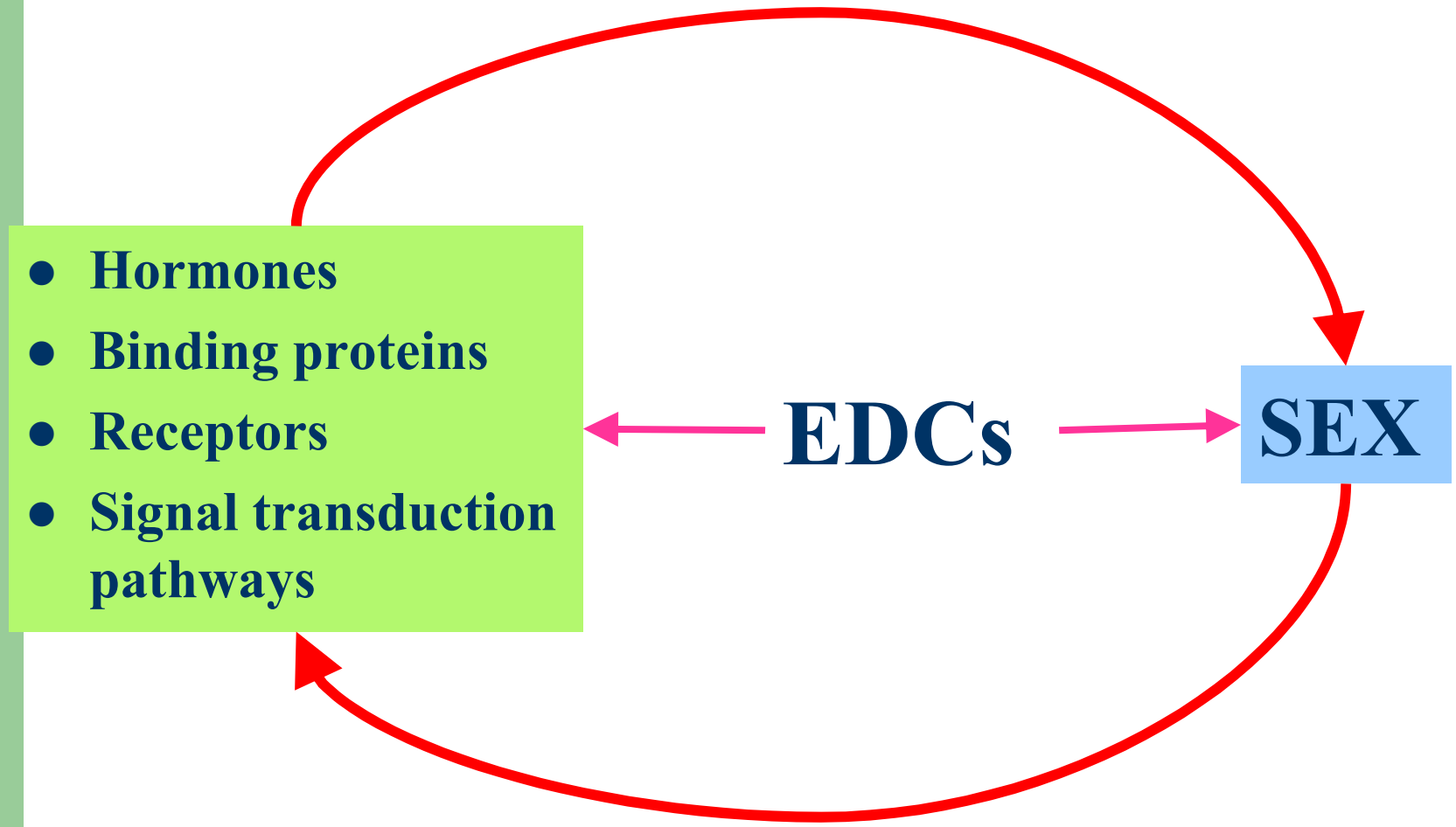
- **Alterations in excretion causing toxicity or reduced effectiveness of the drug:**
  - **Increased or decreased reabsorption (e.g. Li and Na).**
  - **Alterations in drug actions.**
- **Diet-drug interactions & toxicity:**
  - **Interactions can result in toxicity or exacerbate drug side effects *(e.g. MAOIs "antidepressants" and tyramine "found in cheese").***
  - Health professions must understand mechanism of action of drugs & diet-drug interactions for identification &/or prevention.

Endocrine Disruptors:

- Any chemical agent in the environment that can alter normal endocrine system actions leading to deleterious effects on an organism or its progeny.
- **Disruptors may act directly or indirectly:**
  - **Direct acting disruptors** are usually hormone agonists or antagonists that interfere with hormone actions on target cells.
  - **Indirect acting disruptors** alter hormone dynamics in circulation, change hormone metabolism, or interfere with hormone regulation.
- **Endocrine disruptors may include:** Pesticides (herbicides, insecticides, …), Plasticizers, Natural plant metabolites, Pharmaceuticals (contraceptives, drugs,…), Detergents, Chemicals from cooking & burning, Antibiotics, Metals.
- **Results of disruption may include:** 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.

Endocrine Disruptors (EDCs):

Targets for Endocrine Disruption



Mechanisms of Endocrine Disruption:

- **Receptor Mediated:**
  - Agonistic & Antagonistic.
  - Pesticides.
  - Polychlorinated biphenyls (PCBs).
- **Altered Enzyme Action:**
  - Nitrate/nitrite.
  - Pesticides.
  - Phthalates.
- **Altered Metabolism:**
  - Pesticides.
- **Altered Hormone Availability:**
  - PCBs/ Polybrominated biphenyls (PBBs).
- **Altered Gene Expression:**
  - Nitrates/nitrite.
  - Pesticides.
  - PCBs.

Endocrine Disruptors – Effects on Human:

- Sexual development.
- Fertility and reproductive impairments.
- Nervous system and behavioral Changes.
- Immune function.
- Cancer induction.

Endocrine Disruptors – Effects on Females:

- **Impaired fertility.**
- **Endocrine dysfunction:**
  - Altered hormone profiles.
- **Ovary & reproductive tract structure:**
  - increasing incidence of uterine and oviduct abnormalities.
- **Endometriosis.**
- **Age at puberty.**
- **Brain and behavior:**
  - Altered IQ and behavior, including sexual behaviors.
- **Cancer:**
  - ✓ increasing incidence of breast cancer & reproductive tract cancers.
- **Immune dysfunction.**
- **Multigenerational effects.**

Endocrine Disruptors – Effects on Males:

- **Declining fertility:**
  - Declining sperm counts?
- **Endocrine dysfunction:**
  - Altered hormone profiles.
- **Testis & reproductive tract structure:**
  - increasing incidence of hypospadias and cryptochidism.
- **Age of Puberty.**
- **Brain and behavior:**
  - Altered IQ and behavior, including sexual behaviors.
- **Cancer:**
  - Increasing incidence of testicular & prostate cancers.
- **Immune dysfunction.**
- **Multigenerational effects.**

In conclusion:

- Endocrine disruptors or hormonally active agents have been with us for millennia as elements of plants and cooking.
- The new abundance of synthetic compounds has unleashed a wave of new challenges to our physiology, including the endocrine system.
- The impacts are as pleiotropic as endocrine actions are. Not surprisingly they involve altered reproductive success, growth, and cancer risks because of endocrine controls or inputs in these processes.
- Due care will help minimize impacts, but some increased risks are here permanently.