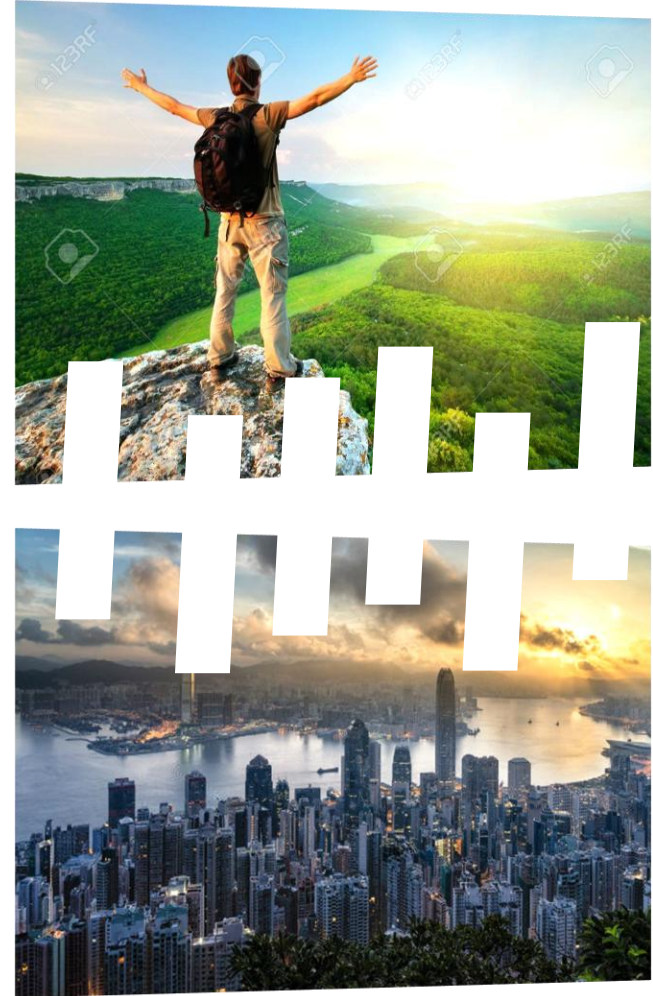


Environmental medicine

Endocrine Disruptors





Endocrine Disruptors:

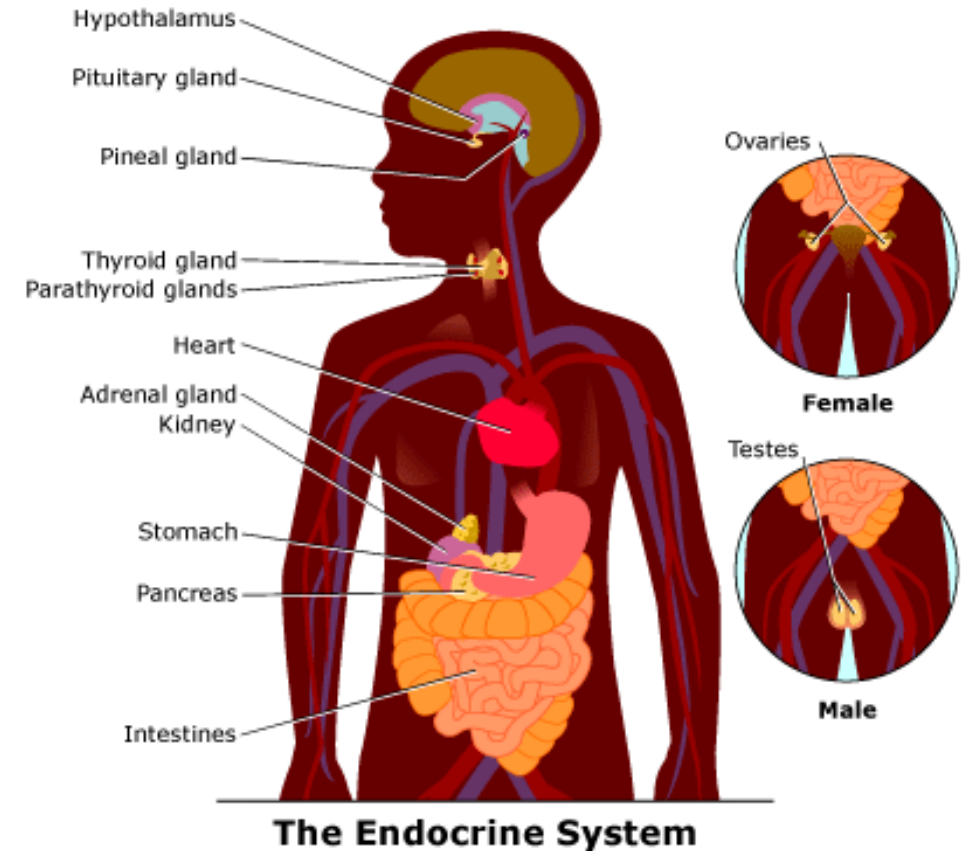
- **Endocrine-disrupting chemicals (EDCs)** are **natural** or **human-made chemicals** that may **mimic, block, or interfere with the body's hormones**, which are part of the endocrine system.
- These chemicals are associated with a wide array of **health issues**.

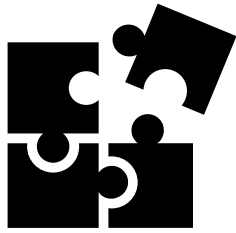




The Endocrine System:

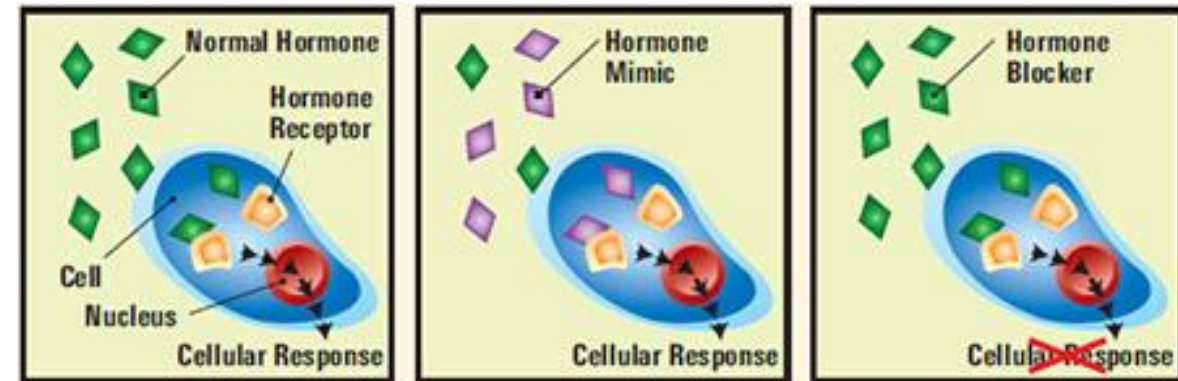
- **Endocrine glands**, distributed throughout the body, produce **hormones** that act as **signaling molecules** after release into the circulatory system.
- The human body is dependent on hormones for a healthy **endocrine system**, which controls many biological processes like normal **growth, fertility, and reproduction**.



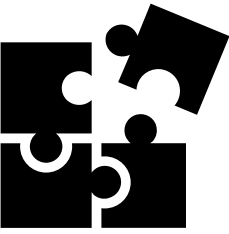


The Endocrine System:

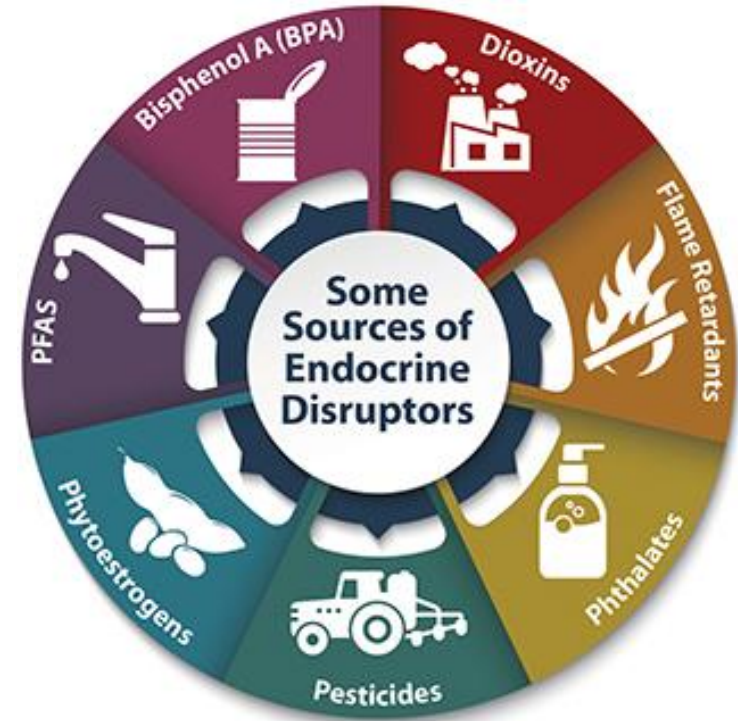
- Hormones act in extremely **small amounts**, and **minor disruptions** in those levels may cause **significant developmental and biological effects**.
- This observation leads scientists to think that endocrine-disrupting chemical (EDC) exposures, **even at low amounts**, can alter the **body's sensitive systems** and lead to **health problems**.

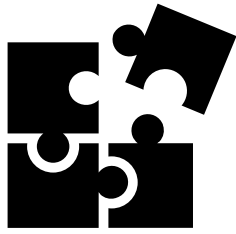


How Do We Encounter These Chemicals?



- Endocrine disruptors are found in many **everyday products**, including some cosmetics, food and beverage packaging, toys, carpet, and pesticides.
- Some chemicals that act as **flame retardants** may also be endocrine disruptors.





How Do We Encounter These Chemicals?

- EDCs have the ability to penetrate the body through ingestion, inhalation, or skin and to mimic the endogenous hormones, leading to the disruption of the endocrine system in both human and animal species.
- The first reported EDCs harmful effects were related to estrogens - breast cancer, endometriosis, fertility problems, and obesity.





How Do We Encounter These Chemicals?

- EDCs have been shown to act through direct or indirect mechanisms.
- In the **direct mechanism**, EDCs **directly bind** to a receptor of the NRs family (**estrogen receptors ER**, thyroid hormones receptors **TR**, androgen receptors **AR**, glucocorticoid receptors **GR**, and peroxisome proliferator-activated receptors gamma **PPAR γ**) or the **aryl hydrocarbon receptor**, leading to **activation or inhibition** of its signaling pathway.



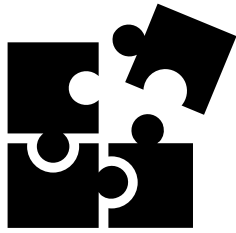


How Do We Encounter These Chemicals?

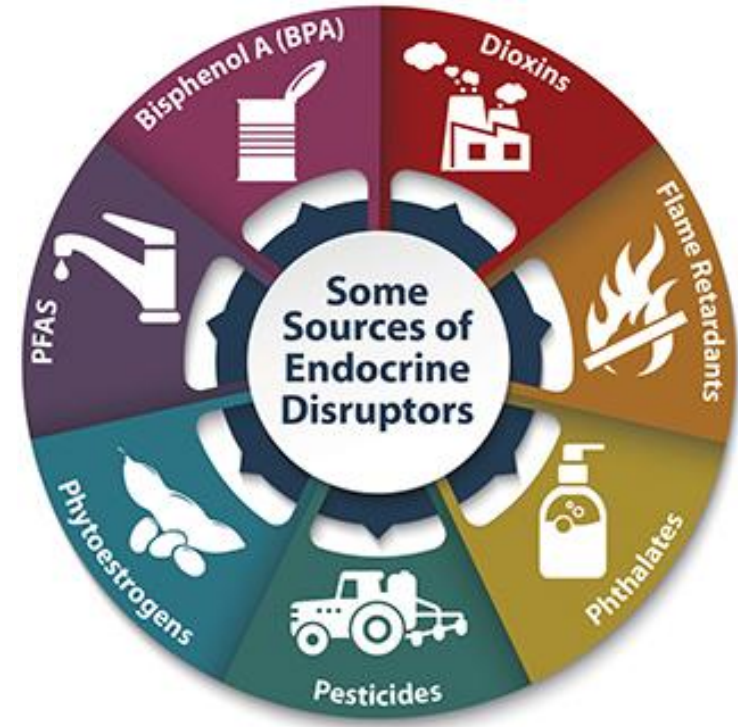
- In the **indirect mechanism**, EDCs affect other transcription factors or hormone metabolism through **interaction with components of the hormone signaling pathway**, stimulation or inhibition of endogenous hormones biosynthesis, binding to circulating hormone-binding protein, stimulation or inhibition of hormone-binding protein synthesis or degradation, stimulation or inhibition of hormone receptor expression



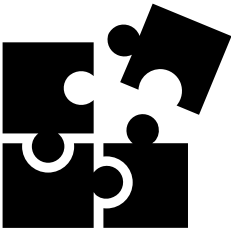
How Do We Encounter These Chemicals?



- The majority of the **in silico studies** dedicated to EDCs focused on the **direct mechanism**.



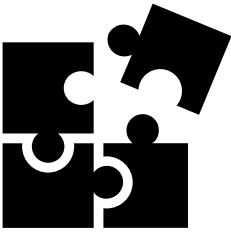
How Do We Encounter These Chemicals?



- EDCs are now considered a **public health threat**, as human exposure to these compounds can **increase the risk of impairment of several biological functions** such as the **reproductive, cognitive, and metabolic functions**.



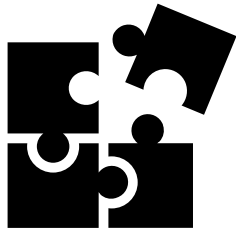
How Do We Encounter These Chemicals?



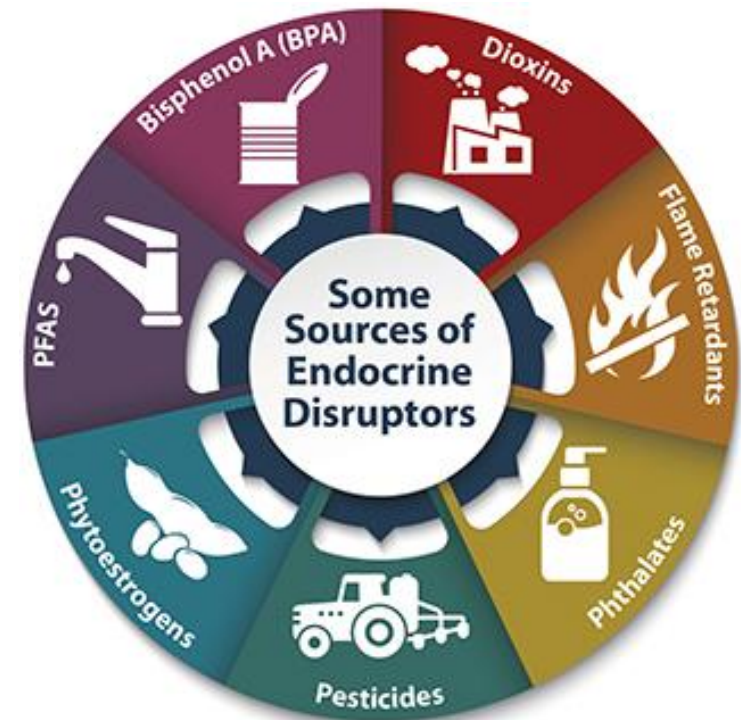
- Contact with these chemicals may occur through **air, food, skin, and water**.
- EDCs **cannot be completely avoided or removed**; however, you can make **informed choices to reduce exposure** and risk of any potential health effects.



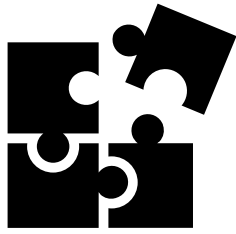
Chemicals That May Disrupt Your Endocrine System



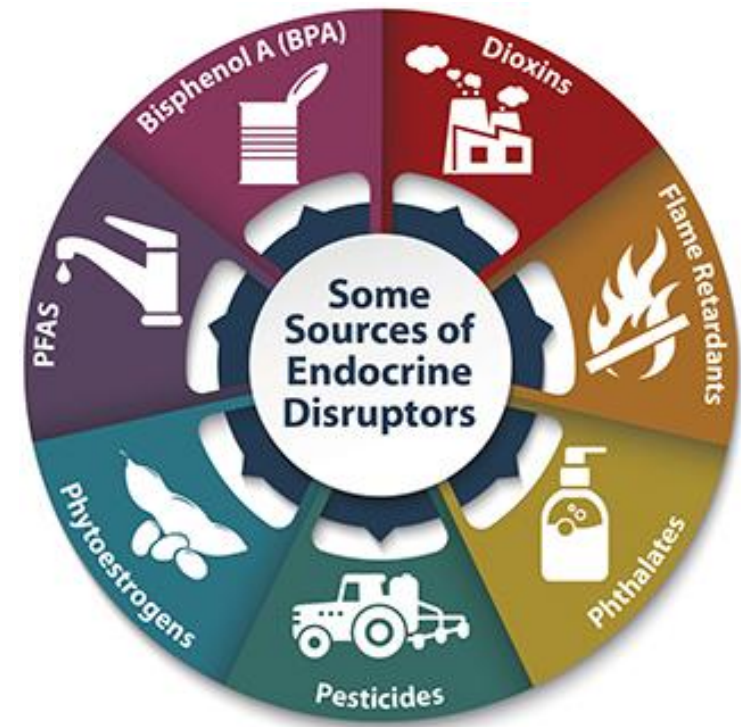
- According to the Endocrine Society, there are nearly **85,000 human-made chemicals in the world**, and 1,000 or more of those could be **endocrine disruptors**, based on their unique properties.
- The following are among the most common and well-studied.



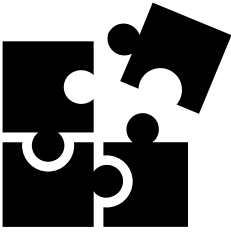
Chemicals That May Disrupt Your Endocrine System



- Some of the most common endocrine disruptors are **bisphenol A**, **phthalates**, perchlorate, perfluoroalkyl, and polyfluoroalkyl substances (PFAs), dioxins, **phytoestrogens**, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCB), triclosan, **atrazine**, lead, arsenic, mercury, organophosphate pesticides, and glycol ethers.



Chemicals That May Disrupt Your Endocrine System



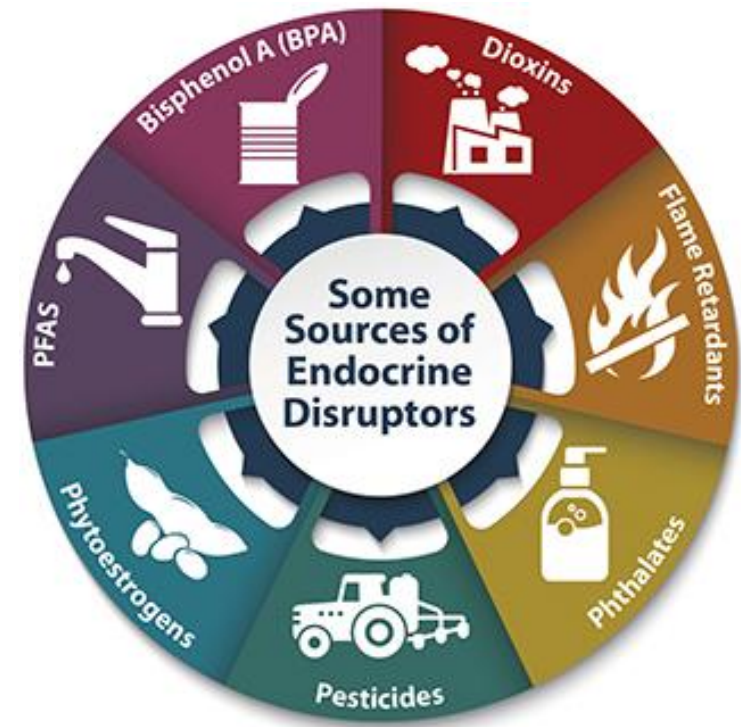
Bisphenol A (BPA)





Bisphenol A (BPA)

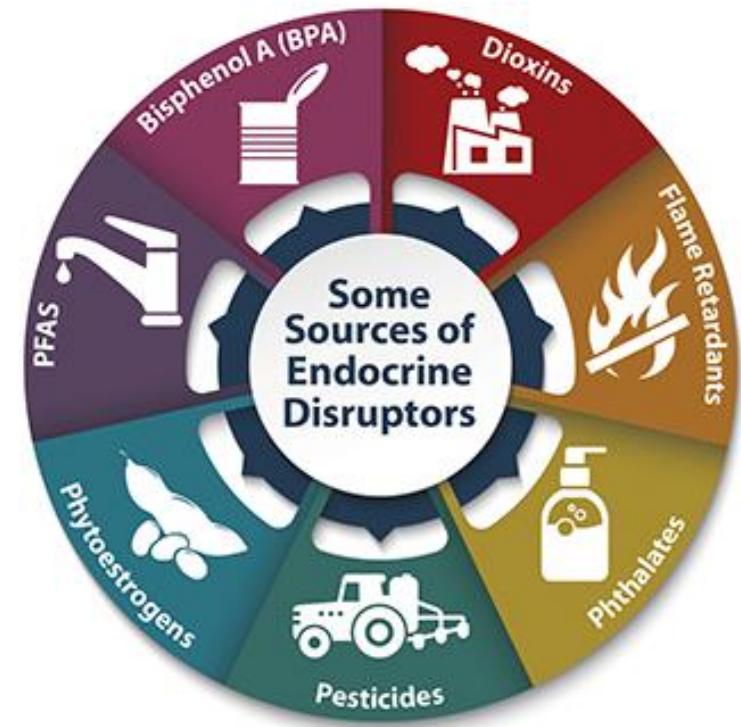
- **Bisphenol A (BPA)** is used to make polycarbonate plastics and epoxy resins.
- It is used in manufacturing, food packaging, toys, and other applications. BPA resins may be found in the lining of some canned foods and beverages.
- It is also widely known for its tendency to leach from those products, which has made it a subject of public health and environmental concern.

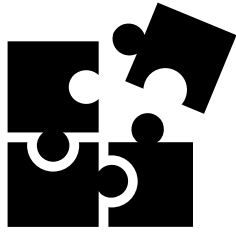




Bisphenol A (BPA)

- BPA was first synthesized in 1891, by Russian chemist Aleksandr P. Dianin, who combined **phenol with acetone** in the presence of **an acid catalyst** to produce the chemical.
- In the 1950s scientists discovered that the reaction of **BPA with phosgene** (carbonyl chloride) produced **a clear hard resin** known as polycarbonate, which **became widely used in the manufacture of plastics**.

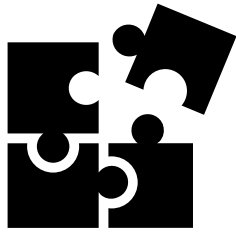




Bisphenol A (BPA)

- Global BPA production amounted to more than 6 billion pounds (2.7 billion kilograms) annually, roughly one-third of which was made in the United States.





Bisphenol A (BPA)

- In general, BPA levels in humans have measured **well below 50 µg/kg of body weight per day**, which is the **maximum acceptable** (or “reference”) dose set by the **U.S. Environmental Protection Agency (EPA)**.
- In **2015**, **EFSA** established a safe level of BPA intake: a temporary tolerable daily intake (t-TDI) for BPA was set at **4 µg/kg body weight per day**.

Types of BPA exposure



Updated tolerable daily intake (TDI) of BPA in food



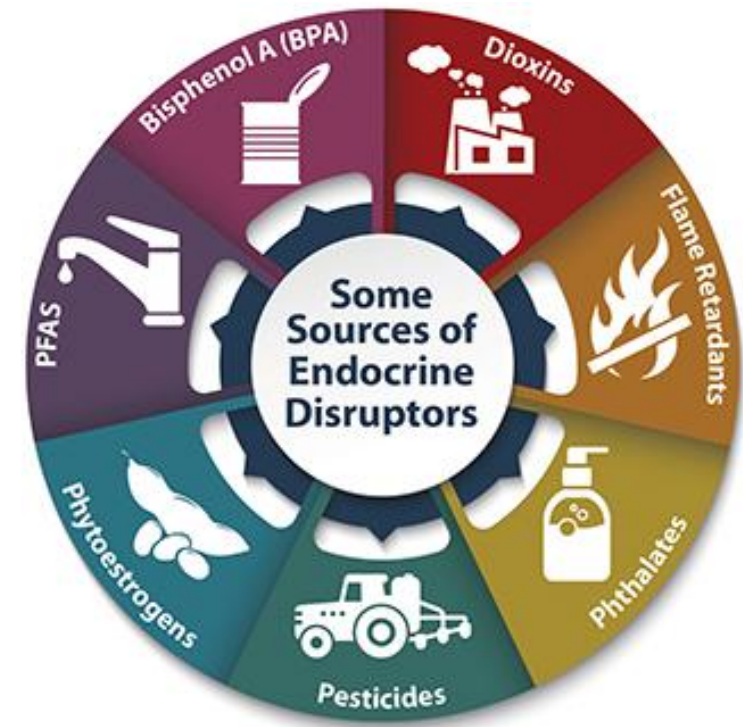
BPA exposure is much higher than the new TDI*





Bisphenol A (BPA)

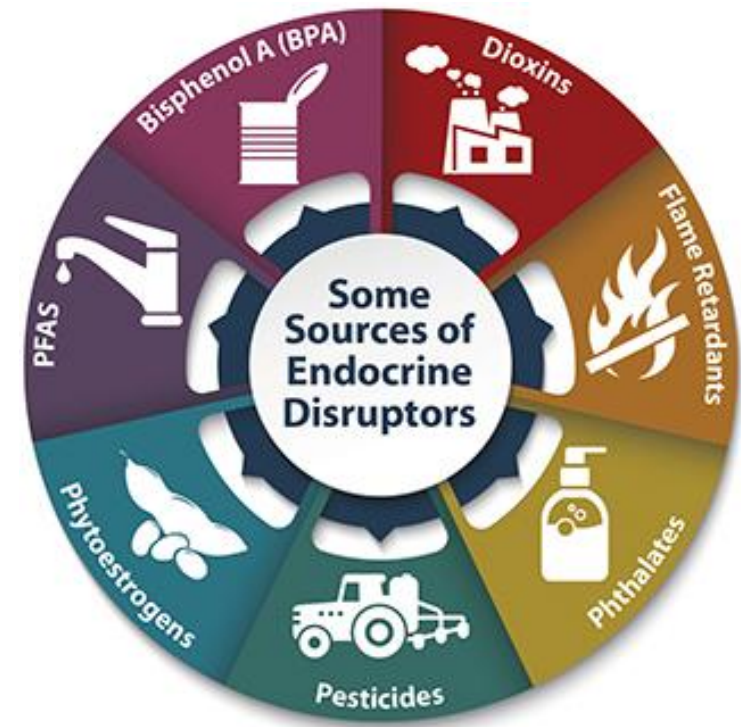
- Despite its presence in human populations and its association with **reproductive and developmental toxicity** in animals, **most countries have not imposed regulations** on the **manufacture, import, or sale of BPA products**.
- That has been due largely to **conflicting scientific evidence** for a **direct association between low-level exposure** and adverse health effects in humans.

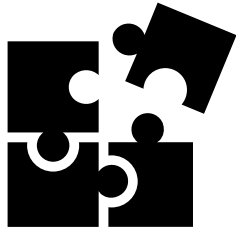




Bisphenol A (BPA)

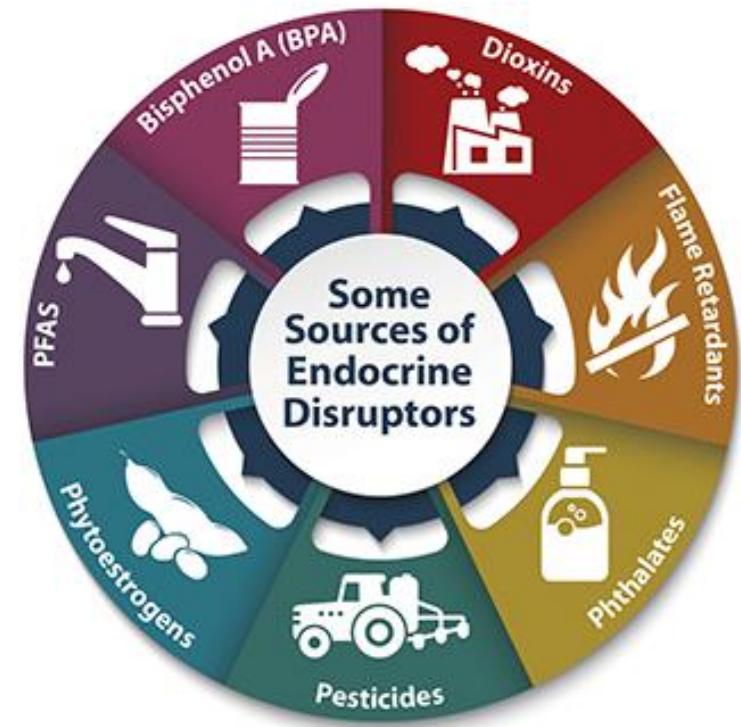
- In the early 1990s, American endocrinologist David Feldman and his team **discovered BPA** in the growth medium of polycarbonate flasks used to culture yeast cells.
- They confirmed that the BPA originated from the plastic used to make the flasks.
- They also found that **BPA produced estrogenic effects** in cells at levels 5 to 10 times lower than those used for safety assessments by companies that manufactured polycarbonate plastics.

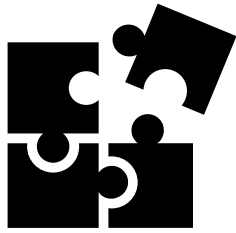




Bisphenol A (BPA)

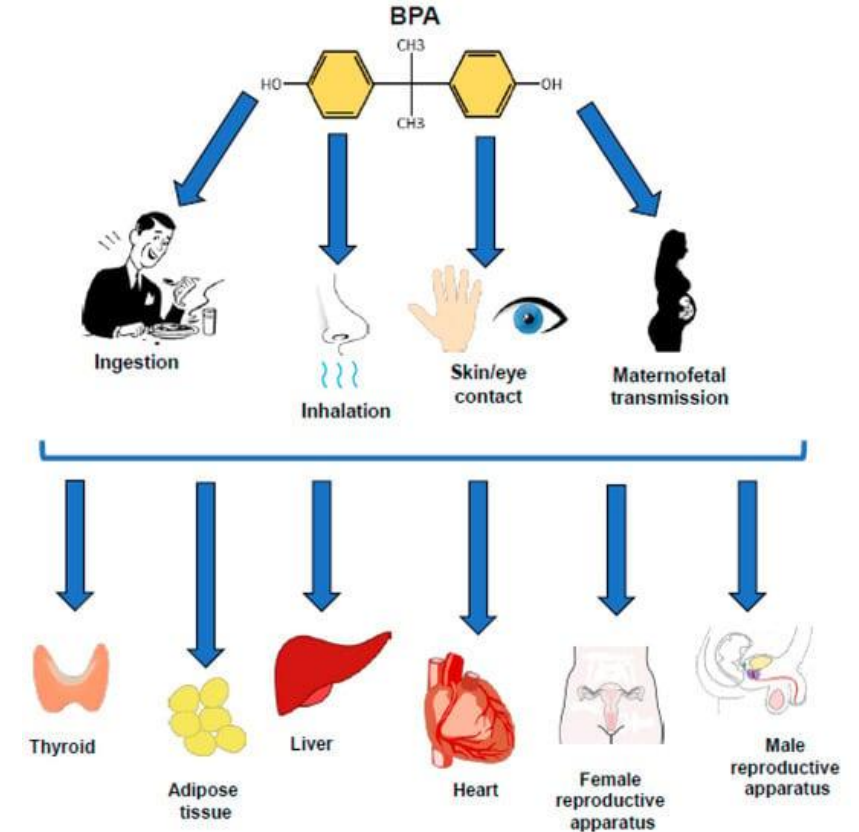
- Various conditions were found to facilitate the **leaching process**, including **photochemical breakdown**, **exposure to high temperatures**, the **presence of ethanol**, and the **age of the plastic or resin**.
- Other research suggested that **free unpolymerized BPA** may always be **present** in plastics and resins.

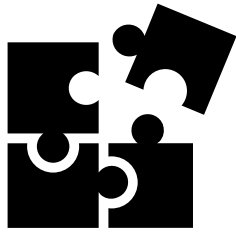




Bisphenol A (BPA)

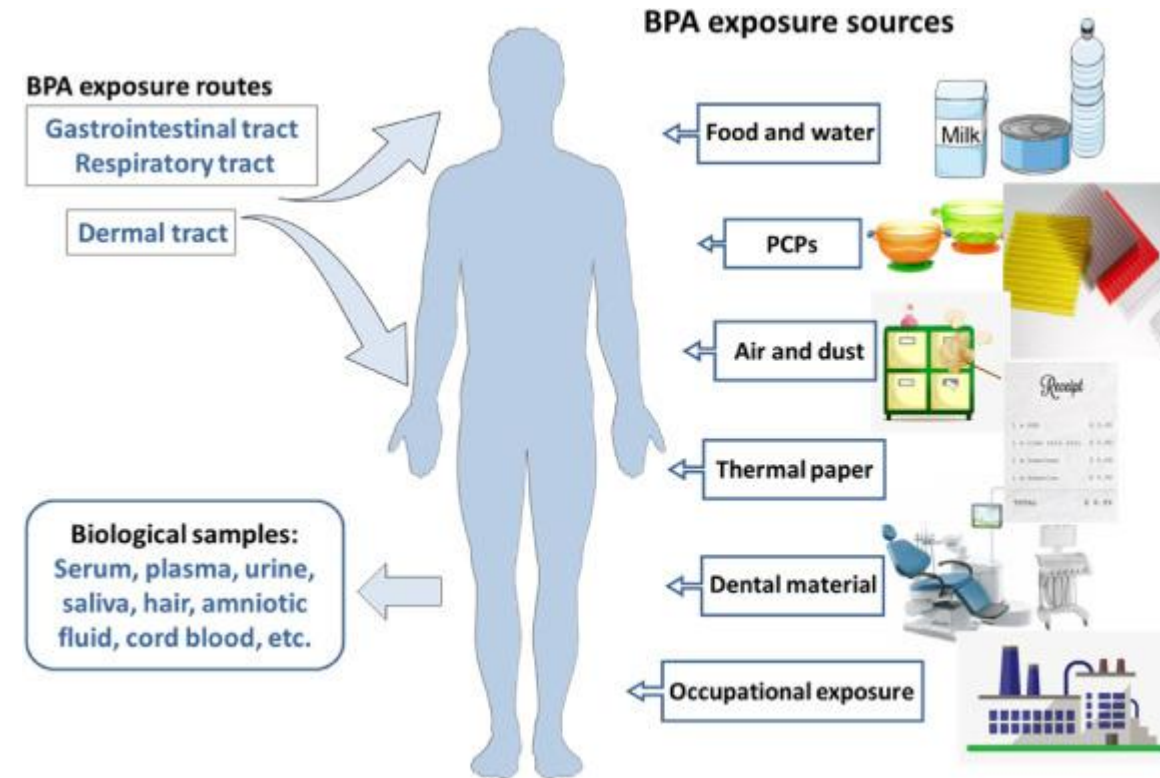
- BPA exposure sources include **ingestion**, **maternofetal transmission**, **inhalation**, **skin**, and **eye contact**.
- Once in the human body, BPA can negatively affect several targets, such as the **thyroid**, **adipose tissue**, **liver**, **heart**, **female**, and **male reproductive apparatus**.

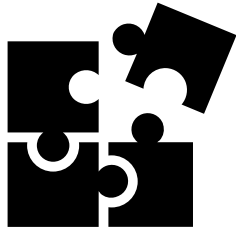




Bisphenol A (BPA)

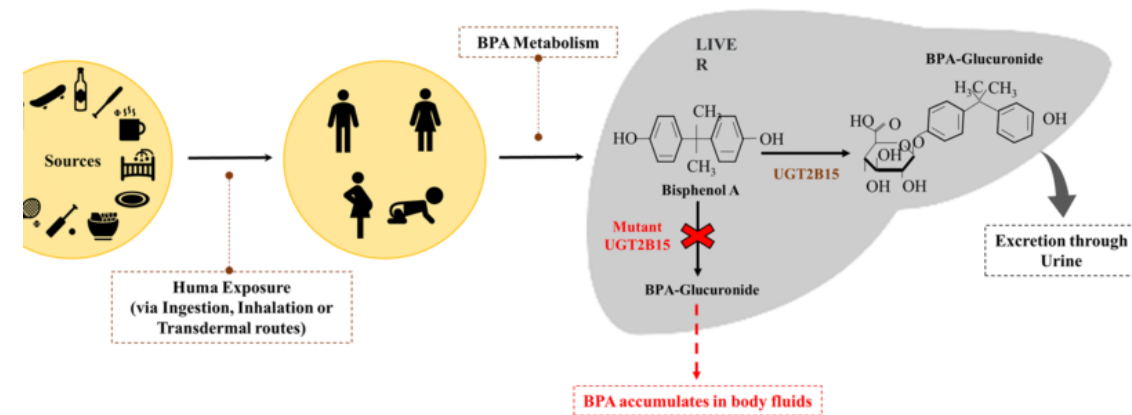
- BPA has a **rapid oral absorption**, once absorbed, this compound is conjugated in the **liver with glucuronic acid**.
- Because of its **lipophilic nature**, BPA has the ability to **accumulate in different human and animal tissues**, compromising their physiological functions and exerting deleterious effects on health.





Bisphenol A (BPA)

- By modulating **PPARs**, BPA induces **adipogenesis**, stimulates **lipid accumulation** in **adipose tissue** and **liver**, and **perturbs** cytokines levels.
- Furthermore, data obtained in human and different cell lines show that BPA **interferes** with **thyroid hormones synthesis**, **secretion**, and **signaling**.





Bisphenol A (BPA)

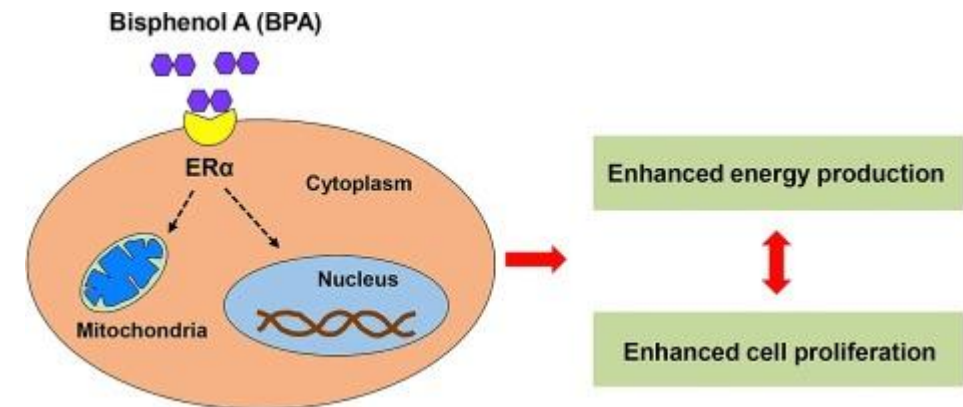
- BPA affects **glucose metabolism**, onset and **progression of several tumors**, and **immune function** by **binding different receptors**, **modulating transcription factors**, and inducing epigenetic changes.
- BPA exposure has been linked to an **increased risk of metabolic disorders**, such as **obesity**, **insulin resistance**, and **type 2 diabetes**, increased susceptibility to **allergies** and **autoimmune diseases**, **oxidative stress** and **inflammation**.

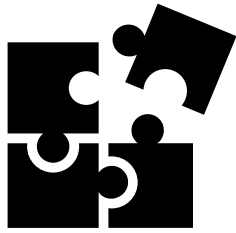




Bisphenol A (BPA)

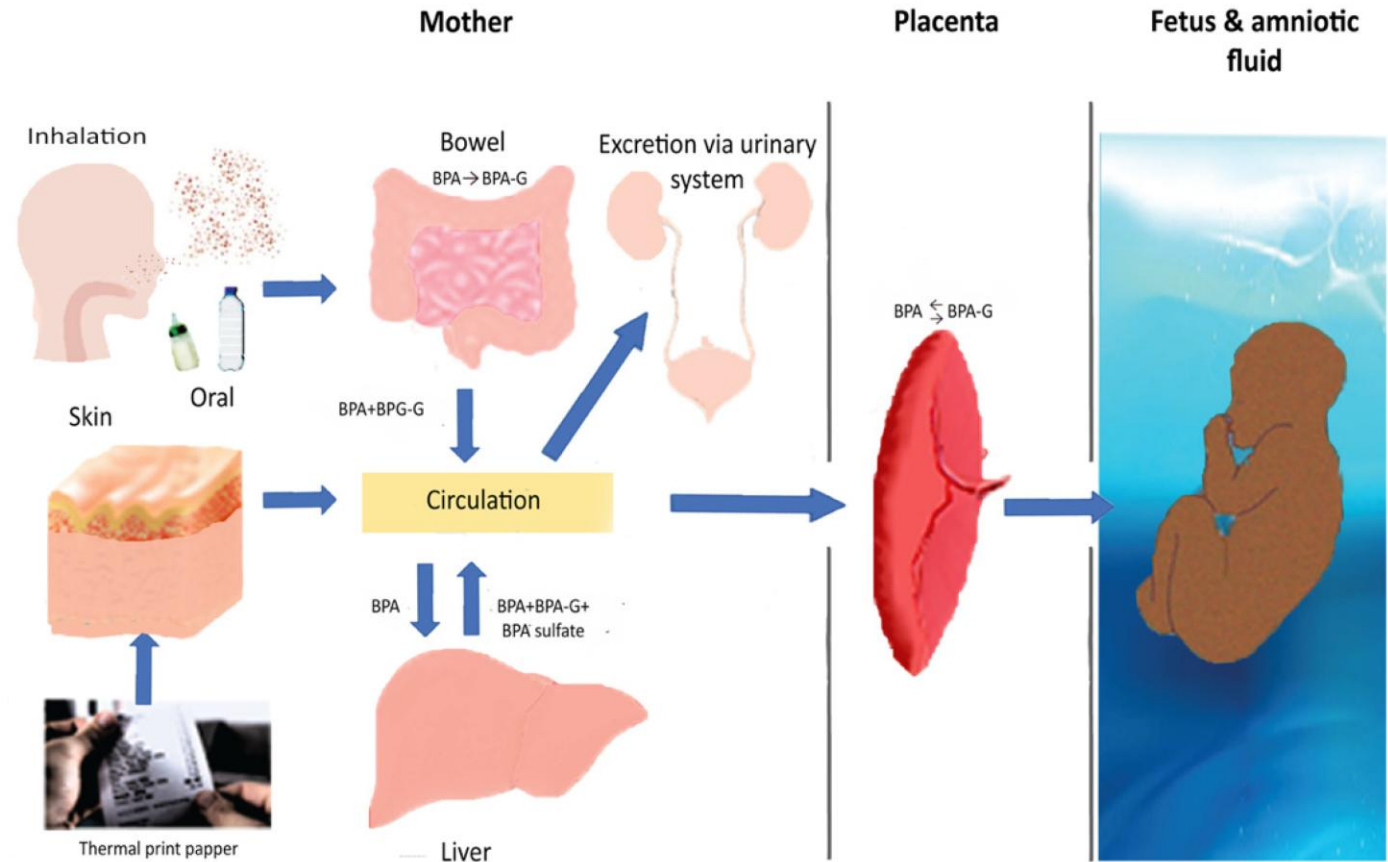
- BPA is known to **mimic estrogen** and can disrupt the **normal functioning of the endocrine system**.
- Due to its anti-androgenic action, BPA works as an **agonist on estrogen receptors** and **antagonist on androgen receptors**.
- It **binds to estrogen receptors** and can **alter hormone levels**, leading to various health issues: altered ovarian function, early puberty, and **infertility**.

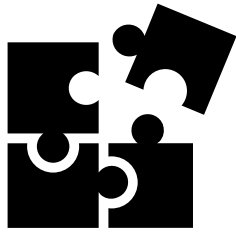




Bisphenol A (BPA)

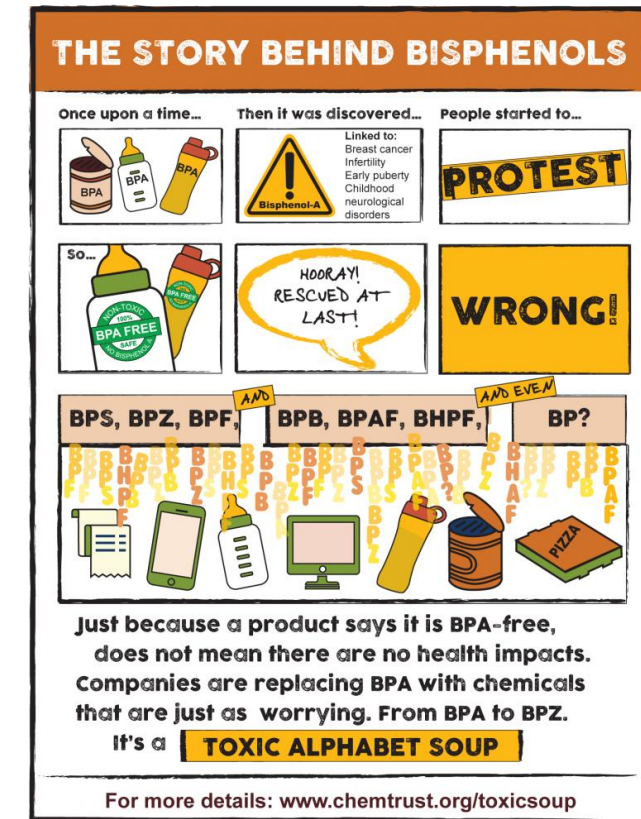
- BPA has been found to **cross the placental barrier** in **mammals** such as **rats and mice**, and it has been detected in **human maternal and fetal serum** and in human placental tissue.



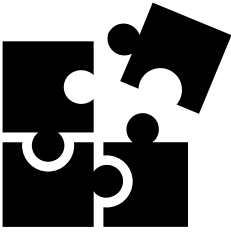


Bisphenol A (BPA)

- Some countries and regions, including **Canada, Europe, Sweden, and the United States**, on the other hand, **have formally banned BPA from infant and children's products**, including, variously, cans of infant formula, baby bottles, and sippy cups.

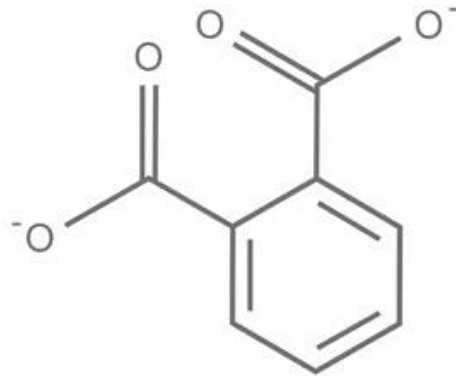


Chemicals That May Disrupt Your Endocrine System



Phthalates

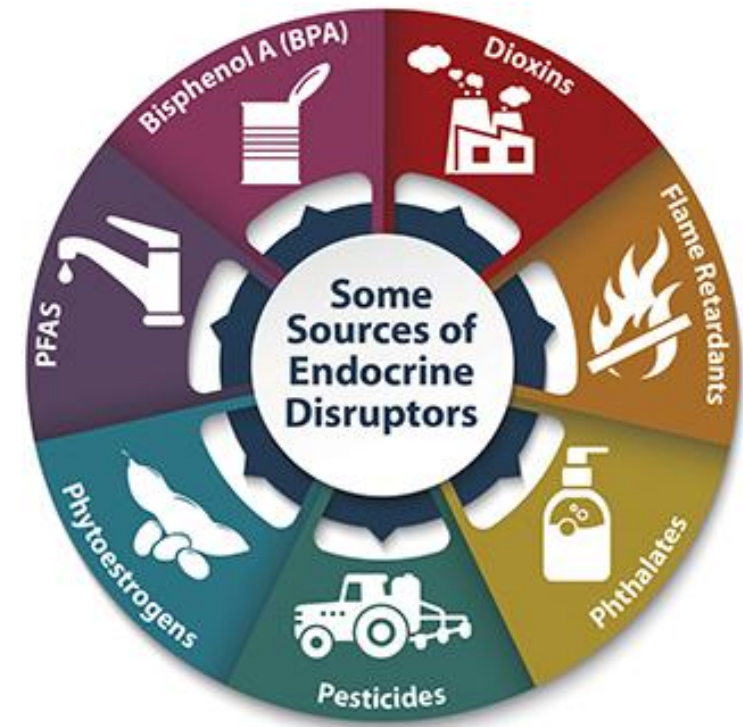
phthalates





Phthalates

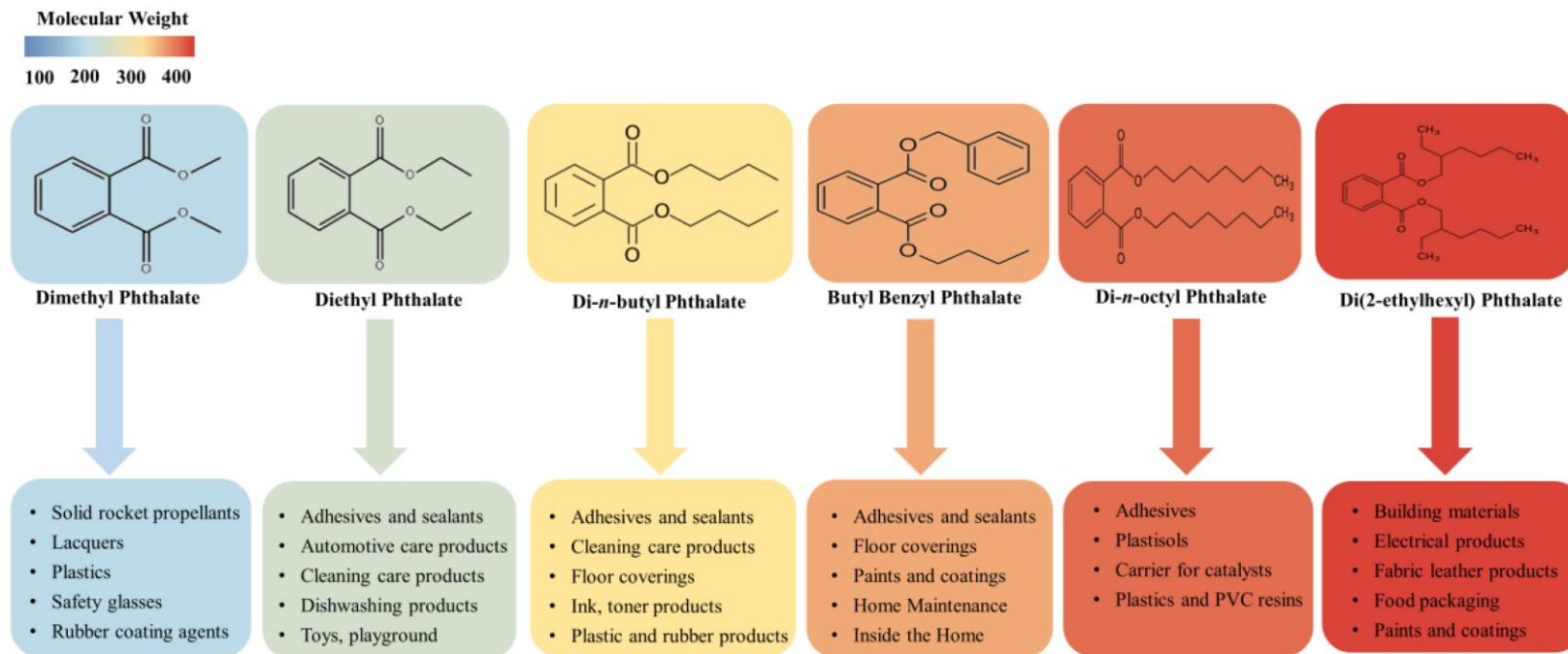
- **Phthalates** are a large group of compounds used as liquid plasticizers.
- They are found in hundreds of products including some **food packaging, cosmetics, fragrances, children's toys, and medical device tubing.**
- **Cosmetics** that may contain phthalates include **nail polish, hair spray, aftershave lotion, cleanser, and shampoo.**

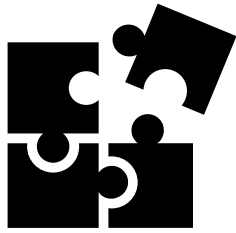




Phthalates

- **Phthalates**, such as diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), diethyl phthalate (DEP), di-isononyl phthalate (DiNP), and di-iso-decyl phthalate (DiDP), are **mainly used in the plastic industries as plasticizers** to produce **polyvinyl chloride (PVC)**.





Phthalates

- The global consumption of DEHP was estimated at 3.07 million tons (Global demand for plasticizers continues to rise, 2017).
- The estimated global market of phthalates in 2020 was expected to reach 10 billion USD and would still be widely used in plasticizers.

Phthalates



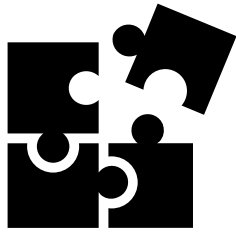
Di-2-ethylhexyl Phthalate (DEHP)



Diethyl Phthalate (DEP)
Dibutyl Phthalate (DBP)

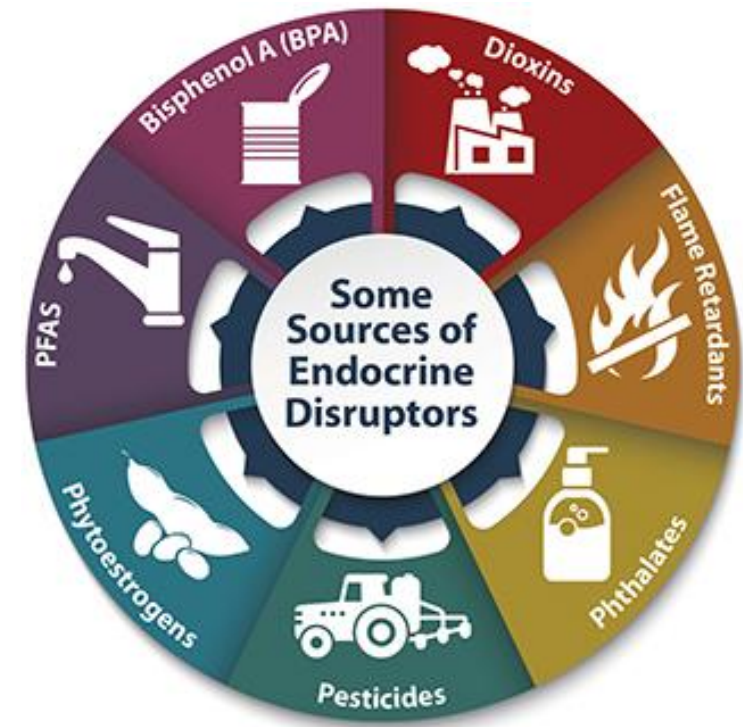


Di-2-ethylhexyl Phthalate (DEHP)
Butylbenzyl phthalate (BBzP)

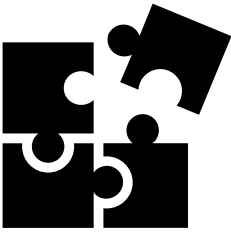


Phthalates

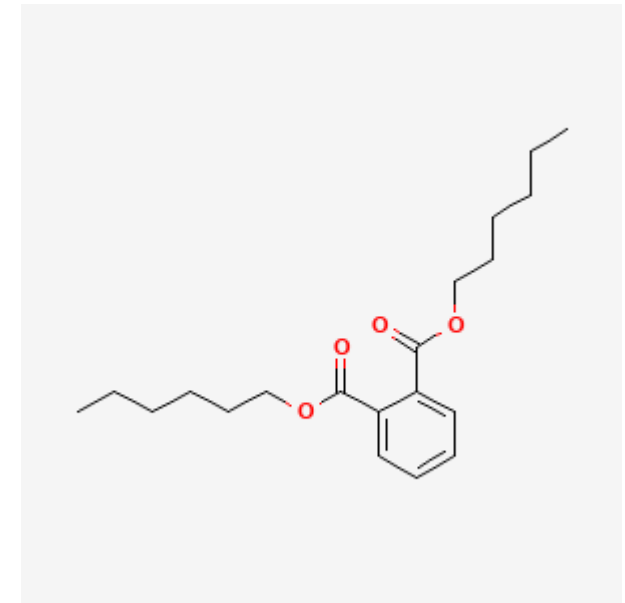
- Phthalates can be easily leaching into food, water, and other products applied directly to the human body.
- The detrimental health and environmental effects have been increasingly studied to assess the extent of the impacts on society.



Phthalates



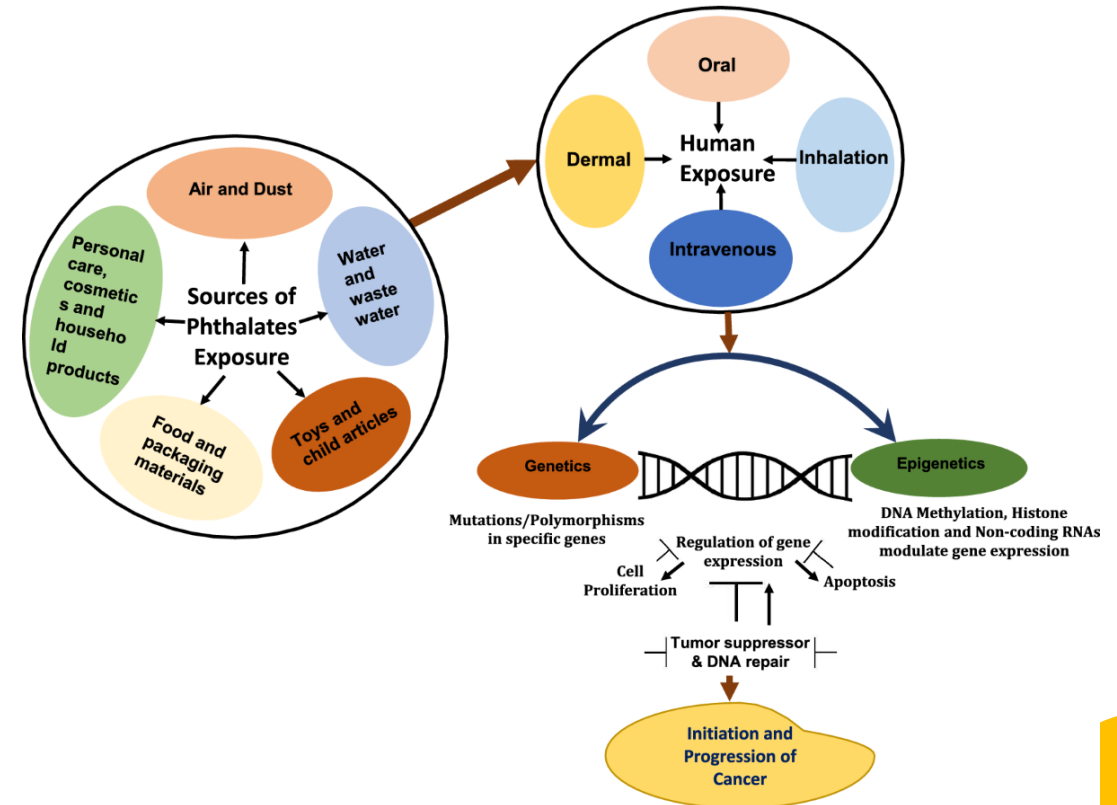
- The bio-metabolism in the human body is **very rapid** since phthalates have short biological half-lives, **about 12 h**.

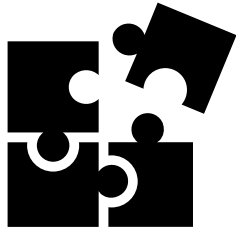




Phthalates

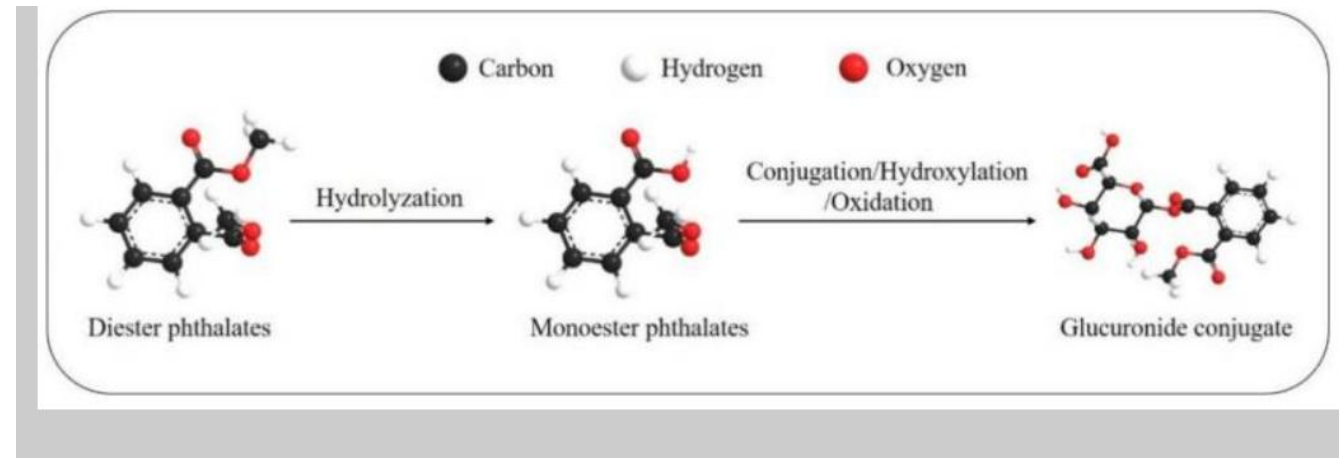
- The first step of metabolism is hydrolyzation after absorption into cells.
- The second step is conjugation to form the hydrophilic glucuronide conjugate, which is catalyzed by the enzyme uridine 5'-diphosphoglucuronyl transferase.
- The type of phthalates determines its toxicological fate in the body.

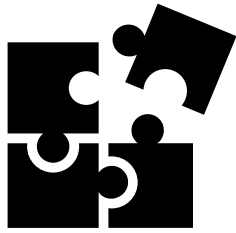




Phthalates

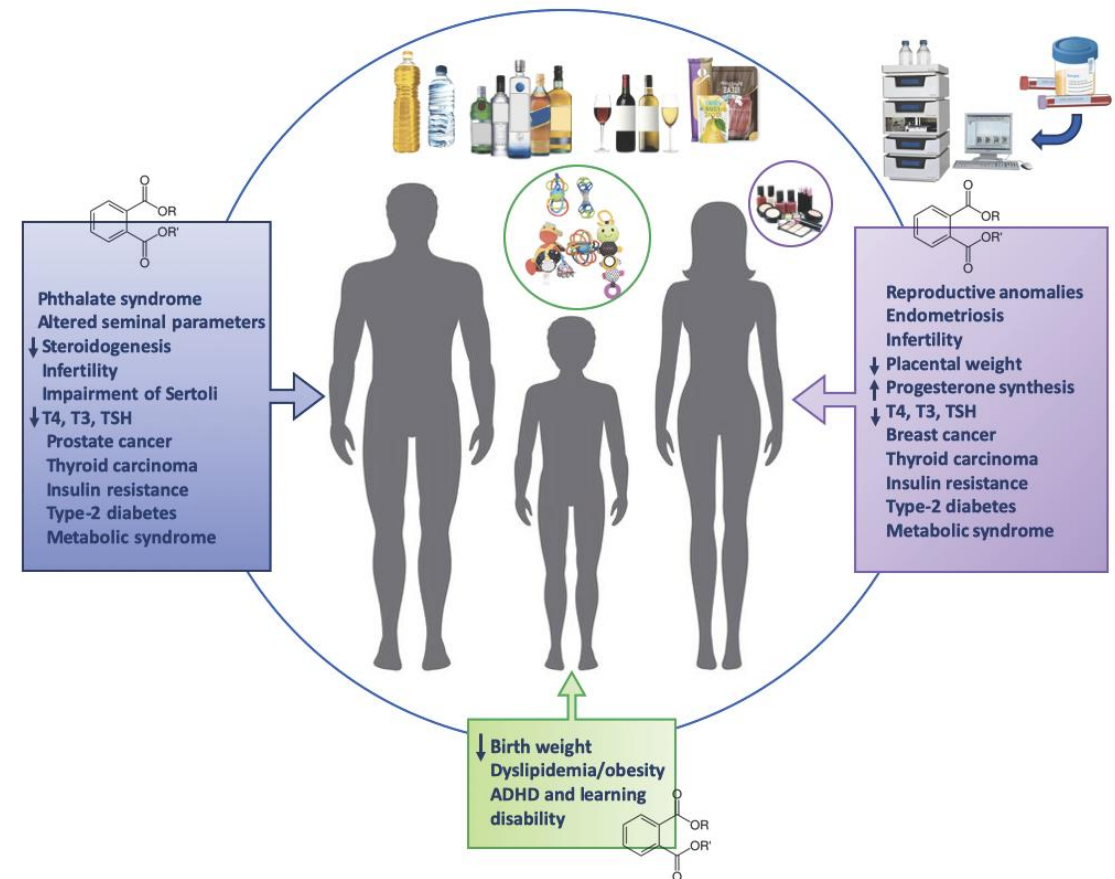
- Short-branched phthalates are often **hydrolyzed to monoester phthalates** and then excreted in the urine,
- Long-branched phthalates mainly **undergo several bio-transformations**, such as hydroxylation and oxidation, and then **excreted in urine and feces as phase 2 conjugated** compounds.

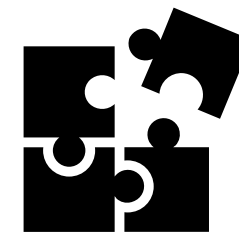




Phthalates

- Despite the **short half-lives in tissues**, **chronic exposure** to phthalates will adversely influence the **endocrine system** and **functioning of multiple organs**, which has **negative long-term impacts on the success of pregnancy, child growth and development**, and reproductive systems in both young children and adolescents.





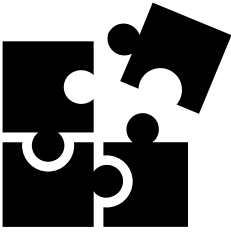
Phthalates

- Children are at a **higher level of exposure** and **more vulnerable to phthalates**.
- Currently, many phthalates are **banned and restricted in multiple countries**.

Restrictions in Japan, Europe, the US, Australia, and China.

Country	Restrictions
Japan [41]	DiNP and DEHP are banned in toys; DEHP is banned in food-handling gloves
Europe [42,43]	DEHP, DBP, DiBP, and BBP are banned in all PVC and plasticized toys and childcare articles; DiNP, DiDP, and DnOP are banned for products that can be placed in children's mouth
The United States [44]	Products containing DEHP, DBP, and BBP at levels >0.1% by weight shall be banned, especially children's toys, and childcare articles; children's products that can be placed in a child's mouth or childcare articles containing more than 0.1% of DiNP, DiDP, and DnOP are banned
Australia [45]	Children's plastic products containing, or have a component containing more than 1% by weight DEHP are banned
China (National Standard of the People's Republic of China)	16 phthalates are restricted in food and food containers, including DNP, DnOP, DEHP, DiNP, DiBP, BBP, etc; dissolved DEHP in transfusion (infusion) equipment is restricted to less than 10 mg/mL; the total amount of DEHP, BBP, DBP in childcare articles should not be more than 0.1%.

Chemicals That May Disrupt Your Endocrine System



➤ **Atrazine**



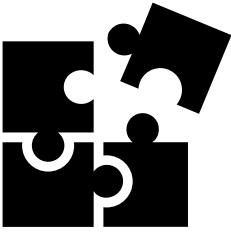


Atrazine

- **Atrazine** is one of the most commonly applied **herbicides** in the **world**, often used to control **weeds** in corn, sorghum, and sugarcane crops.
- Atrazine functions by **inhibiting photosynthesis in plants**, specifically by **blocking the electron transport chain in photosystem II**.

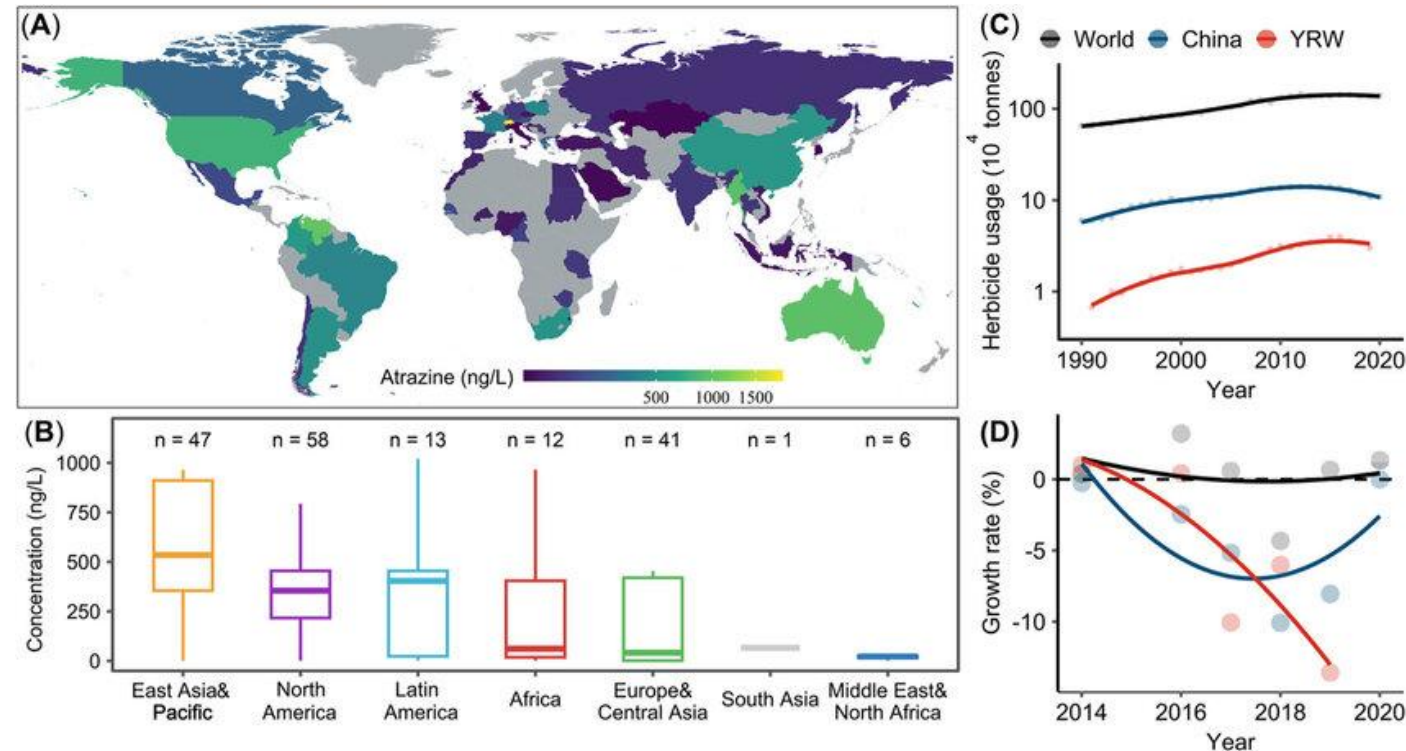


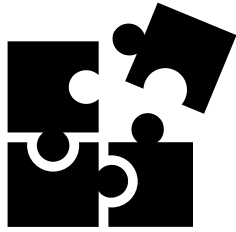
Atrazine



Environmental Impact:

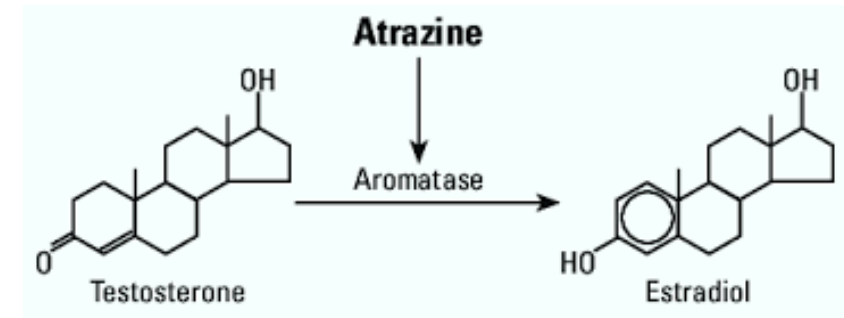
- Atrazine is known for its **persistence in the environment**, leading to concerns about its impact on **soil and water quality**.
- It can **leach into groundwater and contaminate drinking water sources**.
- Atrazine is also **frequently detected in surface waters**, particularly in **agricultural regions** where it is extensively applied.



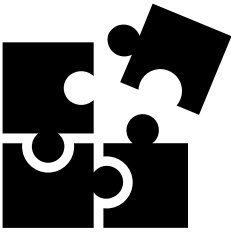


Atrazine

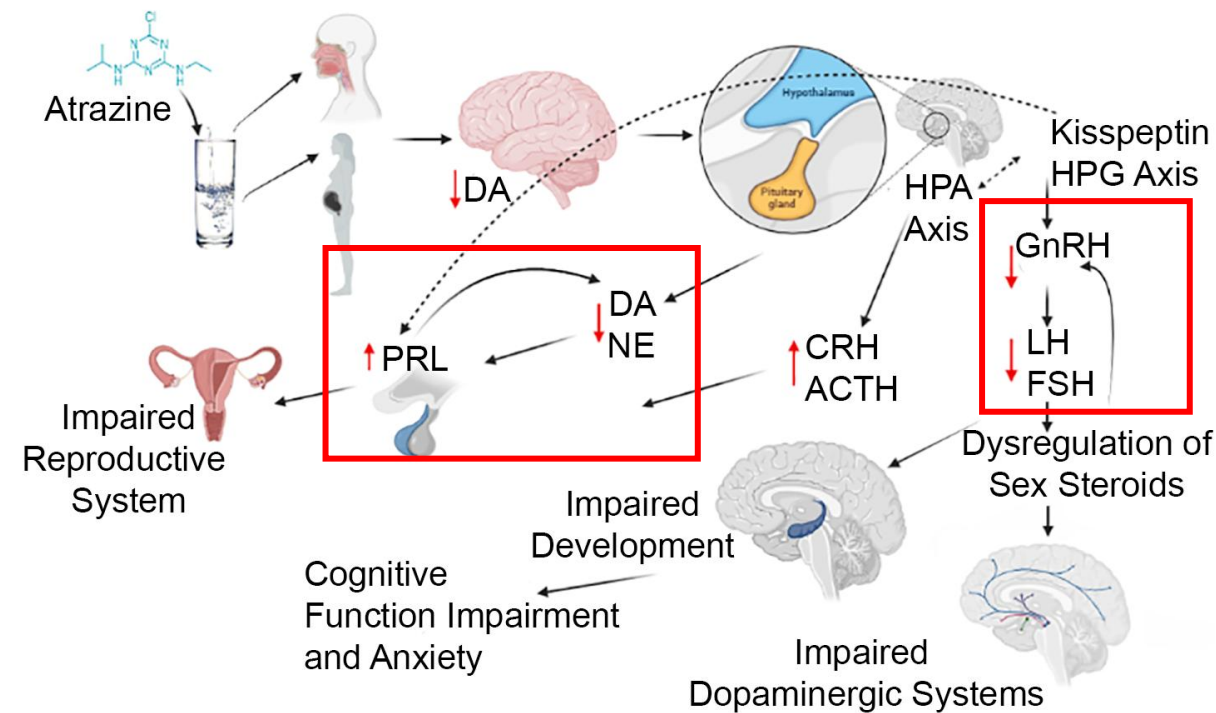
- **Atrazine** affects **reproductive functions** in **different species**, including humans and wildlife (especially amphibians).
- In humans, atrazine has been linked to **irregular estrogen and androgen** levels, **abnormal birth weight** and **potential carcinogenicity**.
- Inhibited luteinizing hormone (LH) and **testosterone** production when applied at concentrations at or above 100 mg/kg per day



Atrazine



- Atrazine- induced changes in cAMP levels (cyclic adenosine monophosphate – secondary messenger) were sufficient to stimulate prolactin release in pituitary cells and androgen production in Leydig cells, indicating that it acts as an endocrine disrupter both in cells that secrete by exocytosis of prestored hormones and in cells that secrete by *de novo* hormone synthesis.

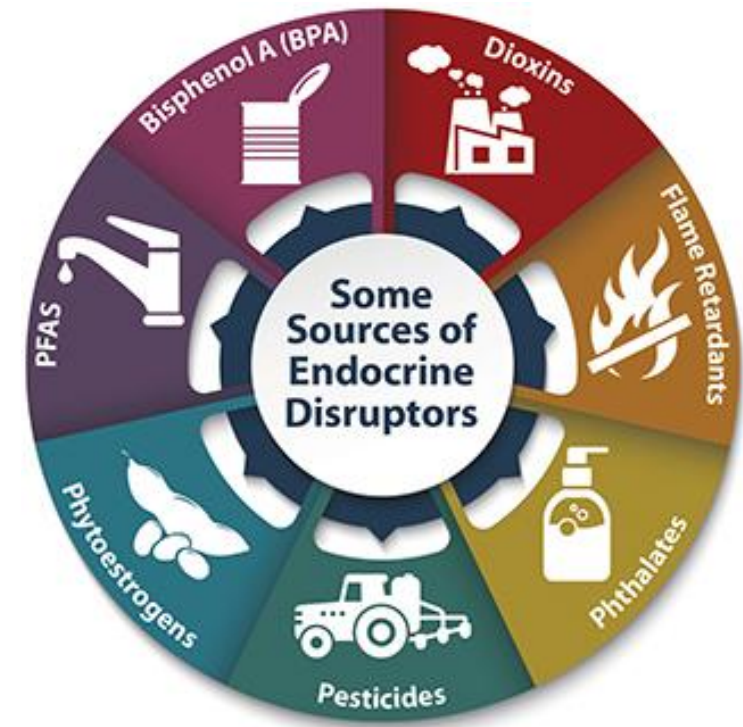




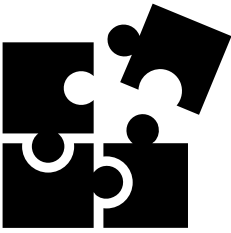
Atrazine

Regulation and Controversy:

- The **use of atrazine** is regulated in **many countries** to minimize **environmental and health risks**.
- In the United States, the Environmental Protection Agency (EPA) sets **maximum allowable levels of atrazine in drinking water** and monitors its presence in the environment.
- The **European Union** banned atrazine in **2004** due to its persistent contamination of water sources.

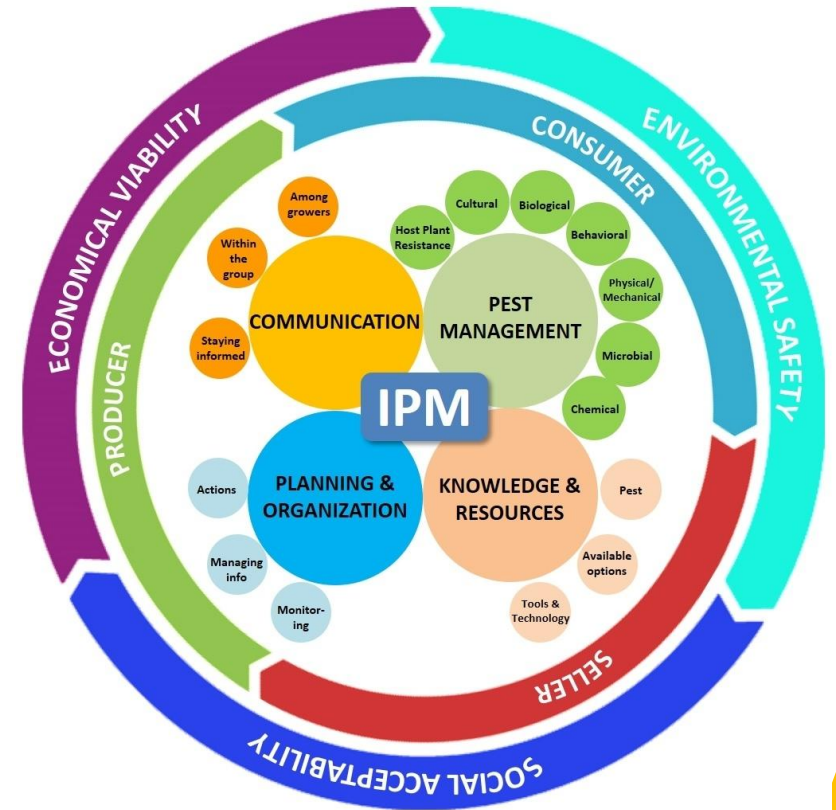


Atrazine

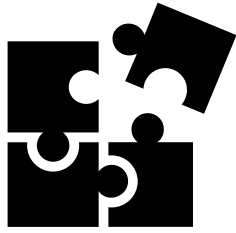


Alternatives and Integrated Pest Management (IPM):

- Alternatives to atrazine include other herbicides with different modes of action, as well as non-chemical methods such as crop rotation and mechanical weed control.
- **Integrated Pest Management (IPM)** strategies aim to reduce reliance on chemical herbicides like atrazine by combining biological, cultural, physical, and chemical tools in a way that minimizes economic, health, and environmental risks.

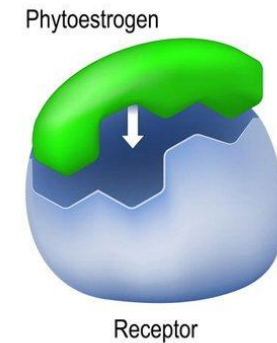
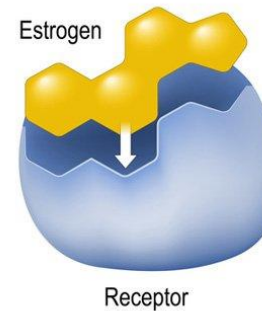
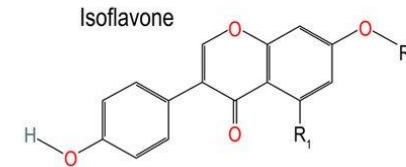
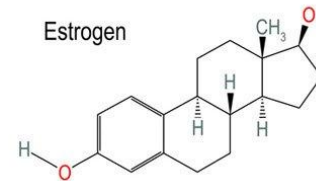


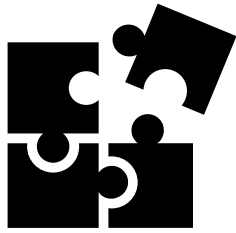
Chemicals That May Disrupt Your Endocrine System



Estrogen and Phytoestrogen

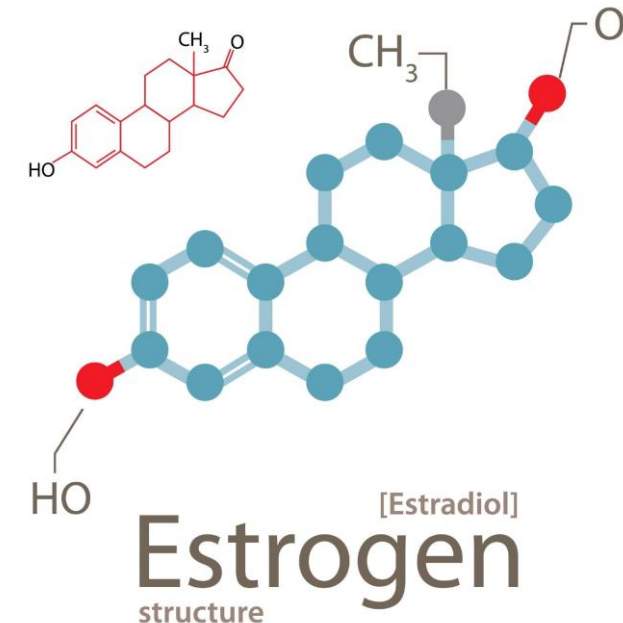
Phytoestrogens

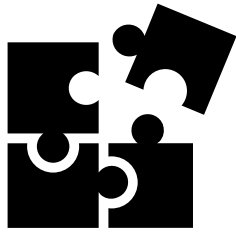




Phytoestrogens

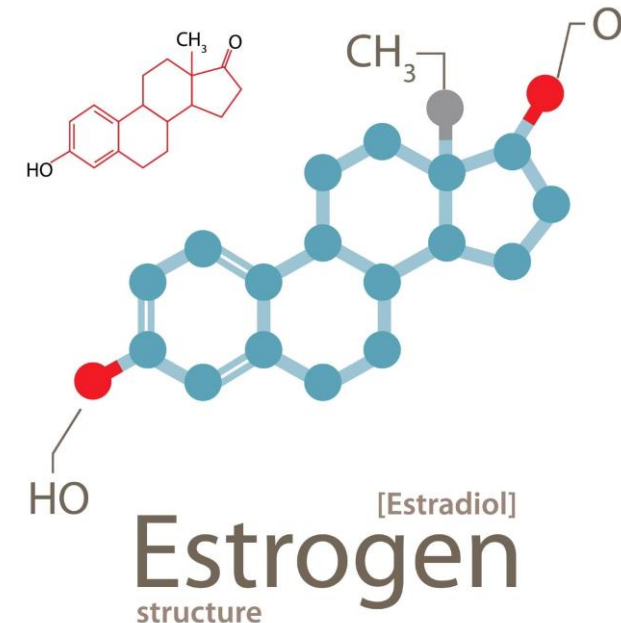
- **Estrogen** - a lipid-soluble steroid hormone, is one of the most important female sex hormones.
- It is predominantly produced by the ovaries, and adrenal cortex, and performs various crucial physiological functions.





Phytoestrogens

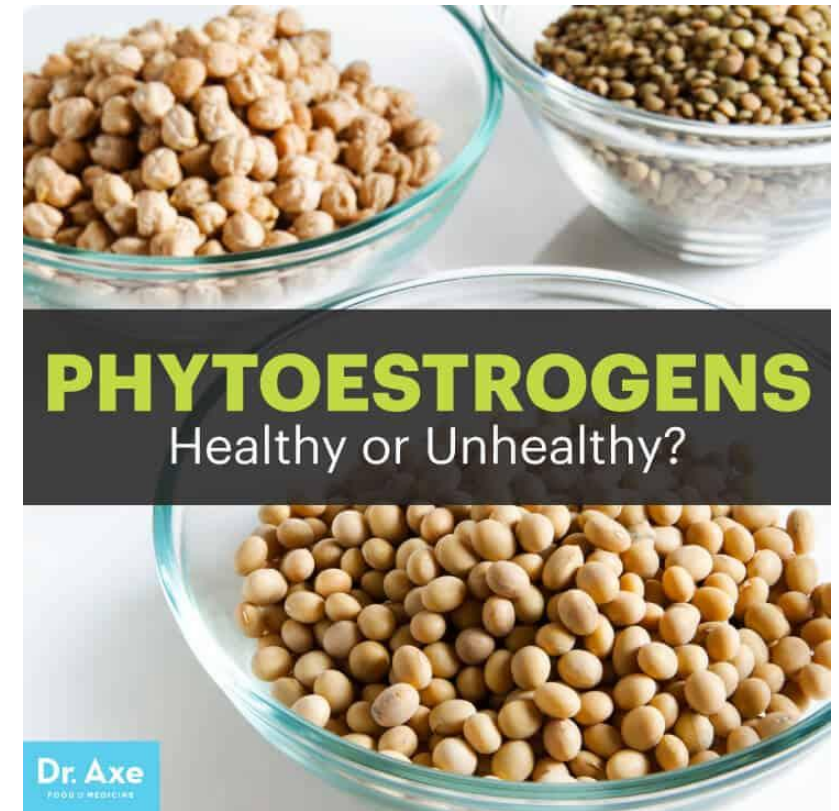
- **Estrogen**, additionally play crucial roles in regulating the cardiovascular system, liver, pancreas, bone, brain, and immune system.
- Is indispensable to **glucose homeostasis, immune robustness, bone health, cardiovascular health, fertility, and neural functions.**

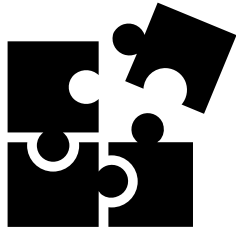




Phytoestrogens

- **Phytoestrogens** are naturally occurring substances with hormone-like activity found in some **plants**; they may have a similar effect to estrogen produced by the body.

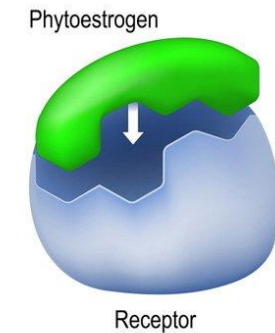
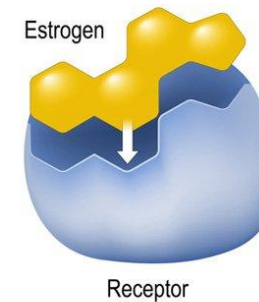
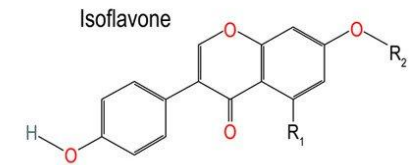
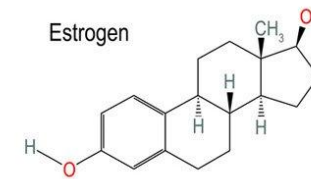




Phytoestrogens

- **Phytoestrogens** have a **chemical structure similar** to the hormone **estrogen**.
- They can interact with estrogen receptors in the human body, exerting both **estrogenic and antiestrogenic effects**.

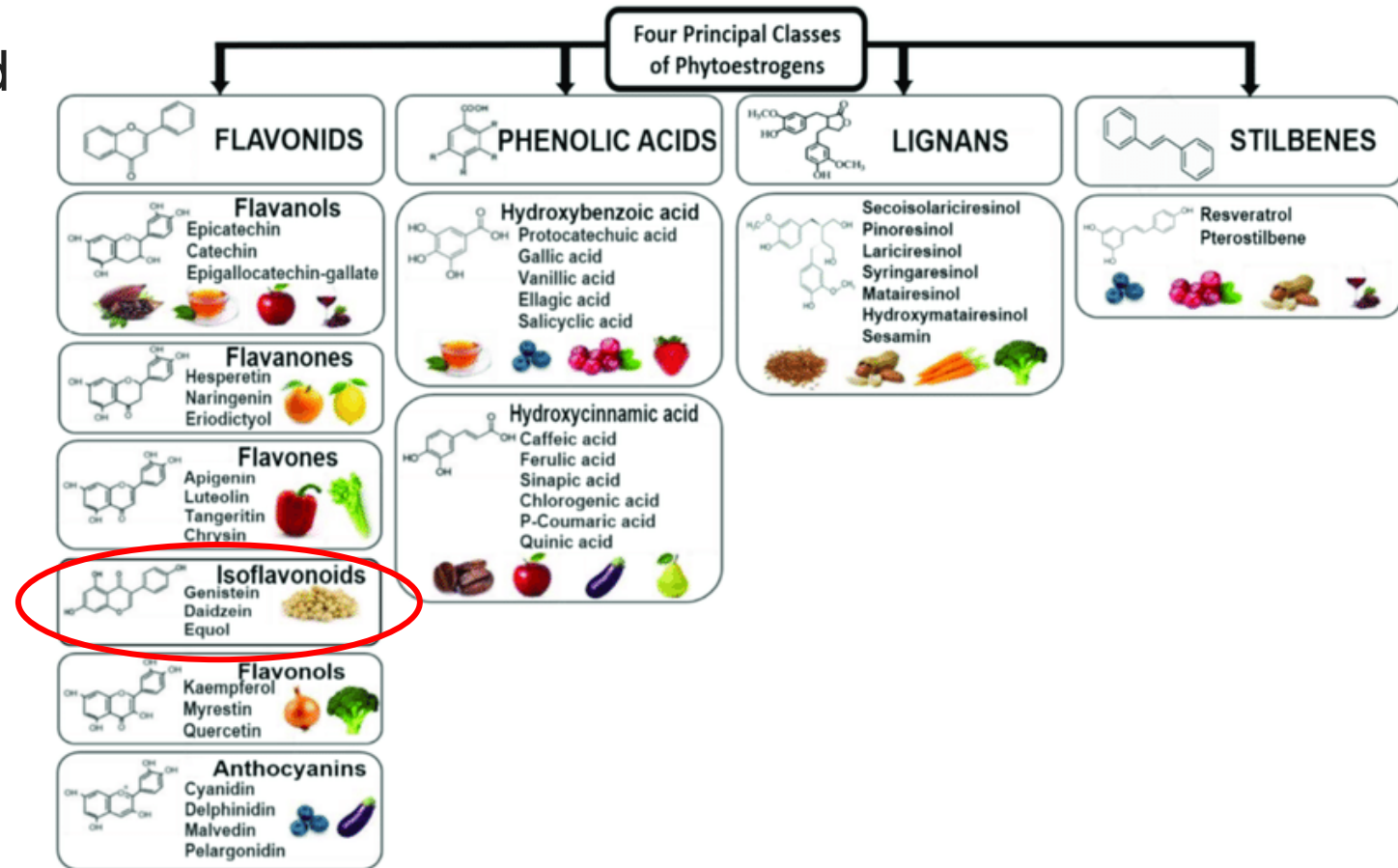
Estrogen and Phytoestrogen

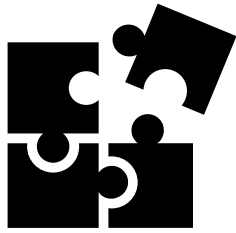




Phytoestrogens

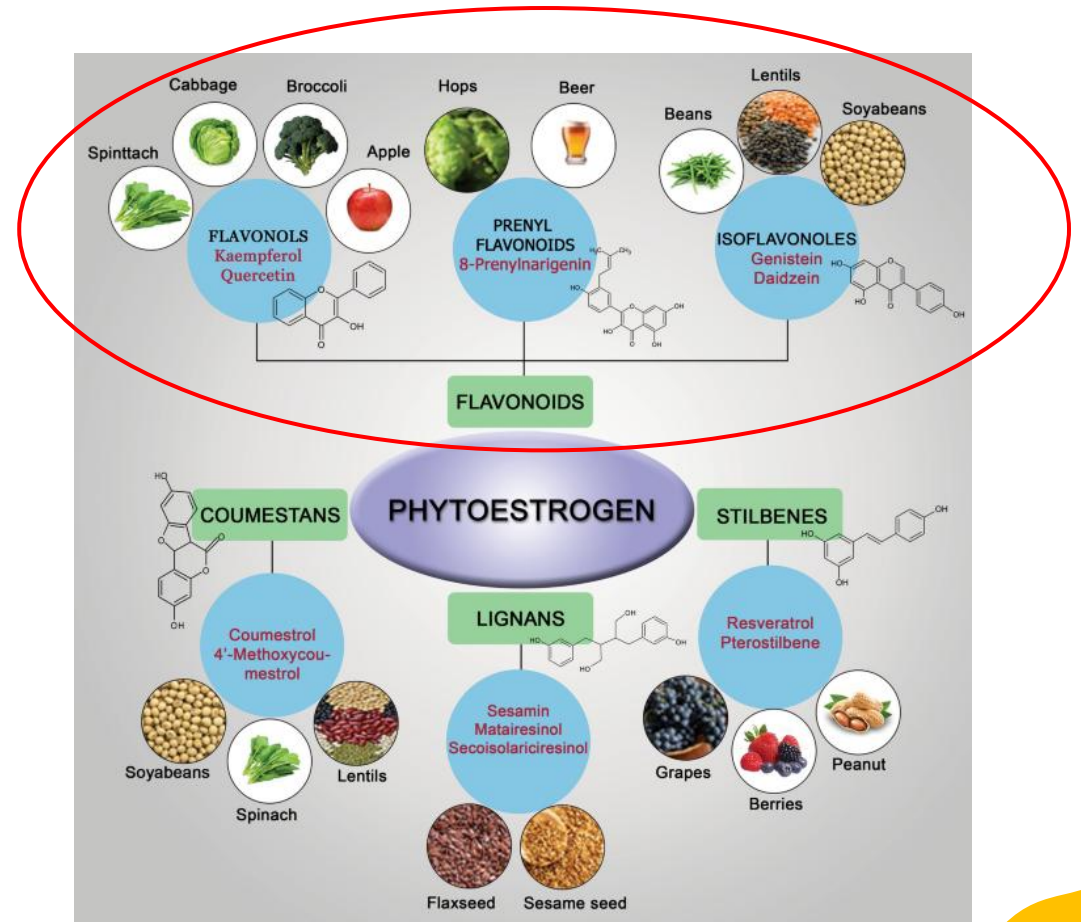
- Four phenolic compounds classified as phytoestrogens are isoflavones, stilbene, coumestan, and lignan.

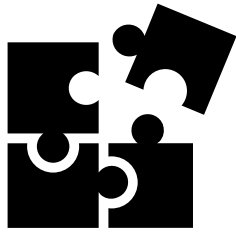




Phytoestrogens

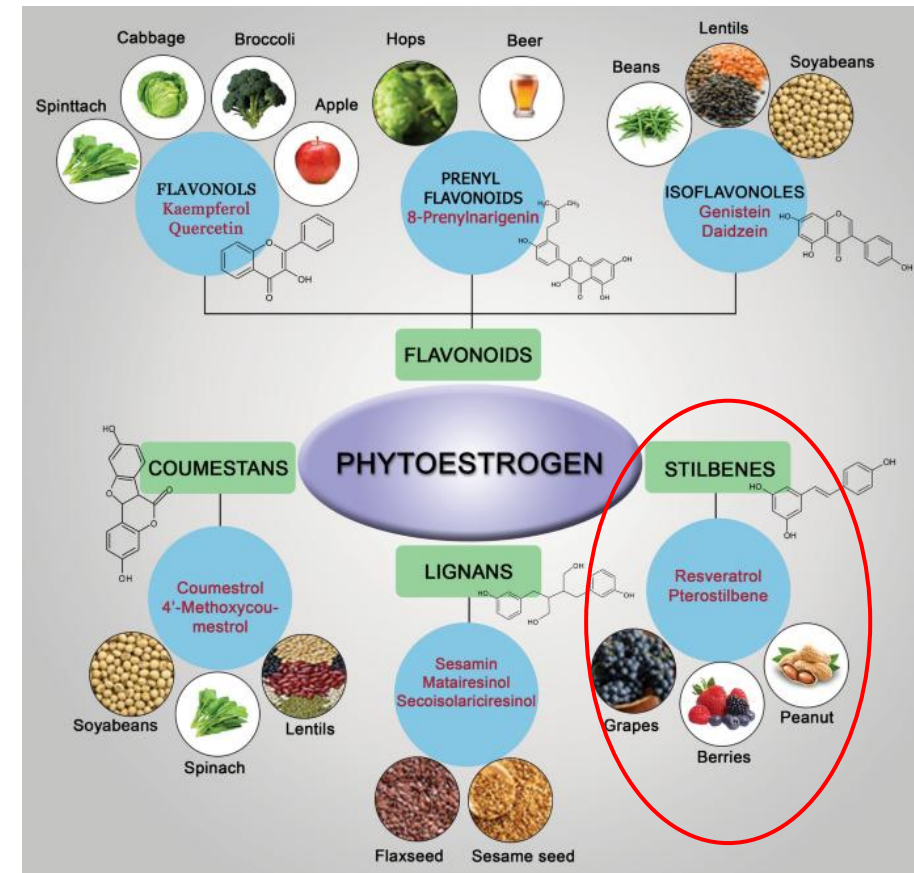
- **Isoflavones** are found in **soybeans** and other legumes.
- The main phytoestrogens in the form of isoflavones are **genistein**, **daidzein**, **glycitein**, **formononetin**, and **biochanin A** contained in soybeans.
- Phytoestrogens that are classified as isoflavones are the **most widely studied**.





Phytoestrogens

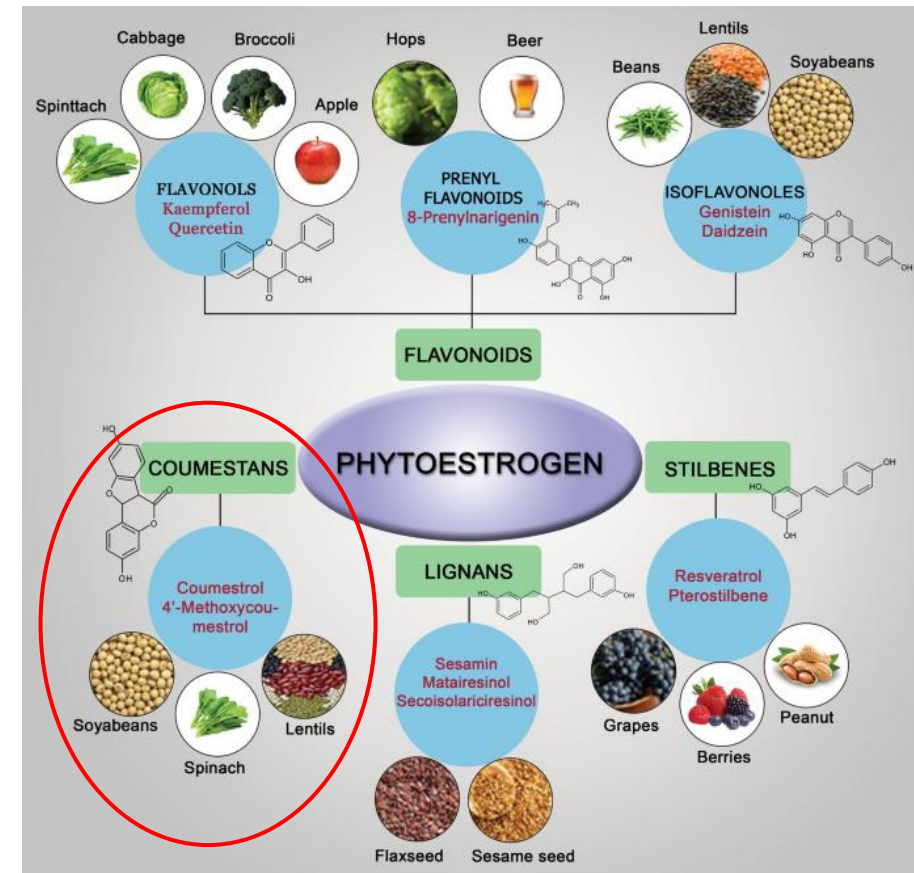
- The most common **stilbene group** is **resveratrol**, which is found in grapes and peanuts.
- Resveratrol consists of **two isomers** namely **cis** and **trans**.
- Trans has a **higher estrogenic** activity.





Phytoestrogens

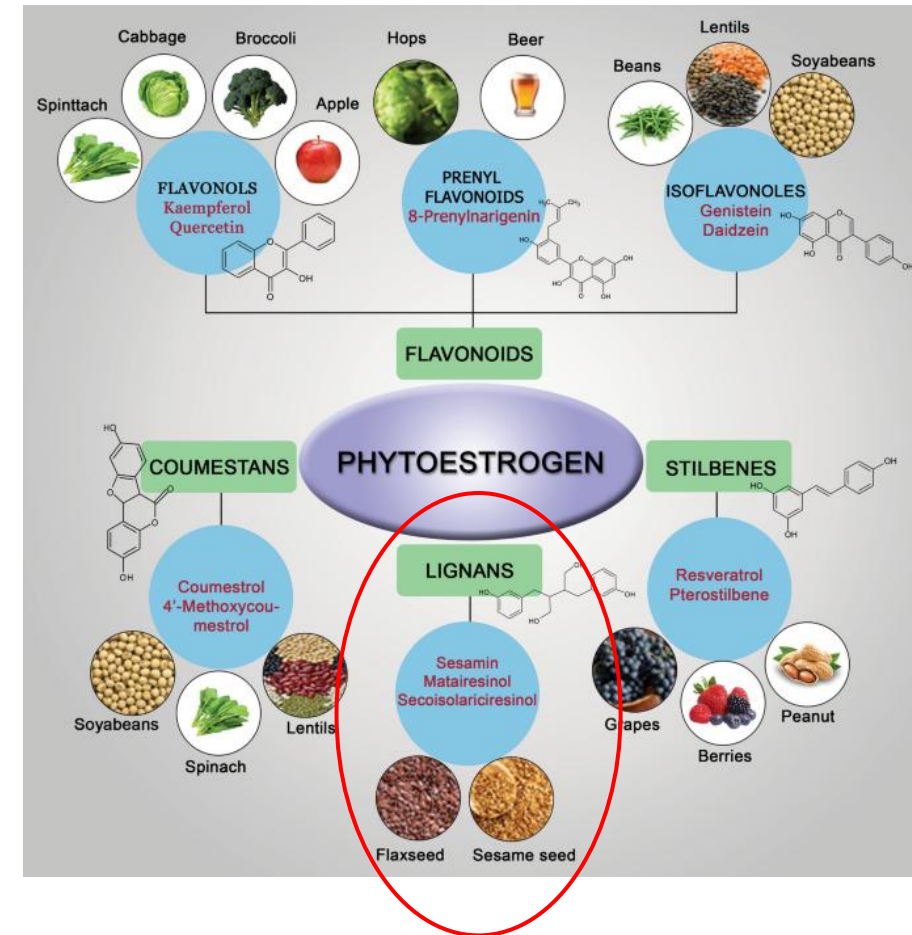
- Coumestans are oxidation products of pterocarpan that are similar to **coumarin**.
- Coumestans, including coumestrol, a phytoestrogen, are found in a **variety** of plants.
- **Coumestans** are **less common** in human diet than **isoflavones**.



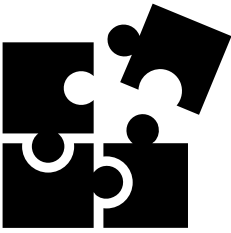


Phytoestrogens

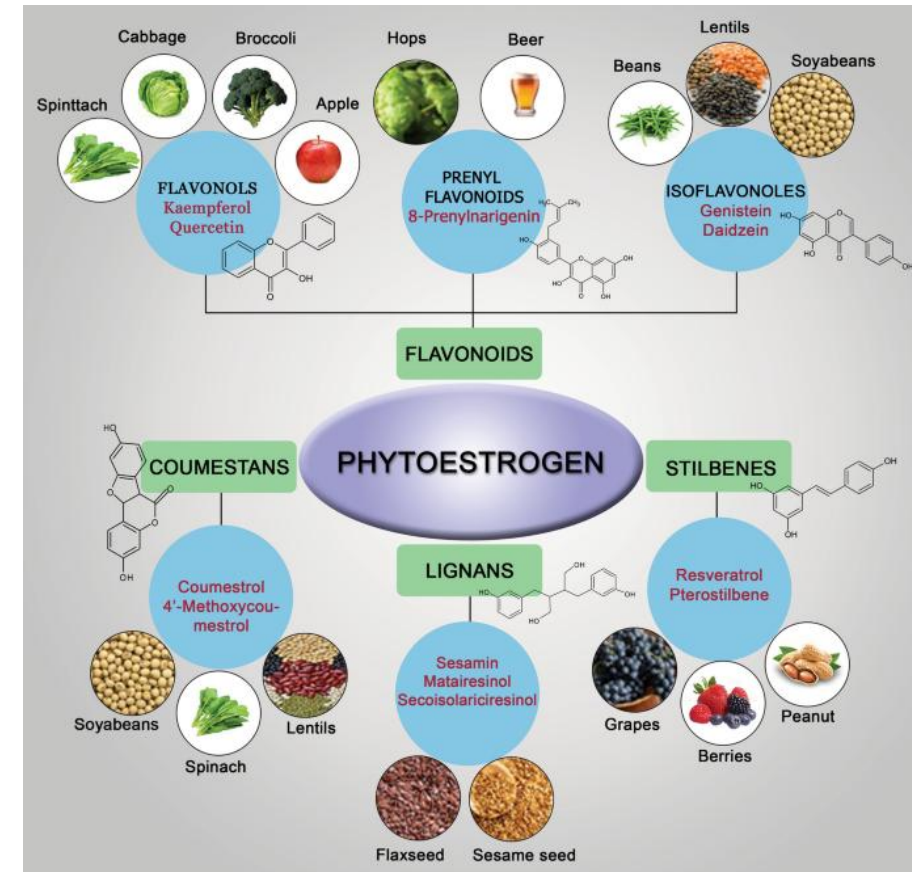
- **Flaxseeds** are the main source of **lignans**, and many contestants are found in clover, alfalfa and soybean sprouts .



Phytoestrogens



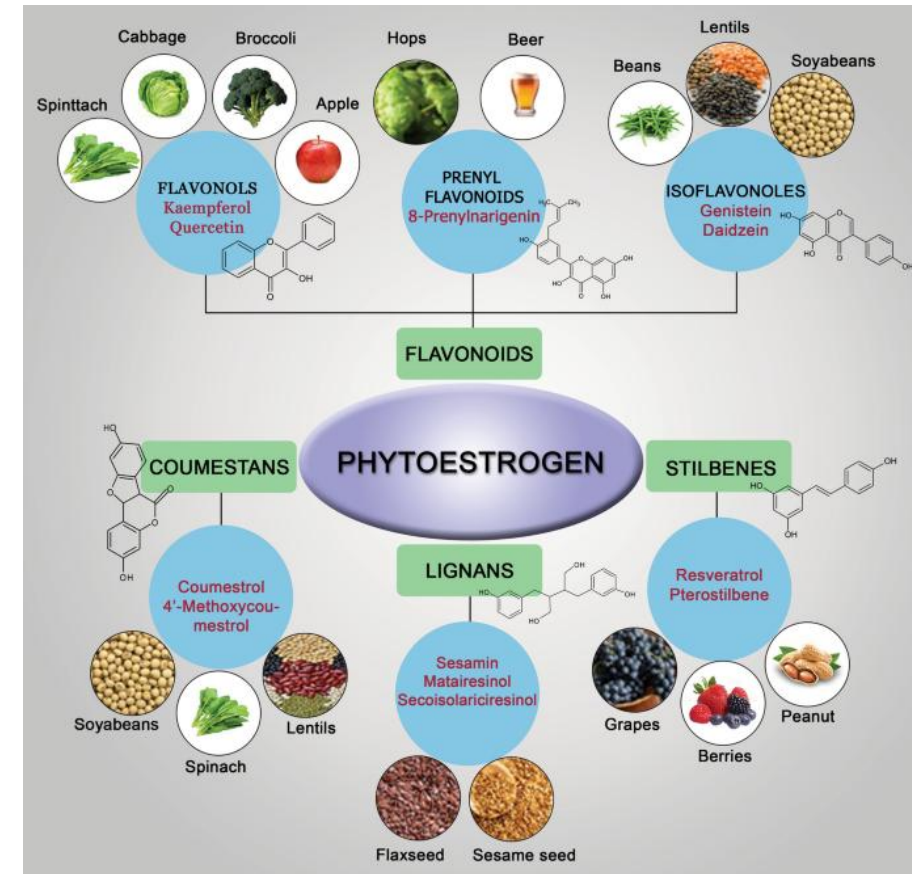
- Phytoestrogens have different effects on the body.
- Endogenous estrogen levels also affect the activity of phytoestrogens.

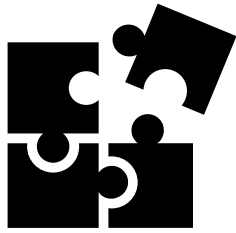




Phytoestrogens

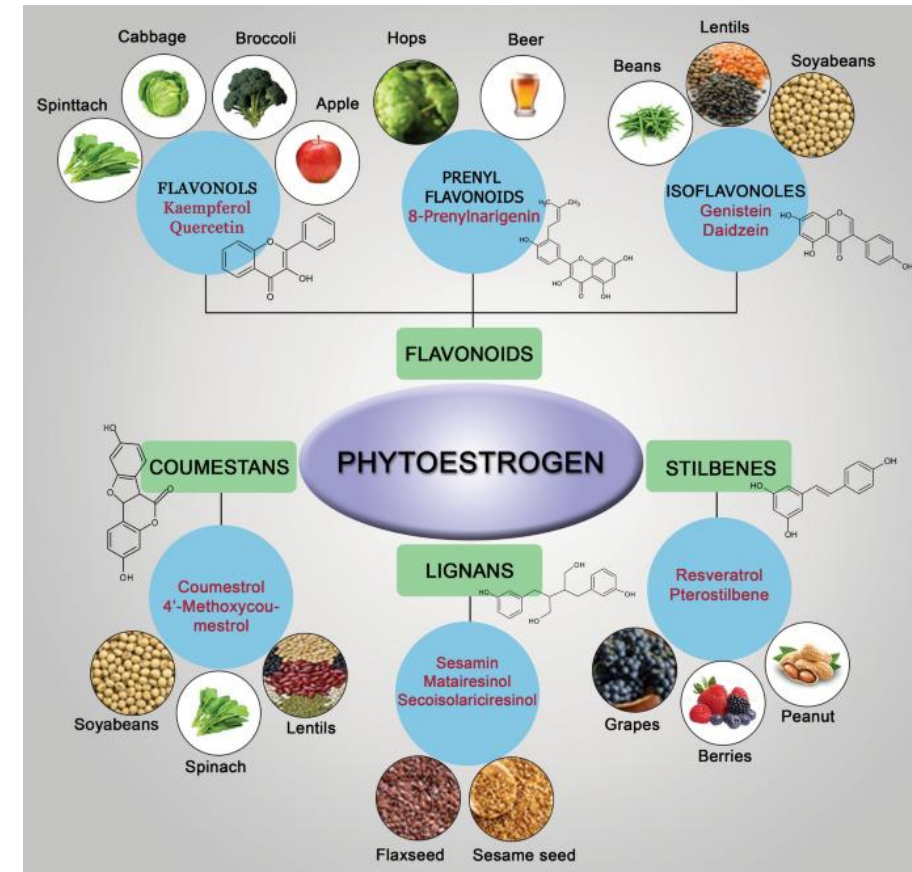
- In women of reproductive age, endogenous estrogen levels is high. In this condition, lignans will compete with endogenous estrogen to bind to estrogen receptors so that they can inhibit estrogen activity.
- In women, higher estradiol (E2) levels were found among those with elevated BP or hypertension than those with normal BP

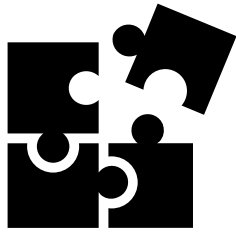




Phytoestrogens

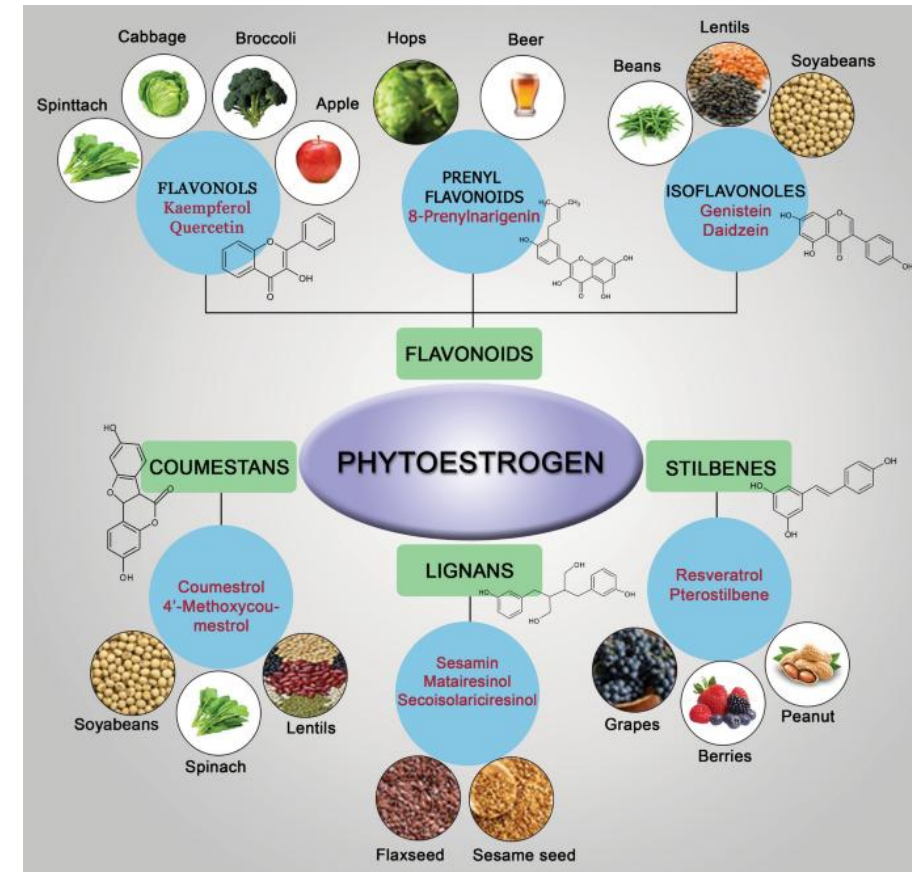
- Isoflavones, lignans also function as **aromatase inhibitors** by inhibiting the action of cytochrome P450 enzymes that convert **androgens to estrogen**.
- Elevated levels of the **cytochrome P450 enzyme** are associated with breast, adrenal and prostate cancers.





Phytoestrogens

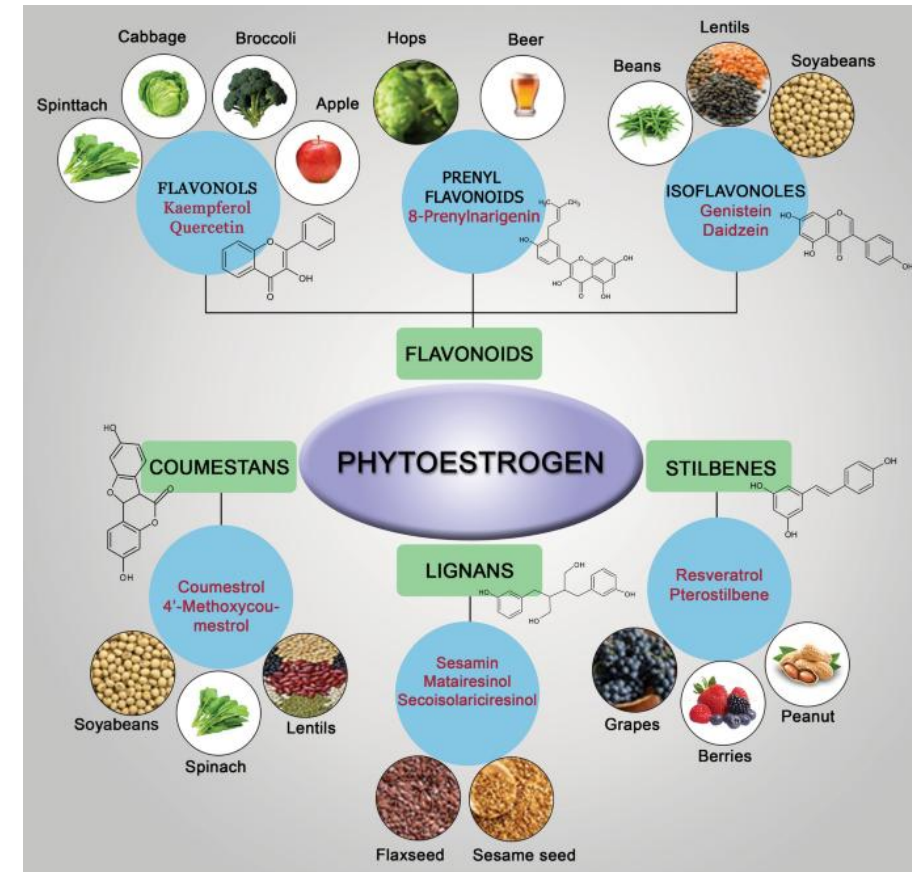
- Genistein can stimulate progesterone stimulation in the ovaries, production of estradiol and cAMP production, oocyte maturation and zygote development in the preimplantation stage.





Phytoestrogens

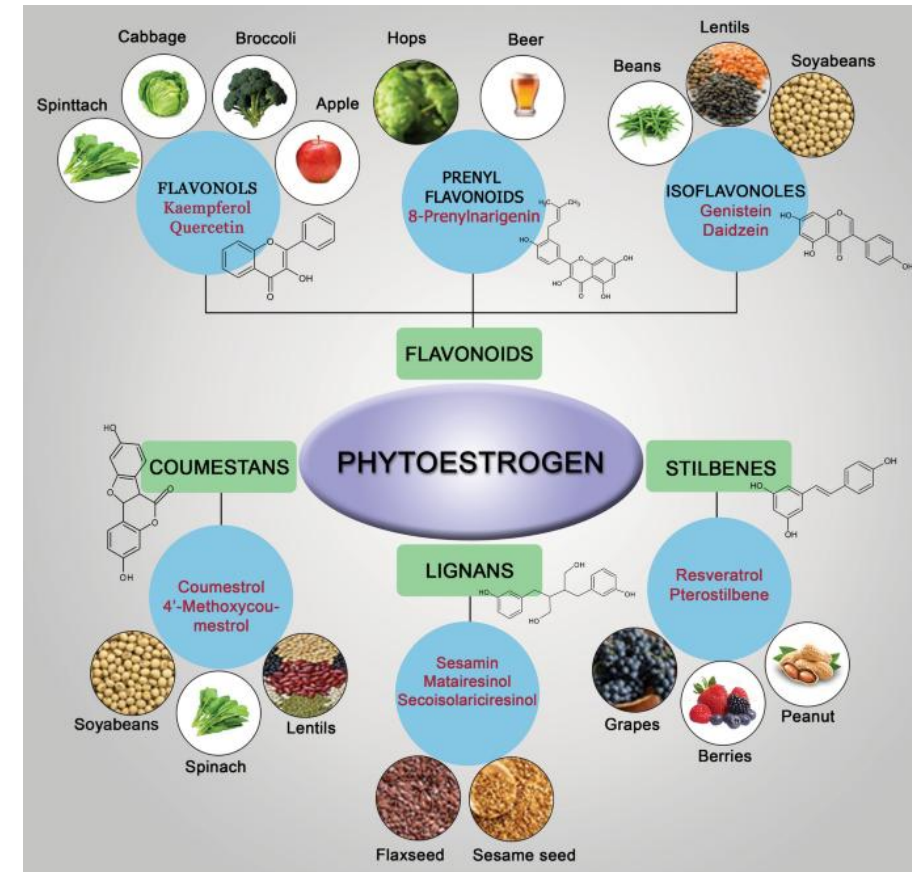
- Several studies have proven the protective effects of phytoestrogens on **cardiovascular disease**.
- Phytoestrogens can **reduce total cholesterol** and improve heart function.





Phytoestrogens

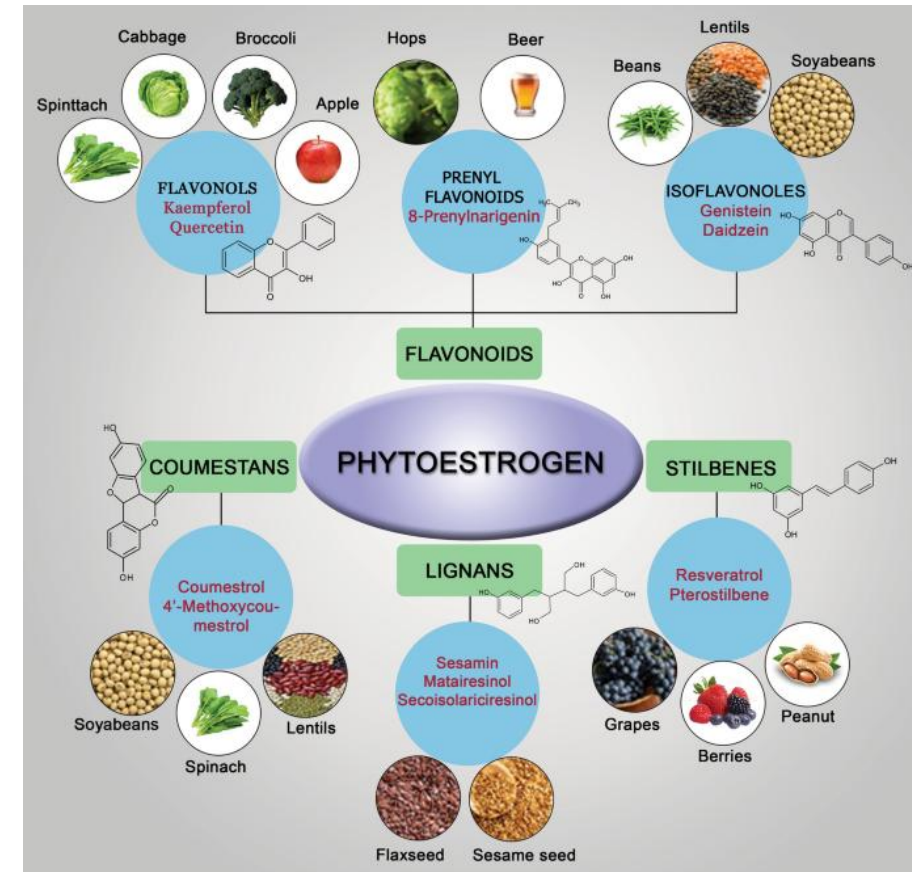
- The results of research on the effects of phytoestrogens on **bone health** are still not consistent.
- A meta-analysis of randomised clinical trials in humans found a **weak link** between increased intake of soy isoflavones and increased bone mineral density





Phytoestrogens

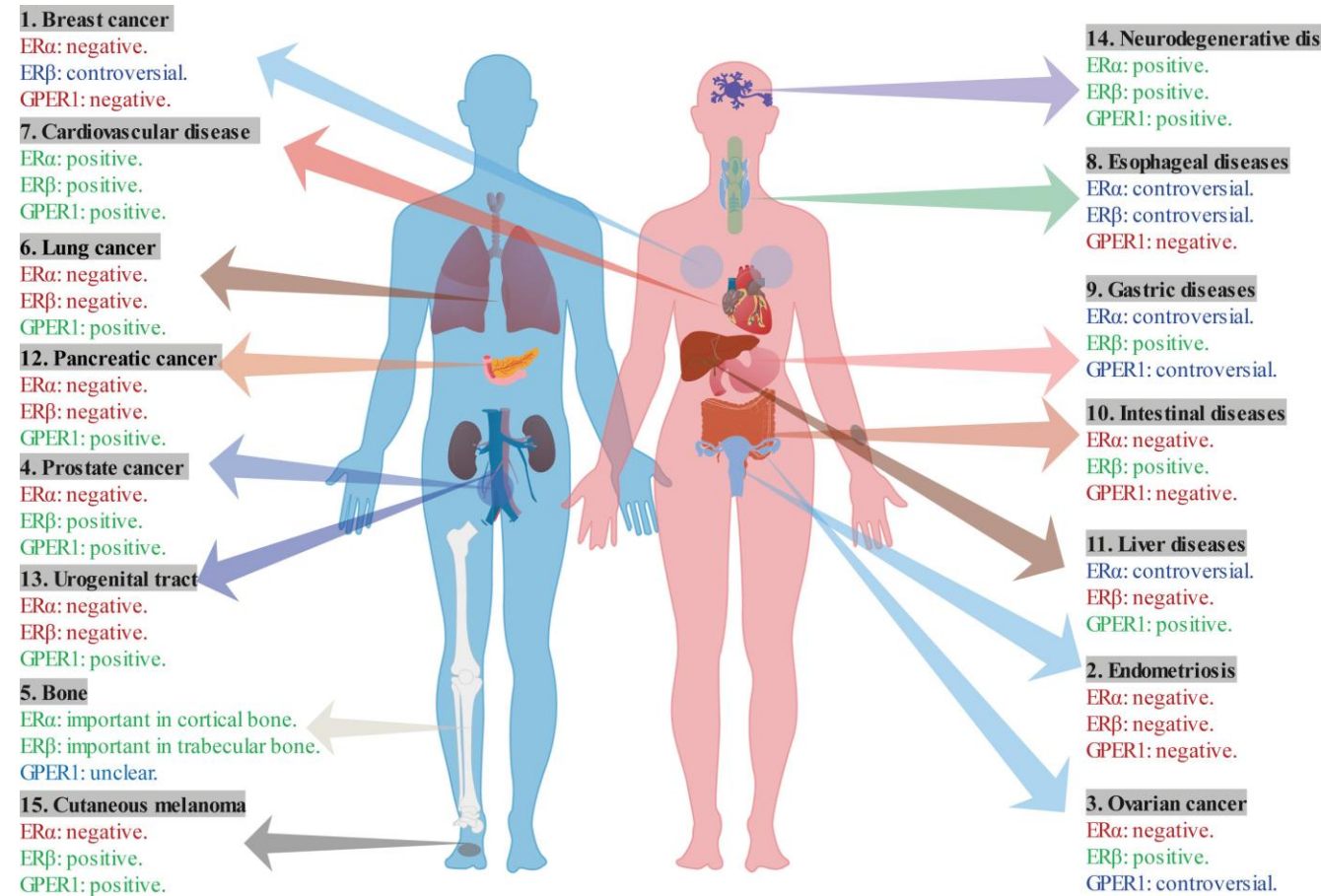
- Phytoestrogens as **neuroprotectors** and **antioxidants** can reduce the risk of Alzheimer's disease.

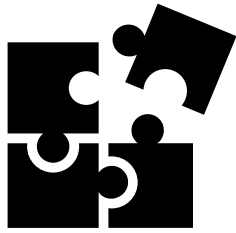




Phytoestrogens

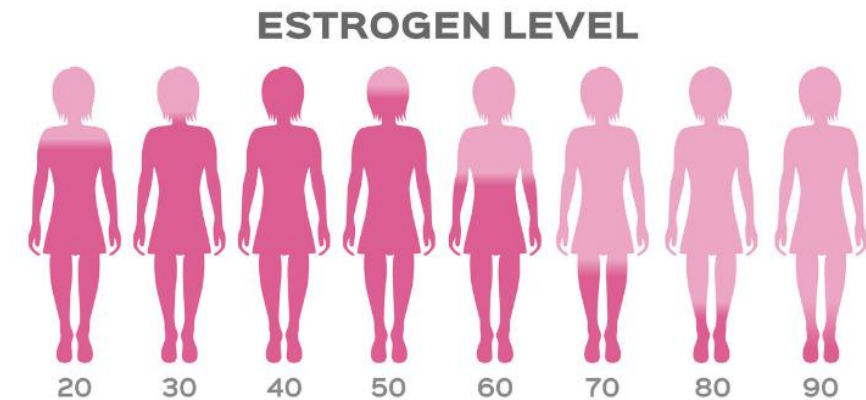
- However, estrogen influence **human pathologies** as autoimmune, metabolic to degenerative.
- Both **hypo and hyper level** of estrogen has been **linked to chronic and acute diseases**.





Phytoestrogens

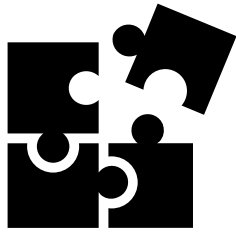
- While **normal aging** is supposed to **lower its level**, leading to tissue degeneration (bone, muscle, neural etc.), and metabolite imbalance, the increment in inflammatory **agents in day-to-day life** are **enhancing the estrogen** (or estrogen mimic) level, fueling '**estrogen dominance**'.



Estrogen Dominance

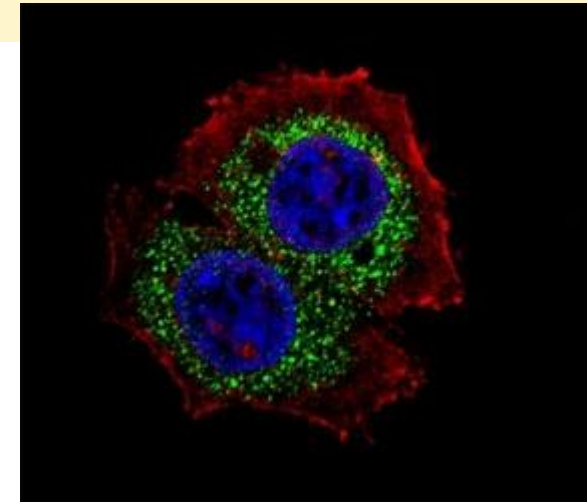
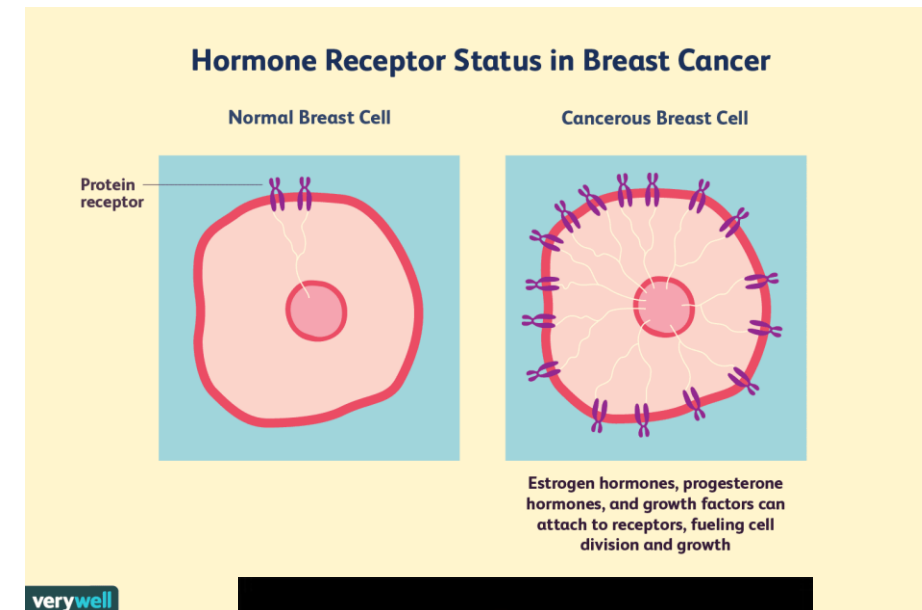
Which are you?





Phytoestrogens

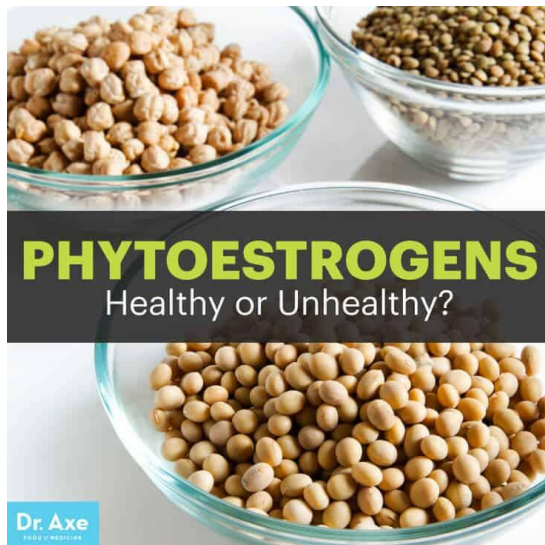
- The resultant excess estrogen is inducing an **overexpression of estrogen receptors** (ER α and ER β), harming tissues, **leading to autoimmune diseases and neoplasms**.





Phytoestrogens

- Breast cancer prevention
<https://www.bcpp.org/resource/phytoestrogens/>



Phytoestrogens



WHAT:

Phytoestrogens are plant nutrients found in soy products, grains, beans, and some fruits and vegetables. When consumed regularly during childhood, phytoestrogen consumption is linked to a decreased risk of breast cancer.

FOUND:

Phytoestrogens are found in foods such as whole grains, dried beans, peas, fruits, broccoli, cauliflower, and especially in many soy products.

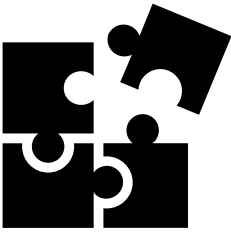
SCIENCE:

Overall, phytoestrogen consumption is believed to be protective against breast cancer. But, some research suggests women with HER-2-positive tumors and pre-menopausal women at high risk should avoid them.

TOP TIPS:

It is best to avoid highly processed soy. Limit intake of concentrated isoflavones, including genistein, in favor of less-processed options such as tofu, edamame and tempeh.

Phytoestrogens



To minimize the potential risks of phytoestrogens on the human body, consider the following strategies:

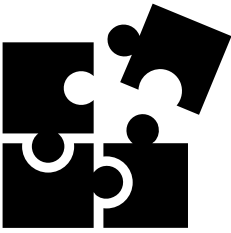
Diversify Your Diet: Instead of relying heavily on a single source of phytoestrogens, such as soy products, **incorporate a variety of phytoestrogen-rich foods into your diet.**

This can help reduce the **risk of overconsumption** of any particular phytoestrogen and provide a wider array of nutrients.



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Phytoestrogens



To minimize the potential risks of phytoestrogens on the human body, consider the following strategies:

Choose Whole Foods: Opt for **whole foods** over processed or highly refined products.

Whole foods like legumes, whole grains, fruits, and vegetables contain phytoestrogens in their natural form and are typically part of a balanced diet.



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