# Sustainability and Chemistry
# CH5106: L10

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Swaminathan Sivaram
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Chemical studies show that $Al^{3+}$ binds $F^-$ more strongly than 60 other metal ions. Al is the most abundant metal on earth. It is ubiquitously present in all foodstuffs and drinking water. [Crit Rev Oral Biol Med 14(2):100-114 (2003); Genes & Diseases, 2023, 10, 1470-1493]

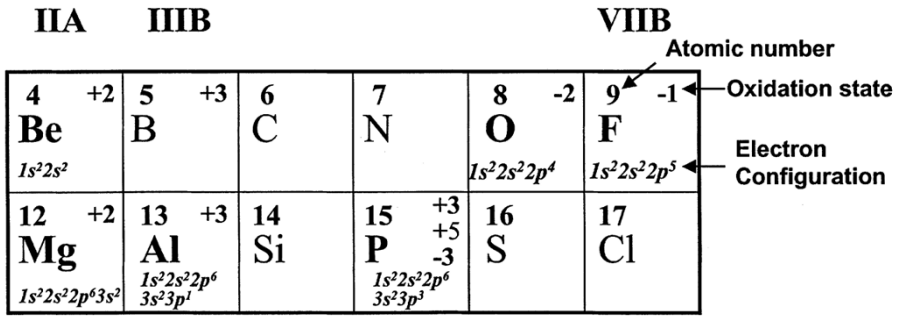
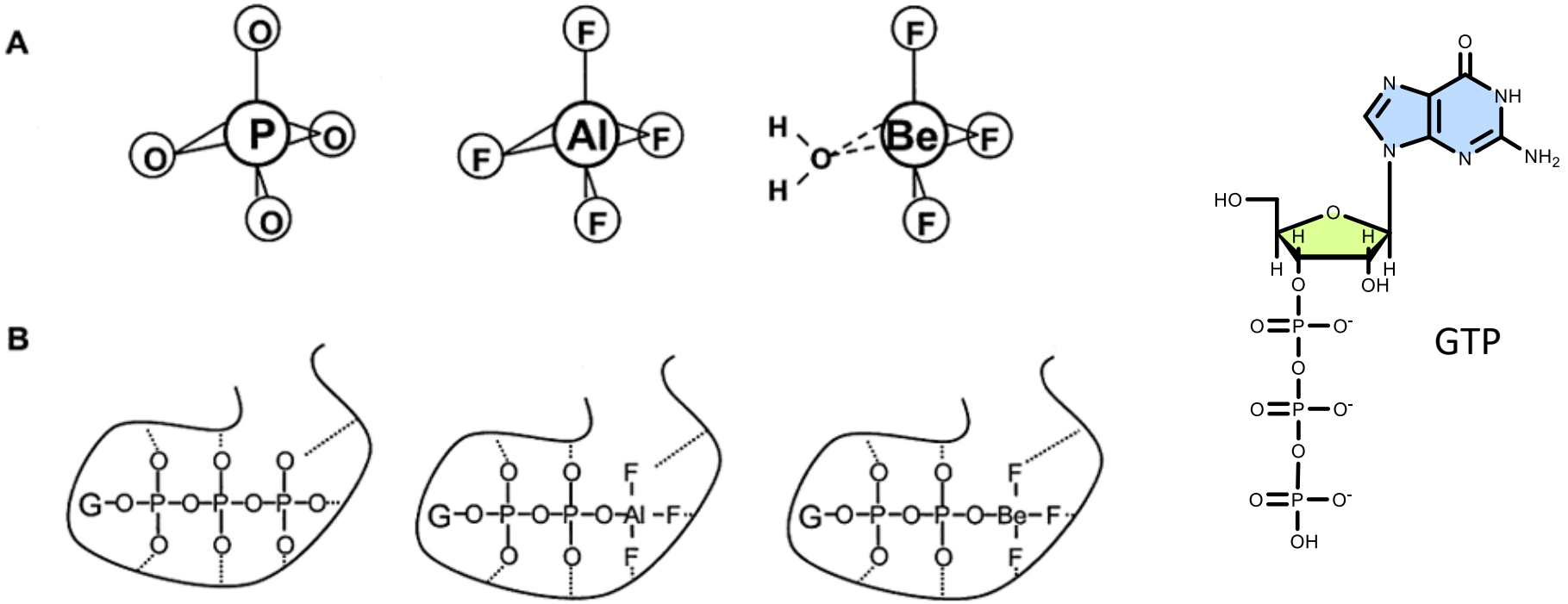



**Figure 1.** A section of the Periodic Table. For the elements related to phosphate or its analogs, their symbols, atomic numbers, oxidation states, and electron configurations are highlighted.

only a μM level of Al is needed to form biologically effective Al-F complexes. $F^-$ is widely added to human drinking water (1 ppm) and in most toothpastes (500-1500 ppm) to prevent dental caries.

- X In biochemical and cellular research, aluminum fluoride complexes ($AlF_x$) and beryllium fluoride ($BeF_x$) are commonly used to interfere with enzyme activity.
- X Both compounds activate G (guanine nucleotide–binding) proteins in eukaryotic cells (Gilman, 1987).
- X $AlF_x$ and $BeF_x$ are small molecules that mimic the chemical structure of phosphate.
- X As phosphate analogues, they modulate the activity of phosphoryl transfer enzymes, including: GTPases; ATPases; Phosphohydrolyases; Phospholipase D
- X Phosphoryl transfer is a fundamental mechanism in cells, underlying both energy metabolism and signal transduction.




Structural similarities among $AlF_4^-$, $BeF_3(OH_2)^-$, and $PO_4^{3-}$. All three compounds exhibit tetrahedral geometry. $BeF_3^-$ has an electron-deficient beryllium atom. Be completes an octet by accepting a pair of electrons from a water molecule. (B) The proposed phosphate model for $AlF_4^-$ and $BeF_3^-$ activation of heterotrimeric G proteins. $AlF_4^-$ and $BeF_3^-$ bind with GDP and mimic the -phosphate of GTP.

## Structural similarities:

- **$AlF_4^-$** is structurally similar to **$PO_4^{3-}$** (both are tetrahedral).
- **Al–F bond length ≈ P–O bond length** in phosphate.
- **$BeF_3^-$** also mimics phosphate because of its similar tetrahedral structure.

A G protein is a molecular switch within a cell that relays signals from activated cell-surface receptors to intracellular effectors, functioning as a signal transducer.

## Phosphate model of G protein activation:

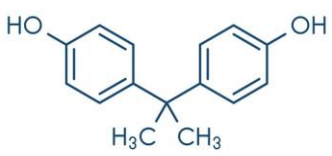
- G protein normally binds GDP permanently.
- **$AlF_4^-$ (or $BeF_3^-$)** binds to the GDP phosphate.
- This mimics the presence of the γ-phosphate of GTP.
- As a result, the G protein adopts the **active G•GTP-like conformation**.

- Relay signals from **cell-surface receptors** to **intracellular effectors**.
- Function as **signal transducers** in pathways.
- Named for binding **guanine nucleotides (GDP & GTP)**.
- Regulate diverse processes: **growth, metabolism, sensation**.

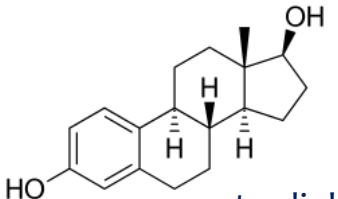
## Stabilization of active state:

- $F^-$ is highly electronegative and forms strong hydrogen bonds with amino acids.
- This makes **$AlF_4^-$ and $BeF_3^-$ resistant to hydrolysis** by GTPase activity.
- Thus, the G protein loses its ability to hydrolyse its bound GTP back to GDP, preventing it from returning to its inactive form.

Bisphenol A (BPA) is an endocrine-disrupting chemical (EDC). It interferes with hormone systems, especially those involving estrogen, and leads to various health issues.



bisphenol A



estradiol

**1. Hormonal Disruption**

- Mimics estrogen: BPA structurally resembles the hormone estradiol, a primary form of estrogen.
- Binds to estrogen receptors: It can bind to ERα and ERβ receptors, mimicking or blocking natural hormone actions.
- Leads to hormonal imbalance: This false signalling can disrupt normal development, metabolism, and reproductive function.

Environ Sci Pollut Res 29, 32631–32650 (2022).
https://doi.org/10.1007/s11356-022-19244-5

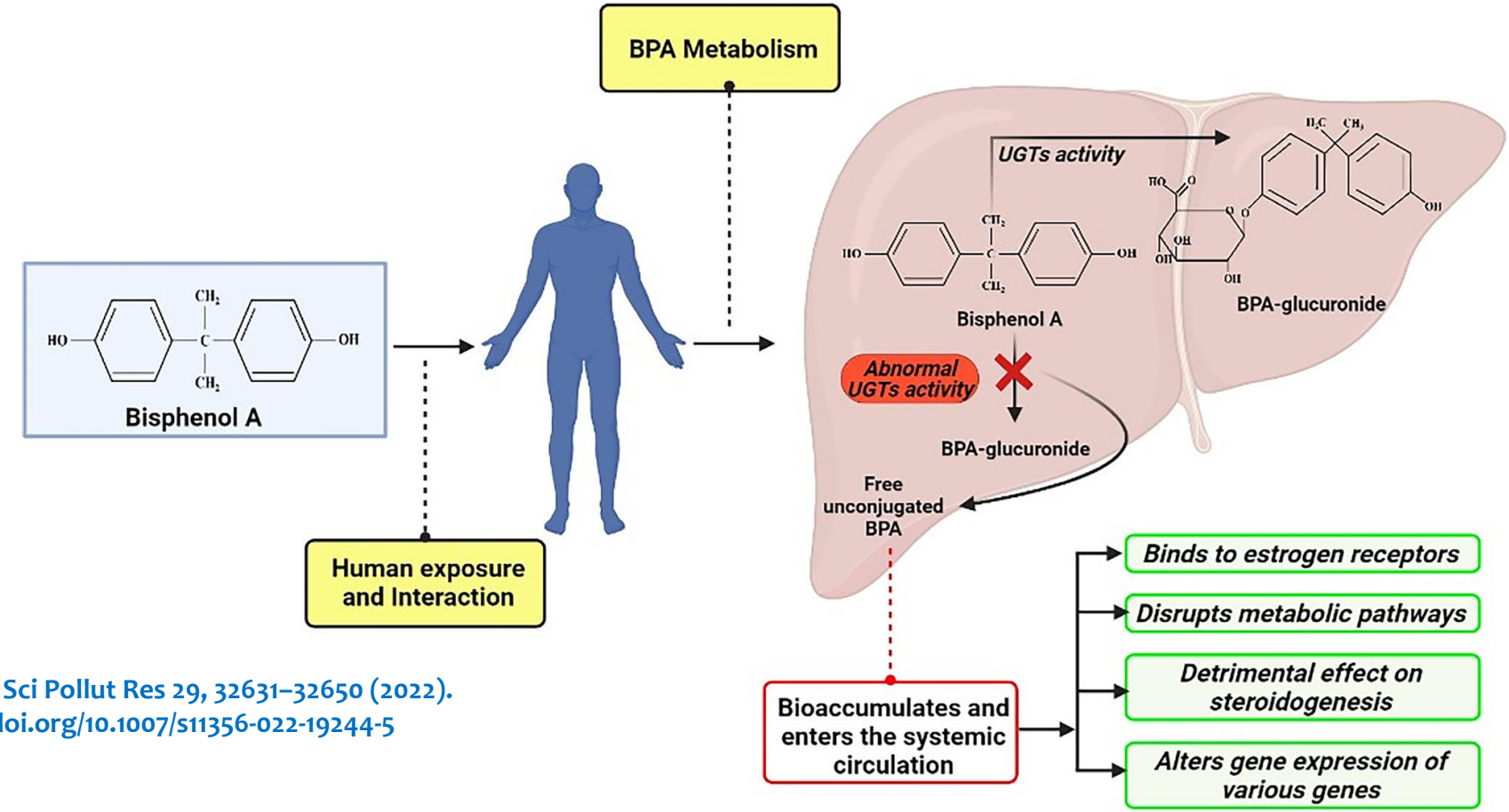
**2. Impact on Fetal and Child Development**

- Crosses placenta: BPA can reach the fetus, interfering with organ development, especially the brain and reproductive organs.
- Linked to neurodevelopmental disorders: Exposure has been associated with ADHD, behavioral problems, and cognitive impairments in children.

**Reproductive Toxicity, Metabolic Disorders, Carcinogenic Potential**

BPA is toxic to human physiology mainly because it mimics natural hormones and interferes with the endocrine system, which controls a wide range of bodily functions from growth and metabolism to reproduction and mood. This disruption can lead to a cascade of chronic health problems, particularly with long-term or early-life exposure.

Additionally, its ability to mimic the behaviour of 17-β estradiol results in the disruption of various pathways, causing moderate acute toxicity in humans. The most common pathological effects include obesity, cardiovascular diseases, hyperinsulinemia, thyroid, hypertension, ovarian and testicular developmental issues, PCOS, and cancer




Environ Sci Pollut Res 29, 32631–32650 (2022).
https://doi.org/10.1007/s11356-022-19244-5

**Uridine-5-diphospho-glucuronosyltransferases (UGTs)** are the important class of enzymes involved in the catalysis of BPA glucuronidation that results in the transformation of BPA to BPA-G, which is biologically inactive. Furthermore, BPA is reported to be majorly excreted in the urine as BPA-G (94.6%). The abnormalities in the functioning of UGTs enzyme cause an increase in levels of unconjugated BPA concentration in the system and the toxicity.

2. **Phase I** Metabolism (Minor Pathway)

- Cytochrome P450 enzymes (CYPs) may oxidize BPA slightly, but this is not the main route.
- Oxidation products may include quinone derivatives or reactive oxygen species (ROS), which can contribute to oxidative stress and DNA damage.

X However, Phase I is not the primary detoxification route for BPA.

3. **Phase II** Metabolism (Primary Pathway: In neonates and fetuses, these Phase II enzymes are underdeveloped, leading to higher levels of free (active) BPA — which increases toxicity risk)

✓ This is the major metabolic route and involves conjugation reactions in the liver, making BPA more water-soluble for excretion.

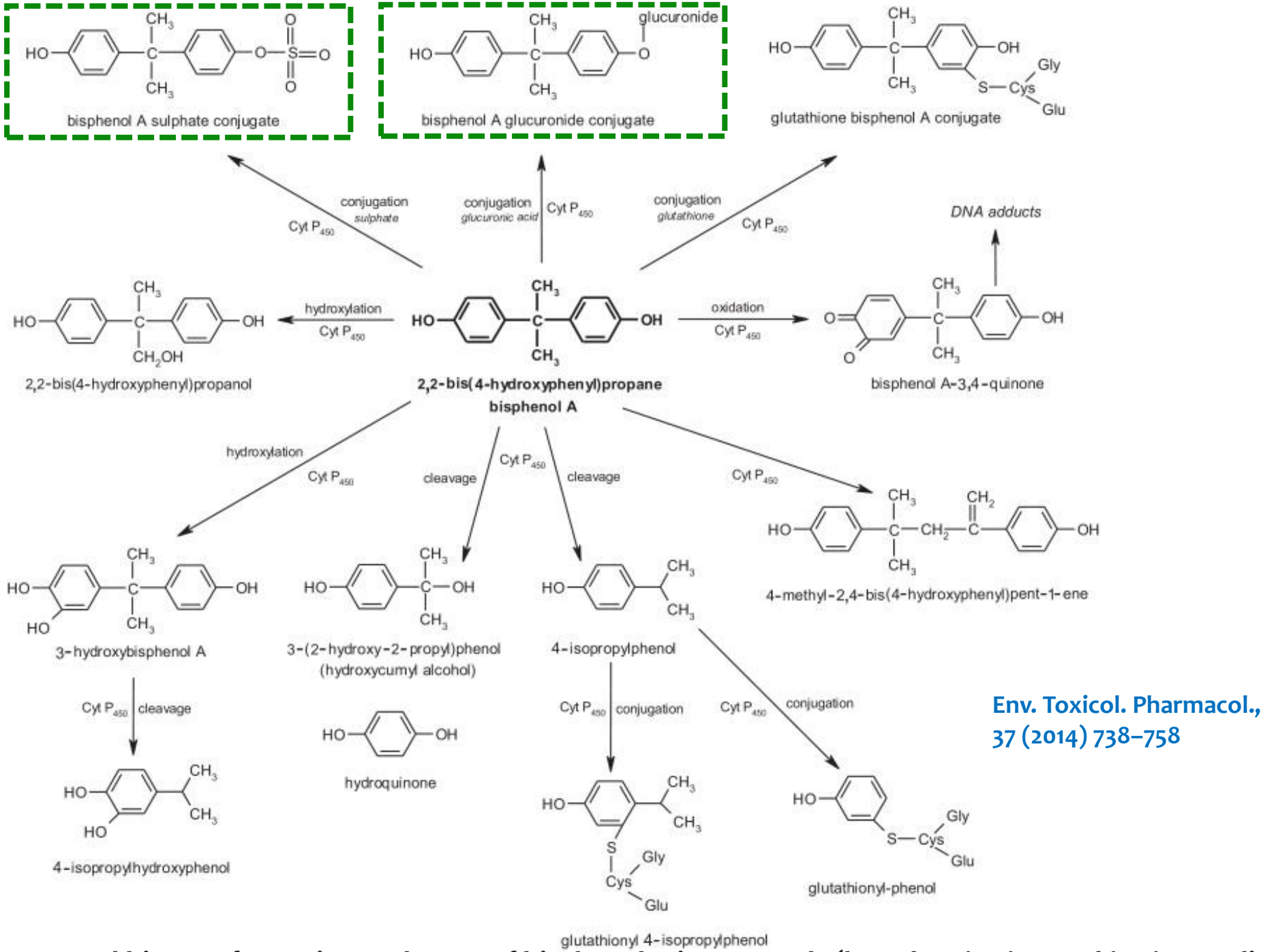
a. Glucuronidation [This is the main detoxification pathway in both adults]

- Enzyme: UDP-glucuronosyltransferases (UGTs)
- BPA is conjugated with glucuronic acid, forming BPA-glucuronide, an inactive and more water-soluble form.

b. Sulfation

- Enzyme: Sulfotransferases (SULTs)
- BPA is conjugated with sulfate groups to form BPA-sulfate, another inactive metabolite.
- Especially important in infants, where glucuronidation is less efficient.

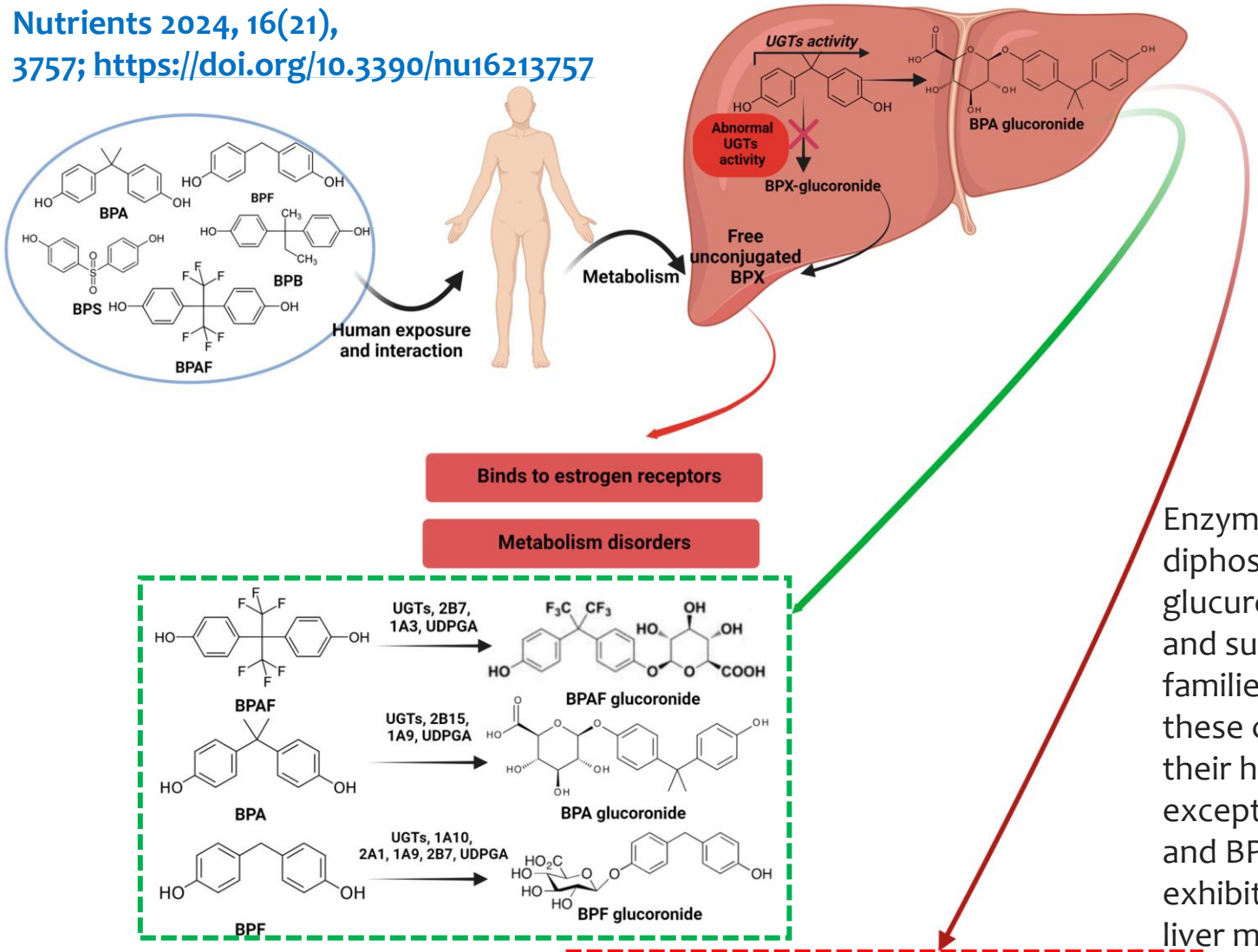
Environ Sci Pollut Res 29, 32631–32650 (2022). https://doi.org/10.1007/s11356-022-19244-5 and AI




Env. Toxicol. Pharmacol., 37 (2014) 738–758

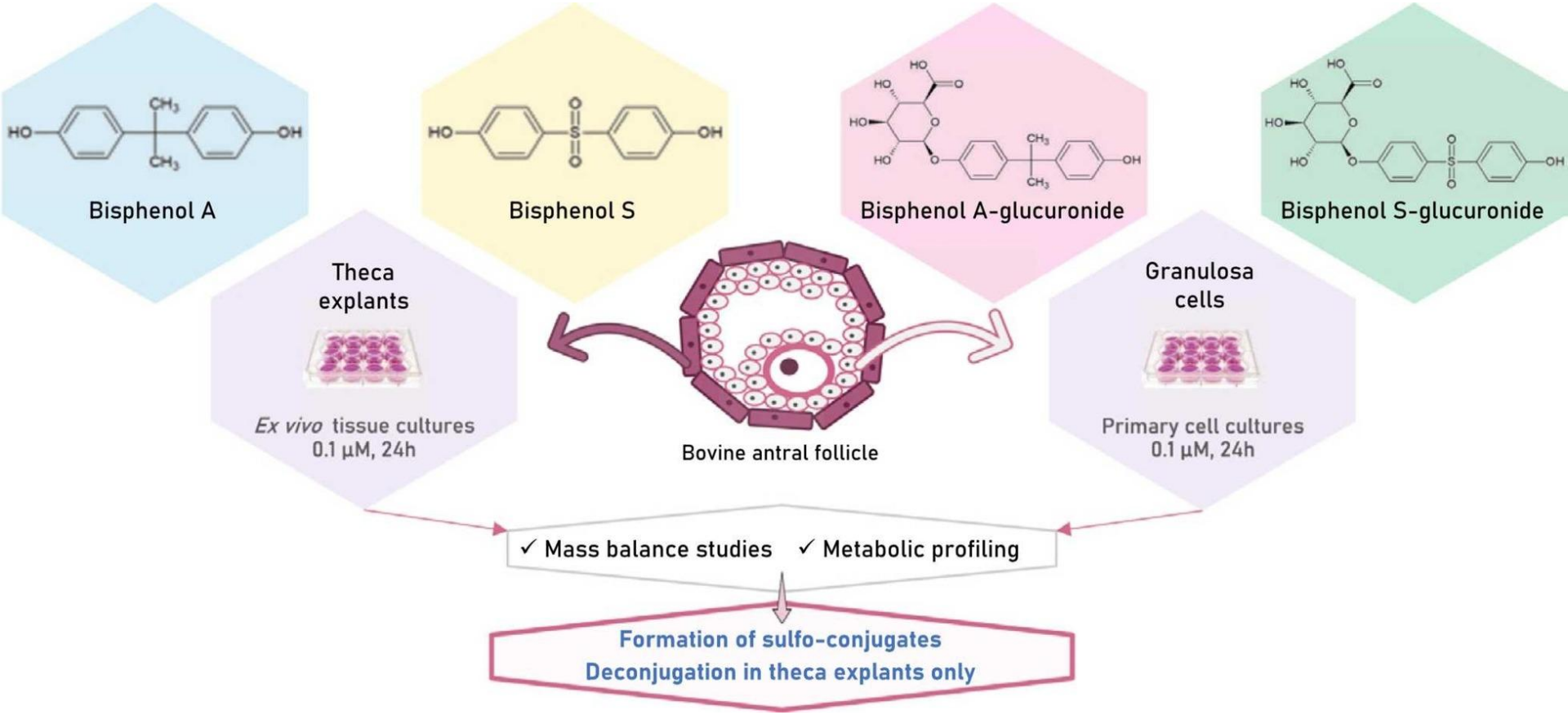
**Proposed biotransformation pathways of bisphenol A in mammals (based on *in vitro* and *in vivo* studies)**

Nutrients 2024, 16(21), 3757; https://doi.org/10.3390/nu16213757




Enzymes like Uridine 5 diphosphate glucuronosyltransferase (UGT) and sulfotransferase (SULT) families reduce the toxicity of these compounds and eliminate their hormonal activity, with the exception of BPB glucuronide and BPS glucuronide, which still exhibit estrogenic activity after liver metabolism.

Toxicology, 2006, 217 (2–3), 81-90



**Bisphenol A (BPA): Precursor for** polycarbonate plastics and epoxy resins and BPA based polymers and resins.

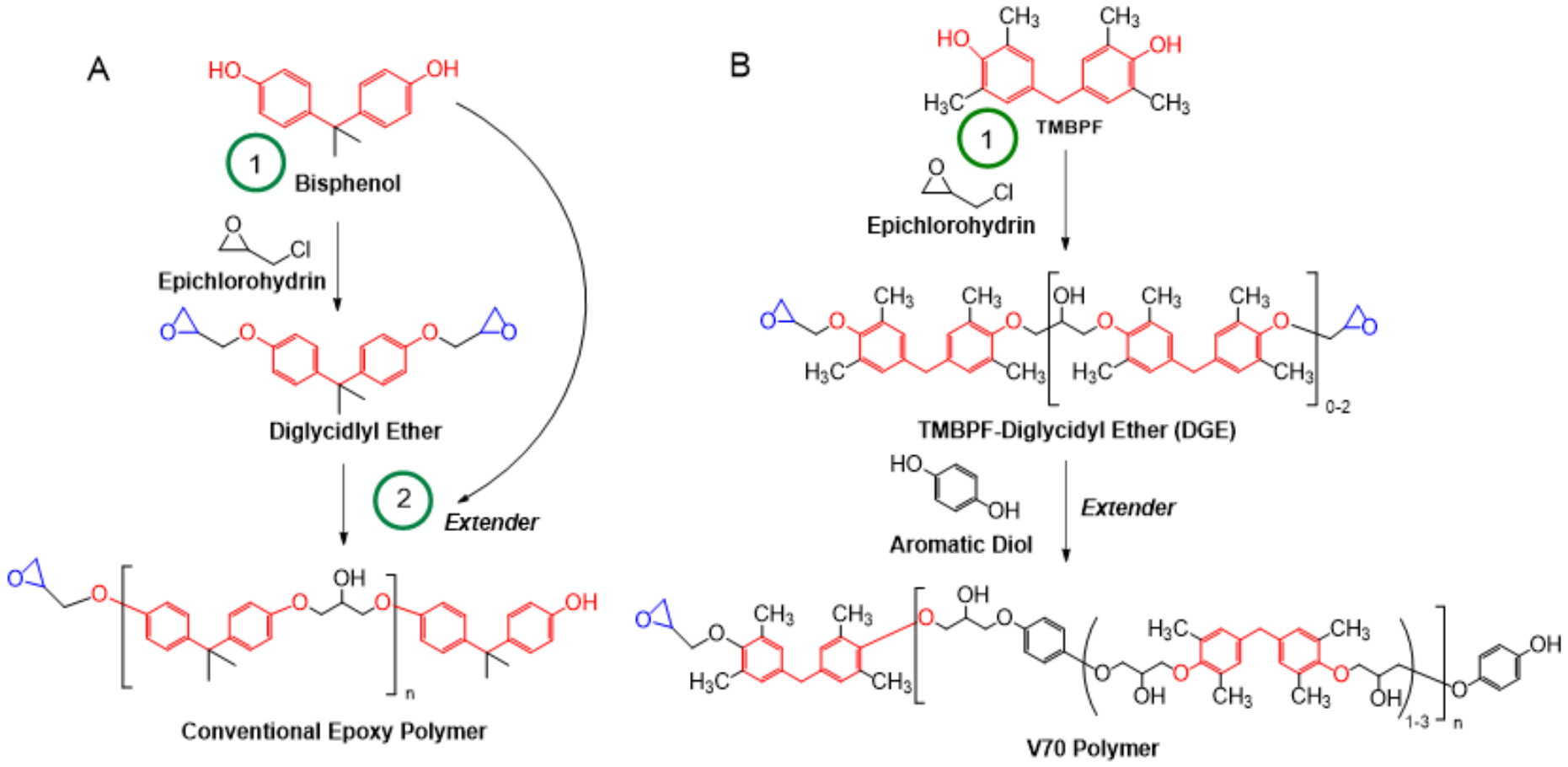



**Figure S1: Conventional versus valPure V70 food packaging epoxy coating manufacturing scheme.**

valPure V70 is a polymer developed by Sherwin-Williams (formerly Valspar) as a BPA-free alternative for safe food packaging. It uses tetramethyl bisphenol F (TMBPF) instead of BPA, which has shown no estrogenic activity in tests. The production process eliminates TMBPF in the final product, and independent tests confirm its absence at the limit of detection.

**valPure V70 is a polymer** developed by Sherwin-Williams (formerly Valspar) as a BPA-free alternative for food packaging that is considered safe. It uses tetramethyl bisphenol F (TMBPF) instead of BPA, which has shown no estrogenic activity in tests. The production process eliminates TMBPF in the final product, and independent tests confirm its absence at the limit of detection.

Creating a technology like valPure V70 demonstrates that our industry can innovate to develop a lasting, sustainable, and safe solution for the packaging industry.
**https://www.cantechonline.com/feature/32647/innovating-sustainably/**


*Safety by Design 7 steps*

Env. Toxicol. Pharmacol., 37 (2014) 738–758

- The Bisphenol A industry capacity was 10.61 million tones per annum (mtpa) in 2023 and will rise at an AAGR of more than 4% from 2023 to 2028.
- Around 95% of BPA is used in the synthesis of polymers, chiefly epoxy resins and polycarbonates. These polymers possess favourable properties such as high mechanical strength, low water absorption, and excellent thermal stability, which make them suitable for a wide array of applications. BPA-based materials are used in manufacturing water pipes, food and beverage containers, bottles, children's toys, baby nipples, medical devices, dental products, electronics, and optical storage media, including CDs and DVDs.
- Additionally, BPA functions as a stabilizer and antioxidant in vinyl chloride production (Nam et al., 2010) and as a coating material in thermal papers used for receipts, tickets, and labels.

~ 100 000 chemicals
on the market

~ 22 600 chemicals
with a use over
1 tonne per year

~ 4 700 chemicals
with a use over
100 tonnes per year
prioritised in
hazard characterisation
and evaluation

RISKS

HAZARDS

EXPOSURES

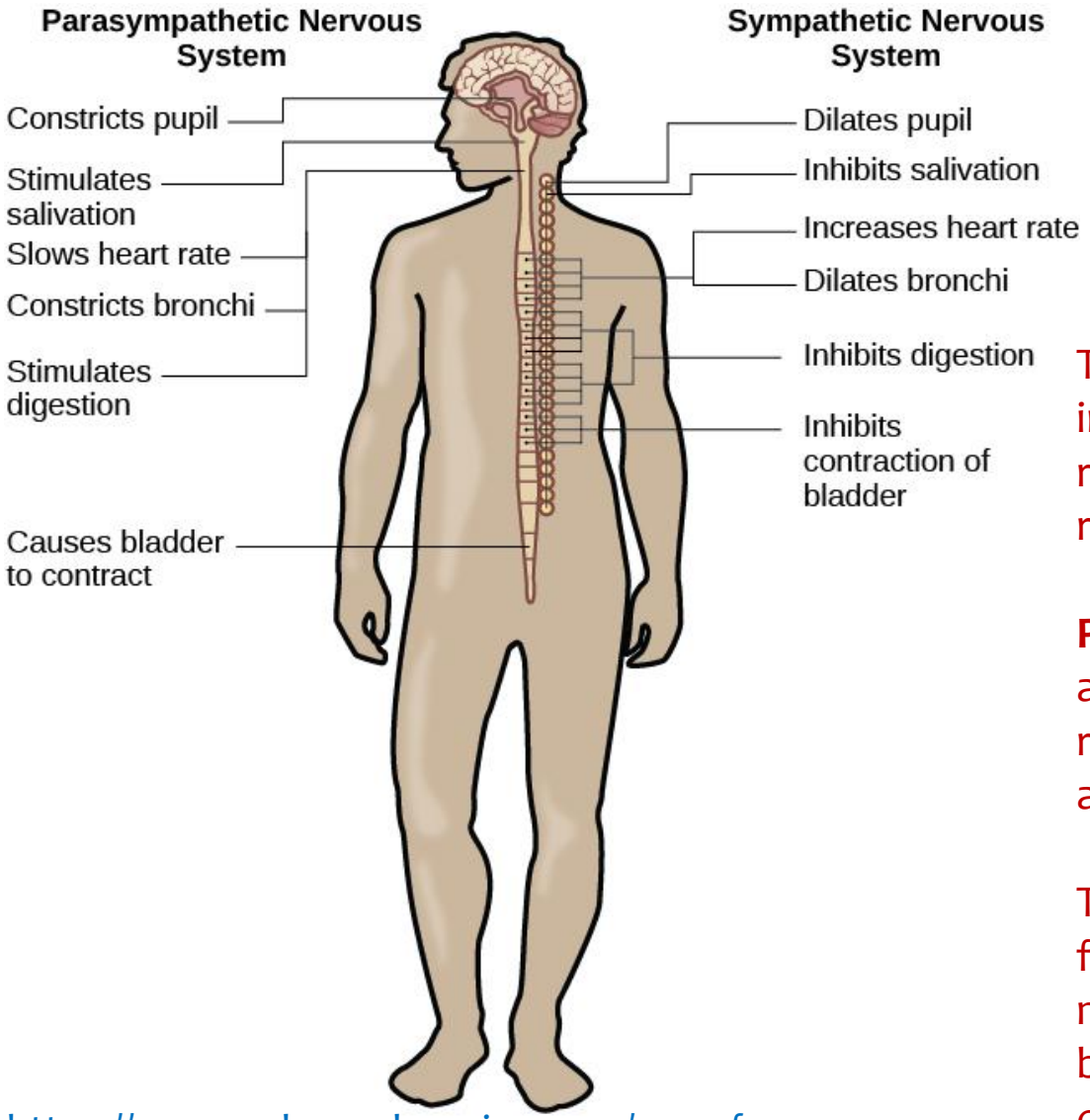
~ 500 chemicals
extensively characterised for
their hazards and exposures

~ 10 000 chemicals
fairly well characterised for
a subset of their hazards and exposures

~ 20 000 chemicals
with limited characterisation for
their hazards and exposures

~ 70 000 chemicals
with poor characterisation for
their hazards and exposures

The **autonomic nervous system** controls our internal organs and glands and is generally considered to be outside the realm of voluntary control. It can be further subdivided into the sympathetic and parasympathetic divisions.



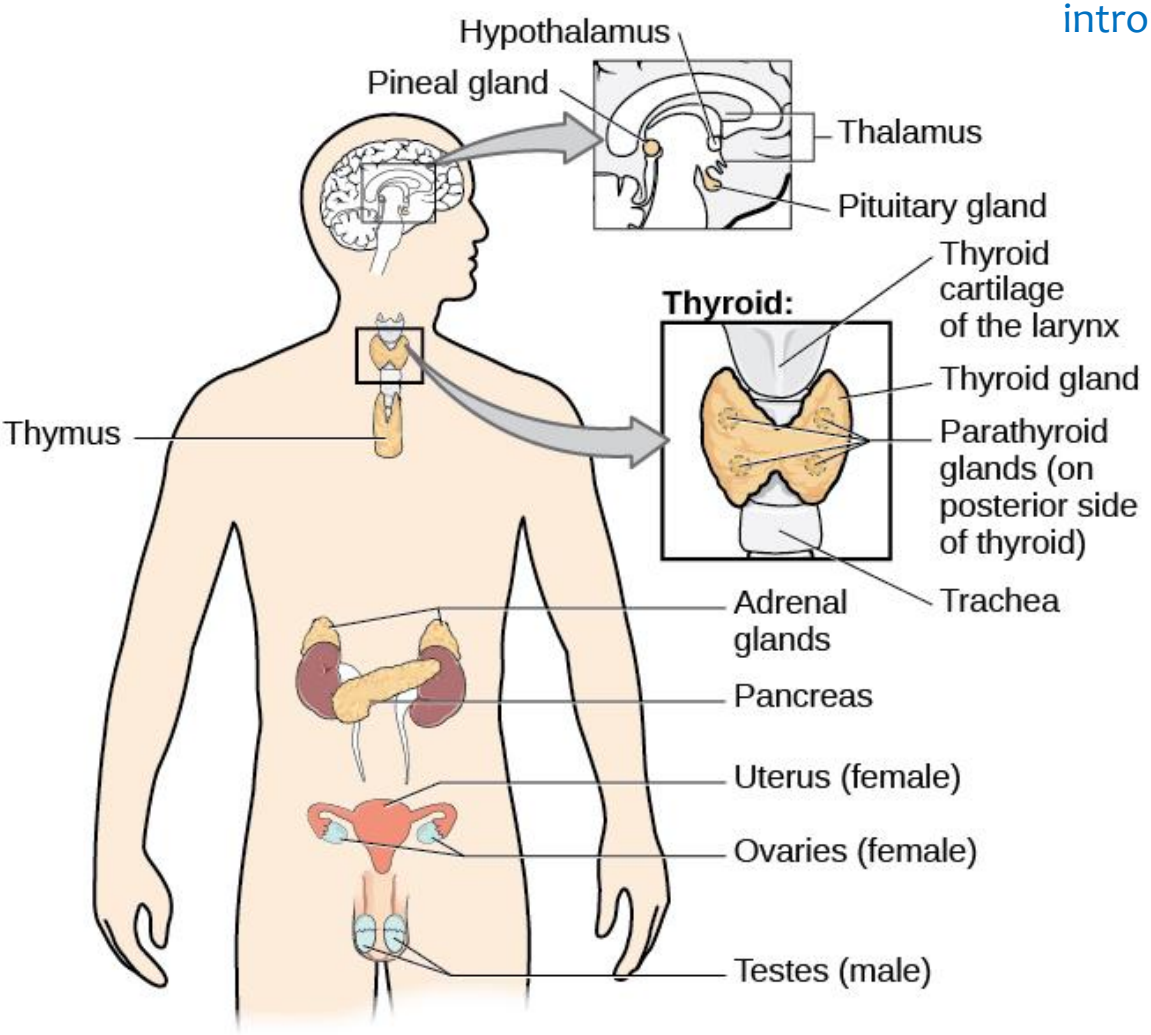

https://courses.lumenlearning.com/suny-fmcc-intropsych/chapter/the-endocrine-system/

The **sympathetic nervous system** is involved in preparing the body for stress-related activities-- "fight-or-flight" responses.

**Parasympathetic nervous system** is associated with returning the body to routine, day-to-day operations--"rest-and-digest" functions

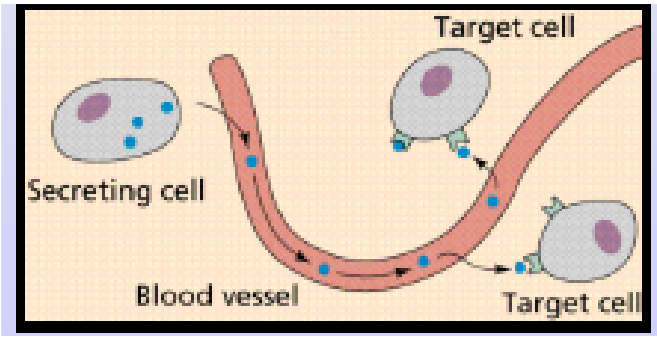
The two systems have complementary functions, operating in tandem to maintain the body's homeostasis—the body's internal balance, keeping conditions like temperature and heart rate within optimal ranges..

https://courses.lumenlearning.com/suny-fmcc-intropsych/chapter/the-endocrine-system/




**Communication Systems:** The nervous system, together with the endocrine system, makes up the body's major signalling pathways in all animals:

A hormone is a chemical message that instructs a specific response




The endocrine system is made up of glands that release hormones, chemical messengers that travel through the bloodstream to target cells with specific receptors. Unlike neurotransmitters, which act quickly and locally, hormones produce slower but longer-lasting, widespread effects throughout the body.

## Small Molecules as Endocrine Disruptors

Small organic molecules—such as bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), and certain organochlorine pesticides—can act as endocrine-disrupting chemicals (EDCs). Due to their lipophilic nature, they readily cross biological membranes and can interact with components of the endocrine system.

**EDCs exert their effects primarily by:**

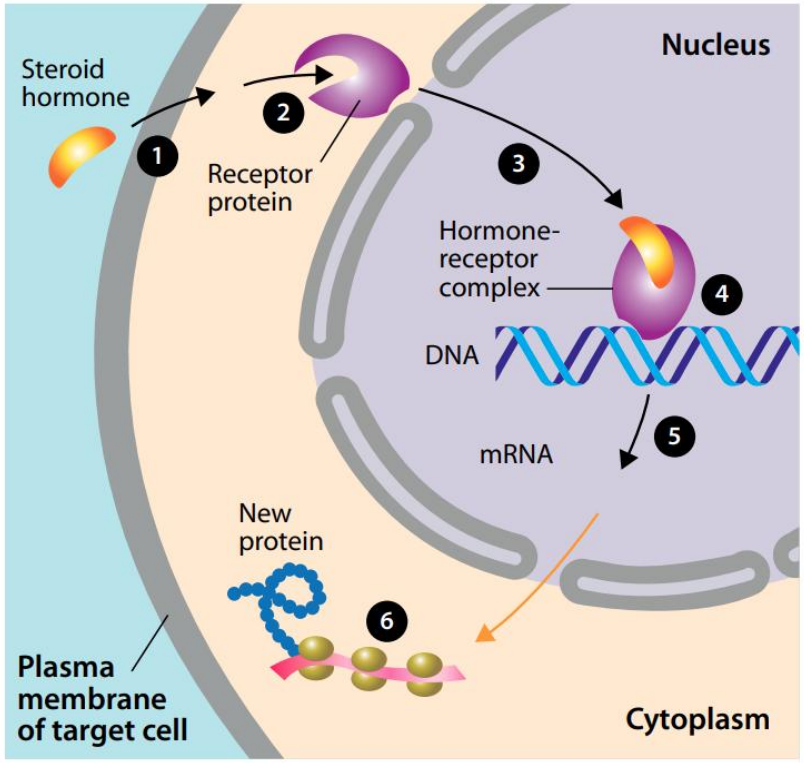
1. Mimicking natural hormones (agonist effect), binding to nuclear hormone receptors such as estrogen (ER), androgen (AR), or thyroid hormone receptors (TR).
2. Blocking hormone binding (antagonist effect), thereby preventing normal receptor activation.
3. Altering hormone synthesis, metabolism, or clearance, changing circulating hormone levels.
4. Modifying receptor expression or signal transduction pathways, resulting in inappropriate gene regulation.

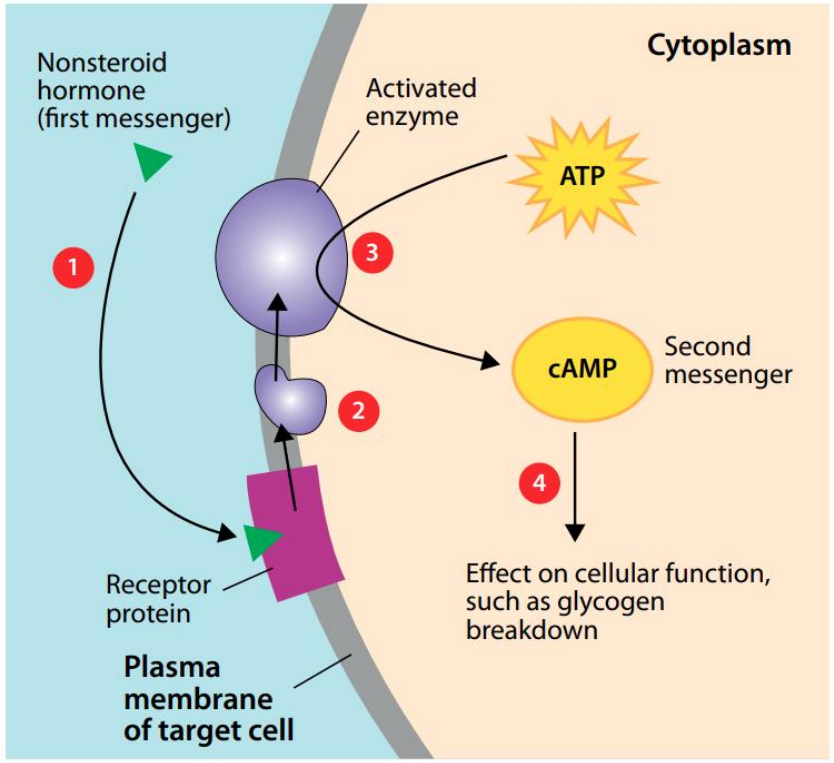
Endocrine signalling is highly sensitive; low concentrations of EDCs can lead to developmental, reproductive, neurological, and metabolic abnormalities. Their persistence and bioaccumulation in the environment further amplify long-term exposure risks.

Endocrine Reviews, 2015, **36**(6), E1–E150, Endocrinology, 153(9), 4097–4110

An **Endocrine disruptor** is 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. A **potential endocrine disruptor** is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations.

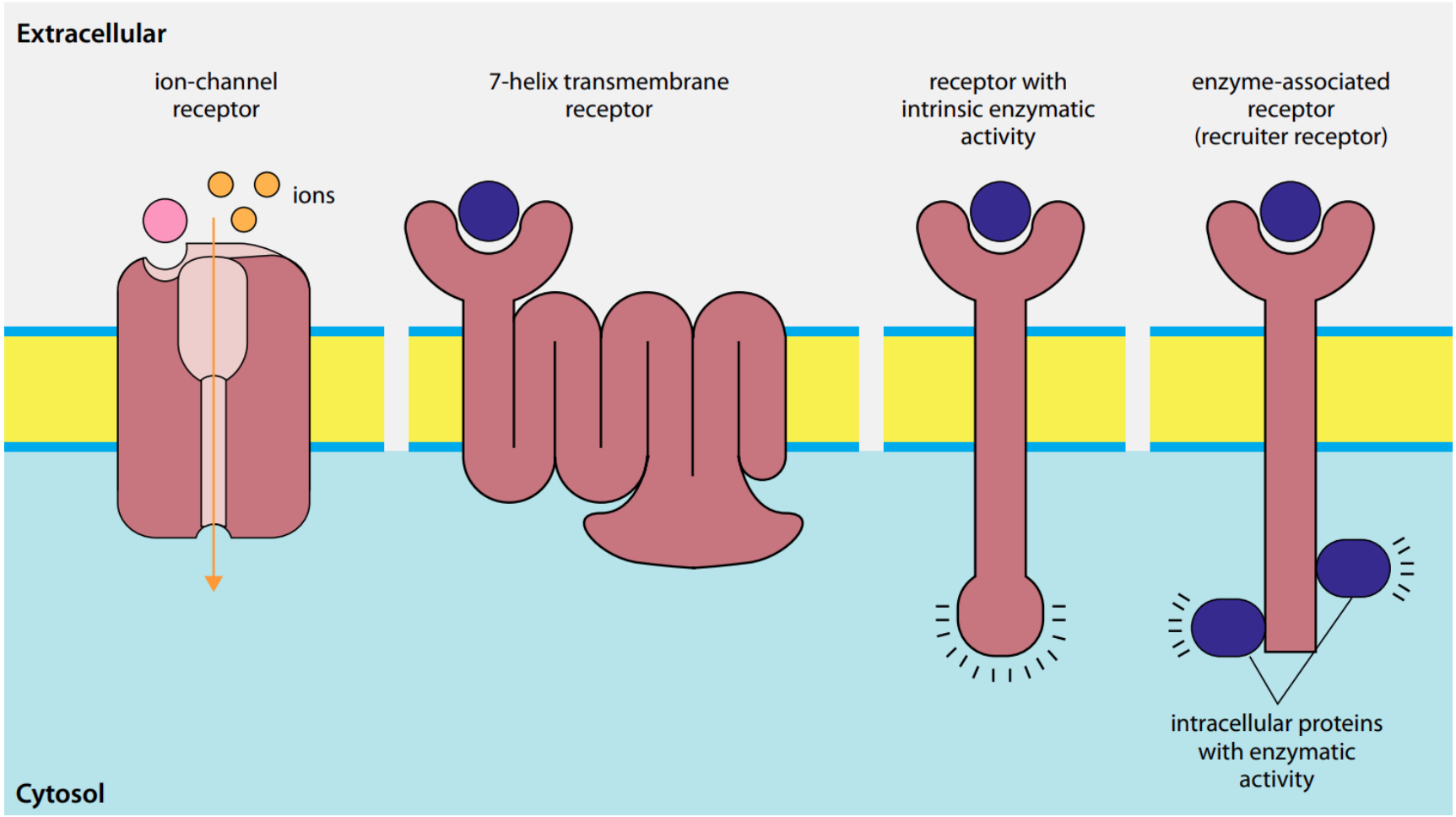
State of the Science of Endocrine Disrupting Chemicals – 2012; A report by UNEP and EHO 2012; 9789241505031_eng.pdf



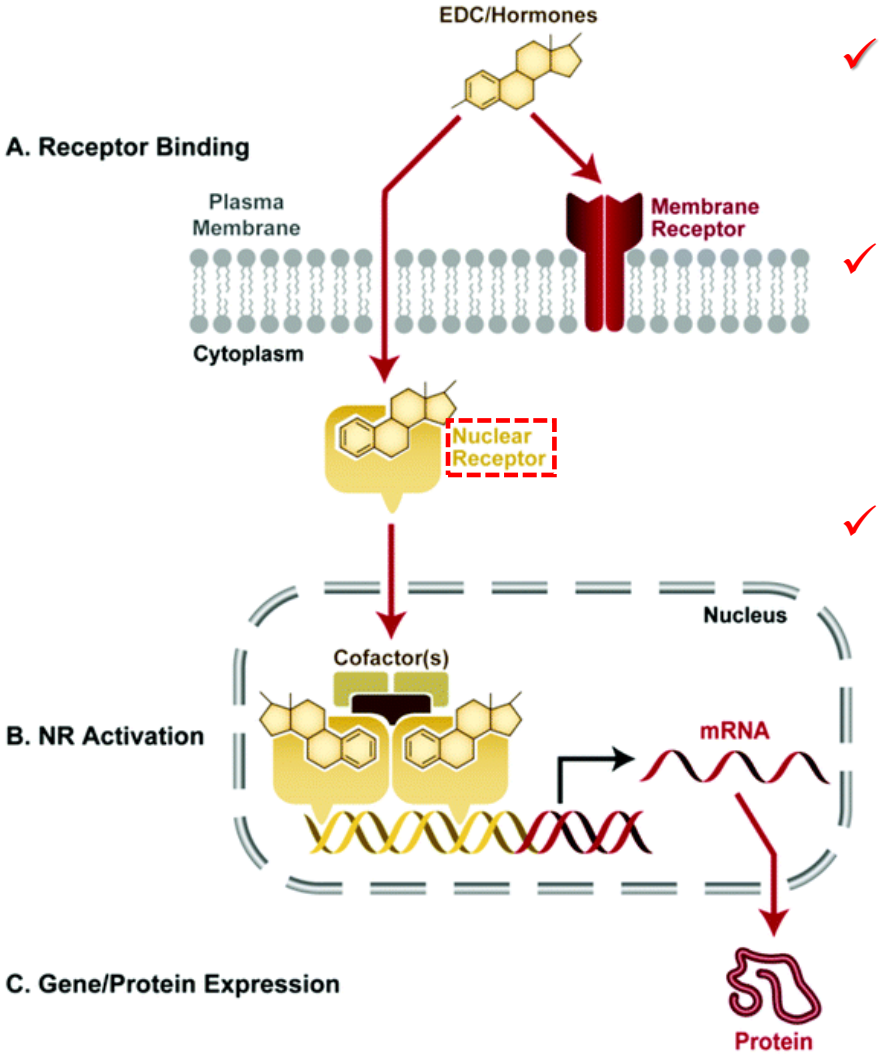

**Nuclear receptors** bind to steroid and thyroid hormones. The hormone–receptor complex crosses the cell membrane and then binds to specific DNA sequences, directly regulating gene transcription and altering protein synthesis to produce long-term physiological effects.

**Membrane receptors** bind to protein and amine hormones, which cannot cross the lipid membrane. Instead, they trigger intracellular effects through a second messenger system (such as cAMP), amplifying the hormone's signal inside the cell.




**Membrane-bound receptors** are specialised proteins that detect extracellular signals, such as protein or amine hormones, and transduce them into intracellular responses. Because these hormones are hydrophilic and cannot cross the lipid bilayer, the receptor activates intracellular signalling cascades via second messengers.

State of the Science of Endocrine Disrupting Chemicals – 2012; A report by UNEP and EHO 2012; 9789241505031_eng.pdf; WHO-IRIS




- ✓ EDCs are small, lipophilic molecules that can cross the cell membrane and bind to nuclear hormone receptors (NRs).
- ✓ Upon binding, the receptor becomes activated and moves into the nucleus, where it recruits cofactors and forms a complex on the hormone response element of target genes.
- ✓ This complex stimulates transcription of DNA into RNA, leading to protein synthesis. Thus, EDC–NR interactions can alter the expression of hormone-responsive genes and their corresponding proteins.

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Transcription is the biological process in which the genetic information stored in DNA is copied into RNA (usually messenger RNA, or mRNA). It is the first step of gene expression, leading to the production of proteins.

- **Initiation**

The enzyme **RNA polymerase** binds to a specific DNA sequence called the **promoter** (located before the gene).

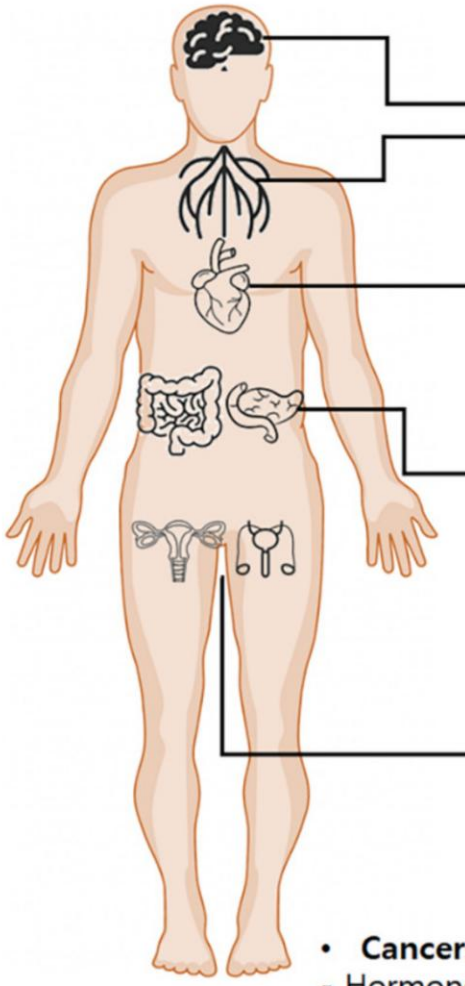
The DNA double helix unwinds near the start site, exposing the **template strand**.

- **Elongation**

RNA polymerase reads the **DNA template strand (3′ → 5′)** and synthesizes a **complementary RNA strand (5′ → 3′)**.

Base pairing rules:

- DNA **A** → RNA **U** (uracil replaces thymine)
- DNA **T** → RNA **A**
- DNA **G** → RNA **C**
- DNA **C** → RNA **G**



- **Brain and nerve system**
  - Brain development ↓
  - Brain function ↓
  - Autism, neurologic disorders
  - Thyroid function ↓

**BPA, OP, Phthalate, D4**

- **Cardiovascular system**
  - Cardiac muscle development ↓
  - Cardiomyocyte differentiation ↓
  - Blood pressure ↑

**BPA, OP, IOX, DES**

- **Metabolic system**
  - Obesity ↑
  - Insulin tolerance ↑
  - Alters fat metabolism
  - Alters calcium absorption
  - Affect gut microbiota by metabolization

**BPA, OP**

- **Reproductive system**
  - premature thelarche and gynecomastia
  - Interrupting normal estrous cycle
  - Disrupt the ovarian function and fertility
  - Alters placental ion transportation

**Alkylphenol, BPA, paraben, phthalates, DES**

- **Cancers**
  - Hormone related cancers e.g. breast, ovary, endometrium, prostate, testis, thyroid cancer

**BPA, OP, pesticide, PCBs**

Exposure to EDCs contributes significantly to the onset and progression of organ development and disorders such as reproductive, metabolic, neurologic, cardiovascular disease, and cancers; these EDCs include Bisphenol A (BPA), octylphenol (OP), octamethylcyclotetrasiloxane (D4), ioxynil (IOX), diethylstilbestrol (DES), polychlorinated biphenyls (PCBs). Int. J. Mol. Sci. 2023, 24(6), 5342; https://doi.org/10.3390/ijms24065342

All embryos start in an undifferentiated state, and in the absence of male signals, development follows the female pathway.

Developmental biology perspective:

All human embryos start out with bipotential (undifferentiated) gonads and common internal structures that can develop into either male or female reproductive organs.

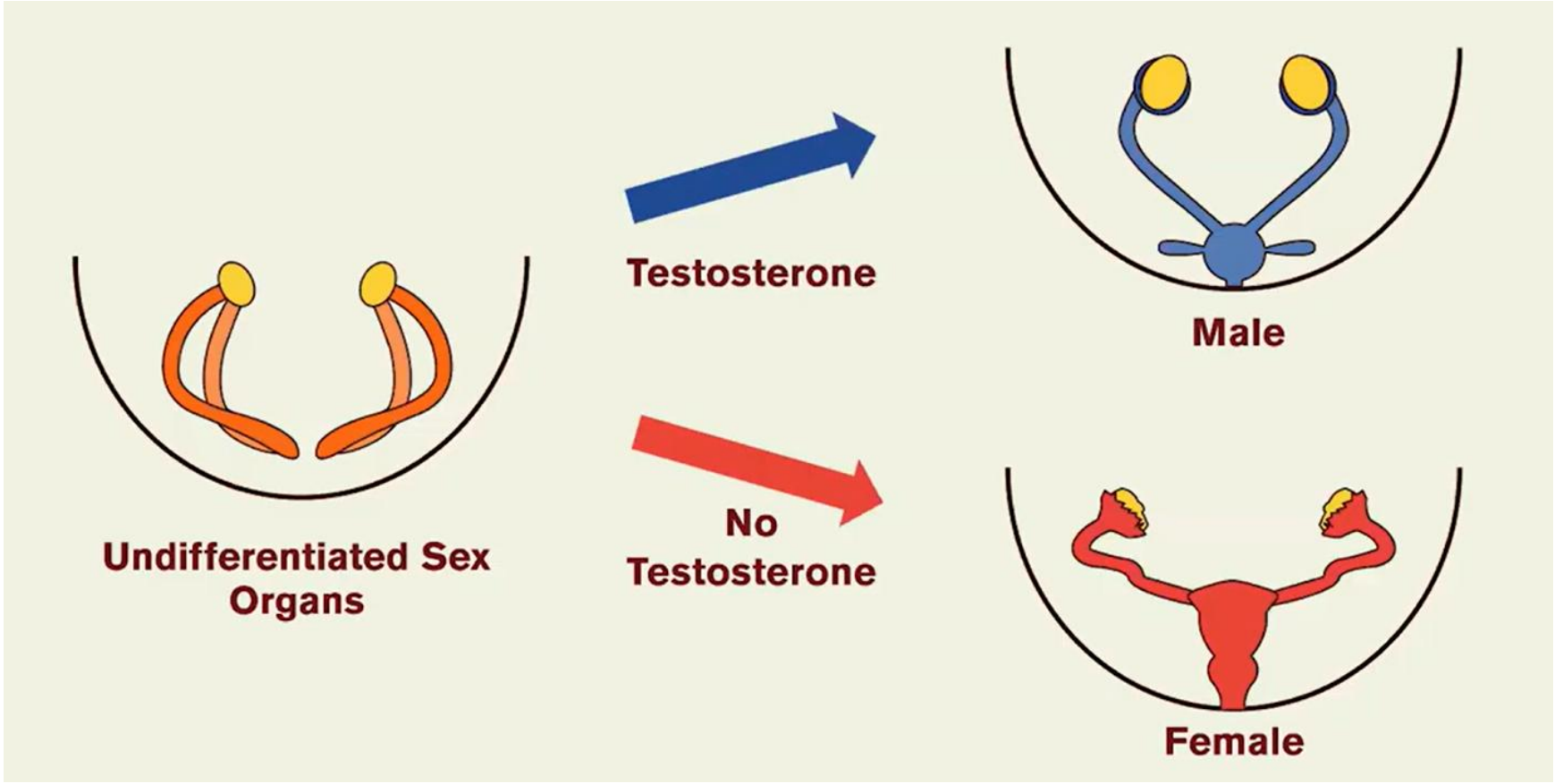
- In the first 6 weeks of embryonic life, there's no anatomical difference between XX (genetic female) and XY (genetic male) embryos.
- Both have Müllerian ducts (which can form female structures) and Wolffian ducts (which can form male structures).

Next, an embryo having a Y chromosome, the SRY gene (Sex-determining Region Y) triggers the development of Testosterone, promoting male organ development and Anti-Müllerian hormone (AMH), which causes regression of female (Müllerian) structures.

If there is no Y chromosome (XX), the default pathway proceeds — gonads develop into ovaries, and female structures form from the Müllerian ducts.

Gilbert, S. F., & Barresi, M. J. F. (2020). Developmental Biology (12th ed.). Chapter 17 Sinauer Associates / Oxford University Press.

# Reproductive Biology



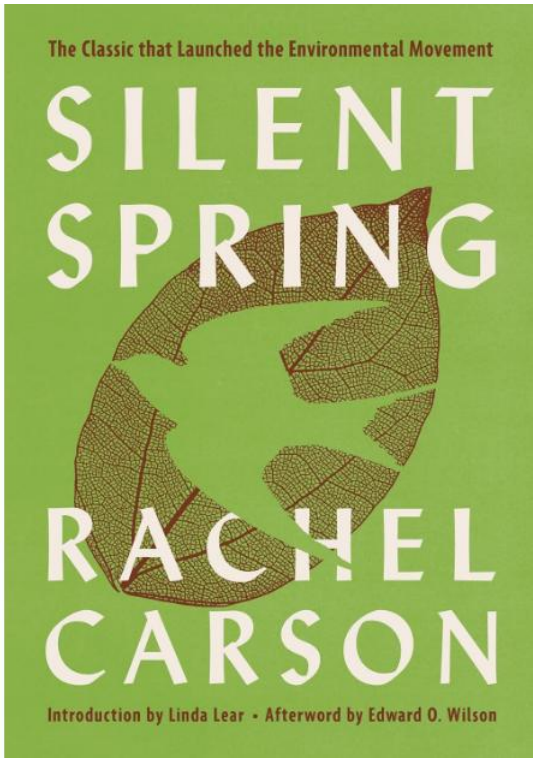
**Mechanisms of Action:**

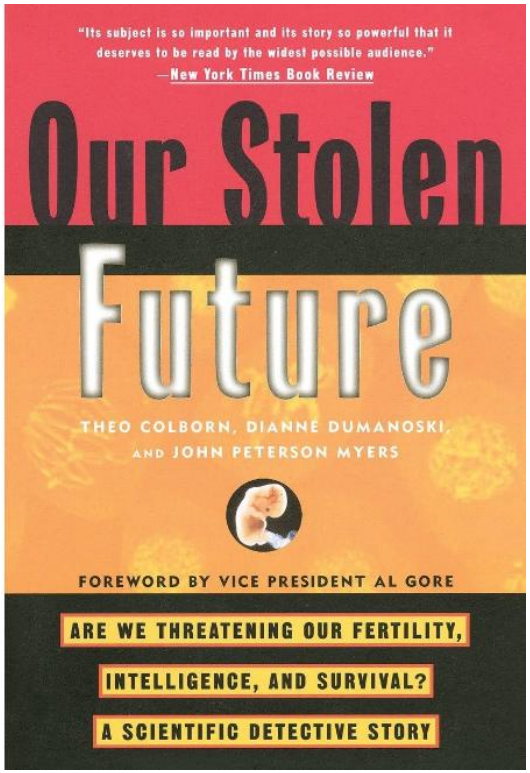
- **Agonist activity:** Chemicals bind to hormone receptors, activating pathways inappropriately.
- **Antagonist activity:** Chemicals block hormone receptors, preventing normal hormonal signalling. Anti-Müllerian hormone (AMH) signals the complete regression and breakdown of the Müllerian ducts.
- **Altered hormone synthesis/metabolism:** Changing circulating levels of sex hormones can disrupt development.

**Impact on Sexual Development and Gender Traits:**

- In prenatal or early postnatal periods, altered hormone signalling can affect the development of reproductive organs, brain sexual differentiation, and secondary sexual characteristics.
- Animal studies and epidemiological evidence suggest that EDC exposure can affect genital morphology, reproductive behaviour, and hormone-dependent traits, potentially influencing gender-related characteristics.

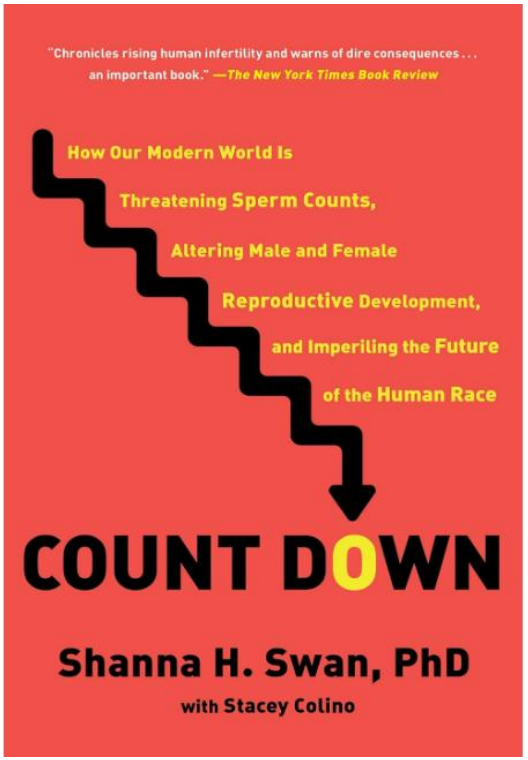
Silent Spring is an environmental science book by Rachel Carson. Published on September 27, 1962, the book documented the environmental harm caused by the indiscriminate use of DDT, a pesticide used by soldiers during World War II.




A Scientific Detective Story is a 1996 book by Theo Colborn, Dianne Dumanoski, and John Peterson Myers. The book chronicles the development of the endocrine disruptor hypothesis by Colborn.

How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development, and Imperilling the Future of the Human Race by Shanna H. Swan and Stacey Colino.

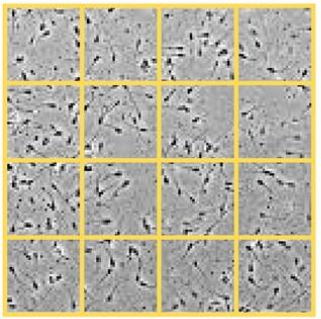


# Temporal trends in sperm count: a systematic review and meta-regression analysis FREE

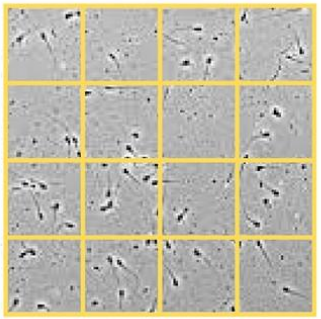
Hagai Levine ✉, Niels Jørgensen, Anderson Martino-Andrade, Jaime Mendiola, Dan Weksler-Derri, Irina Mindlis, Rachel Pinotti, Shanna H Swan

Human Reproduction Update, 2023, 29, 157–176, and Human Reproduction Update, 2017, 23, 646-659

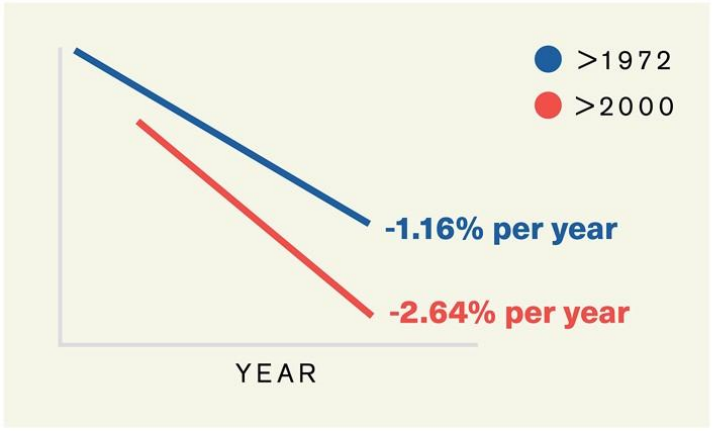
## Sperm count is declining at an accelerated pace globally



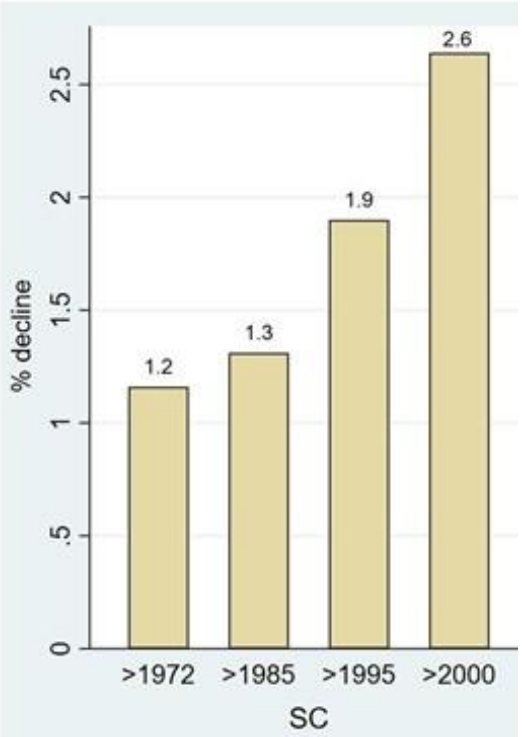
101 mill/ml
(1973)



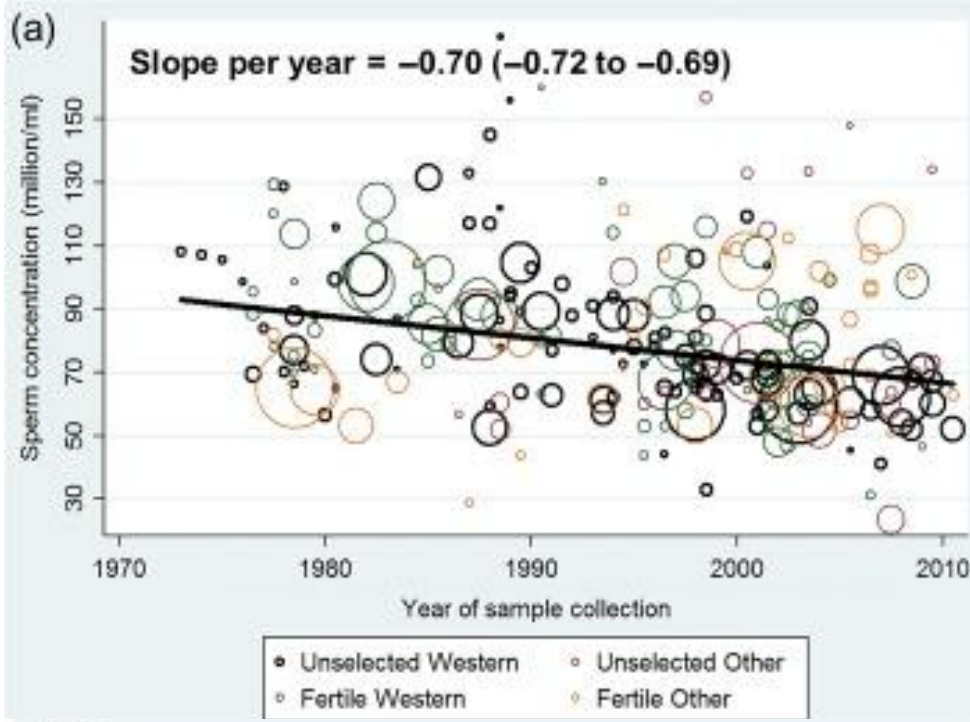
49 mill/ml
(2018)

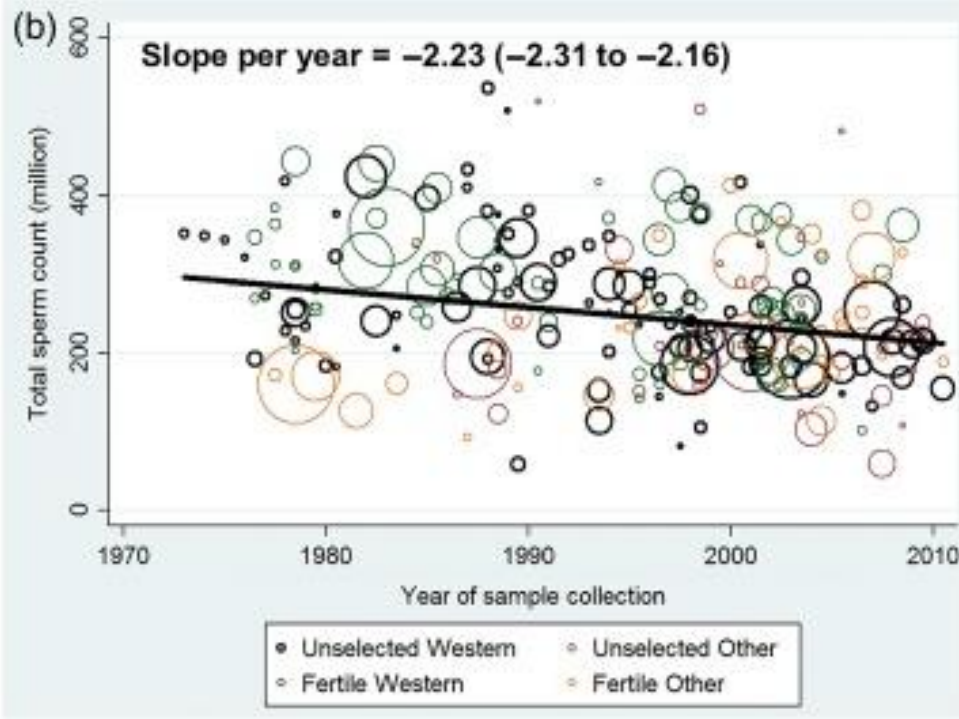


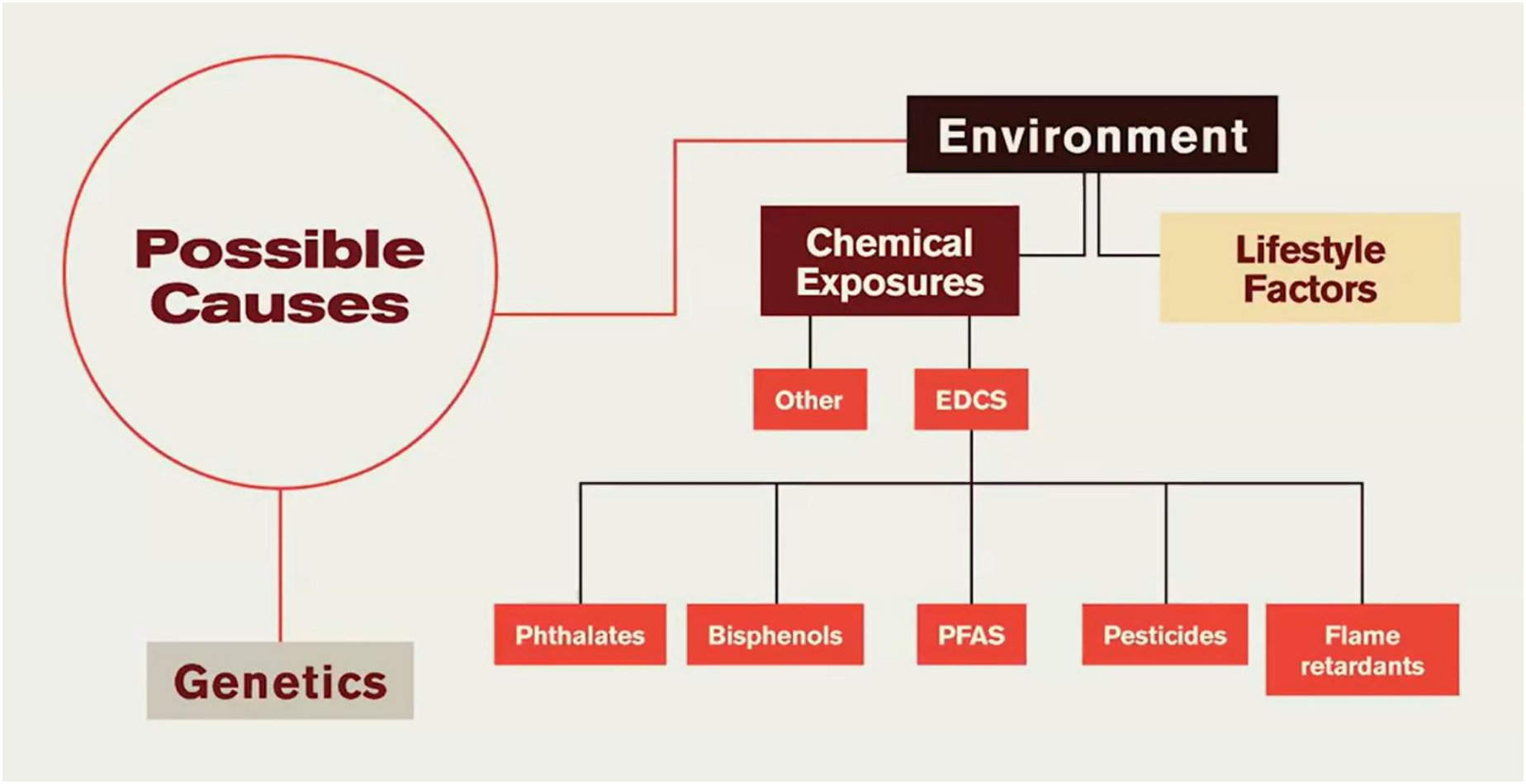

Decline (%) for mean sperm concentration (SC) among unselected men using a stratified meta-regression model.
Human Reproduction Update, 2023, 29, 157–176




(a) Mean sperm concentration and (**b**) Mean total sperm count by year of sample collection in 244 estimates collected in 1973–2011 and simple linear regression.
Hum Reprod Update. 2017, 23, 646–659. doi: 10.1093/humupd/dmx022




Possible Causes
Environment
Chemical Exposures
Lifestyle Factors
Other
EDCS
Phthalates
Bisphenols
PFAS
Pesticides
Flame retardants
Genetics

ANDROLOGY

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# Phthalate exposure and semen quality in fertile US men

S. W. Thurston ✉, J. Mendiola, A. R. Bellamy, H. Levine, C. Wang, A. Sparks, J. B. Redmon, E. Z. Drobnis, S. H. Swan

First published: 24 November 2015 | https://doi.org/10.1111/andr.12124 | Citations: 43

- Nine phthalate metabolites [mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP)], as well as mono-n-butyl phthalate (MBP) and mono-isobutyl phthalate (MiBP), mono (three carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP), and monoethyl phthalate (MEP)] were measured in urine collected at the same time as the semen sample
- Regressed natural log-transformed (ln) sperm concentration, ln(total sperm count), ln(total motile sperm count), percent motile spermatozoa, and percent spermatozoa with normal morphology on each of the nine natural log-transformed metabolite concentrations and on the molar-weighted sum of DEHP metabolites in separate models.

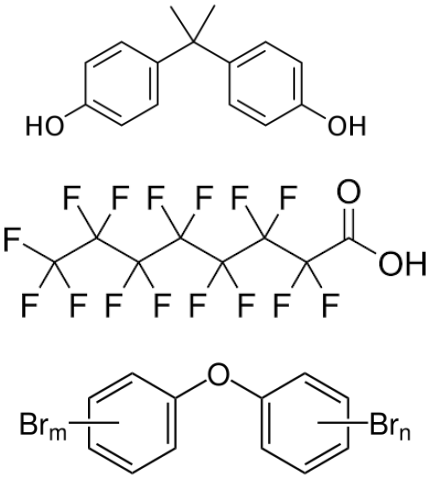
# Our Concerns with Chemicals

In Europe and the US there are Priority Substances for which we have concern because there is good evidence for adverse health effects (e.g. Lead, PCBs).

***Other Chemicals for which there is increasing health concern include:***

**Industrial chemicals:**

- *Bisphenol A:* Polycarbonate polymers and epoxy resins. Associated with various health disorders (e.g. obesity, reproduction)
- *Perfluoro octanoic acid (PFOAs)* - found in the blood of 98% blood US citizens associated with elevated cholesterol and chronic kidney disease
- *Polybrominated diphenyl ethers* - Flame retardants associated with thyroid dysfunction

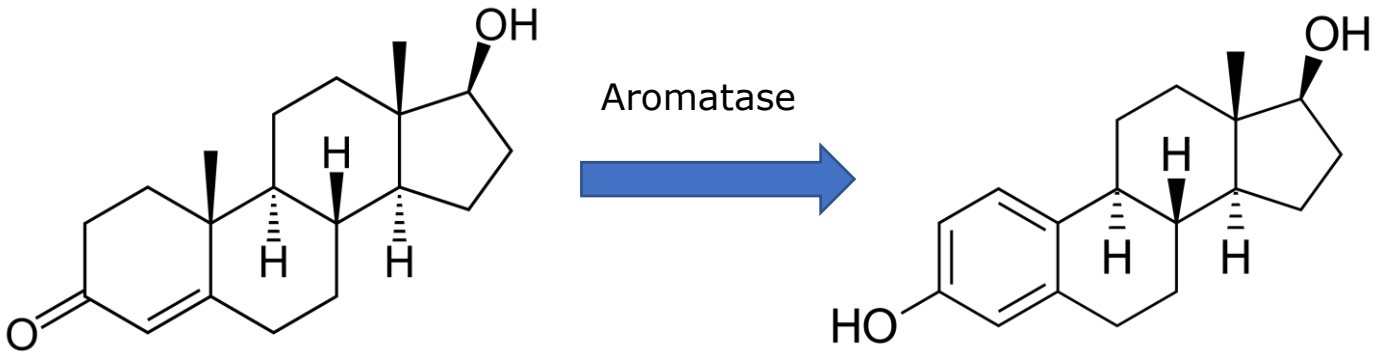



**Pharmaceuticals:**

*17 alpha-ethinylestradiol (EE2), 17 beta-estradiol (E2), Diclofenac.*

*Endocrine Disrupting Chemicals*

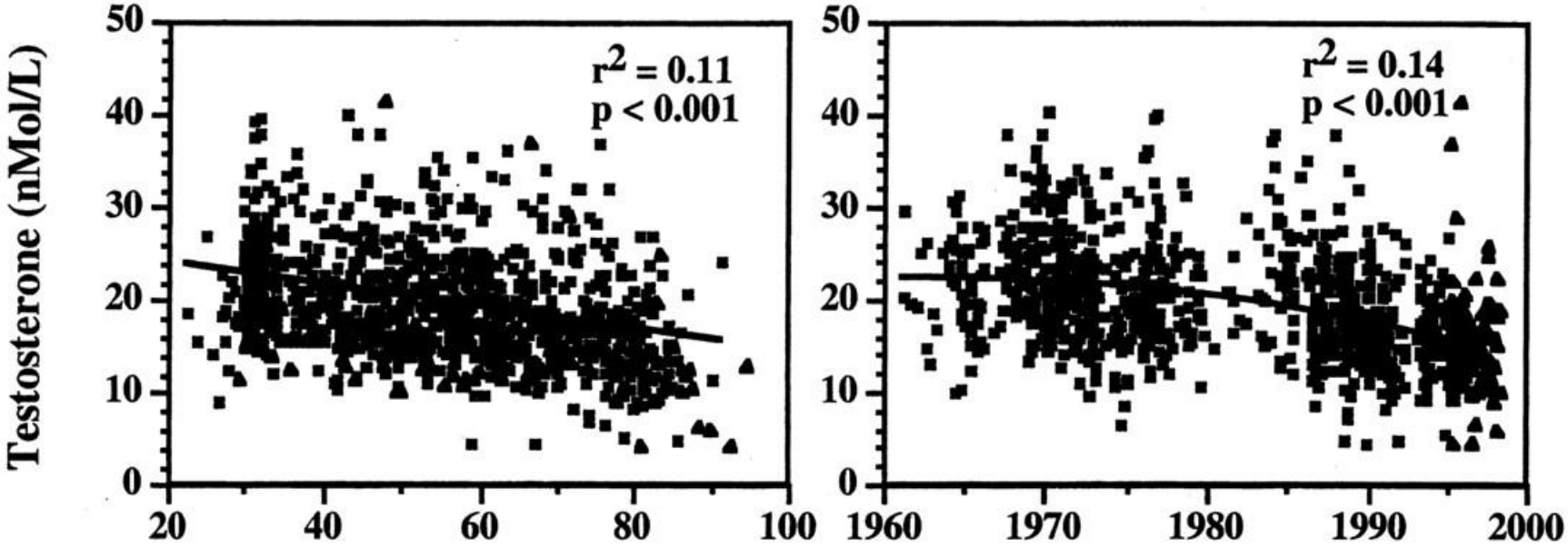
# Testosterone to Estradiol Conversion




Aromatase is a (CYP19A1) Cytochrome P450 family of enzyme

$$\text{Testosterone} \xrightarrow[\text{NADPH, } O_2]{\text{Aromatase}} \text{Estradiol + Formic acid + Water}$$

Certain EDCs upregulate the aromatase expression and disrupt normal endocrine function, leading to hormonal imbalance.




*The Journal of Clinical Endocrinology & Metabolism*, Volume 86, Issue 2, 1 February 2001, Pages 724-731, https://doi.org/10.1210/jcem.86.2.7219

# Perinatal Exposure to the Phthalates DEHP, BBP, and DINP, but Not DEP, DMP, or DOTP, Alters Sexual Differentiation of the Male Rat FREE

L. Earl Gray, Jr., Joseph Ostby, Johnathan Furr, Matthew Price, D. N. Rao Veeramachaneni, Louise Parks

*Toxicological Sciences*, Volume 58, Issue 2, December 2000, Pages 350–365,