Sustainability and Chemistry
CH5106: L11

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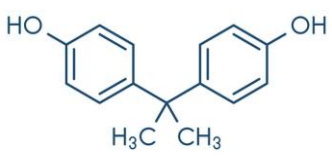
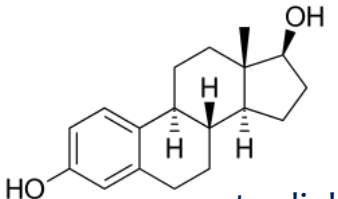
Bisphenol A (BPA) is an endocrine-disrupting chemical (EDC). It interferes with hormone systems, especially those involving estrogen, and leads to various health issues.



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.

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.

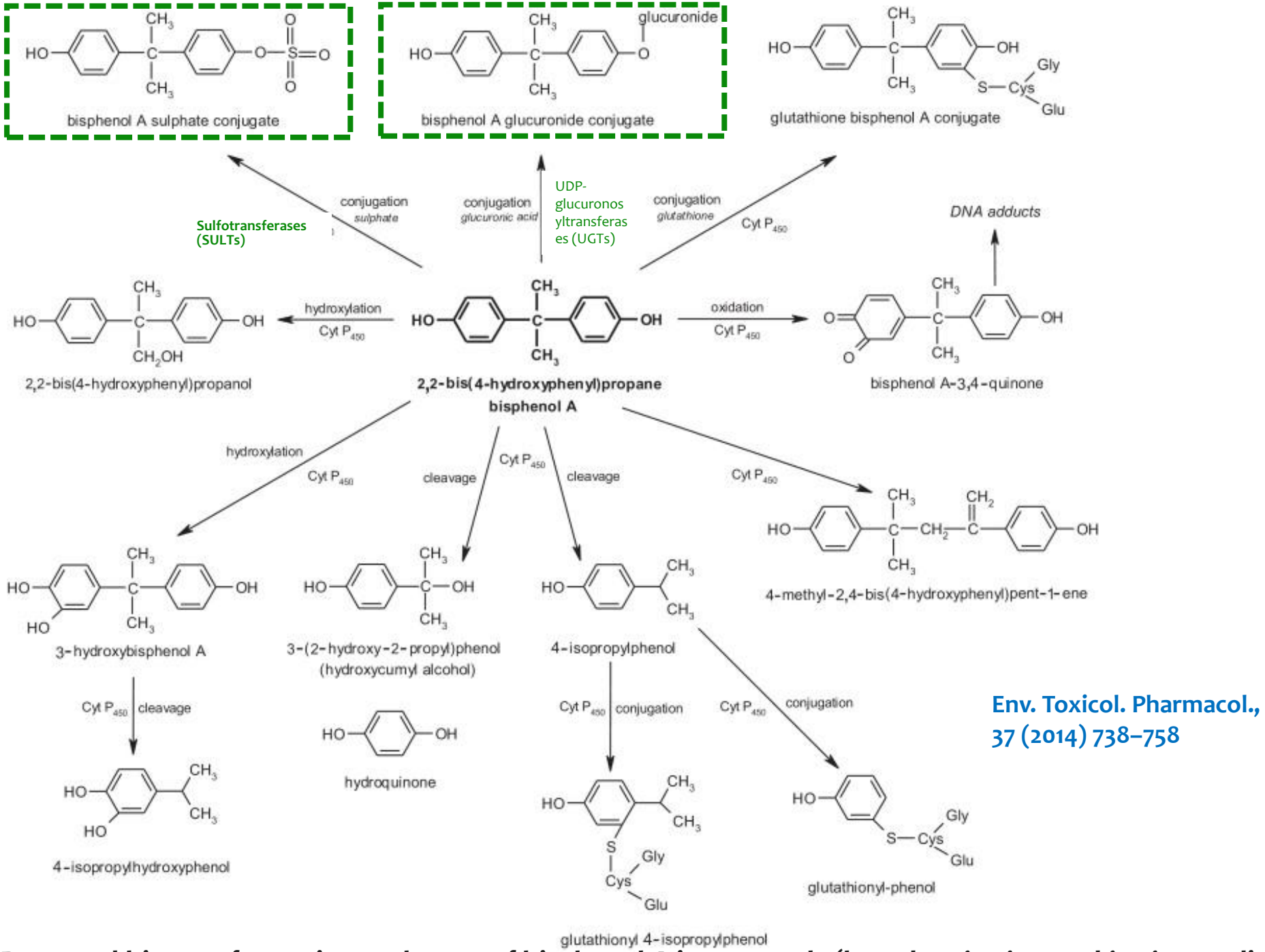
a. Glucuronidation [This is the main detoxification pathway in both adults]

- Enzyme: Uridine Diphosphate-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.

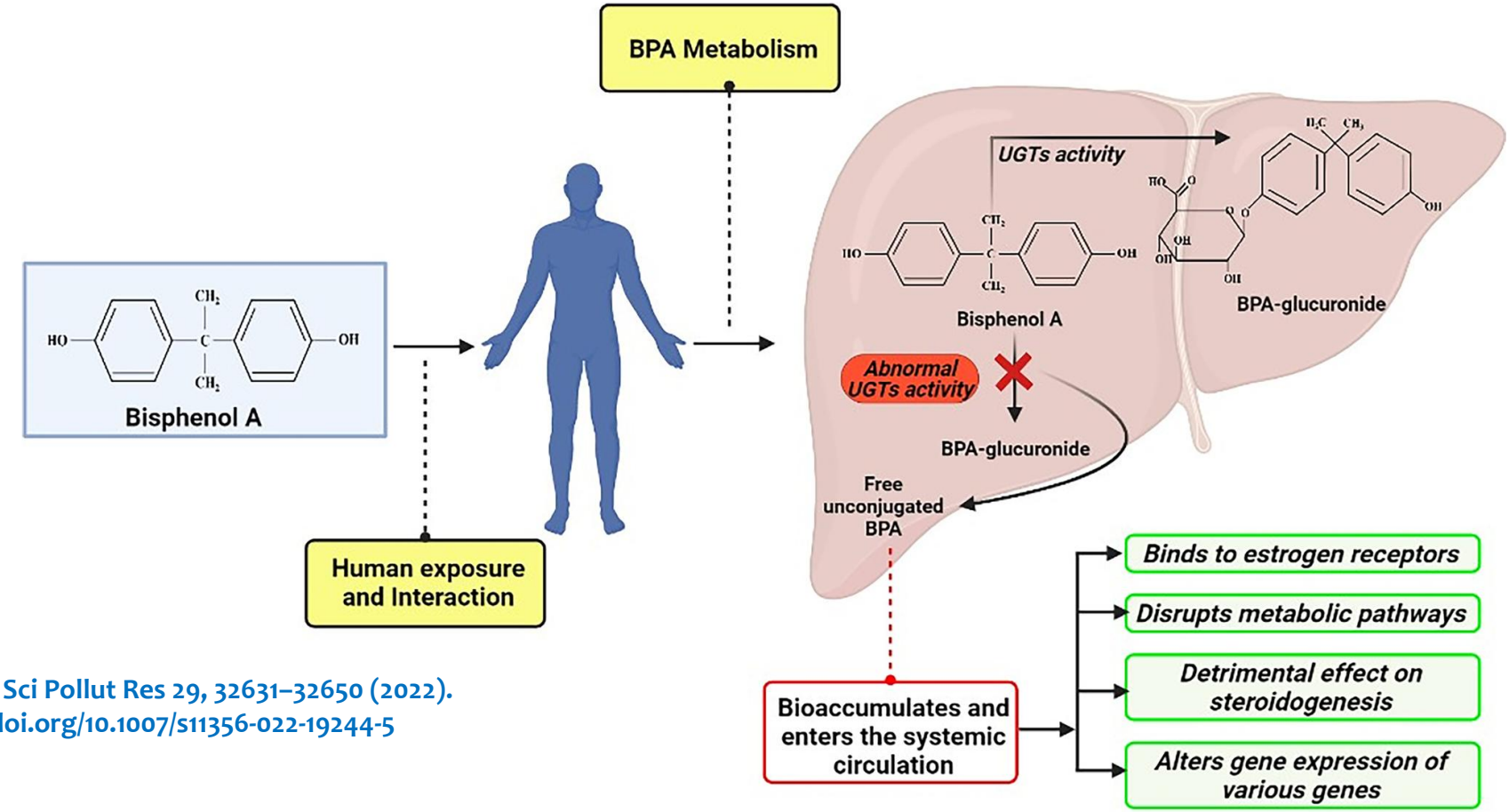
Environ Sci Pollut Res 29, 32631–32650 (2022). https://doi.org/10.1007/s11356-022-19244-5 and AI



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

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

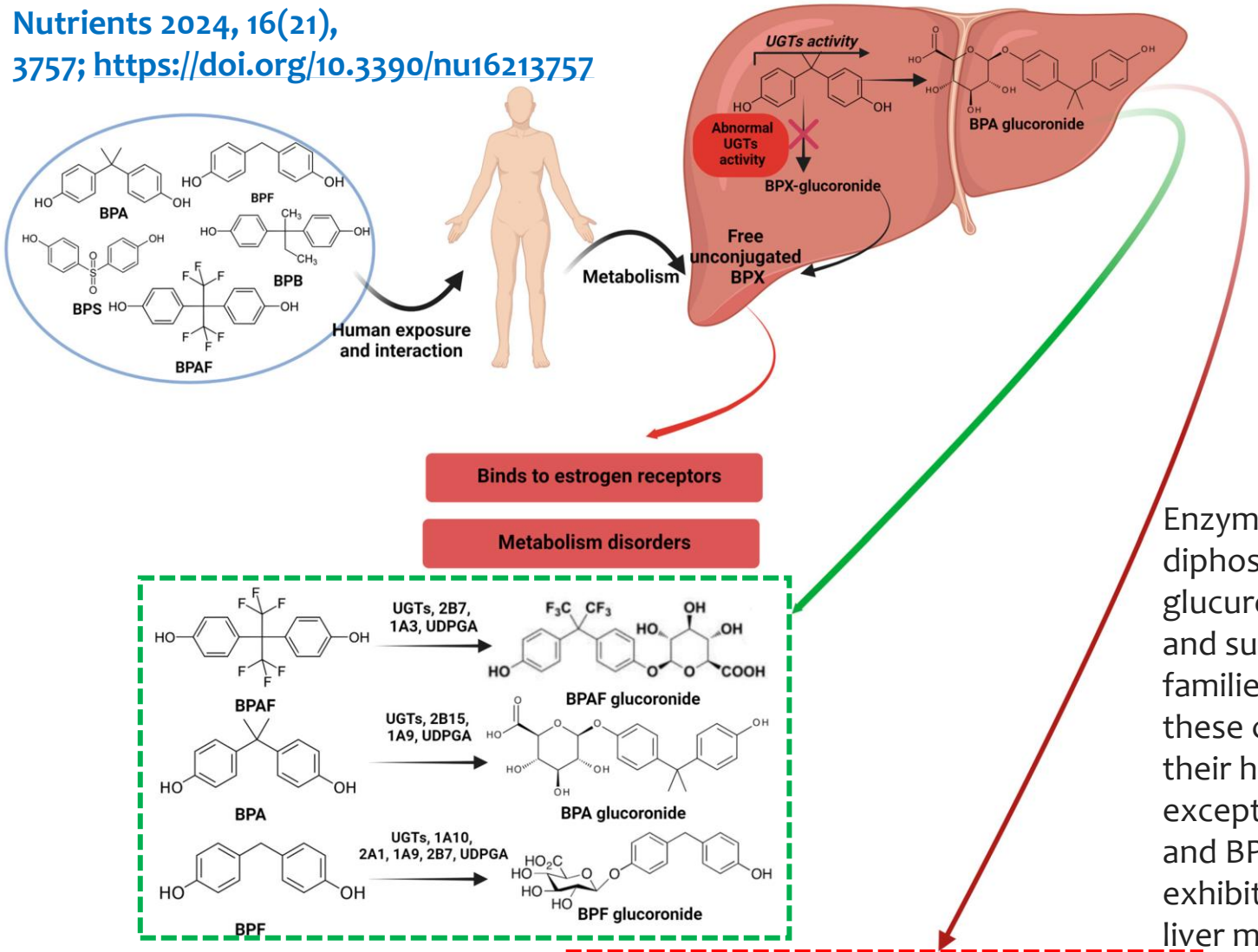
Additionally, its ability to mimic the behaviour of 17-β estradiol results in the disruption of various pathways, causing moderate acute toxicity in humans. The most common pathological effects include obesity, cardiovascular diseases, hyperinsulinemia, thyroid, hypertension, ovarian and testicular developmental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



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

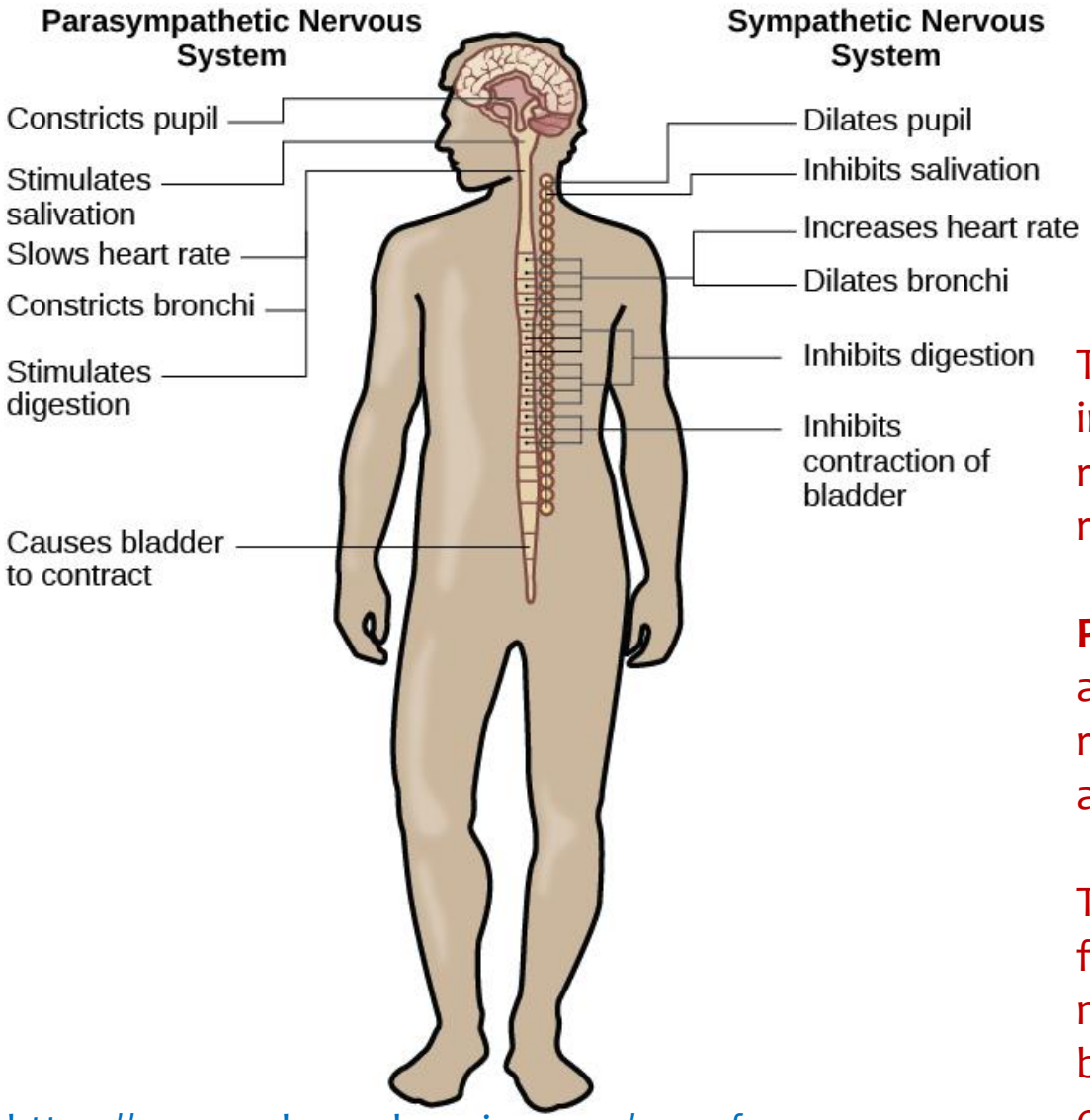
Uridine-5-diphospho-glucuronosyltransferases (UGTs) are the important class of enzymes involved in the catalysis of BPA glucuronidation that results in the transformation of BPA to BPA-G, which is biologically inactive. Furthermore, BPA is reported to be majorly excreted in the urine as BPA-G (94.6%).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

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.

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.



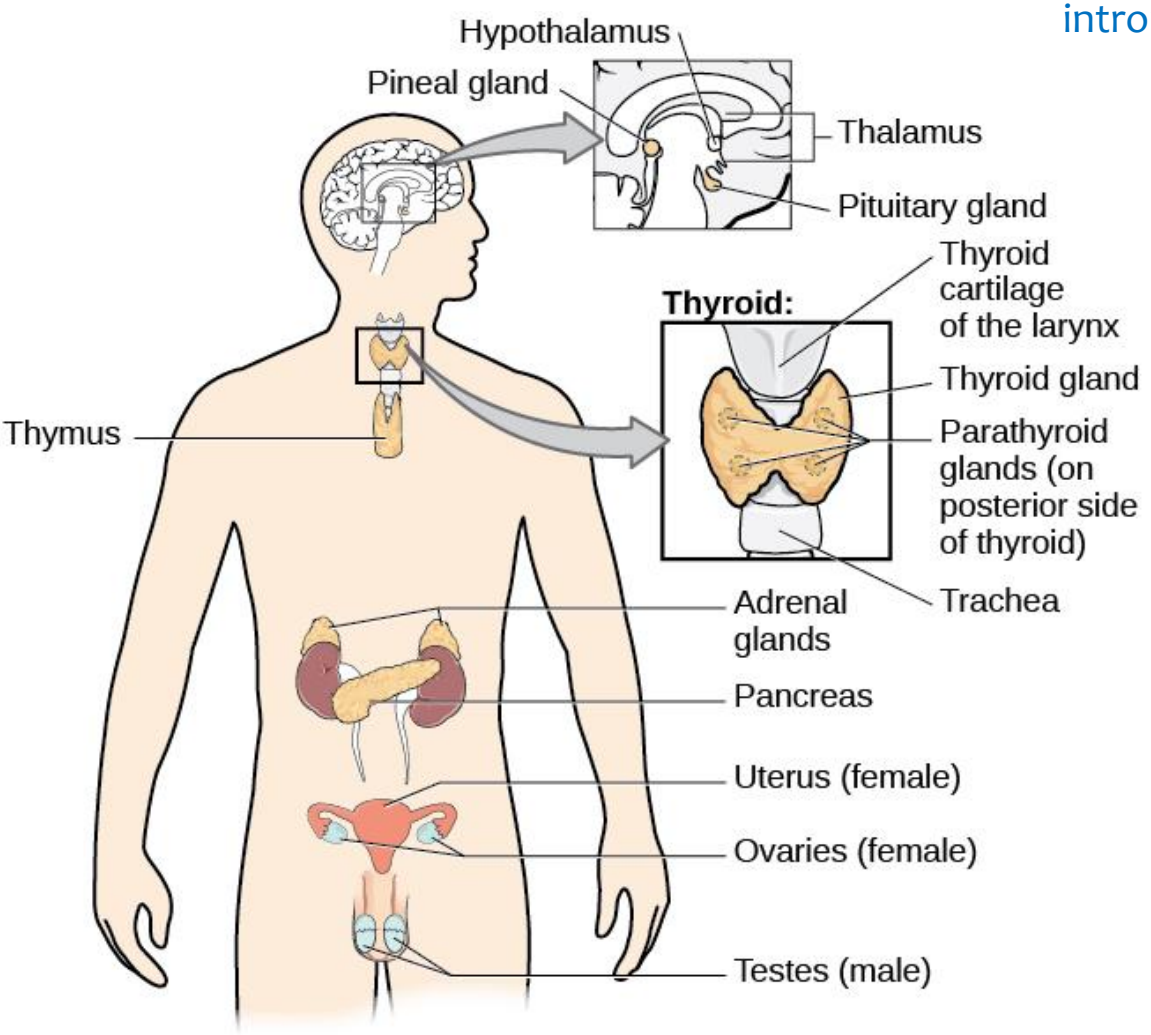
https://courses.lumenlearning.com/suny-fmcc-intropsych/chapter/the-endocrine-system/

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

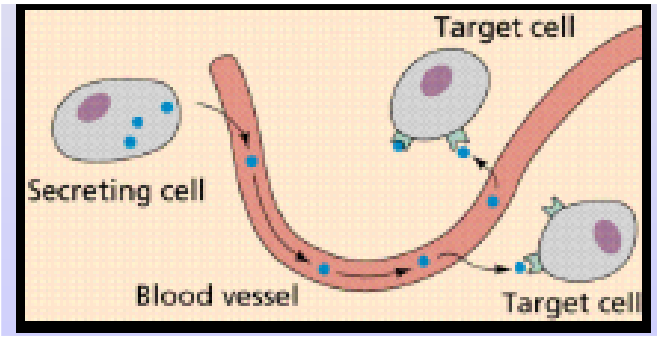
The two systems have complementary functions, operating in tandem to maintain the body's homeostasis—the body's internal balance, keeping conditions like temperature and heart rate within optimal ranges..

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

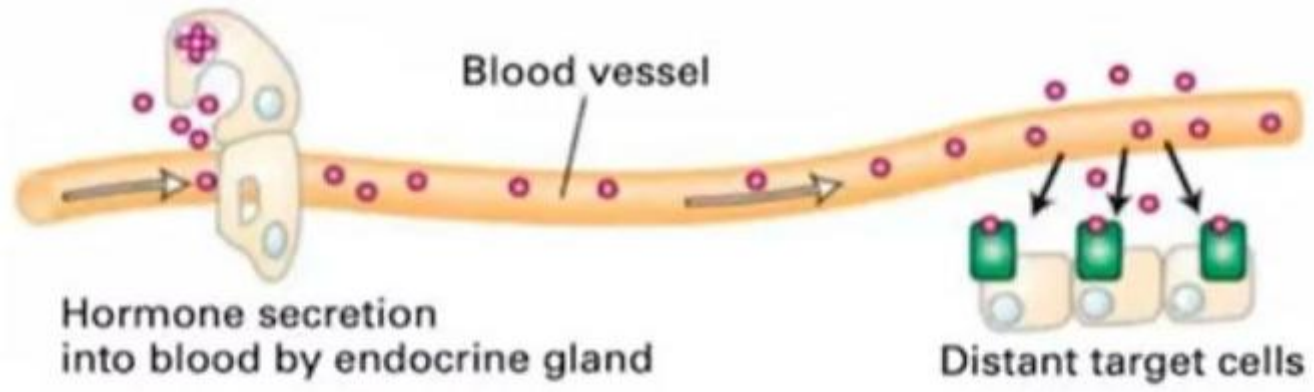


Communication Systems: The nervous system, together with the endocrine system, makes up the body's major signalling pathways in all animals:

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.



Hormones are defined as chemical substances having specific regulatory effects on the activity of an organ or organs. The term hormone was originally applied to substances secreted by various endocrine glands and transported in the bloodstream to various target organs. Thus, hormones are cell-signalling molecules.

In the endocrine type of cell signalling, the chemical substances produced by the gland enter the bloodstream through fenestrated capillaries in the body and travel further to reach various target organs or cells that act as receptors.

Protein Hormone Receptor Activity

Protein hormones are unable to cross the plasma membrane of target cells; hence, their receptors are located on the cell surface. Upon binding of the hormone to its receptor, the receptor undergoes activation, triggering a cascade that generates intracellular second messengers. These second messengers mediate the hormone's effects by promoting the phosphorylation of specific enzymes, ultimately altering cellular activity.

Steroidal Hormone Receptor Activity

Steroid hormones diffuse across the plasma membrane and bind to cytoplasmic or nuclear receptors, regulating gene expression—termed *genomic action*. Some, like estrogen, also trigger rapid *non-genomic actions* via membrane receptors and signaling pathways (e.g., MAP kinase). Receptors lacking identified ligands are termed *orphan receptors*.

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.

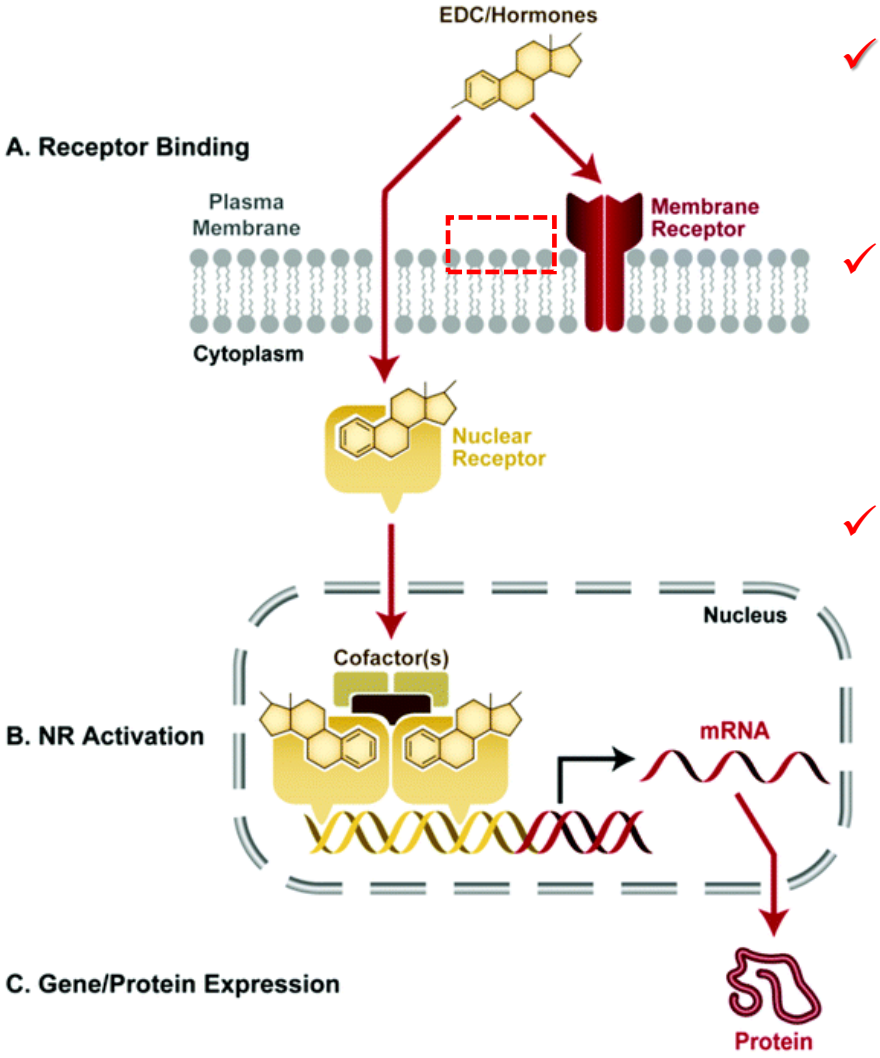
EDCs exert their effects primarily by:

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

EDCs are small, lipophilic molecules that can cross the cell membrane and bind to nuclear hormone receptors (NRs).



- ✓ 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.

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**

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.

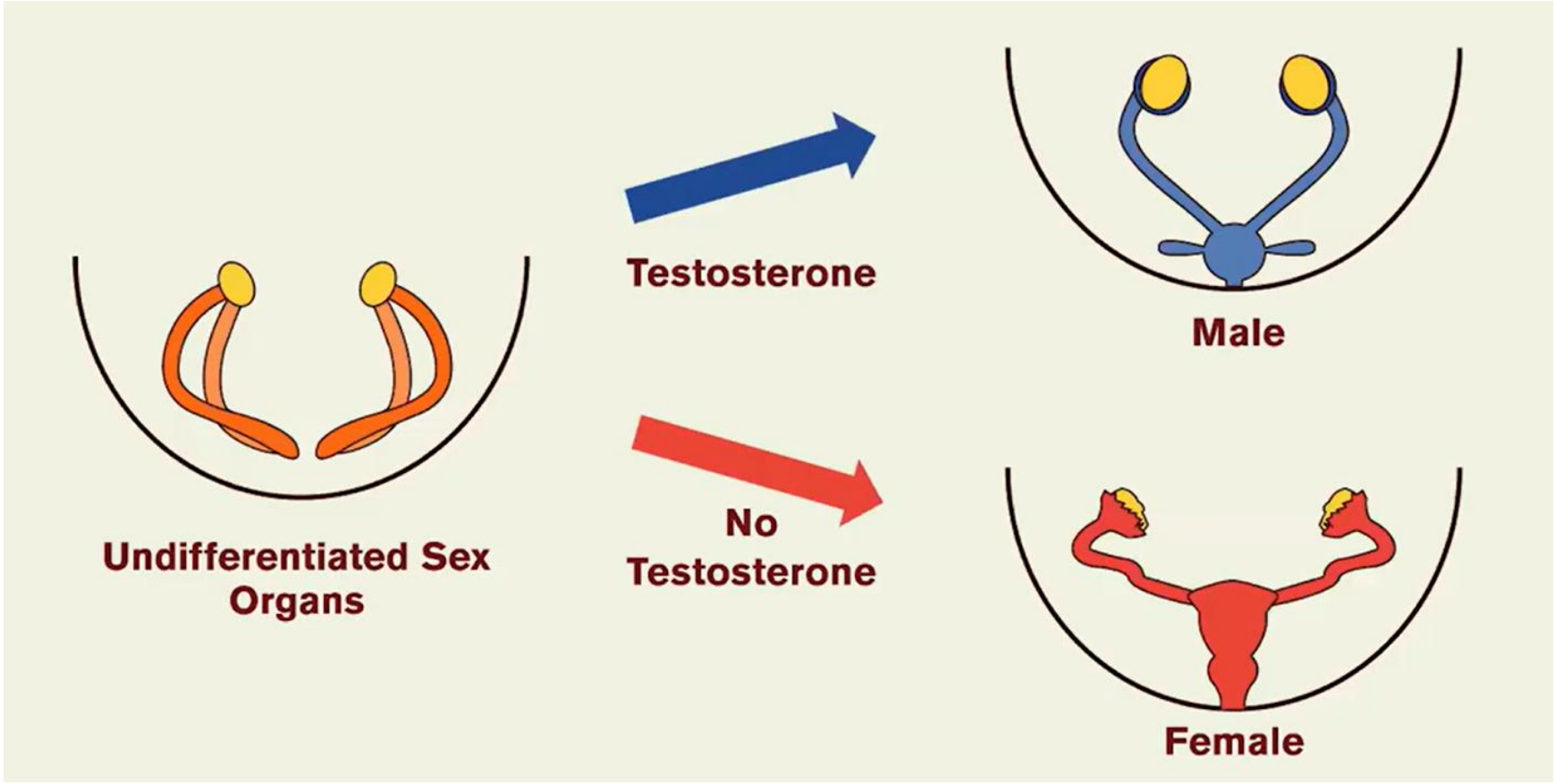
- In the first 6 weeks of embryonic life, there's no anatomical difference between XX (genetic female) and XY (genetic male) embryos.
- Both have Müllerian ducts (which can form female structures) and Wolffian ducts (which can form male structures).

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.

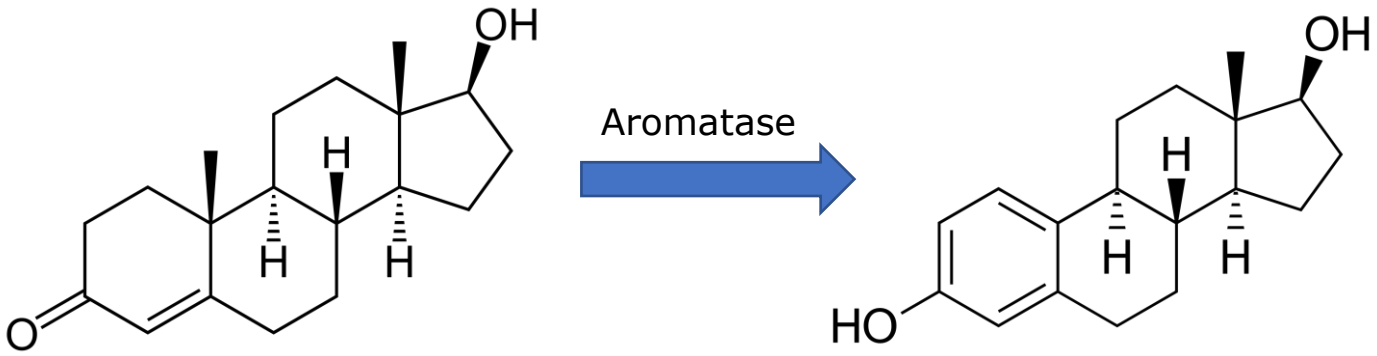
If there is no Y chromosome (XX), the default pathway proceeds — gonads develop into ovaries, and female structures form from the Müllerian ducts.

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

Reproductive Biology



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.

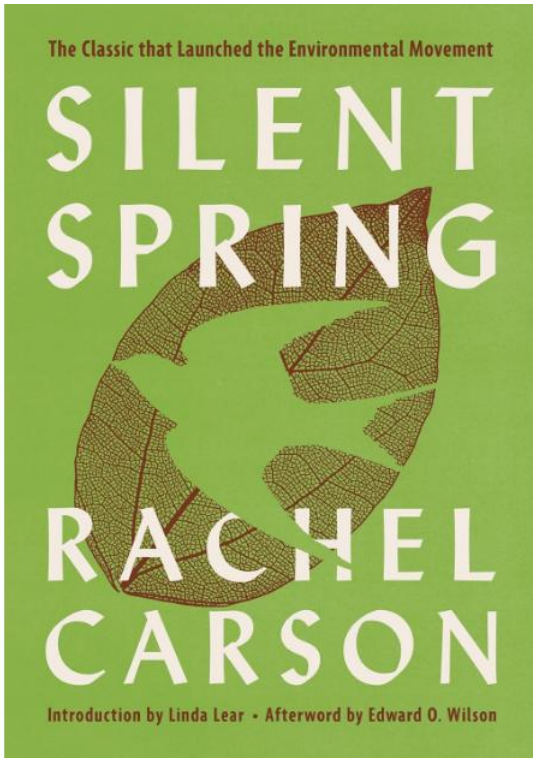
Mechanisms of Action:

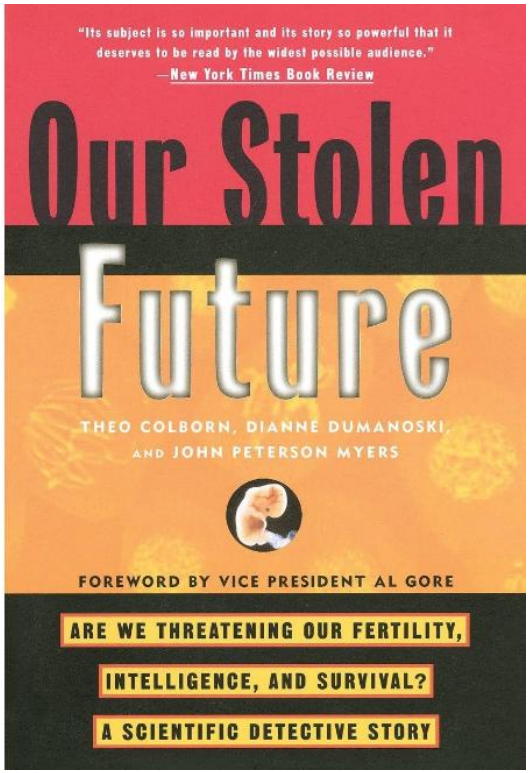
- **Agonist activity:** Chemicals bind to hormone receptors, activating pathways inappropriately.
- **Antagonist activity:** Chemicals block hormone receptors, preventing normal hormonal signalling. Anti-Müllerian hormone (AMH) signals the complete regression and breakdown of the Müllerian ducts.
- **Altered 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.

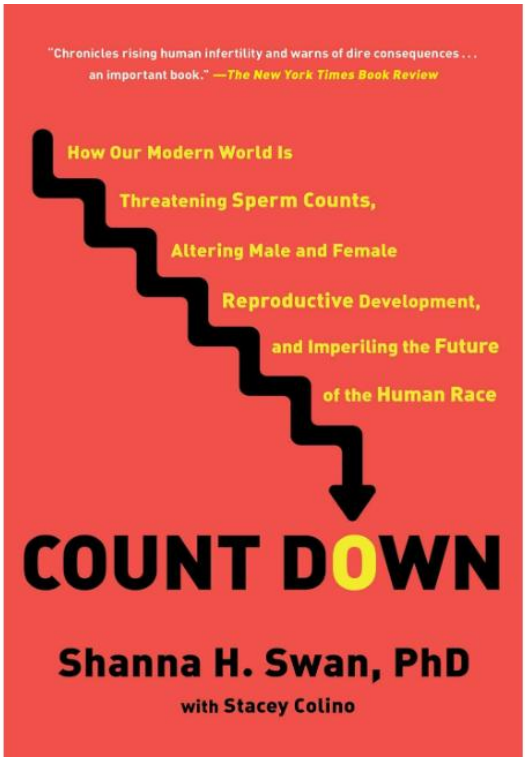
Silent Spring is an environmental science book by Rachel Carson. Published on September 27, 1962, the book documented the environmental harm caused by the indiscriminate use of DDT, a pesticide used by soldiers during World War II.



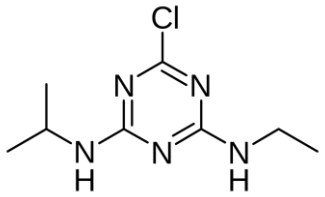


A Scientific Detective Story is a 1996 book by Theo Colborn, Dianne Dumanoski, and John Peterson Myers. The book chronicles the development of the endocrine disruptor hypothesis by Colborn.

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.



Atrazine is a widely used triazine herbicide and one of the most studied endocrine-disrupting chemicals (EDCs). Its persistence in soil and water, combined with high usage in agriculture, has raised concerns regarding toxicological effects on human and animal physiology, particularly on the reproductive system.



General Toxicity of Atrazine:

- Endocrine disruption: Atrazine interferes with the hypothalamic–pituitary–gonadal (HPG) axis, altering hormone signalling.
- Metabolic effects: It induces oxidative stress, mitochondrial dysfunction, and DNA damage.
- Carcinogenic potential: Some studies link atrazine exposure to increased risk of breast, ovarian, and prostate cancers, though epidemiological data remain debated.

Mechanistic Insights:

- **Aromatase induction:** Key mechanism where atrazine increases estrogen production, shifting the hormonal balance.
- **Oxidative stress:** Reactive oxygen species damage gonadal tissues and germ cells.
- **Epigenetic changes:** Evidence suggests atrazine alters gene expression linked to reproductive development and function.

Atrazine acts as an endocrine disruptor that interferes with hormone synthesis and signalling, impairing male and female reproductive health. Its effects include reduced fertility, altered sexual development, and increased risk of hormone-related reproductive disorders.

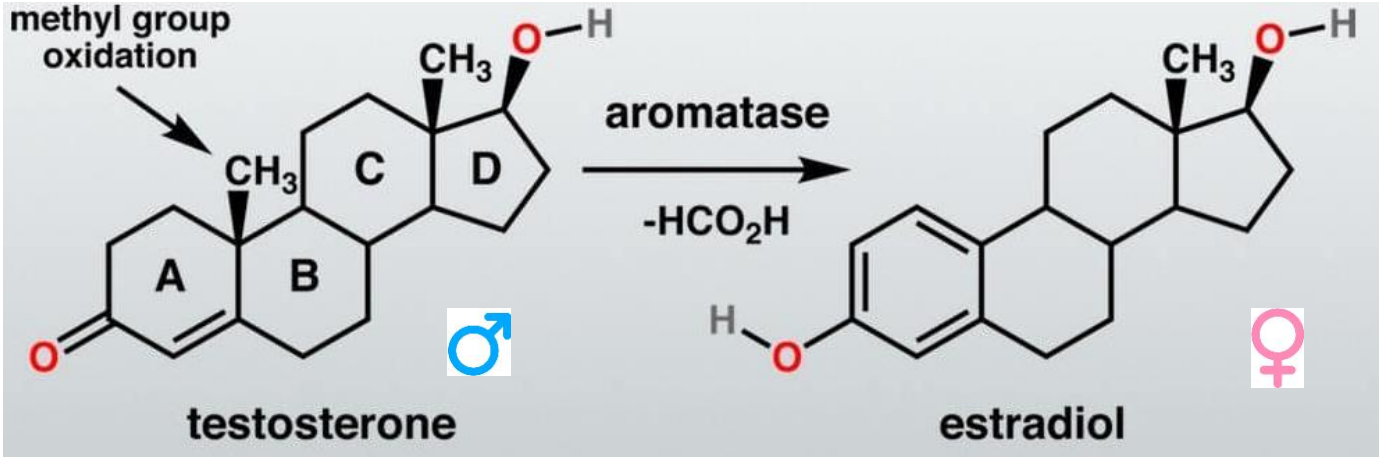
Effects on the Reproductive System:

In Males

- **Hormonal imbalance:** Atrazine reduces testosterone by increasing aromatase activity, which converts androgens to estrogens.
- **Testicular toxicity:** Reported effects include reduced sperm count, abnormal sperm morphology, impaired spermatogenesis, and testicular atrophy.
- **Developmental impact:** Prenatal exposure alters sexual differentiation and reproductive capacity in adulthood.

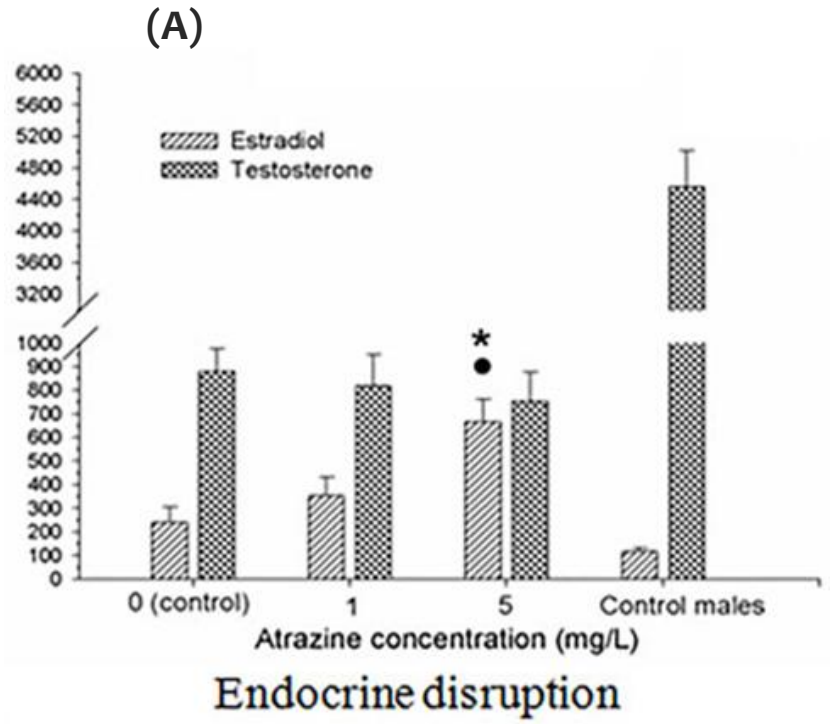
In Females

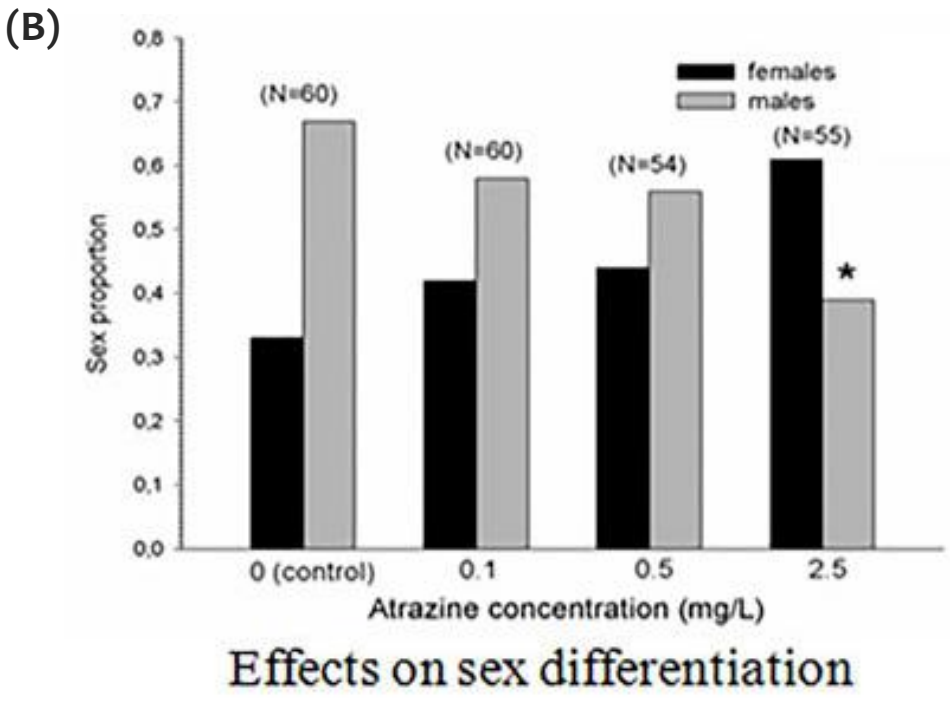
- **Ovarian dysfunction:** Atrazine disrupts folliculogenesis, reduces ovulation rates, and alters estrous/menstrual cycles.
- **Pregnancy outcomes:** Animal studies show increased risk of spontaneous abortion, delayed puberty, and impaired fertility.
- **Endocrine-mediated effects:** By altering luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, atrazine affects ovarian steroidogenesis, leading to decreased progesterone and estrogen dysregulation.



Testosterone —(Aromatase; NADPH, O2)→ Estradiol + Formic acid + Water

Atrazine is a well-recognized endocrine disruptor that alters hormone balance and developmental processes across diverse organisms. One of its key mechanisms involves the induction of aromatase (CYP19), the enzyme responsible for converting testosterone into estrogens such as estradiol. By upregulating aromatase expression, atrazine disrupts normal endocrine function, leading to hormonal imbalance. In male amphibians, this manifests as feminization, reduced testosterone levels, and impaired reproductive development, highlighting its profound effects on reproductive physiology. [PNAS, 2002, 99, 5476–5480; PNAS, 107, 4612–4617; Environ. Health Persp., 2007, 115, 720–727].





(A) Changes in steroid in the hemolymph of *Procambarus clarkii* (red swamp crayfish) after 1 month of exposure. Asterisk and dot indicate significant differences ($p < 0.05$) with respect to control and the lowest concentration, respectively; control male data are also included for comparative purposes.

(B) Proportion of sex in early juveniles of *Cherax quadricarinatus* (Redclaw crayfish) exposed during 4 weeks. Asterisk indicates significant differences ($p < 0.05$) with respect to control; number of animals is indicated in brackets. **[Front. Physiol., Sec. Aquatic Physiology, 2022, 13, doi.org/10.3389/fphys.2022.926492]**

https://youtu.be/HuoIXMTFY9Q

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.

•**Atrazine** (commonly applied herbicides)

•**Bisphenol A (BPA)** is used to make polycarbonate plastics and epoxy resins. BPA based polymers and resins.

•**Dioxins** (byproduct of certain manufacturing processes) Also released into the air from waste burning and wildfires.

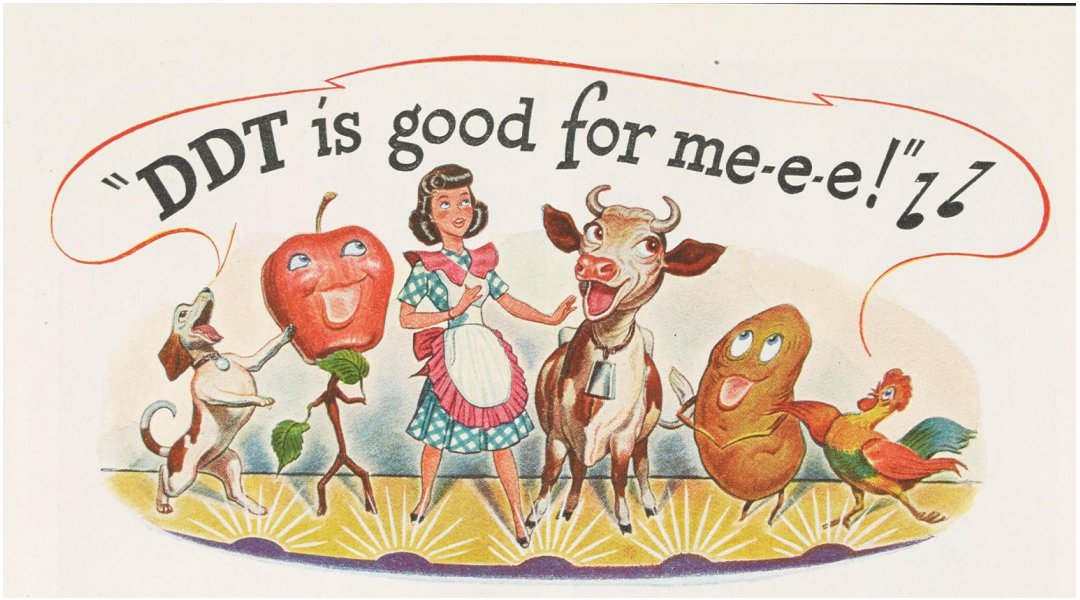
•**Perchlorate** (Used in explosives, and fireworks)

•**Per- and polyfluoroalkyl substances (PFAS)** (firefighting foam, nonstick pans, paper, and textile coatings, etc).

•**Phthalates** (liquid plasticizers, food packaging, cosmetics, fragrances, children's toys, and medical device tubing, Cosmetics (nail polish, hair spray, aftershave lotion, cleanser, and shampoo).

•**Polychlorinated biphenyls (PCBs)** (electrical equipment, such as transformers, and are in hydraulic fluids, heat transfer fluids, lubricants, and plasticizers) were banned in 1979.

During World War II, the U.S. military declared this revolutionary biocide to be “the most powerful of the new weapons the army is now using in its war on insect-borne diseases,” specifically malaria, yellow fever, typhus and bubonic plague. After the war, planes “broadcast sprayed” leftover stockpiles across the United States and many other countries to kill weeds, crop-eating insects and to control mosquitoes.



https://news.mongabay.com/2022/05/rachel-carsons-silent-spring-60-years-on-birds-still-fading-from-the-skies/

DDT was the world’s first modern synthetic insecticide, a chlorinated hydrocarbon and persistent pollutant. It is toxic to wildlife and humans, stores in fatty tissues, and bioaccumulates in greater and greater concentrations up the food chain.

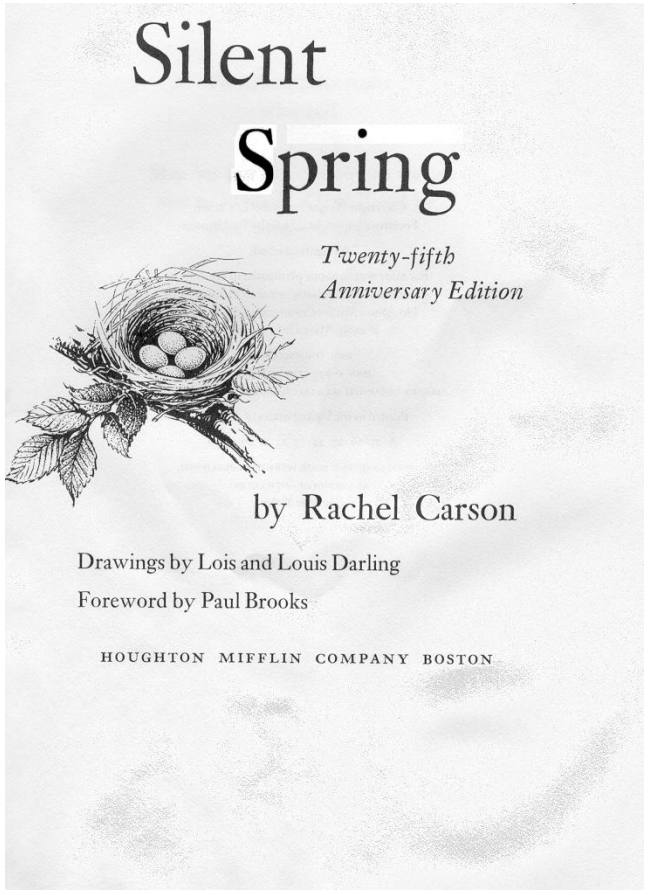
DDT sparked a global avian catastrophe. The biocide interferes with Ca^{2+} metabolism in egg production, particularly in birds of prey, which were “catastrophically impacted”. Thin-shelled, fragile eggs fractured in bird nests, unable to support the weight of a growing embryo.

Rachel Carson Biography

Born, May 27, 1907, Springdale PA

Educated at Pennsylvania Women's College, Pittsburgh and MA in zoology from Johns Hopkins University in 1932

Employment at Marine Biological Laboratory, Woods hole, MA, Bureau of Fisheries

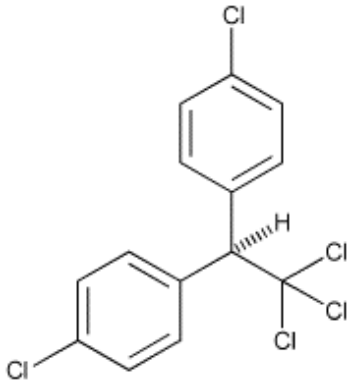


"Only within the moment of time represented by the present century has one species—man—acquired significant power to alter the nature of his world."

“Silent Spring Becomes A Noisy Summer”

- Opposition From Chemical Firms – Monsanto and Velsicol; Agricultural Chemical manufacturers Association
- Review by William Darby in *Chemical and Engineering News*, “Silence, Miss Carson”
- Opposition from Entomologists at Land Grant Universities
- Opposition from those who saw the book as a powerful force in undermining the idea that science and technology mean progress

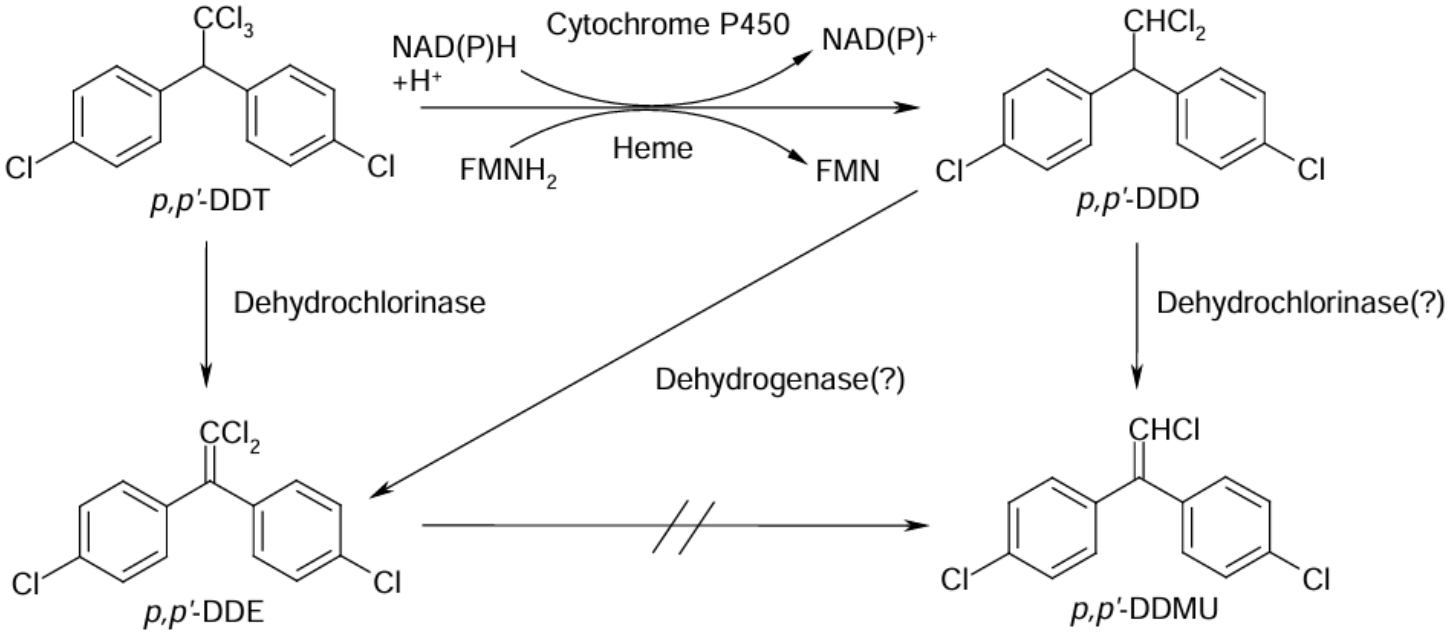
- While working for the Fish and Wildlife Service from 1935 to 1952, Rachel Carson knew of the early studies of DDT's lasting effects on the environment.
- 1945 she proposed an article to *Reader's Digest* about the dangers of DDT. The article was turned down.
- What finally led Carson to take a larger role was a letter from her friend, who owned a two-acre private bird sanctuary in Duxbury, MA, which was hit in 1957 by pesticides sprayed by planes to control mosquitoes.
- Because many of their birds died, an irate Mrs. Huckins wrote a detailed letter to *The Boston Herald* and sent a copy and a note to Rachel Carson.
- Planning her next book to be about humans and ecology, Rachel Carson began assembling background information which was evidence of the dangers on the environment by man's use of pesticides.



Early problems with DDT

During the summer of 1949 studies were conducted at Princeton, New Jersey, to determine the effects on wildlife of DDT used in the control of Dutch elm disease. An intensive search for dead birds determined direct mortality after spraying.

Population declines during the 1950s–1970s were largely driven by a combination of reproductive failure due to eggshell-thinning, egg breakage and embryonic death attributable to DDT and its metabolites [Journal of Raptor Research, 2017, 51(2):95-106]



Drug Metab Dispos. 2002; 30(2):113-8. doi: 10.1124/dmd.30.2.113

Dichlorodiphenyltrichloroethane (DDT): First synthesized in 1857 [Othmar Zeidler]

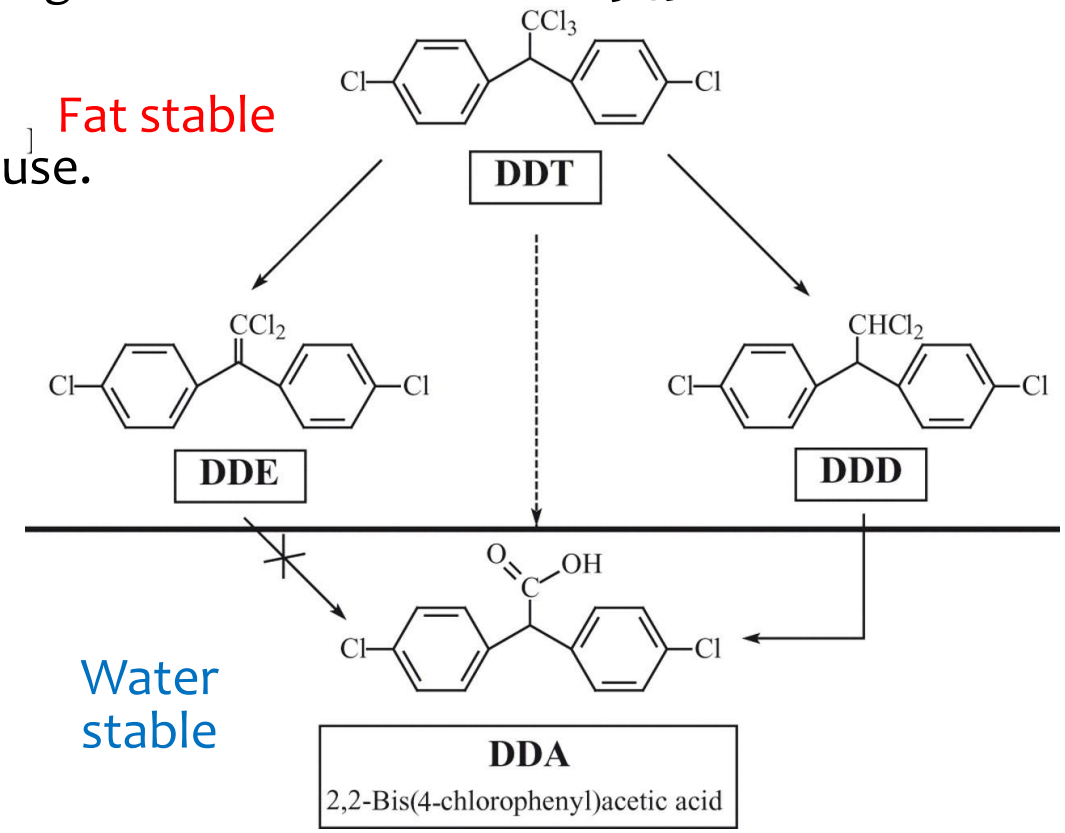
Insecticide action: Paul Muller (1939) [Nobel Prize in Physiology or Medicine, 1948]

DDT as an insecticide: First used as an agricultural insecticide in 1945.

Banned in the USA: 1972

Banned in India: 1989 for agricultural use.

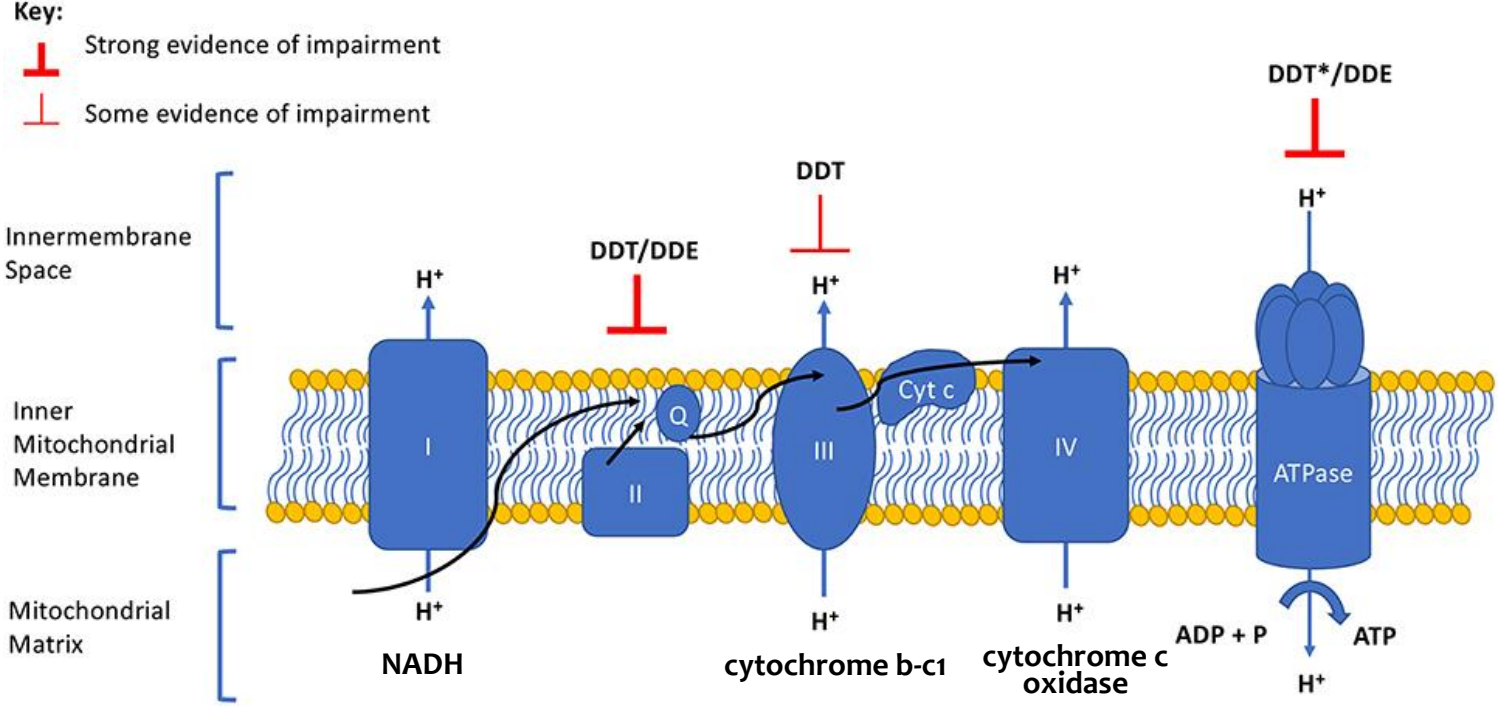
Fat stable

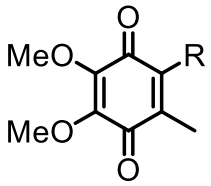


Water stable

DDT metabolism in humans forms DDA, a stable, water-soluble metabolite that is a useful urine biomarker of active DDT exposure and ideal for DDT exposure monitoring and surveillance.

International Journal of Toxicology 28(6) 528-533 ª The Author(s) 2009

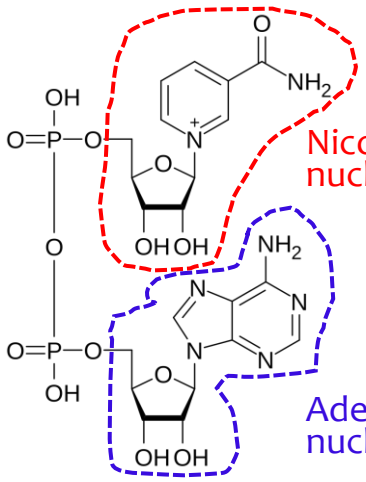




R: $(CH_2CH=C(Me)CH_2)_{10}H$

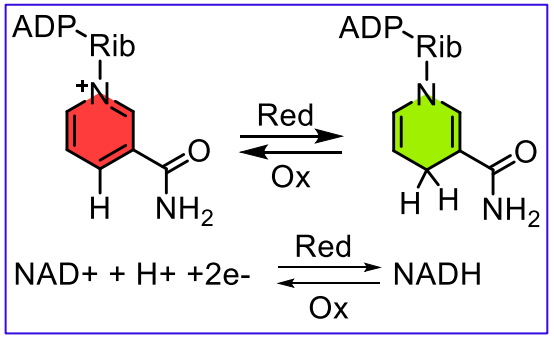
Ubiquinone

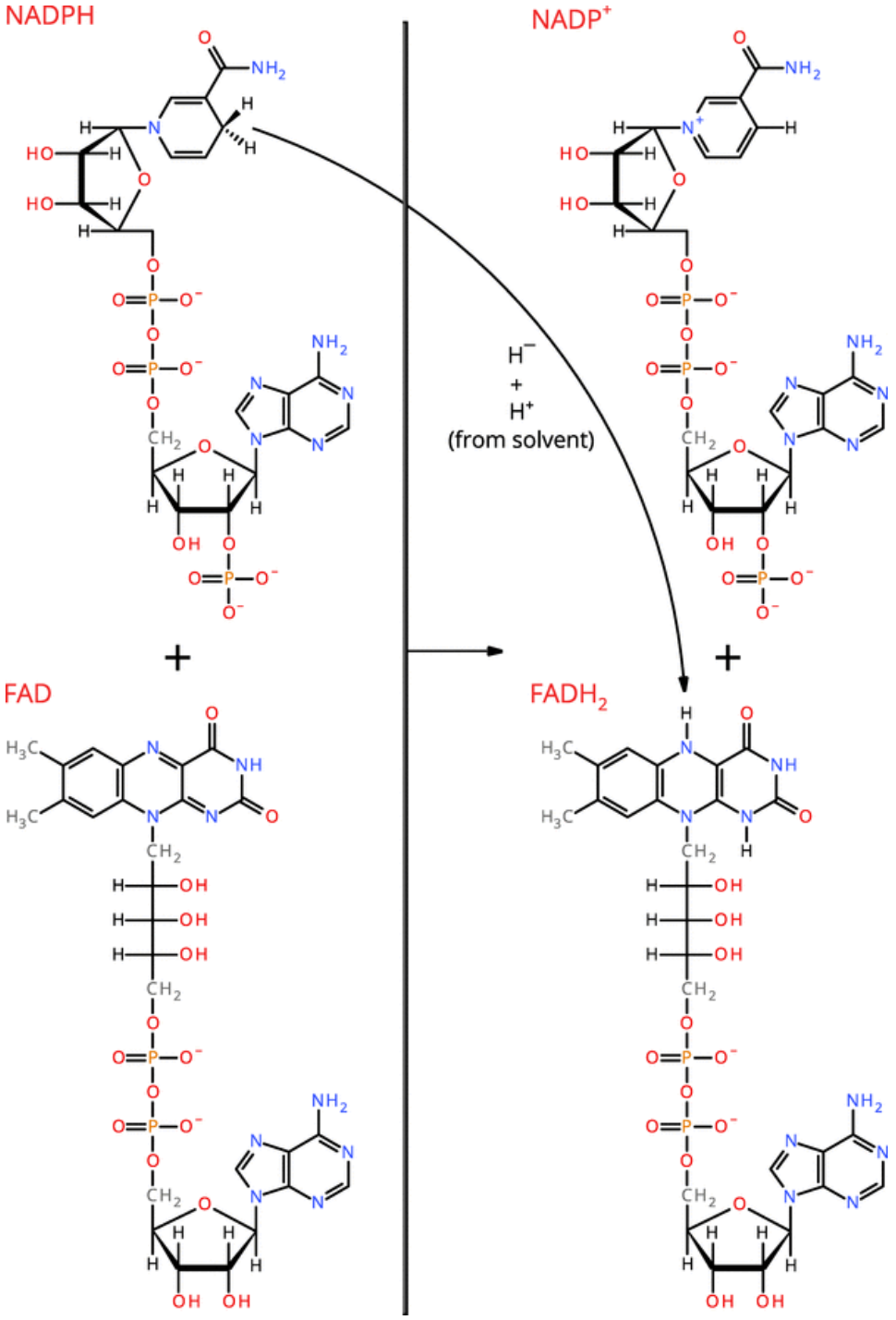
Oxidative phosphorylation occurs in the inner mitochondrial membrane. It couples the oxidation of NADH and $FADH_2$ (generated in glycolysis, TCA cycle, and β-oxidation) to the production of ATP via the electron transport chain (ETC) and ATP synthase (Complex V).



NAD: Nicotinamide Adenine Dinucleotide.

NADH is a coenzyme central to metabolism.



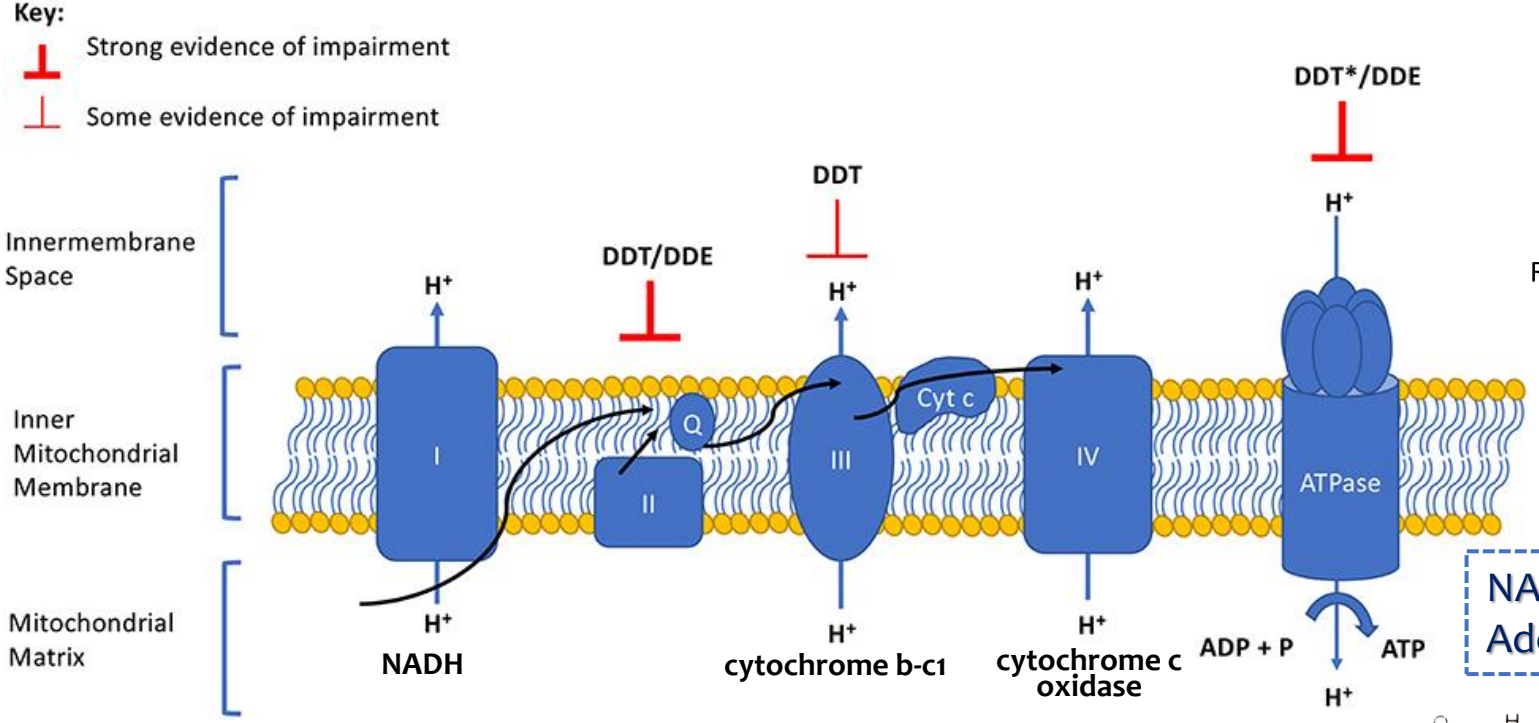


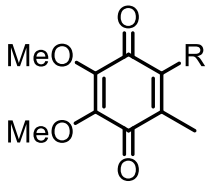
Reduction of FAD by NADPH. The nicotinamide group of NADPH transfers a hydride ion (H^-) to the isoalloxazine ring of the FAD, forming $FADH^-$. After reaction with an additional H^+ from the solvent, $FADH^-$ becomes FADH2

J. Mol. Evolu. 2017, 85(5-6)
DOI: 10.1007/s00239-017-9821-9

FADH2 is the reduced form of FAD (flavin adenine dinucleotide): Flavin-N (5)-oxide, quinone, semiquinone, and hydroquinone are the four, redox forms of FAD. Quinone is the fully-oxidized form while hydroquinone or FADH2 is the fully-reduced from, which has accepted two electrons (2e–) and two protons (2H+). FAD, along with proteins, form flavoproteins.

https://pediaa.com/difference-between-nadh-and-fadh2/





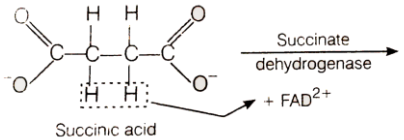
R: $(CH_2CH=C(Me)CH_2)_{10}H$

Ubiquinone

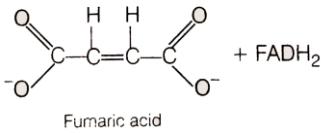
NAD: Nicotinamide Adenine Dinucleotide

Complex I – NADH:Ubiquinone Oxidoreductase (Coenzyme Q: CoQ)

$NADH + H^+ + CoQ \rightarrow NAD^+ + CoQH_2$



Complex II – Succinate Dehydrogenase Succinate+CoQ → Fumarate + $CoQH_2$



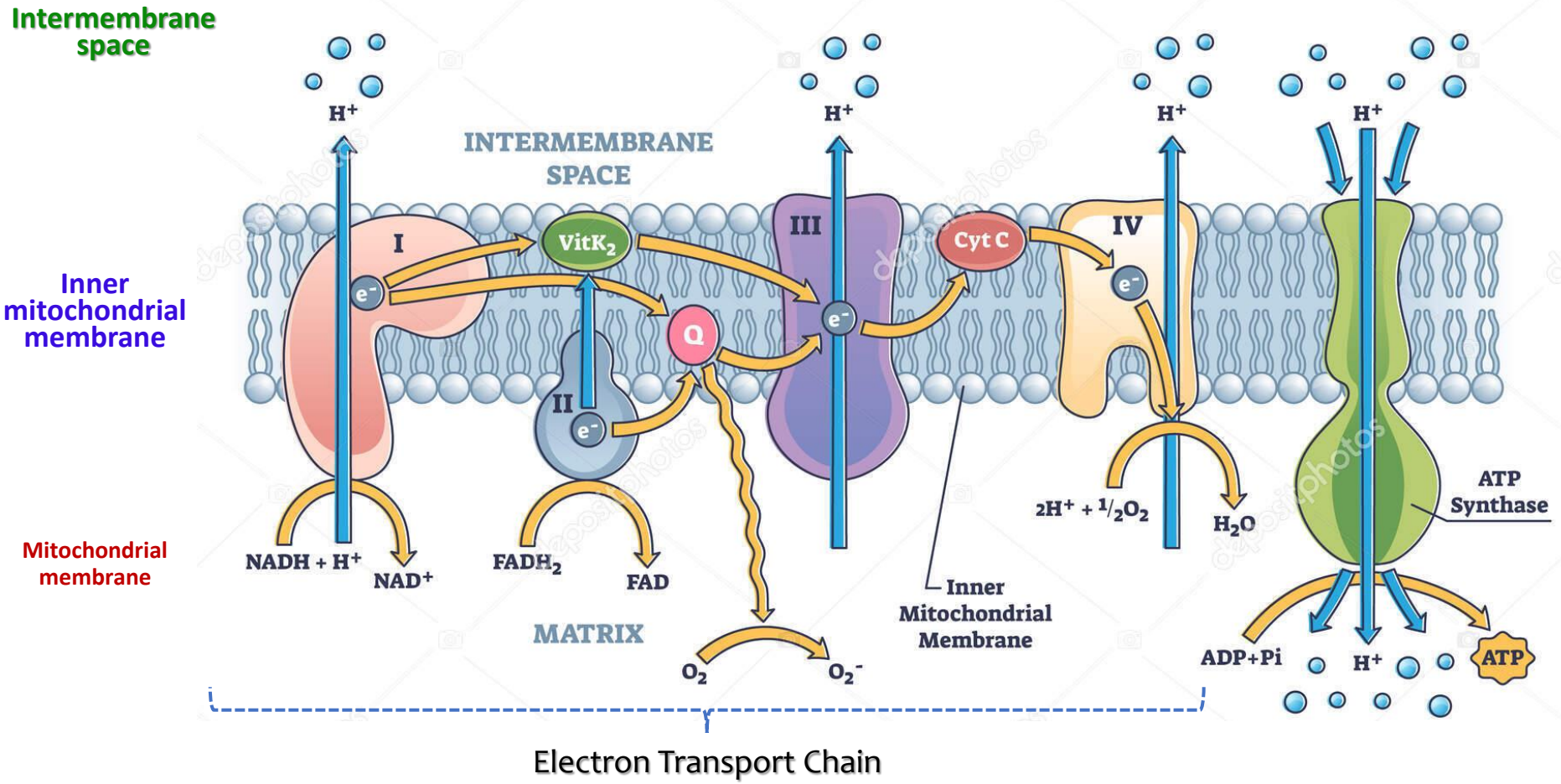
Complex III: cytochrome bc_1 complex or ubiquinol–cytochrome c oxidoreductase

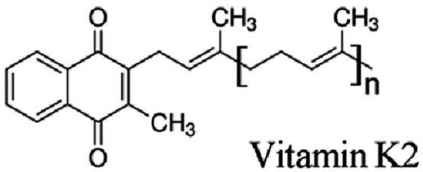
Transfers electrons from **ubiquinol ($CoQH_2$)** to **cytochrome c**, while **pumping protons (H^+)** into the intermembrane space to help build the **proton motive force** used for ATP synthesis.

Overall reaction: $CoQH_2 + 2Cyt\ c\ (Fe^{3+}) \rightarrow CoQ + 2Cyt\ c\ (Fe^{2+}) + 4H^+_{(intermembrane\ space)}$

Complex IV: cytochrome c oxidase, is the segment where $4e^-$ are removed from four molecules of cytochrome c and transferred to oxygen to produce two water molecules.

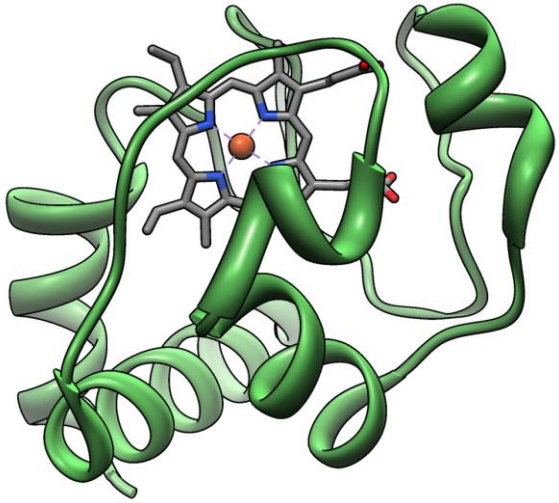
Role of NADH and FADH2 in the Electron Transport Chain



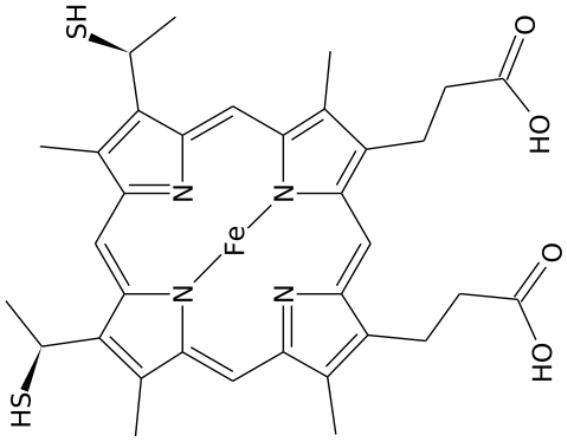


Vitamin K2

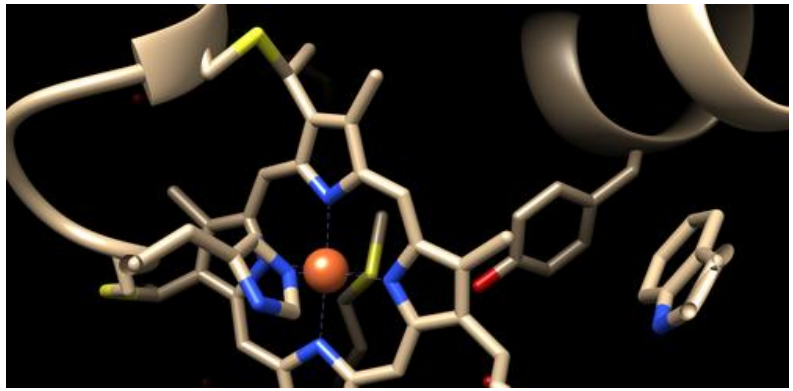
Author: Vector Mine
https://depositphotos.com/vector/electron-transport-chain-as-respiratory-embedded-transporters-outline-diagram-530772006.html



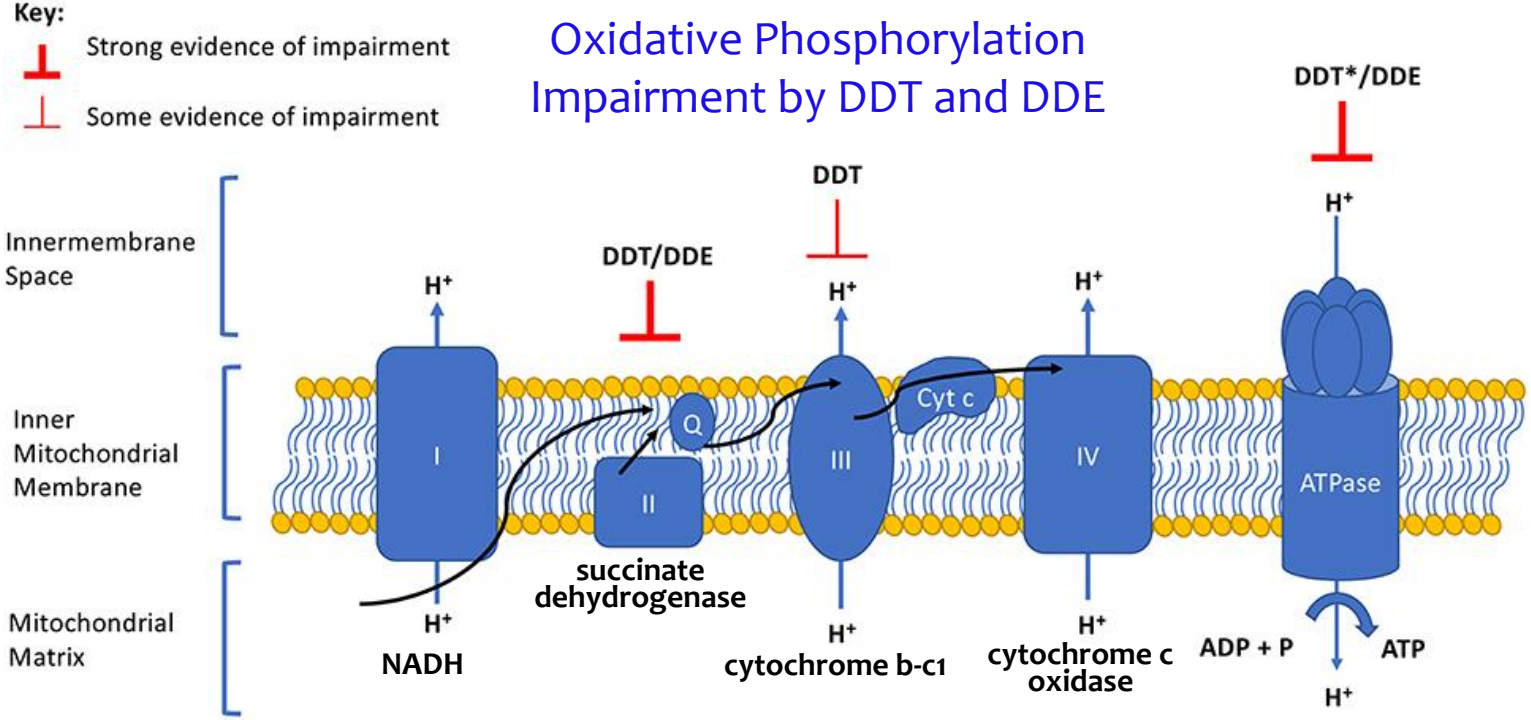
High-resolution three-dimensional structure of horse heart cytochrome c." J Mol Biol. 1990 Jul 20;214(2):585-95

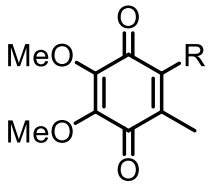


Heme prosthetic group of cytochrome c, consisting of a rigid porphyrin ring coordinated with an iron atom.



The cytochrome complex, or cyt c, is a small hemeprotein found loosely associated with the inner membrane of the mitochondrion. It transfers electrons between Complexes III (Coenzyme Q – Cyt c reductase) and IV (Cyt c oxidase). It is capable of undergoing oxidation and reduction as its iron atom converts between the ferrous and ferric forms, but does not bind oxygen. In humans, cytochrome c is encoded by the CYCS gene.
[https://en.wikipedia.org/wiki/Cytochrome_c]





R: $(CH_2CH=C(Me)CH_2)_{10}H$

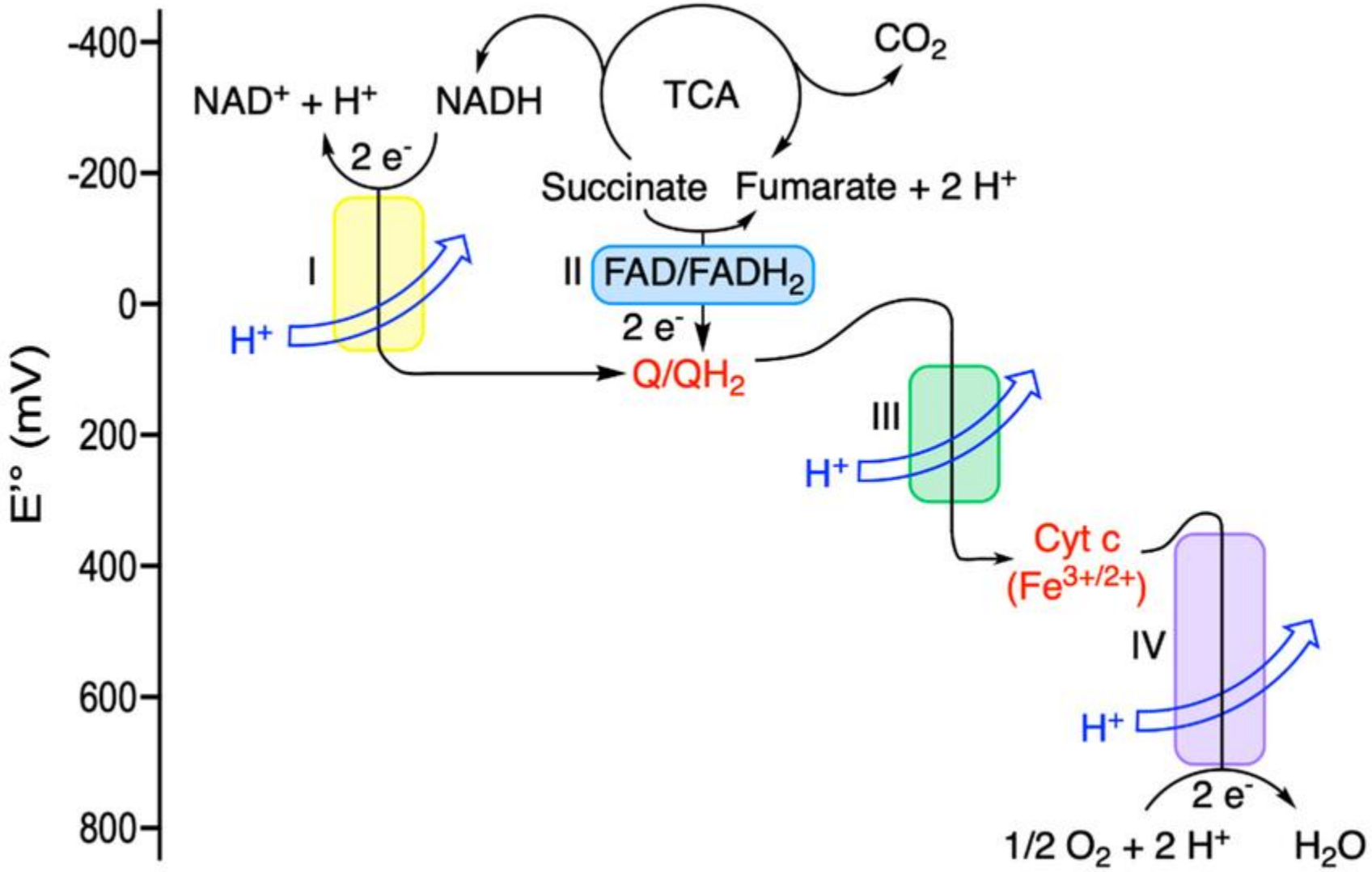
Ubiquinone

Summary of DDT and DDE effects on the electron transport chain and oxidative phosphorylation process. Arrows indicate the direction of the electron flow.

A cyclic flow of these electron carriers occurs within the whole respiratory system in the mitochondrial inner membrane. Thus, starting upstream in the redox potential gradient, the oxidised UQ is reduced upon interaction with Complex I or II, proceeding via an intermediary, the semiquinone UQH, on either complex to become the fully reduced ubiquinol (UQH_2), which is then released to carry electrons to Complex III, where UQH_2 is re-oxidised by releasing its protons and transferring its electrons to Complex III, before returning for repeated cycles.

Complex IV: cytochrome c oxidase, is the segment where $4e^-$ are removed from four molecules of cytochrome c and transferred to oxygen to produce two water molecules. Simultaneously, protons are moved from the mitochondrial matrix to the inner membrane thus contributing to the mitochondrial proton gradient.

Endocrinol., 2019: Sec. Translational and Clinical Endocrinology, Volume 10 – 2019; https://doi.org/10.3389/fendo.2019.00122



Electron flow from NADH and FADH2 to O2 in the mitochondrial respiratory chain. While the first reactions involve the transfer of $H^- + H^+$ to the acceptor Q, complexes III and IV act as electron wires coupled to proton pumps.

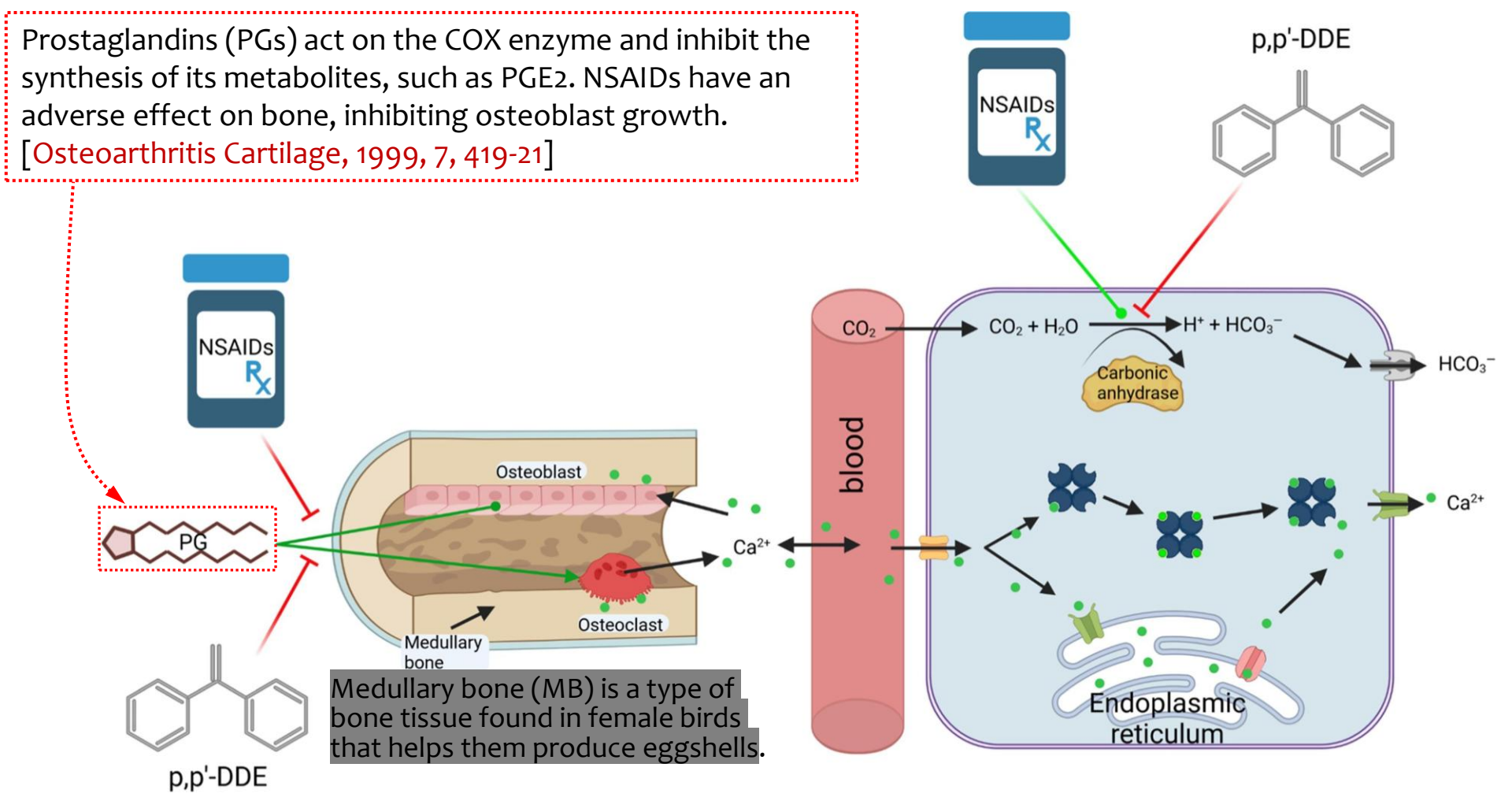
Osteoblasts and osteoclasts are special cells that help your bones grow and develop. Osteoblasts form new bones and add growth to existing bone tissue. Osteoclasts dissolve old and damaged bone tissue so it can be replaced with new, healthier cells created by osteoblasts.

Osteoblasts and osteoclasts work together to maintain healthy bones through two key processes—bone formation and bone resorption.

•Bone formation: Osteoblasts are responsible for producing new bone tissue. They secrete collagen and other proteins that form the bone matrix, which later hardens as minerals like calcium and phosphate are deposited. Osteoblasts are triggered by chemical reactions or hormones when a bone grows or changes. They create and release (secrete) a mix of proteins called bone matrix. Bone matrix is made of proteins like collagen mixed with calcium, phosphate and other minerals.

•Bone resorption: Osteoclasts dissolve and remove old or damaged bone by releasing acids and enzymes that break down the mineralised matrix. Osteoclasts release enzymes that break down old bone. They trigger chemical reactions on the surface of old bone tissue that dissolve it and create space for newer, stronger tissue to form in its place.

Prostaglandins (PGs) act on the COX enzyme and inhibit the synthesis of its metabolites, such as PGE2. NSAIDs have an adverse effect on bone, inhibiting osteoblast growth. [Osteoarthritis Cartilage, 1999, 7, 419-21]



Role of Non-steroidal anti-inflammatory drugs (NSAIDs) and p,p'-DDE in regulating osteocytes (osteoblasts and osteoclasts) through suppression of prostaglandin, and the regulation of long-term, calcium (Ca^{2+}) stores from medullary bone, as a source of $Ca^{2+}$for epithelial cells in the shell gland for the eggshell formation.

[The hormone calcitonin decreases blood calcium levels by inhibiting osteoclasts, stimulating osteoblasts, and calcium excretion by the kidneys]

How does p,p'-DDE cause thin-shelled egg?

$CO_2 + H_2O \Rightarrow H^+ + HCO_3^- + Ca^{2+} \Rightarrow CaCO_3$

Affects medullary bone.

Carbonic anhydrase inhibition

Inhibition of CaATPase

Calcium ATPase (CaATPase) is a pump that moves calcium across a membrane, often against a concentration gradient. It uses the energy of adenosine triphosphate (ATP) to do this.

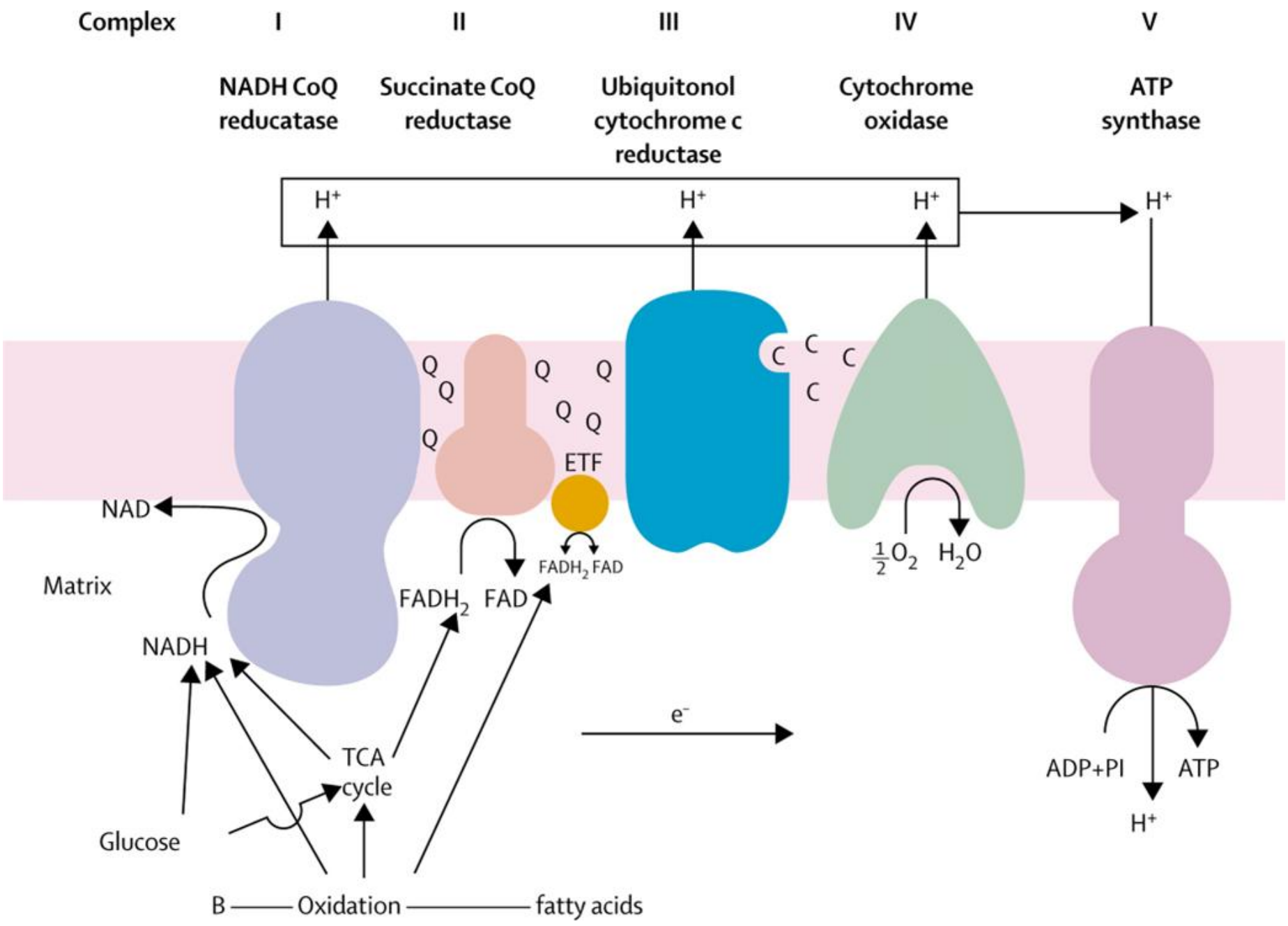
Inhibition of prostaglandin synthetase: inhibits prostaglandin synthesis in the eggshell gland mucosa of sensitive bird species, which can lead to eggshell thinning.

There is evidence that prostaglandin (PG)F-2a decreases blood flow to the ovary or corpus luteum but this does not occur in the guinea pig. J. Reprod. Fert. 1982, 64, 227.

The carbonate ions are formed from metabolic CO_2. The first step in the carbonate ion formation, i.e. $CO_2 + H_2O \Rightarrow H^+ + HCO_3^-$, is catalyzed by carbonic anhydrase (CA), an enzyme family consisting of at least 14 different isozymes.

In the EE2-treated HD birds, both the reduced endothelial CA activity and the decreased number of capillaries in the shell gland mucosa negatively affect egg-shell formation by reducing the availability of calcium and carbonate ions.

- CA is present in the glandular cell membranes as well as in capillaries and the CO2 is supplied via the blood plasma and cellular metabolism. Thus, a reduced CO_2 diffusion, as a result of a decreased amount of CA in the capillaries in treated birds, could therefore reduce HCO_3^- transfer to the shell gland lumen.
- Large amounts of calcium are transported by the blood to the shell gland, and blood flow in the shell gland increases significantly during shell formation. Altered microcirculation and/or a reduced number of capillaries in the exposed birds may therefore reduce the amount of calcium available for shell formation.
- In addition, impaired transport or reduced concentration of HCO_3^- ions may also reduce the availability of Ca^{2+} since transport of these two ions through the shell gland mucosa is, to some extent, coupled.
- Oxidative Phosphorylation Impairment by DDT and DDE. Oxidative phosphorylation is a metabolic pathway that uses enzymes to oxidize nutrients and produce adenosine triphosphate (ATP). [Reproduction (2004) 128 455–461]

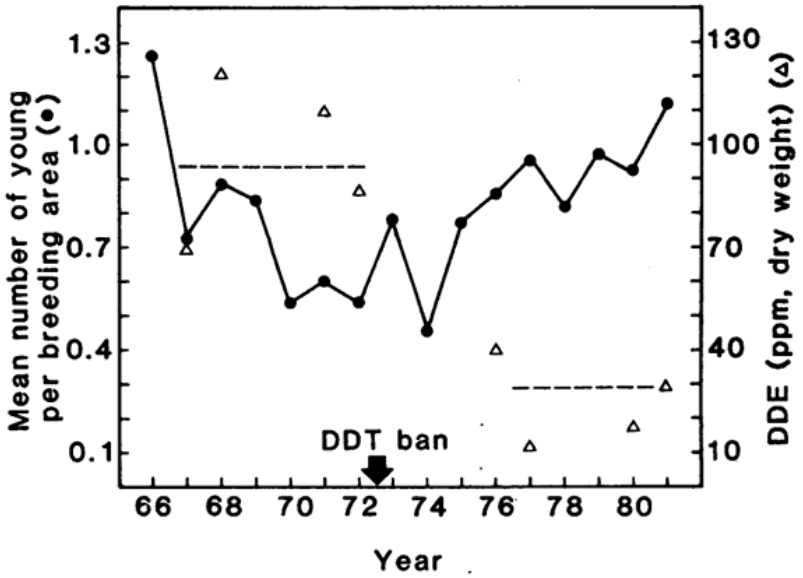


Review article on Mitochondrial Disease: Lancet 2006; 368: 70–82

Eggshell development is a crucial and complex reproductive event achieved through a sequence of steps relying on an array of hormones, signalling molecules, enzymes, organic compounds, and minerals. Mineralization begins during the egg's travel from the ovary to the uterus when it enters the isthmus. The eggshell consists of approximately 95% inorganic minerals, mostly calcite, and ~3.5% organic matrix, with the remaining portion consisting of water. The unshelled egg contains two uncalcified protein layers that enter the shell gland (i.e., uterus), increasing prostaglandin E2 (PGE2) levels.

- ✓ Simultaneous with the influx of PGE2, the uterine lining (epithelium) floods the intrauterine fluid with calcium (Ca^{2+}) and bicarbonate (HCO_3^-) ions primarily through uterine glandular cells. These spontaneously precipitate into calcite and are deposited onto the outer organic eggshell membranes, forming the hard eggshell.
- ✓ The calcified egg contains numerous pores that allow water and gas to be exchanged during embryonic development.
- ✓ Prostaglandin E2 (PGE2) levels drop rapidly following oviposition. Calcium needed to form eggshells is obtained from the diet and continuously replenishes in the blood.
- ✓ Excess calcium is stored in the medullary bone, an estrogen-dependent, specialized tissue produced only in female laying birds, and which serves as a long-term calcium repository. The medullary bone acts as a labile source of calcium when demands exceed dietary supplies. [Environment International 171 (2023) 107638]

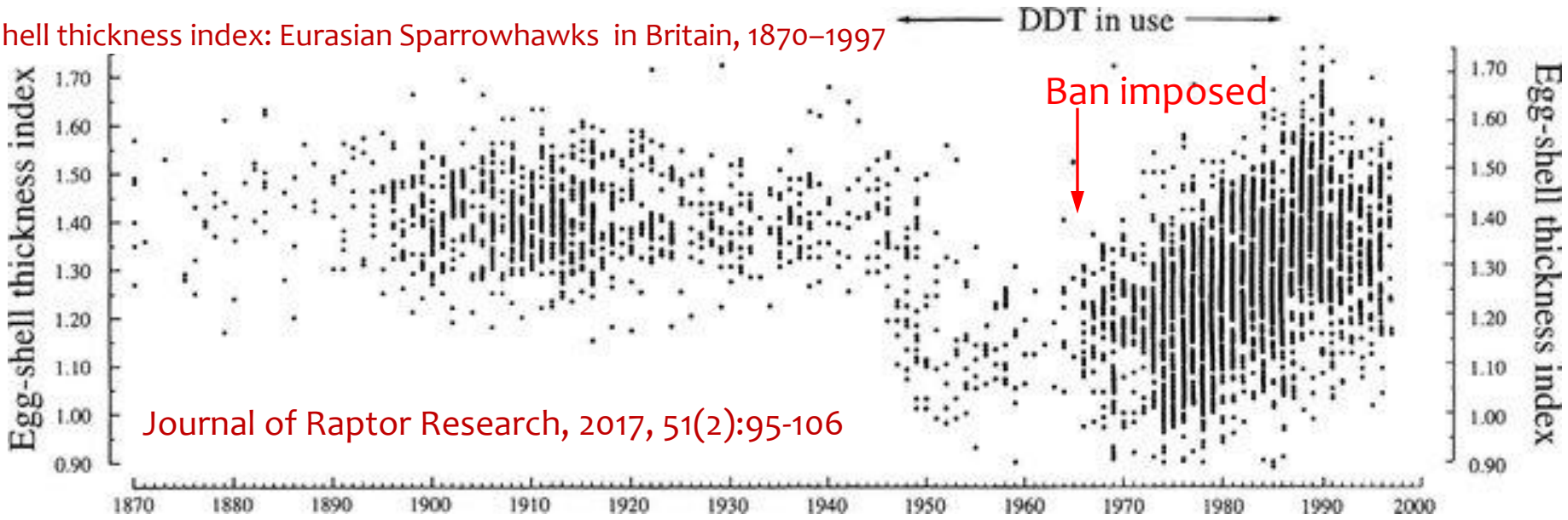
Laboratory experiments showed that DDE could cause eggshell thinning. Field studies showed that field exposures to DDE, a metabolite of DDT, were sufficient to cause effects in many species of birds based on the stressor-response relationship



Science, 1982, 218, 1232-1235

Summary of average annual bald eagle reproduction and DDE residues in addled eggs in northwestern Ontario, 1966 to 1981. Dashed lines indicate weighted mean concentrations of DDE residues in clutches before (94 ppm) and after (29 ppm) the ban of DDT. Means for the 16-year period are 57 ppm DDE (weighted mean) and 0.82 young per breeding area

Shell thickness index: Eurasian Sparrowhawks in Britain, 1870–1997

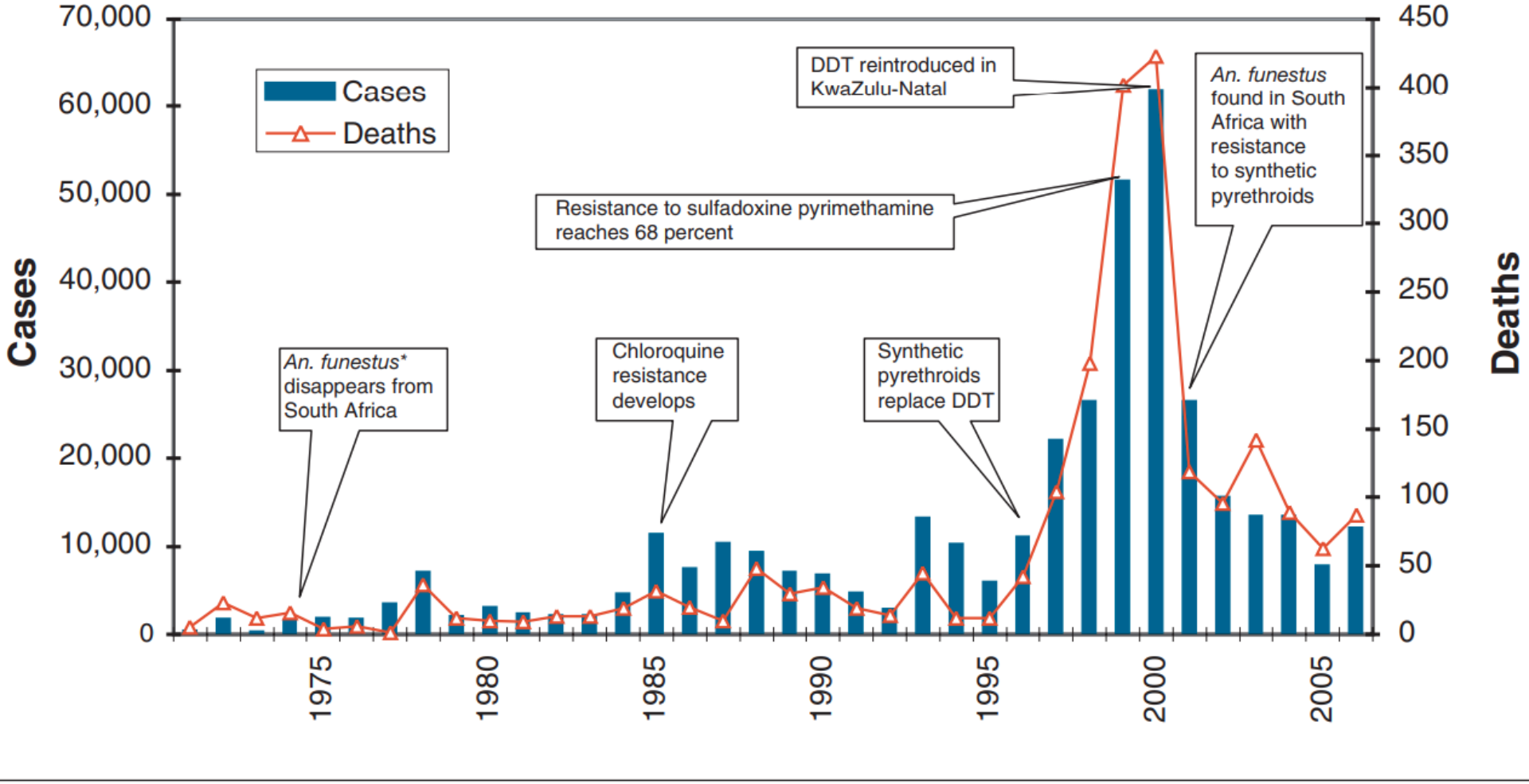


Journal of Raptor Research, 2017, 51(2):95-106

Environmental groups that had previously shown no interest in malaria, such as the World Wildlife Fund, started to profess expertise in alternatives to DDT use—any alternative, as long as it was not DDT. Between 1997 and 2000, member states of the United Nations Environment Program negotiated

the Stockholm Treaty on Persistent Organic Pollutants, with DDT as one of the "dirty dozen" chemicals targeted. Green groups wanted the chemical banned and set 2007 as the year for its demise. Ironically, because of the disastrous surge in malaria cases in South Africa, coupled with Johannesburg being chosen as the final negotiating location in December 2000, DDT was not banned; instead, it was to be phased out when "cost-effective alternatives" were available. In 2000, the South African Department of Health reintroduced DDT. In just one year, malaria cases fell nearly 80% in KwaZulu-Natal province, which had been hit worst by the epidemic. In 2006, malaria cases in the province were approximately 97 below the previous high of 41,786 in 2000. DDT remains an essential part of South Africa's malaria control program, and the success of its use in that country has encouraged other countries in the region to follow suit.

Malaria Cases and Deaths in South Africa, 1971–2006

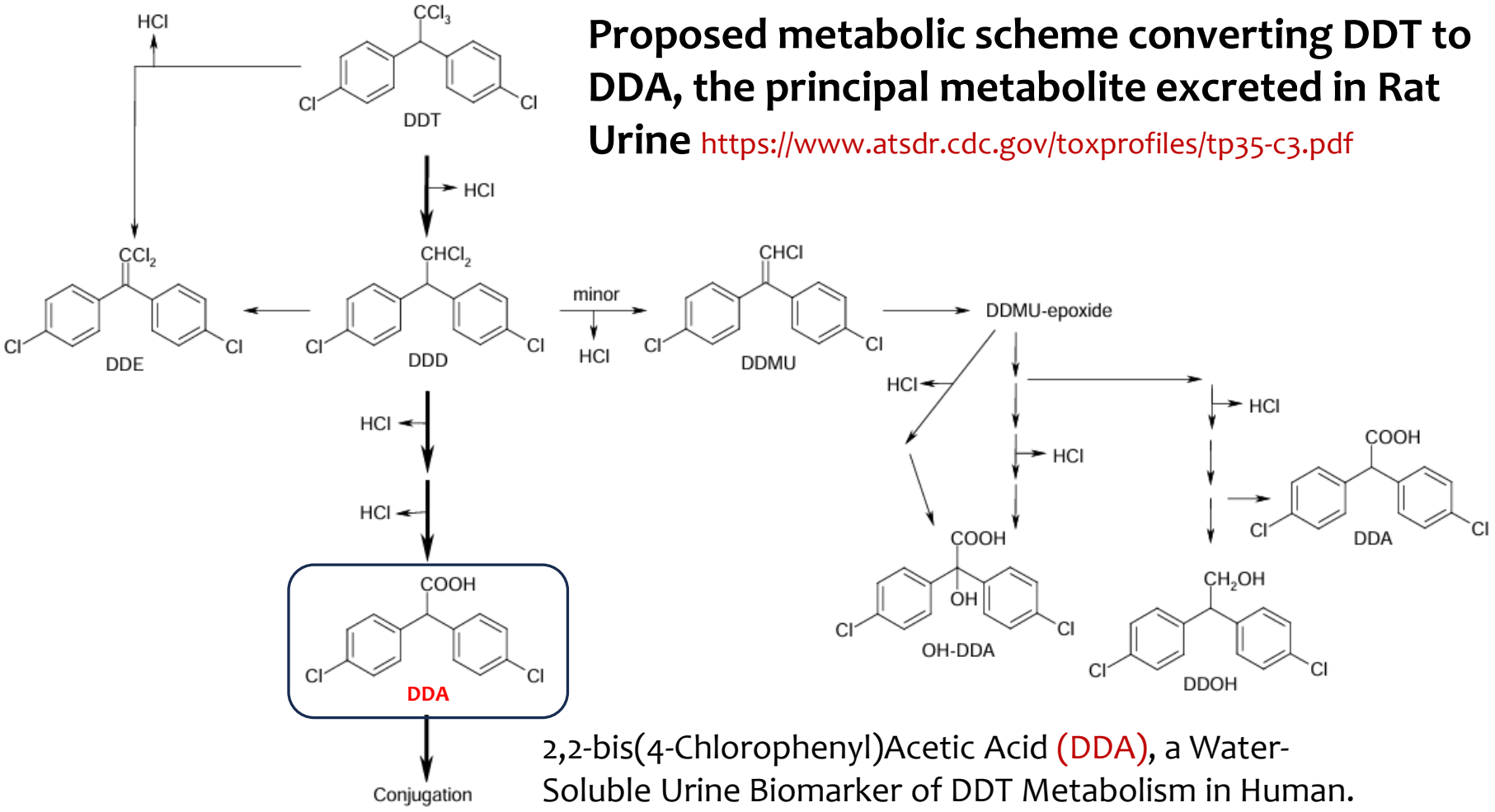


SOURCE: South African Department of Health, *National Malaria Update*, 2007, available through www.doh.gov.za/facts/index.html (accessed October 21, 2007)
NOTES: **An. funestus* is a malaria-transmitting mosquito species common in sub-Saharan Africa.
N.B. According to experts in South Africa, the recent increase in malaria in 2006 is largely due to refugees from Zimbabwe, where the disease is more prevalent

The Rise, Fall, Rise, and Imminent Fall of DDT By Roger Bate
A report: American Enterprise Institute for Public Policy Research

As priority persistent organic pollutants (POPs) and endocrine-disrupting chemicals (EDCs), an exposure to DDT can cause a wide range of acute and chronic effects including carcinogenesis, estrogenic action, and endocrine disruption, posing a serious risk to environmental and human health. Sci Rep. 2016; 6: 21332

Proposed metabolic scheme converting DDT to DDA, the principal metabolite excreted in Rat Urine https://www.atsdr.cdc.gov/toxprofiles/tp35-c3.pdf



2,2-bis(4-Chlorophenyl)Acetic Acid (DDA), a Water-Soluble Urine Biomarker of DDT Metabolism in Human. http://ijt.sagepub.com/cgi/content/abstract/28/6/528