Sustainability and Chemistry CH5106: Chemicals –Selected Slides

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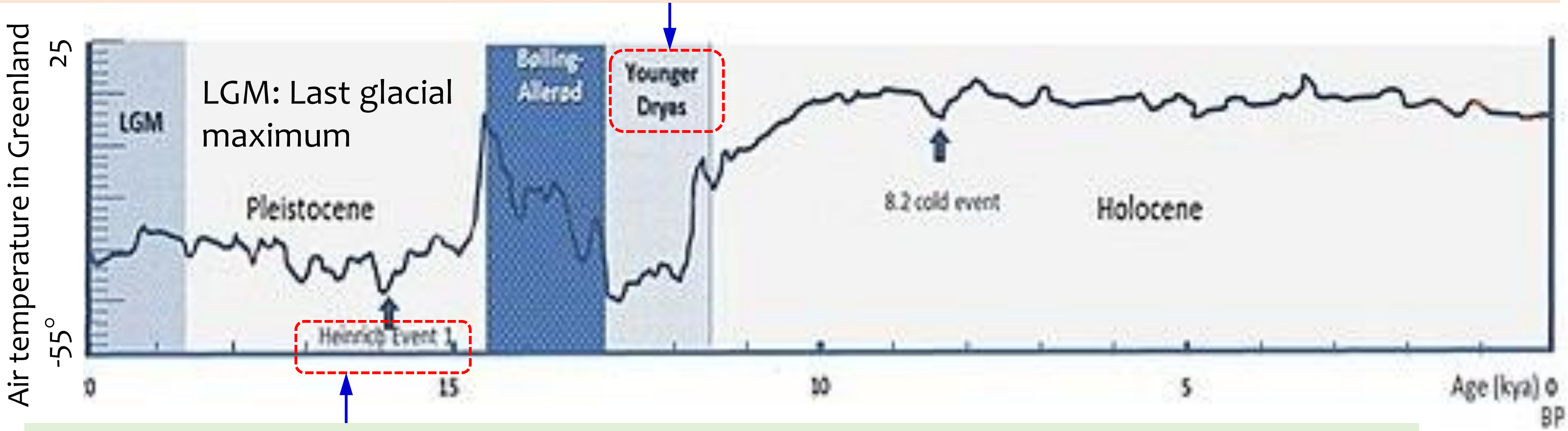
The Neolithic Revolution, or First Agricultural Revolution, marked a major shift in Afro-Eurasia during the Neolithic period, as many human societies transitioned from hunting and gathering to agriculture and permanent settlement. This change enabled population growth and allowed people to study plant growth, eventually leading to the domestication of crops.

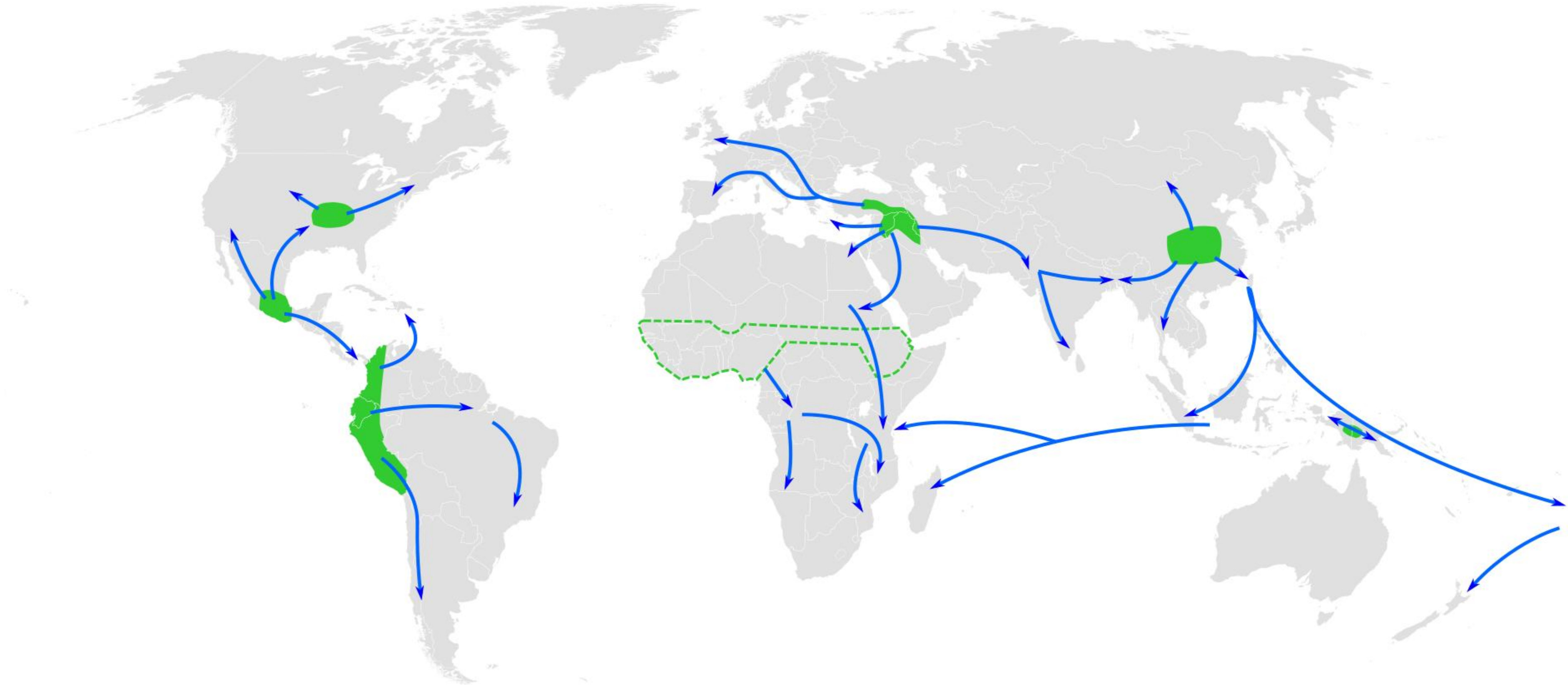
Younger Dryas: A period of abrupt cooling (in the Northern Hemisphere) that interrupted the warming trend following the last glacial period, roughly 12,900 to 11,700 years ago.



Heinrich Event 1 (H1) was a significant climatic event during the last glacial period, specifically during the last deglaciation, approximately 16,000 years ago.

https://en.wikipedia.org/wiki/Neolithic_Revolution https://en.wikipedia.org/wiki/Neolithic_Revolution

Diamond, J.; Bellwood, P. (2003). "Farmers and Their Languages: The First Expansions". Science. 300 (5619): 597–603.



Map of the world showing approximate centres of origin of agriculture and its spread in prehistory.

Carbon has three main isotopes: carbon-12 (^{12}C), carbon-13 (^{13}C), and carbon-14 (^{14}C). ^{12}C and ^{13}C are stable, while ^{14}C is radioactive and decays over time.

This radioisotope exists in trace amounts and is mainly created when carbon atoms in the upper atmosphere encounter cosmic radiation. It takes in the thousands of years for this isotope to decay into a stable nitrogen atom (^{14}N).

Decay of ^{14}C provides scientists with a useful tool in dating biological material, otherwise known as radiocarbon dating. $\%^{14}C$ remaining in non-living biological material helps in estimating the age of this material.

The expansion of grasslands contributed to the extinction of several large animals (chiefly herbivores), especially those dependent on woody vegetation for food and shelter. Although climate change and human activity were also influential, the transition from forests to grasslands particularly affected megafauna (the large mammals of a particular region) adapted to forested habitats.

Carbon Fixation

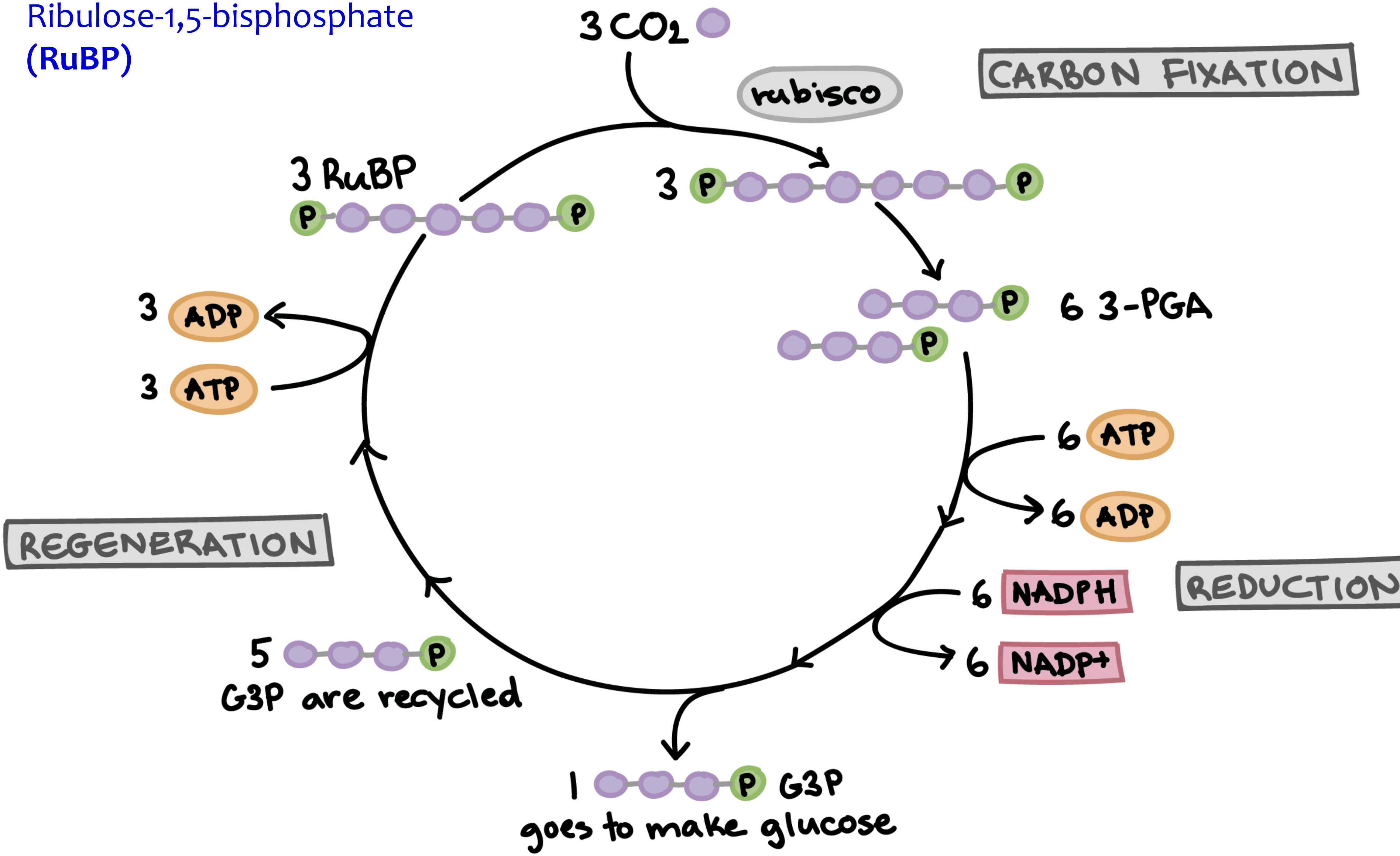
The process by which the inorganic CO_2 is integrated into an organic sugar (through photosynthesis) is called carbon fixation, and C_3 and C_4 plants "fix" the carbon in different manners.

C_3 Pathway (or Calvin Cycle): Woody plants primarily utilize the C3 photosynthetic pathway, also known as the Calvin cycle.

RuBisCO, or Ribulose-1,5-bisphosphate carboxylase/oxygenase, is a crucial enzyme in photosynthesis that facilitates the initial step of carbon fixation in the Calvin cycle. It's found in all plants and other photosynthetic organisms. RuBisCO's primary function is to catalyze the carboxylation of ribulose-1,5-bisphosphate (RuBP), a 5-carbon molecule, using carbon dioxide.

Ribulose-1,5-bisphosphate

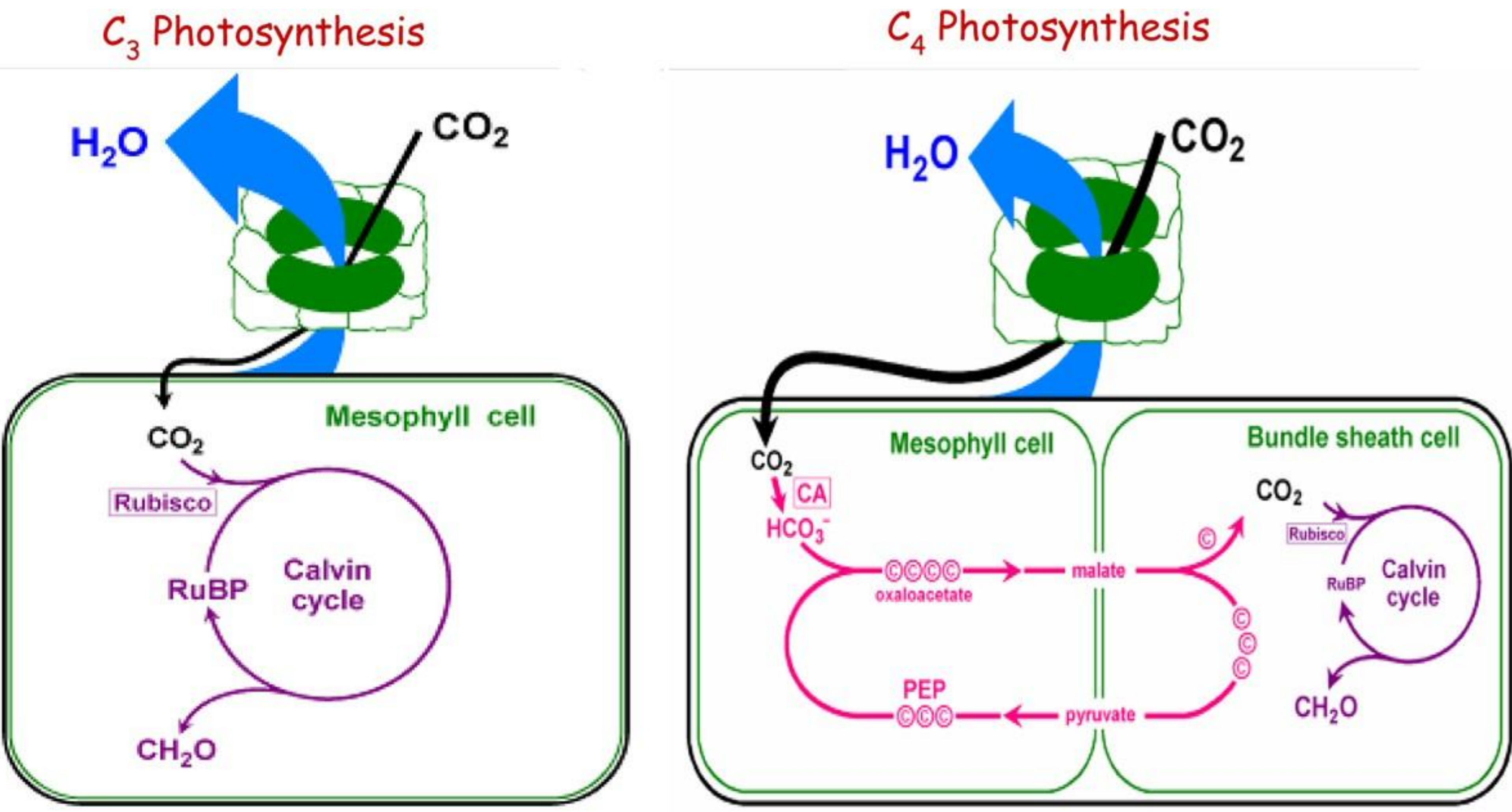
(RuBP)



https://www.khanacademy.org/science/ap-biology/cellular-energetics/photosynthesis/a/calvin-cycle

Hatch and Slack Pathway or C_4 pathway

BMC Syst Biol **6** (Suppl 2), S9 (2012)

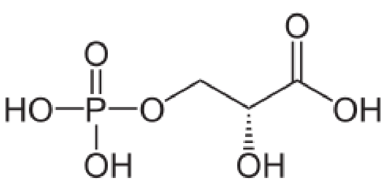


The C4 pathway, also known as the Hatch-Slack pathway, is a photosynthetic adaptation that enhances carbon fixation in plants, especially those in hot, arid environments. C4 plants, like maize and sugarcane, have evolved a system where CO_2 is initially fixed into a four-carbon compound in mesophyll cells, before being transported to and released in specialized bundle sheath cells for use in the Calvin cycle.

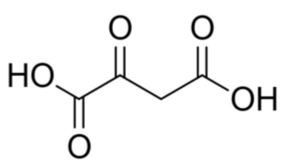
Mass spectrometry can determine the nature of fossilized plants by analyzing the molecular composition of preserved organic material. Techniques likepyrolysis-gas chromatography-mass spectrometry (Py-GC-MS) and mass spectrometry imaging (MSI) help identify specific biomarkers and structural components, providing insights into the plant's identity, evolutionary relationships, and even its functional traits.

Mass spectrometry can distinguish between grassland/woodland and fossils by analysing the unique molecular compositions and stable isotope ratios within the samples. Fossils, especially those with preserved organic matter, will exhibit distinct molecular signatures compared to living plant material, due to degradation and fossilization processes.

Mass spectrometry, specifically stable carbon isotope analysis (^{12}C and ^{13}C), can distinguish between grassland and woodland ecosystems, and even identify fossilised remains of these ecosystems. The technique leverages the different photosynthetic pathways of C3 (woody plants) and C4 (grasses) plants, which result in distinct carbon isotope signatures.



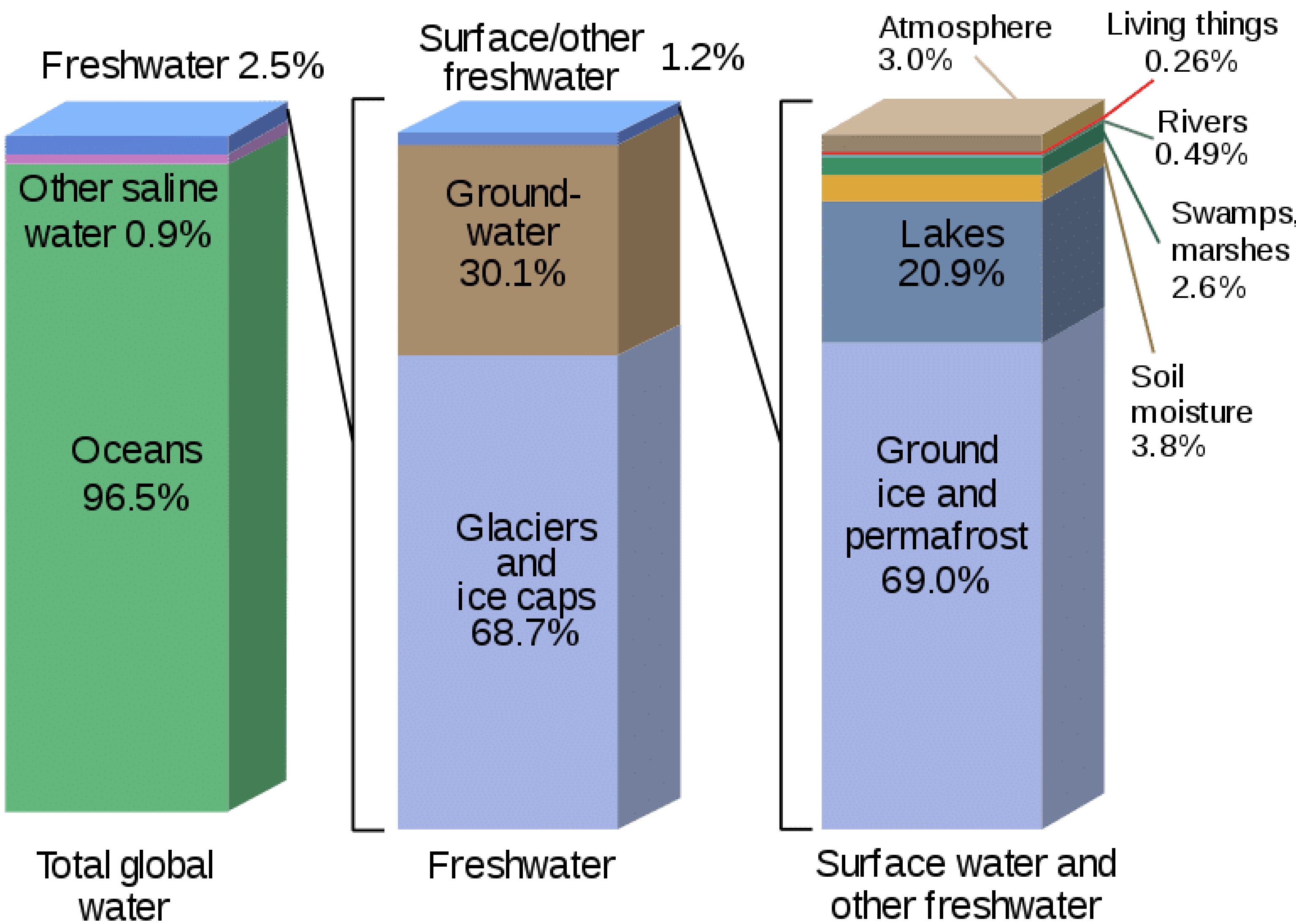
3-phosphoglyceric acid



Oxaloacetate

C3 and C4 plants utilize different photosynthetic pathways. C3 plants (mostly woody plants) use the Calvin cycle directly to fix CO_2 into a C3-compound (3-phosphoglyceric acid or 3-phosphoglycerate). C4 plants (found mostly in grassland) have an initial step where CO_2 is fixed into a 4C-compound (oxaloacetate) in mesophyll cells, before being transferred to bundle sheath cells for the Calvin cycle. This process enhances efficiency in high-light, high-temperature, and dry conditions.

Where is Earth's Water?



https://lotusarise.com/water-resources-upsc/

The categorization based on status of ground water quantity is defined by Stage of Ground Water extraction as given below:

Stage of Ground Water Extraction	Category		
≤ 70%	Safe	> 90% ≤ 100%	Critical
> 70% ≤ 90%	Semi-Critical	> 100%	Over Exploited

GEALL = GEIRR + GEDOM + GEIND [Groundwater draft or extraction is to be assessed as follows]; Where,

GEALL = Ground water extraction for all uses;

GEIRR = Ground water extraction for irrigation

GEDOM = Ground water extraction for domestic uses;

GEIND = Ground water extraction for industrial uses

Stage of Ground Water Extraction (%) =

(Existing gross ground water extraction for all uses / Annual Extractable Ground water Resources) x 100

Fast Track Initiative – Final report; ADA Project No. 2725-00/2014

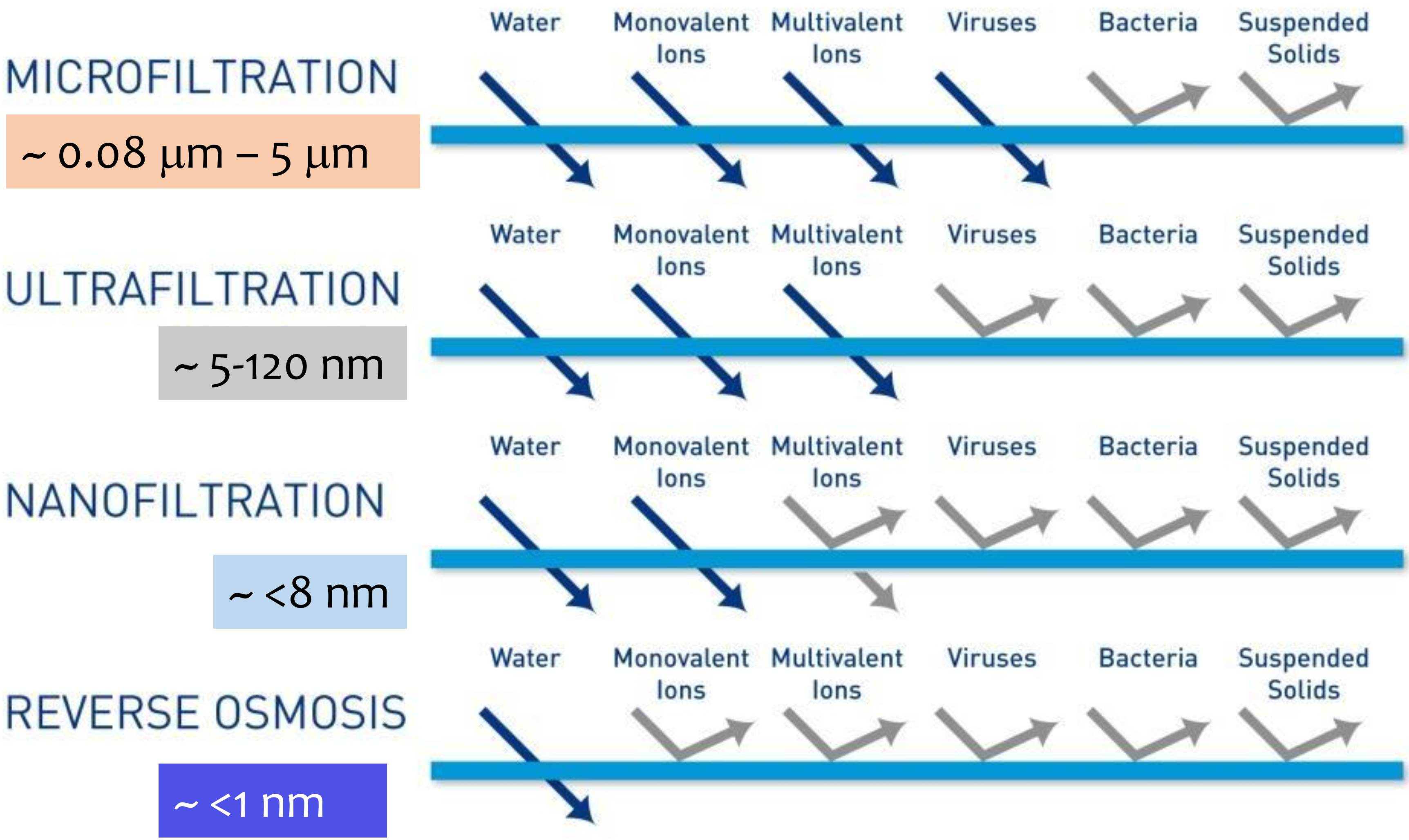
Groundwater Abstraction		[km^3/year]				Change rate
Ranking	Countries	2010	Share	2050	Share	(% of 2010)
1	India	201	25%	278	25%	139
2	USA	103	13%	118	11%	114
3	China	102	13%	152	14%	150
4	Iran	60	8%	73	7%	122
5	Pakistan	60	8%	70	6%	116
6	Mexico	25	3%	32	3%	127
7	Russian Federation	22	3%	37	3%	168
8	Saudi Arabia	22	3%	29	3%	135
9	Bangladesh	11	1%	13	1%	117
10	Japan	11	1%	12	1%	109

Alternate source of water

Traditionally, freshwater has come from rivers, lakes, streams, and groundwater aquifers. These traditional sources are becoming unavailable for various reasons. Need to switch to alternative sources of water, including rainwater, storm water, grey water, reclaimed water, and brackish & seawater desalination.

National policy for identifying appropriate technologies for securing the supply of fresh water as per the need.

TYPE OF MEMBRANES AND CHARACTERISTICS



Major Research Focus: Potable Water through desalination of sea water/ brackish water/ pathogen removal/ removal of contaminants like Fluoride/ Arsenic/ iron/ etc

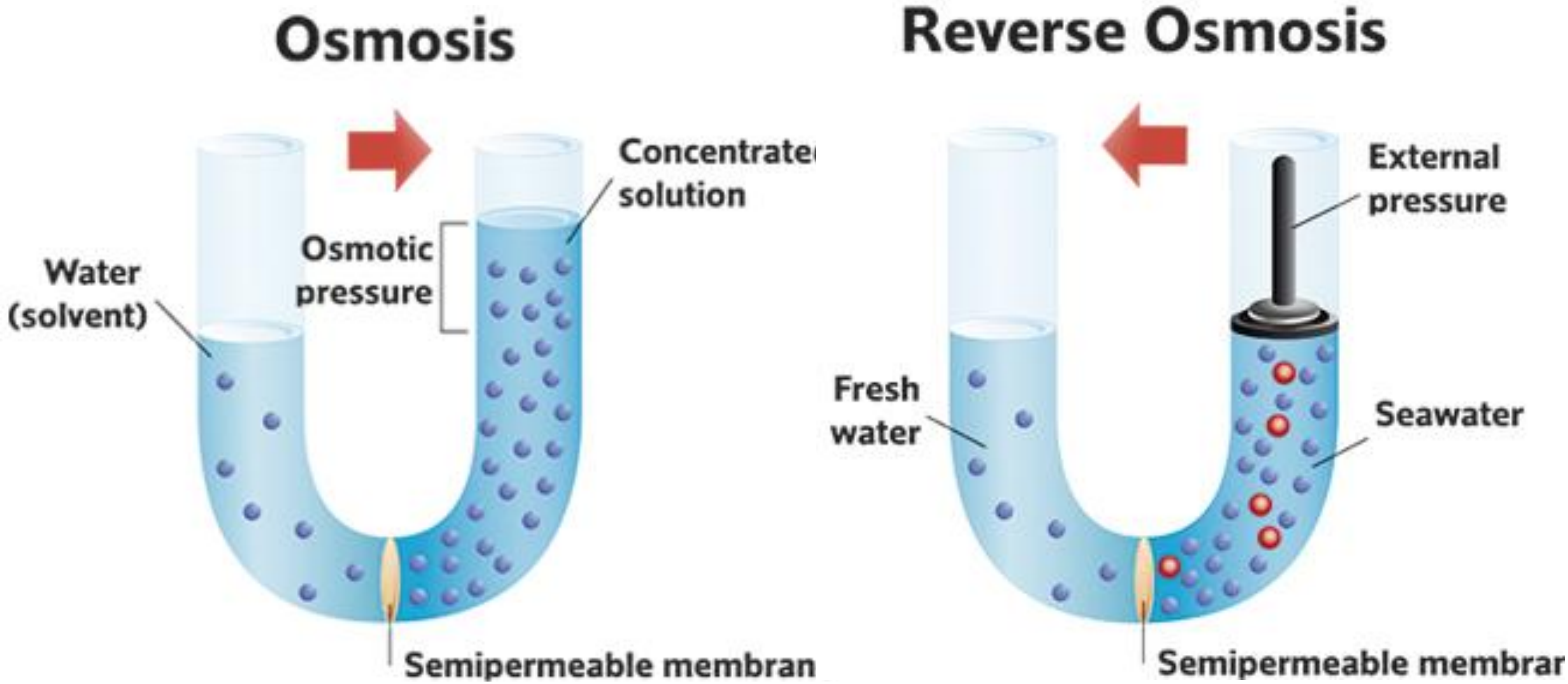
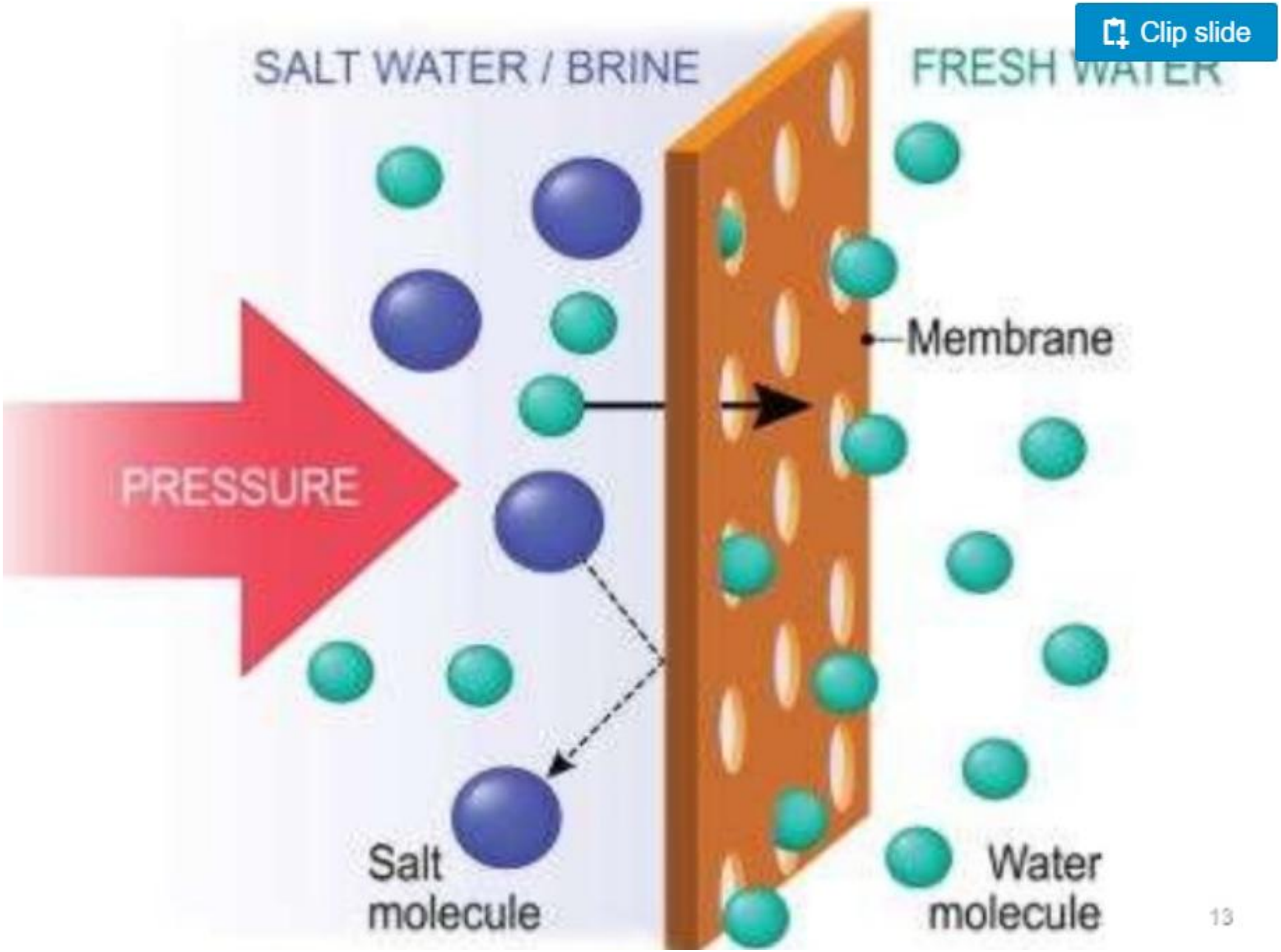
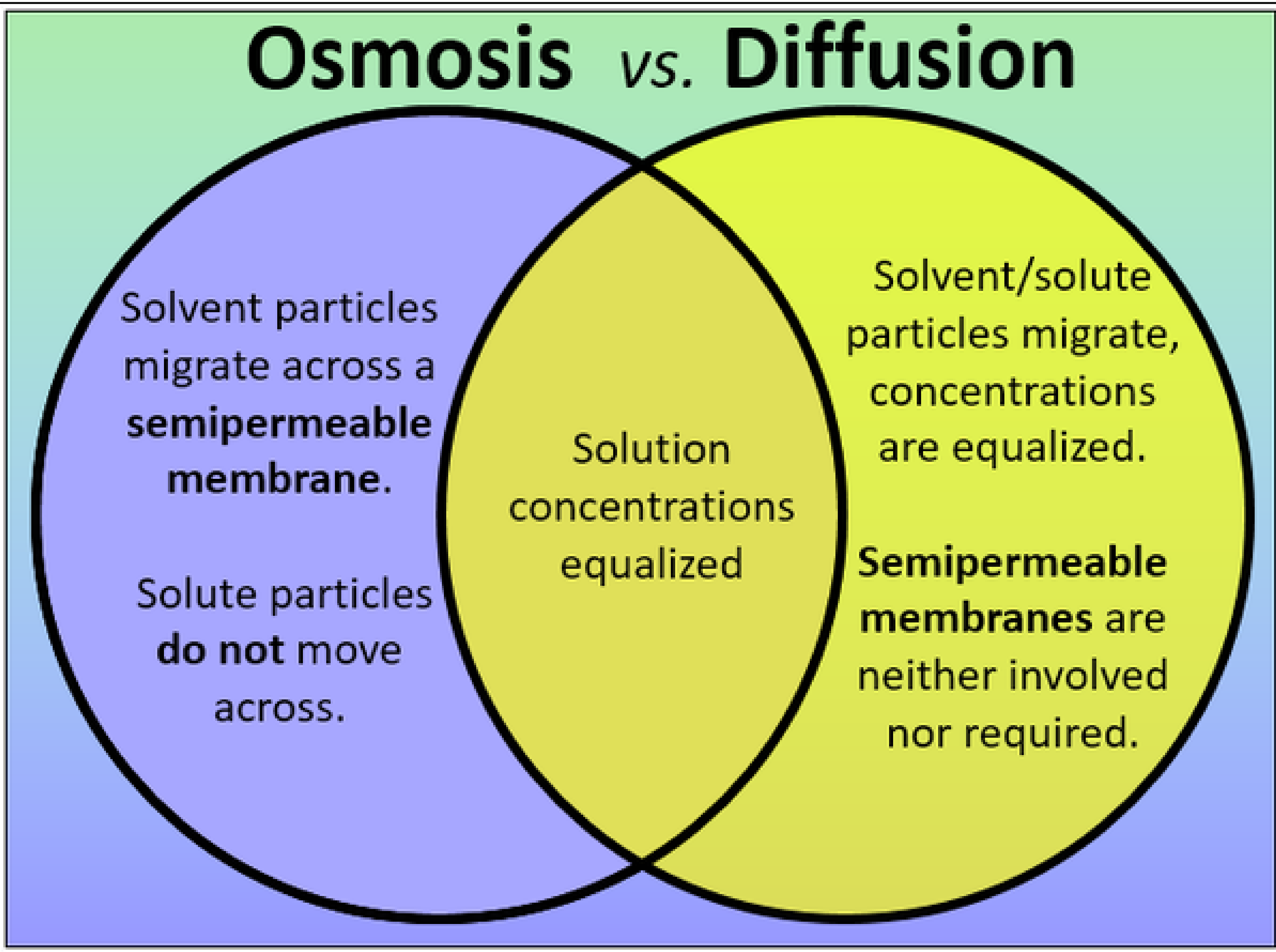


Diagram of osmosis in a U-shaped tube through a dialysis membrane that separates two solutions having different solute concentration.

Osmosis is a process that is fundamental to the physiology of all living things. It is the selective transport of water across a semipermeable membrane from high to low chemical potential caused by a difference in solute concentrations and/or hydrostatic pressures.



https://www.slideshare.net/9495094029/reverse-osmosis-based-desalination



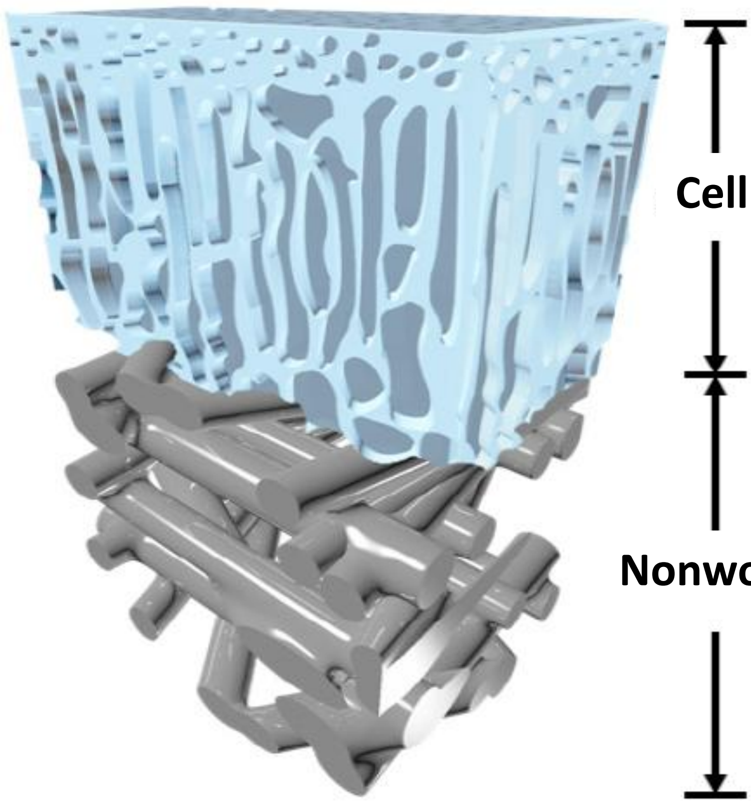
Osmosis vs. Diffusion
Solvent particles migrate across a **semipermeable membrane.**
Solute particles **do not** move across.
Solution concentrations equalized
Solvent/solute particles migrate, concentrations are equalized.
Semipermeable membranes are neither involved nor required.

Eighteenth-century **French physicist Jean Antoine Nollet (1748)** gets the credit for first conceptualization of RO membrane. However, two centuries after Nollet's discovery, RO was still not much more than a laboratory phenomenon until a Thayer student project helped create a new multi-million dollar RO industry.

Researchers from both University of California at Los Angeles and the University of Florida successfully produced fresh water from seawater in the mid-1950s, but the flux was too low to be commercially viable. Two UCLA engineering graduate students, **Sidney Loeb** and **Srinivasa Sourirajan**, made that process possible. The pair created the first practical RO membrane using cellulose acetate. They filed for a patent on the new membrane in 1960.

The middle porous structure was created by phase-inversion Method. The top skin layer of cellulose acetate membrane was generated by solvent evaporation to have a dense layer. This combination is used for the selective separation of water molecules and sodium/ chloride ions.

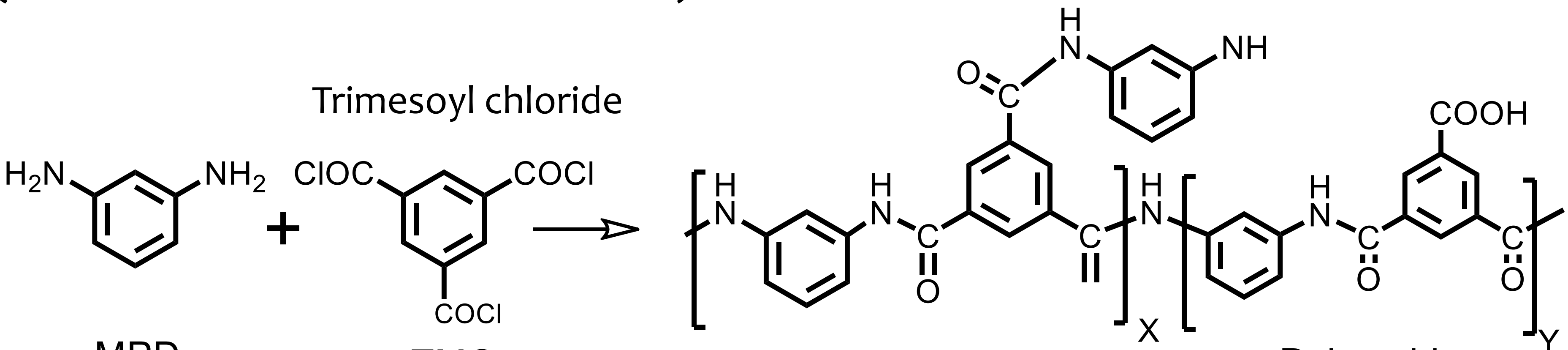
PET: Polyester (e.g., polyethylene terephthalate, PET) non-woven substrate to provide the mechanical strength. The middle and top layers are cellulose acetate fabricated by different approaches.



Phase inversion is a chemical phenomenon used for fabrication of artificial filtration membranes. Solvents are removed from a liquid-polymer solution, leaving a porous, solid membrane.

https://www.slideshare.net/9495094029/reverse-osmosis-based-desalination

Thin Film Composite membranes (for Flat Sheet Membrane)

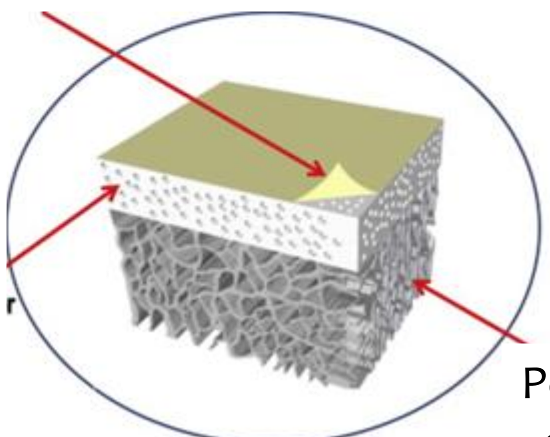


MPD
M-phenylene diamine

TMC

Polyamide

Active layer (< 200 nm)
of Polyamide



Polysulphone
Layer

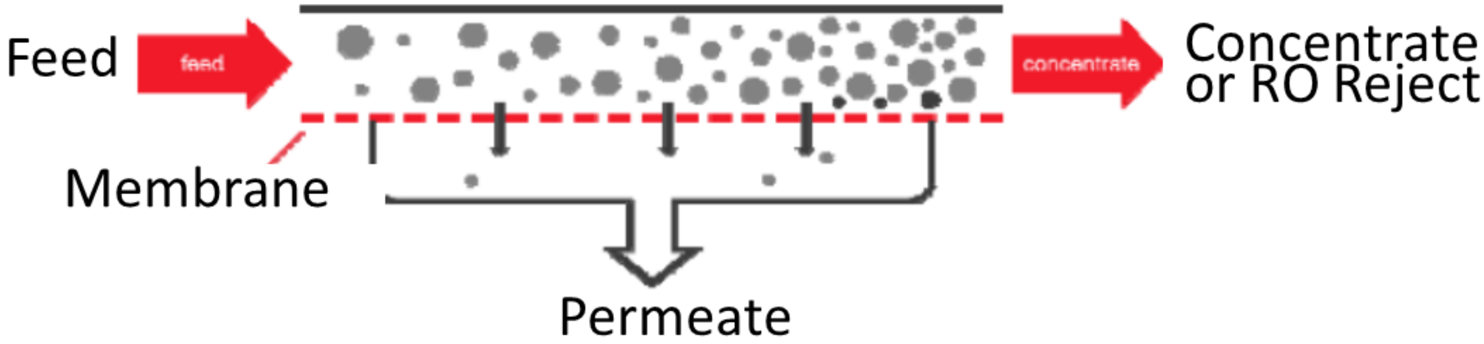
Polyester web
~120 µm

Membrane performance under BW condition: 50-65 l/m²hr, salt rejection 97-98% at 225-250 psi applied pressure……*feed water quality dependent*

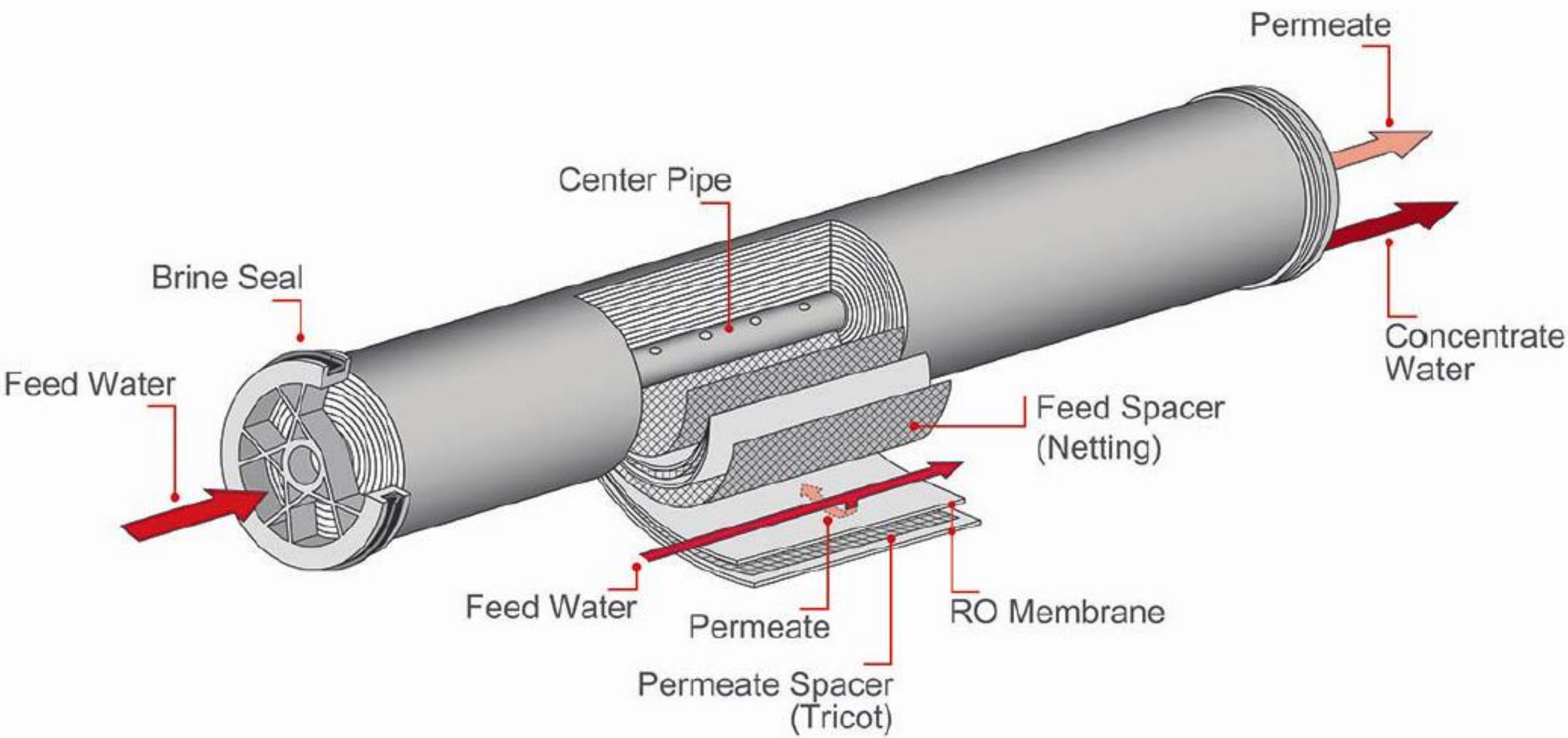
Steps:

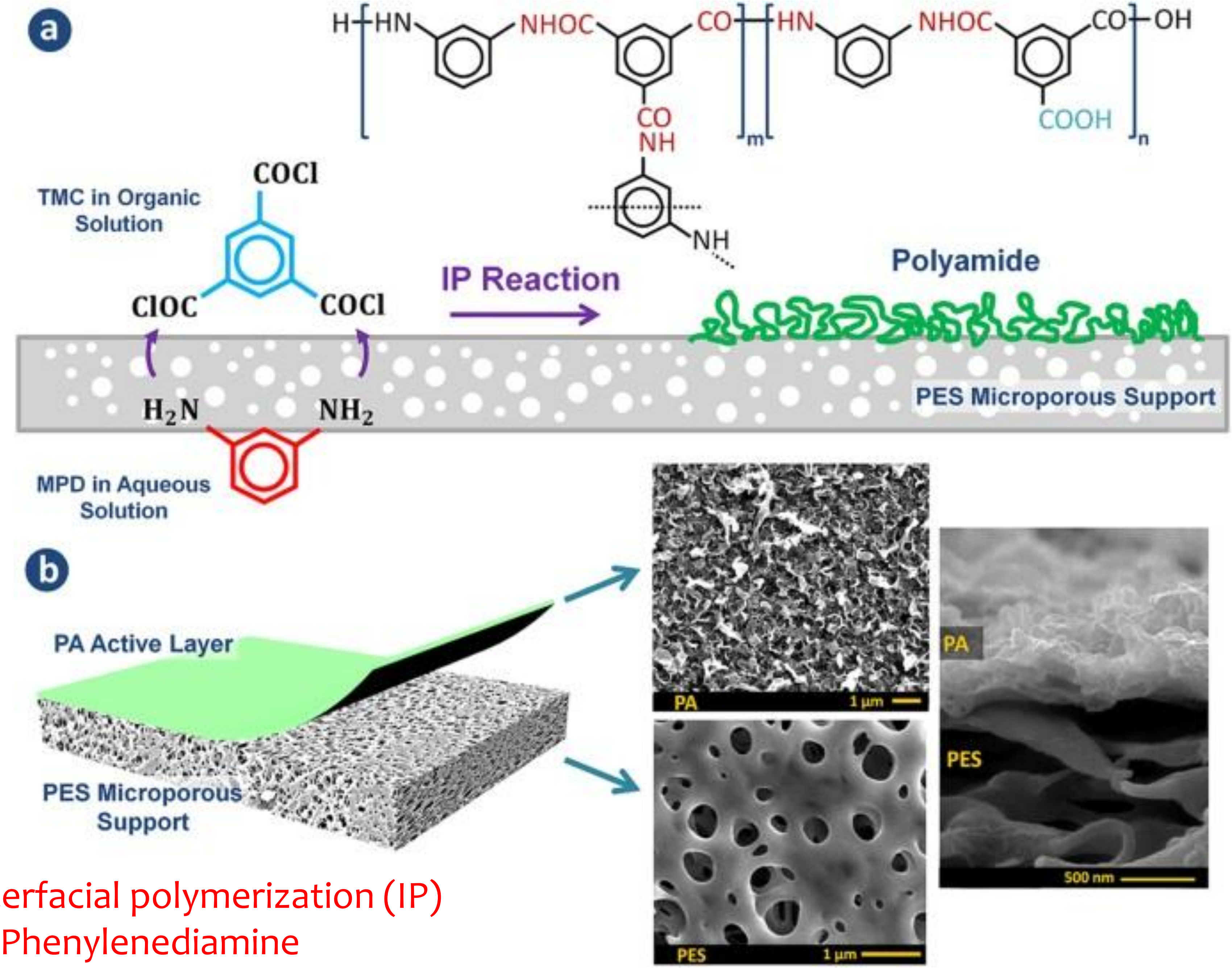
Ultrafiltration membrane casting on polyester fabric following phase separation method

Polyamide coating following *in situ* interfacial polymerization reaction



Typical spiral-wound element construction



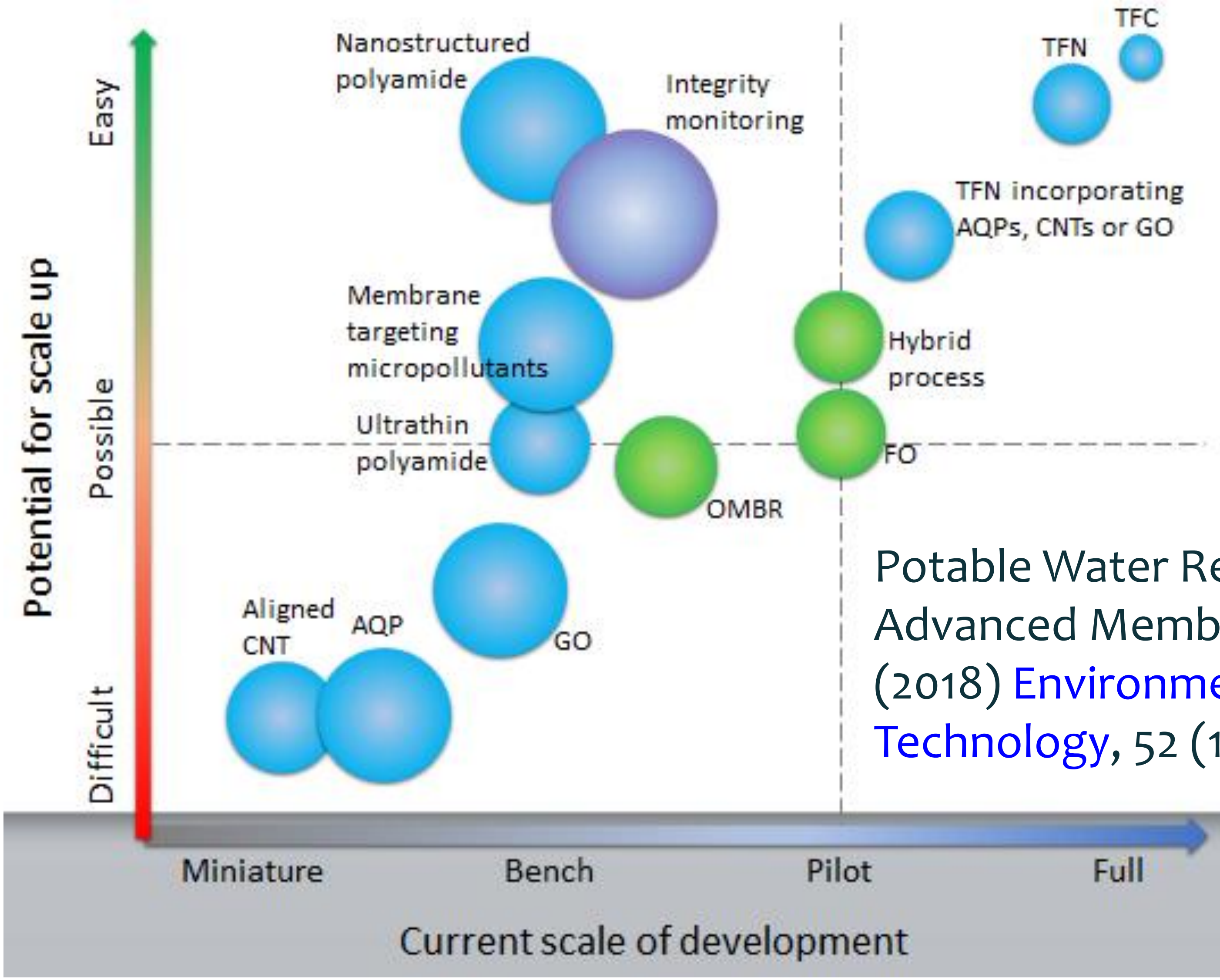


interfacial polymerization (IP)

m-Phenylenediamine

polyethersulfone (PES)

Sci Rep 2016, 6, 22069



(TFN) Thin film nanocomposite

Potable Water Reuse through Advanced Membrane Technology (2018) Environmental Science and Technology, 52 (18), pp. 10215-10223

Outlook of water reuse technologies. Both axis have the usual meaning.

Size of the sphere represents the potential impact of a particular technology--larger sphere indicates enhanced reliability, reduced cost, and energy consumption, and/or improved water quality.

Reverse Osmosis based processes

Brackish Water Desalination: ~3000 – 7000 ppm

One Step Process

Working pressure: 225 - 250 psi (or ~ 30 bar pressure)
Water recovery: ~ 65%
Capacity: 500 - 10000 LPH
Cost: ~ Rs.0.07/- per L
Rejection: > 98% (~ 200-300 ppm)

Sea Water Desalination: ~30,000 – 35,000 ppm

Two Step Process

Working pressure: 800 plus psi (or ~60 bar pressure)
Water recovery: ~ 55%
Capacity: 500 - 10000 LPH
Cost: ~ Rs. 0.12/- to 0.15/- per L
Rejection: > 98% (~200 – 300 ppm)

Electro dialysis based processes

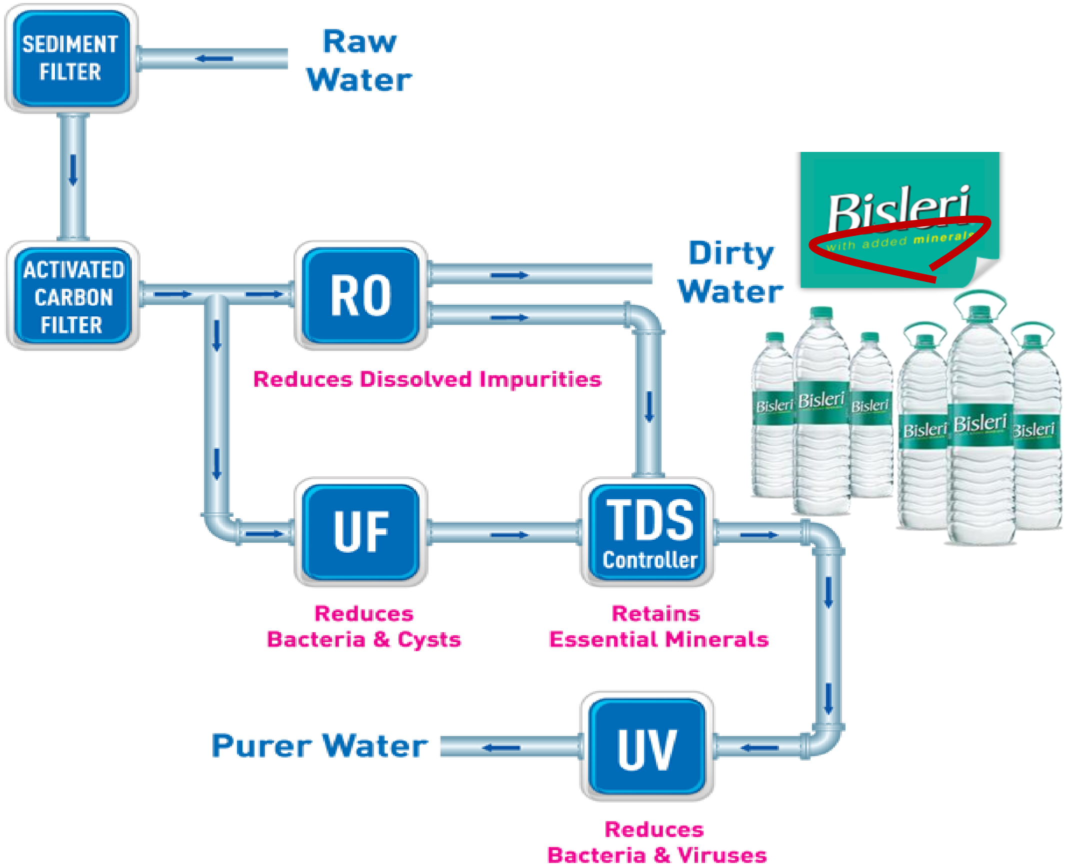
Brackish Water Desalination: < 3000 ppm

~ 140 - 200 mAmp current
Water recovery: ~ 85%
Capacity: ~ 350 - 400 LPH [for 40 cm x 80 cm stack]
Cost: ~ Rs.0.04/- per L [For Solar panel driven]
TDS in water: > 200-250 ppm

During desalination, the salinity is lowered – which is desired – but the concentrations of nutritious constituents may also be reduced excessively—which is not desired.
Nature 452 (2008) 301.

Remineralisation is one approach to correct the imbalance but this is not practiced always.
Water Sci. Technol. 49 (2003) 69; 55 (2007) 127.

Nutritious constituents depletion is an issue in water obtained through RO process.
Science 318 (2007) 920.



ED process with mono-valent selective ion-exchange membranes can be used for the retention of nutritious bulky ions (HCO_3^-/bivalent ions) to produce nutritious drinking water during brackish water desalination.

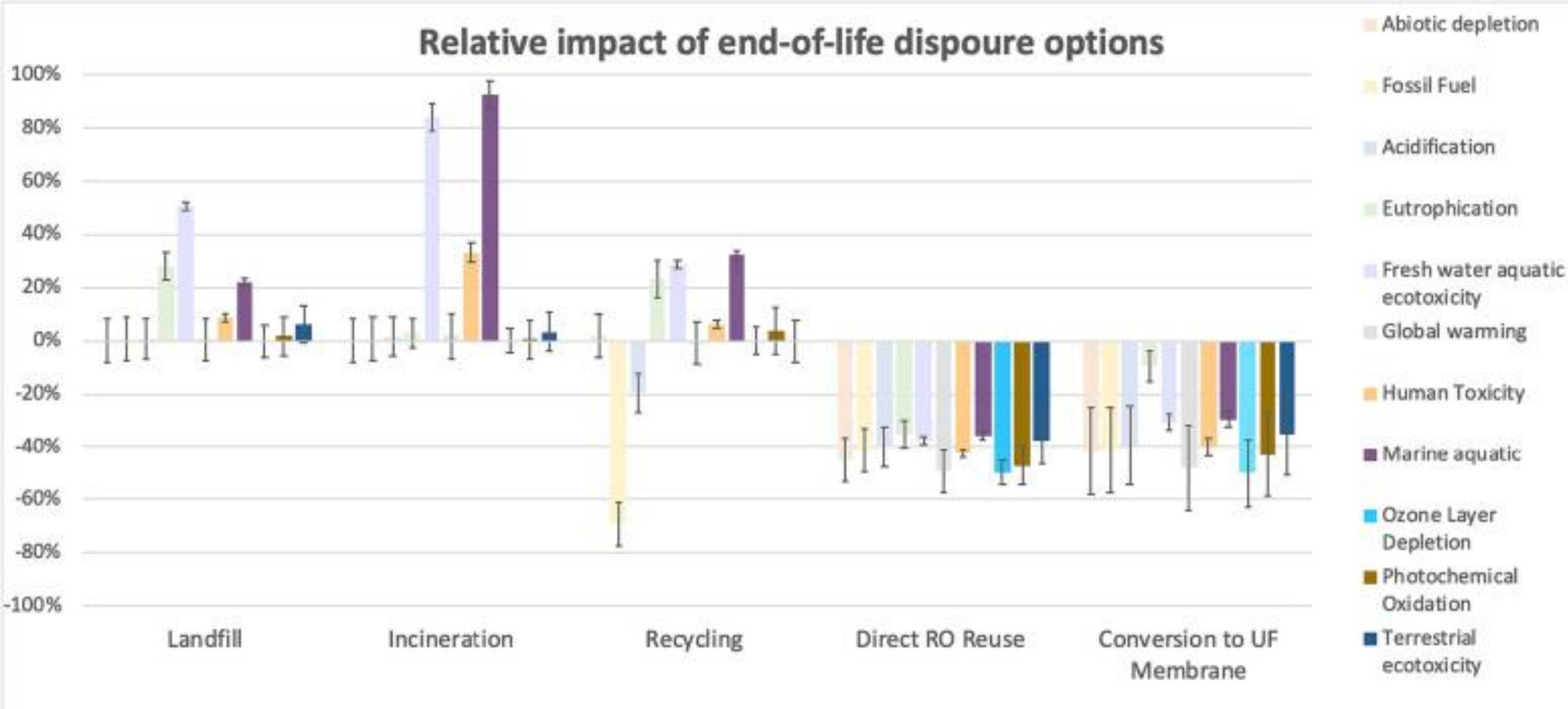
Comment
Environ. Sci. Technol. 2019, 53, 3999–4000

The Unintended Consequences of the Reverse Osmosis Revolution

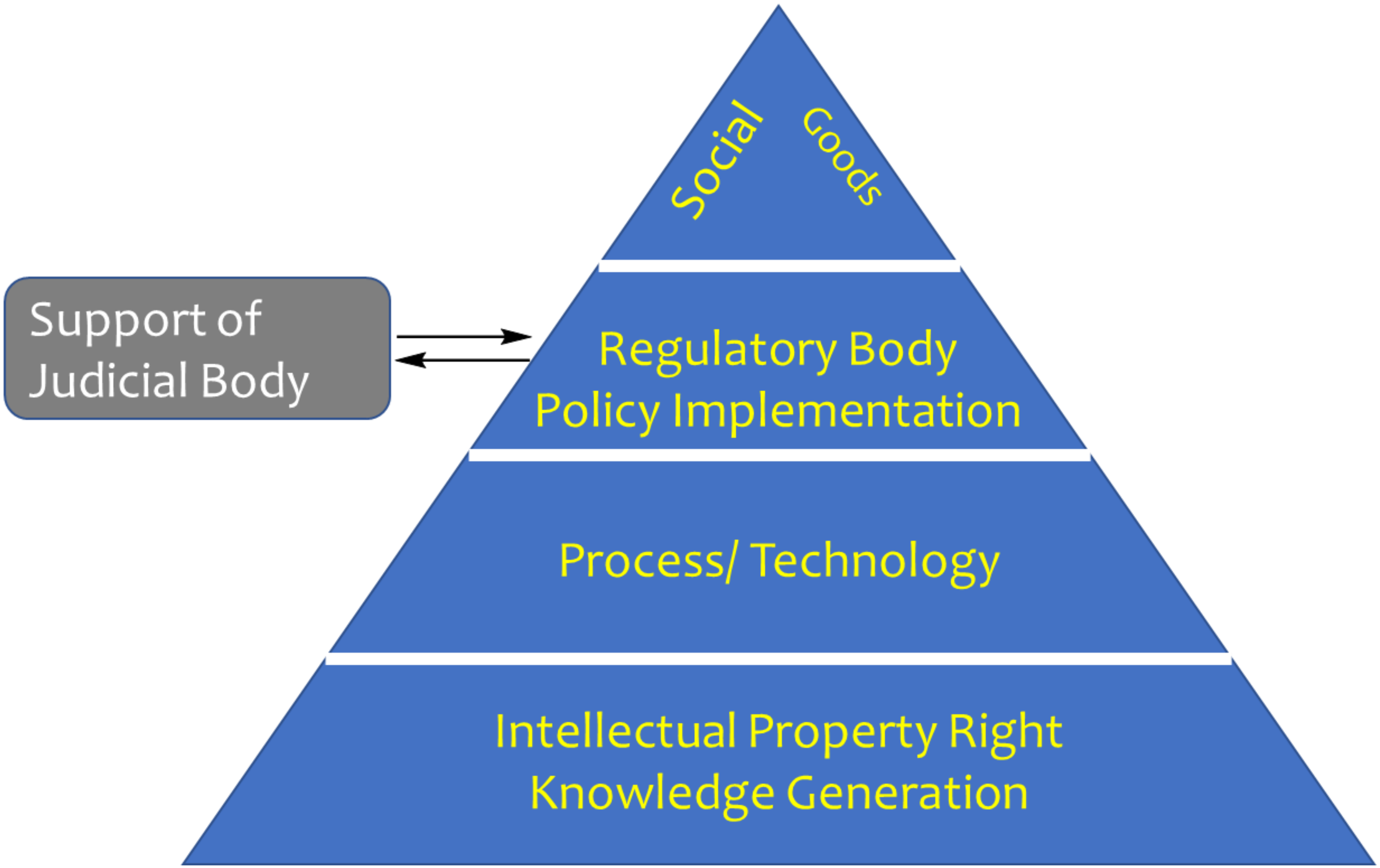
As reverse osmosis creates additional fluoride-deficient drinking water supplies, **public health experts will have to pay more attention to the need to augment dietary fluoride sources. This issue is particularly important in lower income communities,** where fluoride containing toothpaste is less common. For example, failure to appreciate the impact of reverse osmosis on fluoride led to decreases in height and increases in caries among children in communities in China where reverse osmosis systems had been installed at primary schools.

About 10 years ago, **epidemiologists reported increased rates of suicide in communities where lithium concentrations in drinking water are low.** Although not all of the subsequent studies supported the lithium deficiency hypothesis, **the concentrations of lithium in desalinated seawater are at the low end of the range reported in places where increased suicide rates have been observed.** It would be possible to add a small amount of lithium, or other needed trace elements, to reverse osmosis water or to supplement diets in other ways in deficient populations, but without additional research to establish the validity of these ideas, this is unlikely to happen.

At full-scale water treatment plants, where corrosion of water distribution pipes is a major concern, lime (i.e., $Ca(OH)_2(s)$) is used for remineralization because it is inexpensive and readily available. Unfortunately, the near absence of **magnesium in water produced by this process has resulted in deficiencies in magnesium that increase the risks of heart disease.** When this problem first came to light, water providers in Israel initiated an effort to develop cost-effective and reliable approaches for introducing magnesium during remineralization.



Desalination
Volume 575, 16 April 2024, 11733

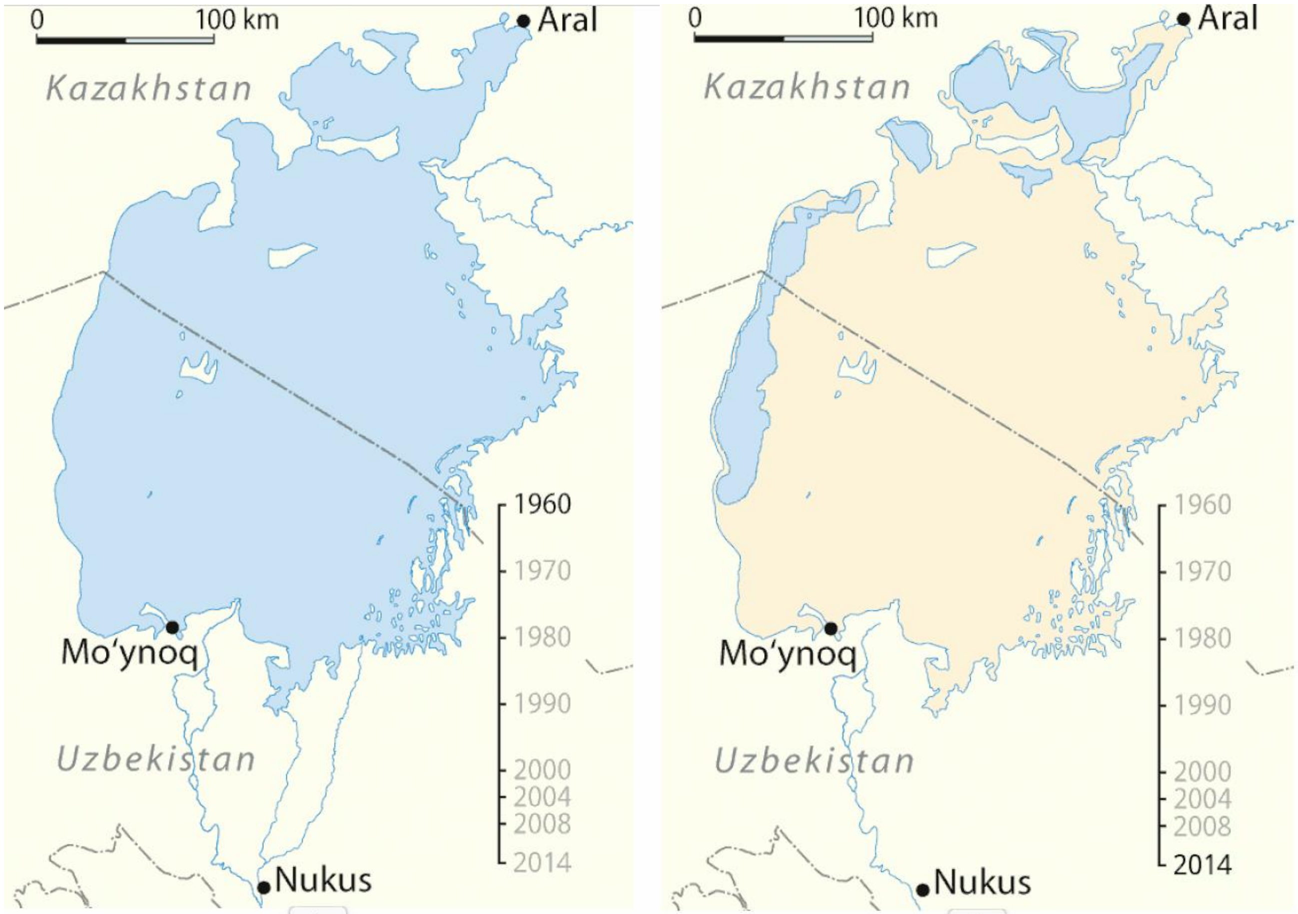

Social Goods
Support of Judicial Body
Regulatory Body
Policy Implementation
Process/ Technology
Intellectual Property Right
Knowledge Generation

Desiccation of the Aral Sea: **Aral Sea Catastrophe: One of the Worst Ecological Calamities of the Last Century and** An Example of Misplaced Economic Priorities over Environmental One

The Aral Sea is a lake located east of the Caspian Sea between Uzbekistan and Kazakhstan in Central Asia—is a part of the Turkestan desert, which is the fourth largest desert in the world. Satellite images revealed that the water level has decreased 40-fold in the past five decades.
The lake is divided into two parts: the large Aral in the territory of Uzbekistan and the small Aral in Kazakhstan.

It is produced from a rain shadow effect by Afghanistan's high mountains to the south. Due to the arid and seasonally hot climate, there is extensive evaporation and limited surface waters in general. Summer temperatures can reach 60°C. The water supply to the Aral Sea is mainly from two rivers, the Amu Darya and Syr Darya. In the early 1960s the then-Soviet Union diverted the Amu Darya and Syr Darya Rivers for irrigation of one of the driest parts of Asia to produce rice, melons, cereals, and especially cotton (white gold)—to become a major exporter. They were successful and today Uzbekistan is one of the world's largest exporters of cotton. Unfortunately, this action essentially eliminated any river inflow to the Aral Sea and caused it to disappear almost completely.

Aral Sea, formerly the fourth-largest freshwater lake in the world with an area of 68,000 square kilometres, has transformed into the expanses of the Aralkum Desert that emerged in its place.

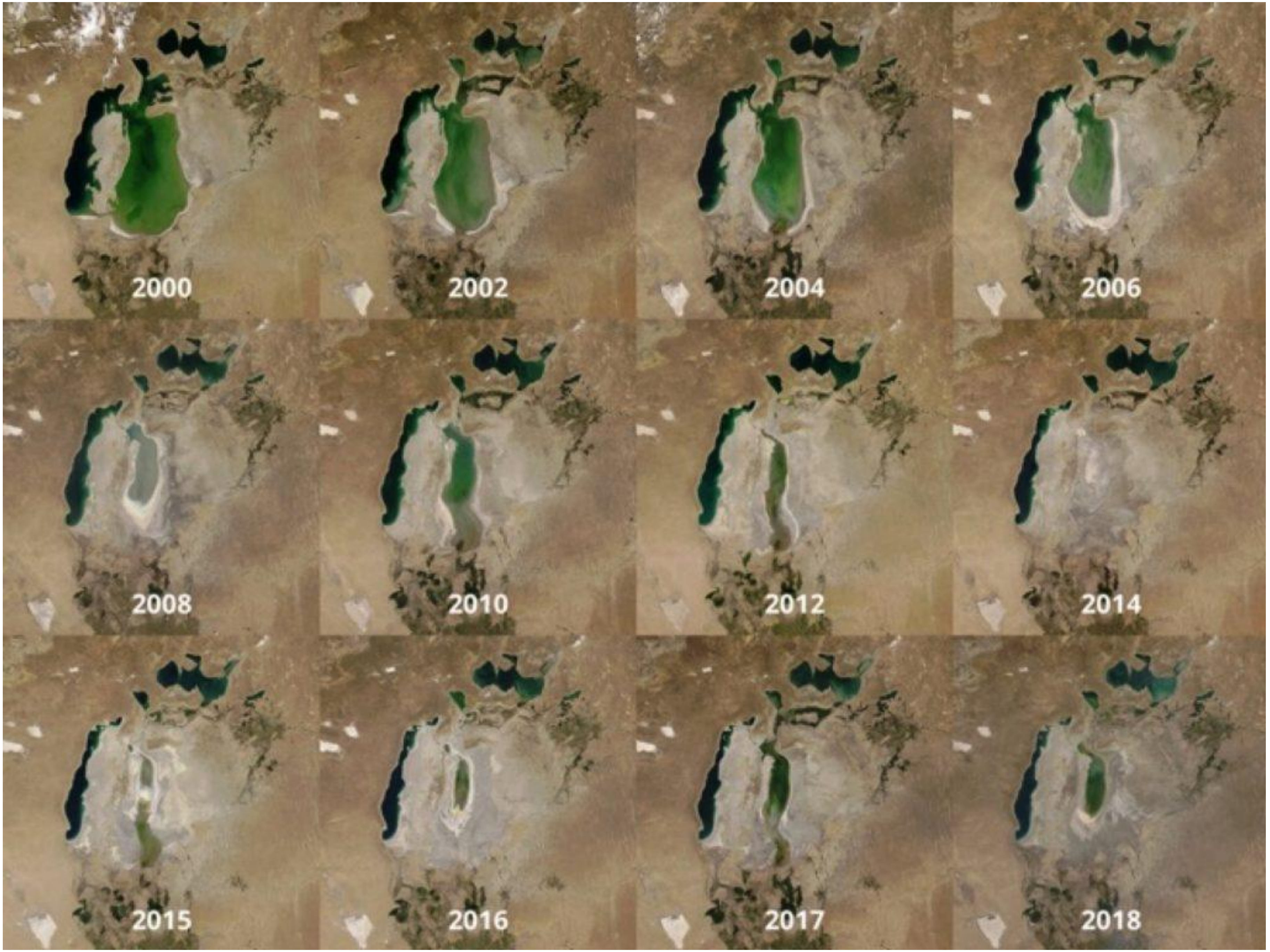


https://adarshbadri.me/politics-society/aral-sea-and-bad-politics/

The United Nations Development Programme called the Aral Sea the "most staggering disaster of the twentieth century" (Grabish 1991). It is a prime example of what unsustainable growth—i.e., economic growth that disregards ecological concerns—can produce.

Besides aquatic species, the Aral Sea used to be a crucial stopover point for millions of migratory birds travelling along the Central Asian flyway. As the sea shrank, wetland habitats vanished, forcing birds to alter their migration patterns.

Aral Sea Transformation



Impact on the Aral Basin Due to Economic Policies of **the Soviet Union.**

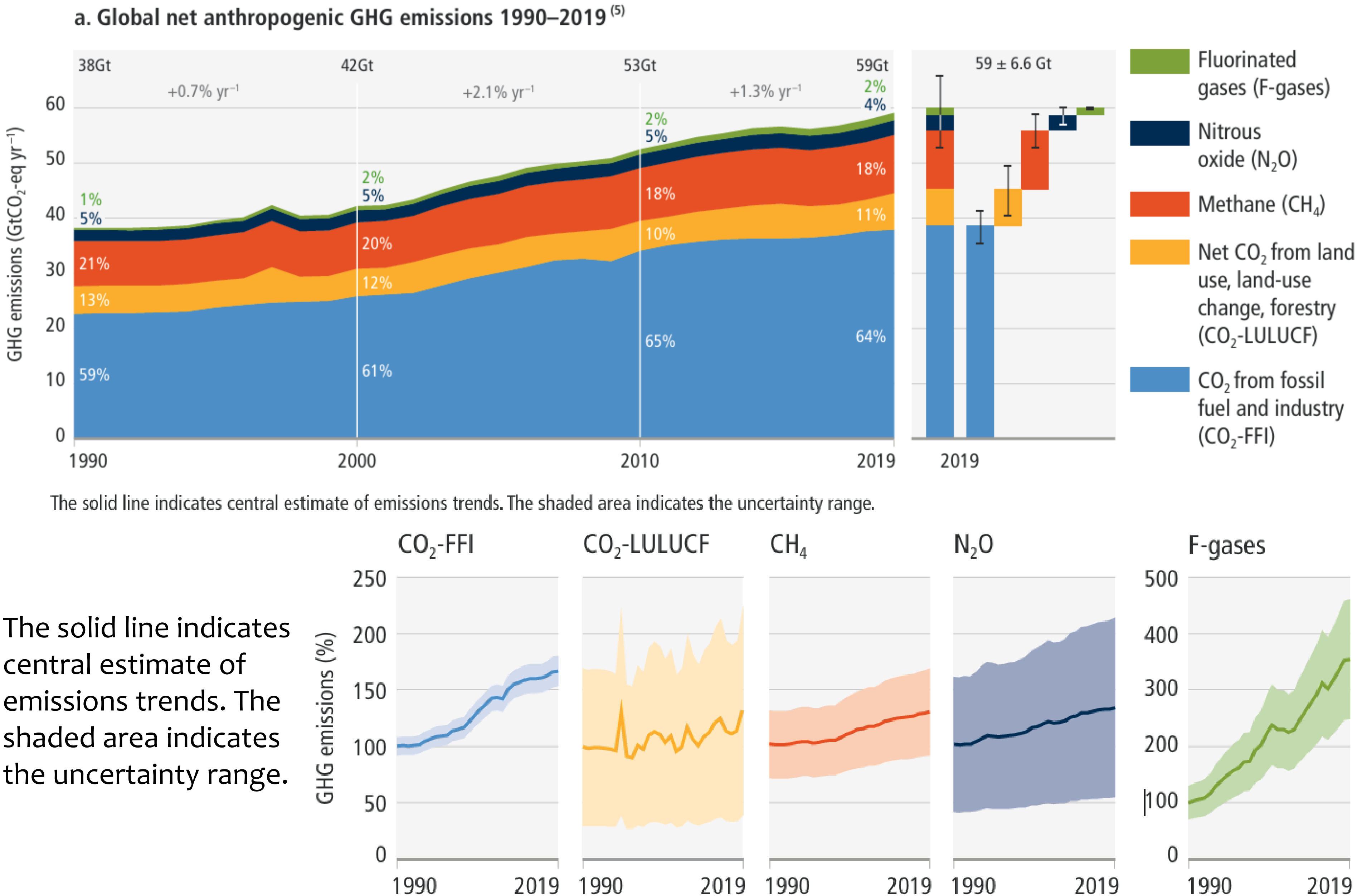
The Collectivisation of Agricultural Land in the Soviet Union.

Human Impact of the Aral Sea Crisis.

Salination of Water in the Aral Sea; Health Crisis in the Aral Sea Basin; the varieties of fish in the region have also reached extinction (Micklin and Aladin 2008). The 20 fish species in the sea, which were crucial for the region's economy and nutrition, have perished.

Societies find it difficult to balance between the economy and ecology. In economics, we are taught "opportunity cost"—the value of gaining something at the cost of something else. It is a trade-off.

Global net anthropogenic emissions have continued to rise across all major groups of greenhouse gases.



The solid line indicates central estimate of emissions trends. The shaded area indicates the uncertainty range.

https://www.ipcc.ch/report/ar6/wg3/

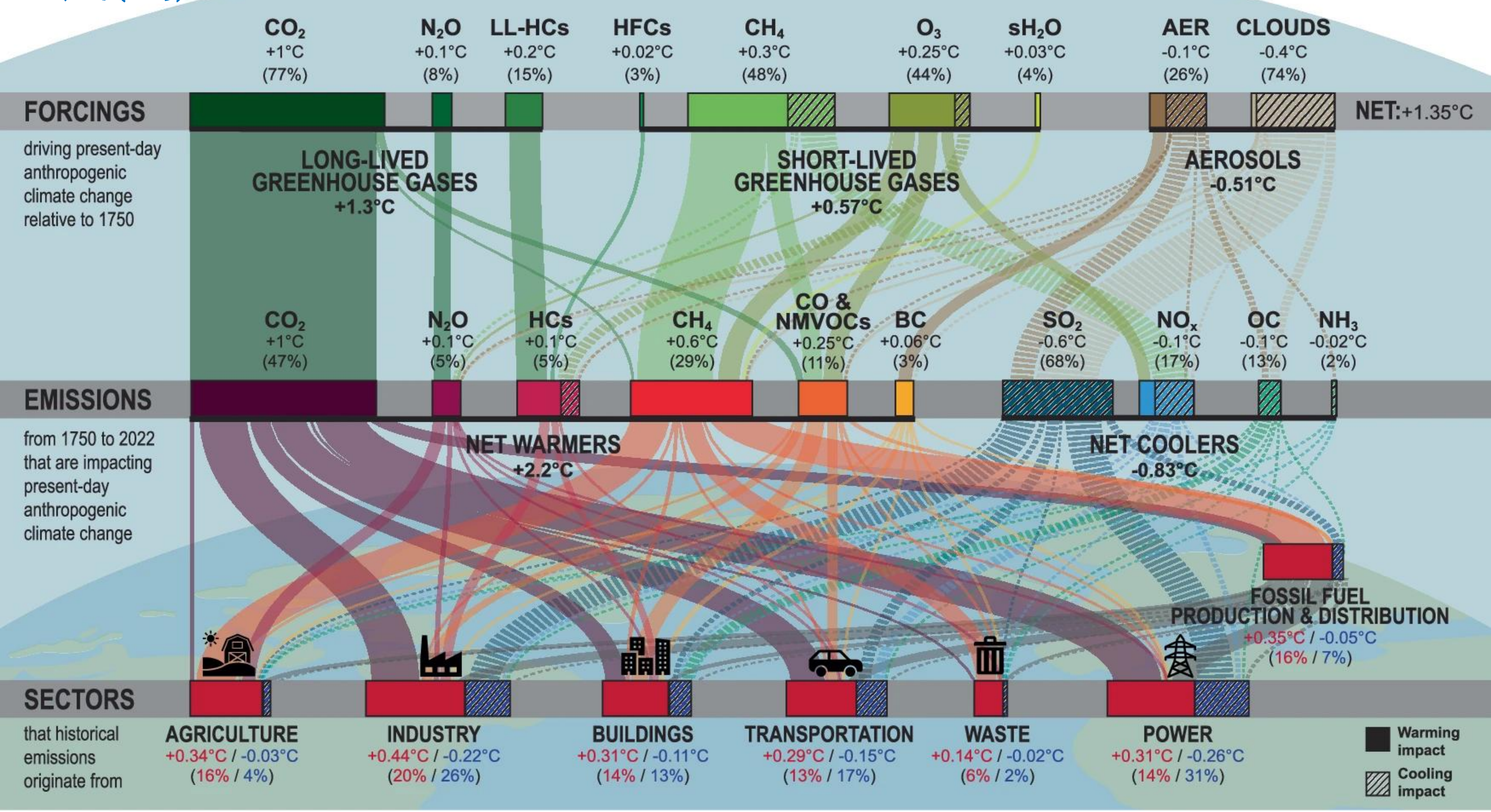
Greenhouse Gas (GHG)	Atmospheric Lifetime (yrs)	Global Warming Potental (GWP)	Primary Current Sources
Carbon dioxide (CO_2)	50-200	1	Fossil fuel use, land use, cement
Methane (CH_4)	12±3	21	Fossil fuel use, agriculture
Nitrous oxide (N_2O)	120	310	Mostly agriculture, ~1/3 are anthropogenic
Hydrofluorocarbons (HFCs)	1.5 to 209	150 to 11,700	Alternative to ozone depleting substances
Perfluorocarbons (PFCs)	2,600 to 50,000	6,500 to 9,200	Primary aluminum production; semiconductor manufacturing
Sulfur Hexafluoride (SF_6)	3,200	23,900	Used in electric power transmission, magnesium and semiconductor industries

High GWP gases

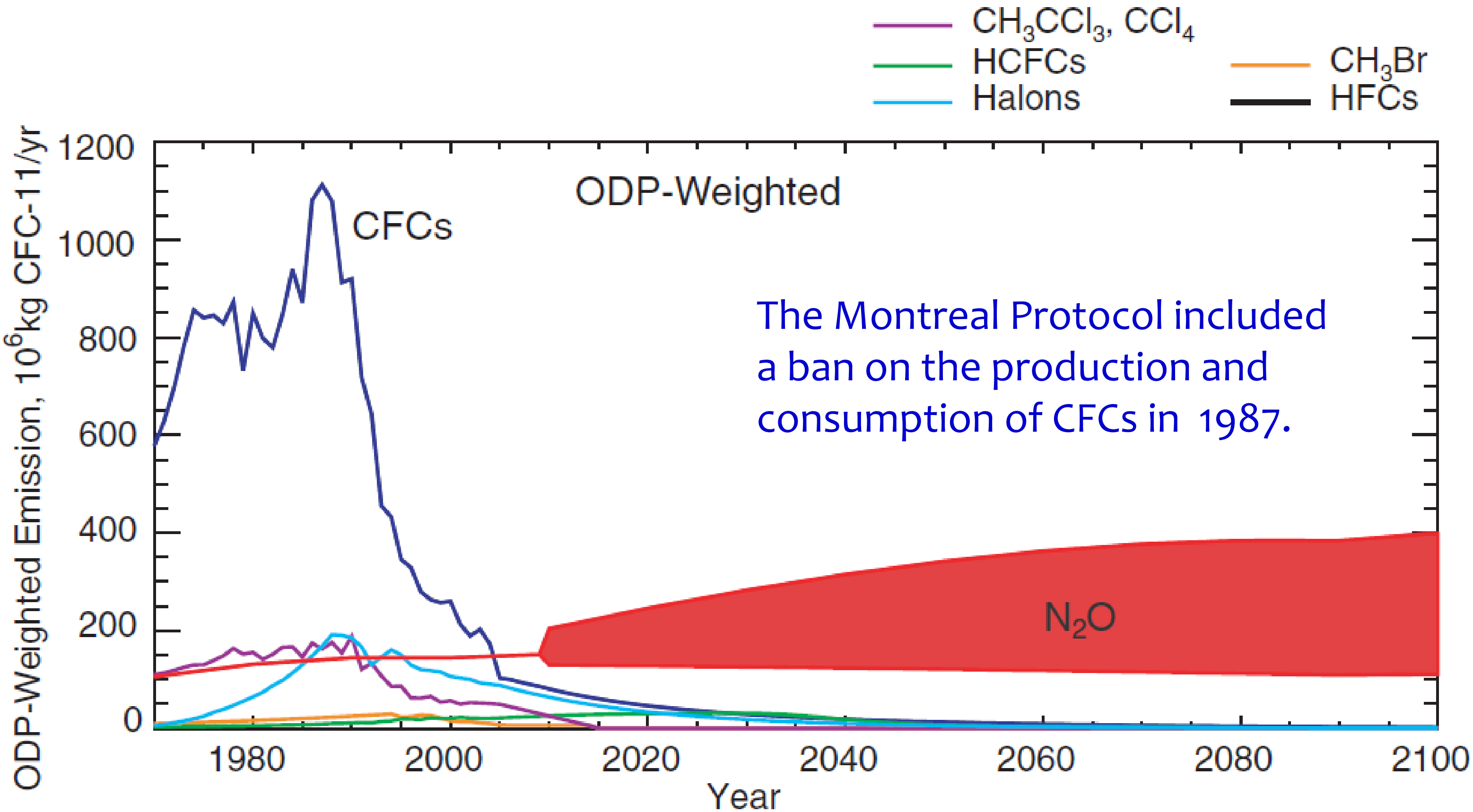
https://www.global-climate-change.org.uk/6-5-2.php

The Kyoto Protocol fixed the use of GWP values published by the IPCC in 1996 in its Second Assessment Report. Since then, the IPCC has updated its GWP values four times, in 2001, 2007, 2013, and 2021. The result has been a proliferation of GWP values out there that leads to a lot of confusion.

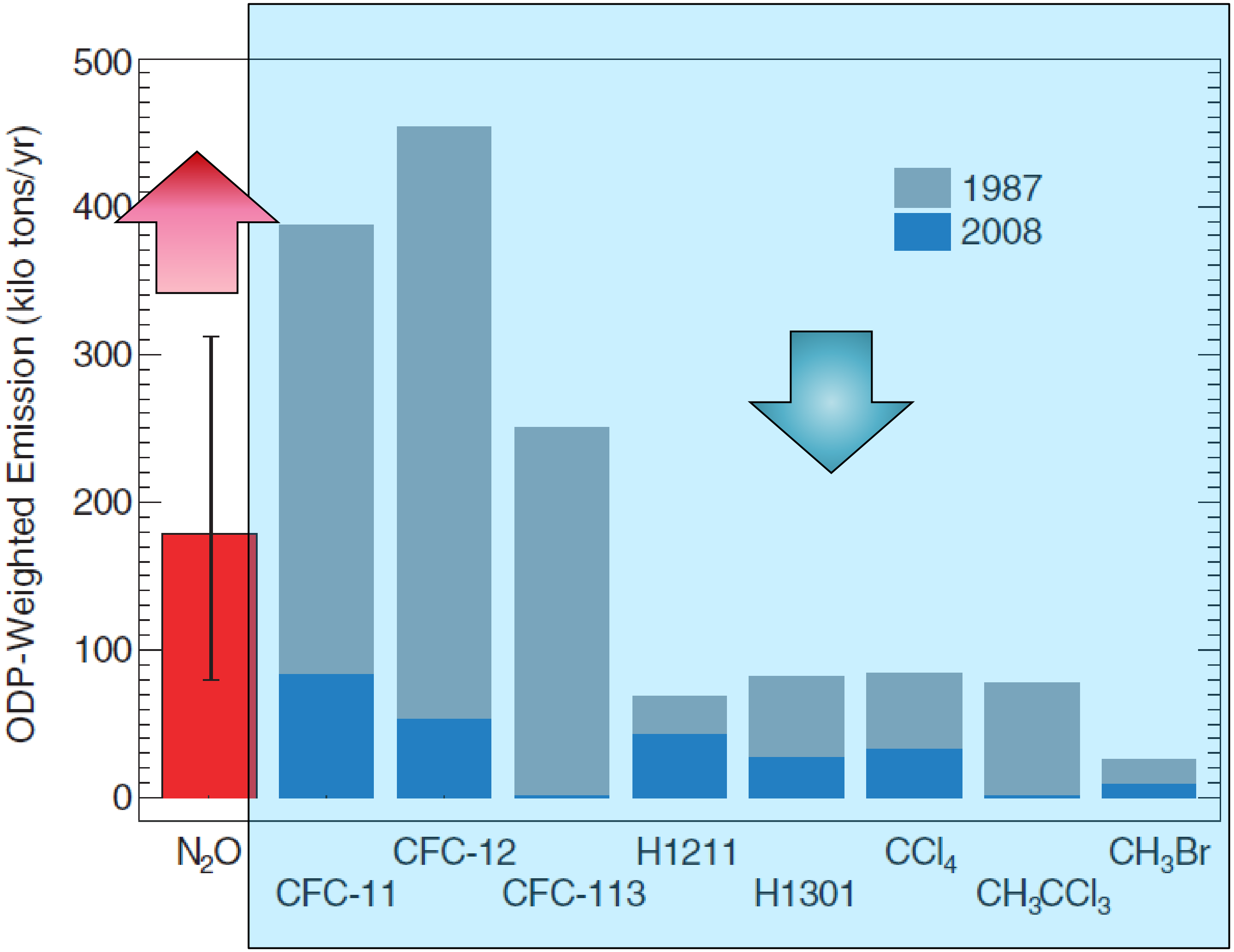
npj Clim Atmos Sci 8, 287 (2025)



Halogenated Compounds [LL-HCs: long-lived HCs] including Chlorofluorocarbons (CFCs), Hydrochlorofluorocarbons (HCFCs), Hydrofluorocarbons (HFCs); CH_4: Methane; O_3: Tropospheric & Stratospheric Ozone; sH_2O: Stratospheric Water Vapor; AER: Aerosol direct effects; Clouds: Aerosol-induced cloud effects; CO & NMVOCs: Carbon Monoxide & Non-Methane Volatile Organic Carbons; BC: Black Carbon; SO_2: Sulfur Dioxide; NO_x: Nitrogen Oxides; OC: Organic Carbon; NH_3: Ammonia. Sector to emissions data taken from the analysis herein (including emissions contributions to net temperature change), emissions to forcings data taken from ref. [2]. Biomass burning and land use changes not included. Agriculture includes energy-use emissions from forestry and fisheries. Power represents power generation.



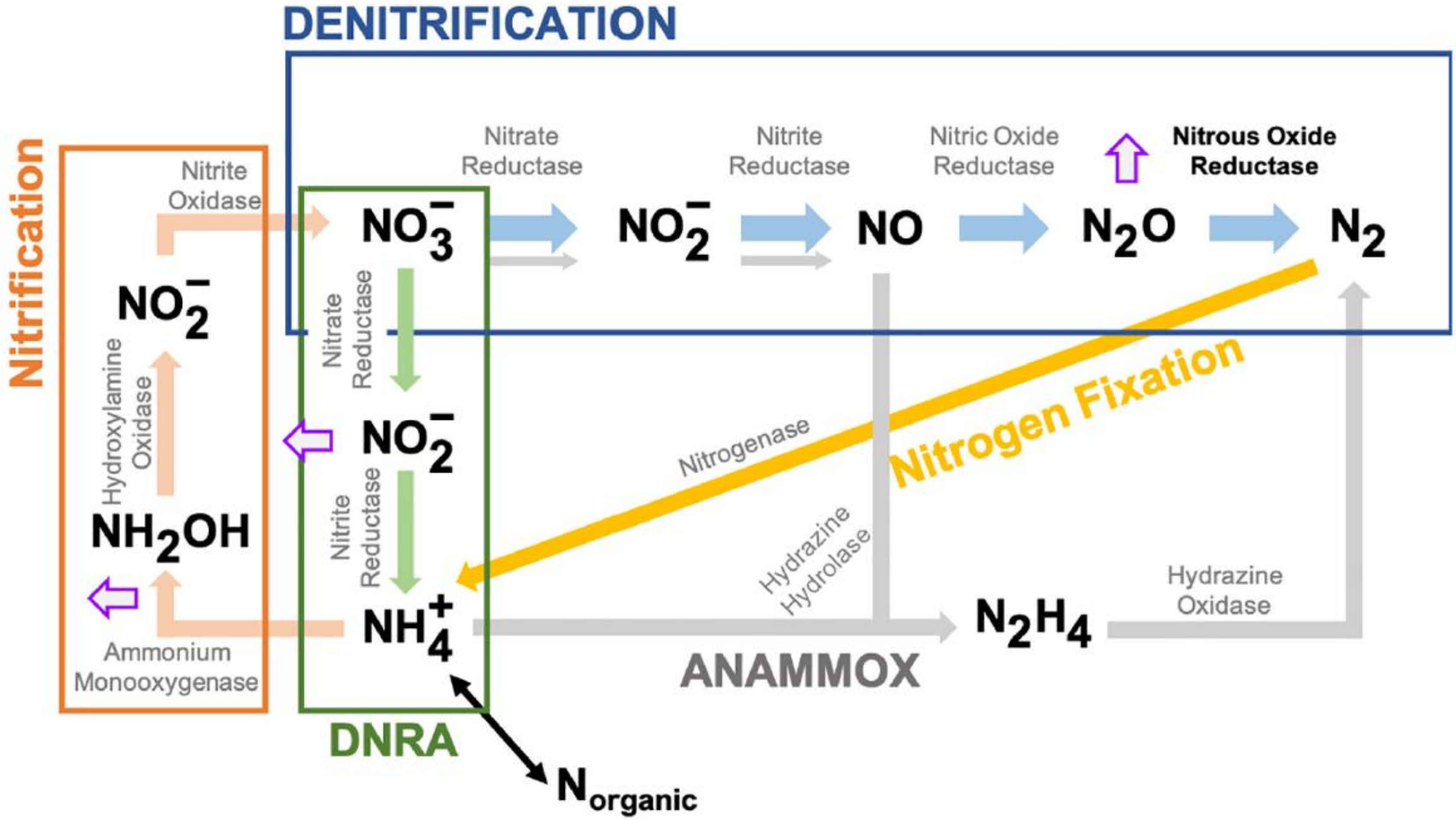
Historical and projected ODP-weighted emissions of the most important ODSs and non-CO2 greenhouse gases. Non-N2O ODS emissions are taken from WMO (Global Ozone Research and Monitoring Project Report No. 50, Geneva, Switzerland, 2007). Hydrofluorocarbon (HFC) projections are taken from Velders et al. Proc. Natl. Acad. Sci. U.S.A. 2009, 106, 10949 & Science, 2009, 326, 123-125



Ozone depleting potential (ODP) is a measure of how much damage a chemical can cause to the ozone layer compared with a similar mass of trichlorofluoromethane (CFC-11). **CFC-11, with an ODP of 1.0,** is used as the base figure for measuring ozone depleting potential.

Montreal Protocol included a ban on the production and consumption of CFCs in 1987.

Comparison of annual N_2O ODP-weighted emissions with emissions of other Ozone Depleting Substances (ODSs). A report from the Global Monitoring Division, Earth System Research Laboratory, National Oceanic and Atmospheric Administration for CFC-11, CFC-12, Halon 1211 (H1211), Halon 1301 (H1301), and CH3Br; all other emissions are taken from WMO. Science, 2009, 326, 123-125



ANAMMOX: Anaerobic NH_4^+ oxidation, **DNRA**: Dissimilatory nitrate reduction to $NH4^+$

In O2-limited environments (anaerobic conditions), denitrifying bacteria can switch from O2-dependent respiration to nitrate (NO_3^-) respiration in which the NO_3^- is sequentially reduced via nitrite (NO_2^-), nitric oxide (NO) and N_2O to N_2.

Coordination Chemistry Reviews 387 (2019) 436–449

N_2O accumulates during biological nitrogen removal from wastewater as a byproduct of nitrification by ammonia oxidizing bacteria and/or as a result of incomplete denitrification by heterotrophic denitrifying bacteria in the activated sludge (Schreiber et alFront. Microbiol., ., 2012, 3, 372).

A significant proportion of the rise in atmospheric N_2O is microbial in origin. This implies that the enzyme responsible for reduction, **nitrous oxide reductase (NO2R)**, does not always carry out the final step of denitrification either efficiently or in synchrony with the rest of the pathway. FEMS Microbiol. Letts. 365, 2018, fnx277

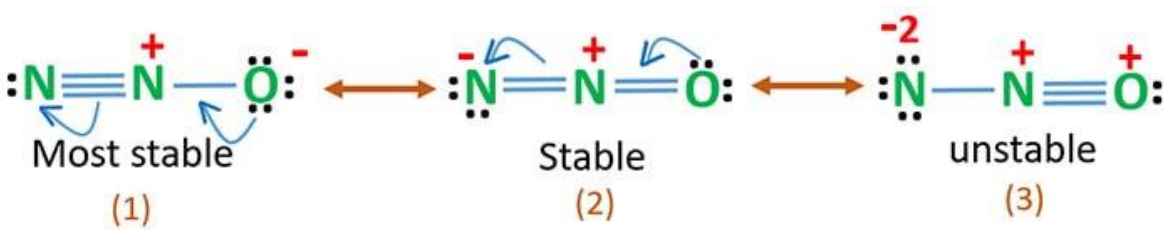
Under anaerobic conditions, denitrifying organisms perform the reduction of inorganic NO_3^- or NO_2^- in sequential steps that involve the abstraction of an oxygen atom at each step, with the production of gaseous molecules at intermediate stages:

$$\mathrm{NO3} \xrightarrow{\boxed{\mathrm{Nar}}} \mathrm{NO2} \xrightarrow{\boxed{\mathrm{Nir}}} \mathrm{NO} \xrightarrow{\boxed{\mathrm{Nor}}} \mathrm{N2O} \xrightarrow{\boxed{\mathrm{NO2R}}} \mathrm{N2}.$$

Each step is catalyzed by a distinct enzyme—nitrate reductase (Nar), nitrite reductase (Nir), nitric oxide reductase (Nor), and nitrous oxide reductase (N_2OR)—located either in the inner membrane or the periplasm of various α-, β-, γ-, and ε-proteobacteria.

N_2O is a linear asymmetrical molecule, and its electronic and structural properties can be described with the resonance structures.

N2O reduction is highly exergonic ($\Delta G^o = -339.5$ kJ mol^{-1}) , and this molecule is a stronger oxidant than N2, as seen by its redox potential (E° (pH 7.0) = 1.35 V). Although this reaction is thermodynamically favorable, a high activation barrier (250 kJ mol^{-1}) makes this process kinetically unfavorable--consistent with a spin-forbidden process. J. Am. Chem. Soc. 1987, 109, 5539-5541



The reduction of N_2O to molecular nitrogen (N_2) requires two protons and two electrons, according to Eq. (1):

$$N_2O + 2H^+ + 2e^- \rightarrow N_2 + H2O, \quad E^o \text{ (pH7.0)} = 1.35 \text{ V}; \quad G^o = -339.5 \text{ kJ/mol}^{-1}$$

This is a challenging reaction to be catalyzed by a metalloenzyme, as nitrous oxide is not just kinetically inert to decomposition but also a poor transition metal ligand, due to its weak σ–donating and π-accepting properties

For **nitrous oxide (N_2O)** in its **ground electronic state,** the **spin multiplicity** is **1.**

- The ground-state electron configuration of N_2O has **all electrons paired** → total spin quantum number S=0.
- Spin multiplicity is given by 2S+1 = 1 [**singlet state**]. This is the stable atmospheric form.

N_2O can be excited via **UV absorption** or photodissociation, leading to various states:

State	Notation	Spin multiplicity	Notes
First excited singlet	$^1\Delta$, $^1\Pi$	1	Spin-allowed from ground state via electric dipole transitions. Short-lived.
First excited triplet	$^3\Delta$, $^3\Pi$	3	Spin-forbidden from ground state; often accessed via intersystem crossing.
Rydberg states	ns, np	1 or 3	Higher energy; lead to ionization or dissociation.

Photodissociation Pathways & Multiplicity: N_2O absorbs UV light (< 200 nm), it can dissociate:

N_2O → **N_2 (singlet) + O(^{1}D)** → Both products singlet (multiplicity 1)

$\boxed{N_2O \rightarrow \mathbf{N_2\ (singlet) + O(^3P)} \rightarrow \text{O atom triplet state (multiplicity 3)}}$

The O(^{3}P) channel is spin-forbidden from the singlet ground state.

Triplet channels lead to slower, spin-forbidden reactions; singlet channels are faster but require higher-energy UV photons

- In quantum mechanics, spin selection rules for electronic transitions state

$$\Delta S = 0$$

The total electron spin must be conserved during the transition/ reaction.
If a reaction or transition changes the spin state (e.g., singlet $\rightarrow$ triplet or triplet $\rightarrow$ singlet), it is spin-forbidden.

- Spin-forbidden processes occur more slowly than spin-allowed ones because they rely on **spin–orbit coupling** to mix states of different spin multiplicities.
- Often occur through **intersystem crossing (ISC)**—a non-radiative process that changes multiplicity.
- Important in **atmospheric chemistry**

For **N_2O photodissociation**:

$N_2O(^1\Sigma^+) \rightarrow N_2(^1\Sigma_g^{\,+}) + O(^3P)$

N2O reduction is thermodynamically favored ($N_2O + 2H^+ + 2\ e^- \longrightarrow N_2 + H_2O$; $E^{Red}{}_0$: pH 7:0 is + 1:35V; $\Delta G_0{}' = -339.5\ kJ{\cdot}mol^{-1}$), its activation energy barrier of 250 $kJ{\cdot}mol^{-1}$ leads to substantial kinetic stability and chemical inertness. The biological reduction of N_2O to N_2 is catalyzed by a specialized enzyme, nitrous oxide reductase (usually referred as NO2R), a periplasmic, homodimeric metalloprotein of 130 kDa that contains with two distinct multinuclear Cu centers per subunit, a binuclear Cu_A ET site, and a catalytic Cu_Z center, a novel μ_4-sulfide-bridged tetranuclear Cu cluster. N_2O reductase (N2OR) catalyzes the final step of denitrification, that is, the two-electron reduction of N_2O to N_2.

The crystal structures of N_2OR from *Pseudomonas nautica* and *Paracoccus denitrificans* at 2.4 Å and 1.6 Å resolutions, have revealed a novel μ_4-sulphide-bridged tetranuclear Cu_Z cluster.

The reduction of nitrous oxide is the last step in the denitrification process of the geo-biological nitrogen cycle:

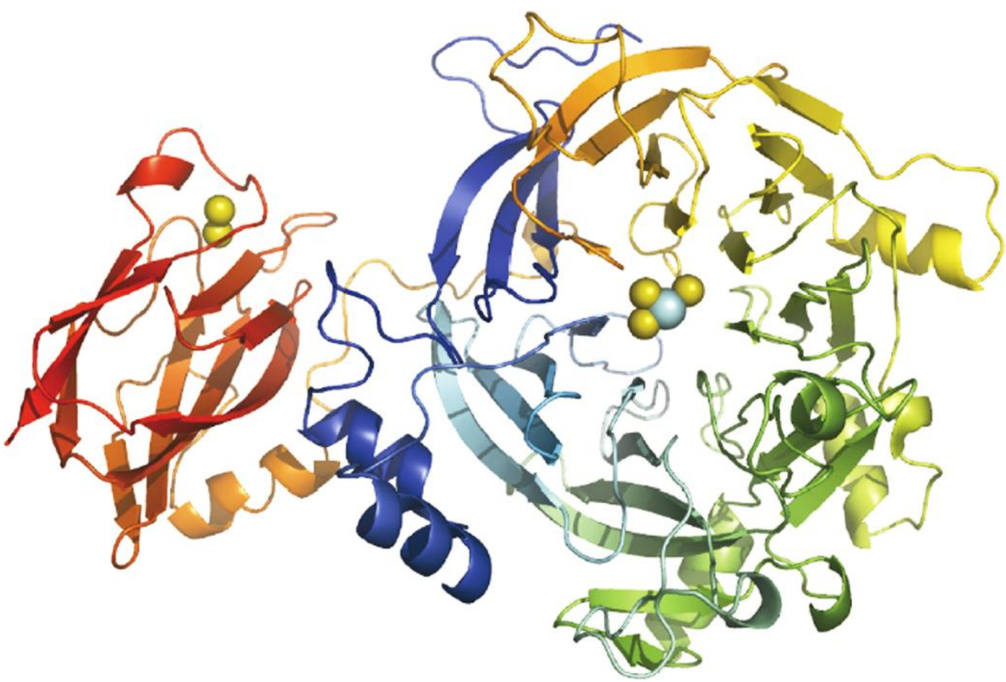
$N_2O + 2\,H^+ + 2\,e^- \rightarrow N_2 + H_2O$ (E_o (pH 7.0)=+1.77 V)

N_2ORs have been characterised from a wide variety of bacteria including *Achromobacter cycloclastes* (*Ac*N_2OR), *Alcaligenes xylosoxidans* (*Ax*N_2OR), *P. nautica* (*Pn*N_2OR) and *P. denitrificans* (*Pd*N_2OR).[3,4]

The reduction of N_2O is thermodynamically favourable but it is kinetically inert, and is a poor ligand for transition metals. N_2ORs are a highly conserved protein family of ~130 kDa homodimers containing multiple Cu atoms. Since the original spectroscopic work in the 1980s, more recent, extensive spectroscopic and mutational studies have shown these Cu atoms to be organised into two distinct types of Cu-centres.

Journal of Molecular Biology, 2006, 362, 55-65

Extensive spectroscopic and mutational studies have shown these Cu atoms to be organized into two distinct types of Cu centres. Subsequent X-ray crystal structure analysis of *Pn*N_2OR (from *P. nautica*) and *Pd*N_2OR (*P. denitrificans*) confirmed the presence of two multi-nuclear Cu-centres per monomer. This includes a Cu_A site that, in analogy to the role of this centre in cytochrome *c* oxidase, is proposed to mediate electron transfer to the second multi-nuclear catalytic Cu_Z centre. The Cu_Z centre is a novel μ_4-sulphide-bridged tetranuclear Cu cluster ligated by seven His ligands and is the site of N_2O reduction.



Overall structure of a monomer of *Ac*N_2OR showing two domains; a C-terminal domain that contains the Cu_A cluster (left) and an N-terminal domain that contains the catalytic Cu_Z site (right). Copper atoms are shown as yellow spheres.

isolated under aerobic conditions

Journal of Molecular Biology, 2006, 362, 55-65

Incomplete denitrification terminating with release of N_2O is a major contributor to the detrimental environmental effects of excessive fertilizer use, and consequently the application of recombinant N2O reductase (NO2R) in a suitable host is of major interest for bioremediatory applications.

Nitrous oxide reductase is inhibited under low pH, and is highly sensitive to oxygen. High O_2 concentration and low pH favours N2O as the end product.

Present emphasis is to elucidate the mechanism of N_2O reduction and on enzyme engineering through a combination of environmental chemistry and synthetic biology to develop biotechnological tools for the efficient bioremediation of N_2O emissions. (https://www.slideserve.com/cala/chapter-9-biogeochemical-cycling and PNAS, 2019, 116 (26), 12822–12827.

Demand drivers: Energy transition drives chemical demand

The energy transition is generating a wave of manufacturing activity that depends on chemicals and materials for support. New government policies and incentives have spurred investment in the energy transition of 2021 and 2022.
The Infrastructure Investment in 2021: US$70 billion to electric vehicle (EV) infrastructure and clean energy transmission.
In 2022: US Congress passed the Creating Helpful Incentives to Produce Semiconductors (CHIPS), infusing another US$469 billion in tax incentives and funding into sectors such as domestically manufactured semiconductors, lithium-ion batteries, solar panels, and other clean energy technologies, as well as the components and material inputs for these products. Healthcare is another dominant sector that drives the demand and investments.

So, while total demand for chemicals was soft in 2023, demand for chemicals and materials that are needed to support the energy transition is expected to rise in 2024 and beyond as the impact of these policies reverberates through the economy.

https://www2.deloitte.com/us/en/insights/industry/oil-and-gas/chemical-industry-outlook.html

Impact on demand

How might the energy transition impact overall demand in 2024? In 2023, an estimated US$2.8 trillion was invested globally in energy, with more than 60% invested in clean energy technology, such as renewables, EVs, and battery storage.

Persistent, Bioaccumulative, and Toxic (PBT) Chemicals:

1.Persistent (P):

A chemical is considered **persistent** if it resists degradation in the environment (through processes such as hydrolysis, photolysis, or biodegradation). It typically remains in soil, water, air, or organisms for long periods, leading to long-term exposure.

2.Bioaccumulative (B):

A chemical is **bioaccumulative** if it tends to build up in the tissues of living organisms (often in fatty tissues) over time, rather than being excreted or metabolized efficiently. Bioaccumulation can occur through food chains, leading to higher concentrations in predators (biomagnification).

3.Toxic (T):

A chemical is **toxic** if it causes harmful effects to organisms, including humans, at relatively low concentrations. Toxicity may involve carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption, or organ-specific damage.

In short, **PBT chemicals** are long-lasting in the environment, accumulate in organisms, and are harmful to health or ecosystems (e.g. polychlorinated biphenyls (PCBs), dioxins, and certain pesticides (like DDT)

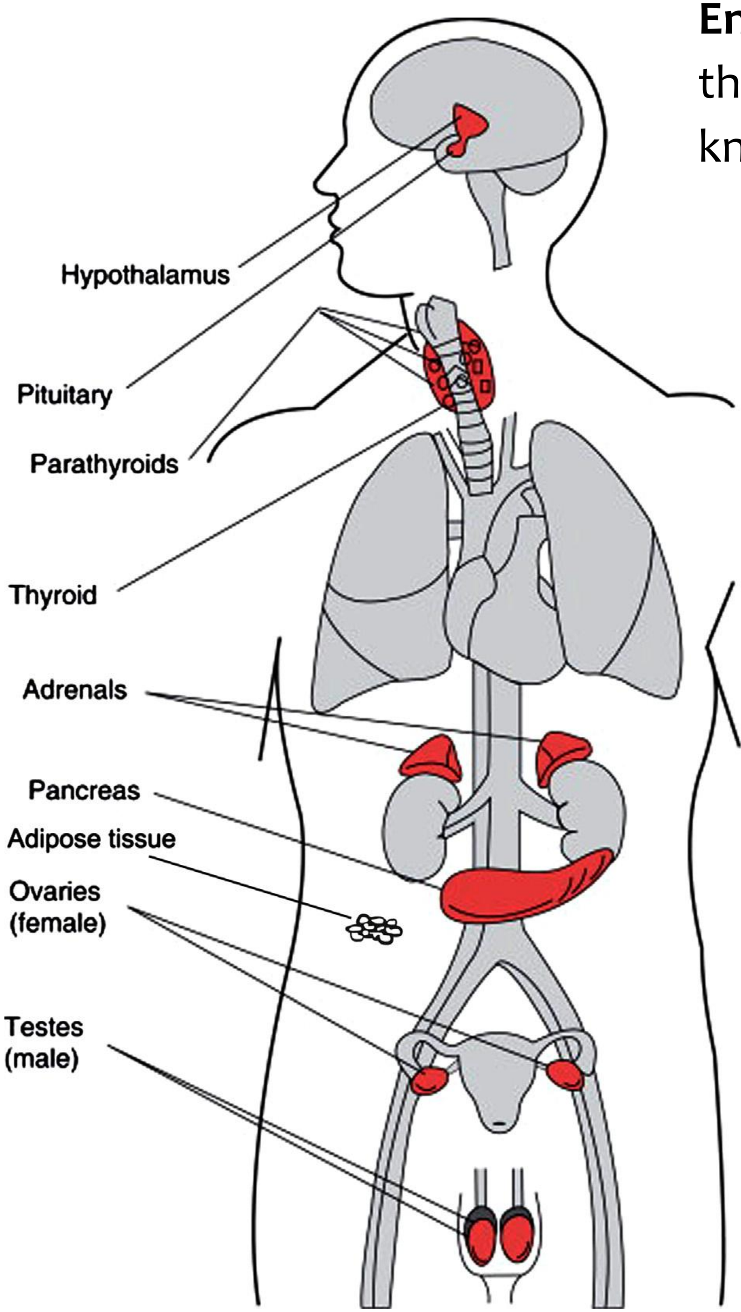
3. Toxicity (T): A chemical is considered **toxic** if it causes harmful effects at low concentrations.

- **REACH (EU criteria):**
- Chronic **NOEC (No Observed Effect Concentration)** for aquatic organisms < **0.01 mg/L**
- Evidence of **carcinogenicity, mutagenicity, or reproductive toxicity (CMR, category 1A or 1B)**
- Evidence of **chronic toxicity** in mammals

EPA stands for the **United States Environmental Protection Agency**

U.S. EPA Criteria (similar but slightly different focus):

- **Persistence:** Half-life in water, sediment, or soil consistent with above thresholds.
- **Bioaccumulation:** BAF or BCF > **1,000** often considered bioaccumulative.
- **Toxicity:** Based on **acute and chronic toxicity data**, including potential for endocrine disruption, neurotoxicity, carcinogenicity, etc.



Endocrine disruptors are natural or man-made chemicals that may mimic or interfere with the body's hormones, known as the endocrine system

The Endocrine System:

Endocrine glands, distributed throughout the body, produce the hormones that act as signalling molecules after release into the circulatory system. This controls many biological processes like normal growth, fertility, and reproduction. Hormones act in extremely small amounts, and minor disruptions in those levels may cause significant developmental and biological effects.

Encyclopedia of Toxicology, 2014 (third ed.) Volume 2, Page 332 http://dx.doi.org/10.1016/B978-0-12-386454-3.00377-8

The chemical pollutant challenge for humanity: Discussion and questions:

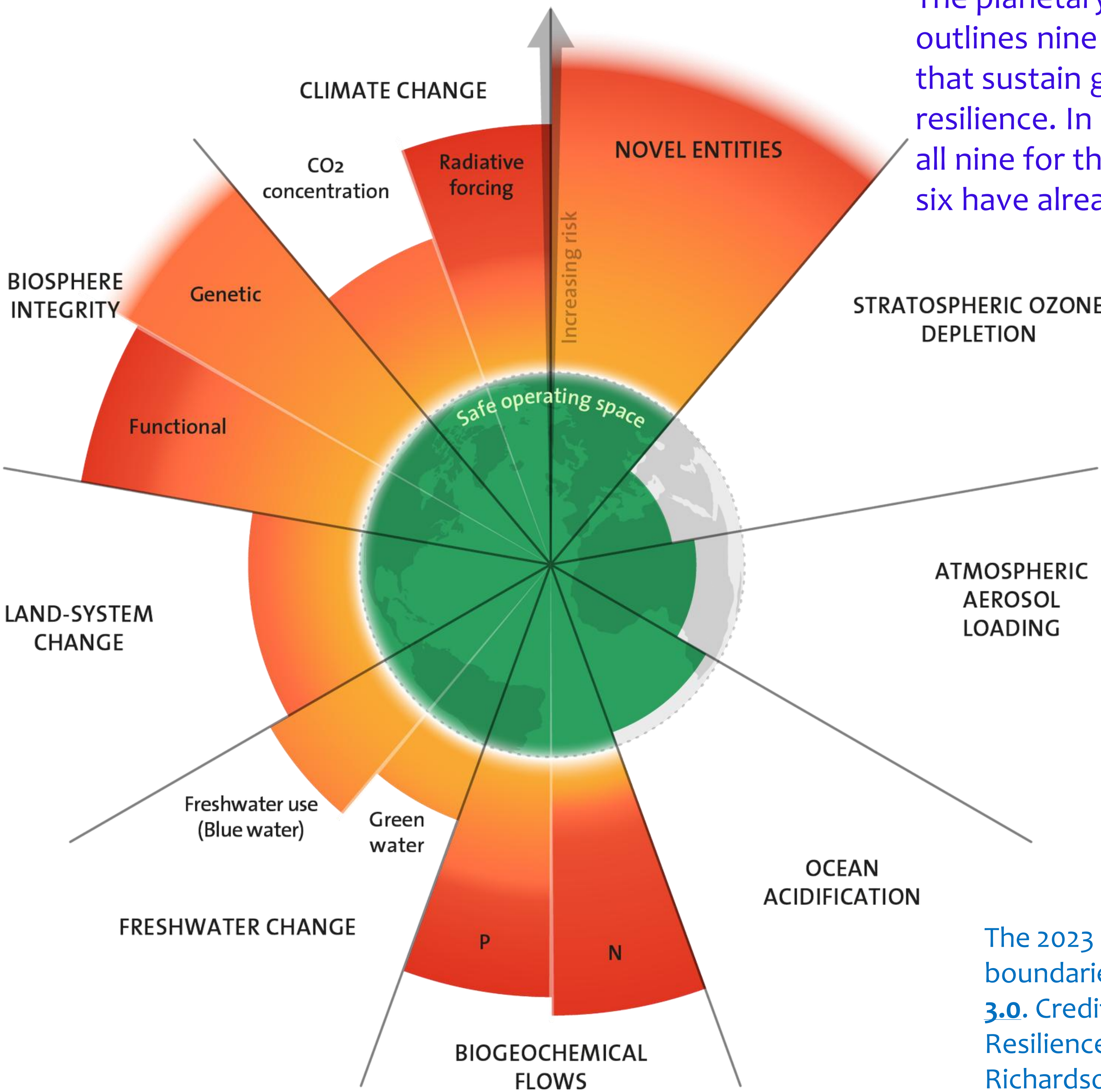
methodological constraints and the varying susceptibility to toxins among humans, only a few reports are showing direct quantitative, whole life-span analyses of fatalities attributed to environmental pollutants. Nevertheless, compilation of the substantial evidence of the health burden caused by chemical pollution both shows and predicts the impairment of normal human life expectancy by direct exposure to pollutants, food contamination and fertility decline.

The concept of the planetary boundary is so pertinent in this regard.

It is likely humanity is approaching a dangerous tipping point due to our release of geogenic, anthropogenic synthetic chemicals. This raises the issue that, as yet, no scientifically credible estimate has been made of humanity's combined chemical impact on the Earth and on human health. This gap exists as the 'global boundaries' chart was unable to include a boundary for chemical emissions because of a lack of data and a suitable methodology.

Consequently, humanity is unaware of how near or far it is from exceeding the Earth's capacity to 'absorb' or safely process our total chemical releases, which grows by many billions of tonnes with each passing year. This represents a potential catastrophic risk to the human future and merits global scientific scrutiny on the same scale and urgency as the effort devoted to climate change.

The planetary boundaries framework outlines nine key Earth system processes that sustain global stability and resilience. In 2023, scientists quantified all nine for the first time and found that six have already been transgressed.



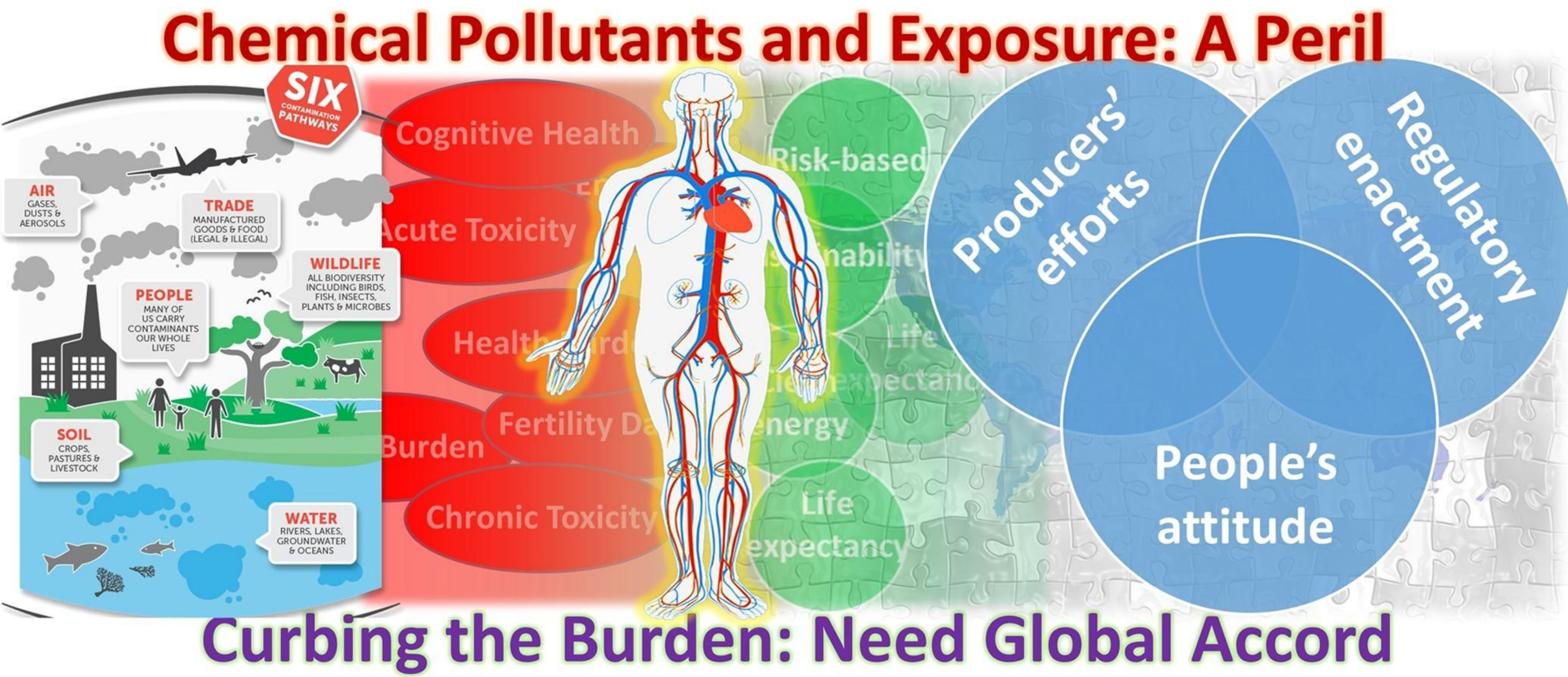
Emerging contaminants (ECs) are a diverse group of unregulated pollutants increasingly present in the environment. These contaminants, including pharmaceuticals, personal care products, endocrine disruptors, and industrial chemicals, can enter the environment through various pathways and persist, accumulating in the food chain and posing risks to ecosystems and human health.

Emerging contaminants pose significant risks to wildlife and ecosystems by disrupting animal hormones, causing genetic alterations that diminish diversity and resilience, and altering soil nutrient dynamics and the physical environment.

Ecotoxicology and Environmental Safety 278 (2024) 116420

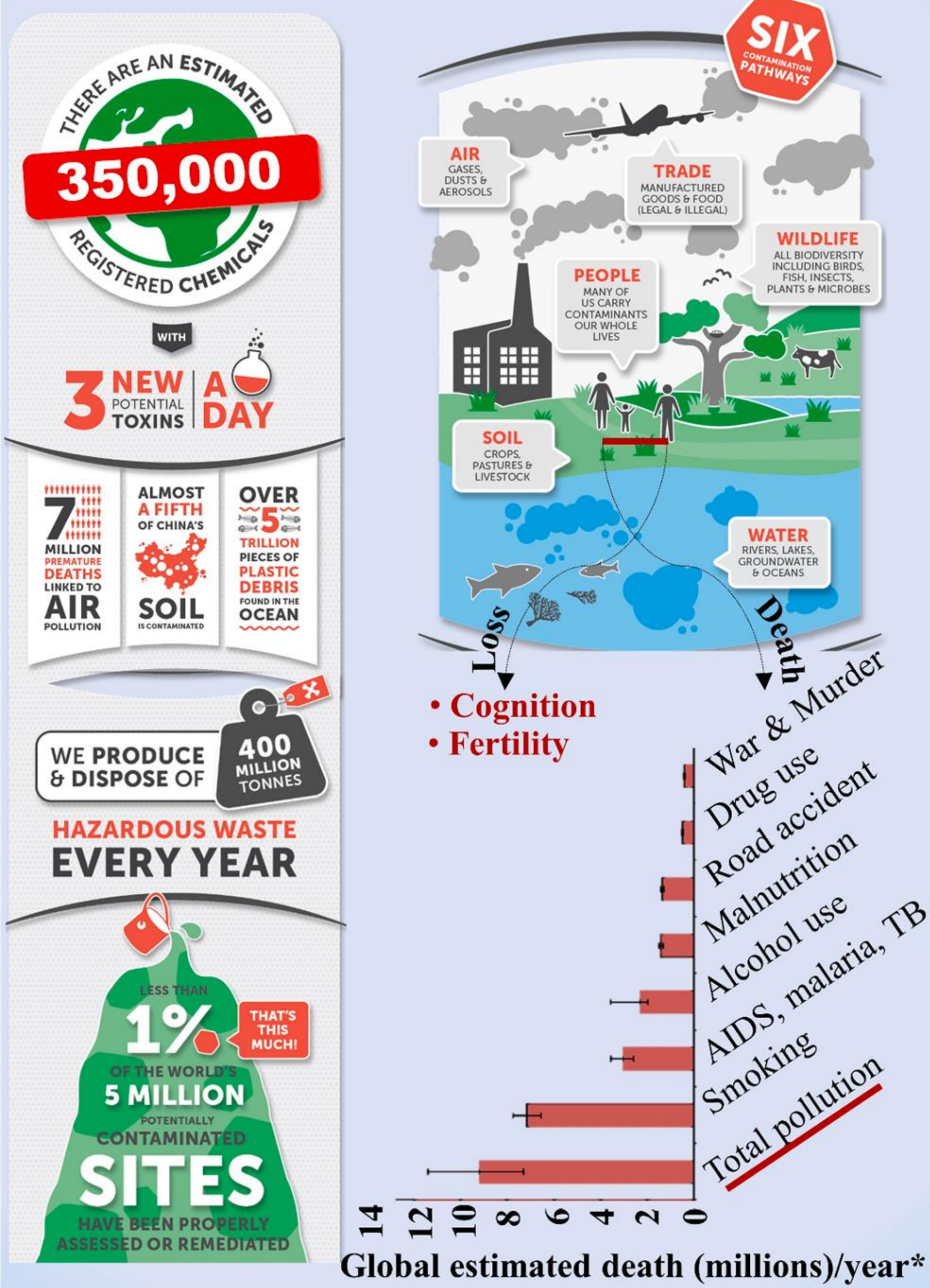
One Health is a collaborative, multisectoral, and transdisciplinary approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognises that the health of humans is interconnected with the health of animals and the environment, and therefore requires integrated efforts from medical, veterinary, agricultural, and environmental sciences to prevent and manage complex health challenges effectively.

Chemical pollution poses an escalating threat to humanity—undermining male fertility, cognitive health, and food security—yet critical knowledge gaps remain about the risks from chemical dispersal, mixtures, and recombination in the environment.



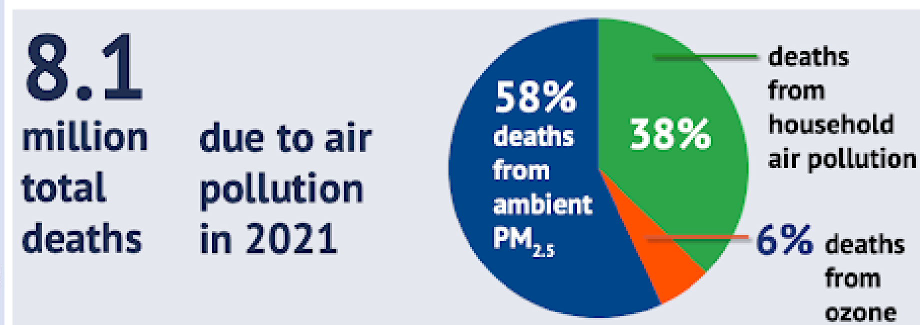
Environment International, 2021, 156, 106616

Chemical pollutant: Global PICTURE



Chemical pollution moves through six major pathways—soil, air, water, wildlife, people, and trade—causing severe environmental and health impacts. Pollution-related deaths, estimated at 9–10 million annually, exceed those from any other major risk factor, far surpassing the 2 million global deaths from COVID-19 in its first year (WHO 2021).

Fig. 1. The number of "silent" deaths caused by environmental pollution exceeds any other widely recognized risk factor.



https://healthpolicy-watch.news/air-pollution-kills-a-child-every-minute/, **2024 data.**

[Environment International 156 (2021) 106616]

International regulation of toxic chemicals began with treaties such as the Vienna Convention for the Protection of the Ozone Layer (1985) and the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal (1989). These were followed by the Stockholm Convention on Persistent Organic Pollutants (2001) and the Minamata Convention on Mercury (2013). Among these, the Stockholm Convention is the most comprehensive one for POP, entering into force on 17 May 2004. However, its progress has been modest: of an estimated 350,000 synthetic chemicals in circulation, only 26 (<0.01%) have been banned, with just nine additional substances currently under review. in Annexes B and C.

[http://www.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx (access: 05 February, 2021)] **[Environment International 156 (2021) 106616]**

Pollution impacts on cognitive health:

Recent studies have revealed significant impacts of various industrial pollutants on the human brain and central nervous system. Fine particles, designated PM10, PM2.5, or ultrafine PM0.1, which commonly arise from industrial waste, ash and the combustion products of fossil fuel, can migrate into the brain through the olfactory bulb, the neural structure responsible for the sense of smell. Ultrafine particles also produce cytokines that inflame the lungs or the nasal epithelium and further attack brain cells.

- A 20-year meta-study in China found that children exposed to **fluoride**-contaminated drinking water had a fivefold higher incidence of impaired cognitive performance compared to unexposed children (Tang et al., 2008).
- In vivo studies indicate that per- and poly-fluoroalkyl substances (**PFAS**) are potentially neurotoxic to human neuroblastoma cells. PFAS exposure can alter methylation regulation in brain-derived neurotrophic factor, potentially contributing to behavioural problems (Guo et al., 2017).

Environ. Int. 2021, 156, 106616

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]

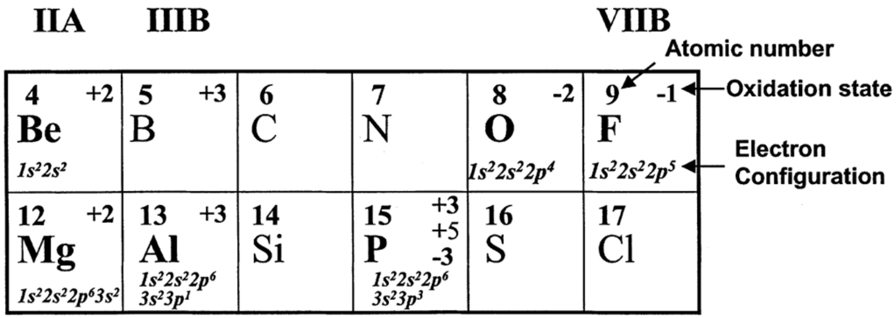
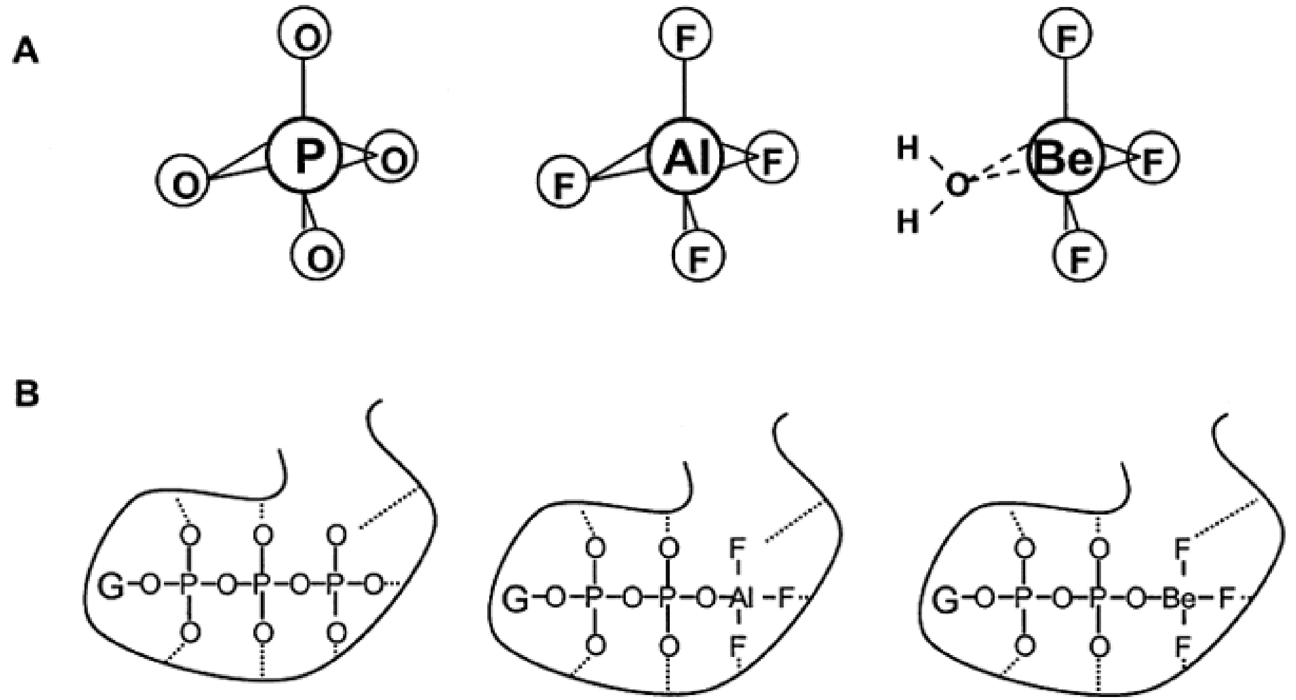
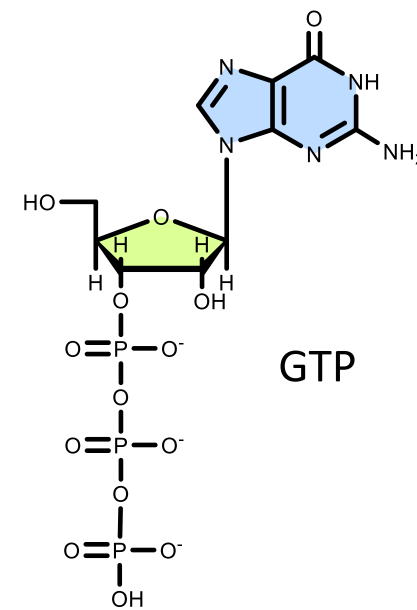


Figure 1. A section of the Periodic Table. For the elements related to phosphate or its analogs, their symbols, atomic numbers, oxidation states, and electron configurations are highlighted.

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.





GTP

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:

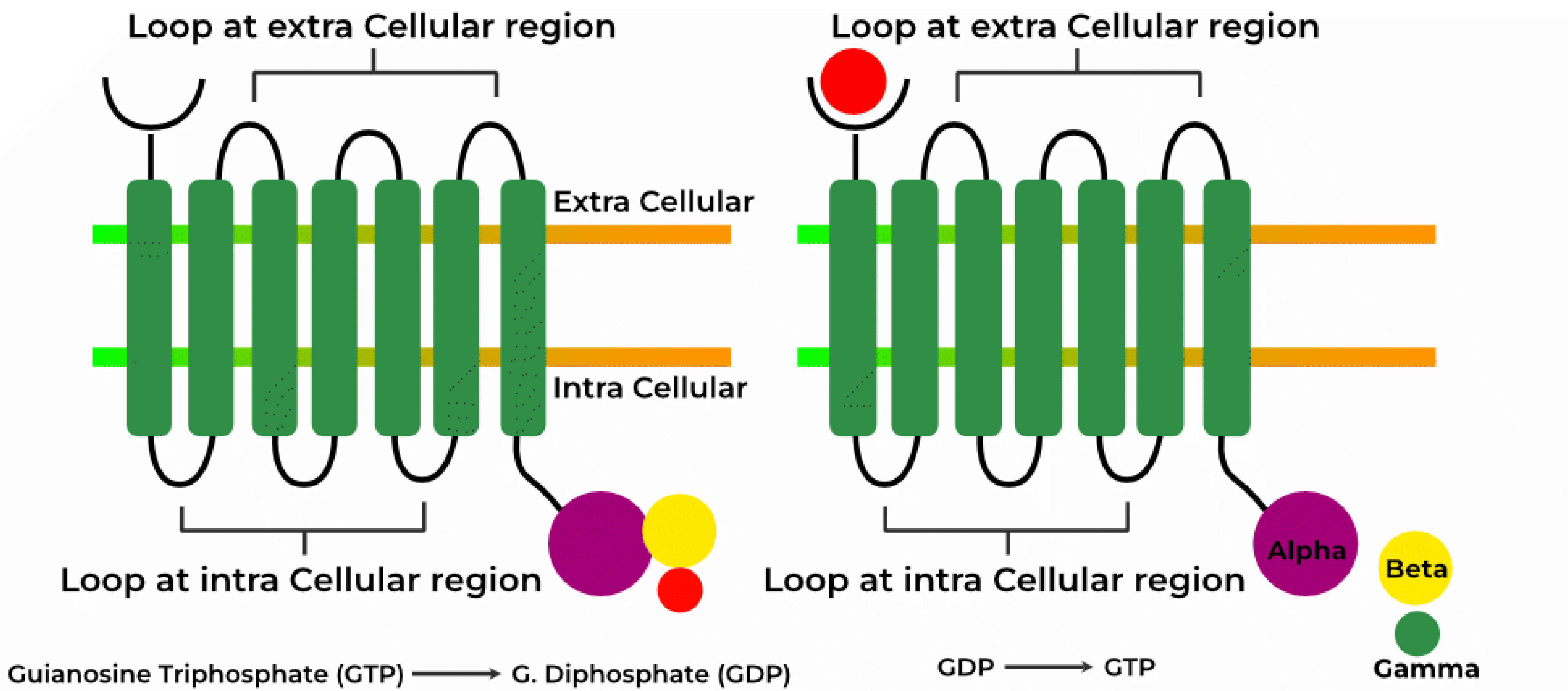
- G protein normally binds GDP permanently.
- **AlF_4^- (or BeF_3^-)** binds to the GDP phosphate.
- This mimics the presence of the γ-phosphate of GTP.
- As a result, the G protein adopts the **active G • GTP-like conformation**.

- 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.

Only eukaryotes, including yeast, choanoflagellates, and mammals, have G protein-coupled receptors. Light-sensitive substances, smells, pheromones, hormones, and neurotransmitters are among the ligands that bind to and activate these receptors. Their sizes range from tiny molecules to peptides to big proteins. Numerous disorders involve G protein-coupled receptors. [https://www.geeksforgeeks.org/biology/g-protein-coupled-receptor/]



Farley et al. (Science, 1983, 222, 330-332) made the first observation that F^- directly increases the proliferation and alkaline phosphatase activity of avian osteoblastic cells in culture. The optimal F^- concentration for this action is about 10 mM/L, which is within the plasma fluoride level in osteoporosis patients receiving F^- treatment (5-30 mM/L).

Fluorosis is an occupational disease among workers in the Al-smelting industry. A high rate of osteosclerosis occurs in the miners of cryolite (Na_3AlF_6). Studies suggest that F^- alone did not affect cell proliferation. In the presence of Al, F^- forms AlF_4^-, which structurally resembles phosphate (PO_4^{3-}) and binds to G-proteins at phosphate sites.

Mimicking phosphate (γ-phosphate of ATP/GTP):

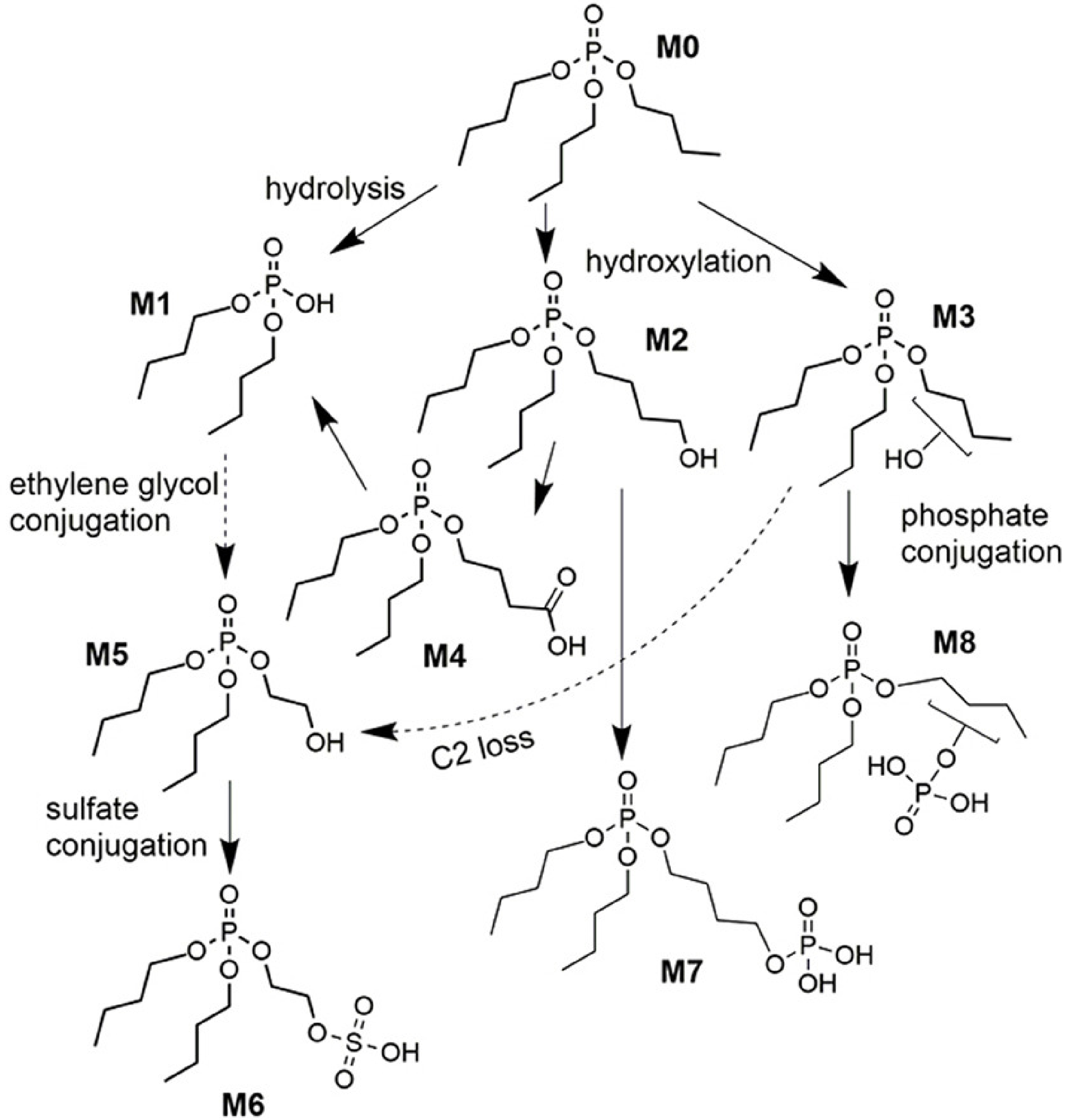
Enzymes and G-proteins contain a binding pocket for the γ-phosphate of ATP or GTP, whose binding and hydrolysis regulate their on/off switch. AlF_4^- can occupy this pocket in place of the γ-phosphate, and because of its structural similarity to PO_4^{3-}, the protein cannot distinguish the difference. As a result, AlF_4^- "tricks" enzymes and G-proteins into adopting the active state without actual ATP or GTP hydrolysis, thereby hijacking normal signalling pathways and promoting uncontrolled growth.

Tri-n-butyl phosphate (TBP) detected in all environmental matrices.

TnBP, when metabolized in the earthworm (*Perionyx excavates*), does not show overt toxicity, unlike in C. elegans:

TBP **tributyl phosphate:**
plasticizer
industrial solvent
anti-foaming agent

metabolic
pathway



Metabolism of TBP in the earthworm, Perionyx excavatus

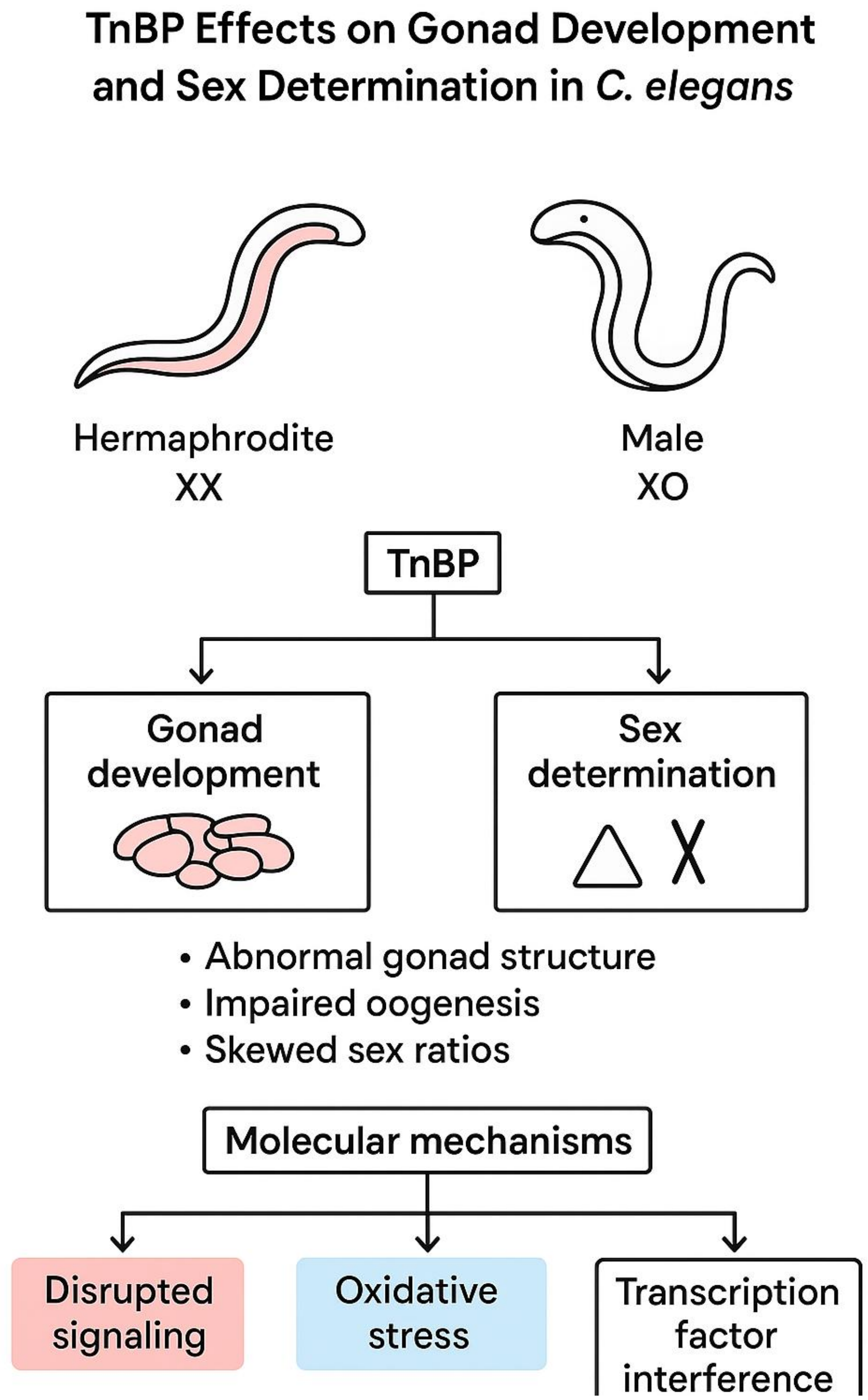
Reproductive toxicity, Estrogen-disrupting effects of TnBP
Ecotoxicol. Environ. Safety 2021, 227, 112896; Environ Pollut. 2018, 234, 389-395

The organophosphate chemical triisobutyl phosphate (TnBP) was used as a case study for exploration of the approach, as its emission to the environment was expected to be inevitable when used as a flame retardant. TBP is also used as a highly polar solvent. It is mainly used as an antifoaming agent in various aqueous systems where it can destroy foam and act as a foam inhibitor.

Effects on Sex Determination & Reproduction

- ***C. elegans*** normally has two sexes: **[Ecotoxicology and Environmental Safety 227 (2021) 112896]**
  - ✓ **Hermaphrodites (XX)** – produce both sperm (early) and oocytes (later). This allows self-fertilization, though they can also mate with males. Represent about **99.9%** of the natural population.
  - ✓ **Males (XO)** – produce only sperm.
- TnBP exposure can disturb **sex-specific gene regulation**, leading to:
  - ✓ Skewed sex ratios (altered proportion of males vs. hermaphrodites).
  - ✓ Impaired sperm or oocyte function → reduced fertility.

Likely mechanisms: disruption of **hormone-like signalling, oxidative stress,** and interference with **transcription factors** (e.g., TRA, FEM, HER-1: proteins that control gene expression by binding to specific DNA sequences and regulating the conversion of DNA into RNA--transcription) that govern sex fate.



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Metabolism of TnBP in *Perionyx excavates*:

Studies indicate that *Perionyx excavatus* can metabolize TBP through **phase I and phase II detoxification pathways**, likely involving **hydrolysis and conjugation reactions**. These processes convert TBP into **less harmful metabolites** that can be excreted, thereby preventing accumulation and toxic effects. Unlike in C. *elegans*, where TnBP induces oxidative stress, apoptosis, and DNA damage, the earthworm's **efficient biotransformation capacity** appears to mitigate toxicity. This highlights species-specific differences in organophosphate metabolism and suggests that *P. excavatus* may tolerate environmental TBP exposure without significant impairment.

The bioaccumulation potential of TnBP in earthworm-soil ecosystem is low at 10 mg kg^{-1} and 50 mg kg^{-1} of TBP. Various phase I and phase II biotransformation products were identified in earthworms. Phase I metabolites include DBP, TBP-OH and TBP-OOH. Novel phase II metabolites were identified: ethanol DBP and its sulfate conjugate, and the phosphate conjugate of hydroxylated TBP, suggesting a unique enzyme system in *P. excavatus* for xenobiotic metabolism.

For hydrophobic xenobiotics, the major detoxification pathway is by bonding of highly polar compounds, thus making them hydrophilic, which can then be easily excreted.

Environmental Pollution; 2018, 234, 389-395

Tri-n-butyl phosphate (TnBP) Exposure:

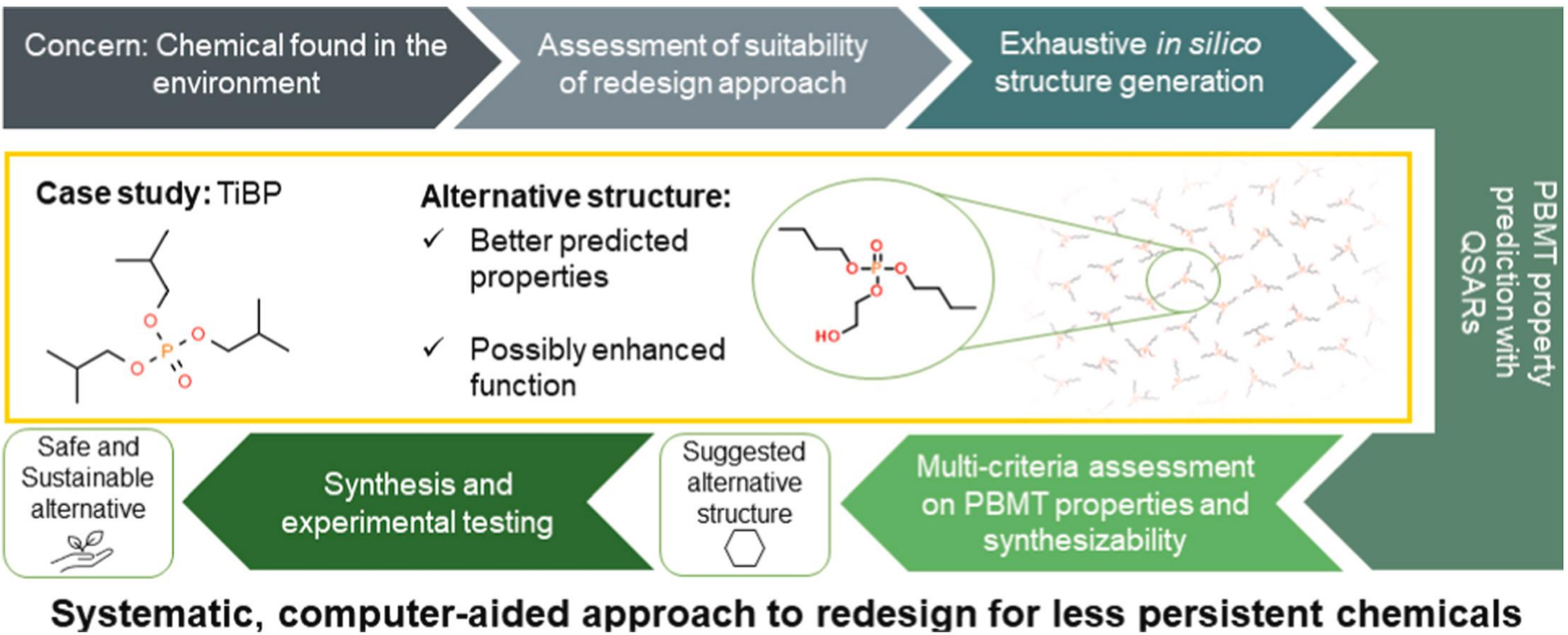
The production volume of TnBP is estimated at 3,000 – 5,000 tonnes worldwide. The major uses of TnBP in industry are as a component of aircraft hydraulic fluid and as a solvent for rare earth extraction and purification. No current consumer product uses of TnBP have been identified. The primary occupational exposure to TnBP results from its use as an ingredient in aircraft hydraulic fluids. The potential for exposure to TBP varies with the type of maintenance activity but is almost always via a dermal pathway.

$$\boxed{BCF = \frac{Concentration_{Biota}}{Concentration_{Water}}}$$

A bioconcentration factor (BCF) is a measure of how much a substance accumulates in an organism's tissues to the concentration of the substance in the surrounding environment.

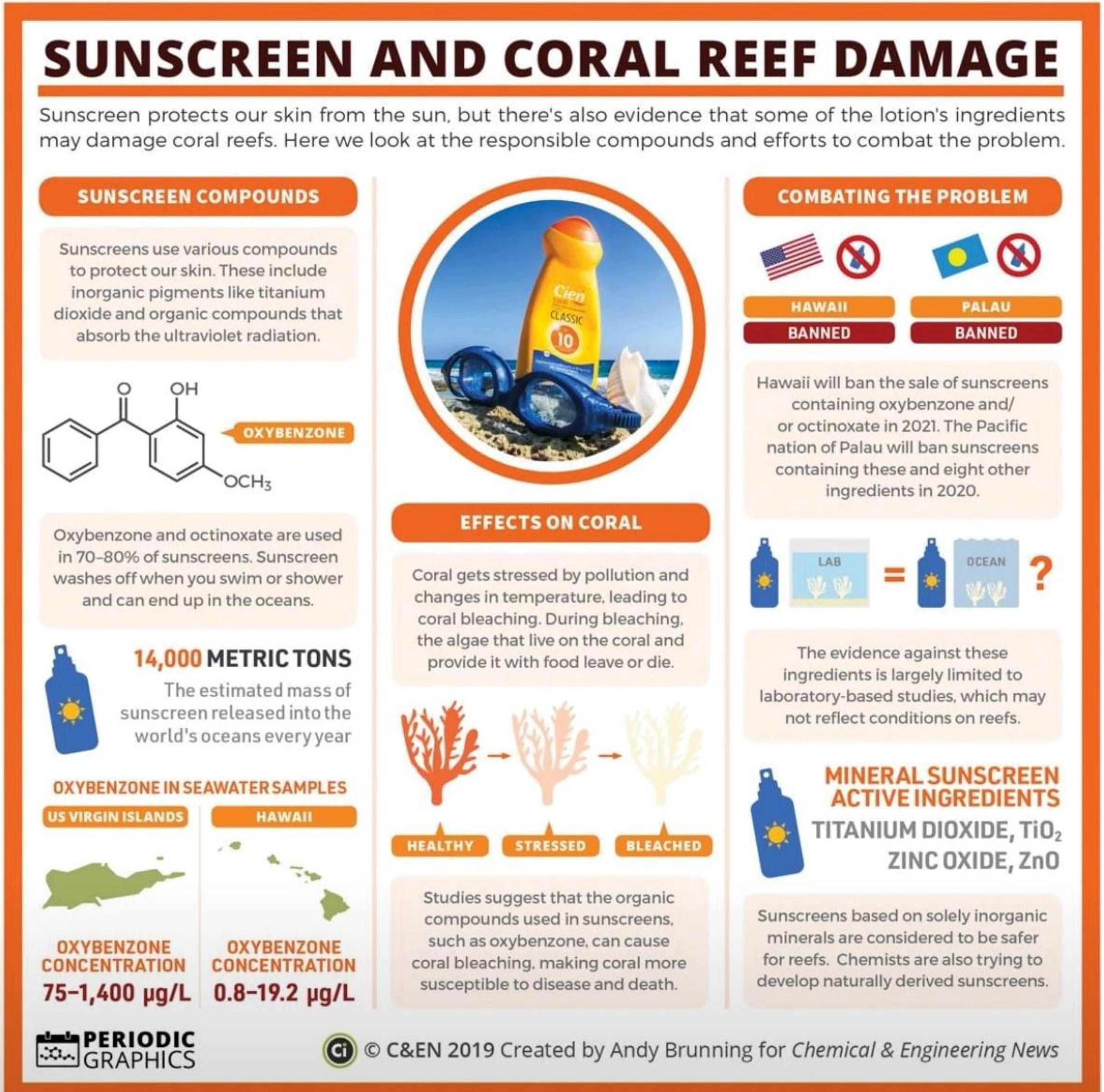
BCF can also be related to the octanol-water partition coefficient, K_{ow}. The octanol-water partition coefficient (K_{ow}) is correlated with the potential for a chemical to bioaccumulate in organisms and can be predicted via software for structure-activity relationship (SAR) or through the linear equation https://www.elsevier.com/en-in/industry/4-key-chemicals-industry-trends

Chemosphere, 2022, 296, 134050



Quantitative structure-activity relationship

Persistence (P), bioaccumulation (B), mobility (M) and toxicity (T) potency properties



Journal of Science Policy and Governance, 2024, 24, https://doi.org/10.38126/JSPG240106

Science, 2022, 376, 644-648

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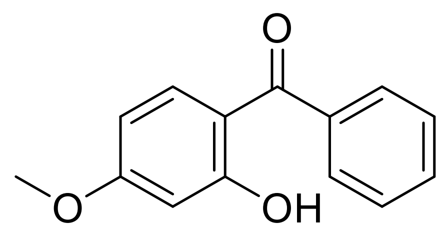
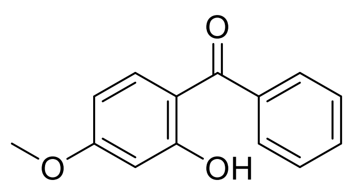
Oxybenzone



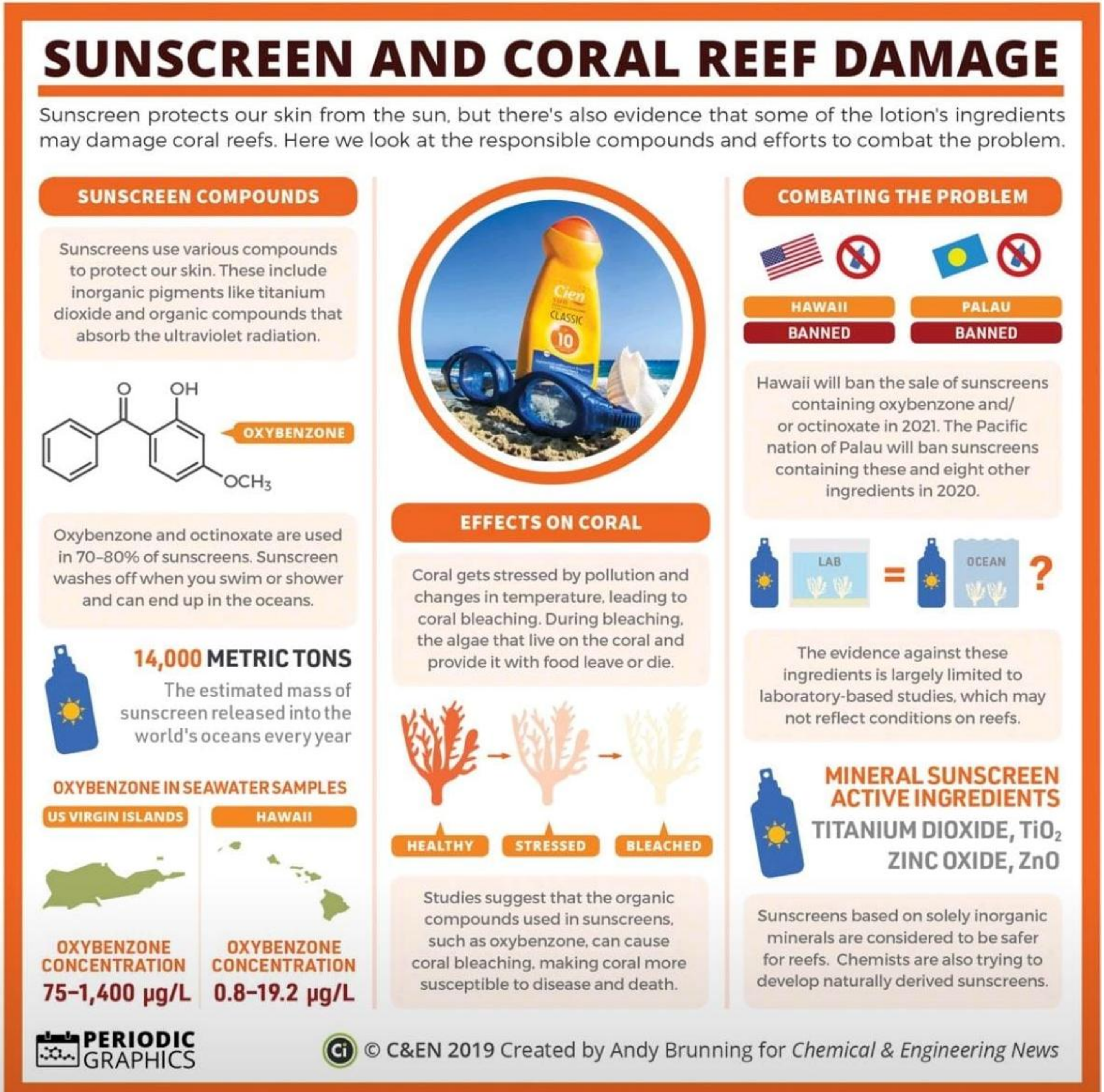
The concentration of oxybenzone at a coral reef can vary widely, depending on factors such as tourist activity and water conditions. Coral-bleaching events on Australia’s Great Barrier Reef, for example, have been linked more closely to trends in water temperature than to shifts in tourist activity. “Mass bleaching happens regardless of where the tourists are,” Hughes says. “Even the most remote, most pristine reefs are bleaching because water temperatures are killing them.”

The metabolic products of oxybenzone-based sunscreen threaten the survival of bleached corals, which have already lost their symbiotic algal partners that could have helped minimize the toxic effects of the chemicals. [Science, 2022, 376, 578-579]

Oxybenzone



A possible relaxation mechanism is the rotation of excited OH groups toward the bulk (water or aq. phase) and the formation of a hydrogen bond after which energy dissipation occurs rapidly due to the increased anharmonicity of the OH vibrational potential. [PNAS, 2013, 18780-18785]



Journal of Science Policy and Governance, 2024, 24, https://doi.org/10.38126/JSPG240106

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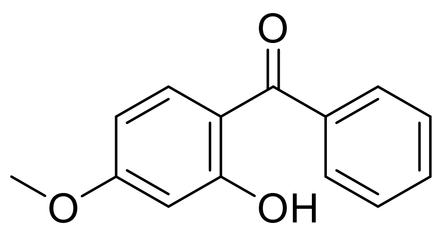

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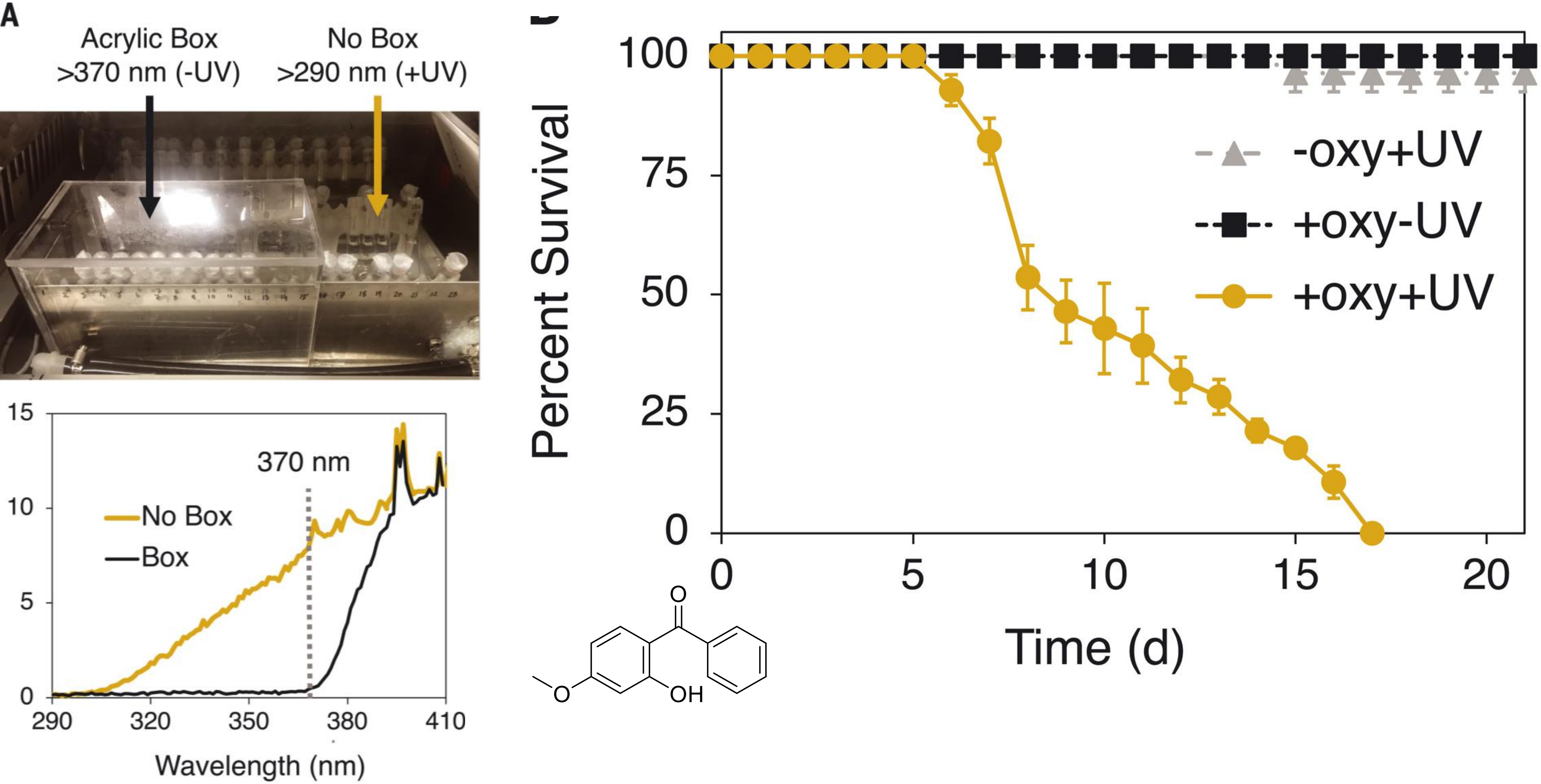
Symbiotic anemones engage in mutually beneficial relationships, primarily with fish and crustaceans, where both organisms benefit from the interaction. One common example is the relationship between clownfish and sea anemones, where the anemone provides protection and a safe haven for the clownfish, while the clownfish helps to clean the anemone and provides it with nutrients.

Molecular Phylogenetics and Evolution
Volume 56, Issue 3, September 2010, Pages 868-877

Clownfish hiding within the anemone in Seacoast Science Center tank.

https://www.seacoastsciencecenter.org/2025/01/30/send-in-the-clowns/

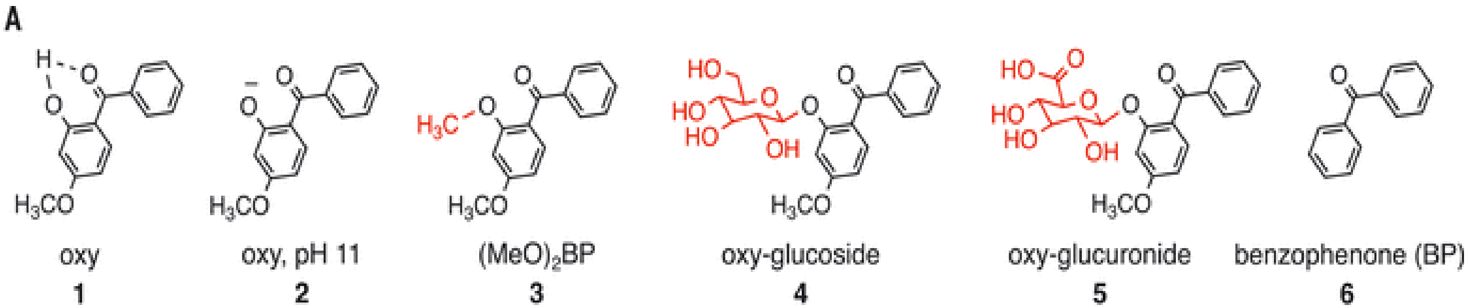


We exposed symbiotic anemones to 8.8 mM (2 mg/liter) oxybenzone in artificial seawater at 27°C in a solar simulator that approximates the 24-hour diurnal sunlight cycle. Mortality was 100% within 17 days. By contrast, negligible mortality was observed over 21 days when exposed to simulated sunlight without oxybenzone or to 8.8 mM oxybenzone without UV light.

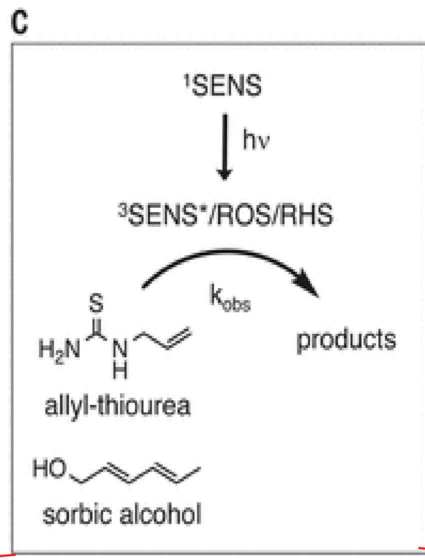
Science, 2022, 376, 644-648

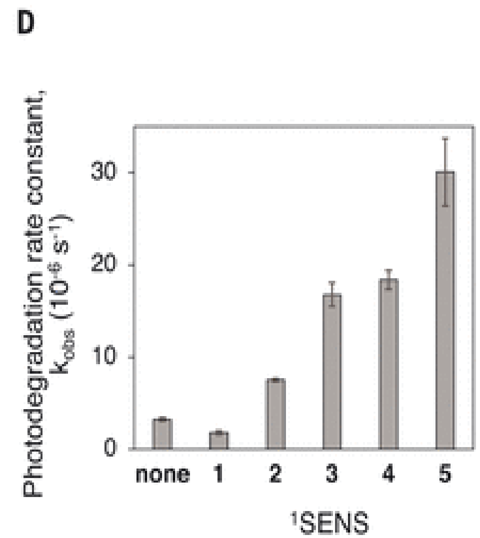
Conversion of oxybenzone sunscreen to phototoxic glucoside conjugates by sea anemones and corals.

Science, 2022, 376, 644-648, DOI: (10.1126/science.abn2600)

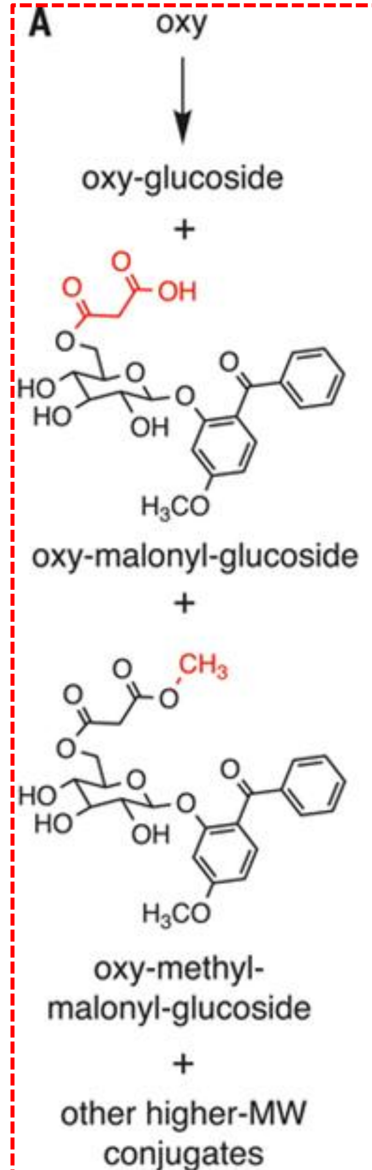


Allyl-thiourea and sorbic alcohol as probes forreactive species. ^{1}SENS, photosensitizing molecule in its ground state; ^{3}SENS*, photosensitizing molecule in its excited, triplet state.
RHS: Reactive halogen species.





Photoexcitation of sensitised molecules to excited triplet states. This excited triplet state degrades biomolecules either directly or indirectly via reactive oxygen species (ROS)and/or reactive halogen species (RHS)



Hypothesized scheme of oxybenzone (oxy) metabolism

Once in a high-energy state, the hydroxyl (–OH) group of oxybenzone can normally dissipate excess energy as heat. However, when corals metabolize oxybenzone, this protective pathway is lost. The resulting oxybenzone glucoside conjugate still absorbs light but can no longer safely release the energy. Instead, it generates reactive oxygen species (ROS), triggering a radical chain reaction that damages cellular components and tissues. In effect, corals transform oxybenzone from a sunscreen into its opposite—a phototoxin.

This suggests that corals that have bleached are even more vulnerable to the sunscreen chemical. Bleaching happens when corals respond to stresses such as increasing ocean temperatures by expelling the symbiotic algae that live in their cells and are a major source of food and energy for the corals. This exodus causes them to turn white. In the group's experiments, bleached sea anemones died about 5 times faster than healthy ones.

https://cen.acs.org/environment/pollution/Sunscreen-chemical-kills-corals-scientists/100/web/2022/05 [C&E News May 9, 2022].

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.

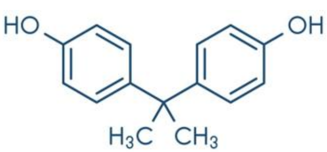
•**Perchlorate** (Used in explosives, and fireworks)

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

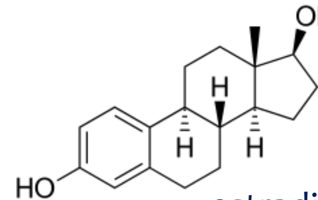
•**Phthalates** (liquid plasticizers, food packaging, cosmetics, fragrances, children's toys, and medical device tubing, Cosmetics (nail polish, hair spray, aftershave lotion, cleanser, and shampoo).

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

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

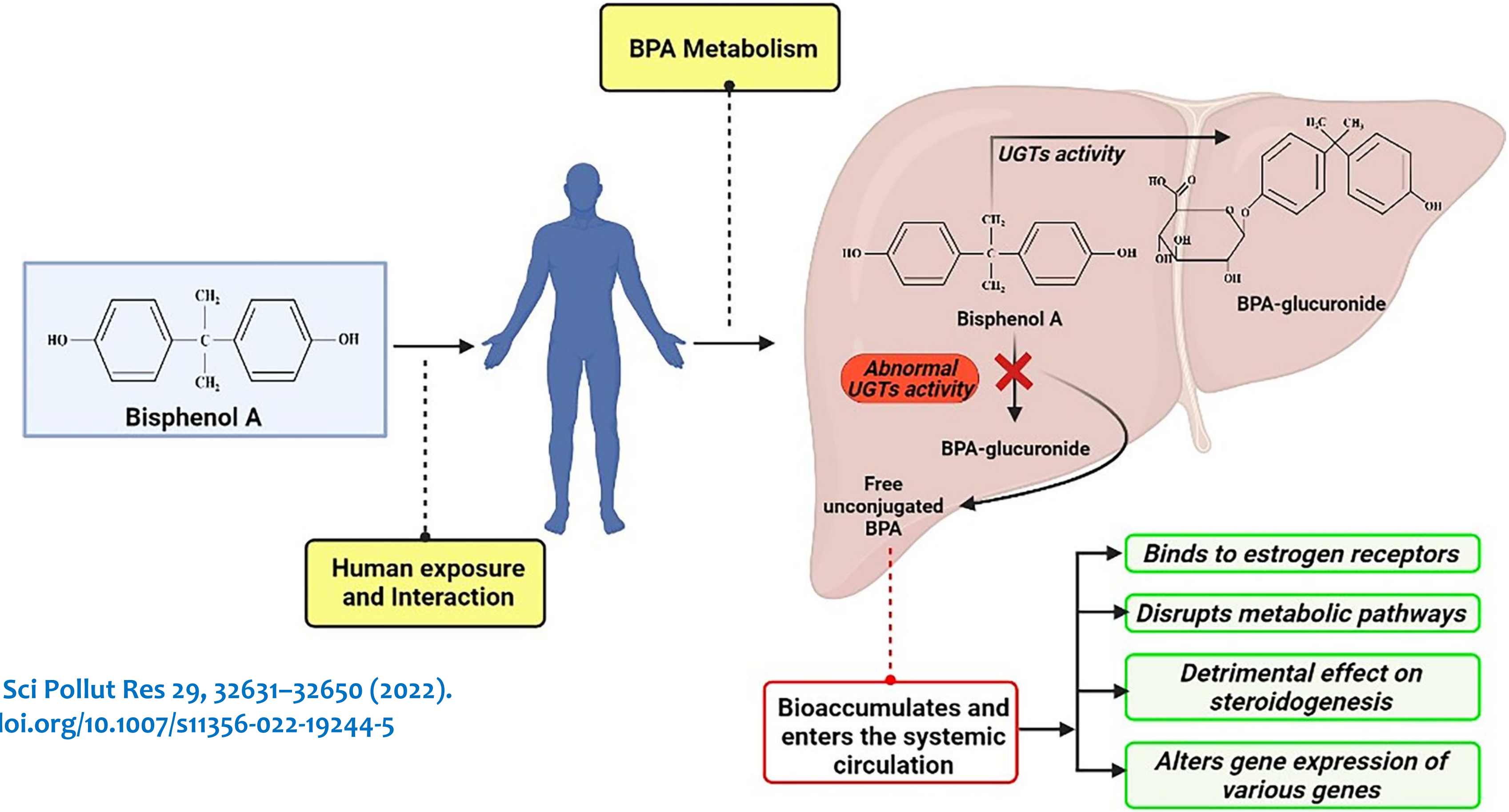
2. Impact on Fetal and Child Development

- 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).
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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.

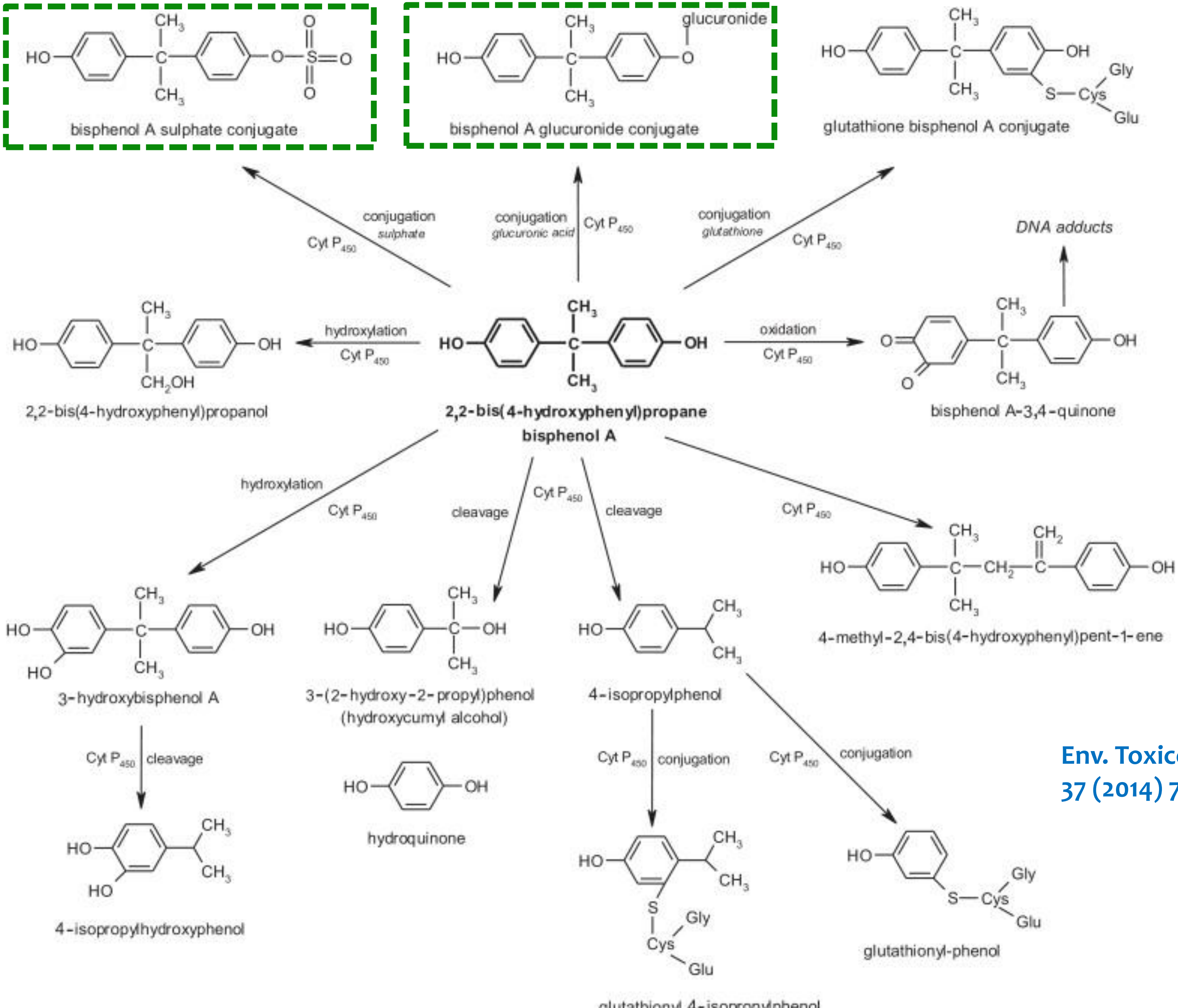
a. Glucuronidation [This is the main detoxification pathway in both adults]

- 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.

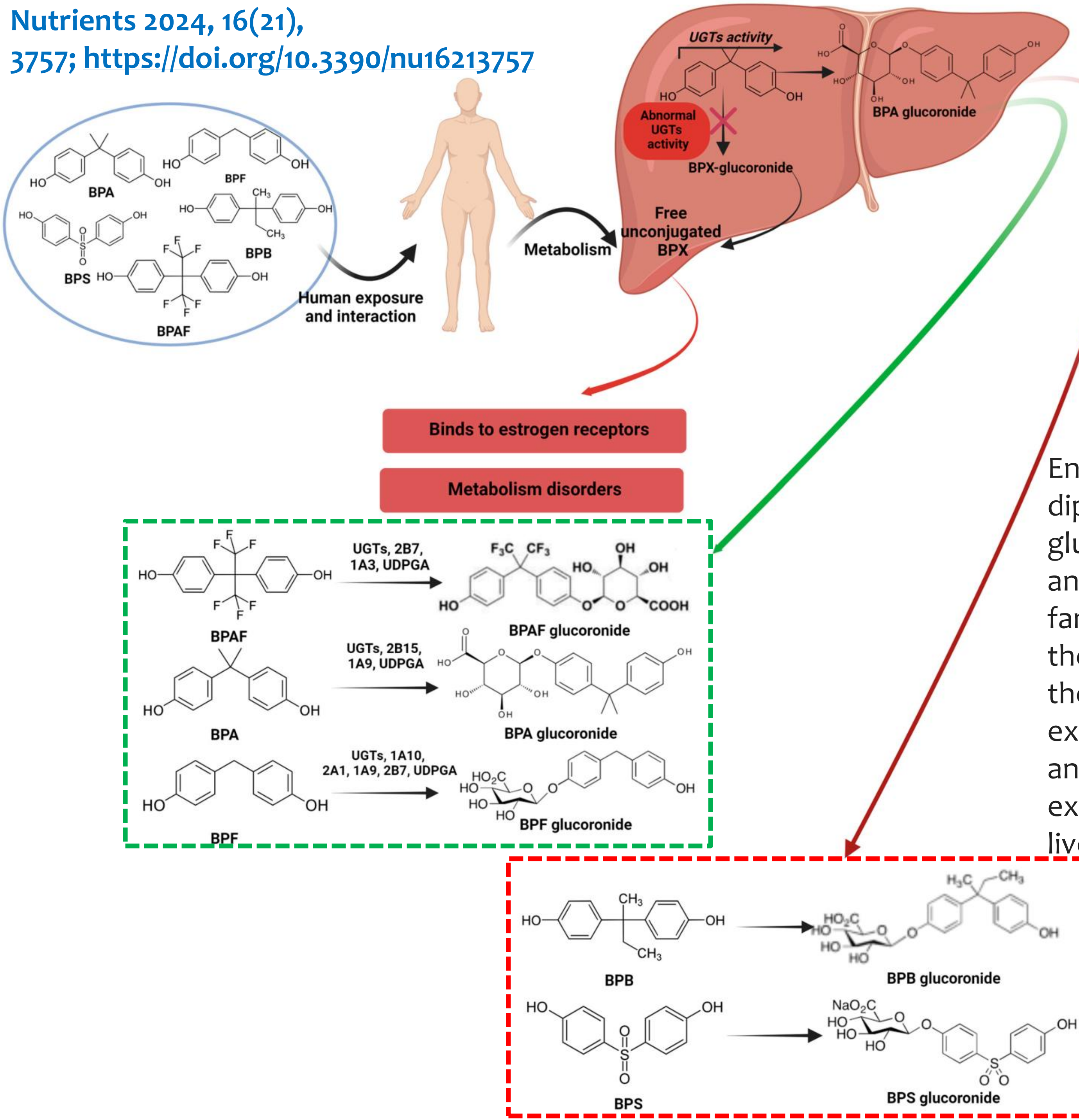
Environ Sci Pollut Res 29, 32631–32650 (2022).
https://doi.org/10.1007/s11356-022-19244-5 and AI



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.

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.

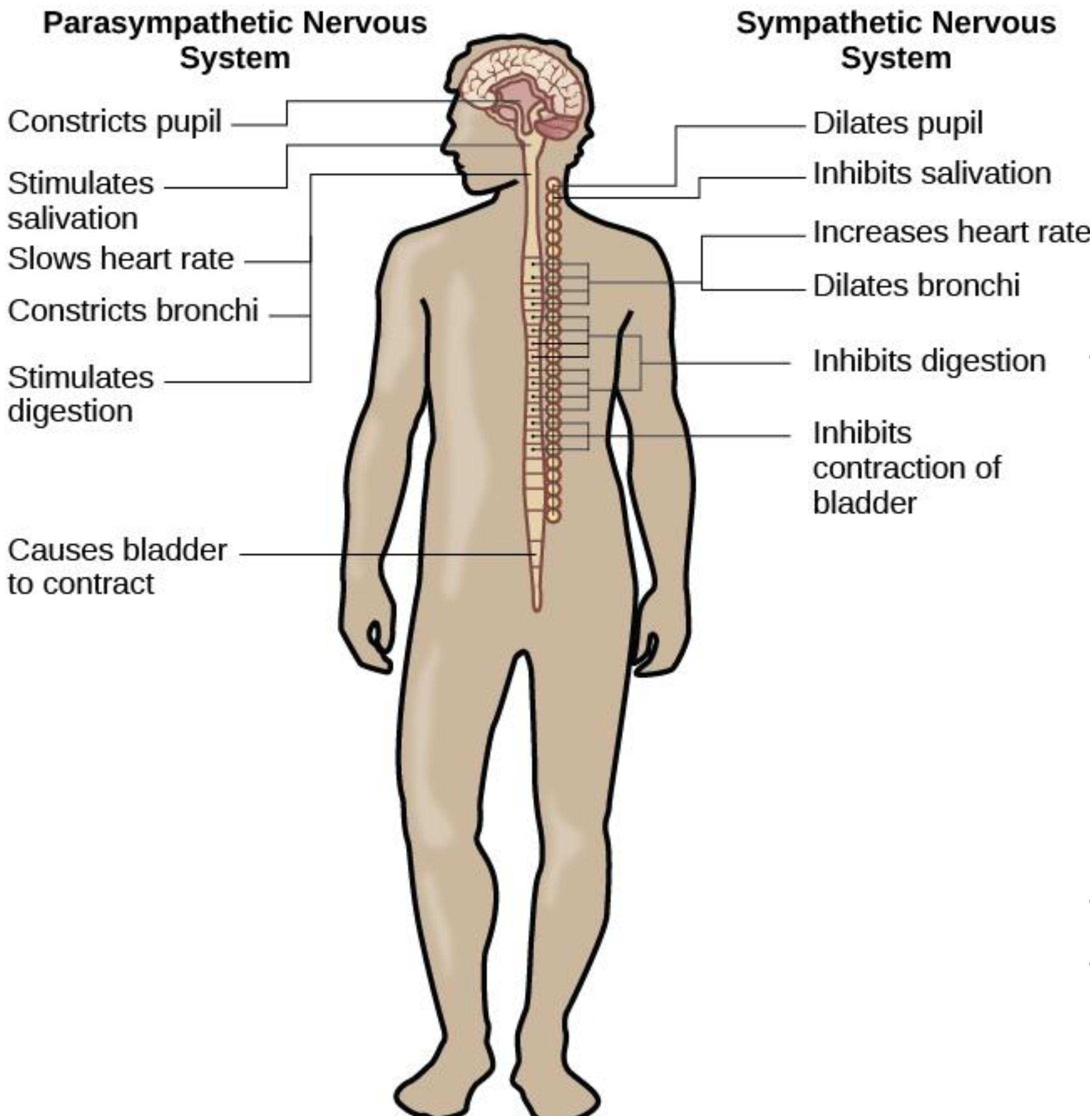
Safety by Design 7 steps

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/

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.

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.



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/

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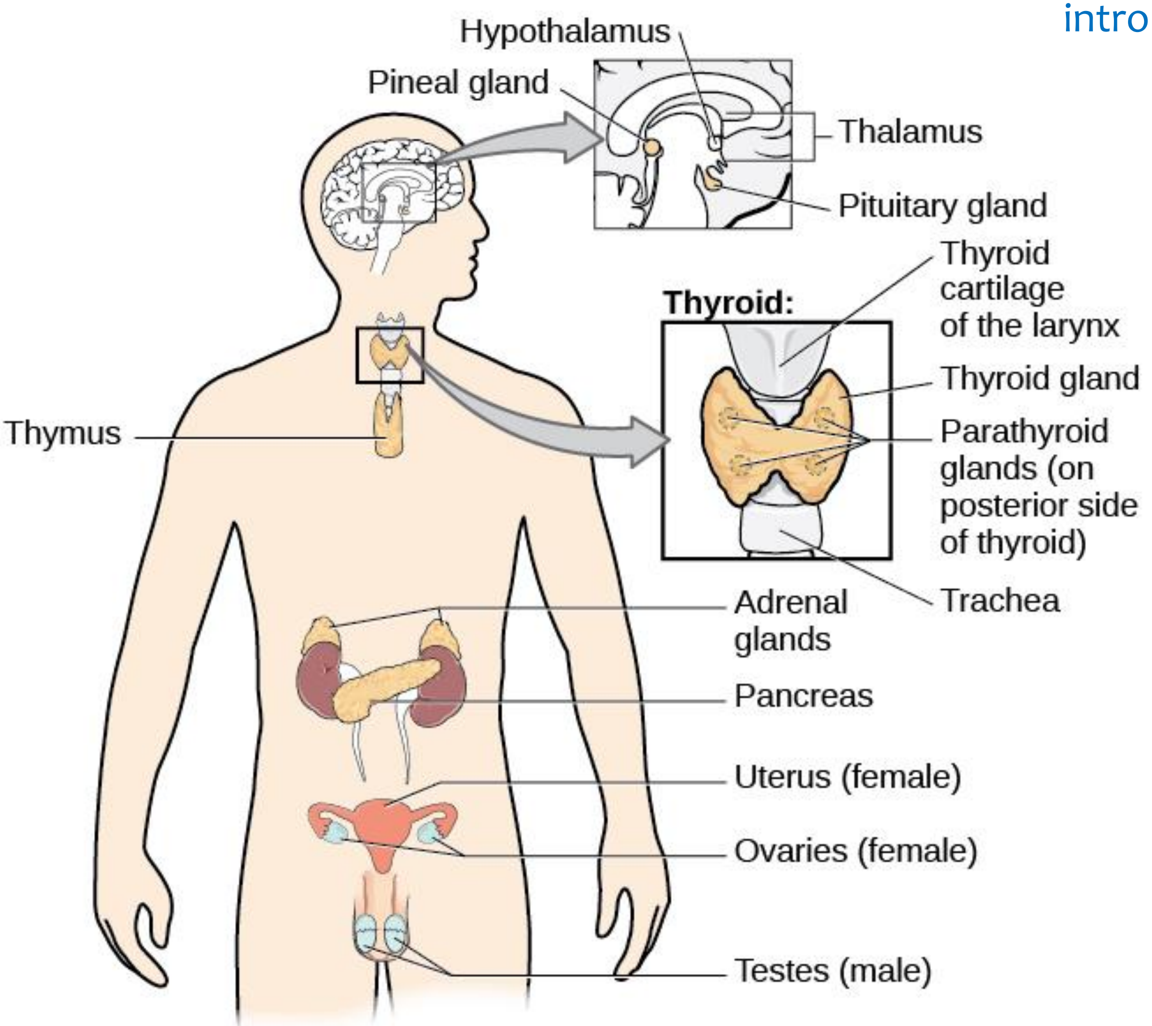
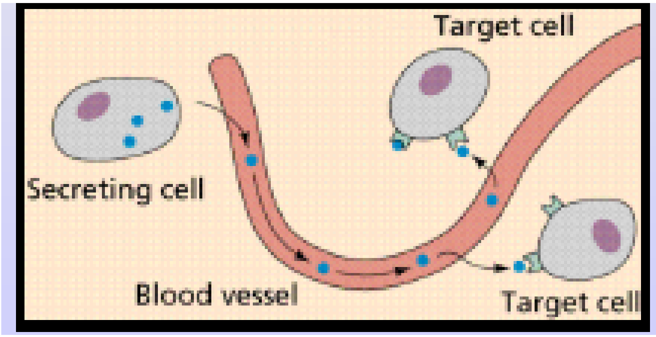
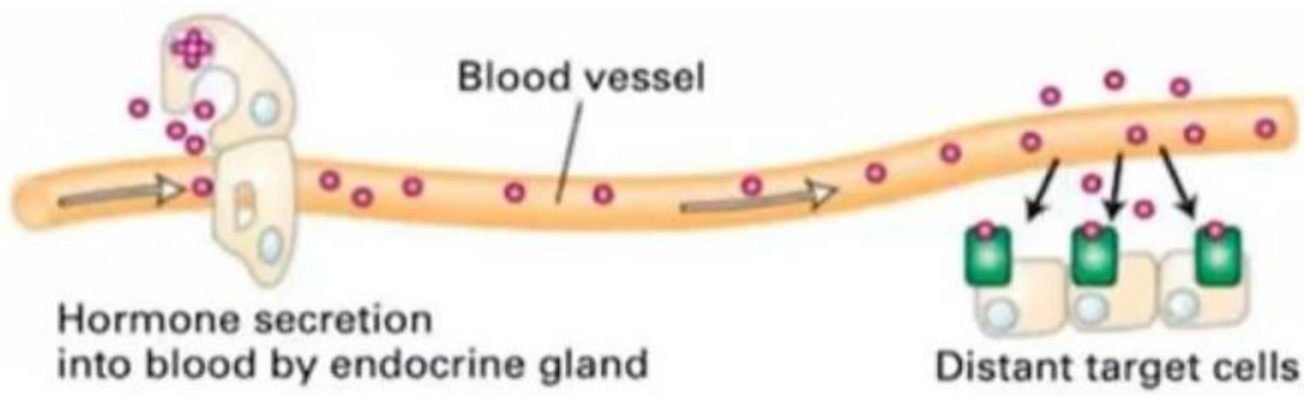


Communication Systems: The nervous system, together with the endocrine system, makes up the body's major signalling pathways in all animals:

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.

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:

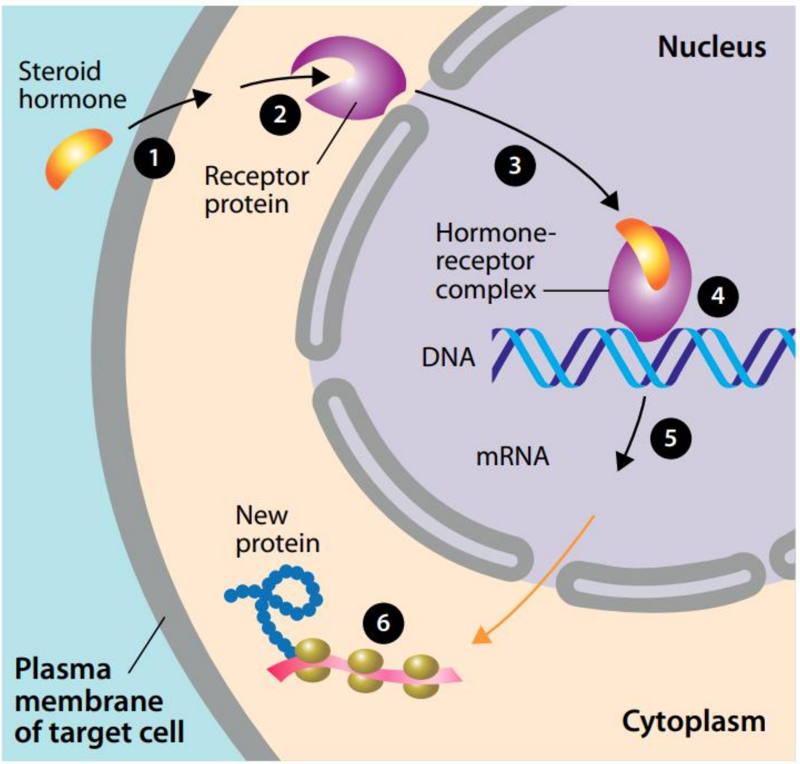
1. Mimicking natural hormones (agonist effect), binding to nuclear hormone receptors such as estrogen (ER), androgen (AR), or thyroid hormone receptors (TR).
2. Blocking hormone binding (antagonist effect), thereby preventing normal receptor activation.
3. Altering hormone synthesis, metabolism, or clearance, 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.

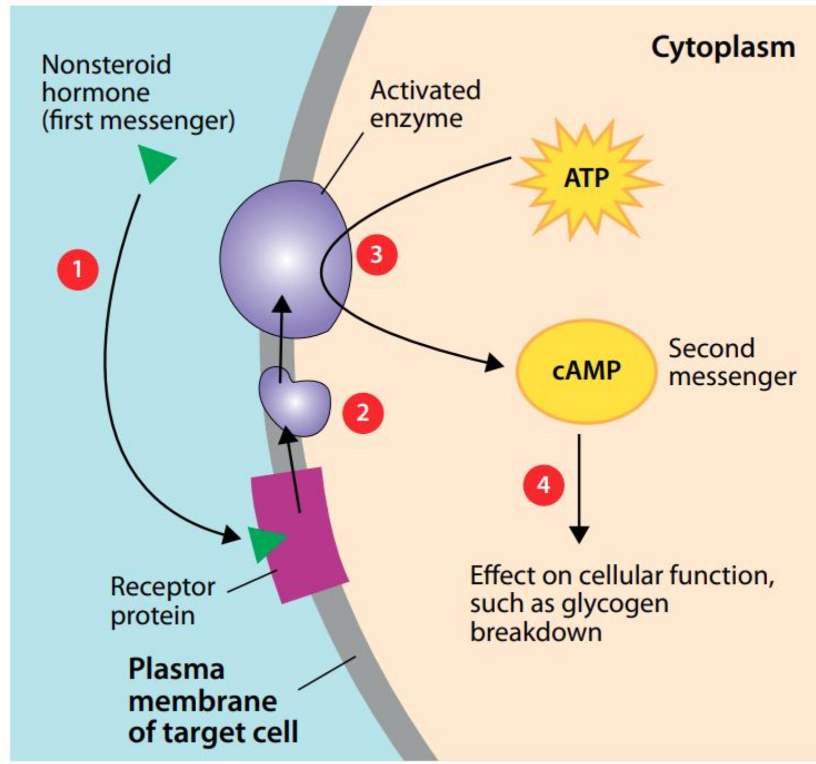
Endocrine Reviews, 2015, **36**(6), E1–E150, Endocrinology, 153(9), 4097–4110

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.

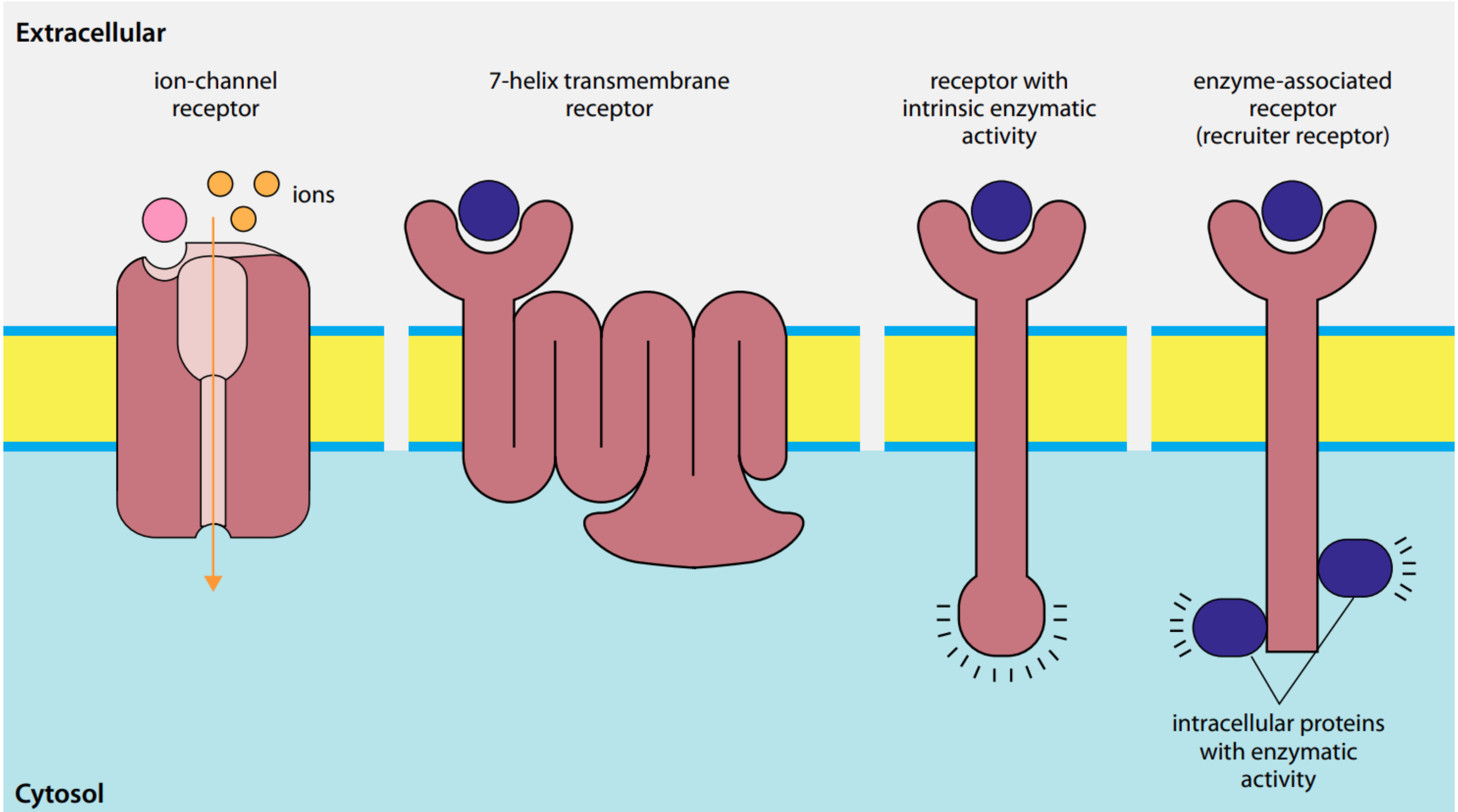
State of the Science of Endocrine Disrupting Chemicals – 2012; A report by UNEP and EHO 2012; 9789241505031_eng.pdf



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.

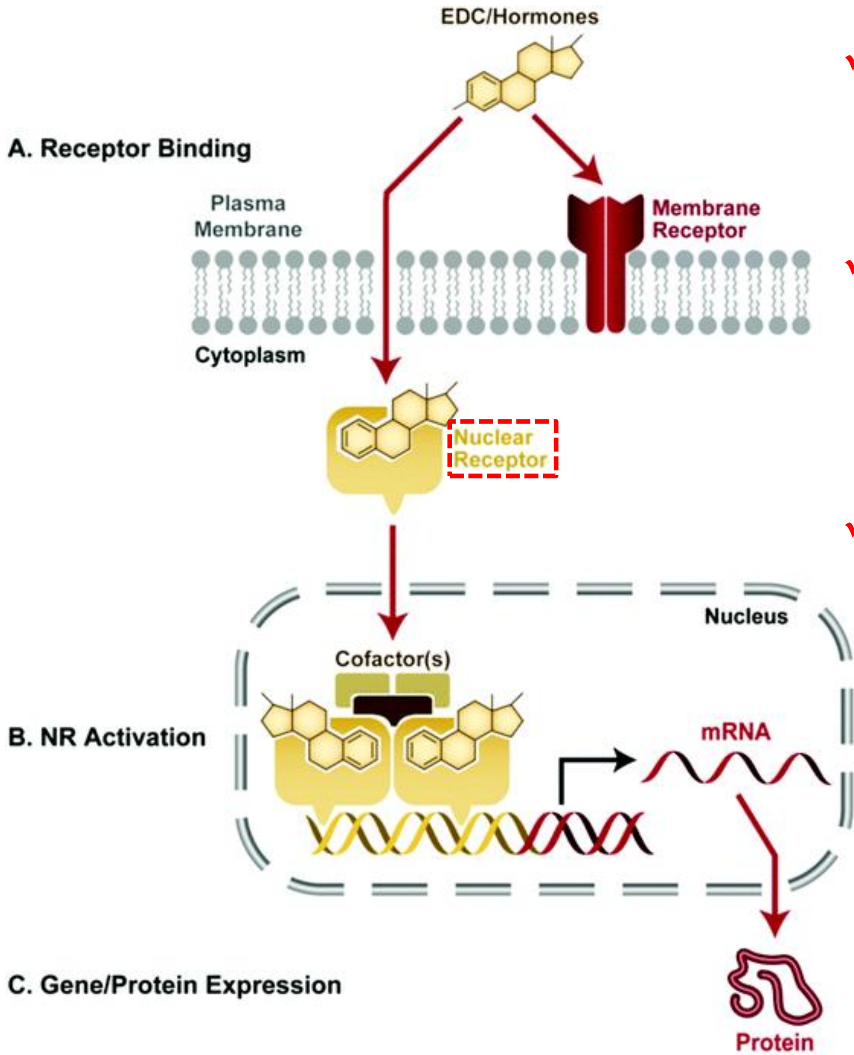


Membrane receptors bind to protein and amine hormones, which cannot cross the lipid membrane. Instead, they trigger intracellular effects through a second messenger system (such as cAMP), amplifying the hormone's signal inside the cell.



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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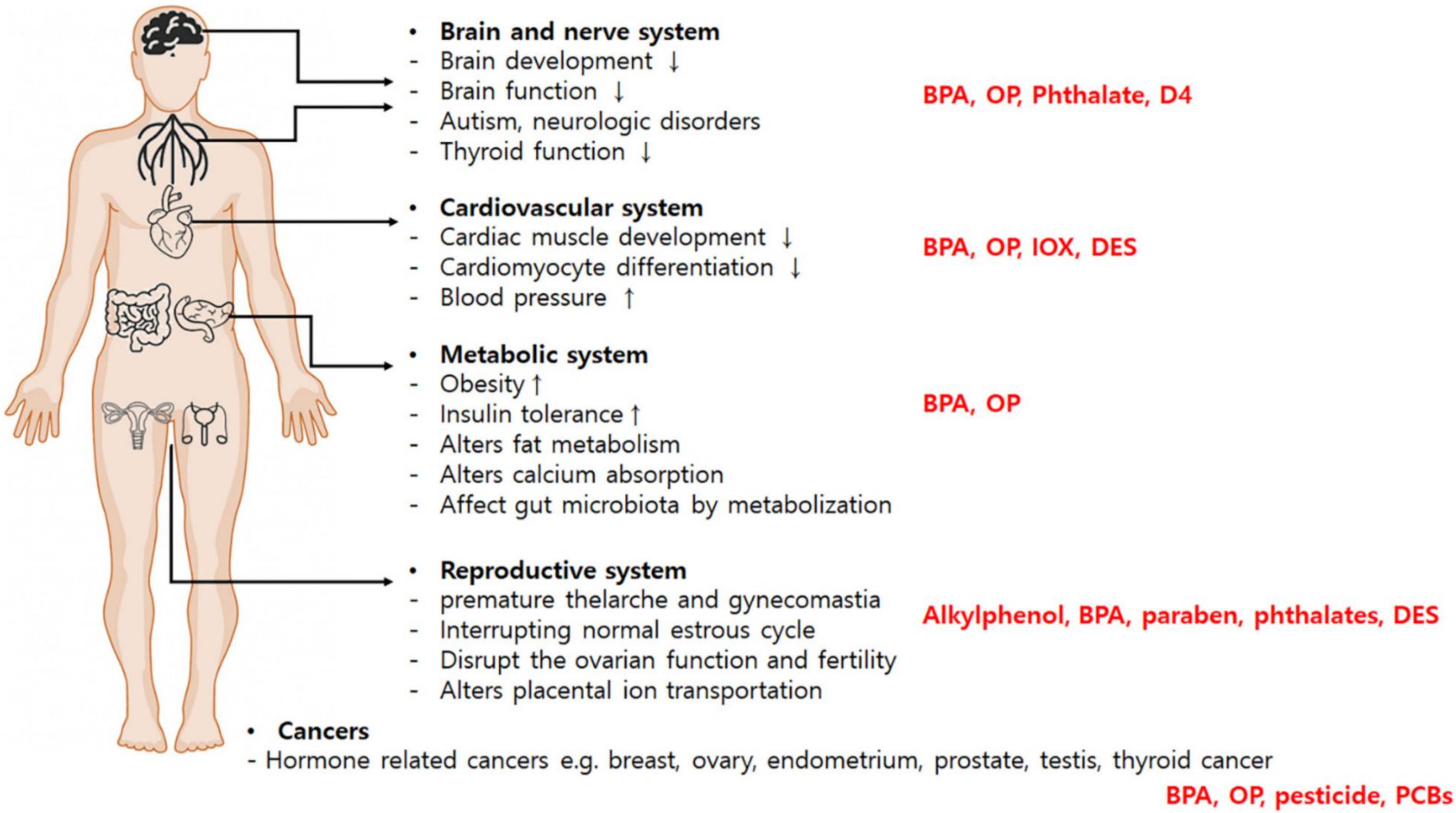


Exposure to EDCs contributes significantly to the onset and progression of organ development and disorders such as reproductive, metabolic, neurologic, cardiovascular disease, and cancers; these EDCs include Bisphenol A (BPA), octylphenol (OP), octamethylcyclotetrasiloxane (D4), ioxynil (IOX), diethylstilbestrol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

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.

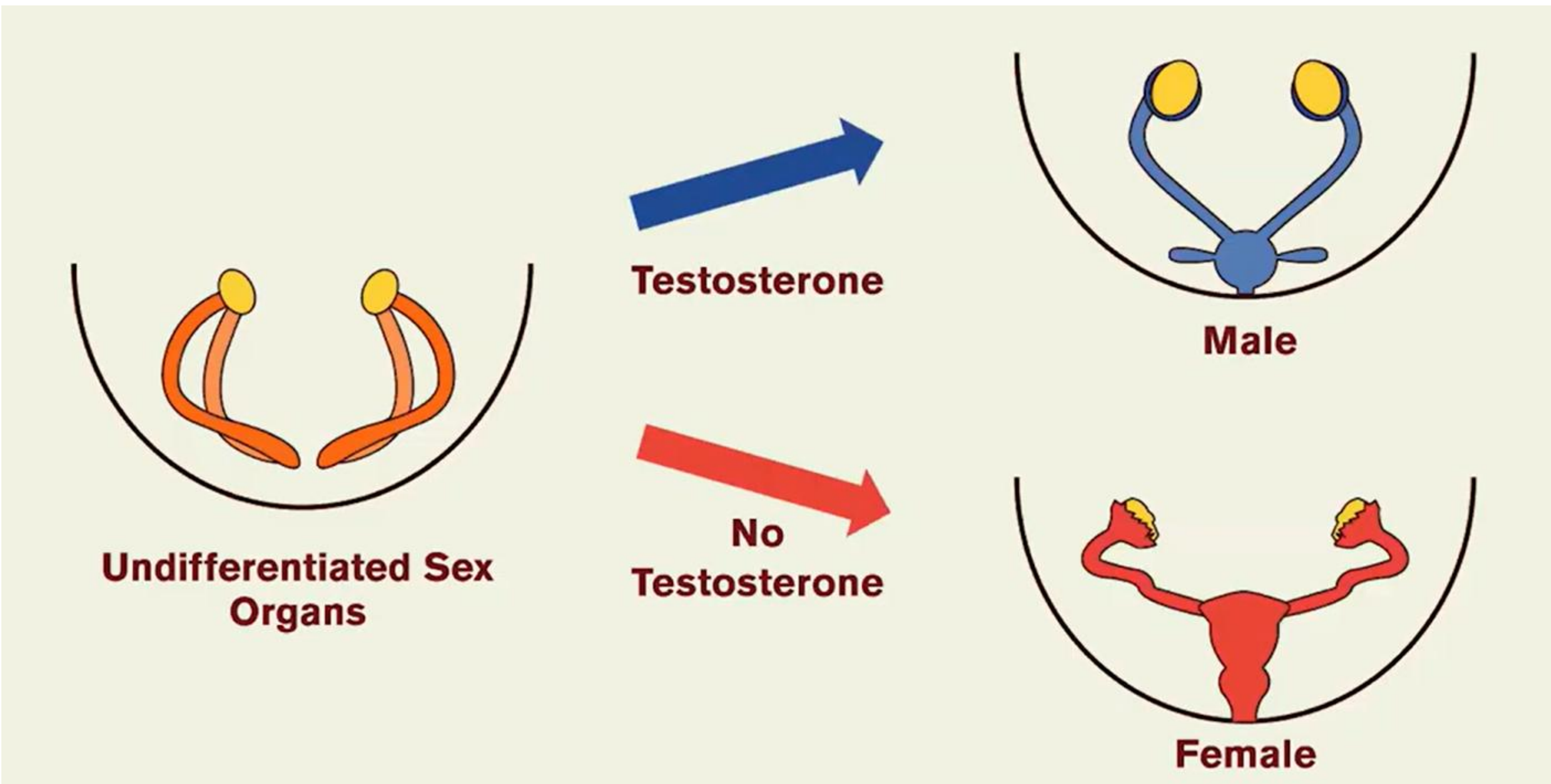
- In the first 6 weeks of embryonic life, there’s no anatomical difference between XX (genetic female) and XY (genetic male) embryos.
- Both have Müllerian ducts (which can form female structures) and Wolffian ducts (which can form male structures).

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



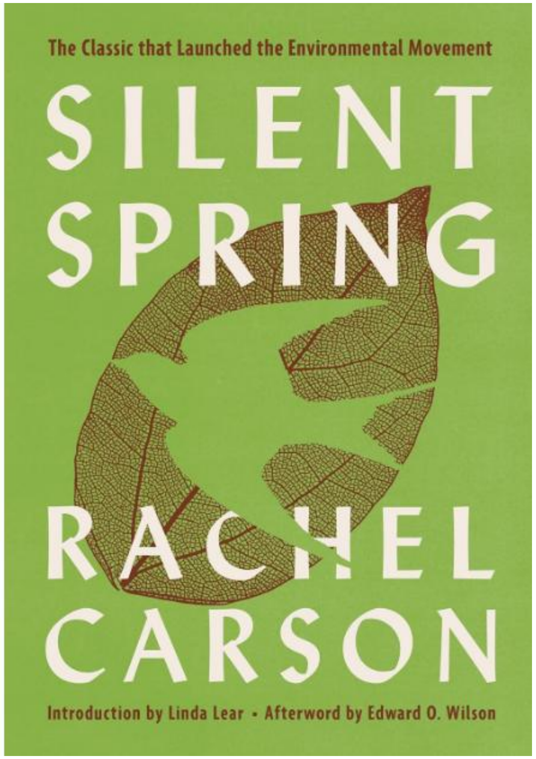
Mechanisms of Action:

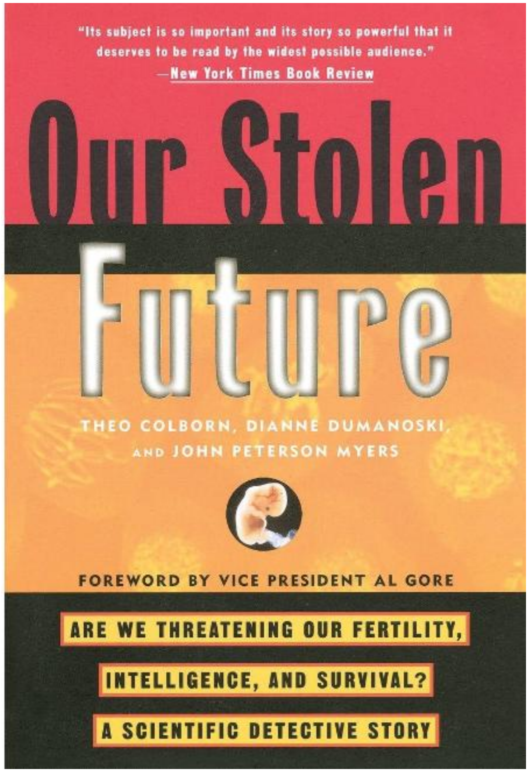
- **Agonist activity:** Chemicals bind to hormone receptors, activating pathways inappropriately.
- **Antagonist activity:** Chemicals block hormone receptors, preventing normal hormonal signalling. Anti-Müllerian hormone (AMH) signals the complete regression and breakdown of the Müllerian ducts.
- **Altered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

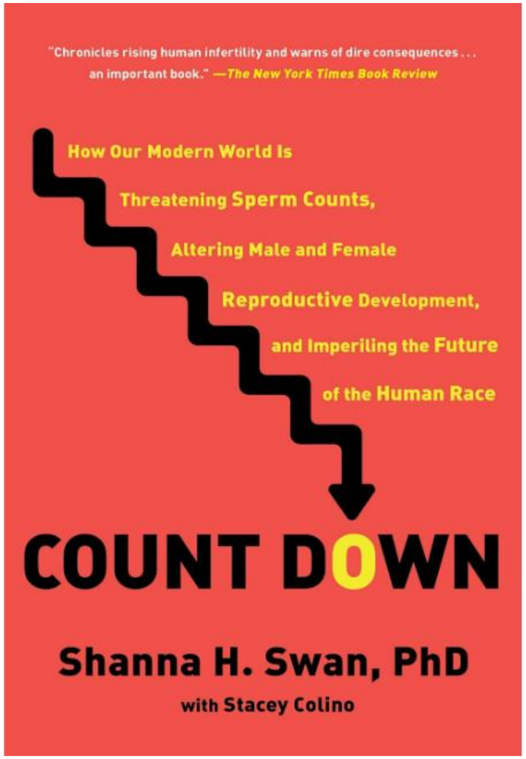
Silent Spring is an environmental science book by Rachel Carson. Published on September 27, 1962, the book documented the environmental harm caused by the indiscriminate use of DDT, a pesticide used by soldiers during World War II.



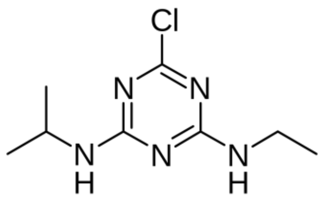


A Scientific Detective Story is a 1996 book by Theo Colborn, Dianne Dumanoski, and John Peterson Myers. The book chronicles the development of the endocrine disruptor hypothesis by Colborn.

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.

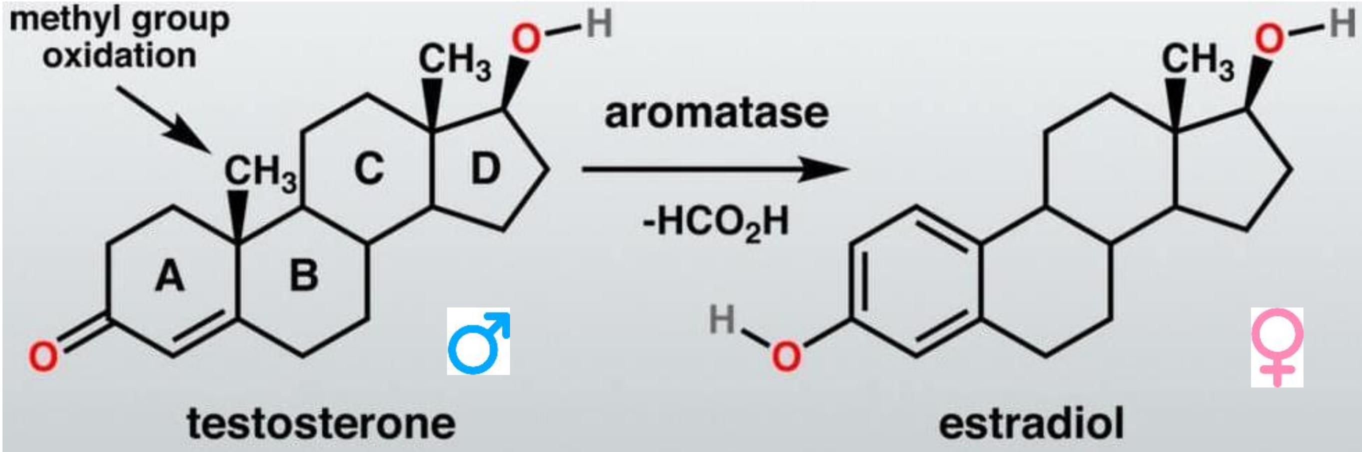
Effects on the Reproductive System:

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.

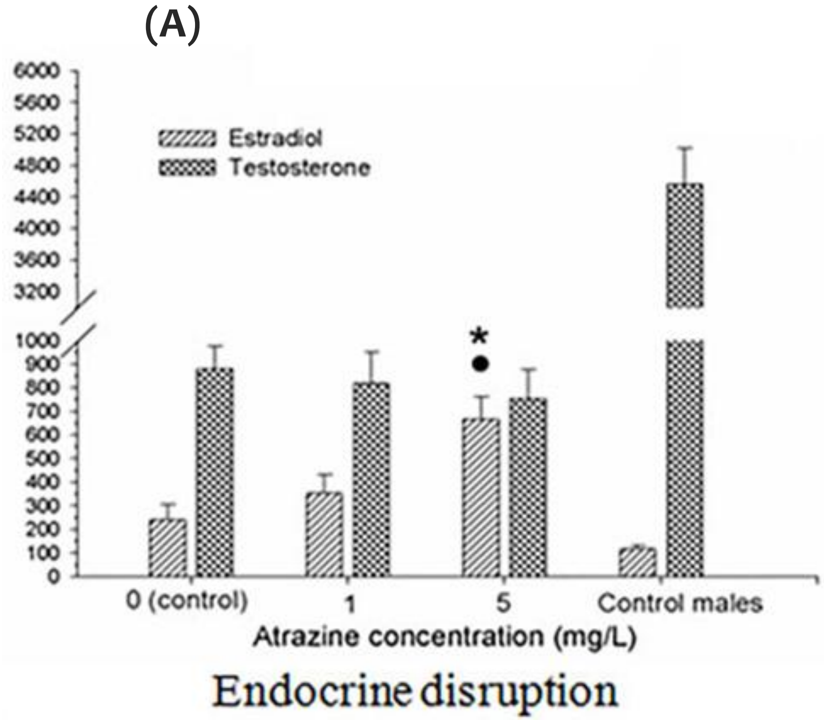
In Females

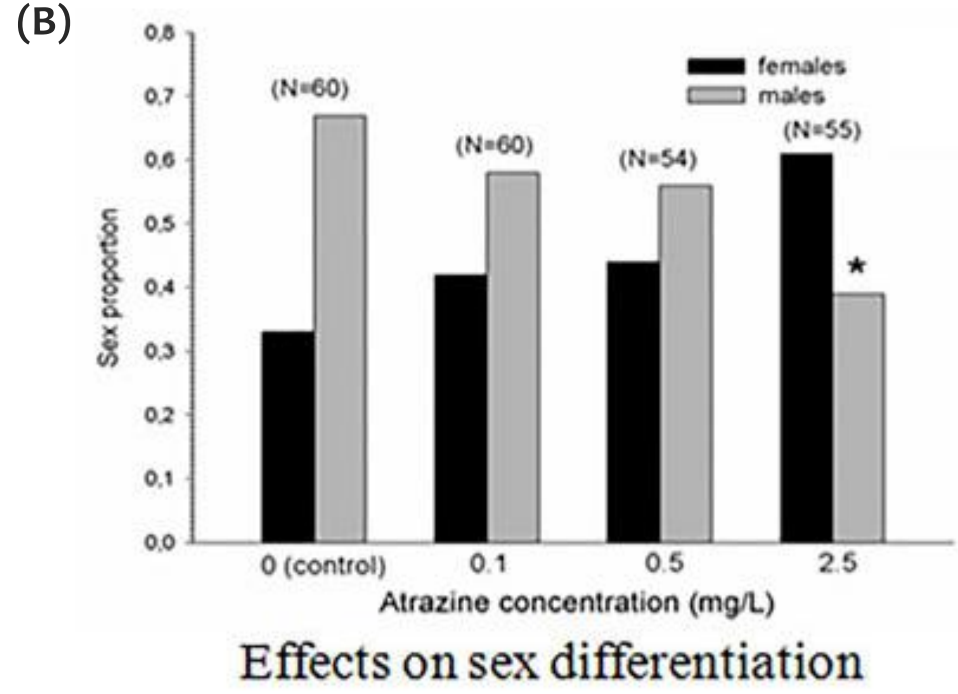
- **Ovarian dysfunction:** Atrazine disrupts folliculogenesis, reduces ovulation rates, and alters estrous/menstrual cycles.
- **Pregnancy outcomes:** Animal studies show increased risk of spontaneous abortion, delayed puberty, and impaired fertility.
- **Endocrine-mediated effects:** By altering luteinizing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



$$\text{Testosterone} \xrightarrow[\text{NADPH, O2}]{\text{Aromatase}} \text{Estradiol + Formic acid + Water}$$

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/Hu0IXMTFY9Q

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.

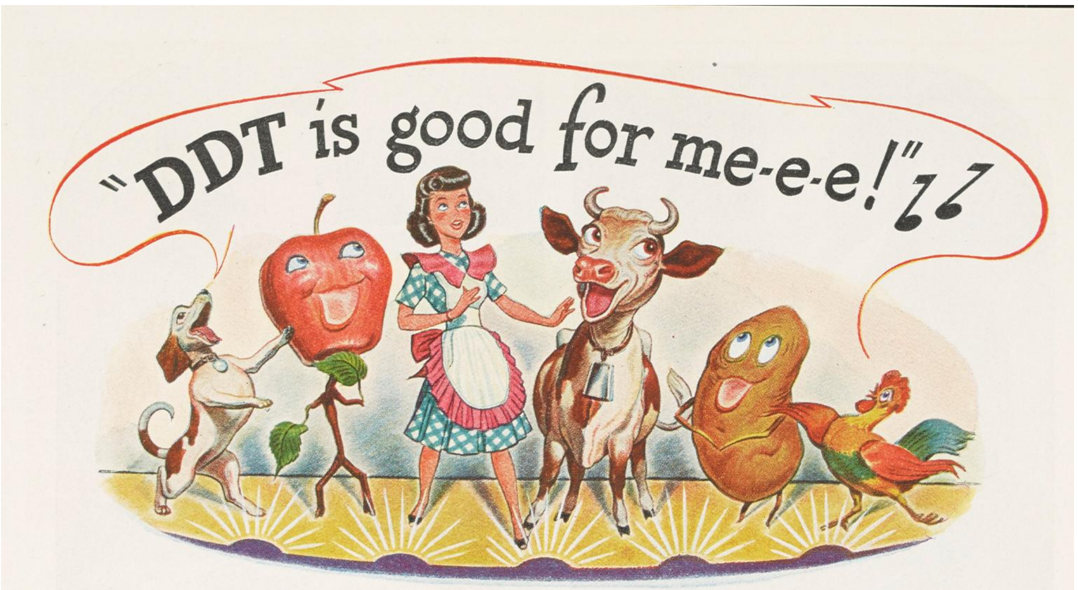
•**Perchlorate** (Used in explosives, and fireworks)

•**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.

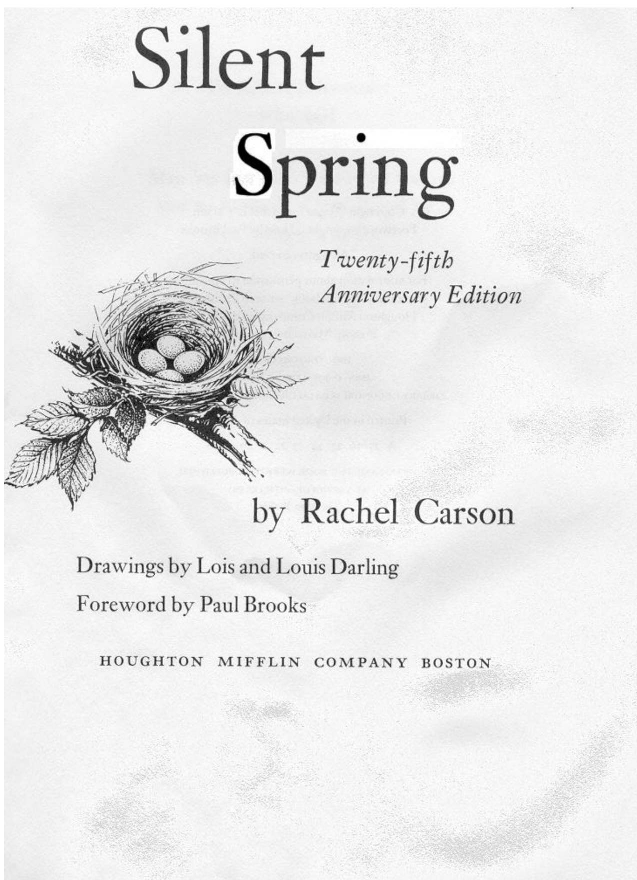
DDT sparked a global avian catastrophe. The biocide interferes with Ca^{2+} metabolism in egg production, particularly in birds of prey, which were “catastrophically impacted”. Thin-shelled, fragile eggs fractured in bird nests, unable to support the weight of a growing embryo.

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

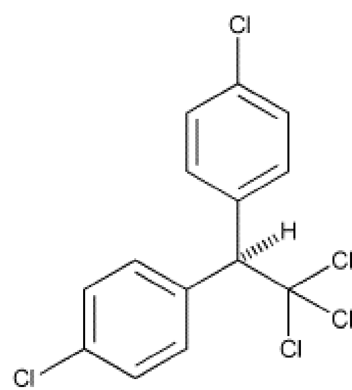


"Only within the moment of time represented by the present century has one species—man—acquired significant power to alter the nature of his world."

“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

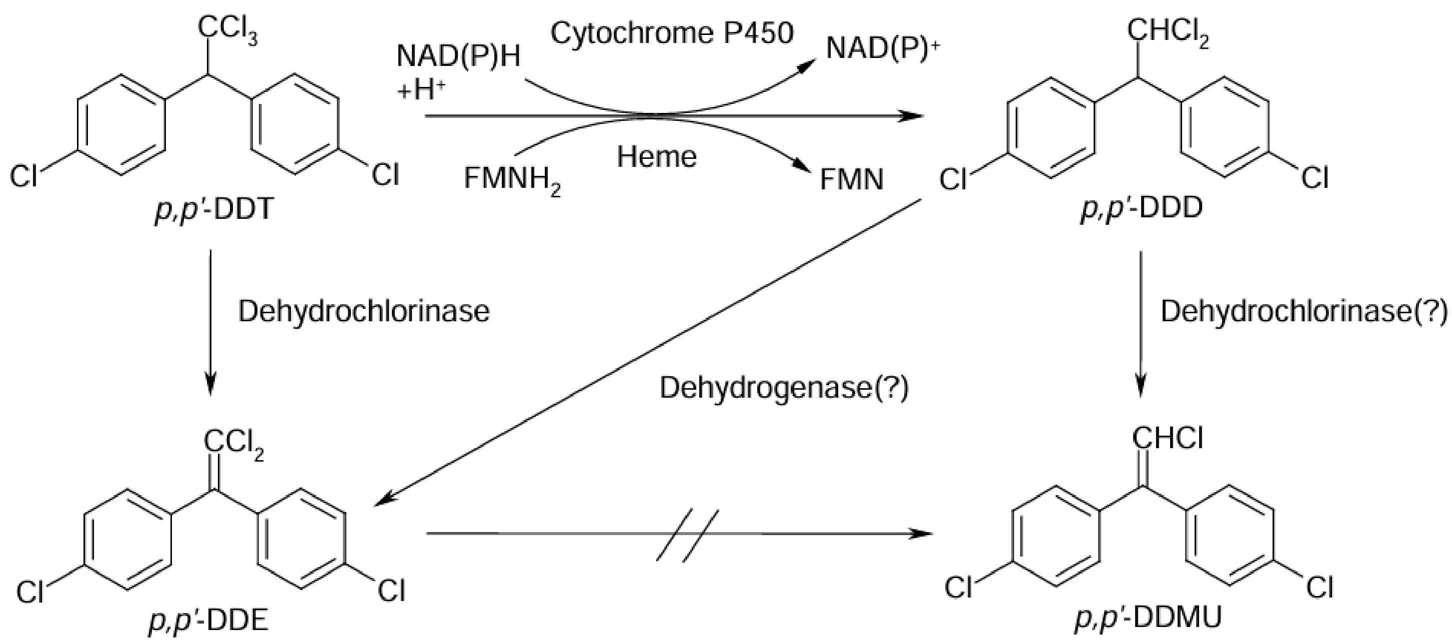
- While working for the Fish and Wildlife Service from 1935 to 1952, Rachel Carson knew of the early studies of DDT's lasting effects on the environment.
- 1945 she proposed an article to *Reader's Digest* about the dangers of DDT. The article was turned down.
- What finally led Carson to take a larger 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

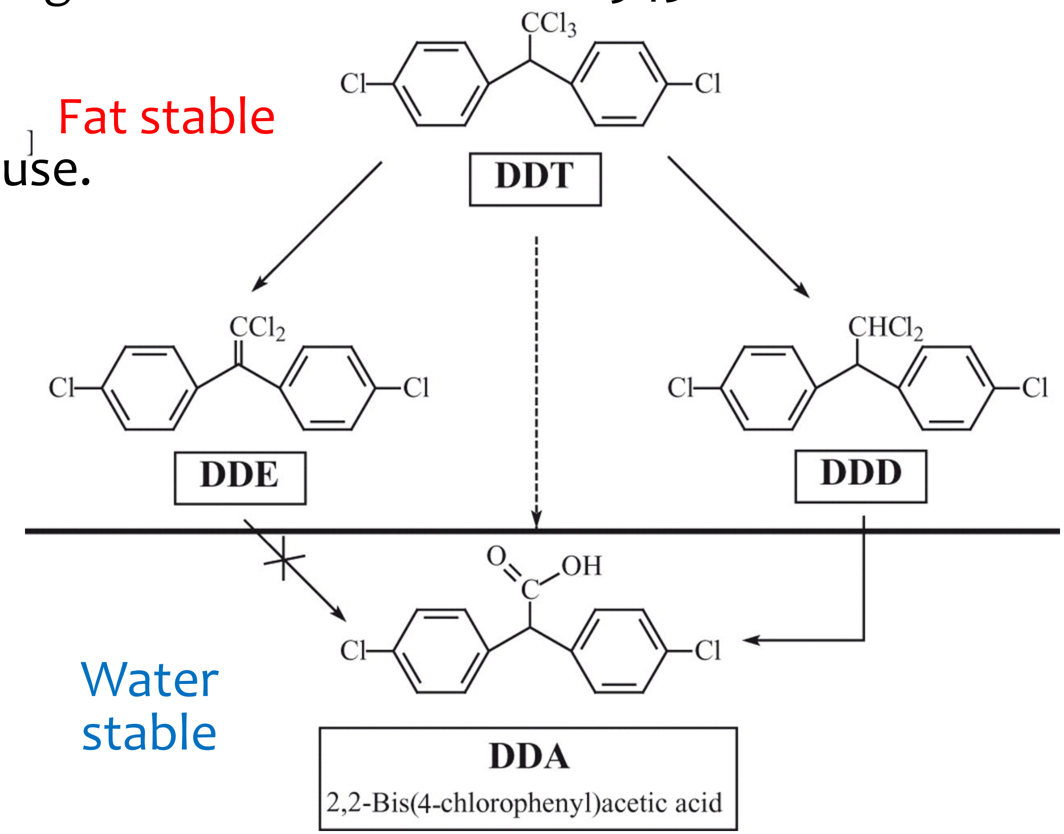
Dichlorodiphenyltrichloroethane (DDT): First synthesized in 1857 [Othmar Zeidler]

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

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

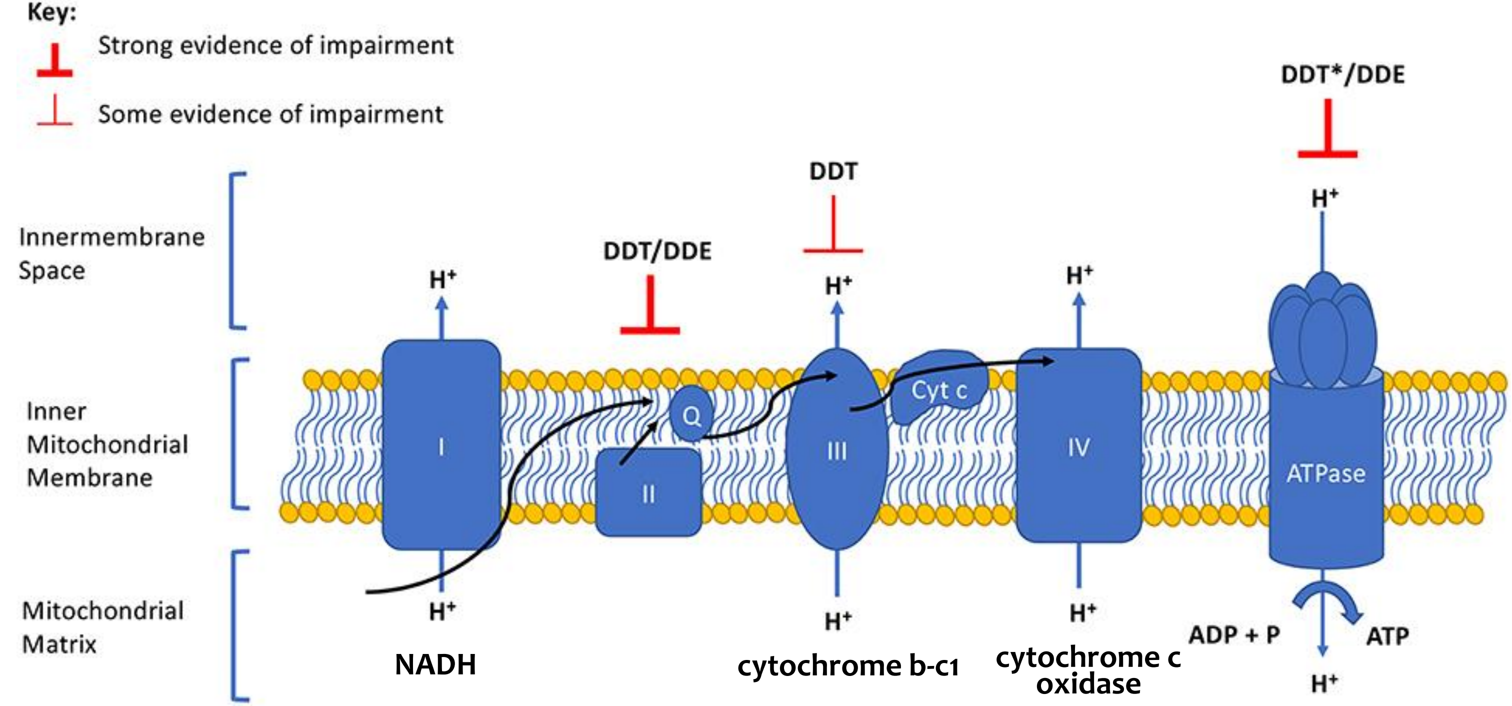
Banned in the USA: 1972

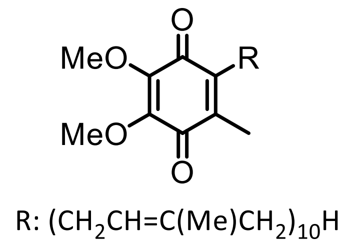
Banned in India: 1989 for agricultural use.



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.

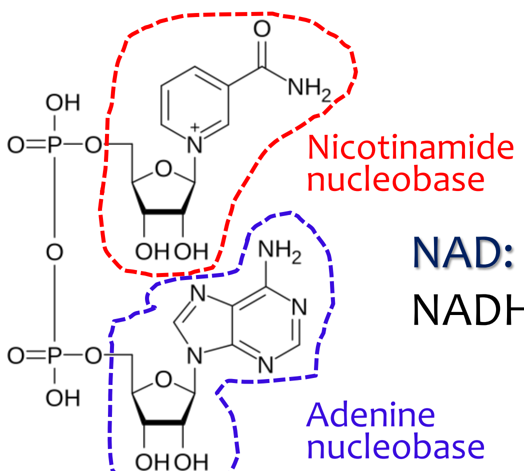
International Journal of Toxicology
28(6) 528-533 ªThe Author(s) 2009





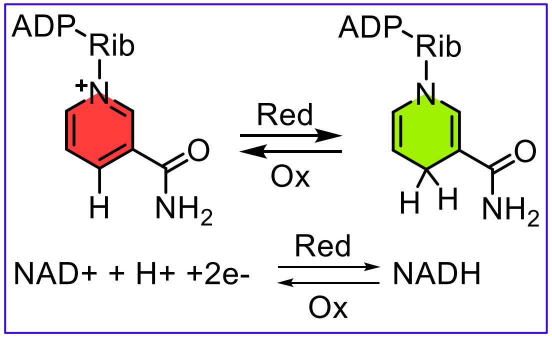
Ubiquinone

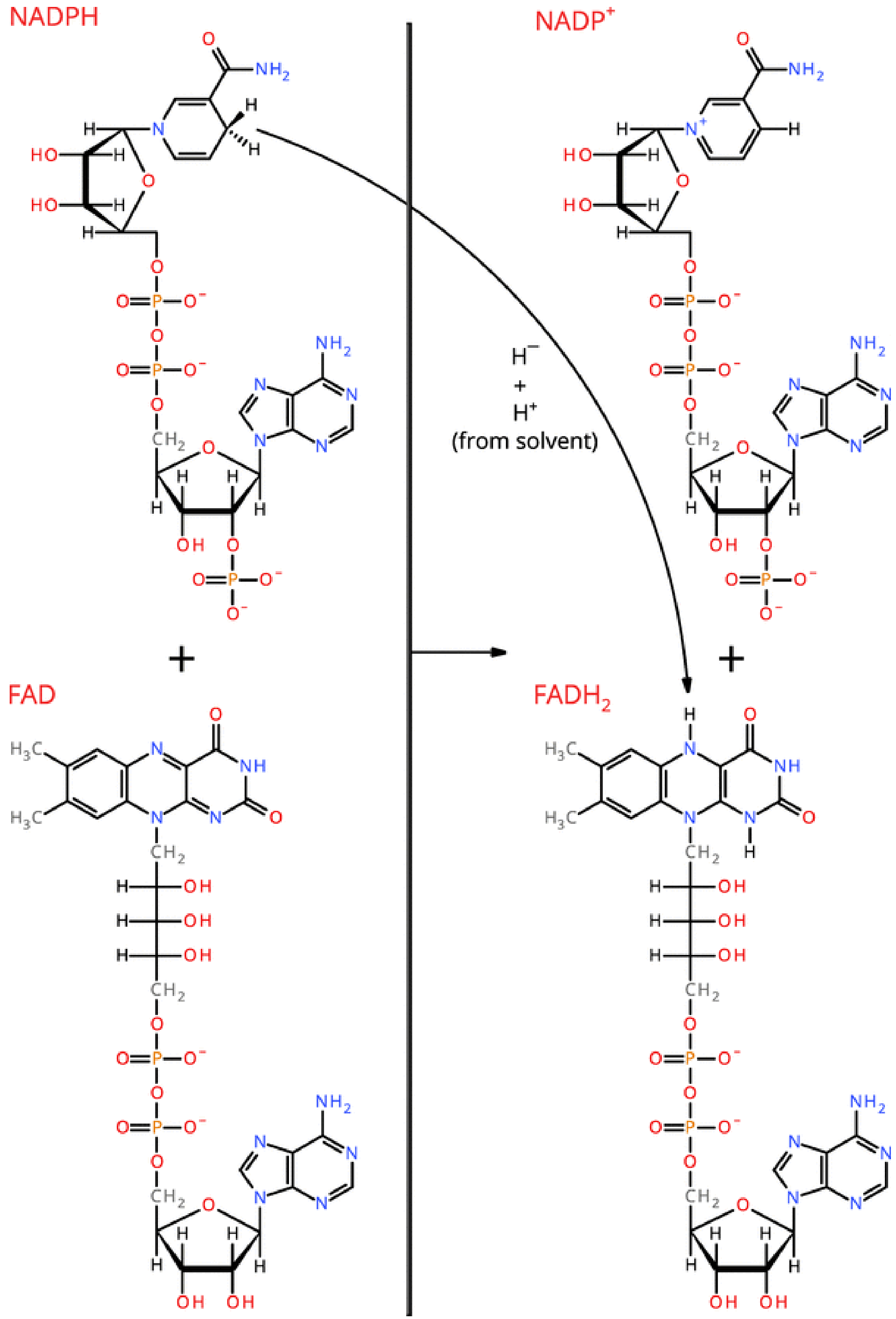
Oxidative phosphorylation occurs in the inner mitochondrial membrane. It couples the oxidation of NADH and $FADH_2$ (generated in glycolysis, TCA cycle, and β-oxidation) to the production of ATP via the electron transport chain (ETC) and ATP synthase (Complex V).



NAD: Nicotinamide Adenine Dinucleotide.

NADH is a coenzyme central to metabolism.



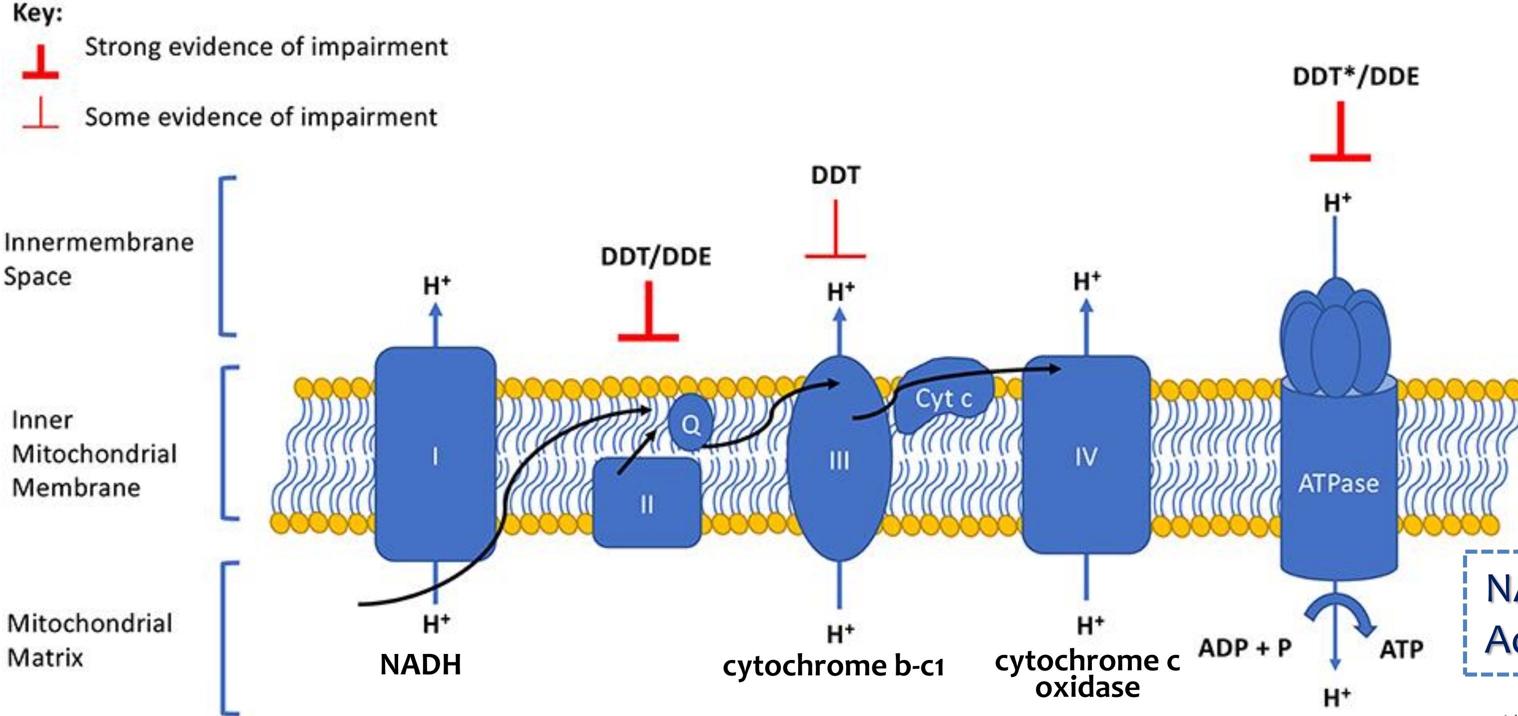


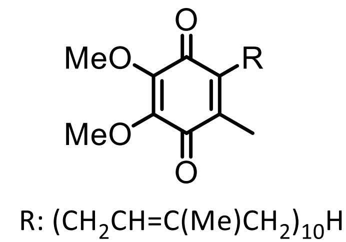
Reduction of FAD by NADPH. The nicotinamide group of NADPH transfers a hydride ion (H^-) to the isoalloxazine ring of the FAD, forming $FADH^-$. After reaction with an additional H^+ from the solvent, $FADH^-$ becomes FADH2

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/



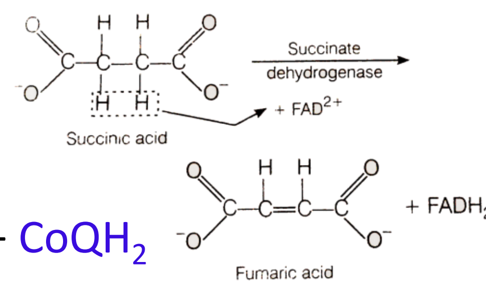


Ubiquinone

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 + $CoQH_2$

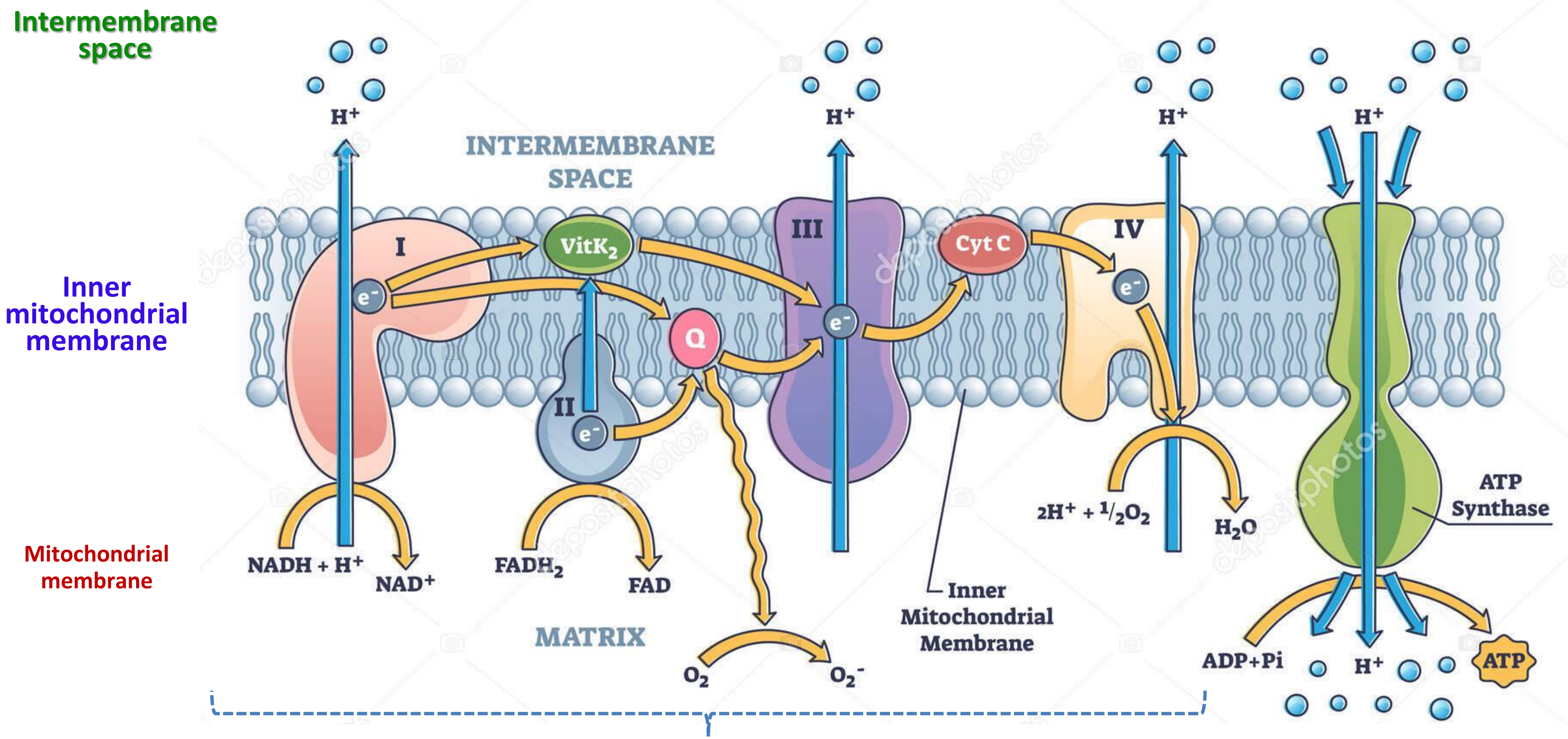
Complex III: cytochrome bc_1 complex or ubiquinol–cytochrome c oxidoreductase

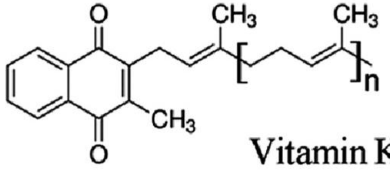
Transfers electrons from **ubiquinol ($CoQH_2$)** to **cytochrome c**, while **pumping protons (H^+)** into the intermembrane space to help build the **proton motive force** used for ATP synthesis.

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.

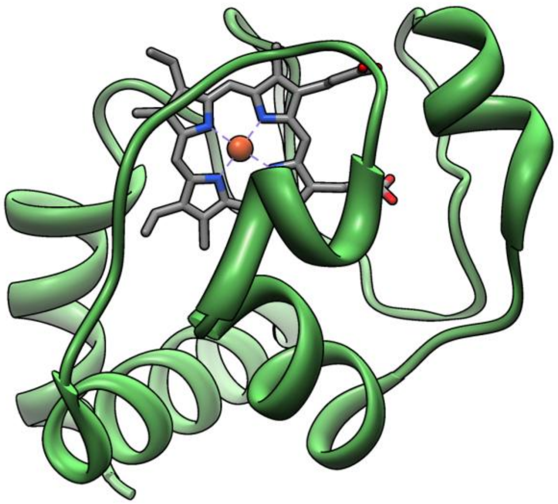
Role of NADH and FADH2 in the Electron Transport Chain



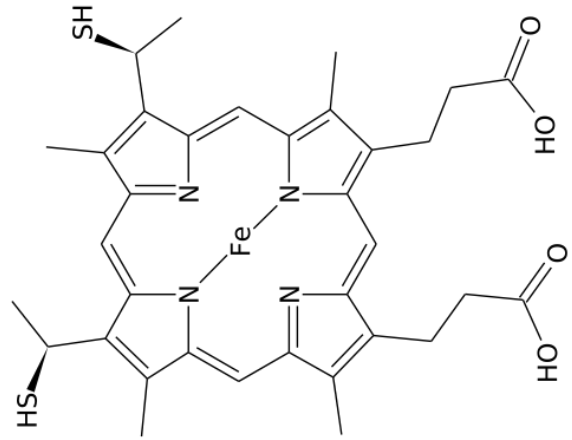


Vitamin K2

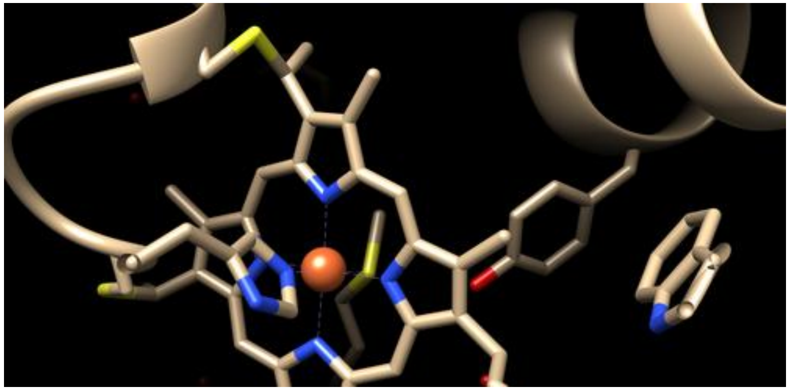
Author: Vector Mine
https://depositphotos.com/vector/electron-transport-chain-as-respiratory-embedded-transporters-outline-diagram-530772006.html



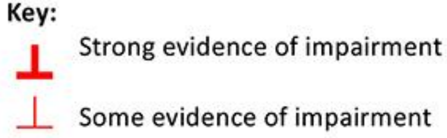
High-resolution three-dimensional structure of horse heart cytochrome c." J Mol Biol. 1990 Jul 20;214(2):585-95



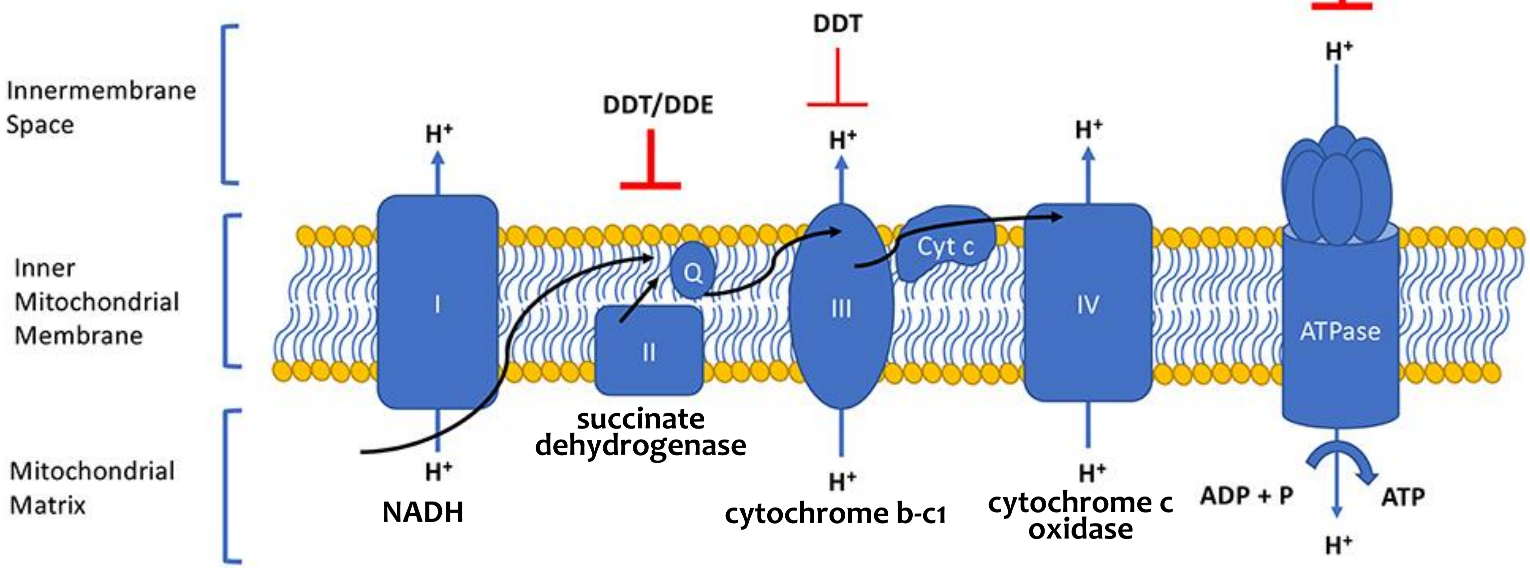
Heme prosthetic group of cytochrome c, consisting of a rigid porphyrin ring coordinatec with an iron atom.

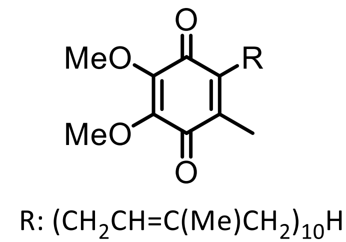


The cytochrome complex, or cyt c, is a small hemeprotein found loosely associated with the inner membrane of the mitochondrion. It transfers electrons between Complexes III (Coenzyme Q – Cyt c reductase) and IV (Cyt c oxidase). It is capable of undergoing oxidation and reduction as its iron atom converts 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]



Oxidative Phosphorylation Impairment by DDT and DDE





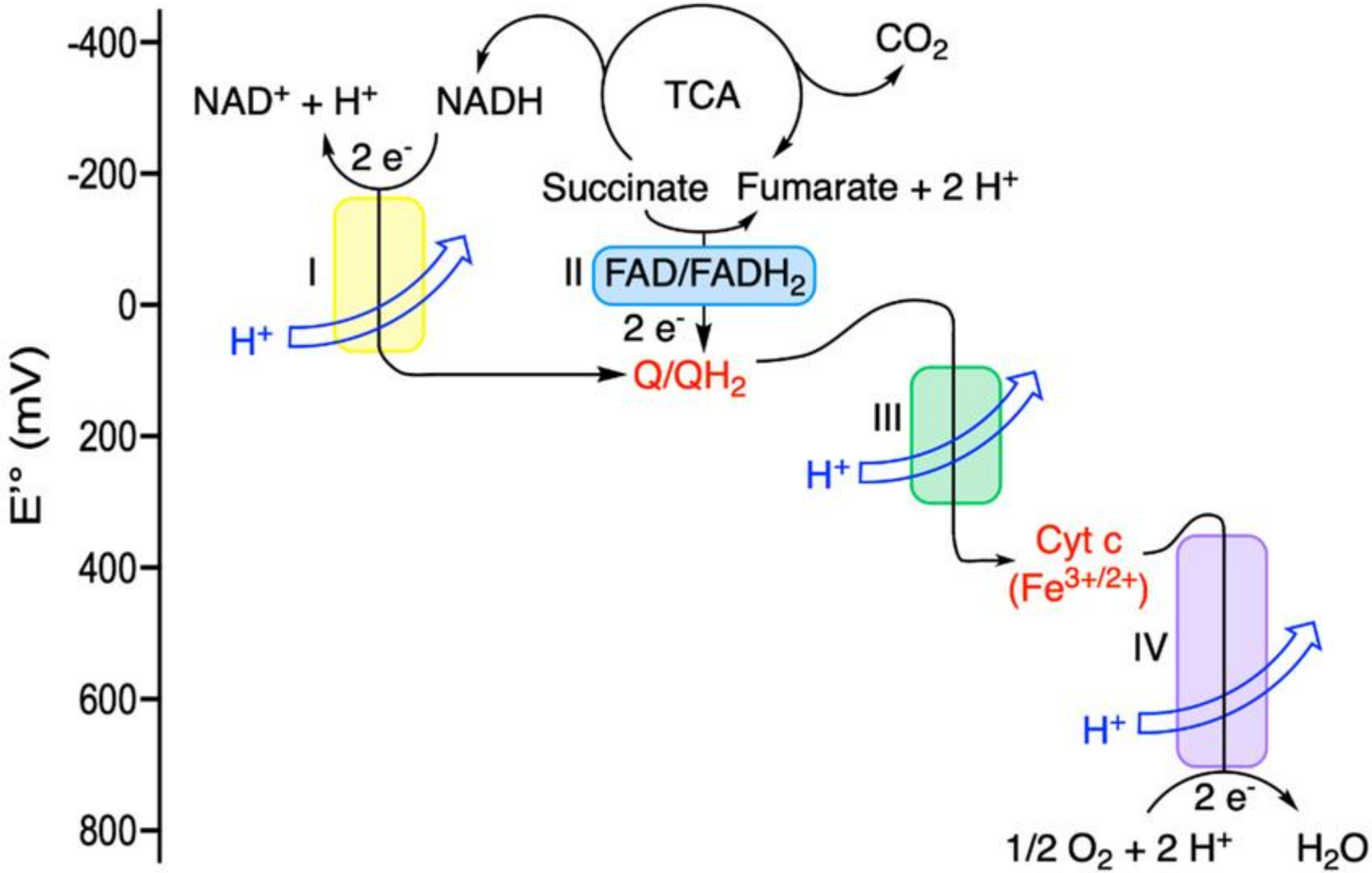
Ubiquinone

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 (UQH2), which is then released to carry electrons to Complex III, where UQH2 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



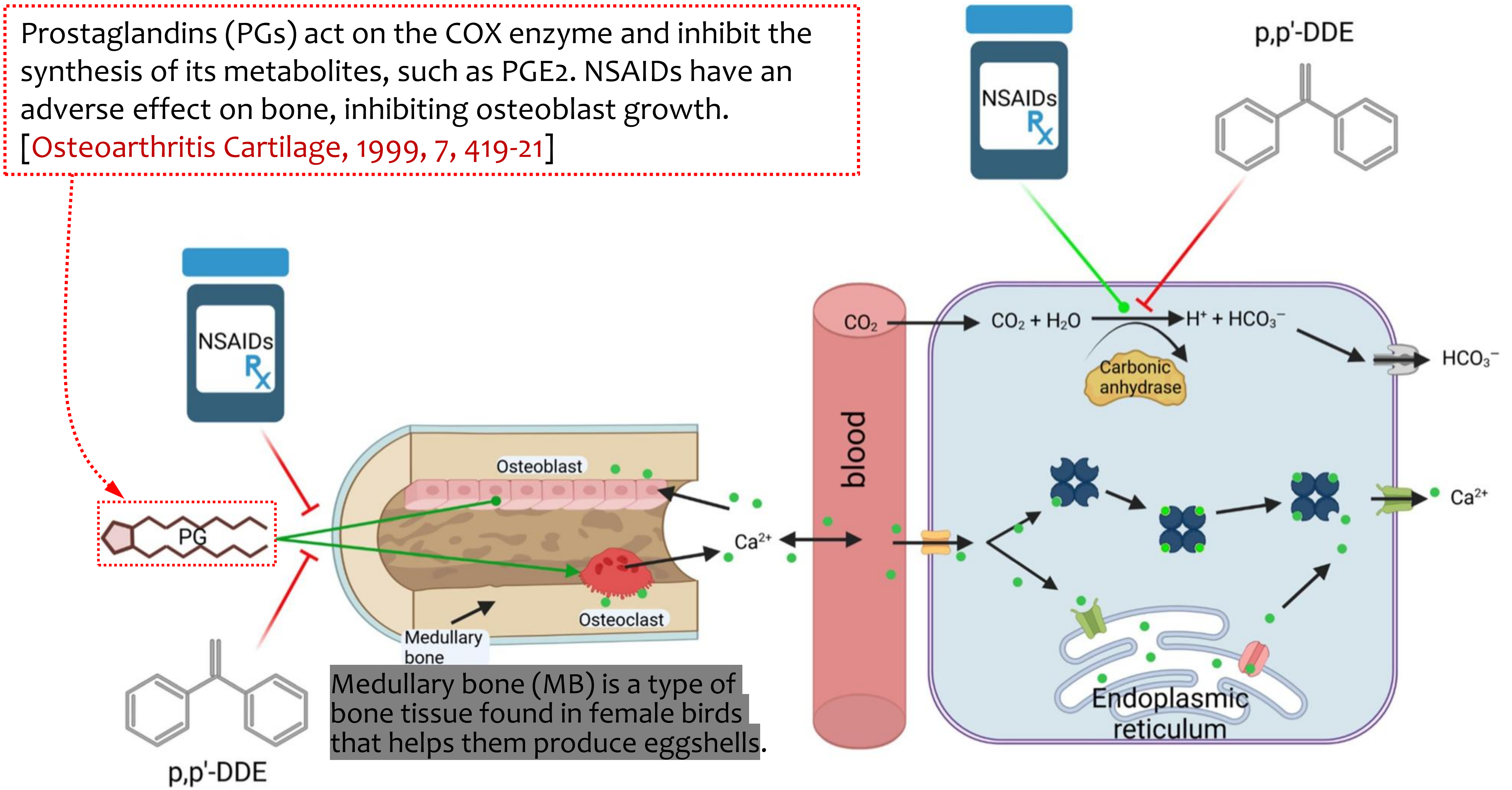
Electron flow from NADH and FADH2 to O2 in the mitochondrial respiratory chain. While the first reactions involve the transfer of $H^- + H^+$ to the acceptor Q, complexes III and IV act as electron wires coupled to proton pumps.

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.



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.

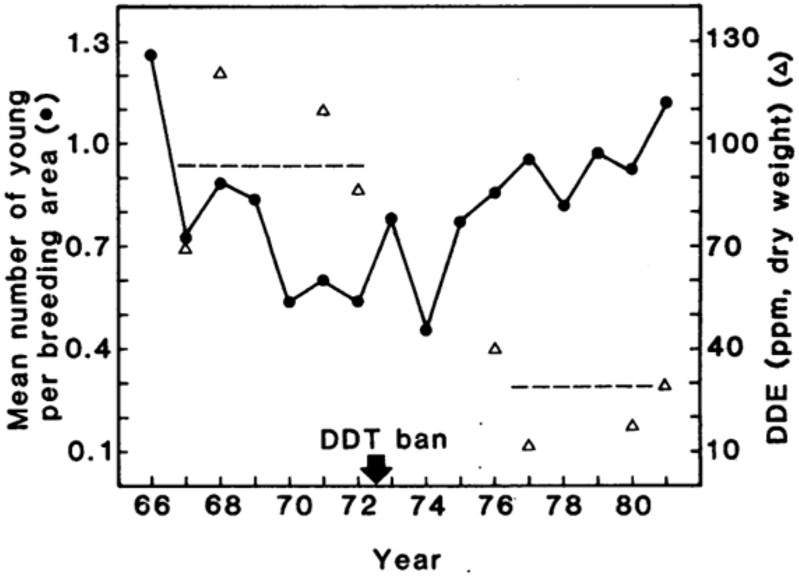
- In addition, impaired transport or reduced concentration of HCO_3^- ions may also reduce the availability of Ca^{2+} since transport of these two ions through the shell gland mucosa is, to some extent, coupled.

- 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]

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]

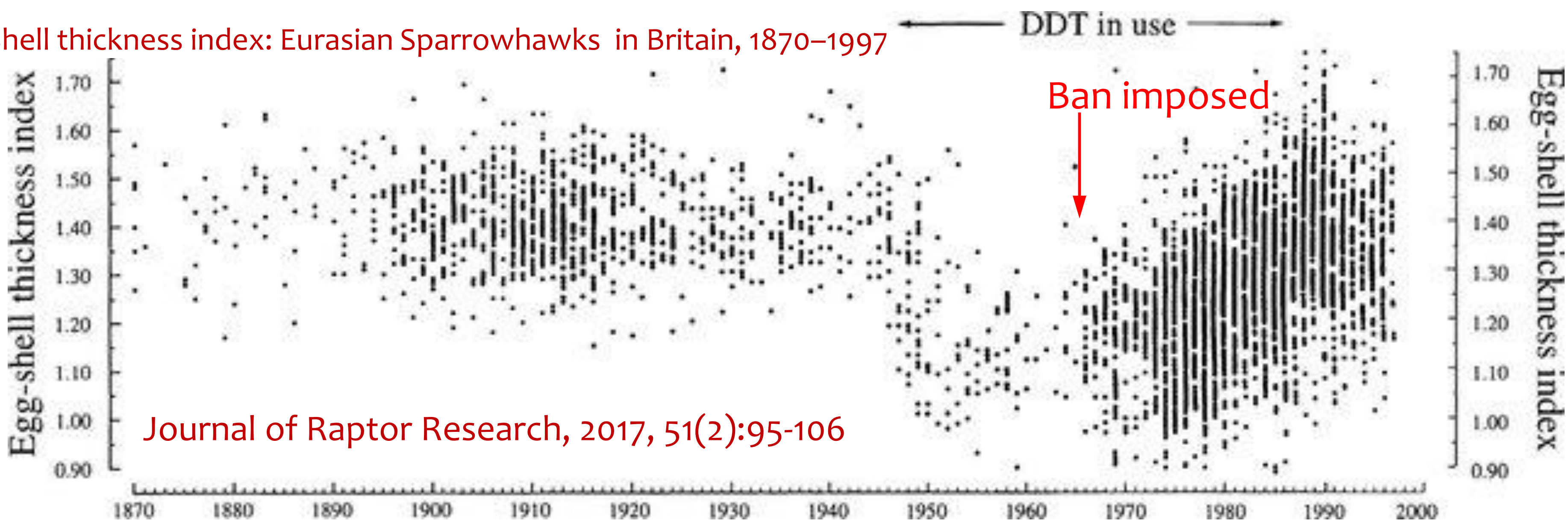
Laboratory experiments showed that DDE could cause eggshell thinning. Field studies showed that field exposures to DDE, a metabolite of DDT, were sufficient to cause effects in many species of birds based on the stressor-response relationship



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

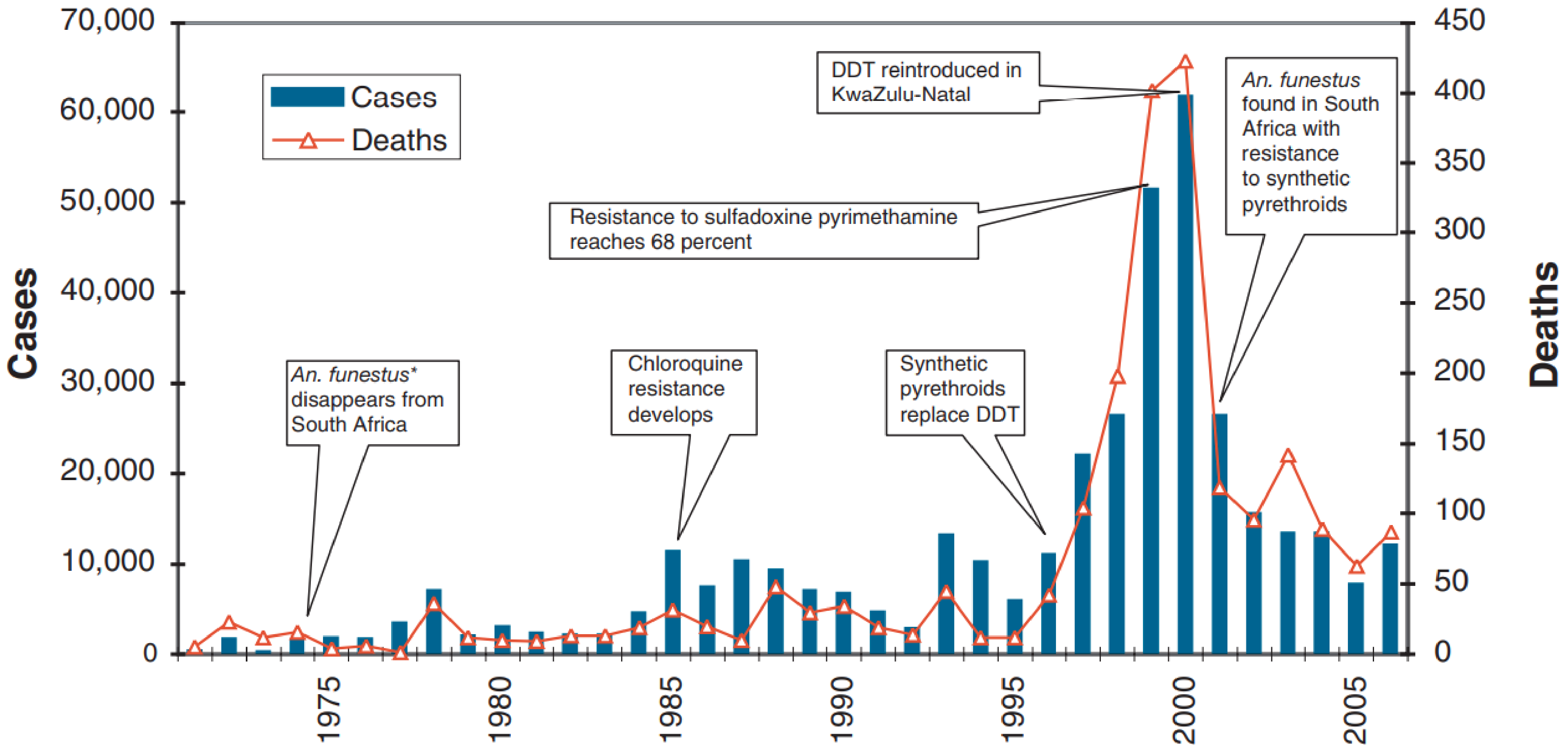


Journal of Raptor Research, 2017, 51(2):95-106

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

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Du Pont and Nylon:

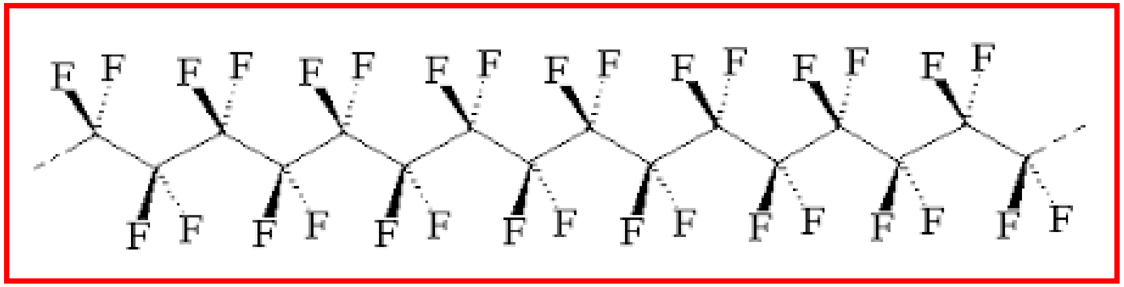
Nylon was first introduced by DuPont around 1939 and was in extremely high demand in the United States, with up to 4 million pairs of stockings bought in one day. During World War II, nylon was used extensively for parachutes and other war materials, such as airplane cords and ropes and the supply of nylon consumer goods was curtailed.

During World War II, Japan stopped using supplies made out of silk, and so the United States had difficulty importing silk from Japan. Eventually, the U.S was unable to import any silk. So, Du Pont thought of an idea to convince the army that nylon is a much more effective material than silk. Du Pont was able to convince the army, and nylon fabric became increasingly popular because of its elasticity and shrink-proof, moth-proof material.

Nylon stockings became increasingly popular on the black market and sold for up to $20 per pair. Because nylon stockings were so widely sought-after, they also became the target of crime. In Louisiana, one household was robbed of 18 pairs of nylons. Similarly, robbery was ruled out as the motive of murder in Chicago because the nylons were untouched.

https://en.wikipedia.org/wiki/Nylon_riots

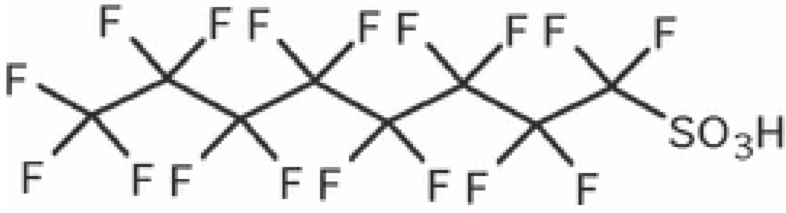
Du Pont and Teflon



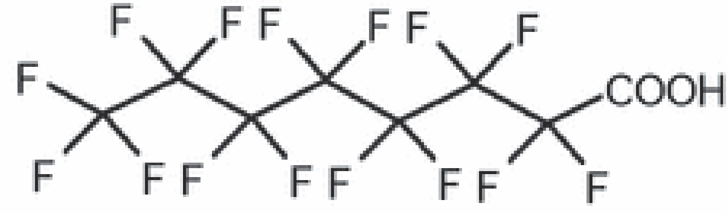
"Teflon"

The story of Teflon™ began April 6, 1938, at the Chemours Jackson Laboratory (by Dr. Roy J. Plunkett) in New Jersey discovery of Polytetrafluoroethylene (PTFE) in 1938 while working with gases related to Freon™ refrigerants.

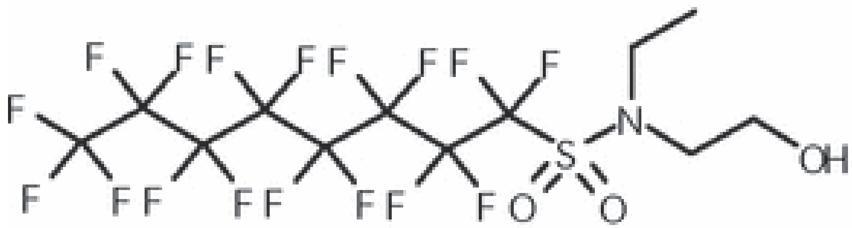
Teflon is the trade name was coined by Chemours (a company created by DuPont) for Polytetrafluoroethylene (PTFE) in 1945. PTFE is inert to virtually all chemicals. Teflon, a product best known for its use in non-stick cookware, but also widely used in a variety of other consumer products, including waterproof clothing and furniture, food packaging, self-cleaning ovens, airplanes and cars.



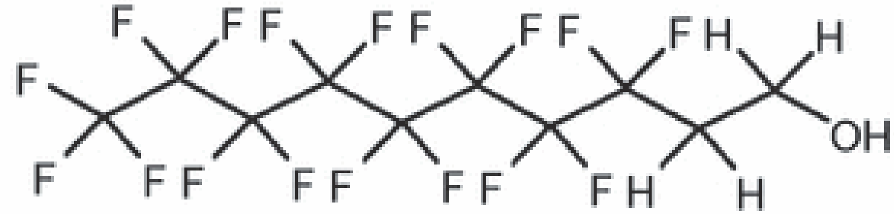
PFOS, perfluorooctane sulfonic acid, $C_8HF_{17}SO_3$



PFOA, perfluorooctanoic acid, $C_8HF_{15}O_2$



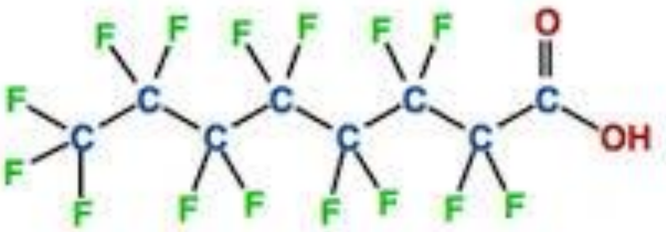
N-Ethylperfluorooctane sulfonamidoethanol (EtFOSE)



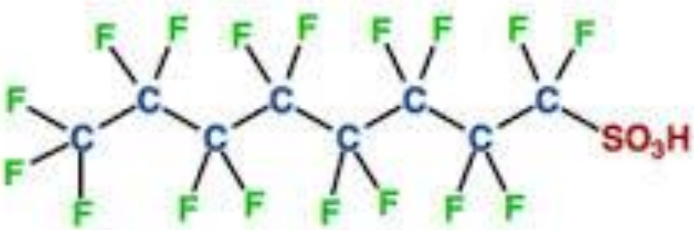
Fluorotelomer alcohol 8:2 FTOH (1H,1H,2H,2H-Perfluorodecanol)

One of the key ingredients in DuPont's Teflon was C8, a toxic, man-made chemical developed by Minnesota Mining and Manufacturing Company (3M). The chemical, also known as PFOS or PFOA, is what gave Teflon its non-stick properties.

Perfluorooctanoic acid ($C_7F_{15}COOH$, PFOA) is an aqueous anionic surfactant and a persistent organic pollutant.



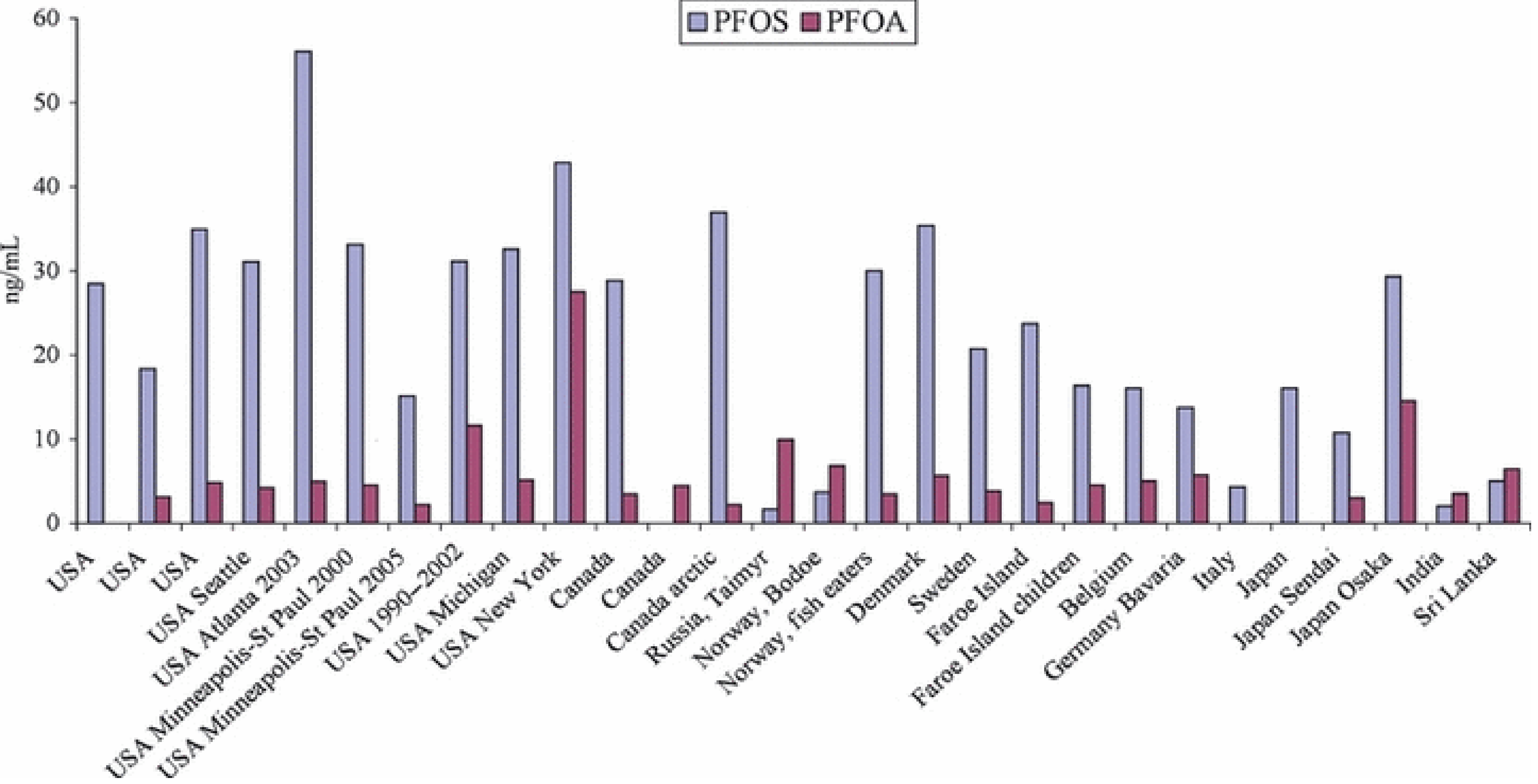
PFOA - perfluorooctanoic acid



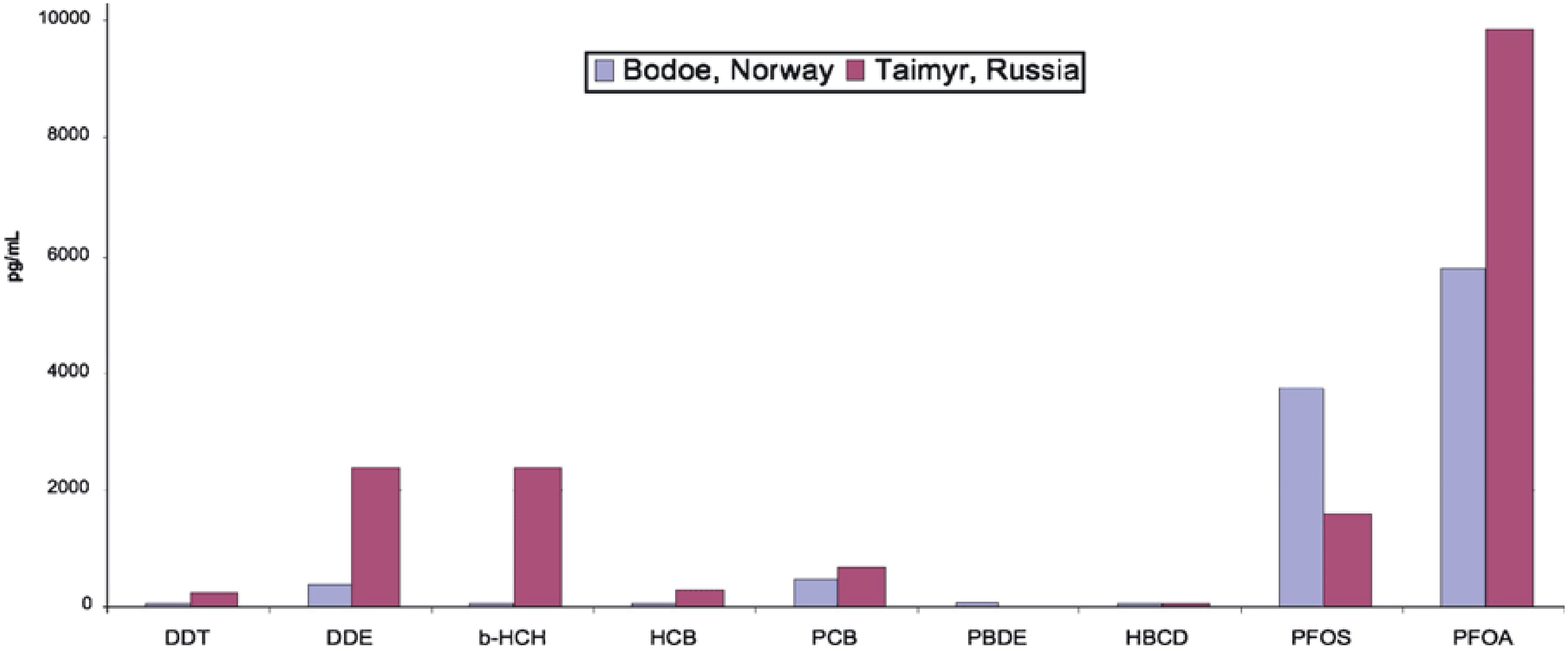
PFOS - perfluorooctanesulfonic acid

PFOA is found in the blood of an estimated 99.7 % of Americans. The eight main fluoropolymer manufacturers, including DuPont, participate in the U.S. Environmental Protection Agency's 2010/2015 PFOA Stewardship Program, which seeks to eliminate PFOA and related chemicals from products and factory emissions by 2015.

Exposure to C8 in drinking water is linked to six different diseases: kidney cancer, testicular cancer, ulcerative colitis, thyroid disease, preeclampsia and high cholesterol.



Typical average concentrations of perfluorooctane sulfonic acid and perfluorooctanoic acid in blood (serum/plasma) from various countries [Int. Jr. Andrology, 2007, 31, 161–169 and refe. Therein]



Persistent organic pollutants in blood plasma from pregnant women living in Norwegian and Russian Arctic [Int. Jr. Andrology, 2007, 31, 161–169 and refe. Therein]

The effects on hormone levels in rodents are reflected in changes in the exposure to perfluorooctanoate and results in Leydig cell hyperplasia and eventually the development of Leydig cell adenomas. A study with adult rats exposed to ≥5 mg perfluorododecanoic acid/kg bw daily for 2 weeks also showed a reduced gene expression of many genes involved in a reduced serum testosterone level, which accounts for the compromised fertility in the adults.

Leydig cell hyperplasia is common among infertile men who, as a group, also show lower testosterone levels than comparable normal controls. [Int. Jr. Andrology, 2007, 31, 161–169 and refe. Therein]

The international awareness and concern is increasing. In 2000, the main producer (3M Company), voluntarily stopped the production of one of the chemicals (PFOS), and a ban of some fluorotelomers has been introduced in Canada. In Europe, the EU countries will ban PFOS and its derivatives from the summer of 2008. However, PFOS is only a small part of the problem. The family of PFCs consists of several hundreds other unrestricted chemicals. Because the exposure to polyfluorinated substances is so considerable, and uses seem to increase, there is an urgent need to resolve, what effect such exposure has on humans. [Int. Jr. Andrology, 2007, 31, 161–169 and refe. Therein]

Rob Bilott was a corporate defense attorney for eight years. Then he took on an environmental suit that would upend his entire career, and expose a decades-long history of chemical pollution. In March 2001, Robert Bilott embarked on an ambitious plan to force DuPont to come clean — to tell what it knew about C8 and, he hoped, eliminate the chemical from the water consumed by the large section of the population of the country.

Possibly the first whistle blower:

The farmer, Wilbur Tennant of West Verginia, said that his cows were dying. He believed that the DuPont chemical company, which until recently operated a site in that region was responsible. Till that time, Bilott worked almost exclusively for large corporate clients. His specialty was defending chemical companies. Several times, Bilott had even worked on cases with DuPont lawyers.

https://www.nytimes.com/2016/01/10/magazine/the-lawyer-who-became-duponts-worst-nightmare.html

In his law suit he presented documents showing that DuPont, which since the early 1950s had used C8 to manufacture Teflon and other products in its Parkersburg plant, had known for years that C8 posed health dangers and had spread beyond the company's West Virginia plant into local sources of drinking water.

By some measures, Bilott has in fact been successful in slamming DuPont, but 14 years after he sent his evidence to the EPA, the company has managed to avoid a full reckoning for its actions. And C8, which is in the bloodstream of 99.7 percent of Americans, remains unregulated at the national level. Although Bilott and his clients eventually prevailed in a ground-breaking class-action lawsuit filed the same year he approached the EPA, that settlement had limited applicability. Action by the EPA could hold DuPont accountable nationally.

Environmental Health Perspectives, 2013, volume 121, number 11-12, A 340
Toxicology and Applied Pharmacology, 2017.07.001, 330, (9-21); 10.1016/j.taap.
Environ. Sci. Technol. 2018, 52, 14, 8005–8015
Encyclopedia of Toxicology, 3rd Edn. 2014 Elsevier, Inc.

https://theintercept.com/2015/08/20/teflon-toxin-dupont-slipped-past-epa/

A Timeline of DuPont and C8

https://theintercept.com/2015/08/20/teflon-toxin-dupont-slipped-past-epa/

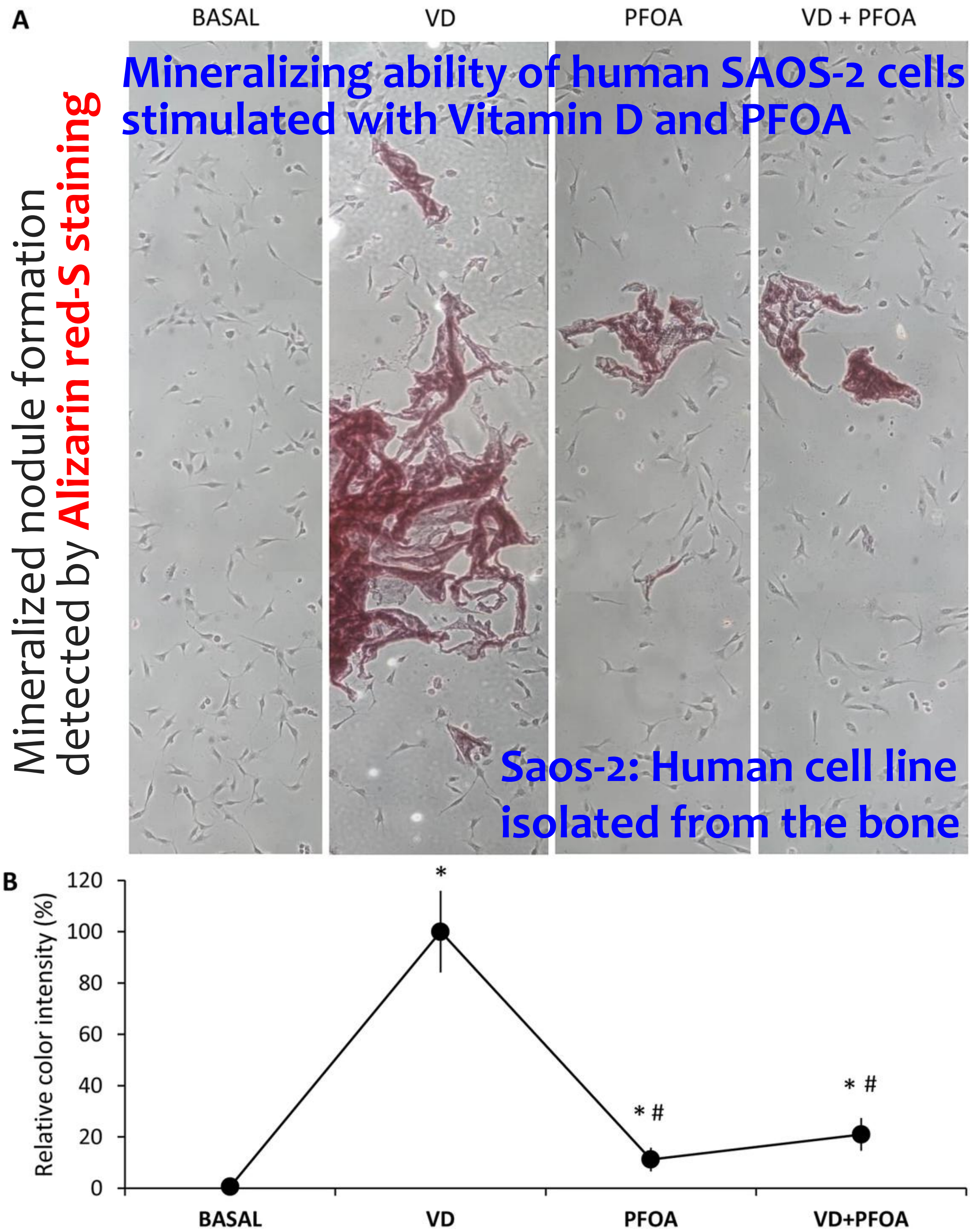
- **1945** — DuPont registers the Teflon trademark.
- **1951** — DuPont begins using C8 in the manufacture of Teflon at its West Virginia plant.
- **1954** — DuPont becomes aware of C8's possible toxicity, the same year a French engineer first applied Teflon to a pan.
- **1961** — DuPont researchers confirm that C8 is toxic.
- **1978** — 3M and DuPont become aware that C8 is accumulating in workers' blood and body tissues, causing elevated liver enzyme; several Rhesus monkeys deteriorate and die after being fed C8 in a 3M study.
- **1981** — 3M releases rat study finding birth defects; DuPont employee Sue Bailey's child Bucky born with birth defects.
- **1984** — DuPont monitors local drinking water for C8 contamination; concludes that reducing C8 emissions is not "economically attractive."
- **1999** — Wilbur Tennant's cows die after drinking water contaminated with C8 and he files suit against DuPont.
- **2000** — 3M decides to stop making C8; Bernard Reilly warns his DuPont colleagues that C8 communications may be subject to discovery.
- **2001** — DuPont settles with Tennant for an undisclosed sum; attorney Robert Bilott files class action suit against DuPont and provides the EPA with DuPont's internal documents on C8.
- **2002** — The EPA initiates a priority review of C8.
- **2005** — DuPont settles $343 million class action lawsuit and agrees to fund C8 health project to study the chemical's health affects; EPA fines DuPont $10.25 million for failing to report "substantial risk of injury to human health" from C8 (PFOA).
- **2006** — DuPont agrees to phase out its use of C8 by 2015.

Endocrine disruption of vitamin D activity by PFOA.

Perfluorooctanoic acid (PFOA) induces severe health consequences, such as neonatal mortality, neurotoxicity, and immunotoxicity.

PFAS accumulates in bone tissues and causes altered bone development. Epidemiological studies have reported an inverse relationship between PFAS and bone health, however, the associated mechanisms are still unexplored.

Interference of PFOA on vitamin D (VD) is established. First, PFOA competes with calcitriol on the same binding site of the VD receptor, leading to an alteration of the structural flexibility. Second, this causes an altered response of VD-responsive genes in two cellular targets of this hormone, osteoblasts and epithelial cells of the colorectal tract. Third, mineralization in human osteoblasts is reduced upon co-incubation of PFOA with VD. Finally, in a small cohort of young healthy men, parathyroid hormone (PTH) levels were higher in the exposed group, but VD levels were comparable. These results provide evidence of endocrine disruption by PFOA on VD pathway by competition on its receptor and subsequent inhibition of VD-responsive genes in target cells. [Sci Rep 10, 16789 (2020). https://doi.org/10.1038/s41598-020-74026-8]



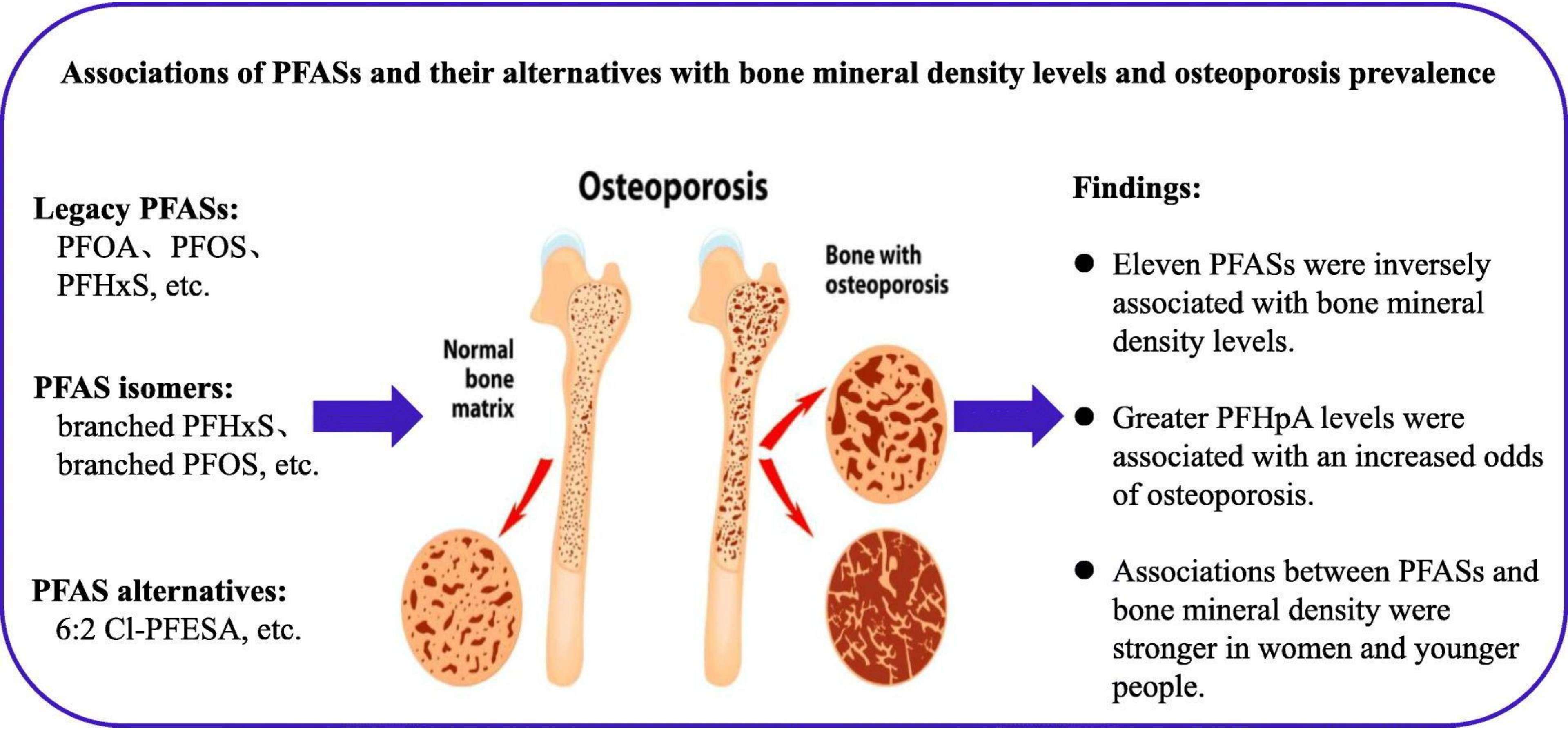
1: PFOA competes with calcitriol on the same binding site of the vitamin D receptor (VDR).

2: this interference leads to an altered response of vitamin D-responsive genes in two cellular targets of this hormone, osteoblasts and epithelial cells of the colorectal tract.

3: mineralization in human osteoblasts is reduced upon co-incubation of PFOA with calcitriol.

4: VD was not decreased in the exposed group, but PTH levels were higher in association with PFAS exposure, suggesting a compensatory mechanism in response to functional hypovitaminosis D.

[Sci Rep 10, 16789 (2020).]



Science of the Total Environment, 2023, 862, 160617

The Human Predicament:

Conflict of Socio-economic development and Human welling/Environment

"Everybody knows everybody's business," Higgs said, but nobody talked about C8. It was a matter of “not wanting to bite the hand that fed you.”

Higgs, now an emergency room physician living in Richmond, Virginia

A lasting legacy: DuPont, C8 contamination and the community of Parkersburg left to grapple with the consequences. [Environmental Health News, Jan. 2020]
https://www.ehn.org/dupont-c8-parkersburg-2644262065.html