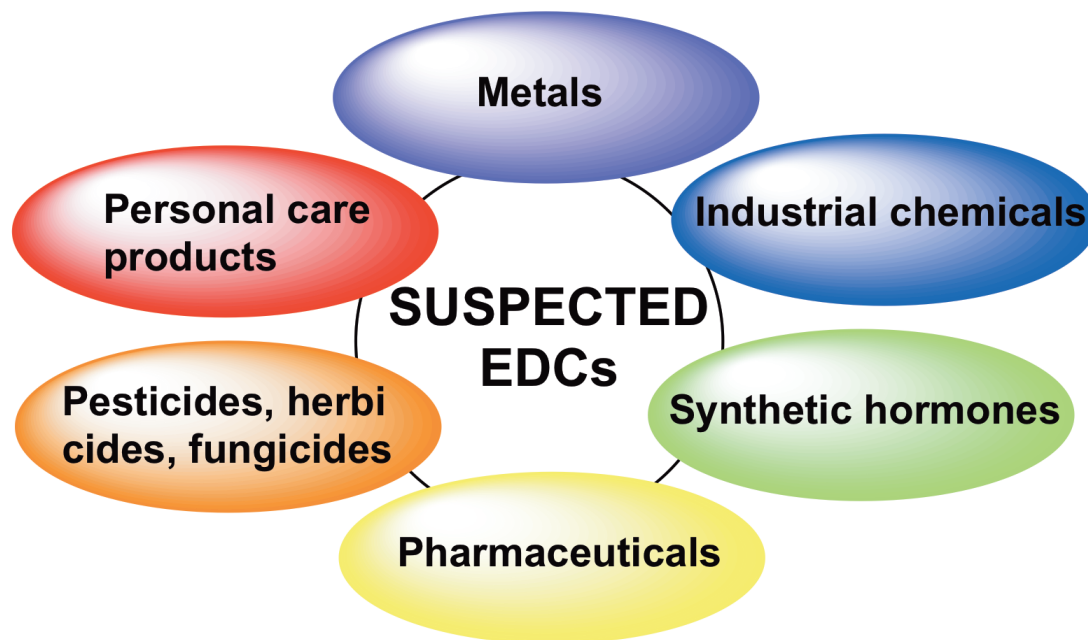


11. ENDOCRINE DISRUPTORS

Endocrine Disrupting Compounds (EDCs)

- Any exogenous chemical that interferes with the production, release, transport, binding, action, or elimination of natural hormones responsible for the maintenance of homeostasis and regulation of developmental processes.
- Interactions with the functions of estrogens, androgens, and thyroid hormones have been the most highly studied.

- Pesticides
- Herbicides
- Fungicides
- Plasticizers
- Surfactants
- Drugs
- Organometals
- Halogenated PAHs
- Phytoestrogens



Endocrine Disrupting Compounds (EDCs)

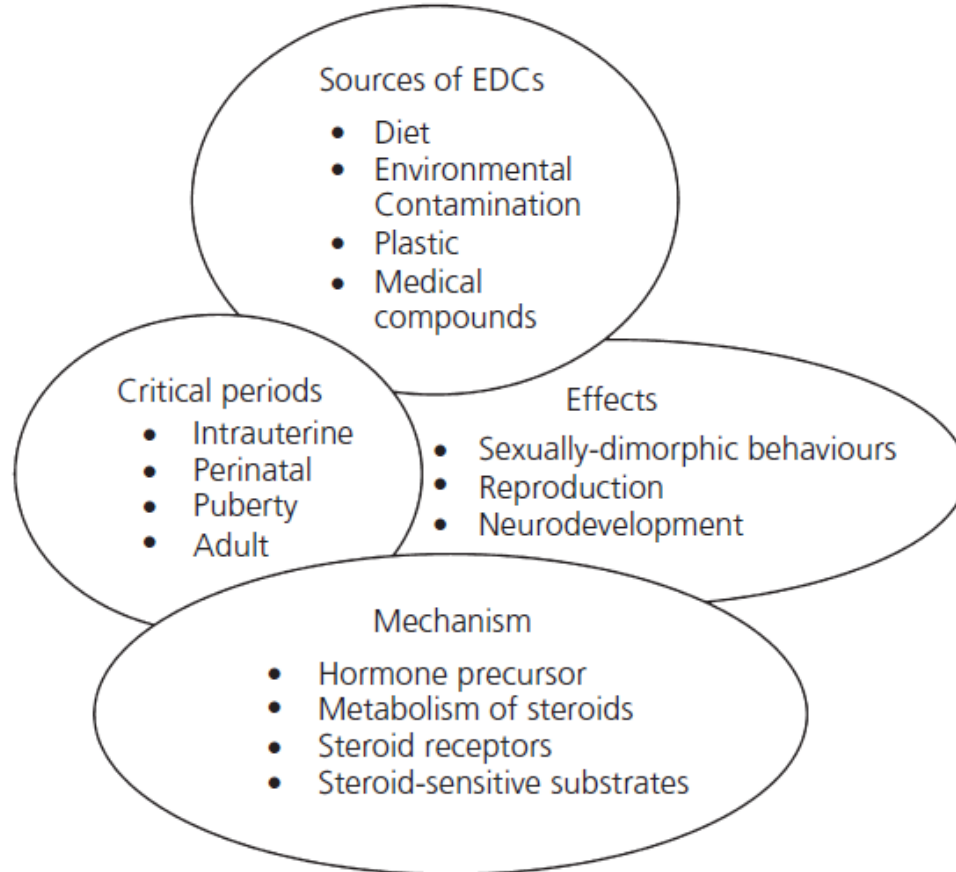
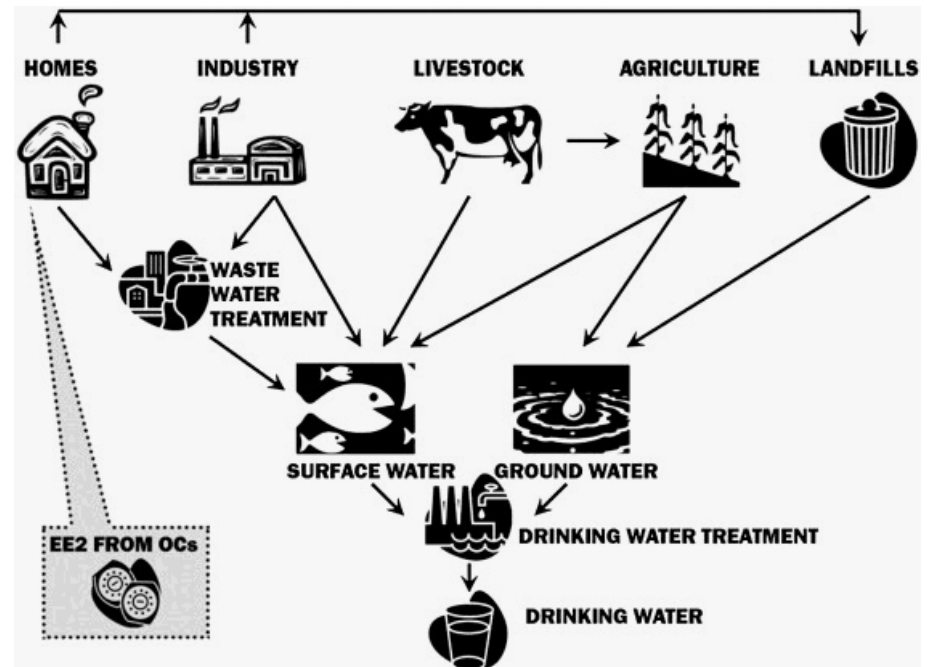
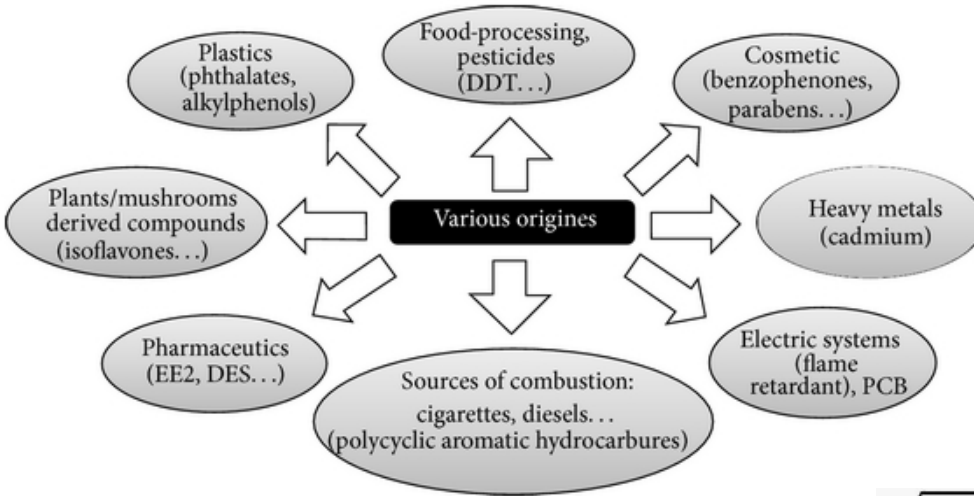


Fig. 1. A schematic representation of varied sources of endocrine disrupting chemicals (EDCs) and how they may influence sexually-dimorphic, reproductive and neurodevelopmental processes, in particular through their actions during critical periods of development. Some of the steroids mechanisms that may mediate the actions of EDCs are included.

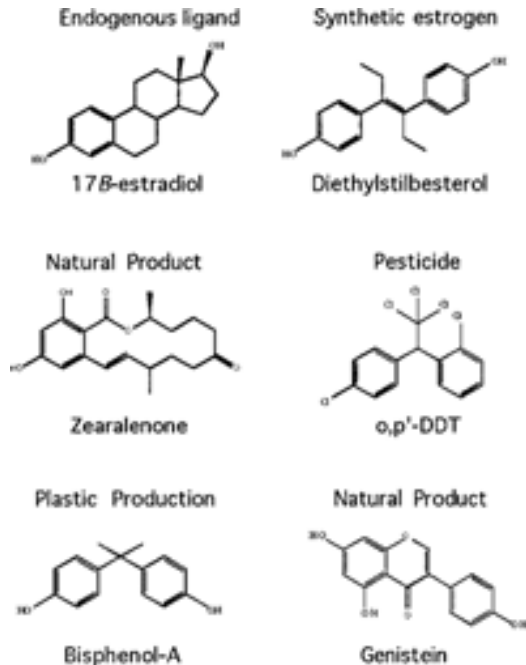
J Neuroendocrinol. 2012 Jan;24(1):144-59.
Endocrine disruptors: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. Frye CA1, Bo E, Calamandrei G, Calzà L, Dessì-Fulgheri F, Fernández M, Fusani L, Kah O, Kajta M, Le Page Y, Patisaul HB, Venerosi A, Wojtowicz AK, Panzica GC.

Endocrine Disrupting Compounds: Exoestrogens or Xenoestrogens



Prototypical Exoestrogens: Note the Diverse Chemical Structures

Table Table 1.. Different classes of alleged exoestrogens^a



Natural products	Environmental pollutants	Industrial chemicals	Pharmaceuticals	Complex mixtures
Genistein	DDT	Bisphenol A	Ethinyl estradiol	Effluents
Naringenin	Kepone	Nonionic surfactants	Diethylstilbestrol	Sediment extracts
Coumestrol	PCBs/HO-PCBs	Phthalate esters	Gestodene	Air particulate matter
Zearalenone	PAHs and dioxins	Endosulfan	Norgestrel	Tissue extracts

^a DDT = dichlorodiphenyltrichloroethane; PCBs = polychlorinated biphenyls; HO-PCBs = hydroxylated PCBs; PAHs = polycyclic aromatic hydrocarbons.

Exoestrogens: Mechanisms of action and strategies for identification and assessment

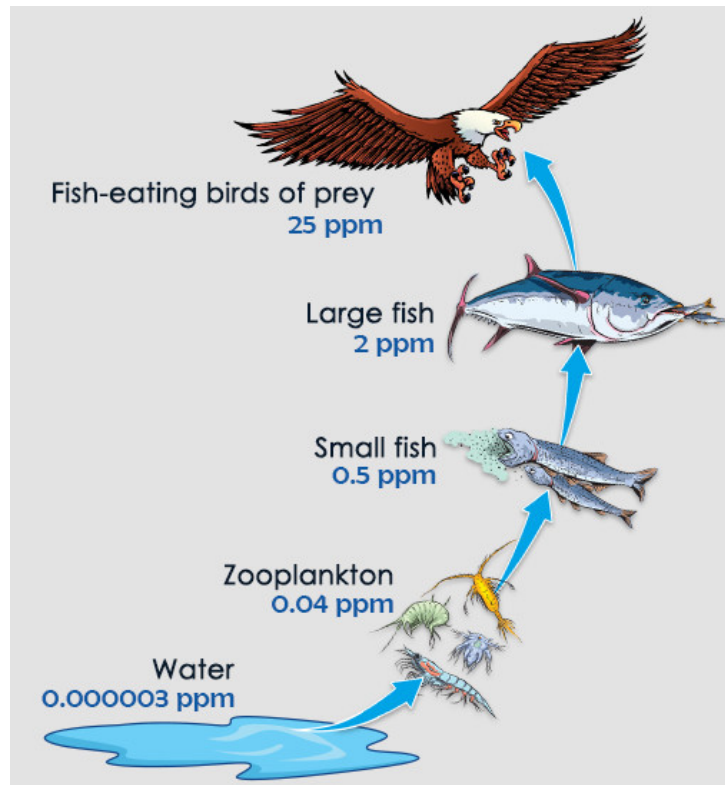
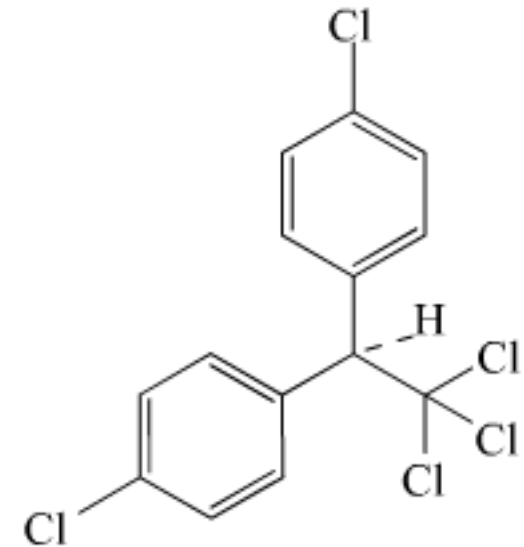
Environmental Toxicology and Chemistry

Volume 17, Issue 1, pages 3-14, 26 OCT 2009 DOI: 10.1002/etc.5620170102

<http://onlinelibrary.wiley.com/doi/10.1002/etc.5620170102/full#fig3>

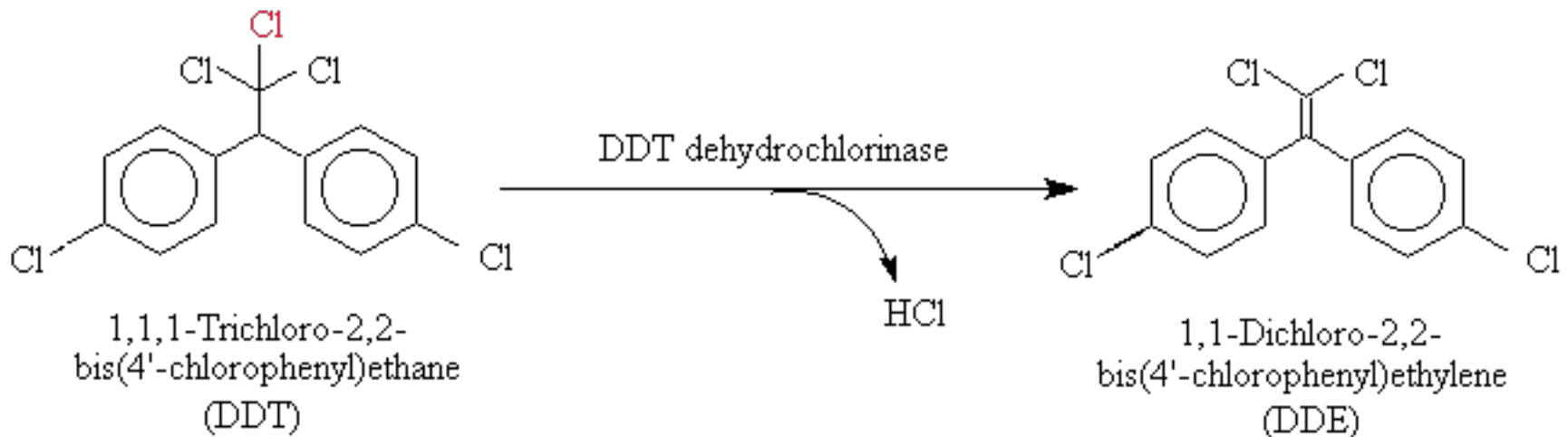
Pesticide-DDT

- 1950's to 1960's – DDT
 - Estrogenic
 - Affected reproduction system of birds
 - Disrupted the eagle's endocrine system, interfering with calcium metabolism and produced weak egg shells, feminized frogs
 - DDT metabolite (DDE) → anti-androgens



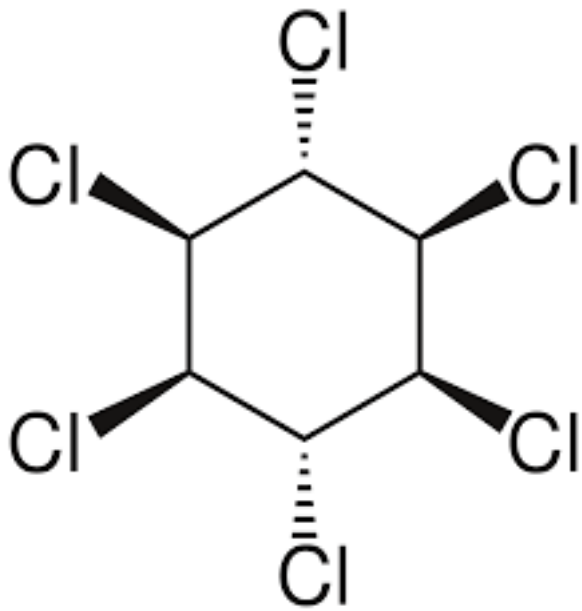
Pesticide-DDT

- Several small studies published in the late 1980s and early 1990s reported a higher level of DDE in the fat of women with breast cancer compared to women without breast cancer. Yet, the small scale of these studies and the lack of control of other factors that may have affected breast cancer risk made the significance of these studies questionable.
- These studies were followed by a larger, well-controlled study of New York City women published in 1993. Researchers reported a four-fold higher risk of breast cancer in women with the highest levels of DDE in their blood compared to the women with the lowest levels.

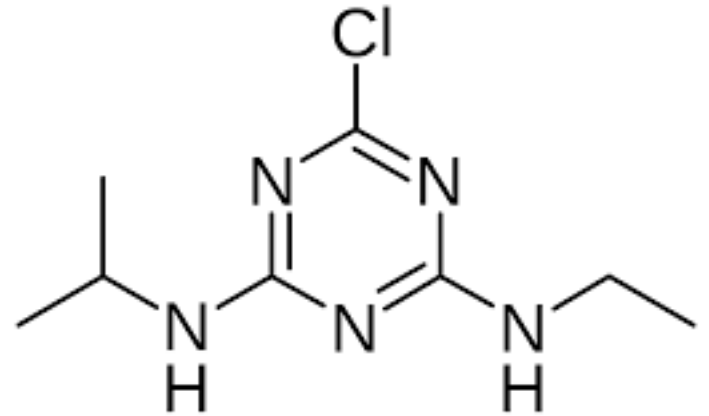


Insecticides and herbicides

Lindane is estrogenic

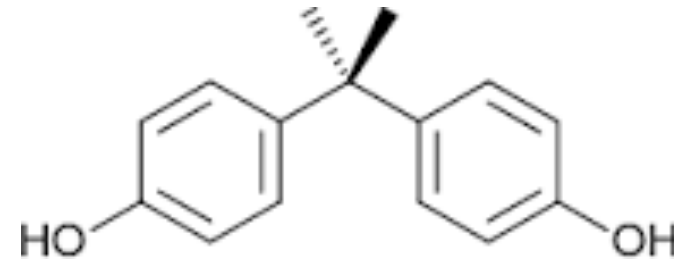


Atrazine induces aromatase expression

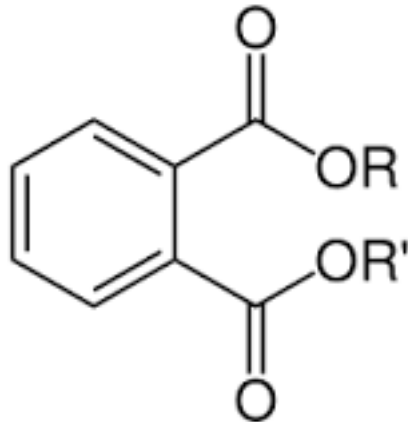


Bisphenol A and Phthalates

- Bisphenol A
 - Used in the manufacture of some clear plastics (e.g. baby feeding bottles), and used in the resin which lines most tin cans
 - Potency 4 to 6 times less than 17β -estradiol
 - Weakly estrogenic, anti-androgenic

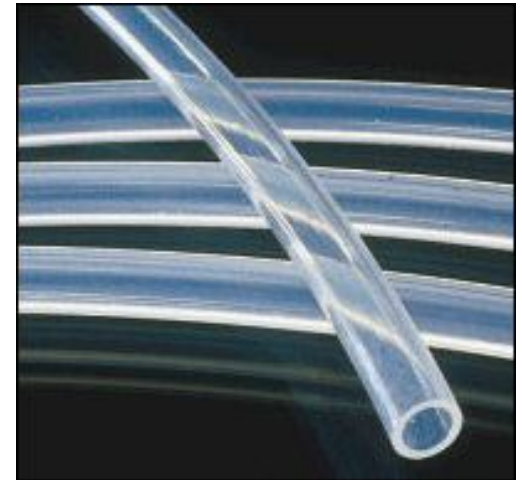


- Phthalates
 - Potency 6 to 7 times less than 17β -estradiol
 - Weakly estrogenic

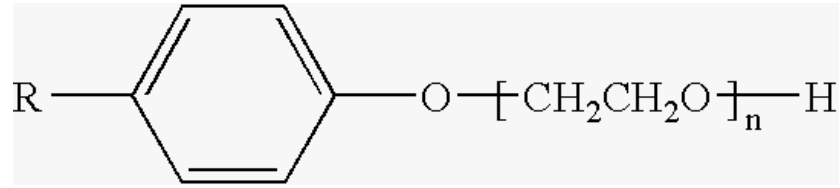


Phthalates

- Exposure of patients to phthalates from polyvinyl chloride PVC tubes and bags during dialysis
 - A group of patients not yet on dialysis treatment was used as control
 - The DEHP concentration was 0.8-4.2 mg/mL serum in the 17 hemodialysis patients after dialysis
 - In all of the pre-dialysis patients, DEHP could not be detected (less than 0.1 mg/mL).



Surfactants



- APEs: alkylphenol polyethoxylates
 - Used in detergents, cleaning products, paints, and pesticides
 - Degradation product → 4-octylphenol
 - Estrogenic
 - Found in surface water
 - Feminized male fish downstream from sewage treatment plants
 - Impaired testicular development
- Fish with both male and female sex tissue have been discovered near Colorado wastewater treatment plants on the South Platte River and Boulder Creek
- Newborn male fish become female fish after exposure to hormones
- “There are *many* reports of alkylphenols causing production of a female associated liver protein, vitellogenin, in male fish” –EPA
- **help mix oily and watery substances and that help other chemicals adhere to surfaces**
- Unfortunately, the APEs and their degradation products have been detected with increasing frequency in surface water.
- Conventional drinking water treatment technologies fail to remove these chemicals. The degradation products octylphenol and nonylphenol have been reported previously as weakly estrogenic, but the health effects have been relatively unexplored.
- Estrogen from biosolids has been found to migrate to nearby surface water mainly through surface runoff, while testosterone percolates down to the groundwater (Drewes and Shore 221)

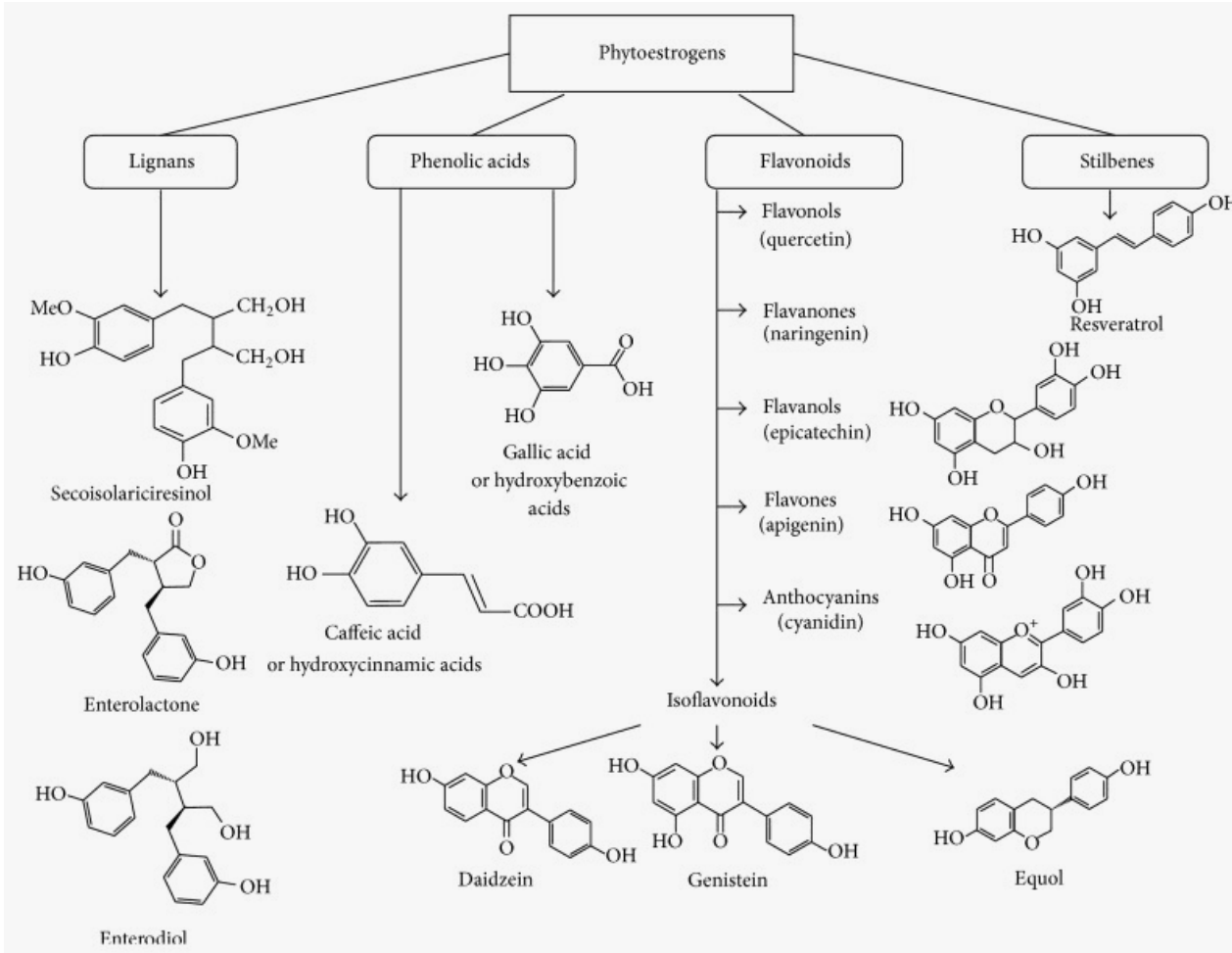
Endocrine-Disrupting Effects in Wildlife

Species	Contaminant/Effect
Mammals	
Panther	Hg, DDE, PCBs/cryptorchidism
Baltic seals	PCBs/sterility, adrenocortical hyperplasia
Beluga whales	PCBs, Dieldrin, 2,3,7,8-TCDD/hermaphroditism
European otter	PCBs/reproductive impairment
Dall's porpoises	PCBs, DDE/reduced testosterone levels
Birds	
Western gull	DDT compounds, methoxychlor/feminization, female-female pairing
Peregrine falcon	DDE/egg shell thinning
Fish-eating birds (U.S., Great Lakes)	PCDD, PCDF/reproductive failure, deformities
Common tern	PHAHs/reduced hatching, morphological abnormalities
Reptiles	
Snapping turtles	Organochlorine compounds/developmental abnormalities, feminization
American alligator	DDE/low hatching rates, abnormalities in males and females
Fish	
Roach	Steroid estrogens/increased vitellogenin in males, intersex
Flounder	Nonylphenol, octylphenol/vitellogenin in male fish
Flounder	Estrogens/vitellogenin in male fish
Rainbow trout	Estrogens, nonylphenol/vitellogenin in male fish

EDCs in Cosmetics & Toiletries

- Alkylphenol Ethoxylates
- Benzophenone-3 (Bp-3)
- Butyl Benzyl Phthalate
- Butylated Hydroxyanisole (BHA)
- Butyl-methoxydibenzoylmethane (B-MDM)
- Dibutyl Phthalate
- Diethyl Phthalate
- Homosalate (HMS)
- Methyl-benzylidene Camphor (4-MBC)
- Nitro Musks
- Octyl-dimethyl-PABA (OD-PABA)
- Octyl-methoxycinnamate (OMC)
- **Parabens**
- Polycyclic Musks
- Resorcinol

Phytoestrogens



Sources of Phytoestrogens

Isoflavones

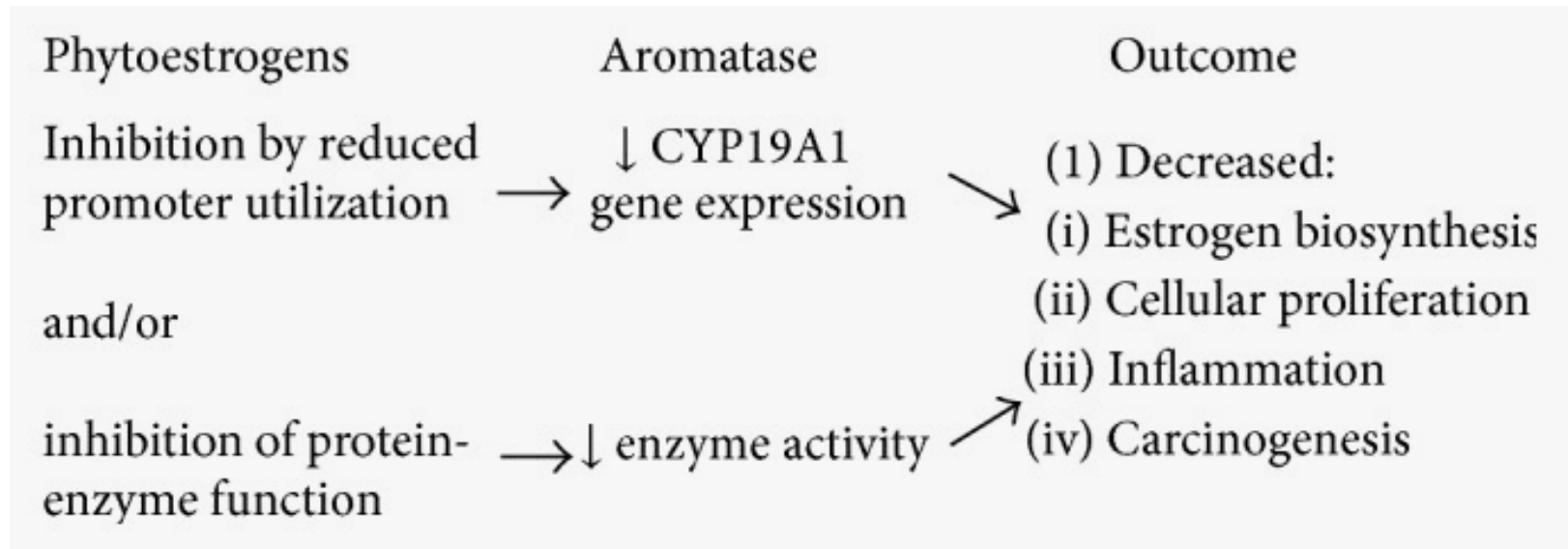
Soybeans
Lentils
Beans
haricot
broad
kidney
lima
Chick peas
Wheat
Barley
Hops
Rye
Bran
Oats
Rice

Lignans

Flaxseed
Wheat
Oats
Bran
Garlic
Asparagus
Carrot
Broccoli
Mushroom
Pear
Plum
Banana
Orange
Apple
Strawberry

Phytoestrogens

- Phytoestrogens are a group of plant derived naturally occurring compounds that have chemical structures similar to estrogen.
- Since phytoestrogens are known to be constituents of animal/human food sources, these compounds have received increased research attention.
- Phytoestrogens may contribute to decreased cancer risk by the inhibition of aromatase enzyme activity and CYP19 gene expression in human tissues.
- The impact on health and phytoestrogen's potential as anticancer treatments, but well-controlled, large-scale studies are warranted to determine the effectiveness of phytoestrogens on breast cancer and age-related diseases.



Mechanisms of Endocrine Disruption

- Binding and activating the estrogen receptor (thereby acting as an estrogen)
- Binding but not activating the estrogen receptor (thereby acting as an anti-estrogen)
- Modifying the metabolism of natural hormones
- Modifying the number of hormone receptors in a cell (reduce or increase the number)
- Modify the production of natural hormones
- Interactions with steroid binding proteins
- Can act through both i) receptor-mediated and non-receptor-mediated mechanisms.
e.g., genistein is a weak estrogen receptor agonist, but can also modulate the activity of tyr kinases and DNA topoisomerases.
- Compounds may act as either estrogens or anti-estrogens depending on the cellular environment.
 - Certain hydroxylated PCBs are able to bind the estrogen receptor and activate gene transcription at high concentrations.
 - However, these PCB metabolites are weak agonists at appropriate concentrations, and they may have the potential to interfere by competing with endogenous estrogens for binding sites.
- We have additive effects: several chemicals binding and activating the estrogen receptor – their combined effects will be additive.
e.g., butylbenzyl phthalate and di-*n*-butyl phthalate can add their effects to any natural estrogen present.

Timing of Exposure

- Sensitivity of an individual to gonadal steroids depends on where (s)he is *temporally* in life.
- Thus, a chemical may have little-to-no impact on a young/older adult, but may have profound development-disrupting effects if exposure occurs *in utero* or during puberty.
- *E.g.*, PCBs and dioxin affect development more during gestational than during lactational exposure.
- Generally, sensitivity to EDCs is greater during fetal and perinatal exposure than during adulthood.
- However, sometimes, fetal serum-binding proteins may protect the fetus from harmful EDCs (lower sensitivity).
 - e.g.*, α -fetoprotein binding 17- β -estradiol protects the fetal male rat from maternal estrogens.

Suspected Effects in Boys and Men

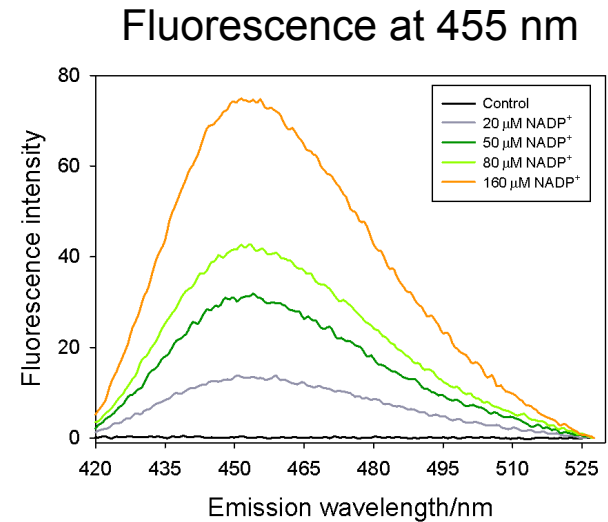
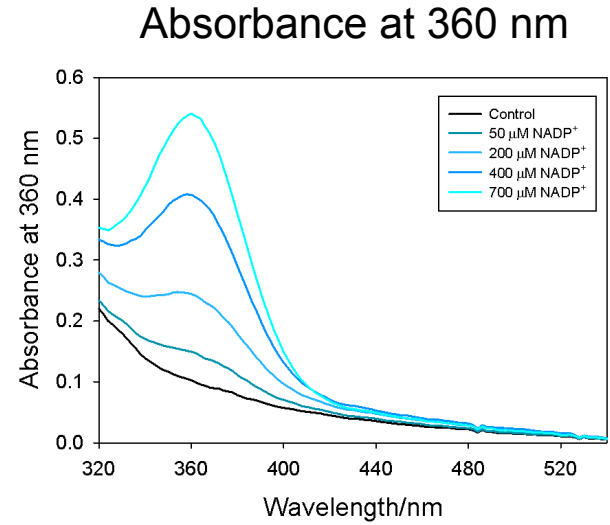
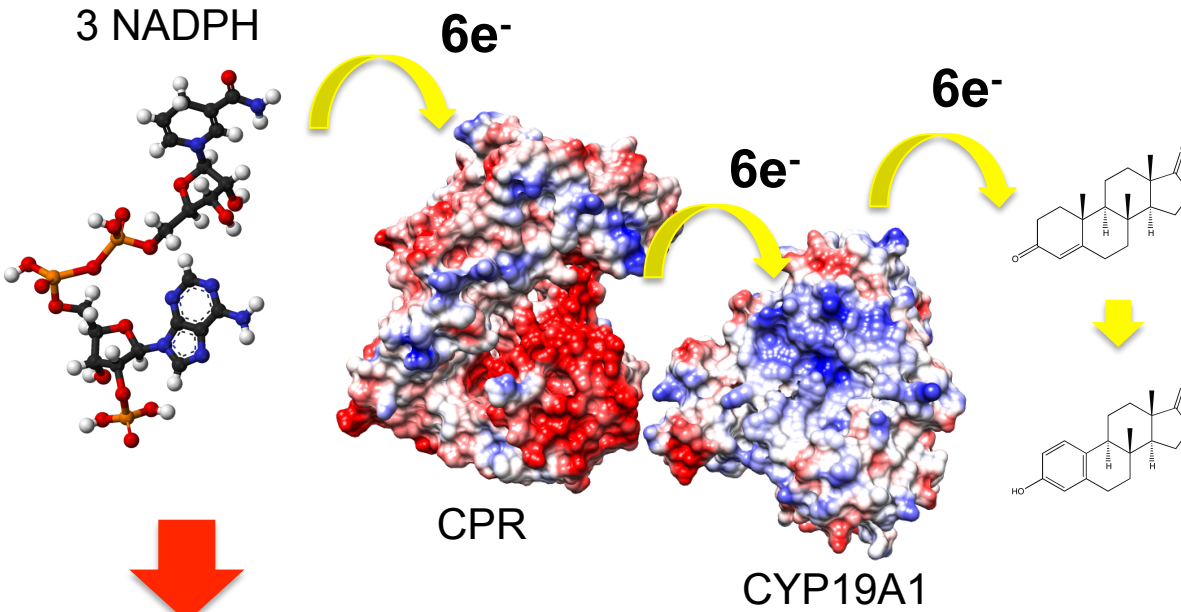
- Male Fertility
 - Reduction in sperm production.
 - Reduced ability of sperm's ability to fertilize an egg.
- Sexual Development Defects and Cancer
 - Undescended testicles in baby boys.
 - “Inter-sex” features (male and female organs) in baby boys.
 - Shorter than normal penises.
 - Increased incidences of cancer of the testicles in younger men.
 - Prostate enlargement in older men.
- Difficulty in becoming pregnant
 - Also difficulty in maintaining pregnancy.
- Breast Cancer
 - This is complex and endocrine disruptors may only be one of multiple contributing factors.
- Endometriosis
 - This is when bits of uterine lining migrate to other pelvic organs causing pain, internal bleeding, and infertility

Additional Suspected Effects

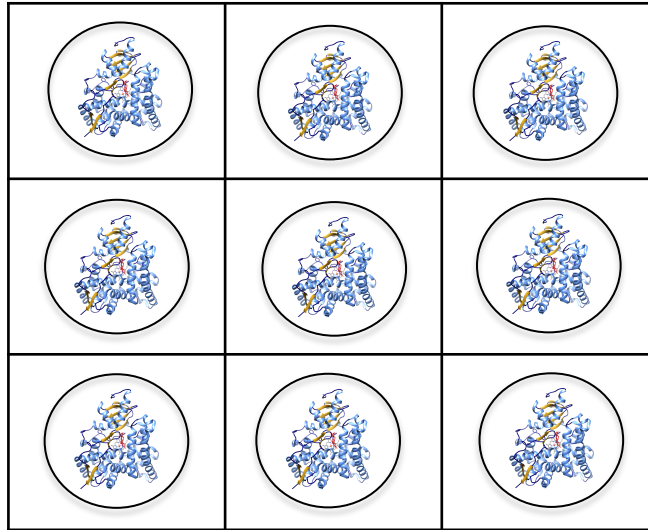
- Increased Incidences of Goiters
 - Goiters are enlargements of the thyroid gland.
 - They can disrupt metabolism and result in the “wasting syndrome”
- Hyperactivity, Learning, & Attention Problems
 - These include neurological disorders such as abnormalities in behavior, difficulty in learning, distorted sensory functions, and immunological disorders that may cause susceptibility to disease, hypersensitivity and allergies.

High-throughput
screening method for
aromatase inhibitors and
endocrine disruptors

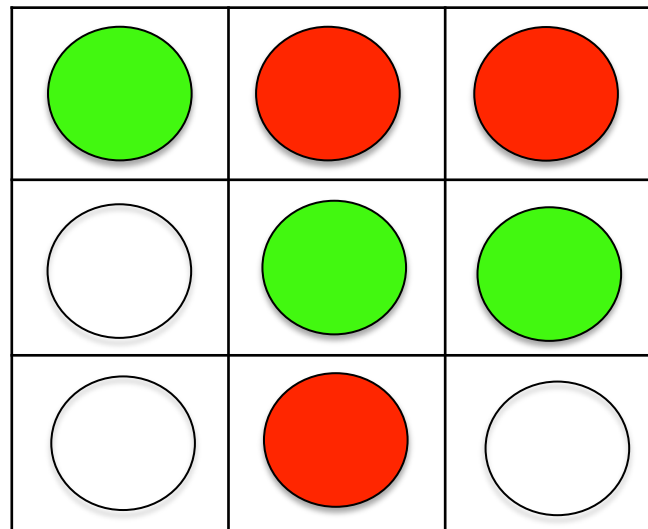
ALKALI ASSAY



ALKALI ASSAY



rArom in a **96-wells plate**

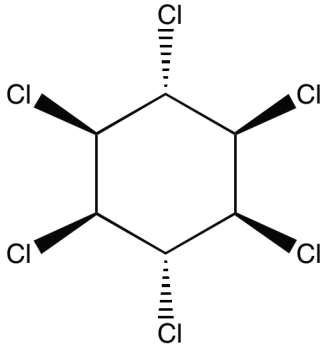


Potential EDCs

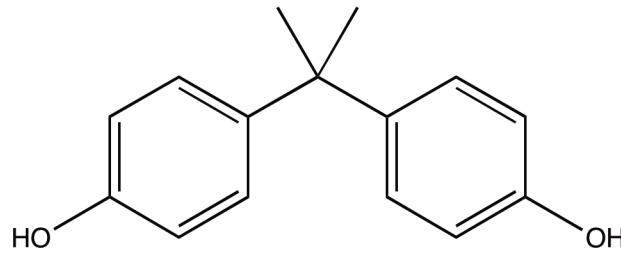
- Green circle: Activator
- Red circle: Inhibitor
- White circle: No effect

ALKALI ASSAY

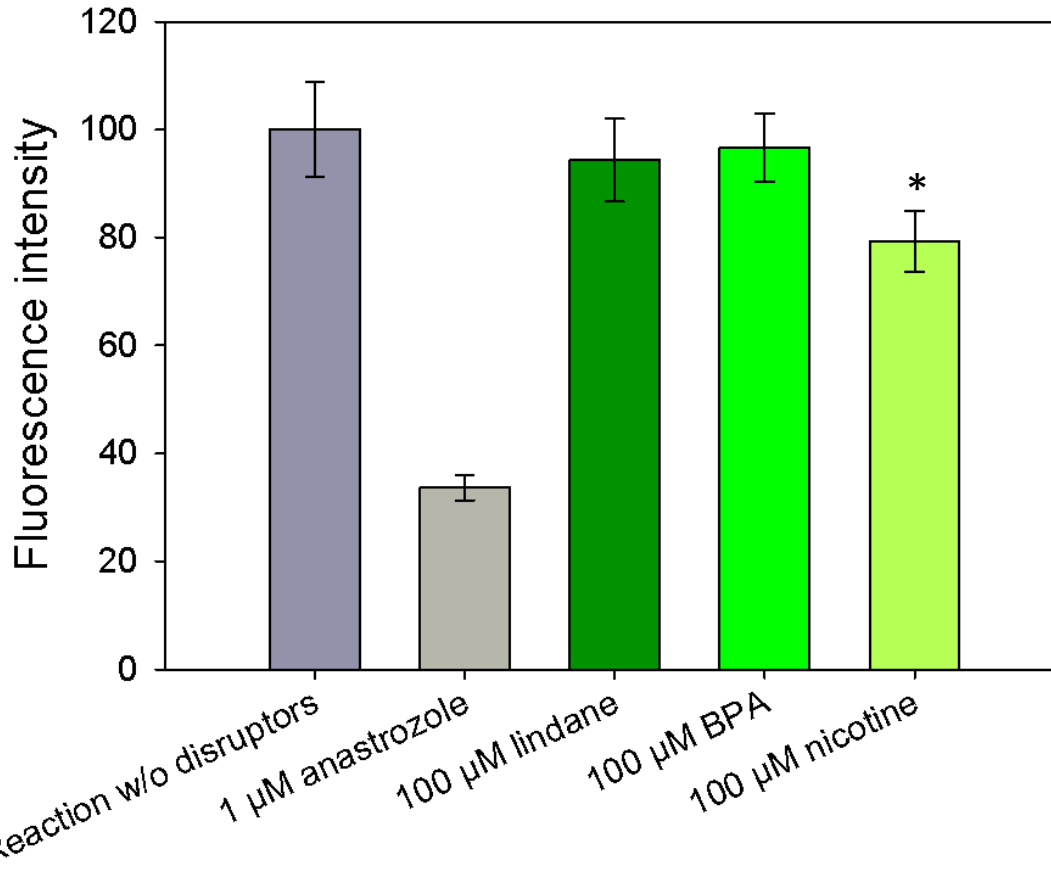
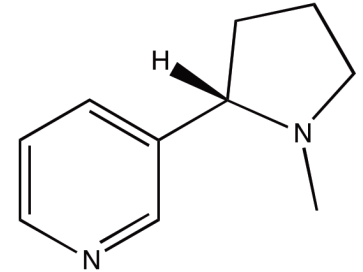
Lindane



Bisphenol A

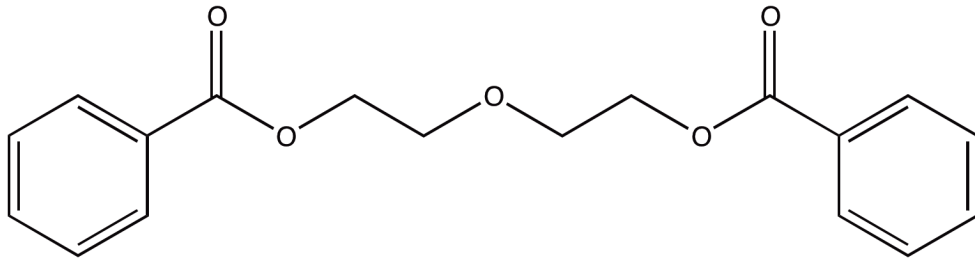


Nicotine

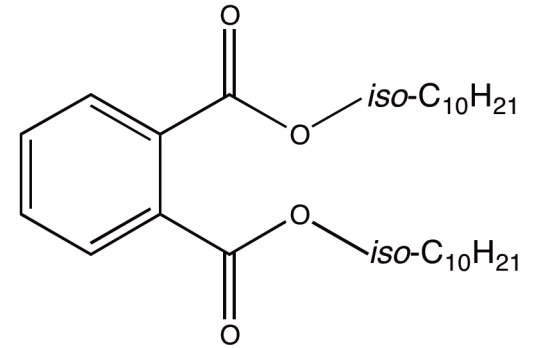


* P-value < 0.05 by ANOVA test

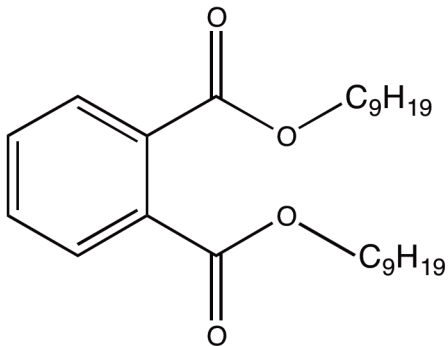
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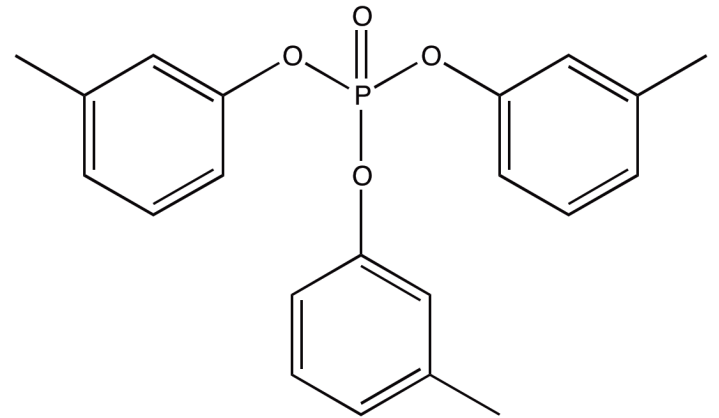
Diethylene glycol dibenzoate



Diisodecyl phthalate

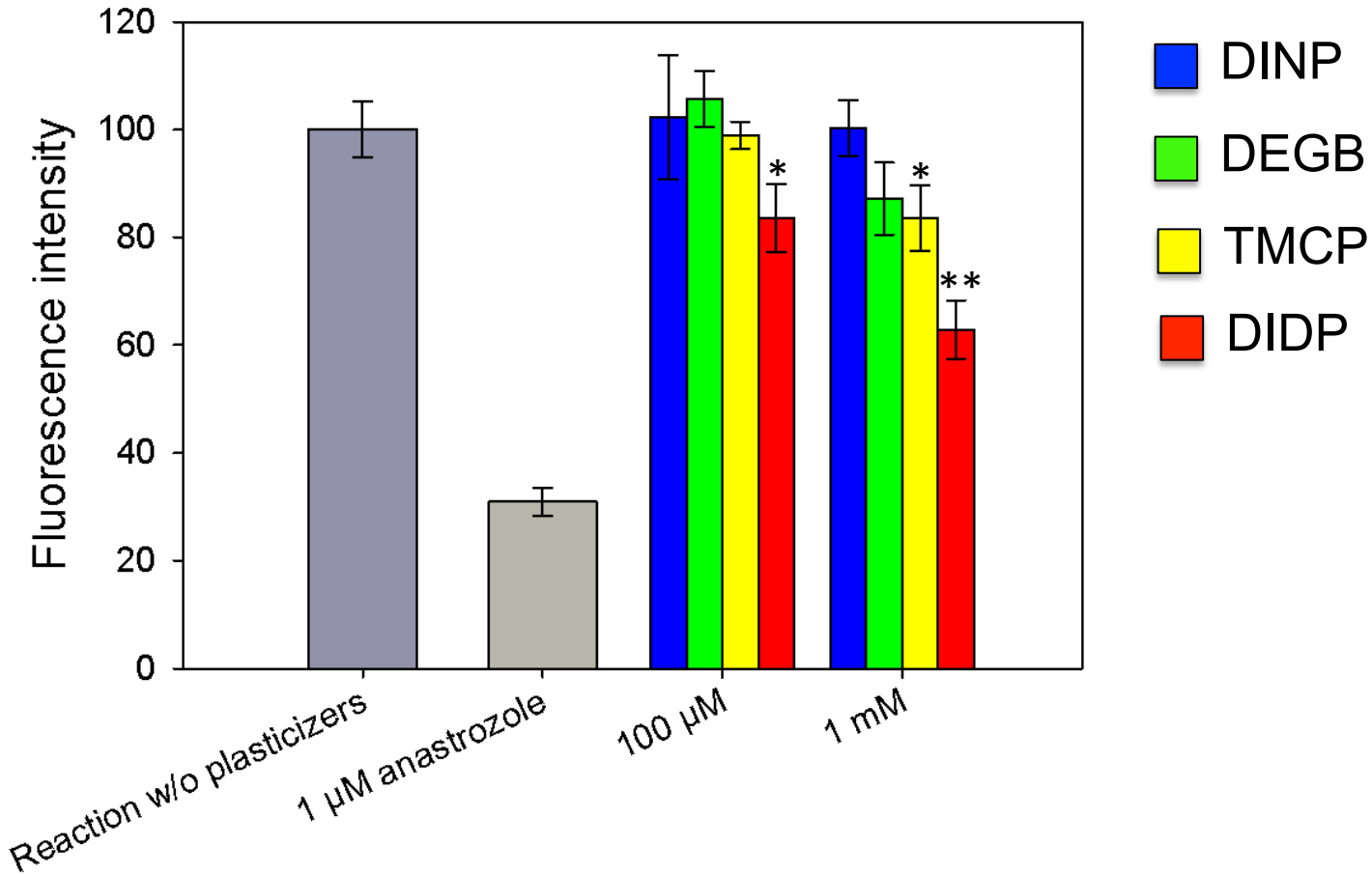


Diisononyl phthalate



Tri-m-cresyl phosphate

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* P-value < 0.05 by ANOVA test

** P-value < 0.001 by ANOVA test