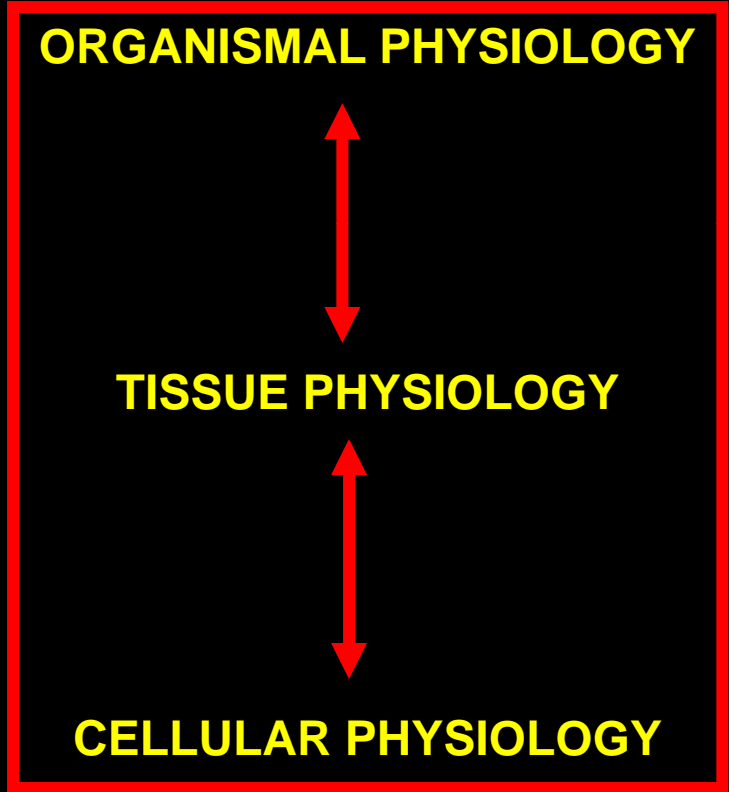


ENDOCRINE DISRUPTION: A COMPARATIVE APPROACH

Dr. Mason email: zedmason@csulb.edu

MULTI-CELLULAR EUKARYOTIC ORGANISM



- Neural
- Contact recognition
- Chemical (hormonal)

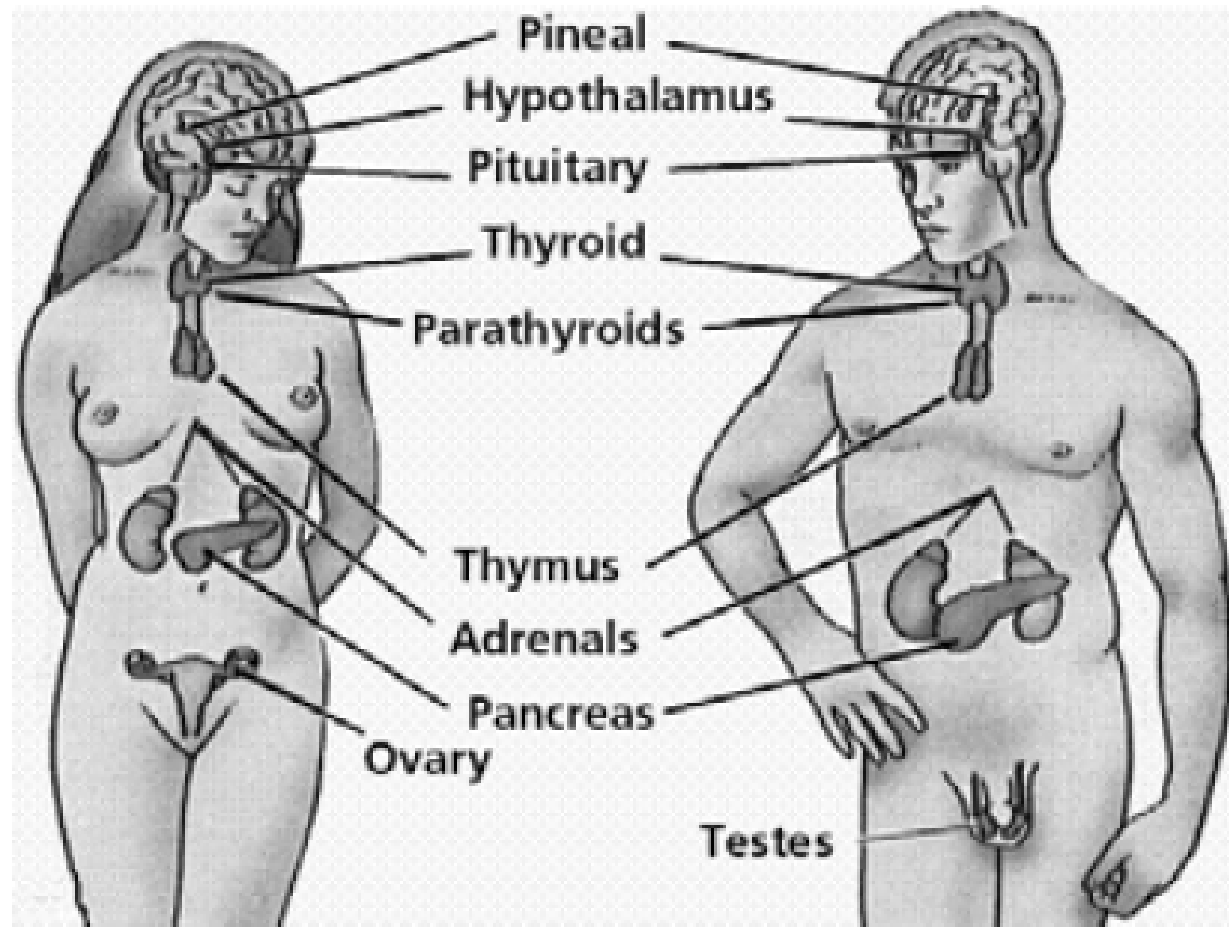
PERCEPTION, RECEPTION, ACTION

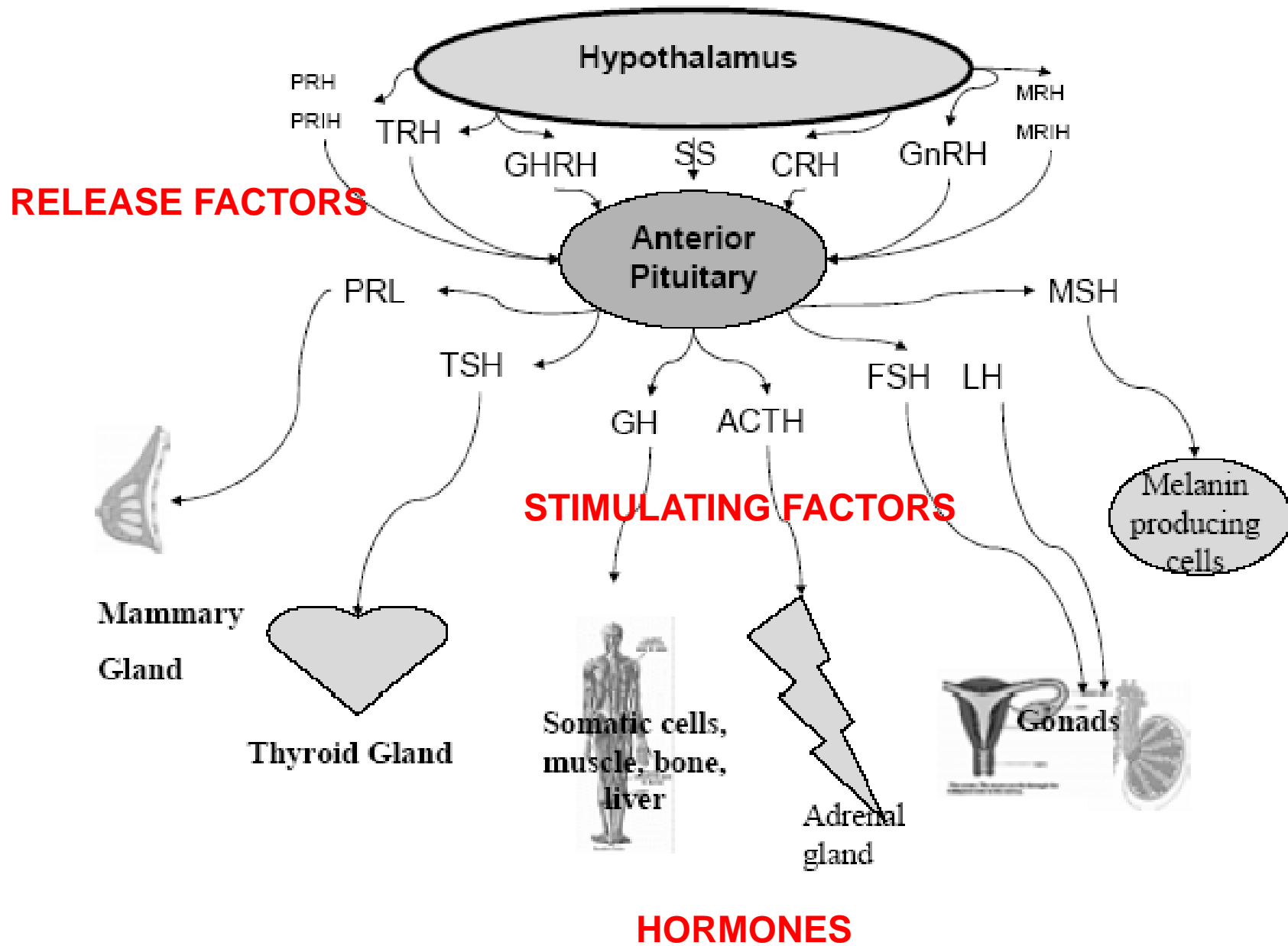
EXTERNAL CUES

- TIME
- PHOTOPERIOD
- TEMPERATURE
- SALINITY
- PRESSURE
- GRAVITY
- OSMOTIC PRESSURE
- ODOR
- PHEROMONES
- BEHAVIOR



MAJOR ENDOCRINE ORGANS IN HUMANS





**ORGANIC CHEMISTS PRODUCE UP TO 50,000
CHEMICALS PER YEAR**

**CHEMICALS AND XENOBIOTICS THAT MIMIC
HORMONES THAT ACCUMULATE IN ORGANISMS
CAN PERTURB ENDOCRINE FUNCTION**

**THESE CHEMICALS ARE TERMED ENDOCRINE
DISRUPTORS**

What is endocrine disruption ?

- Definition of the EU commission (1998):
Exogenic compounds which negatively affect the health of an intact organism or its offspring by interference with its endocrine function.
- Endocrine disruptors (EDCs) are environmental chemicals which directly or indirectly influence the hormonal system and may be active at low concentrations.

Suspected endocrine disrupting compounds

Insecticides

Carbaryl
Chlordan
DDT and DDE
Dicofol
Dieldrin
Endosulfan
Lindan
Methoxychlor
Mirex
Oxychlordan
Parathion
Toxaphen
Pyrethroide

Herbicides

Alachlor
Amitrol
Atrazin
2,4-Dichlorphenoxy-acetic acid
Metribuzin
Nitrofen
2,4,5-Trichlorphenoxy-acetid acid

Nematicides

Aldicarb
DBCP (1,2-Dibrom-3-chlorpropan)

Fungicides

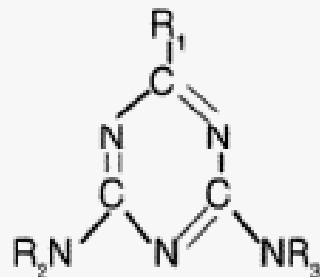
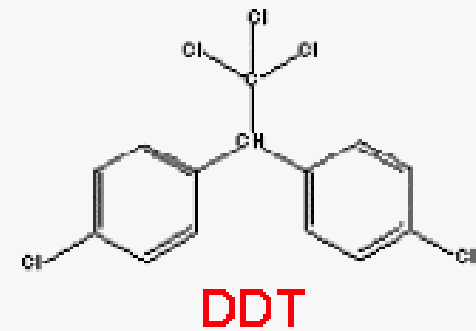
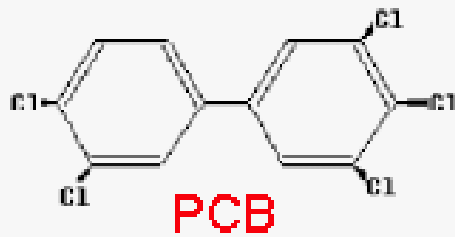
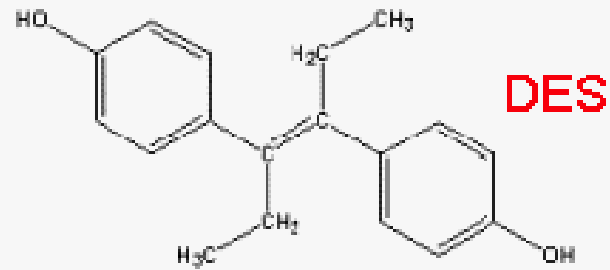
Benomyl
Fenarimol
Mancozeb
Maneb
Tributyltin compounds (TBT)
Triphenyltin compounds (TPT)
Vinclozolin
Zineb

Industrial chemicals

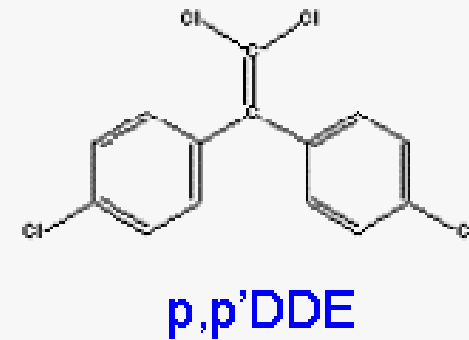
Alkylphenols
Bisphenol A
Dioxine (2,3,7,8-TCDD)
Pentachlorphenol
Phthalate
Polybromated Biphenyls (PBB)
Polychlorinated Biphenyls (PCB)

(from Oehlmann & Markert, 1997)

Endocrine Disruptors



atrazine (?)



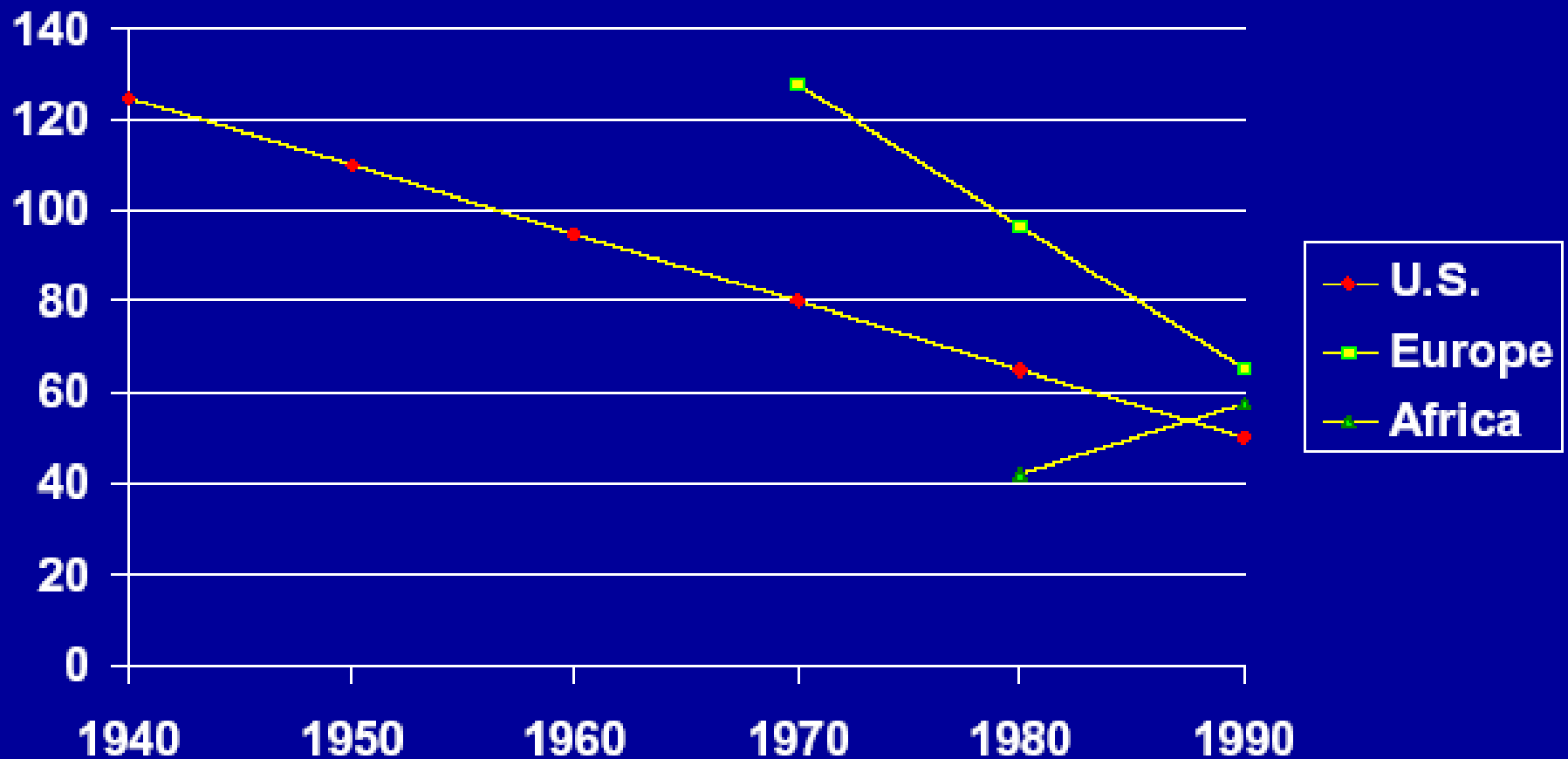
Endocrine Disruption Observations

- Cryptorchidism in the Florida panther.
- Small baculum in young male otters.
- Small penises in alligators.
- Sex reversal in fish.
- Altered social behavior in birds.
- Proposed that EDCs also may have contributed to increases in testicular cancer and hypospadias and the reported decline in human sperm counts.



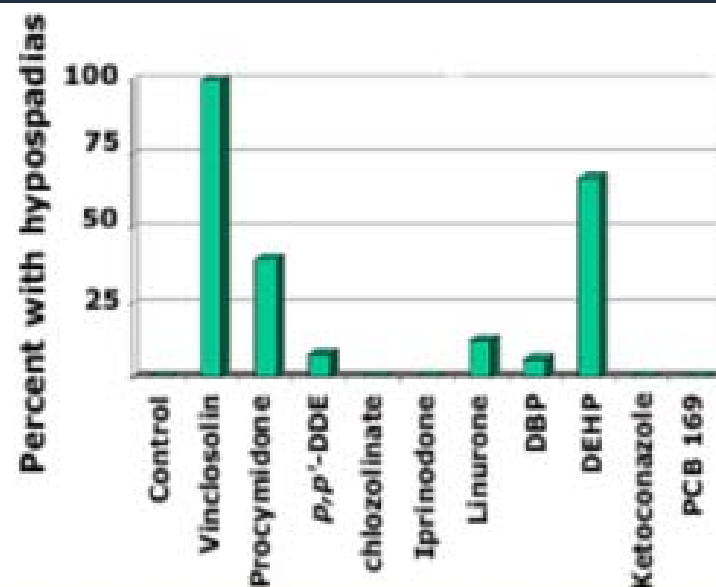
Sperm Density Declines: A Meta-analysis

Swan et. al., Env Hlth Persp 105: 1228-1232, 1997



Incomplete Masculinization of the Reproductive Tract

HYPOSPADIAS in the US



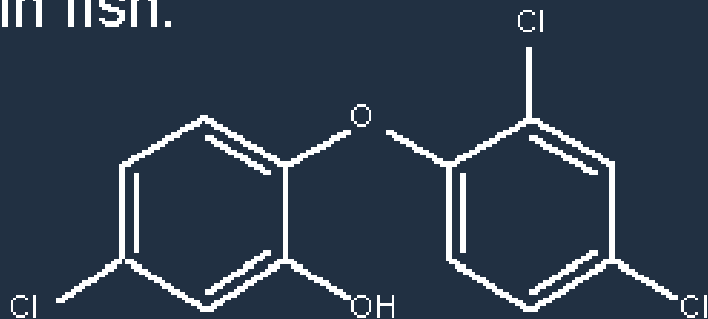
Paulozzi LJ, Erickson JD, Jackson RJ. 1997. Hypospadias trends in two U.S. surveillance systems. *Pediatrics* 100:831-834.

Paulozzi LJ 1999. International trends in rates of hypospadias and cryptorchidism. *Environmental Health Perspectives* 107:297-302.

Gray, LE, C Wolf, C Lambright, P Mann, M Price, RL Cooper and J Ostby. 1999. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinat, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicology and Industrial Health*. 15:94-118.

Example: Antibiotic Soap

- Triclosan, the common antiseptic, was found in 57.6% of the United States water resources surveyed (USGS).
- A broad-spectrum antibacterial - antimicrobial agent classified as a Class III drug by the FDA.
- Bacteriostatic activity against a wide range of bacteria has lead to popular use in:
 - Personal care products, cosmetics, anti- microbial creams, acne treatment, lotions and hand soaps, plastics, polymers and textiles.
- Linked to estrogenic effects in fish.



Male-to-Female Sex Reversal

- Fish: “complete, permanent, and functional male-to-female sex reversal in the Japanese medaka (*Oryzias latipes*, d-rR strain) after a onetime embryonic exposure to the xenoestrogen o,p,-DDT”

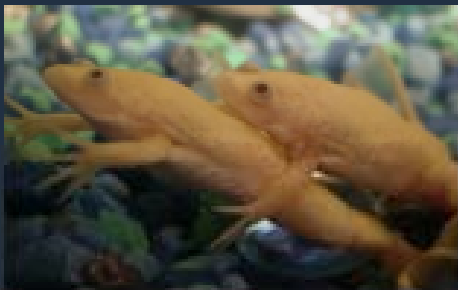
Edmunds, JSG, RA McCarthy and JS Ramsdell.
2000. Permanent and Functional Male-to-Female
Sex Reversal in d-rR Strain Medaka (*Oryzias latipes*)
Following Egg Microinjection of o,p,-DDT.
Environmental Health Perspectives 108:219-224



Hermaphroditism - Demasculinization

- Frogs: “Atrazine (0.1 ppb) induced hermaphroditism and demasculinized the larynges of exposed males (1.0 ppb). Male (African clawed frogs) suffered a 10-fold decrease in testosterone levels when exposed to 25 ppb atrazine.

Hayes, TB, A Cullins, M Lee, M Menduza, N Nuriega, AA Stuart, and A Vonk. 2002. Hermaphroditic, demasculinized frogs after exposure to the herbicide, atrazine, at low ecologically relevant doses. *Proceedings of the National Academy of Sciences (US)* 99:5476-5480.



Sex Ratio, Hermaphroditism Reproductive Failure

- Oysters: “nonylphenol has been found to induce long-term and transgenerational effects in the Pacific oyster ...when larvae are exposed to environmentally relevant concentrations of nonylphenol ...change in the sex ratio ...increase in the incidence of hermaphroditism (up to 30%) ...(next generation) gamete viability, up to 100% mortality.”

Nice, HE, D Morrill, M Crane and M Thorndyke.
2003. Long-term and transgenerational effects
of nonylphenol exposure at a key stage in the
development of *Crassostrea gigas*.
Possible endocrine disruption?
Marine Ecology Progress Series 256:293-300.



Anti-Estrogenic Polycyclic Musks

•“The polycyclic musks (AHTN) and (HHCB) are used as fragrance ingredients in perfumes, soaps, and household cleaning products...are known to be ubiquitously present in the aquatic environment, and because of their lipophilic nature, they tend to bioaccumulate in aquatic biota... musks bioaccumulated in the fish, with concentrations... which were roughly 600 times higher than doses... are shown to be *antiestrogenic* in an *in vivo* fish assay that focuses solely on ER-mediated effects.”

In Vitro and in Vivo Antiestrogenic Effects of Polycyclic Musks in Zebrafish Richard H. M. M. Schreurs,* Juliette Legler, Elsa Artola-Garicano, Theo L. Sinnige, Peter H. Lanser, Willem Seinen, and Bart van der Burg.
Environ. Sci. Technol., 38 (4), 997 -1002, 2004.



Male-to-Female Sex Reversal

- Salmon: “a high incidence (84%) of a genetic marker for the Y chromosome in phenotypic females sampled from the wild... It appears likely that female salmon with a male genotype have been sex reversed, creating the potential for an abnormal YY genotype in the wild that would produce all-male offspring and alter sex ratios significantly.”

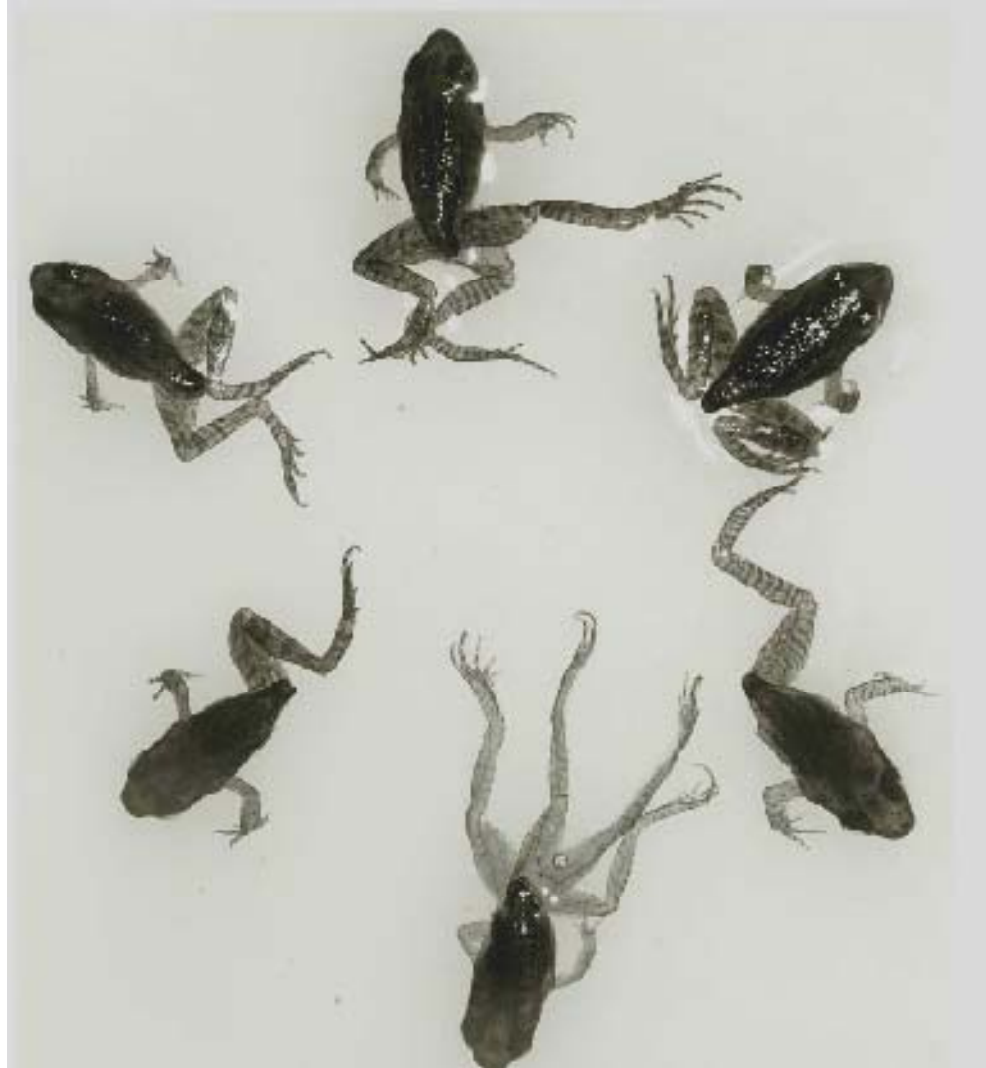
High Incidence of a Male-Specific Genetic Marker in Phenotypic Female Chinook Salmon from the Columbia River. Nagler, JJ; Bouma, J; Thorgaard, GH; Dauble, DD
Environmental Health Perspectives. Vol. 109, no. 1, pp. 67-69. Jan 2001



TERATOGENIC EFFECTS

ATRAZINE AFFECTS MALE TADPOLES 0.1ppb

EPA DRINKING WATER STANDARDS 3.0ppb



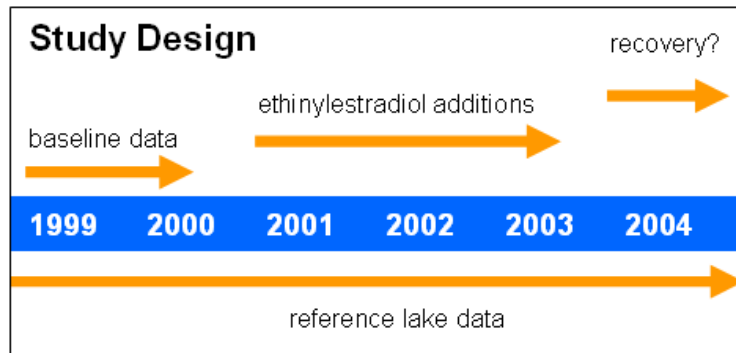
Experimental Lakes Study (1999-2004)

Whole Lake Additions of Ethinylestradiol (EE2)

Collaborators: NERL-Cincinnati, Fisheries and Oceans Canada, USGS



Goal: apply genomic tools to assess exposure of wildlife to EDCs in a field exposure study

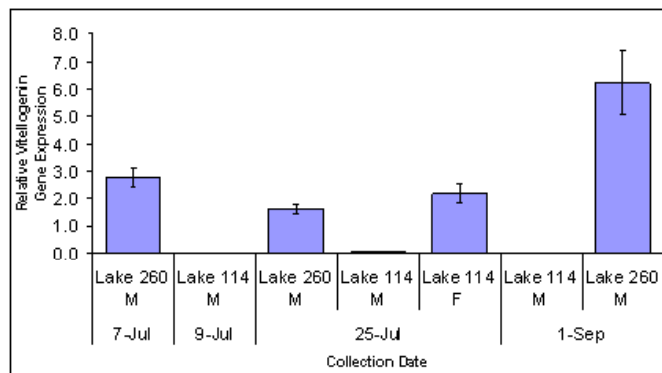


Major Findings

- Fathead minnows and pearl dace had elevated whole body concentrations of vitellogenin within 7 weeks of EE2 additions to Lake 260
- Egg development delayed in fathead minnows and pearl dace; testes development impaired; testes-ova observed in males
- Reproductive failure was observed in both of these minnow species during the second year of additions

Kidd KA, Blanchfield PJ, Mills KH, Palace VP, Evans RE, Lazorchak JM, Flick RW. Collapse of a fish population after exposure to a synthetic estrogen. *Proc Natl Acad Sci U S A*. 2007 May 22;104(21):8897-901.

Vitellogenin gene expression in male fathead minnows



Impact

- Extended the capabilities of EPA/ORD EDC monitoring efforts
- EPA cites the study for developing Ambient WQC for EDCs
- FDA has cited paper for Environmental Assessment testing

Mode of Action of EDCs

EDCs can act

- **directly**

by binding to the receptors as:

- **agonists - acting like natural hormones (e.g. ethinylestradiol, nonylphenol)**
- **antagonists - blocking receptors for natural hormones (e.g. tamoxifen, TCB-77, p,p'-DDE)**

- **indirectly**

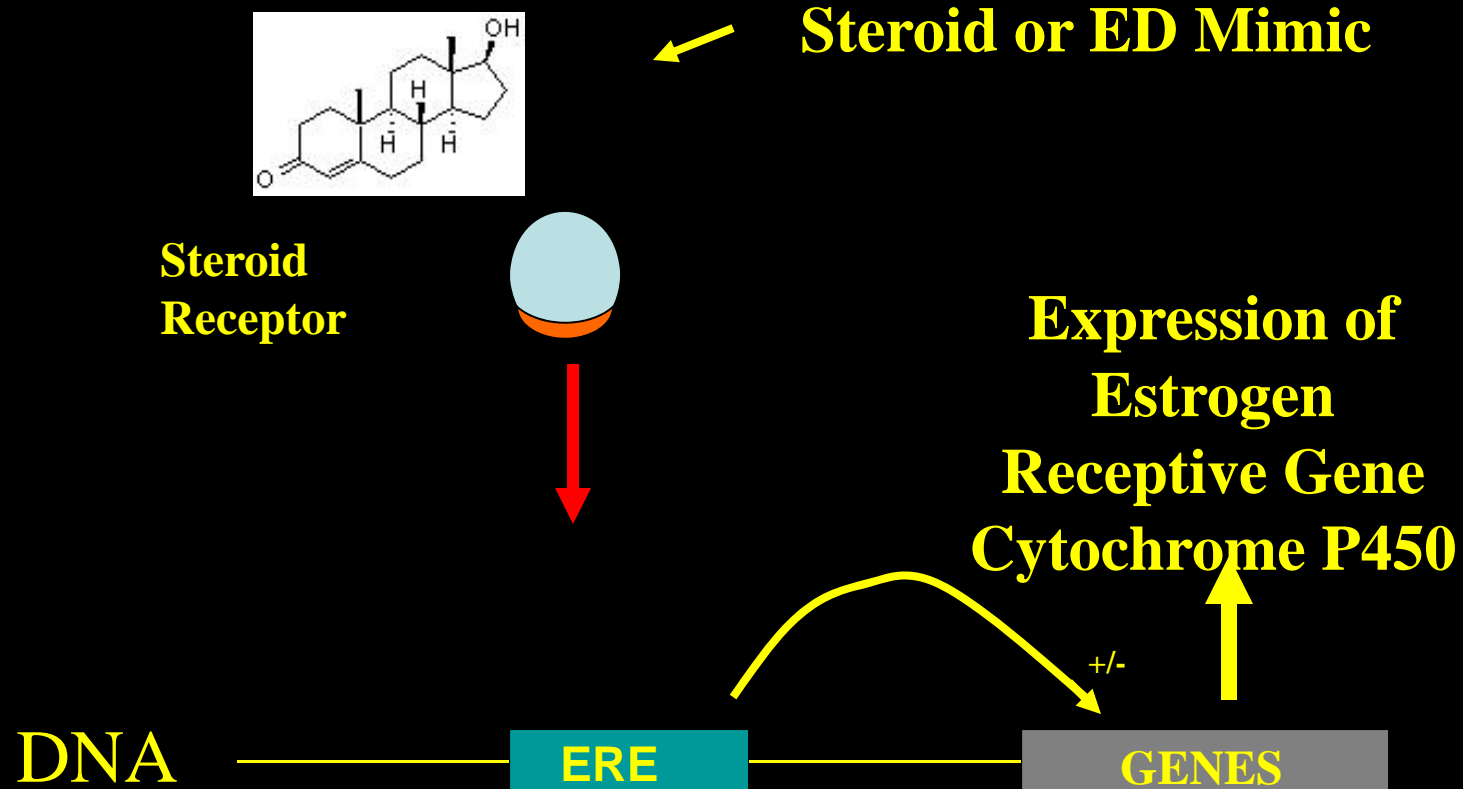
by influencing biosynthesis, metabolism, elimination and/or bioavailability of natural hormones

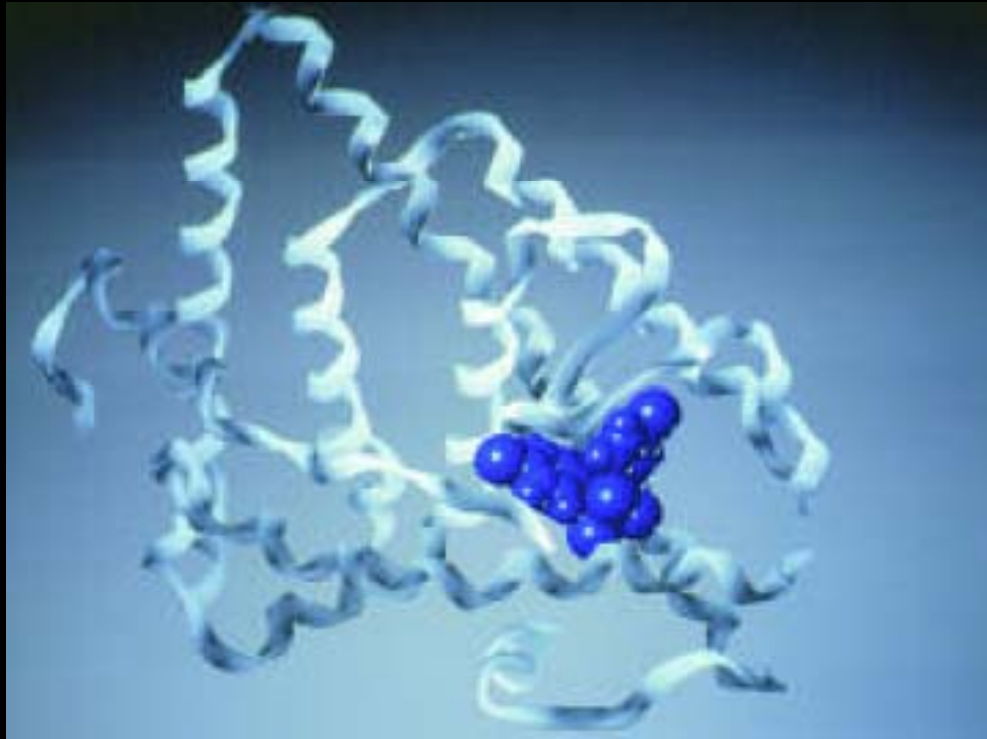
- **inhibition of enzymes such as aromatase - blocking the transformation of androgens to estrogens**

**MECHANISM OF ACTION OF A HORMONE
(STEROID) OR ENDOCRINE
DISRUPTING ENVIRONMENTAL STEROID
(MIMIC)**

Transcriptional Induction of a Steroid Receptive Gene

Regulation and function





Estrogen receptor with docked *pp'* DDT in the binding site plotted from crystal structure coordinates

Courtesy Miriam Jacobs and David Lewis

Abbreviations of receptors

AR	=	androgen receptor
AhR	=	Aryl Hydrocarbon receptor
ER alpha	=	oestrogen receptor alpha
ER beta	=	oestrogen receptor beta
CAR	=	constitutive androstane receptor
LXR	=	liver X receptor
FXR	=	farnesoid X receptor
RAR	=	retinoic acid receptor
RXR	=	retinoid X receptor
PR	=	progesterone receptor
PXR	=	pregnane X receptor
GR	=	glucocorticoid receptor
PPAR	=	peroxisome proliferator-activated receptor