Chemistry 224
Environmental Toxicology

Lecture Seven

Xenoestrogens – the Ultimate Biochemical Feminists

24 September 2007

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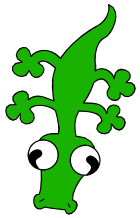

Alligators' penises in USA getting smaller

Human sperm count decreasing

Female dog whelk growing penises

Male trout making Vitellogenin

Guillette article *"Reduction in Penis Size and Plasma Testosterone Concentrations in Juvenile Alligators Living in a Contaminated Environment"*

http://www.brynosaurus.com/funny/alligator/paper/Alligator-Penis-Apopka-Guillette.htm

Reduction in Penis Size and Plasma Testosterone Concentrations

in Juvenile Alligators Living in a Contaminated Environment

General and Comparative Endocrinology 101, 32-42 (1996) Article No. 0005

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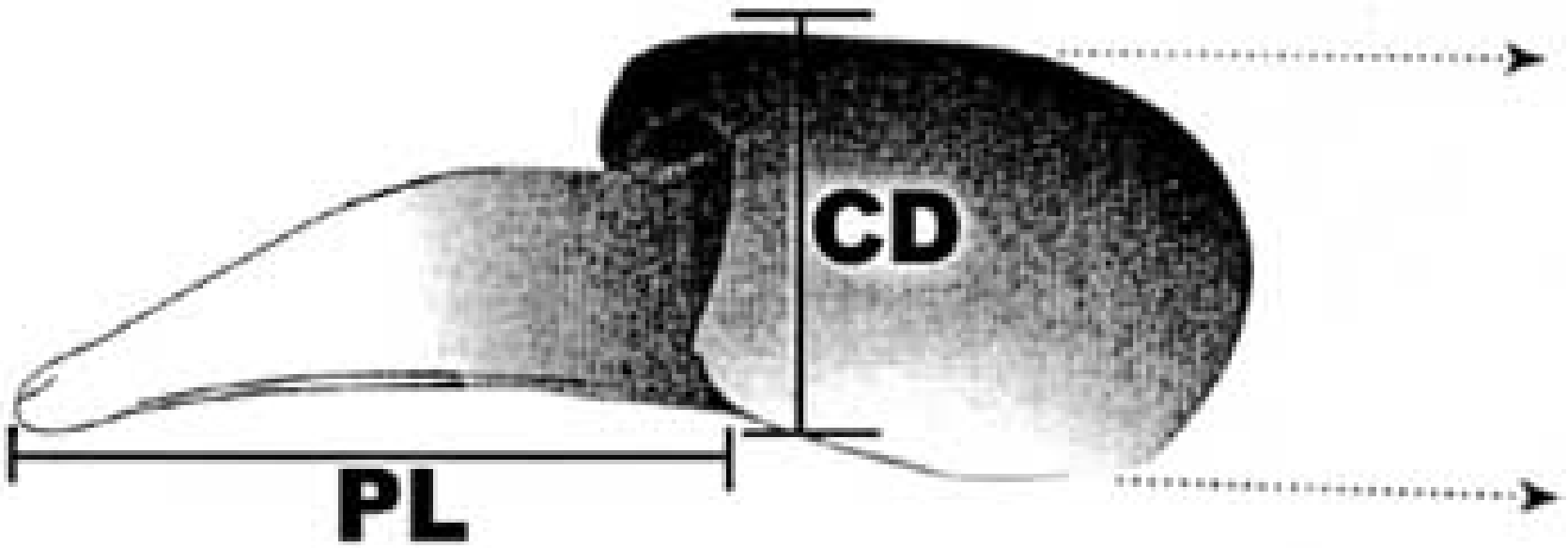
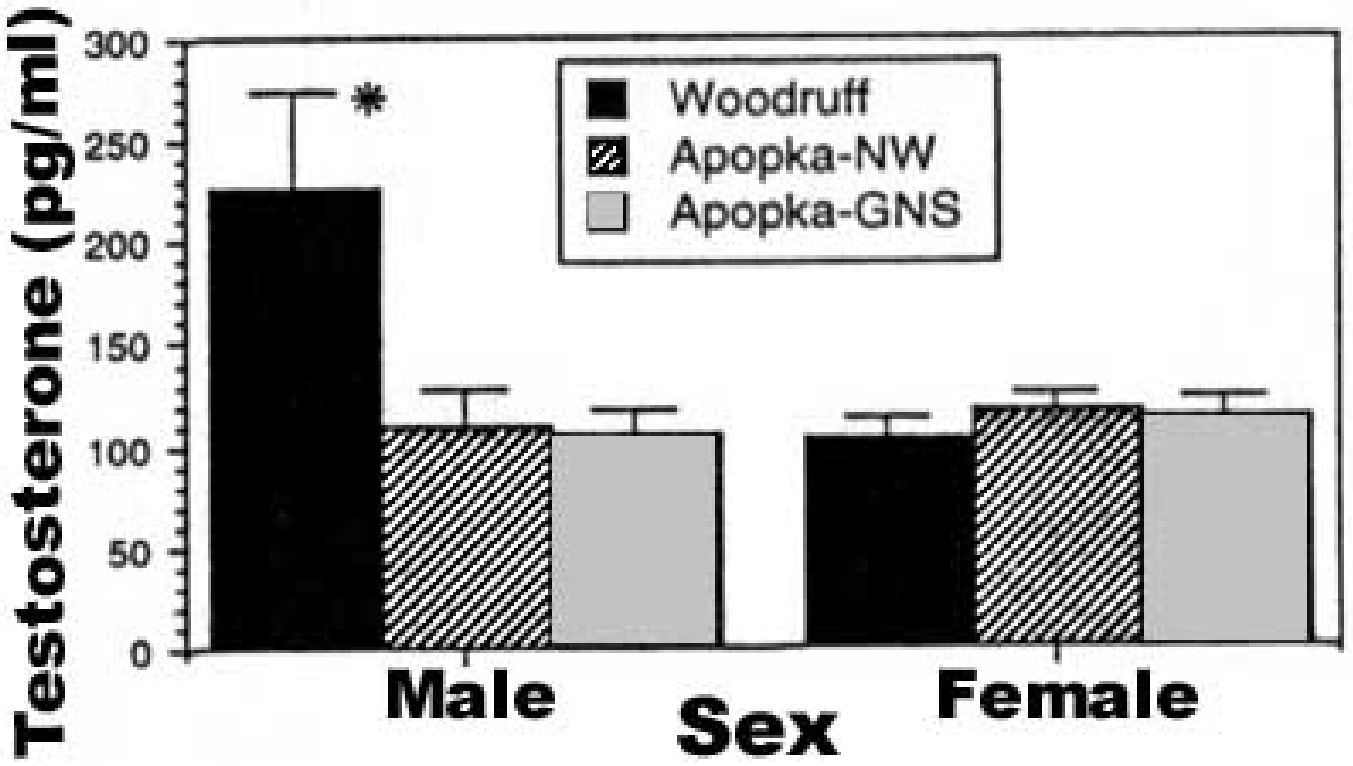
The development of the male reproductive ducts and external genitalia in vertebrates is dependent on elevated androgen concentrations during embryonic development and the period of postnatal growth. We have observed that a population of juvenile alligators living on Lake Apopka exhibit significantly smaller penis size (24% average decrease) and lower plasma concentrations of testosterone (70% lower concentrations) when compared to animals of similar size on Lake Woodruff. In addition to smaller phalli, no relationship exists between plasma testosterone concentrations and penile size in males from Lake Apopka, whereas a positive relationship exists for males from Lake Woodruff. The alligators on Lake Apopka are known to have elevated concentrations of the antiandrogenic DDT breakdown product p,p'-DDE stored in their fat. We suggest a number of hypotheses that could explain the modification in the phenotype of the juvenile male living in Lake Apopka. These modifications in phenotype include a smaller penis size, lower plasma androgen concentrations, and lack of responsiveness of the penis to the plasma androgens present.

In vertebrates, the development of the male internal reproductive ducts and external genitalia is largely dependent on the androgens testosterone and dihydrotestosterone. These sex steroids are responsible for the differentiation of the Wolffian duct into the male internal duct system as well as the formation of the external genitalia in reptiles (see Raynaud and Pieau, 1985). During embryonic development in alligators, secretion of androgens and Müllerian-inhibiting hormone from the testis produces an internal anatomy similar to that commonly described in other reptiles (Austin, 1989, 1990). In addition to embryologically organizing the male reproductive system, androgens are also responsible for stimulating the ontogenetic development of this system during juvenile (especially during puberty) and adult periods (Raynaud and Pieau, 1985). Additionally, seasonal fluctuations in the secretory activity and size of the testis and glands of the reproductive system are androgen dependent (Licht, 1984; Raynaud and Pieau, 1985).



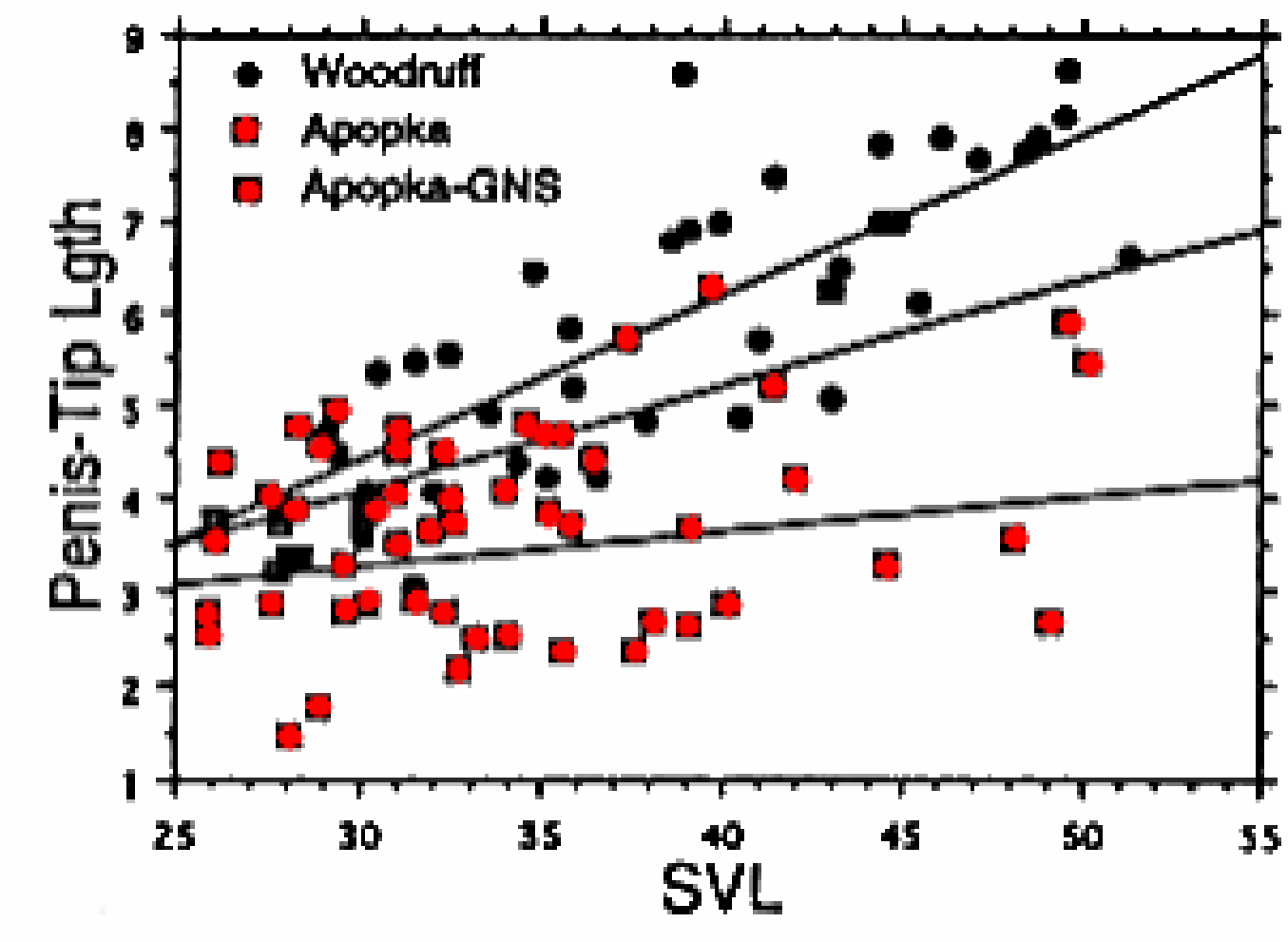
An Alligator's Penis
PL = Penis Length



Mean (+1 SE) plasma testosterone concentrations in male and female juvenile alligators from three lake localities in Central Florida.

***significantly different from all other values**

(Guillette et al, 1996)



Alligators Penis Lengths in Lake Apopka and Lake Woodruff (Guillette *et al*, 1996)

Human Sperm Count

Carlsen *et al* (1992) Evidence for Decreasing Quality of Semen During Past 50 Years

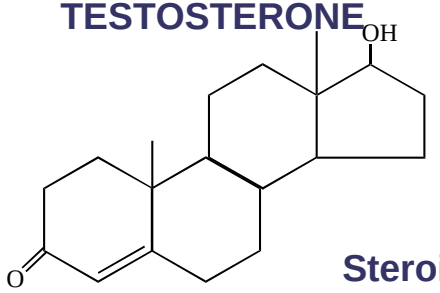
61 Sperm Count Studies 1938 - 1992

	Mean Sperm Count
1940	113 x 10^6/mL
1990	66 x 10^6/mL

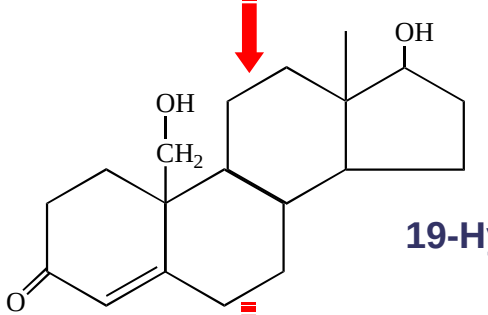
55% DECLINE

THE FINE BALANCE BETWEEN THE SEXES

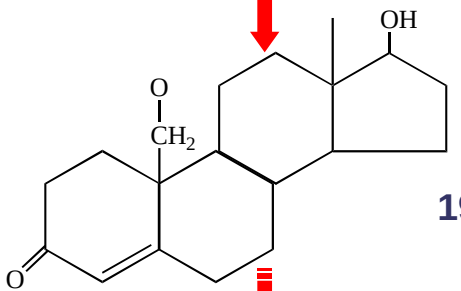
TESTOSTERONE



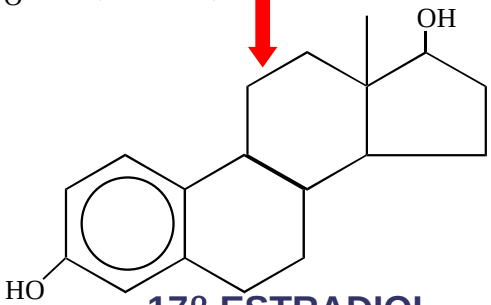
Steroid hydroxylase



19-Hydroxytestosterone



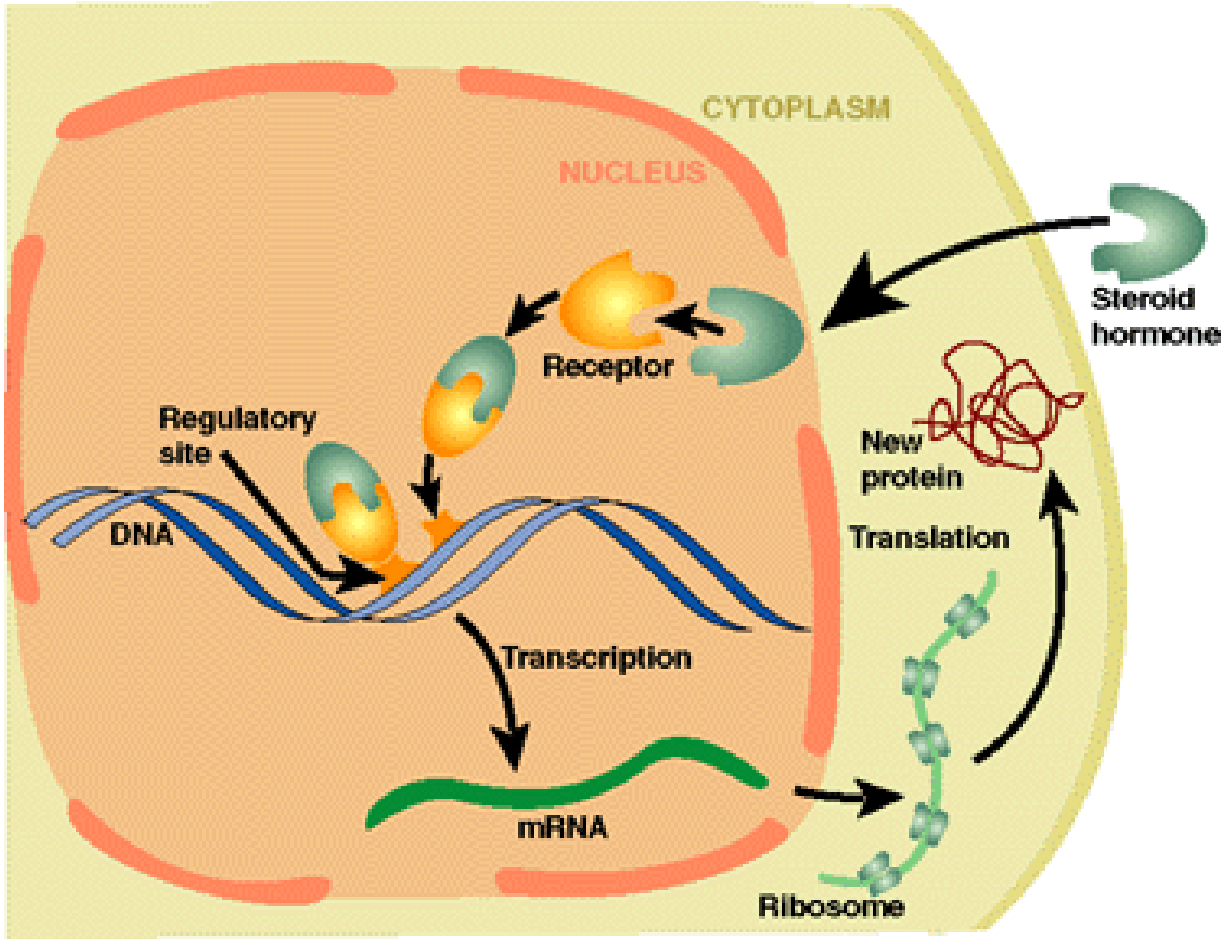
19-Ketotestosterone



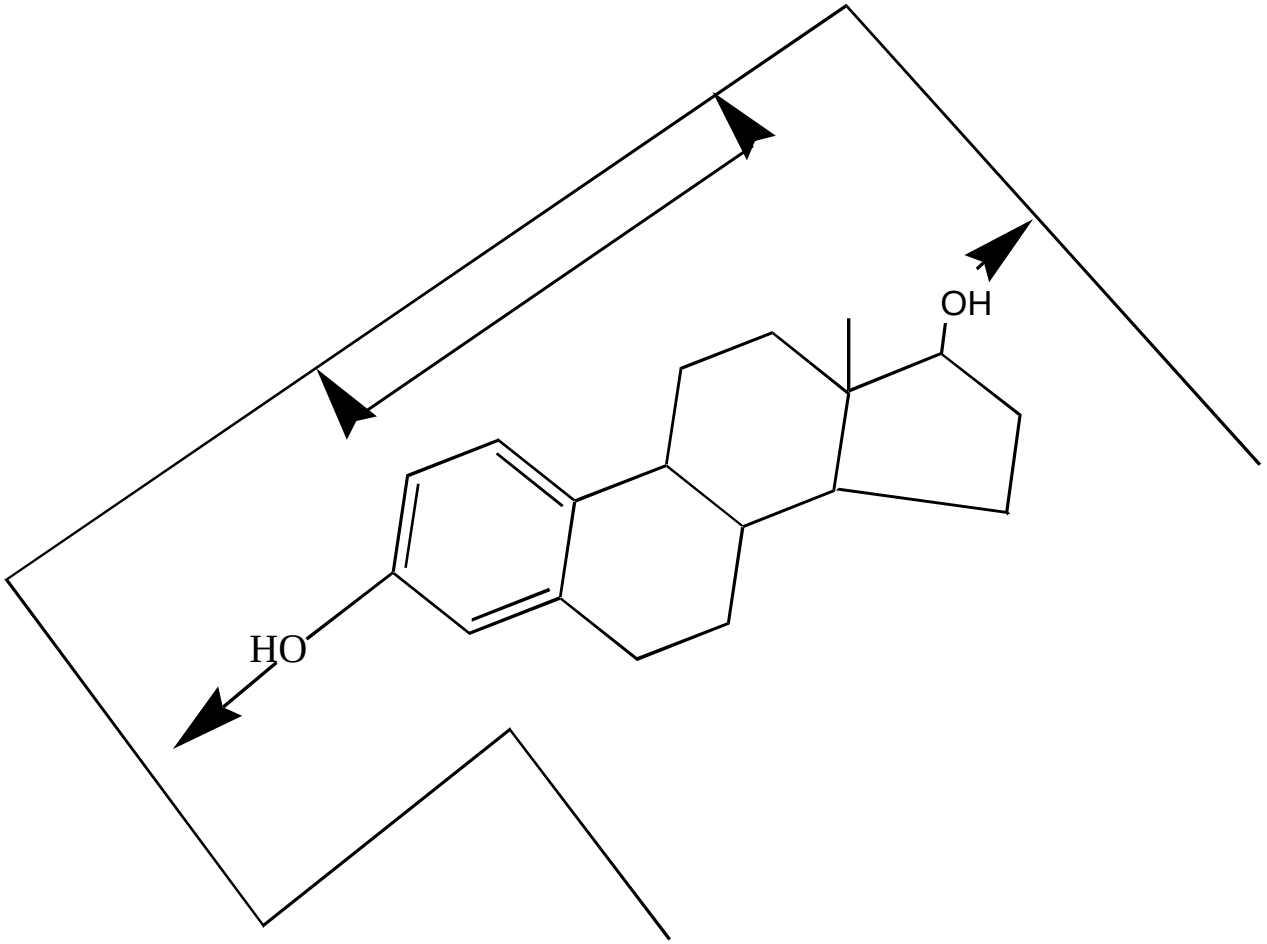
17β ESTRADIOL

BEING A WOMAN IS JUST 3 ENZYMES AWAY!

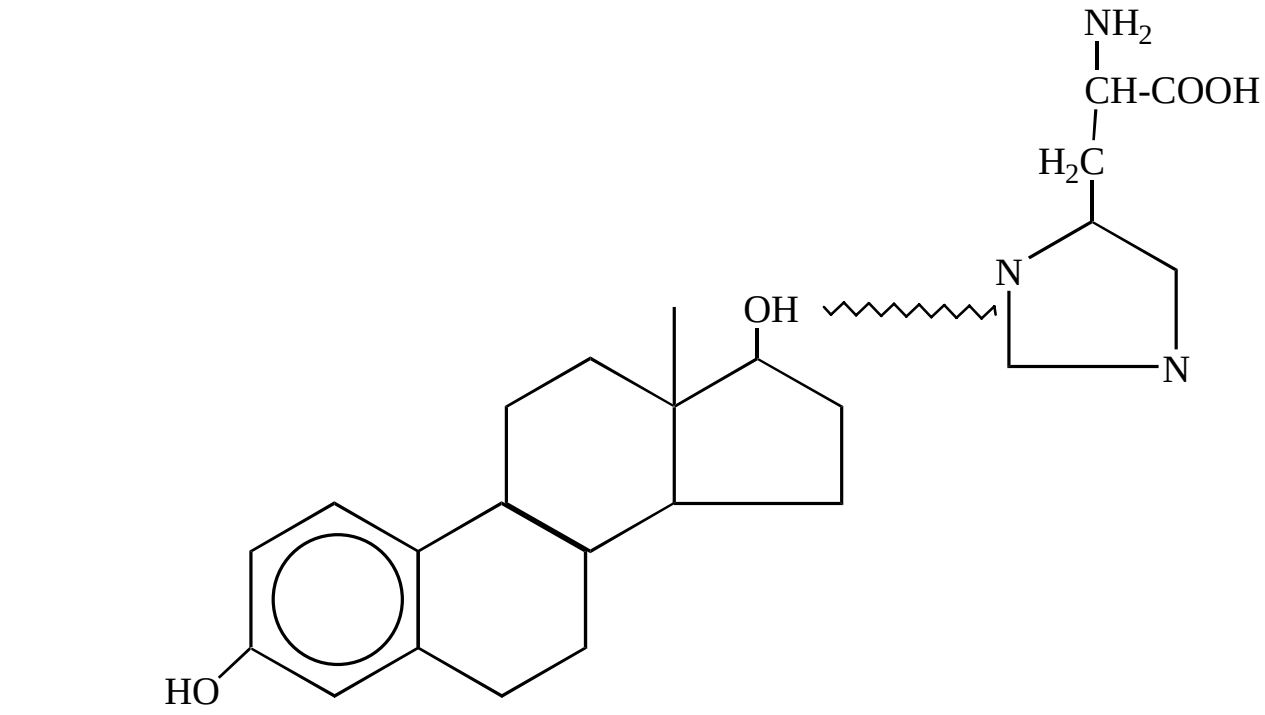
The action of 17β Estradiol



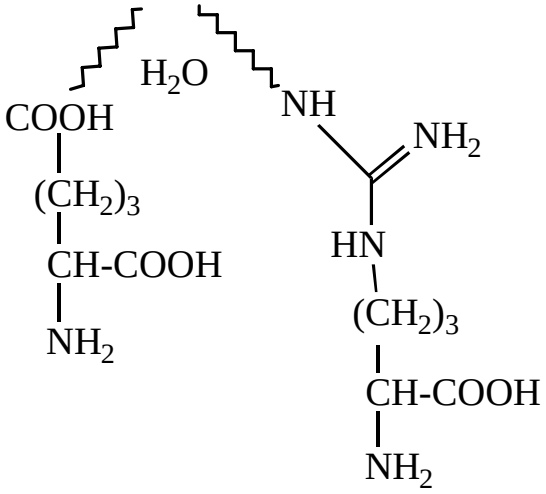
ref: www.utpb.edu/scimath/schafersman/ecoestrogens/



17β-Oestradiol in the oestrogen receptor showing the importance of the phenolic hydroxyl groups and the long hydrophobic region.
(From: Shaw & Chadwick (1998) Principles of Environmental Toxicology, Taylor & Francis)

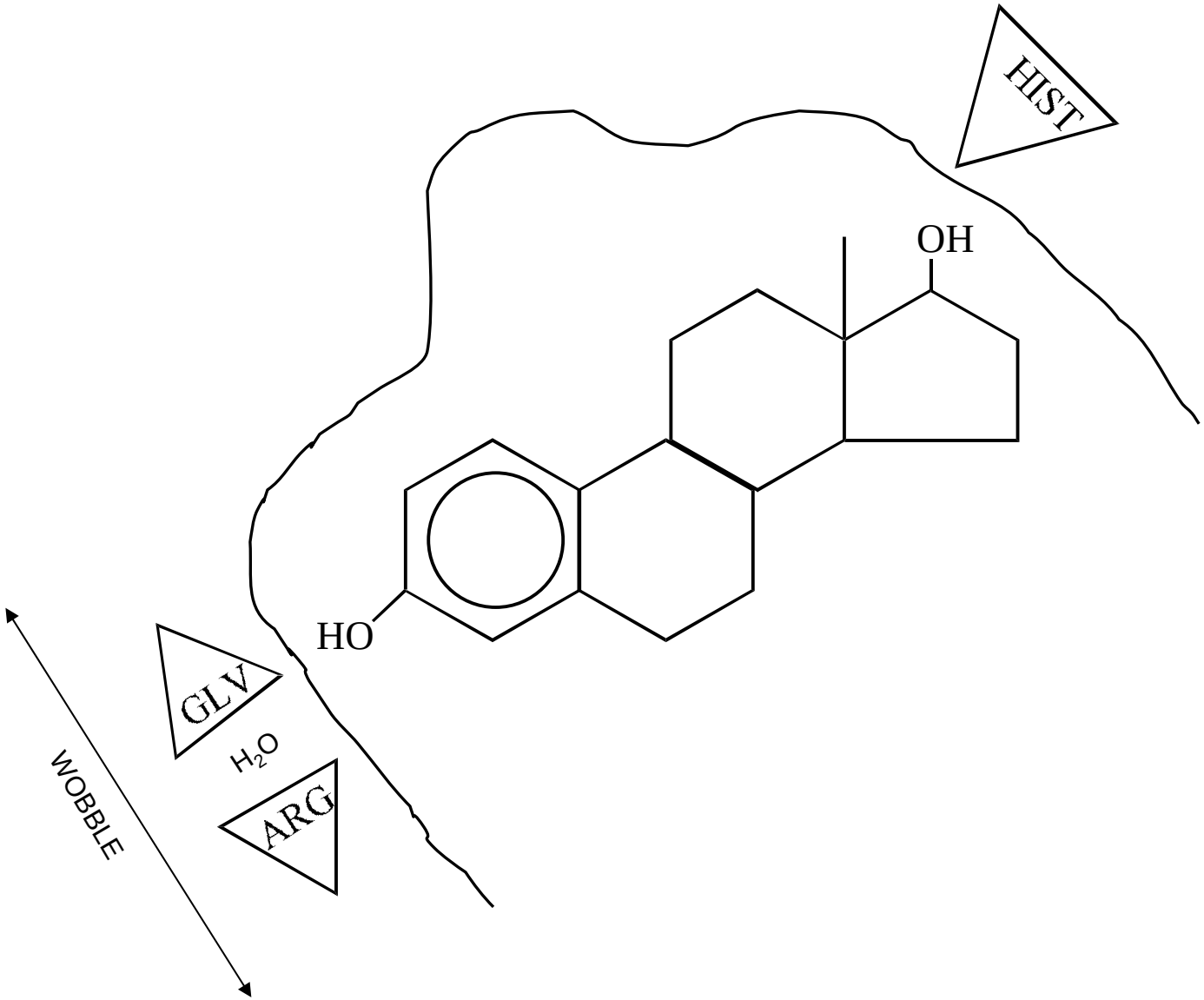


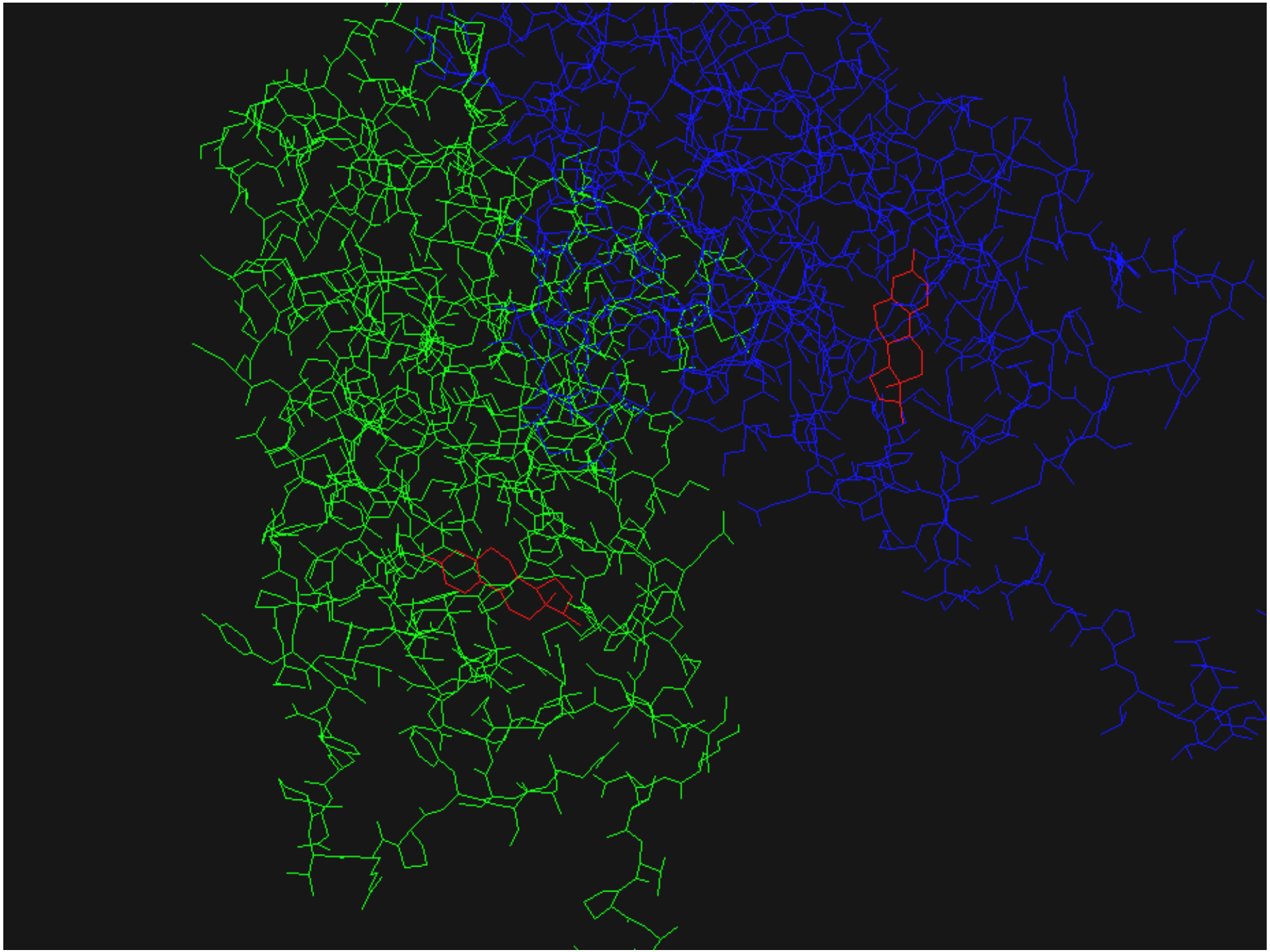
Histidine

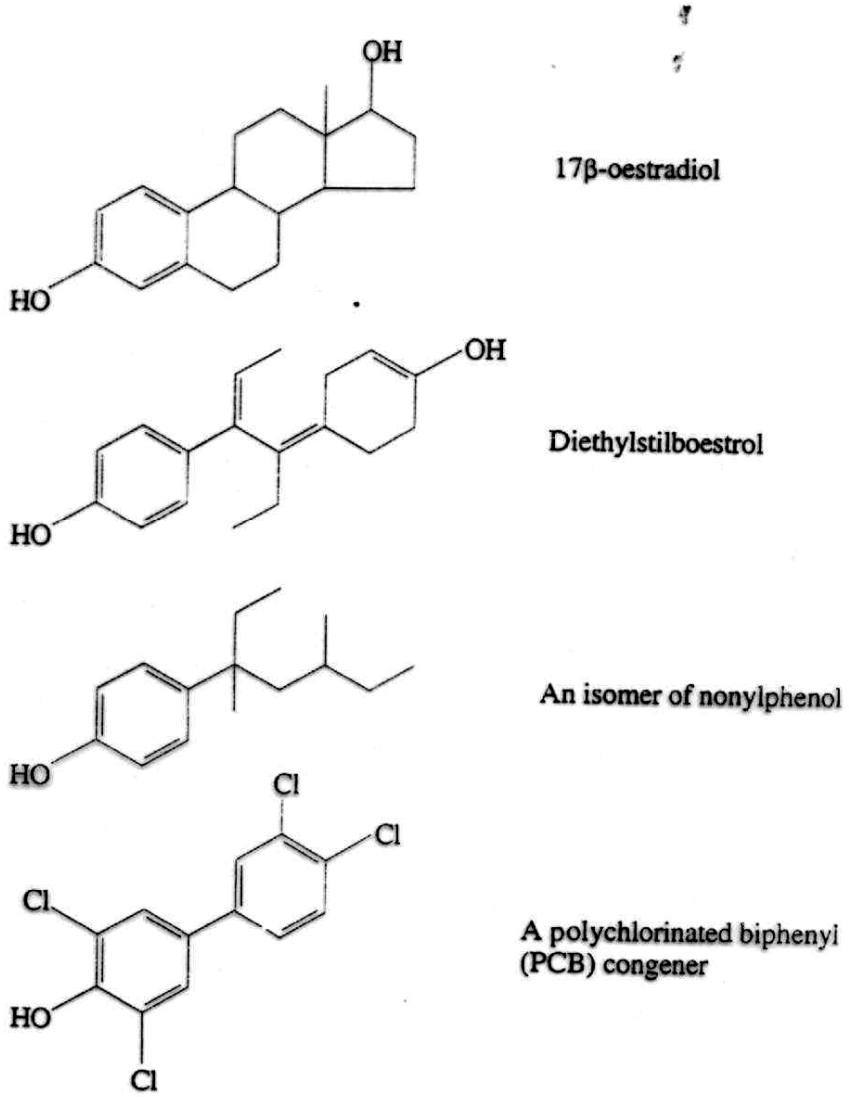


Glutamine

The Estrogen Receptor binding site - showing Amino Acid/Estrogen interactions


HIST
OH
HO
GLV
H_2O
ARG
WOBBLE





Examples of xeno-oestrogens: their structural analogy to oestradiol can be seen clearly. Adapted from Müller *et al*., 1995, *TEN*, 3, 69

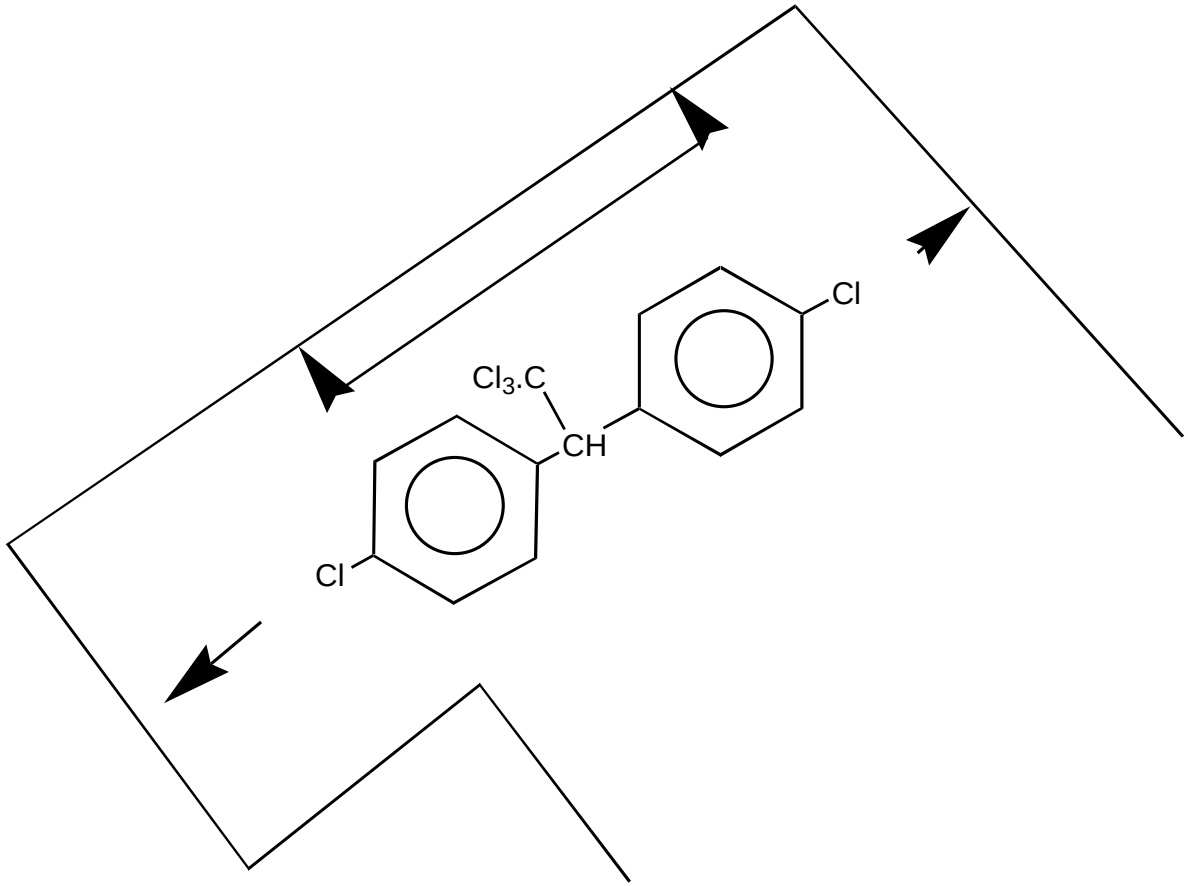


Fig 8.5. DDT in the ER – this shows why DDT unlocks the receptor's feminising activity

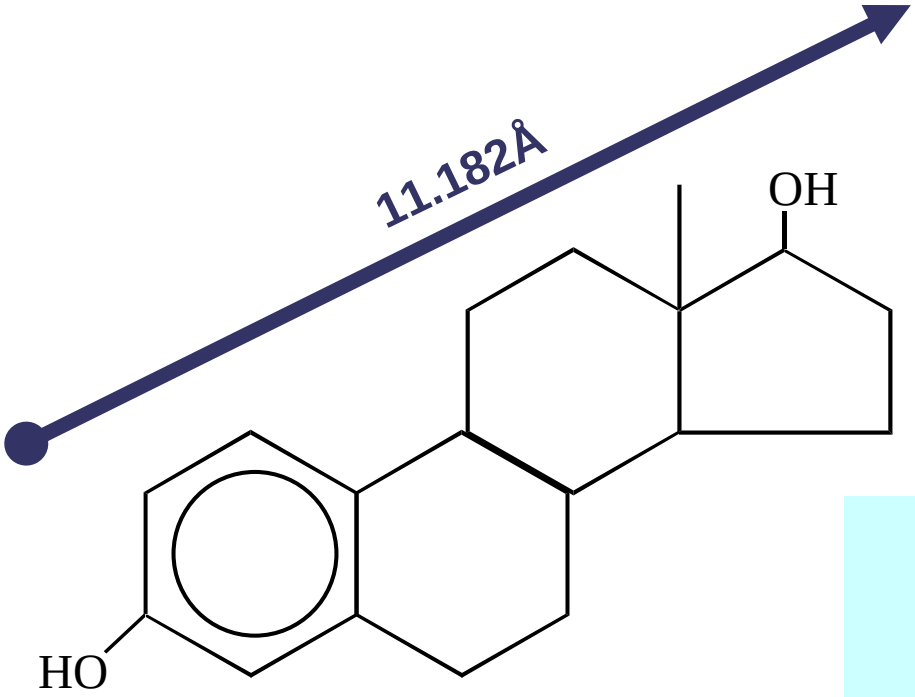
(From: Shaw I C Is It Safe To Eat?, Springer)

Food Chain Concentration of DDT in an East Coast Estuary in the USA

	Diet	DDT residues (parts per million)
Water	**N/A**	**0.00005**
Plankton	**N/A**	**0.04**
Sheepshead minnow	**Plankton**	**0.94**
Pickeral	**Predatory fish**	**1.33**
Heron	**Small fish**	**3.57**
Herring gull	**Scavenger**	**6.00**
Osprey (eggs)	**Larger fish**	**13.8**
Merganser	**Fish**	**22.8**
Cormorant	**Larger fish**	**26.4**

From: Shaw & Chadwick (1998) Principles of Environmental Toxicology

DO XENOESTROGENS FIT THE ER SITE?



	Distance between electronegative groups (Å)
17β estradiol	11.182
Coumestrol	11.406
Genistein	11.773
nonyl-phenol	14.811
Dieldrin	~7.25
Pyrethroid metabolite	10.079
DDT	9.270

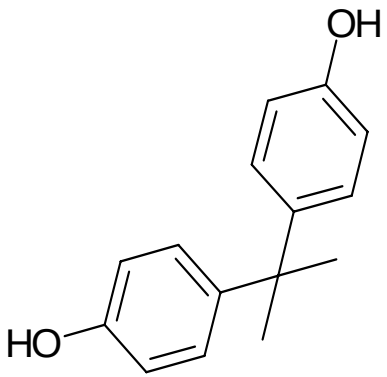
McCarthy, Abell & Shaw (2001) NZIC, Napier

Daily Mail, Wednesday, May 9, 2001

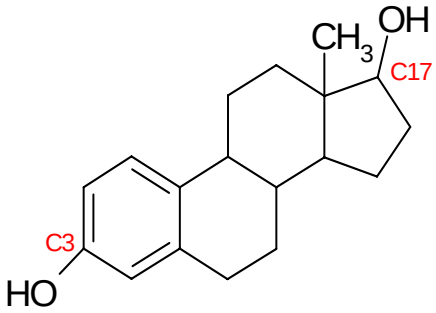
'Gender-bending' chemicals found in canned foods

By **James Chapman**
Science Correspondent

Products which alarmed the experts



Bisphenol A

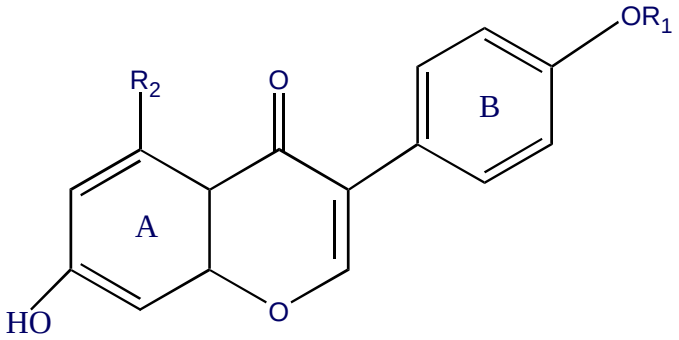


17β-Estradiol

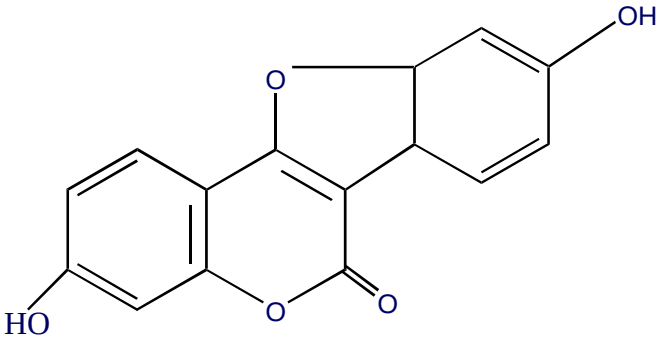
Bisphenol-A and 17B-estradiol – the similarities are clear

STRUCTURES OF THE ISOFLAVONE NUCLEUS, COUMESTROL AND 17-β-OESTRADIOL

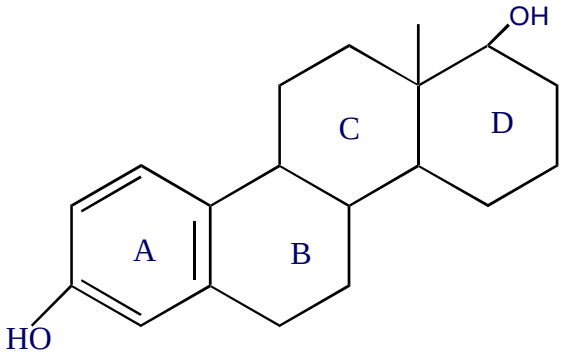
Isoflavone nucleus



Coumestrol



17-β-oestradiol



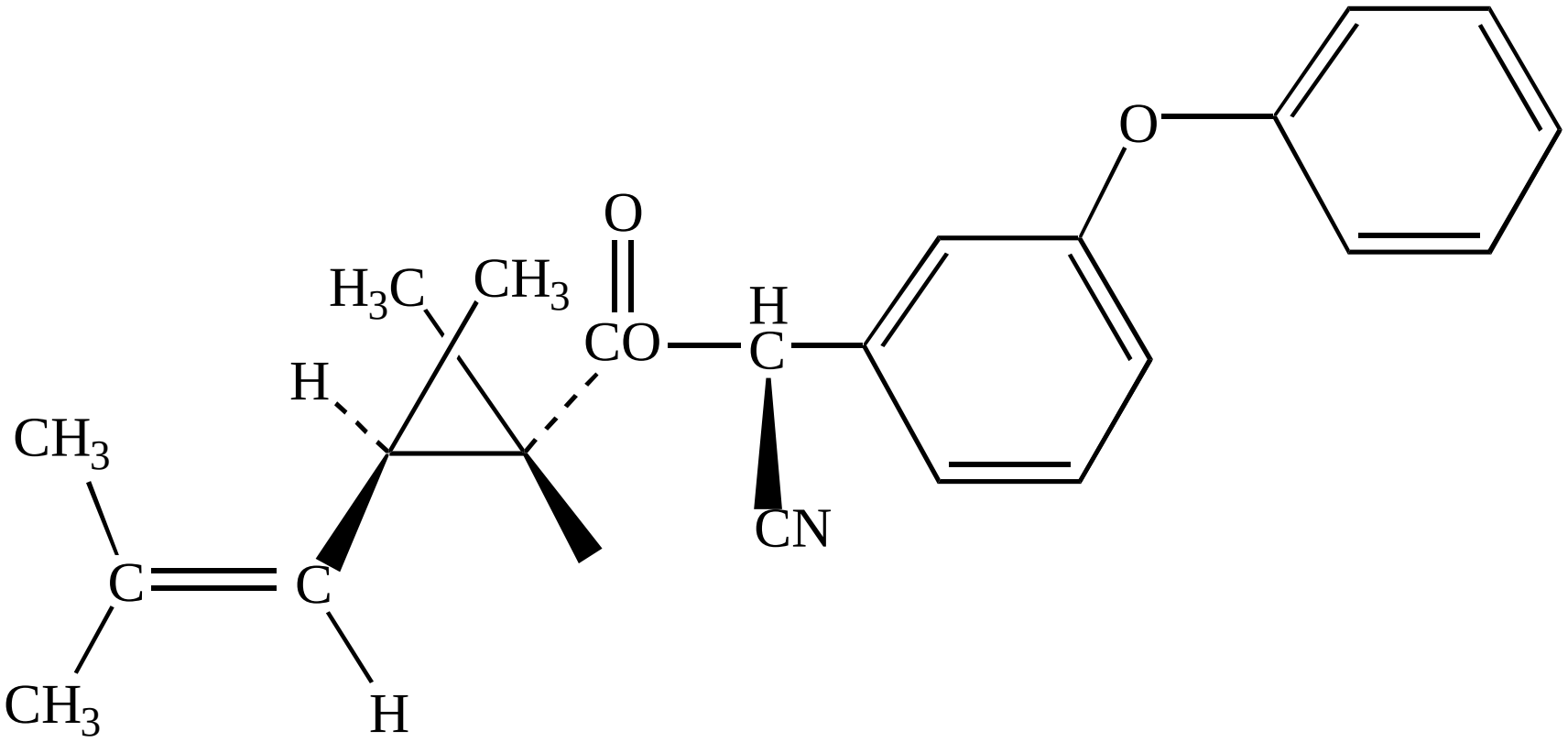
Estrogen Class/Food	Exogenous Estrogen	Theoretical Plasma Concentration ($ng.dm^{-3}$)
Phytoestrogens		
Beans, Peas, Spinach	**Coumesterol**	**11.5**
Soya	**Coumesterol**	**3**
	Genistein/genistin	**143**
Plasticisers	**Bisphenol-A**	**0.1**
	Phthalates	**0.003**
Pesticides	**Total estrogenic pesticides***	**0.005**

Table 3

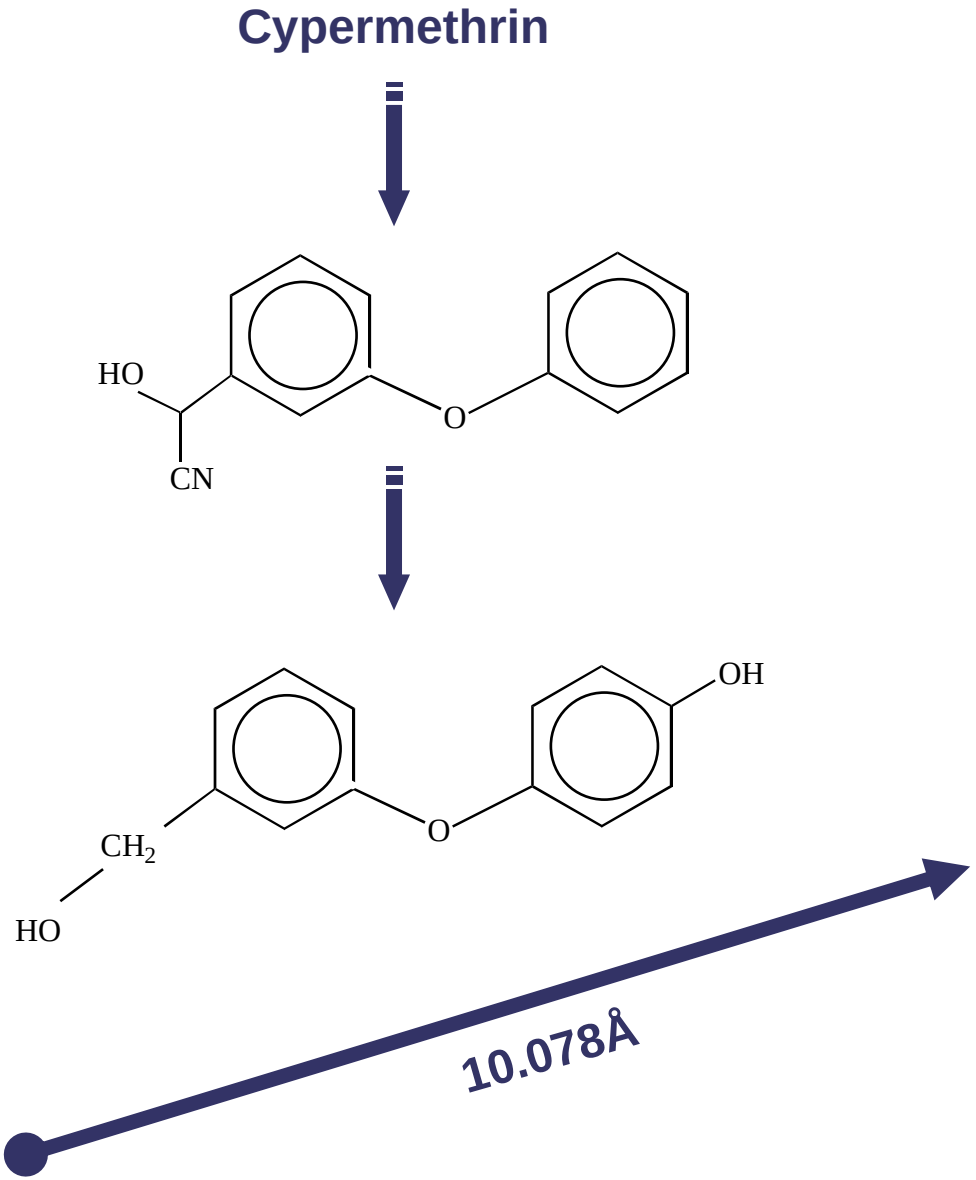
Theoretical plasma concentrations of the main classes of exogenous estrogens
*** Includes DDT, Dicofol, Endosulphan, Dieldrin and β-HCH**

Shaw & McCully (2001) Int. J. Food Sci. Technol. *In Press*

CYPERMETHRIN-
A ‘SAFE’ PESTICIDE



PYRETHROIDS



Cryptorchidism

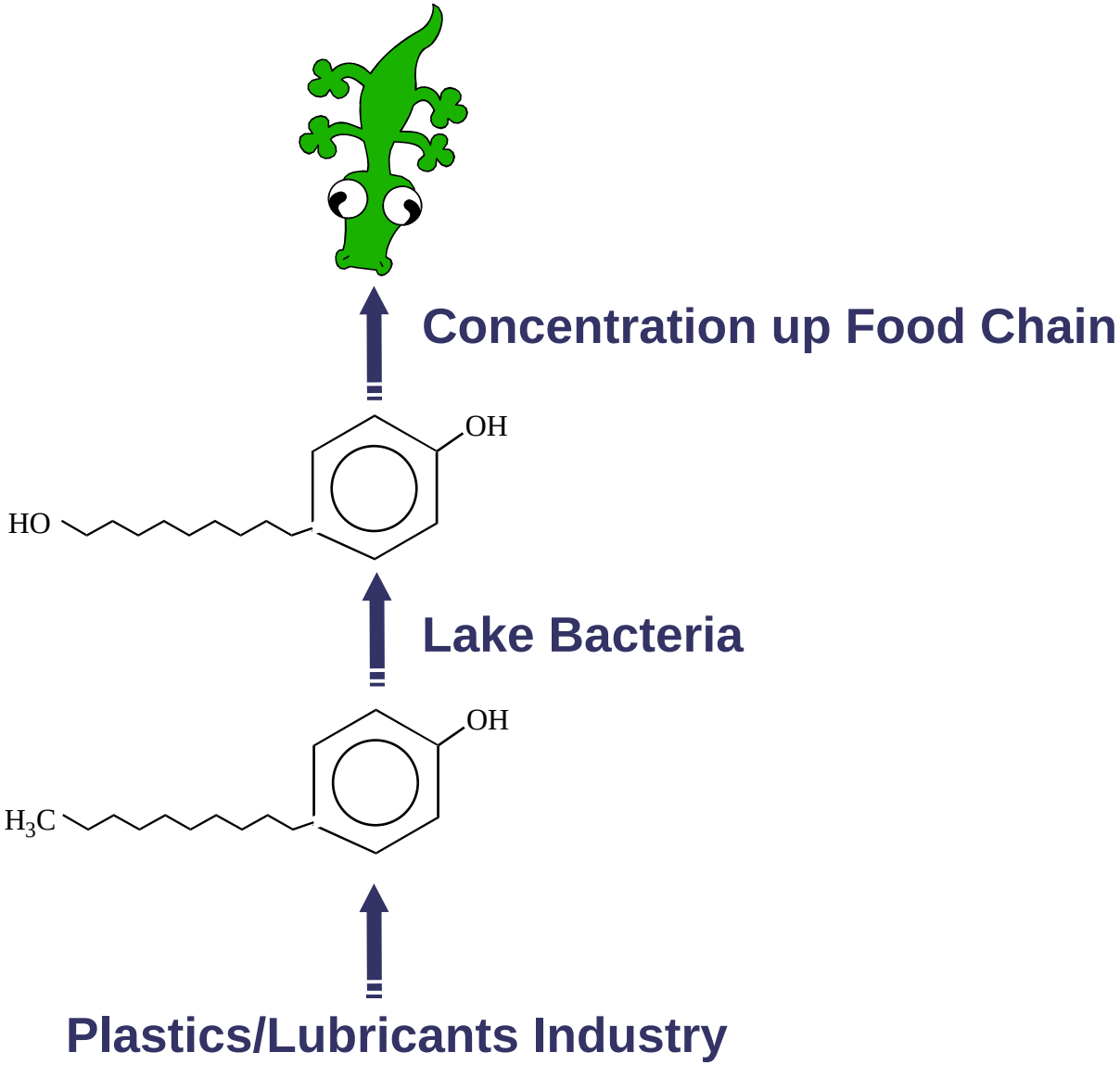
in sons of gardeners and farmers

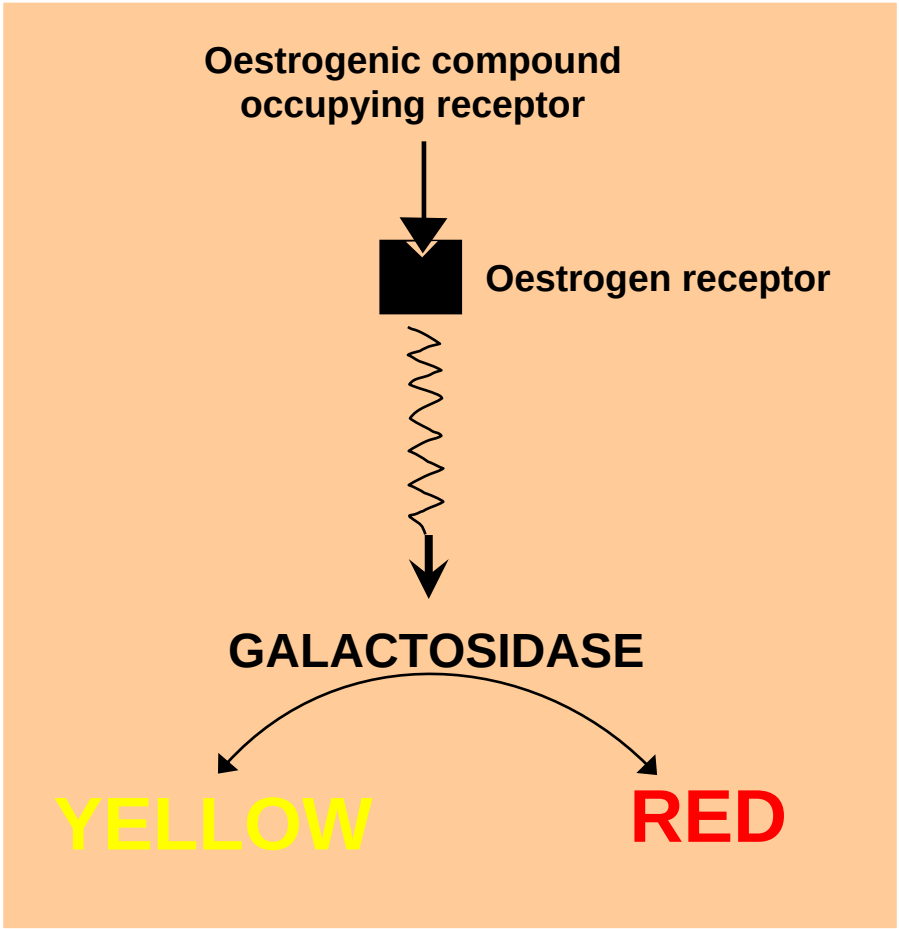
	CONTROLS	CASES
Mothers in farming or gardening	**0.8%**	**1.8%**
Fathers in farming or gardening	**6.4%**	**6.8%**

SUGGESTS *IN UTERO* EXPOSURE

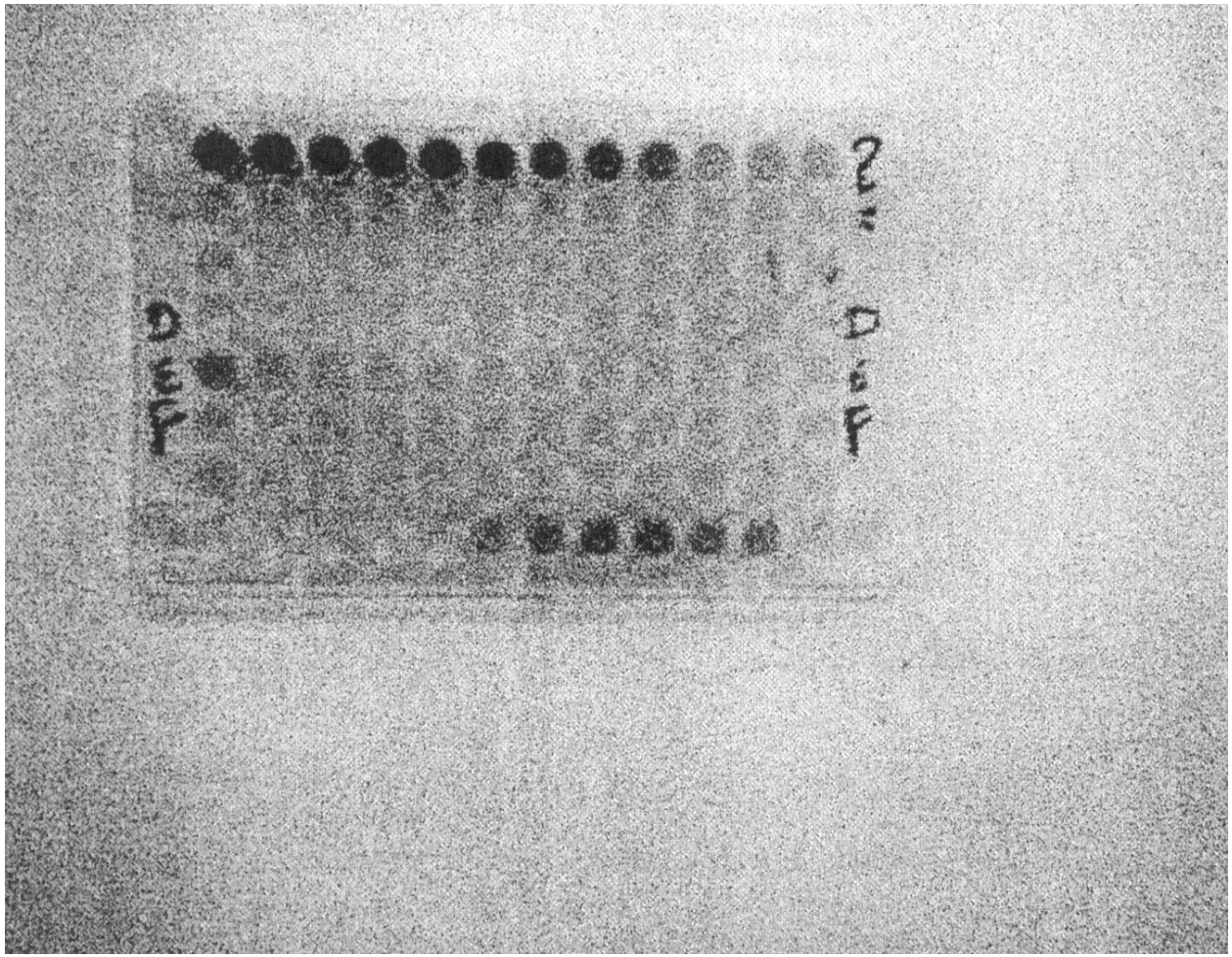
Weidner *et al* (1998) Env. Health Perspect. **106**, 793-796

Nonylphenol in the Lake Apopka Environment





Schematic representation of the yeast oestrogenicity assay showing the oestrogen receptor occupied by an oestrogenic compound with consequent activation of galactosidase. The result is yellow galactoside dye being cleaved to release the red chromophore.



A: 17β Estradiol

E: Cypermethrin

H: Tamoxifen