Interaction of xenobiotics with sex hormone binding globulin

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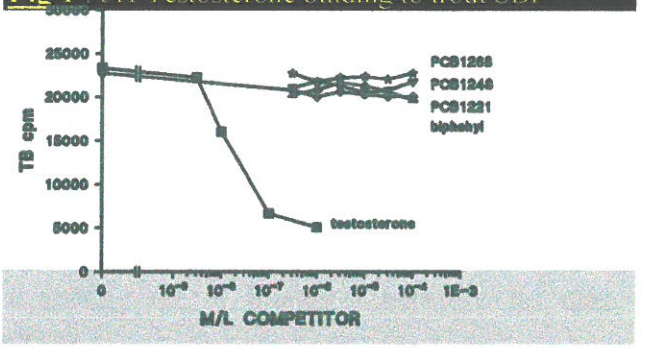
Sex steroid hormones circulate in the blood and extracellular compartments mainly bound to albumin and specific **Steroid Binding Proteins** (SBP). Xenobiotics may interfere with this endocrine equilibrium by occupying the binding sites of the transport protein modify the ratio of bound/free **endogenous testosterone (T) and estradiol** (E2) and therefore the biological activity or the metabolic clearance of these natural hormones (Aldercreutz et al. 1985, 1990). Moreover, binding to SBP may influence **the bioavailability of the xenohormone itself** : it may protect the exogenous molecules against metabolism and promote their accumulation inside the organism , while the absence of binding make them more available for action on their target cells.

We have set up a sensitive and practical in vitro screening method to detect chemicals that modify SBP-sex steroid binding. We incubate increasing concentrations of xenobiotics (10^{-7} to 10^{-4} M) in competition with 10^{-9} M of labelled testosterone or estradiol (-3H-T or 3H-E2), for binding to fish or human blood plasma SBP in vitro (Fig 1).

Fig 1 : 3H-Testosterone binding to trout SBP



30 active pesticides used in French agriculture were screened (exemples in table1): four of them had significant affinity for SBP with ED50 = 0.5 - 5 x 10^{-6} M (Parathion-methyl > Bifenox > Dodemorphe = Triadimefon, in decreasing order of activities) and should be concidered as potential endocrine disruptors.

Among estrogen-like compounds, the phytoestrogens *equol* and, to a lesser extent, *genistein* competed with E2 and T for binding to SBP, as well as *Nonylphenol4* and its *ethoxyl derivatives* (ED50: 2 à 10 10^{-6} M). None of the polychlorinated derivatives of biphenyl (*PCBs*) tested revealed activity.

Table1: Effects of a few pesticides on Testo

Chemicals	INHIBITION OF BINDING TO	
	% inh. at 10 -5 M	ED 50 M/L
Biphenyl	0	
Captan	0	
Chlorothalon	30%	3 x 10 E -5
Dodemorph	60%	3 x1 0 E -6
Pentachlorophen	50%	2 x 10 E -5
Prochloraz	50%	2 x 10 E -5
Triadimefo	85%	3 x 10 E -6
Carbofura	0	
Carbosulfan	20%	> 10 E -4
Deltaméthrin	0	
Lindan	50%	2 x 10 E -5
Parathion-	100%	5 x 10 E -7

Most of the anabolic molecules used in farming, or their metabolites, are able to bind to vertebrate SBP and to inhibit natural hormone binding to their specific blood transport proteins. Exposition of either human or wild vertebrates to one of these compounds could therefore have consequences on free estrogens/free androgens equilibrium or disrupt endogenous steroid hormone action on target tissues, especially if the xenobiotic compound considered is susceptible to bioaccumulate in the organism.

Table2 comparison SBP binding/estrogenic activity

Chemical	*Inhibition T-SBP binding*	*E2 Recept. Activation at 10^{-7} M*
Ethynyl-estradiol	100	137%
Diethylstilbestrol	0	100 %
Zearalenone	0	108 %
α Zearalanol	0	146 %
β Zearalanol	20	62 %
α zearalenol	100	20 %
β zearalenol	15	134 %

The case of ***Zeranol*** and its metabolites is of special interest as their very high estrogenic activity is not "buffered" by binding to an high affinity protein in the extracellular compartment (table2): this could make it more available for action on target cells (as proposed for the action of Diethylstilbestrol on the human foetus).