Review

# Organic Synthetic Environmental Endocrine Disruptors: Structural Classes and Metabolic Fate

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## Abstract

Endocrine disruption is the modification of the endocrine system causing harmful effects in healthy subjects or their offspring. Physiological endocrine hormones act at very low plasma concentrations, and certain chemicals known as endocrine disrupting compounds (EDCs) are suspected of modifying endocrine function at similarly low concentrations. In our review we focus mainly on the structural classes of organic synthetic environmental endocrine disruptors and their common structural elements that enable them to interact with estrogen signalling. EDCs can affect estrogenic signalling directly through interaction with estrogen receptors (ERs) or indirectly through transcription factors such as the aryl hydrocarbon receptor (AhR) or by modulation of critical metabolic enzymes engaged in estrogen biosynthesis and metabolism. However, some structural elements can also pose a great risk of cytotoxicity and genotoxicity, especially after biotransformation to reactive metabolites.

**Keywords:** endocrine disrupting compounds (EDCs), estrogen receptors (ERs), aryl hydrocarbon receptor (AhR), reactive metabolites

## 1. Introduction

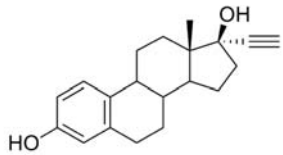
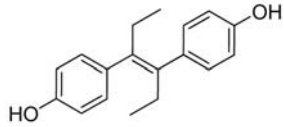
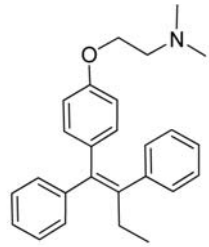
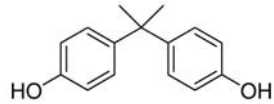
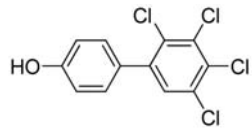
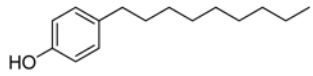
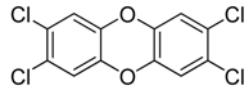
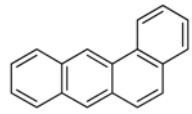
Most structural classes of synthetic endocrine disrupting compounds (EDCs) affect physiological estrogen signalling and are therefore called estrogenic endocrine disruptors, or xeno-estrogens. EDCs can modify genomic and non-genomic estrogen receptor activity through direct interaction with estrogen receptors (ERs). EDCs can also interact with other targets involved in estrogen signalling. They can act as ligands for transcription factors such as the aryl hydrocarbon receptor (AhR) and by modulation of metabolic enzymes that are essential for normal estrogen synthesis and metabolism.[1]

Xeno-estrogens belong to a number of chemical classes that display a broad range of structural diversity. Many structure-activity relationships (SARs) have been studied in which activity was measured using a validated rat uterine cytosol ER competitive binding assay and where the focus was on identification of structural commonalities between diverse ER ligands.[2] Only after discovering crystal structures of ERα and ERβ ligand binding domains could binding properties and selectivity of ER ligands be properly determined.[3,4]

Synthetic estrogenic endocrine disruptors can be divided into eight main structural classes: *steroids, diethylstilbestrol-like compounds, triphenylethylene derivatives, diphenylmethanes, biphenyls* and *phenols,* and two classes of AhR ligands: *polycyclic aromatic hydrocarbons* and *dioxins* (Table 1). For comparison, AhR binds a wide array of structurally different hydrophobic ligands such as polycyclic aromatic hydrocarbons (PAHs) (Figure 9) and halogenated aromatic hydrocarbons (HAHs). Among the high affinity AhR ligands are dioxins, primarily (TCDD), a known EDC.

Involvement of AhR ligands in estrogen signalling is a consequence of intertwined signalling pathways of AhR and ERα (ERα binds to AhR-regulated genes and AhR binds to ERα-regulated genes). AhR ligands 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 3-methylcholanthrene (3-MC) although treated as equivalent compounds, they have distinct effects. TCDD was shown to act solely as antiestrogenic compound, while 3-MC exerts estrogenic properties depending on the cell type. Genomic study from Swedenborg et al. was examining the transcriptional effects of TCDD and 3-MC with regards to ER ligand diethylstilbestrol (DES). All three ligands regulated separate sets of genes, thereby inducing different signaling pathways, with the exception of CYP1A1 and aldehyde dehydrogenase 3A1 genes that were upregulated by both 3-MC and TCDD. It was showed that 3-MC and TCDD control distinct gene expression and probably also have different biological functions. Additionally, 3-MC had an

**Table 1.** EDC structural classes and representative compounds

| EDC structural class | Representative compound |
|---|---|
| Steroids |  ethynylestradiol |
| DES–like chemicals |  diethylstilbestrol |
| Triphenylethylene derivatives |  tamoxifen |
| Diphenylmethanes |  bisphenol A |
| Biphenyls |  2',3',4',5'–tetrachloro–4–biphenylol |
| Phenols |  nonylphenol |
| Dioxins |  TCDD |
| PAHs |  benzo[a]anthracene |

impact on almost 700 genes, hypothesising that many different metabolites were generated in HepG2 cells. The regulation pattern suggests that 3-MC and/or its metabolites have estrogenic effects that are mediated only through ERα.[5] Antiestrogenic effect of TCDD were discovered by Wormke et al. implicating nuclear localization of the AhR, AhR-ERα interactions and finally proteasome-dependent degradation of AhR and ERα.[6] Study of Palumbo et al. showed that AhR agonists reduced vitellogenin synthesis in fish and therefore have opposite effects than estrogen chemicals.[7] However, many EDCs act through multiple mechanisms, as exemplified by compounds that bind to multiple targets, for example ERs and AhRs such as 3-MC.

Some groups of chemicals also influence estrogen synthesis and metabolism, e.g. triazine herbicides and vinclozolin. Triazine herbicides and their metabolites induce the activity and gene expression of the aromatase, also known as the cytochrome oxidase, CYP19A1.[8,9] Apart from estrogenic effects, some EDCs are able to form reactive metabolites that can induce oxidative DNA damage and/or covalent binding to DNA. The role of estrogene reactive metabolites in mammal carcinogenesis is described in more detail in many review articles.[10,11,12] The main pathway leading to carcinogenesis is formation of the catechol estrogen metabolites, especially 4-hydroxy E2. 4-Hydroxy E2 is the most carcinogenic causing DNA damage, kidney tumors in Syrian hamster and uterine tumors in CD-1 mice, what was reported by Newbold et al.[13] NADPH-dependent metabolic oxidation pathway of E2 is well established and consists of the following steps: 1) 2- or/and 4- hydroxylation of E2, 2) subsequent oxidation to semiquinones and ortho-quinones, 3) redox cycling between the ortho-quinones and their semiquinones generating radicals and 4) covalent binding of ortho-quinones, especially of 4-hydroxy E2 to DNA.[8,14] However, when it comes to the extent of 4-hydroxy E2 formation with regards to 2-hydroxy E2 formation, studies on this subject are not uniform. For example, Wilson et al. reported that 4-hydroxy E2 was a predominant metabolite in female ACI rats but on the other side Mesia-Vela et al. found that the main metabolite formed from liver microsomes of ACI rats was 2-hydroxy E2. ACI rat model is very useful, since E2 induced tumours appear in a very short period at low E2 concentrations.[15,16] Authors suggest that the differences could appear due to the possibility of different diet of the laboratory animals or due to existence of other 4-hydroxy E2 formation pathways, meaning that extra hepatic metabolism could play a more important role that was thought before. It is also possible that, especially if contaminated with almost ubiquitous TCDD could influence the metabolism of E2 in the same animal species. In principle reactive intermediates could be formed directly by bioactivation of ingested EDCs or through EDC induction of certain CYPs. For example, Beedanagari et al. examined the induction of *CYP1A1* and *CYP1B1* genes in human MCF-7 breast cancer cells by TCDD that are involved in E2 hydroxylation.[17] Spink et al. proposed the scheme of hydroxylation reactions for E2 and for equine estrogens, which are commonly used in estrogen replacement therapy. Equine estrogens: equilin, equilenin and 8-dehydroestrogene are structurally B-ring unsaturated estrogens. The slight difference in the metabolic behaviour

to the E2 is due to the aromaticity of the steroid B ring that favours C-4 hydroxilation by TCDD induced CYP1A1 and CYP1B1.[18] Wang et al. have developed a sensitive LC-MS/MS method based on the knowledge that 4-hydroxy equine estrogens form their *ortho*-quinones, which form stable DNA adducts. This method could provide a good basis for developing a sensitive assay for monitoring estrogen induced DNA damage.[19] In human MCF-7 breast cancer cells CYP1B1 predominantly catalyzes hydroxylation of E2 at the C-4 position, whereas CYP1A1 predominantly catalyzes 2-hydoxylation.[18] It should be also mentioned that CYP 1A1 and 1B1 are also involved in hydroxylation of PAHs that are consequently forming carcinogenic metabolites. Buters et al. monitored metabolism of dibenzo-[a,l]pyrene that is a very strong carcinogen in mouse skin and rat mammary glands and found that CYP1B1 is the most critical enzyme for formation of its DNA reactive (-)-(11R,-12S,13S,14R)-dibenzo[a,l]pyrene-11,12-dihydrodiol 13,14-epoxide metabolite.[20] Covalent DNA-adducts of such bulky compounds are removed successfully by cellular repair system, if not DNA adducts can cause mutations of proto-oncogenes. Spencer et al. studied the influence of dibenzo[a,l]pyrene adduct formation on carcinogenesis using nucleotide excision repair +/– cell lines.[21]

As we can see, majority of metabolic studies were performed on compounds that are endogenous hormones or synthetic compounds used in estrogen replacement therapy. Undoubtedly, chronic, high-dose intake of estrogens for relieving of menopausal symptoms means a highly statistically significant increase in development of breast cancer.[22] However, it should be mentioned that contribution of reactive metabolite formation to estrogen-induced carcinogenesis is still not clear. The general and most widely recognized mechanism of estrogen mediated carcinogenesis is ER-mediated hormonal activity of ER ligands (as growth factors), inducing uterine growth and malignant genital tract changes.[23] Mechanistically, hypothesis of estrogen induced carcinogenesis via metabolic activation should be expanded to other classes of "orphan" P450s that have bioactivation potential. Many P450s exist for which functions are not fully explained and as such could have important impact on estrogen bioactivation. Recently, Wang et al. have identified the potential of an largely unknown CYP2W1 to mediate bioactivation to reactive metabolites from fluorinated 2-aryl-benzothiazole analogs.[24] Future studies should also focus on other industrial EDCs (eg. bisphenols) and their carcinogenic potential in terms of estrogen activity and their metabolic profile.

# 2. Interaction of EDCs With ERs

## 2. 1. Structures and Features of ERs

ERα ligand-binding characteristics show little differences among vertebrates.[25–27] ER is a ligand-activated transcriptional regulator and a member of the nuclear receptor superfamily. Its endogen ligand is an ovarian steroid hormone E2. Two subtypes of ER are known, ERα and ERβ, which are coded by separate genes.[28] Both possess three major functional domains: the N terminal A/B domain, activation function-1 (AF-1) domain and the DNA binding domain (DBD), which binds the receptor to a DNA helix.[28–31]

ERα and ERβ differ in two features: distribution in the tissues and ligand binding characteristics. This could explain the tissue selective actions of estrogens. ER conformational changes are induced after ligand binding, followed by homodimerization. We should also mention the fact that many cells express both ERα and ERβ, which can form either homo- or heterodimers (heterodimerization).[32] The homodimer binds to a specific estrogen responsive element (ERE), located in the promoter region of the target gene. The role of heterodimerization and ERα/β heterodimers still remains open but it is believed that they regulate ERE, whereas ERβ counteracts the stimulatory effects of ERα through heterodimerization (reduced ERα-mediated cell proliferation).[33] ER agonists induce transcriptional activation through interaction with coactivators. ER antagonists interact preferentially with corepressor complexes.

Selective ER modulators (SERMs) are synthetic ER ligands that act as ER agonists in certain tissues (bone, liver and cardiovascular system), while in other tissues (brain and breast) as ER antagonists.[34–36] In uterus they have mixed agonistic/antagonistic activity. SERMs are chemically categorized into three structural classes: 1) triphenylethylene 2) benzothiophene and 3) benzopyran compounds. The prototype SERM compound from triphenylethylene class is tamoxifen and is still used for the treatment of hormone-dependent breast cancer. The most commonly used SERM today is raloxifene, chemically a benzothiophene, which is indicated for prevention and treatment of postmenopausal osteoporosis.[37] Due to significant presystemic clearance of raloxifene *in vivo* and potential of forming electrophilic diquinone methides and orho-quinones a lot of effort is made to chemically improve the basic structure. As result Liu et al. found that fluoro-substituted desmethyl arzoxifene (4'F-DMA) has improved metabolic profile and represent a safer alternative of SERM.[38] It is worth of noting that tamoxifen bioactivation remains controversial due to carbocation metabolic formation and detection of its DNA adducts in endometrium, what coincides with increased incidence of premalignant and malignant endometrial changes.[39]

Numerous steroidal and non-steroidal compounds can bind to ERs. These compounds have a common phenol group, which is responsible for ER binding, but they contain different core structures. Available ER-ligand 3D structures allow establishment of the structure-activity relationship. ERs can also indirectly alter the expression of genes without directly binding to DNA. This is possible

when interaction with other promoter proteins occurs or by the inhibition of certain transcription factors.[40,41]

Rapid effects of E2 on a time scale of seconds to minutes could not be explained by genomic effects previously described. It is suggested that they are rather conducted through different signalling pathways and are therefore termed non-genomic effects.[42] The presence of membrane impermeable estradiol-protein conjugates may support these effects since membrane initiated estrogen signalling has been reported, implicating the existence of special ERs. In SK-BR-3 breast cancer cell lines that are deficient in nuclear ERs, an orphan receptor, G-protein-coupled ER (GPER; formerly known as GPR30), was discovered.[43–45] GPER was also found in MCF-7 cells, macrophages, keratinocytes, brain cells and vascular cells.[46–48]

Non-genomic effects of E2 were studied on many different cell models. Alyea et al. studied non-genomic estrogen effects on dopamine efflux via dopamine transporter on PC12 cell culture that contains three types of membrane ERs (mERs): mERα, mERβ and GPER. Assay was conducted through measuring the $^3$H-dopamine efflux in the presence of E2, estrone and estriol. Additionally, they showed that for E2-mediated dopamine efflux the protein kinase C and mitogen-activated protein kinases are involved and that the presence of intracellular $Ca^{2+}$ is required.[49] After discovery that platelets contain ERs, Moro et al. studied E2-dependent signaling pathway in platelets. Exposure to E2 leads to rapid phosphorylation of tyrosine kinase Src in platelet membrane and thereby playing an important role in regulating blood aggregation.[50–52] Yu et al. showed that non-genomic effects of E2 help preventing the intestinal injury after traumatic bleeding due to restoring the PI-3K activity, which may prevent neutrophil infiltration and consequent harmful intestinal inflammation.[53]

We should add to this the report on a novel, plasma membrane associated ER with high affinity binding sites named ERX.[54,55] Walsh et al. have demonstrated rapid non-genomic effects of environmental estrogenic compounds at nanomolar concentrations on intracellular concentrations of $Ca^{2+}$ which suggests the existence of an alternative pathway.[56]

## 2. 2. Concept of EDC Binding to ER

Responses to estrogens and other ligands depend on four main features of ERs: *affinity, saturability, ligand specificity* and *receptor distribution that is tissue specific.* Several intracellular pathways are regulated by liganded or non-liganded ERs. Non-liganded ERs may be transcriptionally activated, for example, by selective phosphorylation of certain serine residues of ERα.[28] Structurally different natural and synthetic ER ligands trigger various conformations that interact with other transcription factors in a different way. Sumbayev et al. screened 2,4-dichlorodiphenyldichloroethylene (DDE) and 24 other widely distributed pesticides in order to examine whether they induce ER conformational changes. DDE and several other pesticides (endosulfan, dieldrin, vinclozolin, iprodione, paclobutrazol, fenarimol, prochloraz) were shown to induce a previously unrecognized ER conformational state, which has properties of both E2 (agonist) and 4-hydroxy-tamoxifen (partial antagonist) induced confirmation. This means that pesticide liganded ERs are in equilibrium between two states, one favouring co-regulator binding (agonist liganded receptor) and one preventing co-regulator binding (partial antagonist liganded receptor).[57] High concentrations of hormones that are above the physiological range may also bind to other hormone receptors. For example, E2 present at very high concentrations can bind to androgen receptors.[28,58]

*In vivo* physiological concentrations of endogenous hormones are usually below the dissociation constant ($K_d$) which makes such a system sensitive and effective with respect to hormone concentration fluctuations.[28,59–62] Different responses also require different E2 doses in the same cell systems (e.g. rat pituitary GH3 cells and MCF-7 cells).[63,64] In malignant conditions (e.g. MCF-7 cells) estrogen responsiveness is maintained for a sustained period compared with physiological conditions.[65–68] In addition, chemicals that are inducing growth of MCF-7 cells at lower concentrations can slow or completely stop their growth because of acute toxicity (toxic concentrations). These dual effects can have a wide interval: bisphenol A and octylphenol ranging 1,000 to 100,000-fold and can result in excess of 100 million-fold for DES and E2.[28,62,69–71]

# 3. Aryl Hydrocarbon Receptor (AhR)

AhR is a ligand-dependent transcription factor. Ligands such as TCDD (Table 1) and 3-MC bind to AhR, and the following sequence of events occurs: translocation into the cell nucleus, dimerization with the AhR nuclear translocator (ARNT) and the formation of AhR/ARNT heterodimer complex, leading to gene transcription. The AhR/ARNT heterodimer complex binds to the following specific DNA recognition elements: the AhR responsive element (AHRE), the xenobiotic response element (XRE) or dioxin response element (DRE).[72] Numbers of signalling pathways are cross-connected with the AhR signalling. Observed anti-estrogenic effects after AhR ligand binding are due to AhR/ERα crosstalk. There is certain evidence that activated AhR induces binding of ERα to AhR-regulated genes and that AhR binds to ERα-regulated genes. Genes such as *CYP1A1*, *CYP1B1* and *TiPARP* (poly-ADP ribose polymerase) are expressed as a consequence of TCDD binding to AhR. The same genes are also estrogen responsive (human breast cancer cells), suggesting that AhR and ERs regulate the expression of

common genes.[73] One of the consequences of AhR/ERα crosstalk is impaired DNA binding of inhibitory dioxin response elements (iDREs) in promoter regions of some E2 responsive genes. AhR agonists also mediate degradation of ERs through activation of the proteasome complex, contributing to anti-estrogenic effects.[74] AhR involvement in ubiquitination was confirmed by the inhibition of ER degradation with proteasome inhibitor MG-132.[75] Polyubiquitination of ERα in the presence of AhR ligands occurred when ubiquitin E1 and E2 ligases were supplemented *in vitro*.[75,76]

Beside antiestrogenic effects, AhR ligands can also have proestrogenic effects. AhR agonist, 3-MC, can activate ERs transcriptional activity (especially ERα) in HepG2 or CV-1 cells. It is suggested that these cells are capable of metabolizing parent 3-MC into compounds that act as ER ligands. However, 3-MC itself is not an ER ligand.[77]

## 4. Properties of Synthetic Estrogenic EDCs

EDCs are usually polar and hydrophilic with a low octanol/water partition coefficient ($K_{OW}$). They also have lower binding affinity to organic fractions of sludge or suspended sediments than other persistent organic compounds with higher $K_{OW}$ that are capable of bioaccumulation (PAHs, PCBs, or organochlorine pesticides).[78–81]

**Solubility.** Hydrophilic molecules (e.g. diphenylmethanes) have a tendency to accumulate in aqueous phases and are not distributed in the sediment, body fat or adsorbed to particulate matter in waste water. Compounds with low solubility in water (e.g. p,p'-DDT) are mainly characterized by lipophilic structural fragments. They are largely adsorbed to sediment or particulate matter and tend to accumulate in biological systems, especially in animal fat tissues (Table 2).[82]

**Degradation.** EDCs found in the environment are prone to chemical and microbial degradation (e.g. hydrolysis and photolysis). EDCs with half-lives longer than 2 weeks, some even longer than six months, are considered to be the most persistent (e.g. DDT and PCBs in natural waters).[82] For comparison, BPA has a relatively short biodegradation half-life, ranging from 2–6 days in rivers and is therefore considered less persistent.[84]

**Bioaccumulation.** With the exception of DDT and certain organometallic compounds, EDCs do not accumulate in biological systems significantly.[82] Several active ingredients of oral contraceptives can be traced in aquatic species causing infertility. Active ingredient in birth control pills, ethynylestradiol, has been detected in wild fishes, levonorgestrel, active ingredient in post-coital contraception was found in fishes and mussels.[85] Interestingly, plasma levels of levonorgestrel in fish even exceeded human therapeutic levels.[86] Bioaccumulation in marine animals could present a serious treat for human health because they represent an important source of human nutrition. Relations between ingestion of EDCs and their effects on human cells are very complex and should be studied in more detail (eg. different cell lines with EDCs mixtures). Lasserre at al. studied effects of selected EDCs atrazine and 2, 2', 4, 4', 5, 5'-hexachlorobiphenyl on human MCF-7 cells. Expression of many proteins involved in oxidative stress, DNA repair, cell shape, spermatogenesis were affected.[87]

## 5. Structural Classes of Estrogenic EDCs

Among the ER ligands there are several major categories classified according to their chemical structural characteristics (Table 1). *Steroids* can be divided in two groups. One group has a phenolic A ring (e.g. E2, ethynylestradiol), while the other one lacks a phenolic A ring (e.g. norethynodrel) (Figure 1). *Diethylstilbestrol (DES)*-like *compounds* feature two benzene rings separated by two carbons that are connected by a double bond in DES derivatives (Figure 4), however hexestrol contains only a single bond. *Triphenylethylene* derivatives constitute a group of compounds with an additional phenyl group attached to the ethylene bridge, a common property of synthetic anti-estrogens. The *Diphenylmethane* class includes diphenolalkanes (e.g. bisphenol A and its analogs). *Biphenyls* are chemicals with two connected phenyl rings that may or may not contain halogens (chlorine or bromine). All compounds in the class of *phenols* contain a single phenolic ring, most of them also contain a long alkyl chain substituted at the para position (e.g. p-nonylphenol). In addition to ER ligands two structural classes of AhR ligands are considered: *PAHs* and *dioxins* (Figure 9).

**Table 2.** Comparison of water solubility and log $K_{OW}$ of selected EDCs

| Chemical class | Example of compounds | Solubility in water | log $K_{OW}$ |
|---|---|---|---|
| Diphenylmethanes | Bisphenol A | 120 mg/L[a] [83] | 3,32[83] |
| Steroids | Ethynylestradiol | 11,3 mg/L[b] [83] | 3,67[83] |
| PAHs | Benzo[a]pyrene | $1{,}62 \times 10^{-3}$ mg/L[a] [83] | 6,14[83] |
| Diphenylmethanes | p.p'-DDT | $5{,}5 \times 10^{-3}$ mg/L[a] [83] | 6,91[83] |

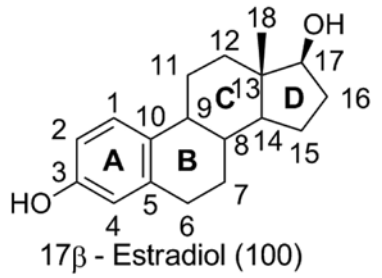
a – at 25 °C b – at 27 °C

## 5. 1. Steroids

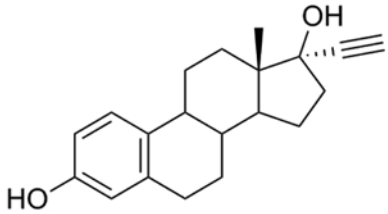
The most active natural estrogen is E2 (Figure 1), a typical prototype for a steroidal compound that acts on ERs and contains a hydrophobic core with two OH groups. EDCs that bind to ERs are actually structural mimetics of endogenous E2. Crystal studies of E2 bound to ER showed that the 3-OH and 17β-OH groups act as H-bond donors and acceptors, respectively. Elimination or modification of these two OH groups significantly reduces ER binding affinity.[2,3,88] The impact of elimination and modification is more drastic at the 3-position than at the 17β-position (Figure 1). Other steroidal hormones like testosterone or progesterone do not bind to ER under physiological conditions because they lack an aromatic hydroxyl group. The precise distance between the 3- and 17β-OH groups of steroids and their spatial orientation significantly impacts binding affinity. The optimal distance between the 3- and 17β-OH groups ranges from 9.7 to 12.3 Å. For comparison the oxygen-oxygen distance in E2 is 10.9 Å.[89] Additionally, steric hindrance at the 7α- and 11β-position of the steroid backbone is also an important feature. The volume of the ER binding pocket is about twice that of E2. Large unoccupied cavities at 7α- and 11β- positions of E2 allow bulky groups to fit in ERs. This observation is of great importance for xenoestrogens such as DES-like chemicals (Figure 4), diphenylmethanes (Figure 5), and biphenyls (Figure 7). For example, the binding affinities of DES, dimethylstilbestrol (DMS) and 4,4-dihydroxystilbene decrease with shortening of the alkyl side chains that mimic the 7α- and 11β- positioned bulky groups. The addition of small substituents such as 11 β-chloromethyl, ethyl and vinyl groups to the 11 β-position usually increases ER binding affinity.[2,88,89]

**Metabolism.** The nature of E2 metabolism is entirely oxidative (Figure 2). The most frequent hydroxylation site is C-2, which is followed by C-16 and C-4.[90–92] The least frequent sites are at C-6, C-7 and C-15. All these hydroxylations are catalyzed by the specific cytochrome P450 with great stereospecificity, since hydroxylations can occur α (below) or β (above) the plane of the steroid backbone. Among the most common P450s that take part in hydroxylations are CYP1A1 for C-2, CYP1B1 for C-4 and CYP3A4/5 for C-16.[93] P450 polymorphic forms differ significantly in reaction rates from that of the major isoform found in populations.[94,95]

a)

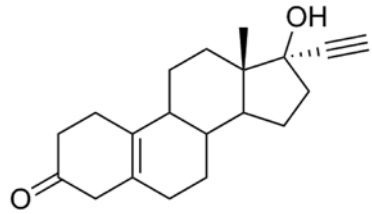



17β - Estradiol (100)




Ethynylestradiol (190)

b)




Norethynodrel (0,22)

**Figure 1.** Steroids (a) with and (b) without phenolic structure (ring A); In each case the ratio of its binding affinity to that of E2 is expressed as a percentage given in parentheses.[2]

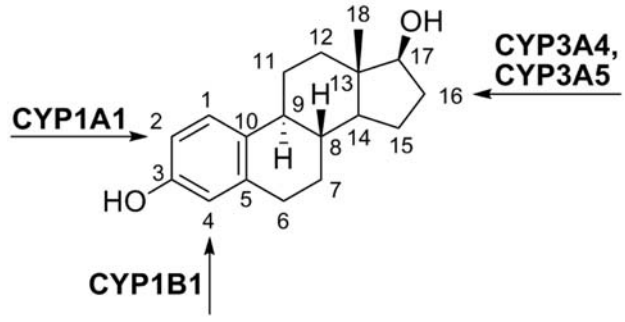



**Figure 2.** The most common P450s that take part in C-2, C-4 and C-16 hydroxylations of E2 *in vitro*[96–98]

Enzyme catechol-O-methyltransferase (COMT) is responsible for O-methylation and therefore inactivation of catecholamine neurotransmitters with S-adenosyl-L-methionine (SAM) as a cofactor. However, any compound with a catechol structure is a potential substrate for COMT. *In vivo* methylation of E2 at C-2, C-4 or less frequently at C-3, results in metabolites with various activities. For example, 2-methoxyestradiol has minimal estrogenic activity but very promising antitumor effects.[99,100] Alternatively, the catechol structures in estrogenic compounds are able to form electrophilic semiquinones and quinones, which can react with glutathione (GSH) and other nucleophilic compounds. While the formation of GSH conjugates *in vivo* may act as a detoxification mechanism, the reaction of semiquinones with DNA leads to stable adducts in the case of the 2,3-catechols, but in the case of the 3,4-catechols depurination adducts are formed, increasing

mutation rate.[101–103] 16α-OH-Estrone has ability to react irreversibly to histones and ERs through the so called Heyns rearrangement, contributing to continuous activation of estrogen signaling.[104–106]

## 5. 2. Synthetic Non-steroidal Compounds

Synthetic non-steroidal estrogens retain phenolic function, but have a remarkable range of structural motifs in core regions that encompass the following possible fragments: simple acyclic, variety of alicyclic systems and heterocycles. Efforts have been made to optimize ER ligand structures to improve tissue selectivity, especially for therapeutic purposes. For example bazedoxifene has improved tissue selectivity with little or no agonistic activity in the uterus in comparison with other SERMs.[107] Synthetic non-steroidal ER agonists have a common structural model and composition: (1) **a core structure**, (2) **an essential phenolic unit** that should not be chemically altered to retain optimal ER binding affinity,[108] (3) **an optional second aromatic group** and (4) **one or two optional substituents** – one of them could be aromatic (Figure 3). It should be mentioned that ER antagonists and partial agonists contain a polar group on the aromatic ring. To achieve high ER-binding affinity, the peripheral groups (2–4) must display a certain geometric arrangement.

Fink et al. have incorporated certain sub-structural motifs into 1,2- and 1,3-azole systems that are outlined in Figure 3. All heterocycles binding affinities to ER were determined with competitive radiometric binding assay using tritium [$^3$H] labelled estradiol.[109] They discovered that **the homodibenzyl structure** is a common structural element in non-steroidal ligands such as benzestrol and raloxifene and can be substituted with sterically very similar 3,5-diaryl-1,2pyrazoles or isoxazoles and 2,4-diaryl-1,3-imidazoles, thiazoles or oxazoles. **The dibenzyl**

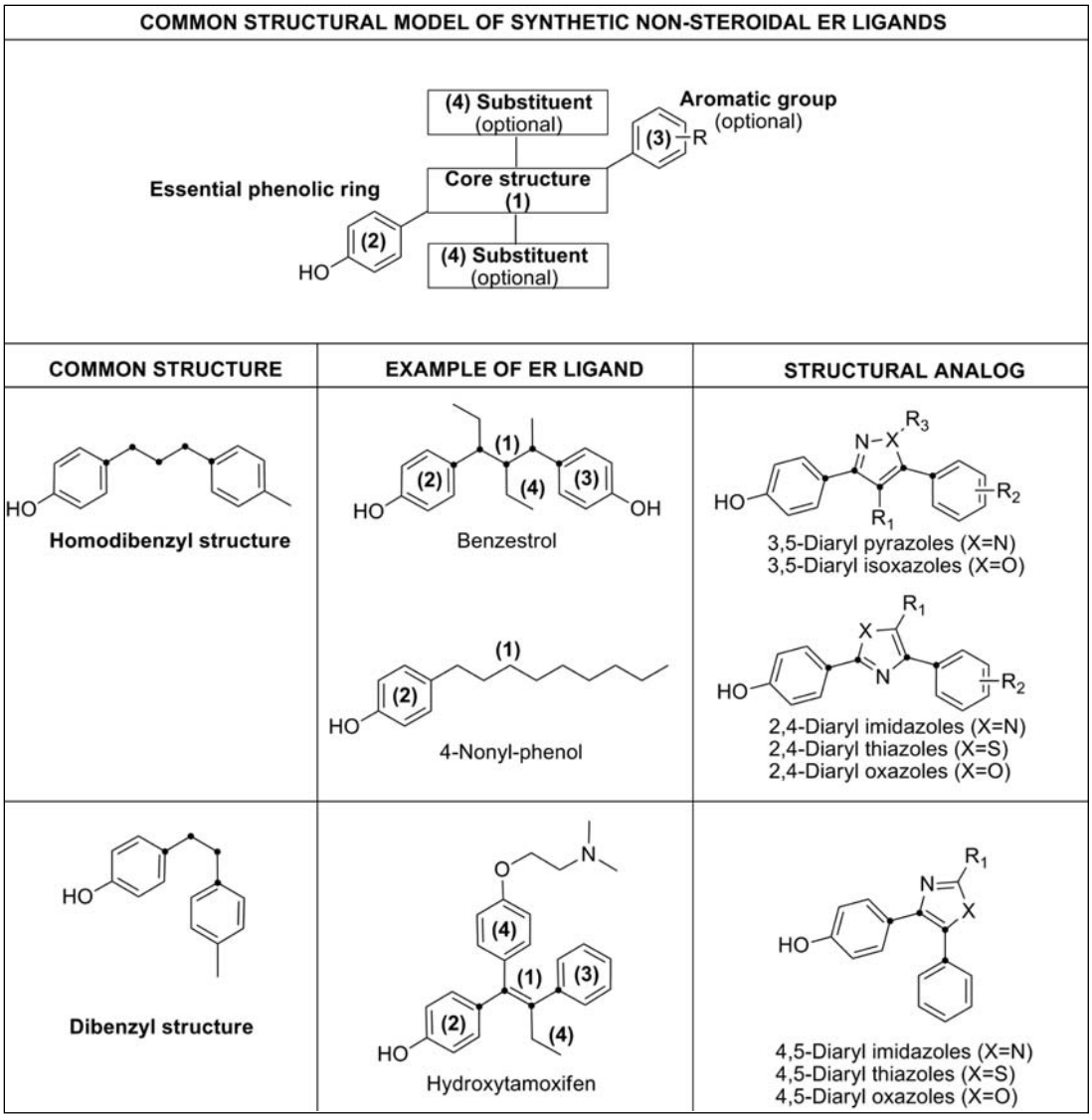



**Figure 3.** Common structures found in ER ligands and proposed experimental analogues[109]

**structure** is a common structural element found in hydroxytamoxifen that can be mimicked with various 4,5-diaryl-1,3-azoles. The diazole *N,N*-systems (namely pyrazoles and imidazoles) can accommodate up to four peripheral substituents, whereas the *N,O*- and *N,S*-heterocycles (oxazoles, isoxazoles and thiazoles) can have a maximum of three attached substituents.[109]

Studies from Fink et al. are important in two ways. First, they have confirmed the hypothesis that bulky core structures contribute to ER binding affinity and second, that simple heterocycles can effectively replace the complex core structures of steroids retaining ER binding.

### 5. 2. 1. DES-like Chemicals

Diethylstilbestrol (DES, Figure 4) is one of the highest-affinity synthetic estrogens, with a relative binding affinity (RBA) of 400, compared to E2 with an RBA of 100. DES molecule seems to have an optimal spatial arrangement for hydrophobic and H-bond interactions.[2] In the case where the OH group is being methylated, ER binding affinity decreases due to loss of H-bonding capability similar to E2. When both OH groups of DES are methylated, the reduction ER binding affinity is even more significant. The two ethyl groups (bulky core groups) increase ER binding activity of DES as significantly as its phenolic OH groups. The two ethyl substituents increase hydrophobicity, maintain rigidity and help to occupy the ER binding pocket. Binding affinity decreases from DES to dimethylstilbestrol and 4,4'-dihydroxystilbene. The ethyl groups may contribute to ER binding. Both ethyl groups resemble the 11β- and 7α-substituents of E2.[2,109]

DES was synthesized in the 1930s and was used as an estrogen supplement, but it was banned in the USA af-

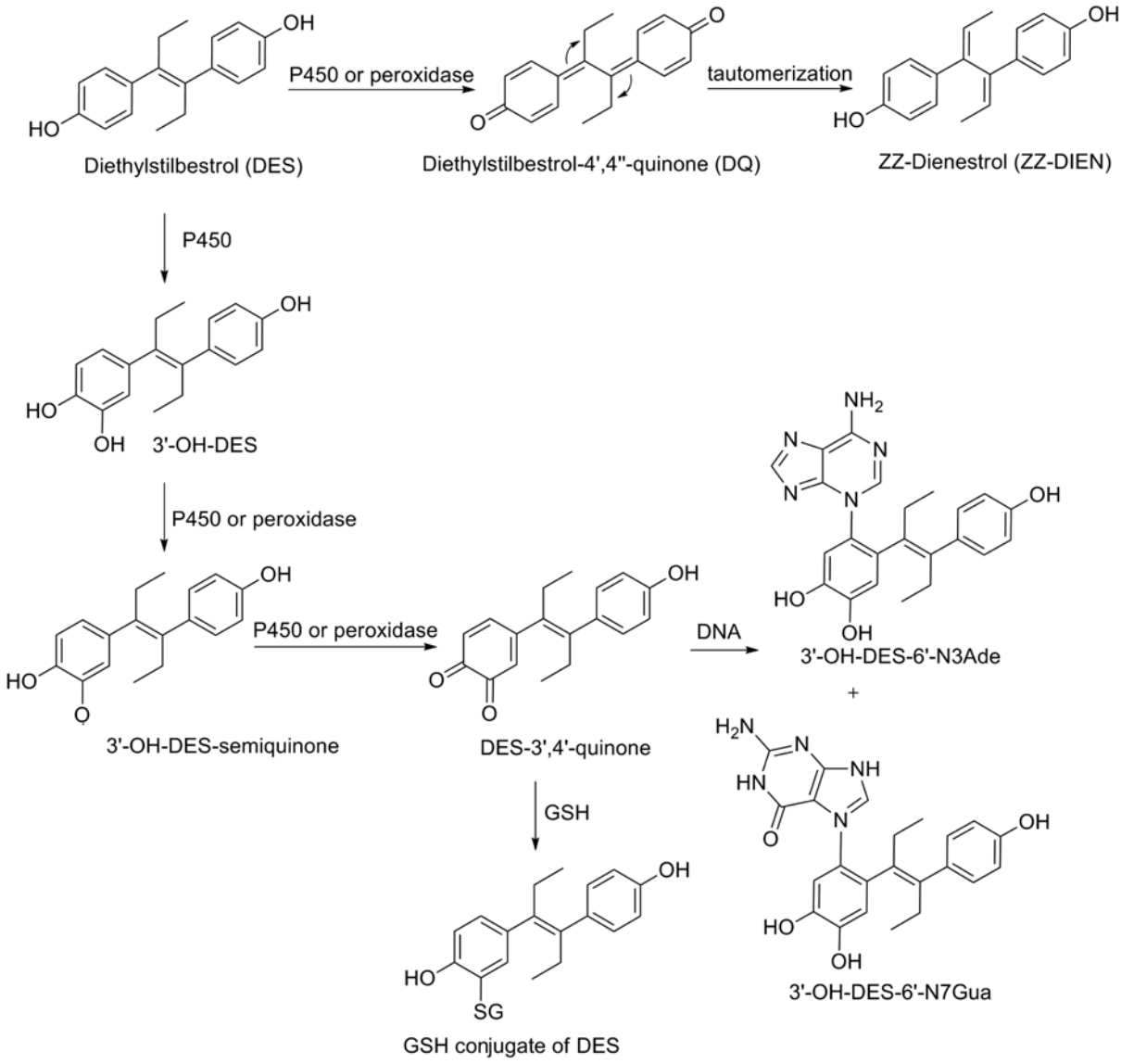



**Figure 4.** *In vitro* and *in vivo* metabolism of DES by cytochrome P450 or peroxidase[110,114]

ter identification of its adverse carcinogenic effects. Moreover, *in utero* exposure to DES leads to increased incidence of cervical cancer in adult females that are exposed to DES before birth.[110] The mechanism of the carcinogenesis is still not known. One hypothesis suggest that reactive metabolites of DES might play a role, since it is metabolized to a number of reactive metabolites, including its oxidative metabolite, diethylstilbestrol-4',4''-quinone (DQ), catalysed by P450 or peroxidase. DQ is further metabolized to a non-carcinogenic metabolite Z,Z-dienestrol (ZZ-DIEN) (Figure 4).[110–113] DES is also metabolized to its catechol, 3'-OH-DES that intercalates into DNA and is then enzymatically oxidized to its quinone which reacts with DNA. The resulting compounds are depurinating adducts 3'-OH-DES-6'-N3Ade and 3'-OH-DES-6'-N7Gua, analogous to those formed by the natural estrogens.[114]

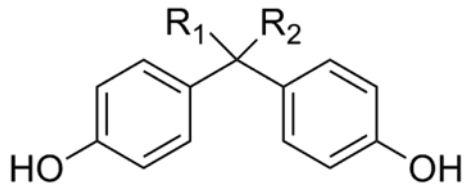
### 5. 2. 2. Triphenylethylene Derivatives

Triphenylethylenes act as anti-estrogens (ER antagonists) and are chemically similar to DES but have an additional phenyl group attached to the ethylene moiety. In the case of ER antagonists and mixed agonist/antagonists, one of the substituents generally contains a basic or polar function. The prototype of this group is tamoxifen, which is used in breast cancer therapy.[108,109]

**Metabolism.** Tamoxifen is a model substance for the triphenylethylene derivatives and is extensively metabolized by human liver enzymes to several primary and secondary metabolites. CYP3A4/5 is the major P450 isoform responsible for the formation of *N*-desmethyltamoxifen. Formation of 4-hydroxytamoxifen or endoxifen is mainly catalyzed by CYP2D6. Other P450 isoforms play a less important role in tamoxifen metabolism. SULT1A1 has been proposed to form an sulphate of 4-hydroxytamoxifen thereby contributing to endoxifen clearance.[115–117]

### 5. 2. 3. Diphenylmethanes

Diphenylmethanes are chemicals with two benzene rings separated by one carbon atom that contain a 4-OH substituent that is critical for binding to ERs. There are three groups of diphenylmethanes: diphenolalkanes, benzophenones and DDTs. Diphenolalkanes (bisphenols) contain two phenol rings separated by one carbon atom; their generic formula is depicted in Figure 5.




**Bisphenol A** ($R_1$=$CH_3$ and $R_2$=$CH_3$)
**Bisphenol F** ($R_1$=H and $R_2$=H)
**Bisphenol AF** ($R_1$=$CF_3$ and $R_2$=$CF_3$)
**Bisphenol B** ($R_1$=$CH_3$ and $R_2$=$CH_3CH_2$)

**Figure 5.** General formula of diphenolalkanes

**Bisphenols.** The most widespread diphenolalkane is bisphenol A (BPA), first synthesized in 1891 by A.P. Dianin. BPA binds to ERβ with an approximately 10-fold higher affinity than to ERα. BPA is used as monomer in epoxy-phenol resin synthesis (canned food) and polycarbonate plastic (medical equipment) or as antioxidant in PVC plastic. Two structural elements enable BPA to bind to ERs: a) 4-OH group on the A-phenyl ring and b) a hydrophobic moiety at the central C-atom. For example, bisphenol F has lower affinity to ERs than BPA and bisphenol B. BPA has approximately 10,000 times weaker affinity for ERs than E2.[118,119]

**Metabolism.** Glucuronidation of BPA is catalyzed with UDP-glucuronosyltransferases (e.g. UGT2B1). The resulting BPA glucuronide is completely without estrogenic activity. Part of BPA is also sulfated by phenol sulphotransferases present in the liver (e.g. ST1A3). BPA sulphate has diminished estrogenic activity.[120–123] Besides metabolic phase II reactions, there is strong evidence to support the hypothesis that the metabolism of BPA in the human liver involves an oxidative pathway and formation of reactive metabolites (e.g. quinones, semiquinones), catalysed mainly by P450s. Jaeg et al. studied BPA metabolism using liver microsomes. Several metabolites have since been discovered: isopropyl-hydroxyphenol, BPA glutathione conjugate, glutathionyl-phenol, glutathionyl-4-isopropylphenol and BPA dimers.[124] The BPA metabolite bisphenol-*o*-quinone was also identified and could bind DNA *in vitro* and *in vivo*. From these results it was suggested that covalent modification of DNA by *in vivo* exposure to BPA may be a factor in the induction of hepatotoxicity.[125] Moreover, it was suggested that the estrogenicity of BPA is increased (two to five times) through its biodegradation by rat liver S9 microsomal and cytosolic fractions. The active estrogenic metabolite was confirmed to be 4-methyl-2,4-bis(*p*-hydroxyphenyl)pent-1-ene (MBP).[126]

**Dichlorodiphenyltrichloroethanes (DDTs).** Dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethane (DDD) and dichlorodiphenyldichloroethylene (DDE) isomers have structural frameworks similar to that of BPA. The o,p'- isomers are active in binding, while p,p'-isomers are not. The *ortho*-chlorine of o,p'-isomers mimics the steric 11β-substituent of E2 and increases structural rigidity, which favours ER binding. p,p'-DDT is metabolized by rat liver microsomes to p,p'-DDD and p,p'-DDE (Figure 6A). p,p'-DDE was also formed from p,p'-DDD. 1-chloro-2,2-bis(4'-chlorophenyl)ethylene (p,p'-DDMU) metabolite is formed via dehydrochlorination of p,p'-DDD.[127] $K_{ow}$ values for DDT (o',p'-DDT: 5.65; p,p'-DDT: 5.50), DDD (o,p'-DDD: 4.87; p,p'-DDD: 4.82) and DDE (o,p'-DDE: 5.43; p,p'-DDE: 5.78) impli-

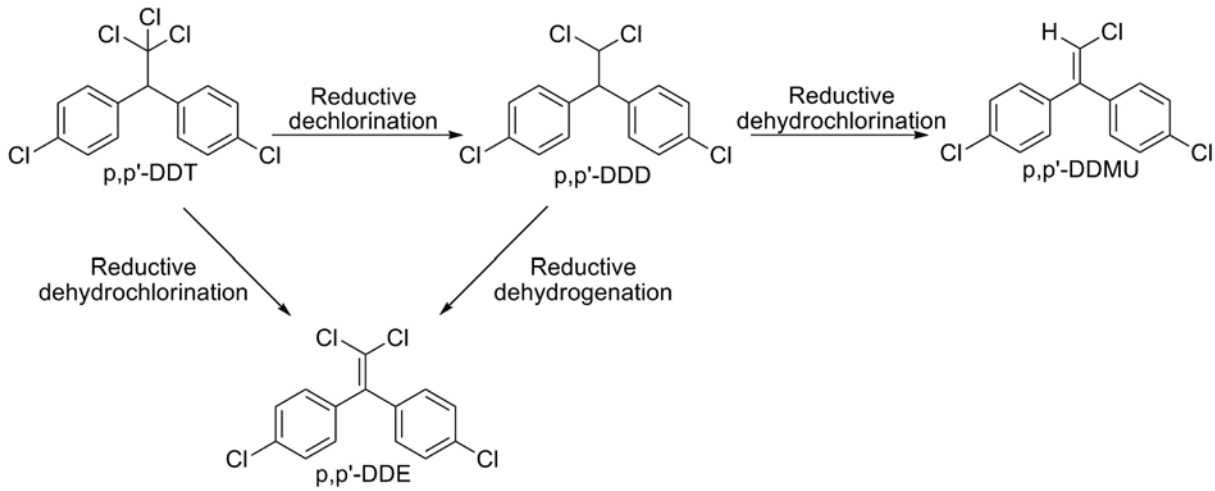



**Figure 6a.** Reductive metabolism of p,p'-DDT in rat liver microsomes by Kitamura et al.[127]

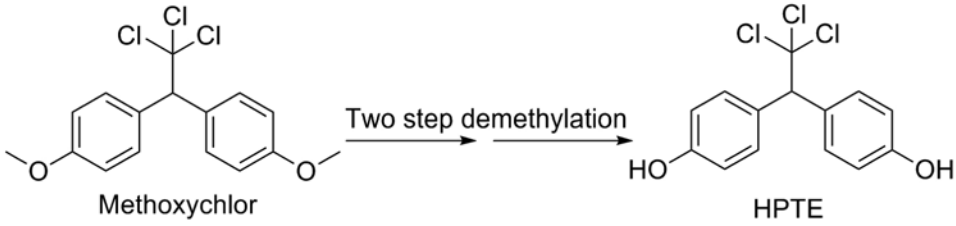



**Figure 6b.** Kupfer et al. proposed a two step demethylation of methoxychlor by using liver microsomes.[130]

cate that the higher $K_{OW}$ values for DDT and DDE increase bioaccumulation in the body fats, whereas DDD and DDMU are mainly eliminated via the kidney.[128,129] The pesticide methoxychlor represents a "safer" version of DDT and also exerts estrogenic effects but is known to induce the enzyme aromatase. It needs metabolic activation for endocrine activity. The resulting active metabolite 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE) with bisphenol structure can act as an ERα agonist. Although it has many toxic endocrine effects (e.g. induction of uterotrophic response, reduced mass of ovaries), it is still used as a pesticide because of its faster metabolism and significantly reduced likelihood of bioaccumulation (Figure 6B).[130]

## 5. 2. 4. Biphenyls

Biphenyls are divided into two types of compounds: polychlorinated biphenyls (PCBs) and phenylphenols.[5] PCBs hydroxylated on position 4 (4-OH-PCBs) are better ER binders than non-hydroxylated PCBs, which is consistent with observations in other chemical classes. With an increasing number of chloro substitutions at the non-phenolic ring, more electron withdrawal is found in the phenolic ring. This results in higher $pK_a$ values and better H-bond formation capabilities. 2',3',4',5'-Tetrachloro-4-biphenylol and 2',5'-dichloro-4-biphenylol are the strongest binders in the group (Figure 7).[131,132]

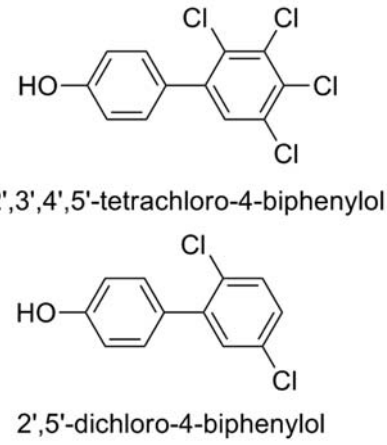



**Figure 7.** Structures of 4-OH-PCBs.

It is evident that PCB compounds with single or multi-orthochlorine substitution patterns that restrict the conformational flexibility of PCBs are among strongest ER binders. From a chemical point of view, PCBs can form rotational isomers since rotation around the central bond is restricted. It was found that three or four orthochlorine substituents are required to prevent racemization. Two ortho-chlorine substitutions at the non-phenolic ring also act as small steric substituents and mimic the 11β-position of E2, leading to improved binding to ERs.[133]

**Metabolism.** Hydroxylated PCBs (OH–PCBs), or polychlorobiphenylols, are the main PCB metabolites. Hydroxy-PCBs are formed through arene oxides by P450. OH–PCBs are polar compounds that are quickly eliminated. Their reported concentrations in humans have been 10% to 20% of the PCB level. OH–PCBs can also be found in the plasma of healthy pregnant women (study in Netherlands). In addition to mentioned hydroxylation reactions, bacterial metabolic reactions of PCBs are also important, since they are responsible for the removal of PCBs from the environment. Anaerobic dehalogenation of highly chlorinated congeners in aquatic sediments is an important process (*Dehalococcoides ethenogenes* and related organisms).[134–136]

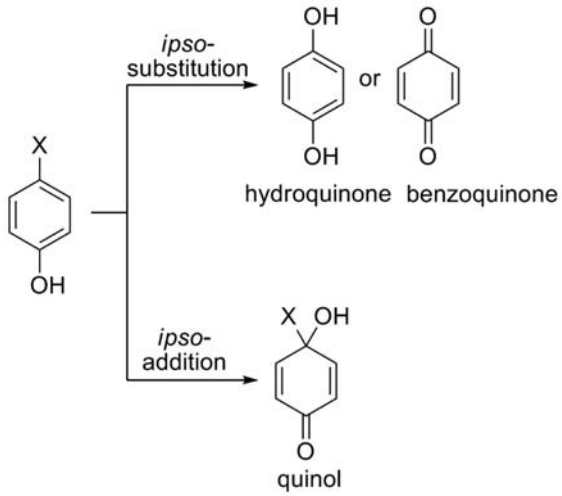



**Figure 8a.** P450 catalysed *ipso*-position reaction of para-substituted phenols[139]

## 5. 2. 5. Phenols

This class is divided into three types of compounds: *alkylphenols, parabens and alkyloxyphenols*. The member of this class having the highest binding affinity is nonylphenol (NP, Table 1).[2] Length of the alkyl side chain at para position has a large impact on binding activity. NP is a mixture of isomers with differently branched nonyl side-chain structures. A number of isomers are generated during the synthesis (an isomeric mixture of p-nonylphenols), the three main NP isomers being 2-(4-hydroxyphenyl)-nonane, 3-(4-hydroxyphenyl)-nonane and 4-(4-hydroxyphenyl)-nonane. NP is most frequently used in the synthesis of nonylphenol ethoxylates, which are components of non-ionic detergents, antioxidants and oil additives.[137,138]

**Metabolism.** The ipso-position biotransformation reaction of para-substituted phenols (para-substituent is an electron donating alkyl group) is catalyzed by P450 with a quinol intermediate formed via an ipso-addition reaction (Figure 8A).[139] When a para-substituent is an electron withdrawing group: halogen, methoxy, nitro, cyano and substituents with carbonyl groups (e.g. acetyl, carboxyl, or benzoyl), a hydroquinone or benzoquinone formation is followed. Estrone and E2 also contain a para-alkylphenol substituent and form quinols through P450 ipso-addition. Ohe et al. confirmed quinol formation from estrone and E2 by CYP1A1, CYP2B6 and CYP2E1 accompanied by 10β-hydroxylation.[140] Estrogens that undergo ipso-addition lose their ER-binding activity. An example of para-substituted phenol is NP, that undergoes an ipso-addition reaction catalyzed by P450, where it forms a quinol intermediate. The benzyl position could also be oxidated by P450, a factor giving rise to ipso-substitution reaction (Figure 8B).[139]

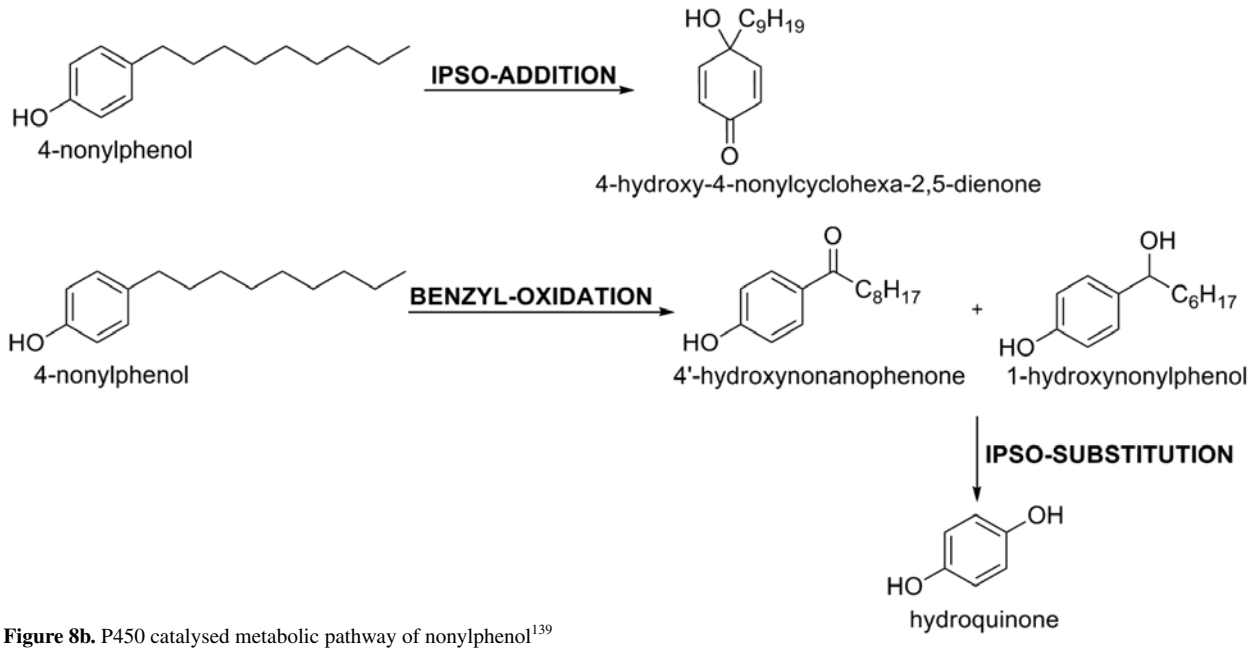



**Figure 8b.** P450 catalysed metabolic pathway of nonylphenol[139]

# 6. AhR Ligands

Studies on the AhR, also known as the dioxin receptor, and its ligands began about 50 years ago when drug-metabolizing enzymes were found to be induced by PAHs such as 3-methylchoranthrene (3MC) and TCDD (Figure 9).[74] The AhR was originally identified as a ligand activated transcription factor involved in induction of the xenobiotic-metabolizing cytochrome CYP1A1. It is known that compounds that bind and activate the AhR are hydrophobic molecules (e.g. synthetic PAHs and HAHs). Many agonists are planar compounds and coplanarity is one of the most important determinants affecting the affinity of the AhR for its ligand.[75] Much attention is given to the intrinsic functions of AhR and its natural or endogenous ligands. Nguyen et al. described different structural types of compounds that act like endogenous activators of AhRs such as indigo and indirubin, equilenin (an equin estrogen), arachidonic acid metabolites (e.g. PGG2 and lipoxin A4), heme metabolites (e.g. bilirubin and biliruverdin), tryptophan derivatives (e.g. tryptamine, indole-3-acetic acid (IAA)), UV photoproducts of tryptophan (e.g. 6-formylindolo[3,2-*b*]carbazole (FICZ)) and AhR agonists derived from dietary sources (e.g. indolo[3,2-b]carbazole (ICZ) and 3,3'-diindolylmethane (DIM)).[75,141] Interestingly, it has been found that harmine and its main metabolite, harmol (β-carboline compounds) significantly inhibit the induction of CYP1A1 by AhRs agonist dioxin. Several AhR antagonists have shown promising results against several carcinogen-activating agents.[142]

## 6. 1. Chlorinated Aromatic Hydrocarbons

TCDD is a prototype compound of chlorinated aromatic hydrocarbons causing a large number of toxic effects: immunotoxicity (strong lymphoid atrophy), cancerogenesis, teratogenesis, skin disorders (chloracne) and infertility. Chlorinated aromatics hydrocarbons are chemically stable compounds with a great bioaccumulation and sorption potential.[143] In the sections above we already described TCDD as a potent AhR-dependent inhibitor of estrogen activity, whereas PCBs exert pro-estrogenic activity.

### 6. 1. 1. Dioxins

Dioxins are a common generic name for polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofuranes (PCDFs), a group of toxic organic contaminants (Figure 9). They are not produced for commercial purposes, but are generated as byproducts in the production of chlorophenols, herbicides (chlorophenoxy acids), and PCBs. Other sources are the paper industry (chlorine bleaching), automobile exhaust (leaded fuel), burning household and industrial waste and the manufacture of PCBs.[144] Most research has been carried out on a representative compound TCDD. Toxicity of PCBs, PCDFs and PCDDs correlates with AhR binding affinity. 3D QSAR studies revealed that sterically favoured regions are present near the 2, 3, 7 and 8 positions of TCDD (this is also the case for PCDFs). However, bulky groups in the medial position (1,4-dioxane ring) of the second benzene ring are particularly unfavourable for binding. When regions near the 2,3 position in TCDD and PCDF are substituted by electronegative halogen molecules the activity increases, but on the medial position of the ring a positive charge is favoured. The first benzene ring makes a greater contribution to the hydrophobic interaction with AhRs than the second benzene ring.[145]

### 6. 1. 2. PAHs

PAHs constitute a major class of environmental organic pollutants. Incomplete combustion of any organic fuel (coal, diesel, gasoline, or biomass) can result in the formation of PAHs. Five PAHs, benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, dibenz[a,h]anthracene and indeno[l,2,3-c,d]pyrene, are known human carcinogens (Figure 9).[146]

Several QSARs studies have been conducted to examine the influence of molecular structure on biodegradation rates, photo-induced toxicity and mutagenicity of PAHs in human cells. Shape, electronic energy and substitution have been determined as significant factors. PAHs are known to bind to AhRs. However, several 4- and 5-ring polycyclic PAHs, heterocyclic PAHs and their hydroxy derivatives were examined to determine their ability to interact with ERα and ERβ. It was determined that only compounds with a hydroxy group were able to compete with $^{3}$H-labelled E2 for binding to glutathione-S-transferase, human ERα, the D, E, and F domain fusion protein or to the full-length human ERβ. PAH structures are homogeneous, but their carcinogenic effects are diverse, ranging from highly active to inactive. Dipple et al. proposed a classification into four classes according to their power: inactive, slight, moderate and high.[147,148] A consistent explanation for the carcinogenic action of many PAHs was given by the so-called K-L-M-"bay region" theory. Schmidt et al. hypothesized that the carcinogenicity of PAHs is related to the distribution of π-electrons.[149] For example PAHs with high π-electron density in the L-region are strong carcinogens. Pullman et al. pointed out the coupling of high π-electron density in the K-region and low density in the L-region to be a determining factor for high carcinogenicity.[150,151] Jerina et al. have found that stabilization of the "bay region" cation is relevant for carcinogenicity.[152] Thus, the diolepoxide formed at the "bay region" was established as the main factor responsible for the toxic action, since it is believed to react directly with a nucleic acid base and give rise to cancer.[146,153–155]

**Metabolism.** It is well known that, *in vivo*, the metabolic processes of PAHs lead to reactive, electrophilic

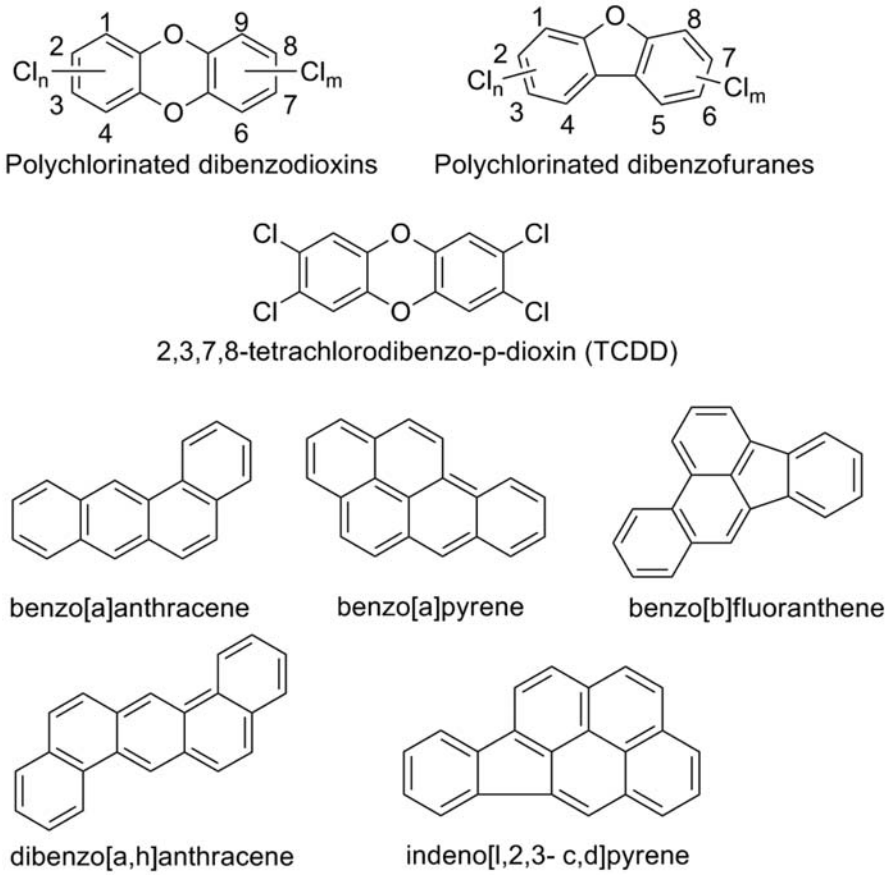



**Figure 9.** Structures of PCDDs, PCDFs and five PAHs that are known human carcinogens

intermediates that can initiate cancer. In the commonly accepted chemical carcinogenesis, a PAH is converted in a stepwise process, by three metabolizing enzymes to a reactive diolepoxide which then intercalates rapidly with the deoxyguanosines or deoxyadenosines in DNA. The first and essential step in DNA adduct formation is a non-covalent interaction of PAH with DNA. The study of such interactions is of great importance in understanding the detailed mechanism of PAH carcinogenesis. Benzo-[a]pyrene, a lead compound for PAHs, is transformed to different arenoxides. Studies of carcinogenicity have revealed that the 7,8-epoxid and 7,8-dihydrodiol forms are proximity mutagens and that 7,8-diol-9,l0-epoxid is a powerful, ultimate carcinogen.[155,156]

## 7. Conclusions and Future Perspectives

Development in the field of estrogenic compounds has evolved significantly from the first synthetic hormones and their use in contraceptives, through aromatase inhibitors used in cancer therapy, and selective estrogen receptor modulators used in hormone replacement therapy, cancer and osteoporosis treatment. Conversely, toxicologists are facing the problem of characterizing EDCs in the environment (mainly industrial chemicals) that present health risks for the population in the form of hormone disruption that affects reproduction and growth. There are a multitude of endocrine disrupters that have widely varying effects and are present in a variety of environments. The persistence of EEDCs in the aquatic environment is governed by biodegradation, sunlight photolysis and other abiotic transformations like hydrolysis. Once they reach surface waters, they can be transformed, mainly via bio- or photo-degradation, or they can be adsorbed onto suspended particles in the aquatic environment. Sorption of hydrophobic contaminants at the particle water interface is one of the most important processes that control their distribution in aquatic environments. A major issue, in terms of metabolism, is the uncertain fate of EDCs through ingestion of food. The increased duration of EDC exposure represents a major risk factor for breast cancer. The underlying mechanisms in the susceptibility of breast tissue to the carcinogenic effect of estrogens remain unclear. It has been shown that estrogen metabolism under normal physiological conditions leads to formation of reactive oxygen species (ROS) playing important roles in cell transformation, cell cycle, migration and invasion (breast cancer). The redox cycling of hydroxylated estro-

gens and their ROS production is especially important.[157,158] However, it may be suggested that unintended exogenous intake of estrogens (EDCs) could lead to excessive formation of ROS, causing oxidative stress and tissue damage. The many examples given here of EDCs forming various oxidized species emphasizes the need for more extensive studies of their oxidative metabolisms.

## 8. References


1. E. K. Shanle and W. Xu, *Chem Res Toxicol.* **2011**, *24*, 6–19.
2. H. Fang, W. Tong, L. M. Shi, R. Blair, R. Perkins, W. Branham, B. S. Hass, Q. Xie, S. L. Dial, C. L. Moland, D. M. Sheehan, *Chem Res Toxicol.* **2001**, *14*, 280–94.
3. A. M. Brzozowski, A. C. Pike, Z. Dauter, G. L. Greene, J. A. Gustafsson, M. Carlquist, *Nature* **1997**, *389*, 753–758
4. A. C. W. Pike, A. M. Brzozowski, R. E. Hubbard, T. Bonn, A. G. Thorsell, O. Engström, J. Ljunggren, J. A. Gustafsson, M. Carlquist, *The EMBO Journal* **1999**, *18*, 4608–4618.
5. E. Swedenborg, M. Kotka, M. Seifert, J. Kanno, I. Pongratz, J. Rüegg, *Mol Cell Endocrinol.* **2012**, *362*, 39–47.
6. M. Wormke, M. Stoner, B. Saville, K. Walker, M. Abdelrahim, R. Burghardt, S. Safe, *Mol Cell Biol.* **2003**, *23*, 1843–55.
7. A. J. Palumbo, M. S. Denison, S. I. Doroshov, R. S. Tjeerdema, *Environ Toxicol Chem.* **2009**, *28*, 1749–55.
8. J. T. Sanderson, R. J. Letcher, M. Heneweer, J. P. Giesy, M. van den Berg, *Environ. Health Perspect.* **2001**, *109*, 1027–1031.
9. J. T. Sanderson, J. Boerma, G. W. A. Lansbergen, M. van den Berg, *Toxicol. Appl. Pharmacol.* **2002**, *182*, 44–54.
10. J. L. Bolton and G. R. J. Thatcher, *Chem. Res. Toxicol.* **2008**, 21, 93–101.
11. J. L. Bolton, M. A. Trush, T. M. Penning, G. Dryhurst, T. J. Monks, *Chem Res Toxicol.* **2000**, *13*, 135–60.
12. J. Russo, M. Hasan Lareef, G. Balogh, S. Guo, I. H. Russo, *J. Steroid Biochem. Mol. Biol.* **2003**, *87*, 1–25.
13. R. R. Newbold and J. G. Liehr, *Cancer Res.* **2000**, *60*, 235–7.
14. Z. Wang, E. R. Chandrasena, Y. Yuan, K. W. Peng, R. B. van Breemen, G. R. Thatcher, J. L. Bolton, *Chem Res Toxicol.* **2010**, *23*, 1365–73.
15. A. M. Wilson and G. A. Reed, *Carcinogenesis.* **2001**, *22*, 257–63.
16. S. Mesia-Vela, R. I. Sanchez, J. J. Li, S. A. Li, A. H. Conney, F. C. Kauffman, *Carcinogenesis.* **2002**, *23*, 1369–72.
17. S. R. Beedanagari, R. T. Taylor, P. Bui, F. Wang, D. W. Nickerson, O. Hankinson, *Mol Pharmacol.* **2010**, *78*, 608–16.
18. D. C. Spink, F. Zhang, M. M. Hussain, B. H. Katz, X. Liu, D. R. Hilker, J. L. Bolton, *Chem Res Toxicol.* **2001**, *14*, 572–81.
19. Z. Wang, P. Edirisinghe, J. Sohn, Z. Qin, N. E. Geacintov, G. R. Thatcher, J. L. Bolton, *Chem Res Toxicol.* **2009**, *22*, 1129–36.
20. J. T. Buters, B. Mahadevan, L. Quintanilla-Martinez, F. J. Gonzalez, H. Greim, W. M. Baird, A. Luch, *Chem Res Toxicol.* **2002**, *15*, 1127–35.
21. W. A. Spencer, J. Singh, D. K. Orren, *Chem Res Toxicol.* **2009**, *22*, 81–9.
22. G. A. Colditz, *J Natl Cancer Inst.* **1998**, *90*, 814–23.
23. B. E. Henderson, R. Ross, L. Bernstein, *Cancer Res.* **1988**, *48*, 246–53.
24. K. Wang and F. P. Guengerich, *Chem Res Toxicol.* **2012**, *25*, 1740–51.
25. B. S. Katzenellenbogen, J. A. Katzenellenbogen, D. Mordecai, *Endocrinology* **1979**, *105*, 33–40.
26. F. Pakdel, C. Le Guellec, C. Vaillant, M. G. Le Roux, Y. Valotaire, *Mol Endocrinol* **1989**, *3*, 44–51.
27. R. White, S. Jobling, S. A. Hoare, J. P. Sumpter, M. G. Parker, *Endocrinology* **1994**, *135*, 175–182.
28. W. V. Welshons, K. A. Thayer, B. M. Judy, J. A. Taylor, E. M. Curran, F. S. vom Saal, *Environmental Health Perspectives* **2003**, *111*, 994–1006.
29. E. Enmark, M. Pelto–Huikko, K. Grandien, S. Lagercrantz, J. Lagercrantz, G. Fried, M. Nordenskjold, J. A. Gustafsson, *J. Clin. Endocrinol. Metab.* **1997**, *82*, 4258–4265.
30. I. Rogatsky, J. M. Trowbridge, M. J. Garabedian, *J. Biol. Chem.* **1999**, *274*, 22296–22302.
31. P. J. Balfe, A. H. McCann, H. M. Welch, M. J. Kerin, *EJSO* **2004**, *30*, 1043–1050.
32. J. M. Hall and D. P. McDonnell, *Endocrinology* **1999**, *140*, 5566–5578.
33. E. Powell and W. Xu, *Proc Natl Acad Sci USA* **2008**, *105*, 19012–7.
34. X. Li, J. Huang, P. Yi, R. A. Bambara, R. Hilf, M. Muyan, *Mol Cell Biol.* **2004**, *24*, 7681–94.
35. D. G. Monroe, F. J. Secreto, M. Subramaniam, B. J. Getz, S. Khosla, T. C. Spelsberg, *Mol Endocrinol.* **2005**, *19*, 1555–68.
36. E. Powell, E. Shanle, A. Brinkman, J. Li, S. Keles, K. B. Wisinski, W. Huang, W. Xu, *PLoS One* **2012**, *7*, 1–13.
37. T. S. Dowers, Z. H. Qin, G. R. Thatcher, J. L. Bolton, *Chem Res Toxicol.* **2006**, *19*, 1125–37.
38. H. Liu, J. L. Bolton, G. R. Thatcher, *Chem Res Toxicol.* **2006**, *19*, 779–87.
39. S. Y. Kim, N. Suzuki, Y. R. Laxmi, B. P. McGarrigle, J. R. Olson, M. Sharma, M. Sharma, S. Shibutani, *Chem Res Toxicol.* **2005**, *18*, 889–95.
40. S. Nilsson and J. A. Gustafsson, *Breast Cancer Res.* **2000**, *2*, 360–366.
41. A. C. Pike, *Best Pract Res Clin Endocrinol Metab.* **2006**, *20*, 1–14.
42. J. Jacob, K. S. Sebastian, S. Devassy, L. Priyadarsini, M. F. Farook, A. Shameem, D. Mathew, S. Sreeja, R. V. Thampan, *Mol Cell Endocrinol.* **2006**, *246*, 34–41.
43. M. H. Wyckoff, K. L. Chambliss, C. Mineo, I. S. Yuhanna, M. E. Mendelsohn, S. M. Mumby, P. W. Shaul, *J. Biol. Chem.* **2001**, *276*, 27071–27076.
44. P. Thomas, Y. Pang, E. J. Filardo, J. Dong, *Endocrinology* **2005**, *146*, 624–632.

45. E. R. Prossnitz, J. B. Arterburn, L. A. Sklar, *Molecular and Cellular Endocrinology.* **2007**, *265–266*, 138–142.
46. M. R. Meyer, E. R. Prossnitz, M. Barton, *Vascul Pharmacol.* **2011**, *55*, 17–25.
47. E. R. Prossnitz, J. B. Arterburn, H. O. Smith, T. I. Oprea, L. A. Sklar, H. J. Hathaway, *Annu Rev Physiol.* **2008**, *70*, 165–90.
48. E. R. Prossnitz and M. Barton, *Nat Rev Endocrinol.* **2011**, *7*, 715–26.
49. R. A. Alyea and C. S. Watson, *BMC Neurosci.* **2009**, *10*, 59.
50. L. Moro, S. Reineri, D. Piranda, D. Pietrapiana, P. Lova, A. Bertoni, A. Graziani, P. Defilippi, I. Canobbio, M. Torti, F. Sinigaglia, *Blood.* **2005**, *105*, 115–21.
51. G. Khetawat, N. Faraday, M. L. Nealen, K. V. Vijayan, E. Bolton, S. J. Noga, P. F. Bray, *Blood.* **2000**, *95*, 2289–96.
52. I. Anwaar, M. Rendell, A. Gottsäter, F. Lindgärde, U. L. Hulthén, I. Mattiasson, *J Intern Med.* **2000**, *247*, 463–70.
53. H. P. Yu, Y. C. Hsieh, T. Suzuki, M. A. Choudhry, M. G. Schwacha, K. I. Bland, I. H. Chaudry, *J Leukoc Biol.* **2007**, *82*, 774–80.
54. C. D. Toran–Allerand, *Exp. Gerontol.* **2004**, *39*, 1579–1586.
55. C. D. Toran–Allerand, X. Guan, N. J. MacLusky, T. L. Horvath, S. Diano, M. Singh, E. S. Connolly Jr., I. S. Nethrapalli, A. A. Tinnikov, *J. Neurosci.* **2002**, *22*, 8391–8401.
56. D. E. Walsh, P. Dockery, C. M. Doolan, *Mol Cell Endocrinol.* **2005**, *230*, 23–30.
57. V. V. Sumbayev, E. C. Bonefeld–Jørgensen, T. Wind, P. A. Andreasen, *FEBS Lett.* **2005**, *579*, 541–8.
58. T. O. Fox, *Proc Natl Acad Sci USA* **1975**, *72*, 4303–4307.
59. F. S. vom Saal, *J Anim Sci* **1989**, *67*, 1824–1840.
60. F. S. vom Saal, B. G. Timms, M. M. Montano, P. Palanza, K. A. Thayer, S. C. Nagel, M. D. Dhar, V. K. Ganjam, S. Parmigiani, W. V. Welshons, *Proc Natl Acad Sci USA* **1997**, *94*, 2056–2061.
61. M. M. Montano, W. V. Welshons, F. S. vom Saal, *Biol Reprod* **1995**, *53*, 1198–1207.
62. W. V. Welshons, S. C. Nagel, K. A. Thayer, B. M. Judy, F. S. vom Saal, *Toxicol Ind Health* **1999**, *15*, 12–25.
63. J. F. Amara and P. S. Dannies, *Endocrinology* **1983**, *112*, 1141–1143.
64. W. V. Welshons and V. C. Jordan, *Eur J Cancer Clin Oncol* **1987**, *23*, 1935–1939.
65. H. D. Soule, J. Vazquez, A. Long, S. Albert, M. Brennan, *J Natl Cancer Inst* **1973**, *51*, 1409–1413.
66. M. E. Lippman and G. Bolan, *Nature* **1975**, *256*, 592–593.
67. M. E. Lippman, G. Bolan, K. Huff, *Cancer Res* **1976**, *36*, 4595–4601.
68. W. V. Welshons, C. S. Murphy, R. Koch, G. Calaf, V. C. Jordan, *Breast Cancer Res Treat* **1987**, *10*, 169–175.
69. W. V. Welshons, K. S. Engler, J. A. Taylor, L. H. Grady, E. M. Curran, *J Cell Physiol* **1995**, *165*, 134–144.
70. J. A. Taylor, L. H. Grady, K. S. Engler, W. V. Welshons, *Breast Cancer Res Treat* **1995**, *34*, 265–277.
71. S. Oesterreich, P. Zhang, R. L. Guler, X. Sun, E. M. Curran, W. V. Welshons, C. K. Osborne, A. V. Lee, *Cancer Res* **2001**, *61*, 5771–5777.
72. Y. Kanno, Y. Takane, Y. Takizawa, Y. Inouye, *Mol Cell Endocrinol.* **2008**, *291*, 87–94.
73. S. Ahmed, E. Valen, A. Sandelin, J. Matthews, *Toxicol Sci.* **2009**, *111*, 254–66.
74. F. Ohtake, Y. Fujii–Kuriyama, K. Kawajiri, S. Kato, J Steroid Biochem Mol Biol. **2011**, *127*, 102–7.
75. Y. Fujii–Kuriyama and K. Kawajiri, *Proc Jpn Acad Ser B Phys Biol Sci.* **2010**, *86*, 40–53.
76. U. A. Bussmann and J. L. Barañao, *Biol Reprod.* **2006**, *75*, 360–9.
77. E. Swedenborg, J. Rüegg, A. Hillenweck, S. Rehnmark, M. H. Faulds, D. Zalko, I. Pongratz, K. Pettersson, *Mol Pharmacol.* **2008**, *73*, 575–86.
78. F. A. Valiman and M. Gavrilescu, *Clean* **2009**, *37*, 277–303.
79. E. Means, A. Ghosh, Z. Chowdhury (Eds.), Endocrine Disruptor and Pharmaceuticals Strategic Initiative Expert Workshop Report, Marina del Rey, California, USA, **2007**, pp. 1–111.
80. C. G. Daughton and T. A. Ternes, *Environ. Health Perspective* **1999**, *107*, 907–938.
81. W. L. Sun, J. R. Ni, T. T. Liu, *Water, Air, Soil Pollut.* **2006**, *6*, 583–591.
82. P. D. Anderson (Eds.), Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment. Water Environment Research Foundation, London, United Kingdom, **2005**, pp. 11–12.
83. http://toxnet.nlm.nih.gov (assessed: March 16, 2012)
84. G. M. Klecka, S. J. Gonsior, R. J. West, P. A. Goodwin, D. A. Markham, *Environ Toxicol Chem.* **2001**, *20*, 2725–35.
85. A. M. Al-Ansari, A. Saleem, L. E. Kimpe, J. P. Sherry, M. E. McMaster, V. L. Trudeau, J. M. Blais, *Environ Pollut.* **2010**, *158*, 2566–71.
86. V. Contardo-Jara, C. Lorenz, S. Pflugmacher, G. Nützmann, W. Kloas, C. Wiegand, *Environ Pollut.* **2011**, *159*, 38–44.
87. J. P. Lasserre, F. Fack, D. Revets, S. Planchon, J. Renaut, L. Hoffmann, A. C. Gutleb, C. P. Muller, T. Bohn, *J Proteome Res.* **2009**, *8*, 5485–96.
88. D. P. Ayan, R. Maltais, J. Roy, D. Poirier, *Endocr Rev* **2011**, *32*, 1–17.
89. G. M. Anstead, K. E. Carlson, J. A. Katzenellenbogen, *Steroids.* **1997**, *62*, 268–303.
90. P. H. Jellinck and J. Fishman, *Steroids.* **1984**, *43*, 559–569.
91. P. H. Jellinck, B. Norton, J. Fishman, *J. Steroid Biochem.* **1984**, *21*, 361–365.
92. P. H. Jellinck, E. F. Hahn, B. I. Norton, J. Fishman, *Endocrinology.* **1984**, *115*, 1850–1856.
93. P. H. Jellinck and J. Fishman, *Biochemistry.* **1988**, *27*, 6111–6116.
94. E. Taioli, H. L. Bradlow, S. V. Garbers, D. W. Sepkovic, M. P. Osborne, J. Trachman, S. Gangulyl, S. J. Garte, *Cancer Prevention Detection.* **1999**, *23*, 232–237.
95. J. Fishman, H. L. Bradlow, T. F. Gallagher, *J. Biol. Chem.* **1960**, *235*, 3104–3107.
96. A. J. Lee, M. X. Cai, P. E. Thomas, A. H. Conney, B. T. Zhu, *Endocrinology.* **2003**, *144*, 3382–3398.
97. S. Lieberman, *J. Steroid Biochem. Mol. Biol.* **2008**, *109*, 197–199.

98. B. T. Zhu and A. J. Lee, *Steroids.* **2005**, *70*, 225–244.
99. N. J. Lakhani, M. A. Sarkar, J. Venitz, W. D. Figg, *Pharmacotherapy.* **2003**, *23*, 165–172.
100. G. Z. Han, Z. J. Liu, K. Shimoi, B. T. Zhu, *Cancer Res.* **2005**, *65*, 387–393.
101. E. Cavalieri and E. Rogan, *Ann. NY Acad. Sci.* **2006**, *1089*, 286–301.
102. E. Cavalieri, D. Chakravarti, J. Guttenplan, E. Hart, J. Ingle, R. Jankowiak, P. Muti, E. Rogan, J. Russo, R. Santen, T. Sutter, *Biochim. Biophys. Acta.* **2006**, *1766*, 63–78.
103. E. L. Cavalieri, P. Devanesan, M. C. Bosland, A. F. Badawi, E. G. Rogan, *Carcinogenesis.* **2002**, *23*, 329–333.
104. R. H. Lustig, C. V. Mobbs, H. L. Bradlow, B. S. McEwen, D. W. Pfaff, *Endocrinology.* **1989**, *125*, 2701–2709.
105. R. Raftogianis, C. Creveling, R. Weinshilboum, J. Weisz, *J. Natl. Cancer Inst. Monogr.* **2000**, *27*, 113–124.
106. G. E. Swaneck and J. Fishman, *Proc. Natl. Acad. Sci. USA.* 1988, 85; 7831–7835.
107. D. M. Biskobing, *Clin Interv Aging.* **2007**, *2*, 299–303.
108. R. Tedesco, J. A. Thomas, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *Chem Biol.* **2001**, *8*, 277–87.
109. B. E. Fink, D. S. Mortensen, S. R. Stauffer, Z. D. Aron, J. A. Katzenellenbogen, *Chem Biol.* **1999**, *6*, 205–19.
110. K. Chae, J. Lindzey, J. A. McLachlan, K. S. Korach, *Steroids.* **1998**, *63*, 149–57.
111. B. Hammes and C. J. Laitman, *J Midwifery Womens Health.* **2003**, 48, 19–29.
112. T. E. Wiese, D. Dukes, S. C. Brooks, *Steroids.* **1995**, 60, 802–8.
113. N. Kalfa, F. Paris, M. O. Soyer–Gobillard, J. P. Daures, C. Sultan, *Fertil Steril.* **2011**, *95*, 2574–7.
114. B. Hinrichs, M. Zahid, M. Saeed, M. F. Ali, E. L. Cavalieri, E. G. Rogan, *J Steroid Biochem Mol Biol.* **2011**, *127*, 276–81.
115. Y. Jin, Z. Desta, V. Stearns, B. Ward, H. Ho, K. H. Lee, T. Skaar, A. M. Storniolo, L. Li, A. Araba, R. Blanchard, A. Nguyen, L. Ullmer, J. Hayden, S. Lemler, R. M. Weinshilboum, J. M. Rae, D. F. Hayes, D. A. Flockhart, *J Natl Cancer Inst.* **2005**, *97*, 30–9.
116. Z. Desta, B. A. Ward, N. V. Soukhova, D. A. Flockhart, *J Pharmacol Exp Ther.* **2004**, *310*, 1062–75.
117. M. Hiratsuka, Y. Agatsuma, F. Omori, K. Narahara, T. Inoue, Y. Kishikawa, *Biol Pharm Bull* **2000**, *23*, 1131–5.
118. L. N. Vandenberg, M. V. Maffini, C. Sonnenschein, B. S. Rubin, A. M. Soto, *Endocr Rev.* **2009**, *30*, 75–95.
119. J. G. Hengstler, H. Foth, T. Gebel, P. J. Kramer, W. Lilienblum, H. Schweinfurth, W. Völkel, K. M. Wollin, U. Gundert–Remy, *Crit Rev Toxicol.* **2011**, *41*, 263–91.
120. A. Atkinson and D. Roy, *Biochem. Biophys. Res. Commun.* **1995**, 210, 424–433.
121. R. Elsby, J. L. Maggs, J. Ashby, D. Paton, J. P. Sumpter, B. K. Park, *J. Pharmacol. Exp. Ther.* **2001**, *296*, 329–337.
122. Y. Nakagawa and T. Suzuki, *Xenobiotica* **2001**, *31*, 113–123.
123. M. Shimizu, K. Ohta, Y. Matsumoto, M. Fukuoka, Y. Ohno, S. Ozawa, *Toxicol. In Vitro* **2002**, *16*, 549–556.
124. J. P. Jaeg, E. Perdu, L. Dolo, L. Debrauwer, J. P. Gravedi, D. Zalko, *J. Agric. Food Chem.* **2004**, *52*, 4935–4942.
125. S. Yoshihara, M. Makishima, N. Suzuki, S. Ohta, *Toxicol. Sci.* **2001**, *62*, 221–227.
126. S. Yoshihara, T. Mizutare, M. Makishima, N. Suzuki, N. Fujimoto, K. Ifarashi, S. Ohta, *Toxicol. Sci.* **2004**, *78*, 50–59.
127. S. Kitamura, Y. Shimizu, Y. Shiraga, M. Yoshida, K. Sugihara, S. Ohta, *Drug Metab Dispos.* **2002**, *30*, 113–8.
128. Y. N. Xing, Y. Guo, M. Xie, R. L. Shen, E. Y. Zeng, *Environ Pollut.* **2009**, *157*, 1382–7.
129. H. Marquardt and S. G. Schäfer (Ed.): Lehrbuch der Toxikologie, Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany, **2008**, pp. 684–85.
130. D. Kupfer, W. H. Bulger, A. D. Theoharides, *Chem Res Toxicol.* **1990**, *3*, 8–16.
131. K. Haraguchi, N. Koga, Y. Kato, *Drug Metab Dispos.* **2005**, *33*, 373–80.
132. V. V. Sumbayev, J. K. Jensen, J. A. Hansen, P. A. Andreasen, *Mol Cell Endocrinol.* **2008**, *287*, 30–9.
133. I. Kania–Korwel, K. C. Hornbuckle, L. W. Robertson, H. J. Lehmler, *Food Chem Toxicol.* **2008**, *46*, 637–44.
134. S. D. Soechitram, M. Athanasiadou, L. Hovander, A. Bergman, P. J. Sauer, *Environ Health Perspect.* **2004**, *112*, 1208–12.
135. K. Furukawa and N. Kimura, *Environ Health Perspect.* **1995**, *103*, 21–3.
136. D. H. Pieper and M. Seeger, *J Mol Microbiol Biotechnol.* **2008**, *15*, 121–38.
137. D. R. Oros and N. David (Eds.), San Francisco Estuary Regional Monitoring Program for Trace Substances, Identification and Evaluation of Unidentified Organic Contaminants in the San Francisco Estuary, Oakland, California, USA, **2002**, pp. 19–22.
138. B. Balakrishnan, E. Thorstensen, A. Ponnampalam, M. D. Mitchell, *Placenta.* **2011**, *32*, 788–92.
139. Y. Tezuka, K. Takahashi, T. Suzuki, S. Kitamura, S. Ohta, S. Nakamura, T. Mashino, *Journal of Health Science.* **2007**, *53*, 552–561.
140. T. Ohe, M. Hirobe, T. Mashino, *Drug Metab Dispos.* **2000**, *28*, 110–2.
141. L. P. Nguyen and C. A. Bradfield, *Chem Res Toxicol.* **2008**, *21*, 102–16.
142. M. A. Gendy, A. A. Soshilov, M. S. Denison, A. O. El–Kadi, *Toxicol Lett.* **2012**, *208*, 51–61.
143. N. S. Fracchiolla, K. Todoerti, P. A. Bertazzi, F. Servida, P. Corradini, C. Carniti, A. Colombi, A. Cecilia Pesatori, A. Neri, G. L. Deliliers, *Toxicology.* **2011**, *283*, 18–23.
144. J. M. Czuczwa and R. A. Hites, *Environ Sci Technol.* **1984**, 18, 444–50.
145. A. Ashek, C. Lee, H. Park, S. J. Cho, *Chemosphere.* **2006**, *65*, 521–9.
146. L. R. Wang , Y. Wang, J. W. Chen, L. H. Guo, *Toxicology.* **2009**, *262*, 250–7.
147. A. Dipple, in: C. E. Searle (Ed.): Chemical Carcinogens, ACS Monograph 173, American Chemical Society, Washington, DC, **1976**, pp. 245–314.

148. A. Dipple, R. C. Moschel, C. A. H. Bigger, in: C. E. Searle (Ed.): Chemical Carcinogens, ACS Monograph 182, American Chemical Society, Washington, DC, USA, **1984**, pp. 41–163.
149. O. Schmidt, *Z. Physik. Chem.*, **1939**, *42B*, 83–110.
150. A. Pullman and B. Pullman, *Rev. Sci.* **1946**, *84*, 145–158.
151. A. Pullman and B. Pullman, *Adv. Cancer Res.* **1955**, *3*, 117–69.
152. D. M. Jerina, R. E. Lehr, R. M. Schaefer, H. Yagi, J. M. Karle, D. R. Thakker, A. W. Wood, A. H. Conney, in: H. Hiatt, J. D. Watson, I. Winstin (Ed.): Origins of Human Cancer, Cold Spring Harbor Laboratories, New York, USA, **1977**, pp. 639–658.
153. S. L. Simonich, O. Motorykin, N. Jariyasopit, *Chem Biol Interact.* **2011**, *192*, 26–9.
154. K. C. Fertuck, S. Kumar, H. C. Sikka, J. B. Matthews, T. R. Zacharewski, *Toxicol Lett.* **2001**, *121*, 167–77.
155. A. Gallegos, D. Robert, X. Gironés, R. Carbó–Dorca, *J Comput Aided Mol Des.* **2001**, *15*, 67–80.
156. J. H. Lin and A. Y. Lu, *Pharmacol Rev.* **1997**, *49*, 403–49.
157. D. R. Thakker, W. Levin, A. W. Wood, A. H. Conney, H. Yagi, D. M. Jerina, in: I. W. Waisser, D. E. Drayer (Ed.): Drug Stereochemistry: Analytical Methods and Pharmacology, Marcel Dakker, New York, USA, **1988**, pp. 271–296.
158. V. Okoh, A. Deoraj, D. Roy, *Biochim Biophys Acta.* **2011**, 1815, 115–33.

## Povzetek

Motnje endokrinega sistema pomenijo tiste spremembe v delovanju endokrinega sistema, ki povzročijo škodljive učinki pri zdravih ljudeh ali njihovih potomcih. Fiziološki endokrini hormoni delujejo v zelo nizkih plazemskih koncentracijah, medtem ko se za določene kemijske spojine, poznane kot endokrini motilci (EDCs), prav tako predvideva sprememba endokrine funkcije pri podobno nizkih koncentracijah. V preglednem članku smo se osredotočili predvsem na pregled strukturnih razredov organskih sinteznih okoljskih endokrinih motilcev ter na njihove skupne strukturne elemente, ki jim omogočajo interakcijo z estrogenim signaliziranjem. Endokrini motilci lahko vplivajo na estrogeno signaliziranje neposredno preko interakcije z estrogenimi receptorji (ERs) ali posredno preko transkripcijskih faktorjev kot je receptor za aromatske ogljikovodike (AhR) ali preko modulacije kritičnih encimov, ki sodelujejo pri biosintezi in presnovi estrogenov. Nekateri strukturni elementi hormonskih motilcev predstavljajo tveganje za citotoksično in genotoksično delovanje, predvsem preko bioaktivacije v reaktivne metabolite.