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Review article

Review on crosstalk and common mechanisms of endocrine disruptors: Scaffolding to improve PBPK/PD model of EDC mixture

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ABSTRACT

Endocrine disruptor compounds (EDCs) are environment chemicals that cause harmful effects through multiple mechanisms, interfering with hormone system resulting in alteration of homeostasis, reproduction and developmental effect. Many of these EDCs have concurrent exposure with crosstalk and common mechanisms which may lead to dynamic interactions. To carry out risk assessment of EDCs' mixture, it is important to know the detailed toxic pathway, crosstalk of receptor and other factors like critical window of exposure. In this review, we summarize the major mechanism of actions of EDCs with the different/same target organs interfering with the same/different class of hormone by altering their synthesis, metabolism, binding and cellular action. To show the impact of EDCs on life stage development, a case study on female fertility affecting germ cell is illustrated. Based on this summarized discussion, major groups of EDCs are classified based on their target organ, mode of action and potential risk. Finally, a conceptual model of pharmacodynamic interaction is proposed to integrate the crosstalk and common mechanisms that modulate estrogen into the predictive mixture dosimetry model with dynamic interaction of mixture. This review will provide new insight for EDCs' risk assessment and can be used to develop next generation PBPK/PD models for EDCs' mixture analysis.

Contents

Abbreviations: 3MC, 3-methylcholanthrene; 5α-R, 5-alpha reductase; ACTH, adrenocorticotropic hormone; Ahr, aryl hydrocarbon receptor; Ahrr, aryl hydrocarbon receptor repressor; AKT, serine/threonine kinase; AMH, anti-mullerian hormone; AMPO, ammonium perfluorooctane; ARC, arcuate cell; Arnt, aryl nuclear translocator; AVPV, anteroventral periventricular nucleus; BAX, BCL2 associated protein; BCL2, apoptosis regulator; BMP, bone morphogenetic protein; BPA, bisphenol A; CAR, constitutive androstane receptor; CREB, cAMP response-element–binding protein; Cx43, connexin X 43; CYP1A1, cytochrome enzyme A; CYP1B1, cytochrome enzyme B; CYP19A, aromatase enzyme; CYP450scc, cytochrome p450 side chain cleavage; DBT, dibutyltin; DEHP, diethylhexyl phthalate; DTCs, dithiocarbamate chemicals; ERE, estrogen response element; E2, estrogen; FAK, focal adhesion kinase; Fas, membrane protein; FasL, fas ligand; Figla, factor in the germline alpha; FOXO3, forkhead box proteins; FSH, follicle stimulating hormone; GATA4, transcription factor; GDF, growth differentiation factor; GH, growth hormone; GJ, gap junction; GJA1, gap junction alpha protein; GnRH, gonadotropin releasing hormone; GVBD, germinal vesicle migration and breakdown; HAT, histone acetyl-transferase; HPA, hypothalamus pituitary adrenal axis; HDAC, histone deacetylases; HMT, histone methyl transferase; HPOA, hypothalamus preoptic nucleus; HSDs, hydroxysteroid dehydrogenases; HSP90, heat shock protein 90; IGF-1, insulin growth factor; IGFR, insulin growth factor receptor; Igf2r, insulin like growth factor 2; INH, inhibin; IP3-DAG, inositol triphosphate-diacylglycerol; LH, luteinizing hormone; LHR, luteinizing hormone receptor; LHX8, LIM homeobox 8; LXR, liver X receptor; LXR, liver X receptor; MAPK, mitogen activated protein kinase; MEHP, mono (2-ethylhexyl) phthalate; MMP2, metalloproteinase 2; NCoA, nuclear coactivator; NCoR, nuclear corepressor; NF-kB, nuclear factor k B; NOBOX, newborn ovary homeobox; NR, notch receptor; p160/SRC, steroid receptor coactivator; P23, protein 23; P4, progesterone; PR, progesterone receptor; PBPK/PD, physiological based pharmacokinetic/pharmacodynamic modeling; PBR, peripheral type Benzodiazepine receptor; PCBs, polychlorinated biphenyl; PCDDs, polychlorinated dibenzodioxins; Peg3, paternal express gene 3; PEPCK, phosphoenolpyruvate carboxykinase; PFASs, poly-fluorinated alkyl substances; PI3, phosphatidylinositol 3-kinase; PMG, primordial germ cell; PPARs, peroxisome proliferator activated receptors; PTEN, phosphatase and tensin homolog; PXR, pregnane X receptor; RIP140, receptor interacting protein; ROS, reactive oxygen species; RXR, retinoid X receptor; SDM, sexual dimorphism; SF, 1-steroidogenesis factor 1; SHBG, steroid hormone binding globulin; SMRT, silencing mediator for retinoid or thyroid-hormone receptors; Sohlh2, spermatogenesis and oogenesis helix-loop-helix 2; SREBP 2, sterol Response Element Binding Protein 2; SREBP1c, sterol Response Element Binding Protein 1c; StAR, steroid acute regulatory protein; SUG 1, suppressor for gal 1; SULTs, sulphotransferase enzyme; TAT, tyrosine aminotransferase; TBG, thyroid binding globulin; TBT, tributyltin; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene; TH, thyroid hormone; TJ, tight junction; TNF α, tumor necrosis factor α; TPT, triphenyltin; TRAIL, TNF-related apoptosis-inducing ligand; TRs, thyroid receptors; TSPO, translocator protein; UDPGT1A1, uridine diphosphate glucuronic transferase enzyme; VCL, vocal adhesion molecule vinculin; VEGF, vascular endothelial growth factor; VTG, vitellogenin; XAP2, X-associated protein 2; ZO-1, zonula occludens-1.

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1. Introduction

The U.S. EPA defines endocrine disruptor compounds (EDCs) as exogenous agents that interfere with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process (Kavlock et al., 1996). The WHO extended this definition linking EDCs to adverse health outcomes in an intact organism, or its progeny or subpopulation (WHO, 2002). The Endocrine Society describes EDCs as chemicals that interfere with any aspect of hormone action (Gore et al., 2014). EDCs can be found in daily use products such as detergents, food cans, plastic bottles, children toys, flame retardants, cosmetics, and processed food (Clarkson, 1995; Rudel and Perovich, 2010). EDCs interfere with hormone kinetics and its dynamics causing alteration in hormone level or expression of hormone responsive element (Crisp et al., 1998).

The aim of hormones is to execute its specific task on specific time with specific amount. There are many studies which link hormone alteration to different disease outcomes. For example, low testosterone and SHBG levels are the early biomarker for the risk of metabolic syndrome (Kupelian et al., 2006); alteration of E2, ERα, PR and the aromatase enzyme is strongly linked with endometriosis and infertility (Kitawaki et al., 2002); alteration in FSH, LH, inhibin B, and testosterone level is associated with decreased sperm quality (Meeker et al., 2006). Earlier assumption that EDCs and hormones would yield the same responses in different cell lines or tissues was found wrong. Now it is well known that EDCs have cell and tissue-specific responses (Lackey et al., 2001). Even at very low concentrations, EDCs can produce significant endocrine disruptive action (Vom Saal and Hughs, 2005; Vandenberg et al., 2012) which challenges classical dose response curve at significantly high doses. Further, EDCs show disparate response at different life-stage dependent physiological concentrations of hormone, challenging current risk assessment methodologies which are not in consonance with life-stage changes (Welshons et al., 2003; Vandenberg et al., 2013). For instance, a study from Ohtake et al. (2003) showed that EDCs can produce a contrary response based on physiological stage of prepuberty and puberty. The interference of EDCs with developmental stages (prenatal-postnatal-early childhood-adulthood) and reproductive stages showed time of exposure as an important factor to determine its potency as well as developmental effect (Haimes, 2009; Gore et al., 2014). For example, there is a strong relationship of EDC exposure affecting HPG axis system and alteration in the age of female puberty showing developmental effect (Wang et al., 2005; Euling et al., 2008). The biological marker like enzyme expression and hormone level can help in assessing developmental risk by knowing the detailed mode of action of EDCs (Rockett et al., 2003).

Humans are subject to continuous and simultaneous exposure to EDCs via its surrounding environment and bioaccumulation becomes inevitable in many cases, which might cause permanent damage following physiological adaptation failure (Vandenberg et al., 2013). Several studies showed that chemicals at the individual level have no observed effect level (NOEL), when exposed simultaneously as a mixture show adverse effect disproving the concept of NOEL and taking more attention towards mixture studies (Rajapakse et al., 2002; Silva et al., 2002). The successive use of the PBPK model in the field of toxicology is commendable since it has great advantage of predicting internal tissue dose by integrating experimental data (both in vivo and in vitro) and extrapolation across species (Caldwell et al., 2012). However, the level of biomarker of exposure (internal tissue dose) is, in many case, not sufficient to predict the toxicity of chemicals and additionally the effect of chemical mixture for certain response deemed to have toxicodynamic interaction. Moreover, many biological responses are the convergence of multiple signaling pathways, which eventually become vulnerable to multiple targets of EDCs. Incorporation of the relationship between the exposure at the sites of action and the response generated can extend the PBPK model to PBPK/PD (Nestorov, 2007). The objective of this review (summarized in Fig. 1) is to understand the mechanism of actions of EDCs which includes interaction of chemicals with molecular receptor, enzymes, proteins, gene regulatory mechanism or epigenetic process thus affecting biological system, including window of exposure. Besides, this review also investigates the normal endogenous pathway of hormone sidewise to better understand the physiology dependent EDCs' action. The last part of the review includes an example showing common as well as crosstalk mechanism of EDC mixture affecting estrogen kinetics. Improved understanding of common as well as crosstalk mode of action and categorization of chemicals based on similar adverse outcomes may provide better scaffolding for integration of pharmacokinetics and pharmacodynamics into predictive mixture toxicological model of EDCs.

2. Molecular mechanism of EDCs on the endocrine system

In general, individual EDCs can affect the endocrine system accounting their synthesis to metabolism; receptor mediated action, various signaling pathways and crosstalk signaling between receptors. In this section, a summarized review of EDCs' effects on major hormones namely thyroid and steroids (corticosteroid and gonadal) is provided.

2.1. EDCs affecting thyroid hormone

Thyroid hormones (THs) are one of the integral parts of the hormone system required for normal brain and somatic development. It has been seen that EDCs can disrupt the function of the thyroid system possibly through multiple mechanisms such as synthesis, transport, and receptors like TR, Ahr, CAR, PPAR and RXR, mediated function for subsequent

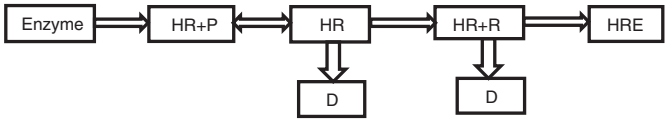

Fig. 1. Effects of EDCs on hormone action at different levels. Enzyme responsible for hormone synthesis, HR-hormone, P-hormone binding protein, R-receptor, D-degradation of hormone and its receptor, HRE-hormone response element.

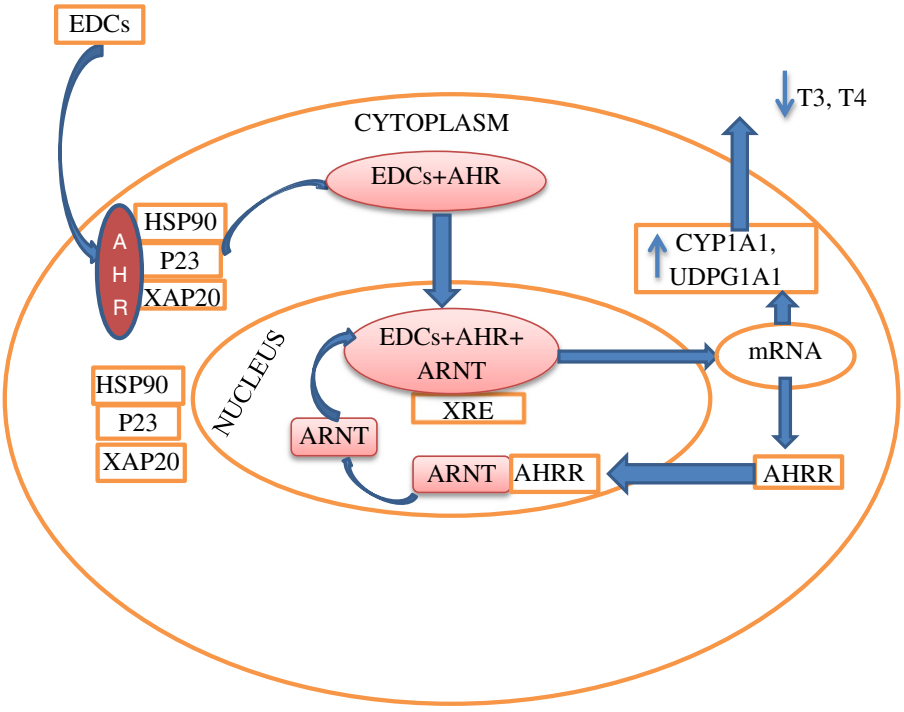

Fig. 2. Summary of molecular mechanism of EDCs binding with Ahr-. The binding of EDCs with Ahr leads to translocation of Ahr receptor to the nucleus from the cytoplasm following dissociation of chaperons, forming Ahr-Arnt complex. This complex binds with XRE (xenobiotic response element) causing induction of CYP enzyme, enhancing metabolism of endogenous hormone.

action and metabolism of hormone. Various chemicals affect homeostasis of hormones including perchlorates, PCBs, PCDDs and PCDFs (Zoeller, 2010). Perchlorates inhibit uptake of iodide into thyroid follicle (Clewell et al., 2004). PCBs, PCDDs and PCDFs that competitively bind with transthyretin impair transportation (Lans et al., 1994) and their affinity towards the Ahr receptor leads to increase metabolism of hormones (Poland and Knutson, 1982).

The toxicology pathway of EDCs via Ahr is shown in Fig. 2; where Ahr receptor is present in the cytosol in conjugation with subunits like chaperon protein HSP90, regulatory protein P23 and immunophilin like protein XAP2 (Perdew, 1988; Kazlauskas et al., 1999; Petrulis et al., 2000). Subsequently binding of EDCs with Ahr forms a complex followed by dissociation of Hsp90, P23 and XAP2 and translocation into the nucleus. In the nucleus, Ahr forms a heterodimer complex with Arnt which then binds with XRE causing increase in expression of CYP1A1 and UDPGT1A; and finally leads to increase in metabolism of thyroid hormone (Hankinson, 1994; Van Birgelen et al., 1995). Simultaneously, there is feedback inhibition of Ahr transactivation by Ahrr (Mimura et al., 1999). Qatanani et al. (2005) reported that EDCs' affinity towards CAR, can be another possible mechanism of metabolism of

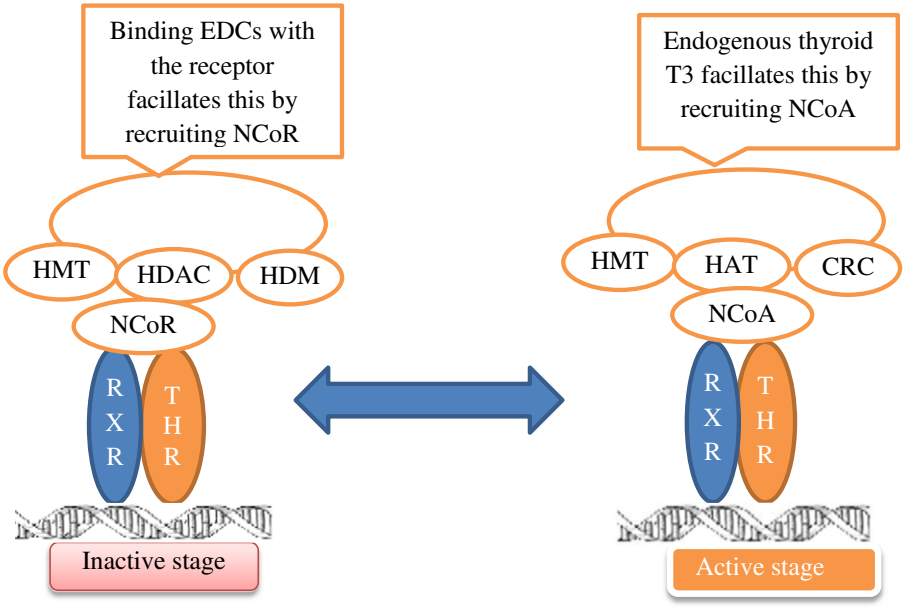

Fig. 3. EDCs affecting dynamic state of receptor. Unliganded thyroid receptor resides in the nucleus in inactive state by recruiting NCoR and thyroid binding facilitates active stage by recruiting NCoA. Binding of EDCs with thyroid receptor induced conformational changes by recruiting NCoR facilitating its inactive stage.

thyroid, that alters the UGTs and SULT mediated glucuronidation and sulfation of TH, respectively.

BPA has been reported as an anti-thyroid agent that is mediated via multiple molecular mechanisms, mainly involved in altering receptor gene expression and dynamic stability. It decreases the TRα and TRβ mRNA levels and subsequently suppresses RXR gene expression which is a heterodimer partner of TR. Additionally, it can also inhibit the binding of T3 to TR by recruiting N-CoR (Moriyama et al., 2002; Iwamuro et al., 2006). The isoform of TR remains in dynamically equilibrium state between inactive and active forms to maintain the physiological action. The binding of EDCs with TR favors its inactive isoform (see Fig. 3) via recruitment of (N-CoR). Subsequently, increase in HDAC, HMT, and HDM levels induces the repression of target gene making TR inactive. In contrast, binding of thyroid to TR induces conformation changes and recruits coactivators of p160/SRC (steroid receptor coactivator). These coactivators have inherent histone acetylase activity that recruits complex like histone arginine methyltransferase (HMT), HAT and chromatin remodeling complex and form active homodimer or heterodimer complex with RXR (Ahuja et al., 2003; Yoon et al., 2005; Flamant et al., 2007). Juge-Aubry et al. (1995) mentioned that RXR was the common partner for both TRs and PPARs to form active heterodimers. Hence, the EDCs having affinity for PPARs or RXR could affect thyroid activity through crosstalk mechanism.

2.2. EDCs affecting steroid hormone

2.2.1. EDCs affecting corticosteroid hormone

Among corticosteroid hormones, glucocorticoids such as cortisol are produced in response to stress and are an integral part of HPA axis involved in cellular homeostasis and different metabolic processes. The enzymes that are responsible for the biosynthesis of these hormones mainly involved CYPs, HSDs and steroid reductases (Miller, 1988). The molecular mechanisms involved in biosynthesis are transfer of cholesterol to inner mitochondrial membrane by regulatory protein StAR (Manna and Stocco, 2005) and conversion of cholesterol to pregnenolone by CYP11A or CYP450scc (Parker and Schimmer, 1995; Manna and Stocco, 2005). Subsequent action of CYP17A and HSD enzyme accomplishes the glucocorticoid synthesis.

The interconversion of cortisol (active) to cortisone (inactive) involves two isoforms of 11β-HSD namely 11β-HSD1 and 11β-HSD2 (Krozowski et al., 1999). This interconversion plays an important role in regulating central adiposity (Stewart et al., 1999) and protecting developing fetus from glucocorticoid excess (Krozowski et al., 1995). EDCs like PFASs, TBT, TPT and dithiocarbamates inhibit 11β-HSD2 isoform (Atanasov et al., 2003; Ohshima et al., 2005; Zhao et al., 2011), and their exposure during pregnancy stage has been found to alter normal fetus development. Wang et al. (2012) reported the role of BPA on increased expression of 11β-HSD1, which results in increased level of cortisol, lipoprotein lipase and PPAR-γ causing higher adipocyte differentiation. The expression of PEPCK and TAT, well characterized metabolic response of glucocorticoid, was shown to be inhibited by DBT which decreases affinity of glucocorticoid towards its receptor (Gumy et al., 2008). Furthermore, one of the metabolic pathways of steroid involves PXR, a xenobiotic receptor which regulates CYP3A expression. Chemicals like phthalic acid and nonylphenol inhibit PXR degradation, thus enhancing CYP3A expression which leads to alteration in metabolism of steroid hormones (Masuyama et al., 2000, 2002).

2.2.2. EDCs affecting gonadal hormone

The effect of EDCs on the human reproductive system has been linked with infertility, mediated through a diverse mechanism that includes: altering gonadal steroidogenesis, affecting HPA axis and feedback mechanism, altering receptor biology, crosstalk of receptor signaling, and direct organ toxicity. For the steroidogenesis, cholesterol is the main precursor which can be affected by the EDCs that alter receptor like PPARα and PXR which regulates transporter protein, such as translocator protein (TSPO) or peripheral type Benzodiazepine receptor (PBR) that transports cholesterol from the cytosol to the mitochondria (Hauet et al., 2005; Fan and Papadopoulos, 2012) and the metabolism of cholesterol by regulating transcription of rat CYP7A1 (cholesterol 7α-hydroxylase) gene (Marrapodi and Chiang, 2000; Staudinger et al., 2001; Li et al., 2011).

Moreover, the involvement of many supplementary pathways initiated via different receptors like GHR, IGF-1 and (RXR/TR) which regulate the function of steroidogenic enzyme and the affinity of EDCs towards these receptors, makes toxicity mechanism more complex (Chandrashekar and Bartke, 1993; Xu et al., 1995; Hull and Harvey, 2000; Manna et al., 2001; N'Diaye et al., 2002). In addition to that, the central system HPG axis which regulates gonadal cell plays an important role in normal reproductive development process. At the hypothalamic level, kisspeptin neurons express both, ligand KiSS-1 and its receptor GPR54 that regulates the release of GnRH in pituitary which in turn controls the expression of FSHR and LHR in gonadal cell. The kisspeptin neurons also express ER-α which is involved in feedback inhibition of GnRH in response to estrogen stimulation. This feed forward mechanism holds an important role during normal fertility cycle of preovulatory to ovulatory phase (Roseweir and Millar, 2009; Silveira et al., 2010; Hameed et al., 2011). It has been shown in rodent models that exposure of BPA affects HPG axis with different mechanisms depending on life stage of exposure; at prepubertal stage damages kisspeptin neuron and at puberty stage alters ERαmRNA expression (Ceccarelli et al., 2007; Patisaul et al., 2009). Xi et al. (2011) showed that the involvement of BPA on transcript levels of GnRH and FSH in the male and female pup via altering Kiss-1 mRNA expressions further supports the notion of multilevel mechanism of EDCs.

Boberg et al. (2008) reported that exposure to phthalates causes the reduction of anogenital distance, sign of male infertility, via the reduction of leptin level which supports the concept of leptin regulation of LH and FSH via leptin-kisspeptin-GnRH pathway (Neurons et al., 1999; Luque et al., 2007). The leptin synthesis was also found to be inhibited by cadmium exposure (Stasenko et al., 2010). In addition to that the local gonadal enzyme CYP19A (aromatase) catalyses the androgen to estrogen conversion to balance androgen-estrogen level which is the prerequisite for the normal fertility in both male and female (Simpson et al., 1994). Several studies have reported that TBT inhibition of aromatase enzyme in granulosa cell results in imposex affecting fertility (Saitoh et al., 2001; Heidrich et al., 2001). Many studies have shown the EDCs' dual action in regard to estrogen level (Ohtake et al., 2003, 2007). For instance dioxin exposure at prepubertal stage, shows estrogenic activity via enhancing binding of ERα to ERE. However at pubertal stage, dioxin-receptor complex represses E2 bound ER function leading to antiestrogenic effects (Ohtake et al., 2003). In another study, Ohtake et al. (2007) reported the antiestrogenic activity of EDCs like TCDD and 3MC via activation of E3 ubiquitin ligase pathway that results in degradation of ERα and Ahr. In contrast to antiestrogenic activity, certain EDCs increase the bioavailability of estrogens via inhibiting principle of estrogen sulphotransferase (SULT1E1) enzyme which causes inactivation of E2 (Kester et al., 2002).

The male sex hormone testosterone biosynthesis has been shown to be affected by TCDD and PFOA via different mechanisms of action that involve altering signaling pathway, regulating expression of enzyme or direct inhibition of enzyme involved in steroidogenesis (Fukuzawa et al., 2004; Lai et al., 2005a; Shi et al., 2009; Zhao et al., 2010; Wan et al., 2011). Saunders et al. (1997) reported that exposure of pregnant mother to octylphenol, decreases the level of testosterone in the fetal rat testis via altering the expression of CYP17α-hydroxylase/C17–20 lyase and steroidogenesis factor 1 (SF-1) leading to reproductive developmental disorder. The local hormone like AMH responsible for sexual differentiation in fetus during embryogenesis also nurtures the testosterone by increasing prenatal proliferation of Leydig cells and maintains the prepubertal stage in male. In parallel, developmental exposure of BPA and PCBs is linked to decreased levels of AMH, LHR, and 17β

HSD3 and reduced aromatase activity in the hypothalamus, affecting sexual maturation (Lee and Donahoe, 1993; Hany et al., 1999; Rey et al., 2003; Nanjappa et al., 2012). In addition to that, TBT or TPT is found to inhibit both 5α-R1 and 5α-R2 isozymes, responsible for production of active androgen (Svechnikov et al., 2010), affecting male sexual characterization (Doering et al., 2002). Castro et al. (2013) found similar results for BPA, reporting inhibition of both 5α reductases at their synthesis level. Simultaneous exposure of both chemicals (TBT and BPA) could lead to more impact on male fertility. Moreover, exposure to EDCs has shown to induce reproductive toxicity by damaging the integrity of blood testes barrier (BTB) in Sertoli cell that causes impairment in spermatogenesis (Cheng et al., 2011).

EDCs like BPA, PFOS, DEHP and cadmium induced reproductive toxicity are found to be mediated via altering MAPK, PI3K/c-Src/FAK, p38 MAPK and ROS signaling pathway leading to alteration in synthesis and metabolism of different proteins like occludin, ZO-1, Cx43 and catenin affecting BTB integrity (Chitra et al., 2003; Sobarzo et al., 2006; Li et al., 2009; Siu et al., 2009; Cheng et al., 2011; Wong and Cheng, 2011; Qiu et al., 2013; Ansoumane et al., 2014). It has also been found that Sertoli cells have functional Ahr, responsible for TCDD dose-dependent toxicity that alters mRNA level of testin, aromatase, sertolin and MIS which are important for germ cell development (Lai et al., 2005a, 2005b). Phthalates are well characterized as reproductive toxic agents that cause apoptosis of germ cell by activating caspase pathway which includes: activation of fas by increased expression of fasl (Richburg and Boekelheide, 1996; Lee et al., 1999; Richburg et al., 1999; Koji et al., 2001), accumulation of lipid in somatic cells via increased LXRα mRNA expression (Muczynski et al., 2012) and downregulation of both GJA1 and vocal adhesion molecule vinculin (VCL) by increasing MMP2 (Yao et al., 2012). Subsequently, activation of NFkB via increased expression of TRAIL-R1(DRP4) and TRAIL-R2 (DRP5) leads to increased apoptosis of germ cell without modification of their proliferation (Giammona, 2002; Lambrot et al. 2009). Fig. 4 shows the mechanism of phthalates causing germ cell apoptosis in fetus.

3. Effect of EDCs in different windows of exposure: case study on female fertility

It has been shown that EDCs have disparate response at different life-stages, depending on the physiological concentrations of hormones (Ohtake et al., 2003). However, primary concerns for female fertility are exposure to EDCs at prenatal and postnatal stages, which are at higher risk of reproductive failure as well as metabolic disorder and hormonal disorders in their later life. EDCs can alter normal cellular and tissue development and function through their interference in developmental programming of the body (Schug et al., 2011). To study the life stage risk assessment on fertility, it is very important to know the detailed mechanism behind development of germ cell into mature oocyte. This involves complex and sequential biological network of signaling pathway.

3.1. Physiology of development of germ cell into mature oocyte

During epigenetic reprogramming of germ cell, at the very first step, involves DNA demethylation to regain differentiation totipotency which subsequently undergoes mitotic division without completing cytokinesis to the formation of germ cell cyst (Pepling and Spradling, 1998). Before birth, germ cells go through meiosis and arrest in diplotene phase of meiotic prophase until puberty comes. Meanwhile germ cell cyst undergoes apoptosis followed by surrounding of pregranulosa cell forming primordial follicles (Borum, 1961; Pepling and Spradling, 2001). After forming primordial follicles, estrogens play a role in maintaining these follicles' pool by inhibiting oocyte nest breakdown through inhibition of BCL-2 gene transcription via both genomic and nongenomic pathways (Perillo et al., 2000; Chen et al., 2007, 2009).

Moreover, additional pathways are also involved in the regulation of primordial follicles which involves Notch signaling, and KIT-KL pathway. Notch signaling activation involves expression of Jagged1 and Jagged2 (ligand), in germ cells and Notch2 (ligand), in granulosa cells to form a receptor ligand complex. The proteolytic cleavage of this complex by γ-secretase produces intracellular domain of Notch (NICD) which translocates into the nucleus and interacts with the CSL family to form the complex. This complex recruits histone acetylase and regulates the expression of LHX8, NOBOX, Figla and Sohlh2 involved in formation of primordial follicles (Baron, 2003; Shih and Wang, 2007; Chen et al., 2014; Vanorny et al., 2014). KIT receptor expressed in oocyte and the KIT ligand that is present in both oocyte and primordial follicle, help in initiation and progression of follicular development (Parrott and Skinner, 1999) via the activation of the MAPK pathway (Jones and Pepling, 2013). GDF9 increases KIT ligand mRNA expression and thus promotes the progression of primary follicle development (Nilsson and Skinner, 2002). BMP4 and BMP7 play a major role in survival and growth of primordial follicle to primary follicle by decreasing KL and TGF-α expression respectively (Nilsson and Skinner, 2003; Lee et al., 2004). Cx43 expressed in both cumulus cell and granulosa cell plays an important role in paracrine signaling and gap junctional intercellular communication between cumulus cell and follicular cell providing follicular development and oocyte quality (Ackert et al., 2001; Gittens et al., 2005; Wang et al., 2009). BMP4, BMP7 and BMP15 downregulate Cx43 in human granulosa cell via smad pathway and thus decrease the gap junctional intercellular communication leading to prevention of premature luteinization (Chang et al., 2013; Chang et al., 2014a, 2014b).

The interplay between paracrine hormones is very important for the transition of primordial follicle to primary follicle to become a mature oocyte. AMH inhibits primordial follicles to enter the pool of growing

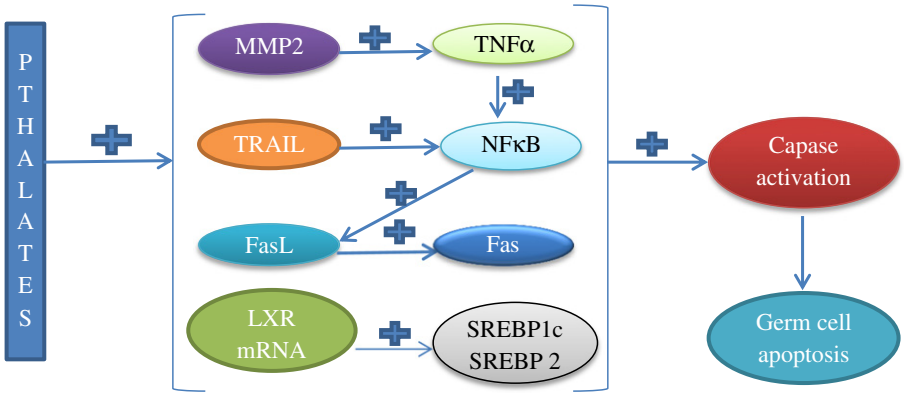

Fig. 4. Mechanism of phthalates causing germ cell apoptosis in fetus. Phthalate exposure at tissue level causes activation of caspase pathway which lead to apoptosis of germ cell through interaction and activation of receptor and gene at the cellular level.

follicles (Durlinger et al., 1999) by decreasing expression of inhibin (Themmen and Themmen, 2009). Billiar et al. (2003) also reported the inhibition of expression of inhibin by the estrogen in pregranulosa and oocyte. Thus, estrogens play an important role in regulating inhibin and follicular development. The TGF-β signaling involves GATA-4 and Smad-3 coordination for activating the inhibin (Anttonen et al., 2006). Androgens play an important role in follicle development via increasing expression of, FOXO-3, GDF9 through PI3/AKT pathway, and, KIT/KL through genomic pathway during primordial follicle to primary follicle stage. Specifically, during the development of primary follicle to antral stage, it inhibits proapoptotic proteins and stimulates FSH mRNA expression, cAMP and p450scc through both genomic and nongenomic i.e. MAPK/ERK pathways which in turn stimulates aromatase enzyme (Prizant et al., 2014). FSH stimulates LHR expression, (Richards et al., 1976) inhibin B production (Lee et al., 1982), and induces aromatase activity in the granulosa cells, which results in more estradiol level (Short, 1962; Richards et al., 1976; Hillier et al., 1981). Moreover, most FSH sensitive called dominant follicle produces the highest levels of inhibin B and estradiol which in turn causes feedback inhibition of FSH production, required for growth of remnant follicles (Hirshfield and Midgley, 1978). After selection of dominant follicle, subsequently progesterone causes germinal vesicle migration and breakdown (GVBD) for resumption of meiosis at puberty by activating p53 and E2F transcription factor 1 (Garcia-reyero et al., 2015) leading to ovulation. The fertilization of ovum results in formation of zygote and matured follicle after releasing ovum called lutein cell which secretes VEGF. It prolongs the lutein cell function that maintains the progesterone level important for pregnancy development. VEGF function is regulated via PPARγ (Fraser et al., 2000; Kaczmarek et al., 2005).

3.2. EDCs' interaction with target molecules and its pathway

Exposure to Lindane, PCBs and PAHs to embryo has been linked with premature reproductive ageing by causing the apoptosis of germ cell through different pathways such as activation of caspase-3 and poly-ADP ribose polymerase cleavage (PPAR) by Lindane and activation of BAX via Ahr by PAHs (Ronnback and de Rooij, 1994; Matikainen et al., 2002; La Sala et al., 2009; Kee et al., 2010). Phthalate exposure induces primordial follicle recruitment via activation of PI3K/AKT pathway, resulting in premature ovarian follicle and infertility (Hannon et al., 2014). Previously, Castrillon et al. (2003) found development of premature oocyte follicle in FOXO3A knock out mouse which is regulated by the PTEN/PI3K/AKT pathway. Both, phthalates and BPA reduce the expression of LHX8, Nobox, Figla, and Sohlh2, involved in oocyte survival and follicular recruitment to form primordial follicle. In addition to this both compounds alter epigenetic reprogramming of Lhx8 by preventing DNA demethylation (Zhang et al., 2012, 2014). However, BPA shows multiple mechanisms of action, altering steroidogenesis and proliferation of granulosa cell such as: induction of PPARγ causing downregulation of FSH-stimulated IGF-1, SF-1, GATA4, aromatase, and E2 (Kwintkiewicz et al., 2010), decreases both StAR and P450scc mRNA impairing hormone production in the antral follicles (Peretz et al., 2011), and activates nongenomic pathway of estrogen via PKA and PKG pathways associated with phosphorylation of transcription factor CREB and the cell cycle regulator Rb (Bouskine et al., 2009). Additionally, BPA delayed maturation of oocyte by inhibiting resumption of meiosis via altering ER expression, following hypomethylation of imprinted gene Igf2r, Peg3, and GVBD, (Chao et al., 2012). On the other hand, other EDCs like methoxychlor inhibit follicular development by stimulating AMH (Uzumcu et al., 2006). This is further supported by the study of impairmaint of follicular development in neonates on exposure of estradiol benzoate found to be via increased expression of AMH (Ikeda et al., 2002). Moreover, Nagel et al. (1999) shown that BPA even at very low doses can affect sexual dimorphism of infants via its estrogenic action in brain, whereas in normal, prenatal estrogen forms complex with Alpha fetoprotein, protecting the female brain from defeminization and masculinization (Bakker et al., 2006).

EDC contamination in the human follicular micro-environment is associated with a lower chance of an oocyte to develop into a top-quality embryo, leading to lowering in fertilization rate (Petro et al., 2012). For instance, PCB exposure affects oocyte quality and competence via multiple mechanisms (altered microtubule organization, mRNA polyadenylation levels, redistribution of cortical granules, mitochondrial disorganization) which leads to polyspermy and transcript instability. It can also directly cause cumulus cell apoptosis which is communicator cell between oocyte and follicle mediated via Ahr signaling (Gandolfi et al., 2002; Brevini et al., 2005; Pocar et al., 2006). MEHP an endocrine disruptor inhibits embryonic genome activation (EGA) initiation and maternal-effect genes resulting in the suppression of maternal-to-embryonic transition by generating ROS (Chu et al., 2013).

Fig. 5 summarizes the life stage development of germ cell to oocyte and the possible targets of EDCs. In this turn, Fig. 6 explains the complex signaling pathway for life stage development of germ cell maturation to oocyte.

4. Grouping strategy and conceptual model of PBPK/PD in assessing risk for chemical mixture

4.1. Grouping strategy

There are numerous classifications of EDCs reported in the literature based on different criteria like pathway of exposure, level of exposure, target hormones, adverse effects, and disease outcomes (Caserta et al., 2008; Wuttke et al., 2010; Craig et al., 2011; Schug et al., 2011; Casals-Casas and Desvergne, 2011; Vandenberg et al., 2012; Hampl et al., 2014). Ongoing discussion of the risk assessment for chemical mixture (EFSA, 2013) needs new grouping strategy which clusters EDCs based on their similar adverse outcomes via independent, crosstalk and common interaction mechanism involving multiple organs and hormones. Similar prerequisite for cumulative risk assessment of chemical mixtures has been cited by EFSA (Kortenkamp, 2007; EFSA, 2013). This type of grouping strategy (based on similar adverse outcomes) could also help in making a decision on whether to go for dose addition or response addition method for mixture interaction study (Culleres et al., 2008). A detailed discussion on classification is beyond the scope of this review. However, a detailed classification for selected chemicals is provided in Annex Table 1. Classification of EDCs proposed in this review is based on target organs, hormones, biomolecule (MOA) and adverse outcomes, which can provide basis for grouping strategy for mixture modeling. Proposed grouping strategy has been illustrated in Fig. 7 by giving a small example of four chemicals (BPA, TCDD, phthalates and PFOS). Some of these chemicals are categorized in one group for mixture study based on their similar adverse outcome including target organs like thyroid gland and Sertoli cell, and in another group with dissimilar mode of action (crosstalk) producing common adverse effect of altering thyroid action and decreasing sperm count, respectively. Similar grouping strategy has been followed in Fig. 9 for the chemicals affecting female fertility.

4.2. Conceptual model of PBPK/PD

A chemical can alter hormone actions by targeting at the level of epigenetic-gene-enzyme/receptor followed by endogenous intracellular signaling pathway (Grün and Blumberg, 2006; Cruz et al., 2014). Therefore, the mixture of chemicals producing similar adverse outcomes via entirely different modes of action can be categorized in one group in order to analyze the combination effect. Furthermore, timing and level of exposure are also important parameters which can make adverse effects temporary or permanent and have to be included when assessing risk (Fenton, 2006; Buck Louis et al., 2008; Palanza et al., 2016). Based on methodologies (Fig. 7), we propose a conceptual model which brings

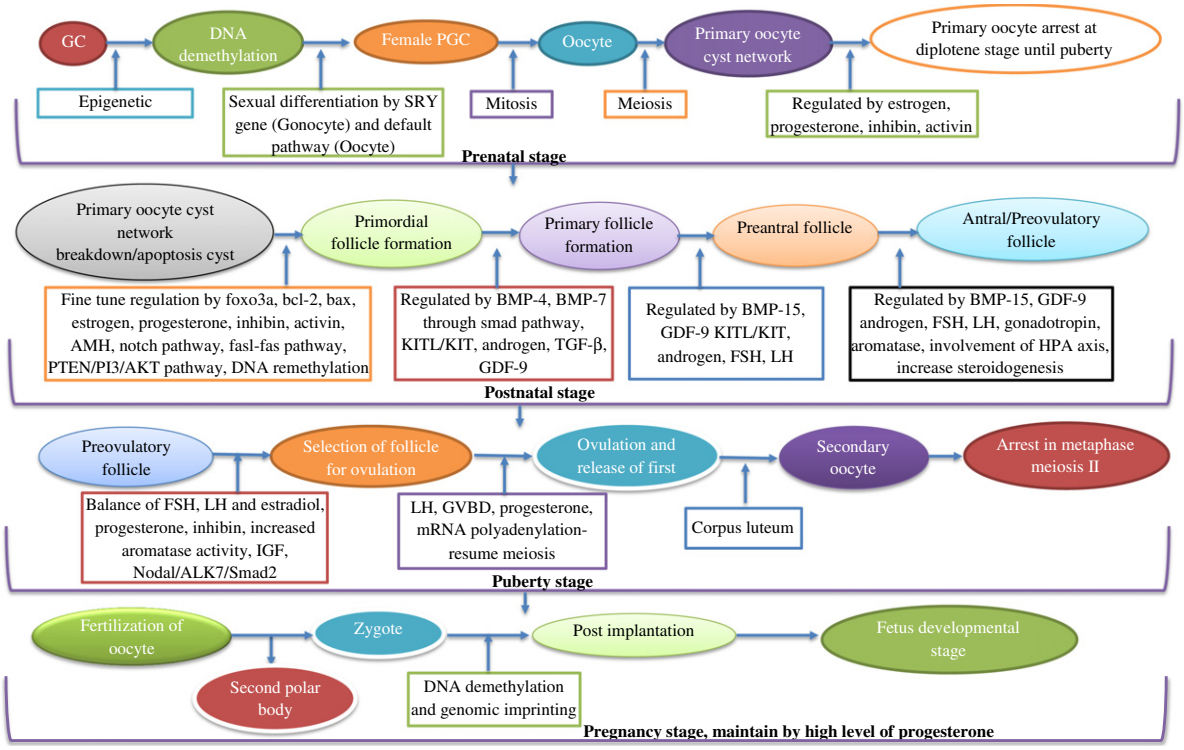

Fig. 5. Life stage development of germ cell and the possible targets of EDCs. The germ cell, basis of future sexual life or transgenerational development, development of oocyte from germ cell starts at embryo stage. Exposure of EDCs to pregnant mother (F0) may cross placental barrier and affect embryonic germ cell in fetus (F1). This could lead to alteration in oocyte quality required for fertilization and transgenerational fetus development (F2). Every stage of development of germ cell to high quality oocyte, demands fine tune balance of endogenous level and interaction pathway. Categorizing development of germ in stages provides information on susceptible targets of EDCs during the journey of germ cell of fetus (F1) residing in mother embryo (F0) to high quality of oocyte, for development of transgenerational fetus (F2).

the fate and the consequence of chemical mixture in the integrated risk assessment framework of exposome-internal exposure-biological effect to the adverse outcome (Fig. 8).

At the dynamic level, integration of individual mechanisms to the dynamic interactions of mixture for assessing risk is still debatable (Lambert and Lipscomb, 2007; EFSA, 2013; Karri et al., 2016). Fig. 9 shows a small example of hypothetical schematic model that integrates individual modes of action based on their target molecule in a system based approach. It includes common, crosstalk as well as dissimilar modes of action based on their targets of common outcome. For instance, the dioxin-like chemicals, DBP, BPA, TOP and PAH-OH alter the estrogen action at different levels of peripheral as well as central mechanism. Their major targets include kisspeptin neuron, CYP19A (aromatase), SHBG, ER, Ahr, ERE CYPA1 and CYPB1 affecting estrogen and progesterone feed forward mechanism, consequently leading to risk of infertility. In fact, EDCs like DBP, BPA and TOP show similar mode of action via targeting CYP19A and SHBG. Dioxin-like substances exhibit dual role such as “antiestrogenic” via Ahr dependent CYPB1 mechanism and “estrogenic” via estrogen receptor showing crosstalk between ER and Ahr. PAH-OH and BPA can interact with other dioxin-like substances in respect to their targets via crosstalk between Ahr and SULTE1 altering metabolism of estrogen. BPA, PAH-OH and other dioxin-like substance are able to simultaneously interfere with the endocrine system through multiple mechanisms. The mixture effects of these chemicals in system based model can be possible by considering estrogen, progesterone and ERE, as end point biomarker of infertility, and integrating available individual toxicological profile data into a dynamic mixture model of EDCs (PBPK/PD).

5. Summary & future perspective

We have summarized the effects of endocrine disruptors on thyroid, adrenal, and sex hormones accounting their effects on synthesis, metabolisms and actions. Mixture of chemicals can simultaneously interfere with multiple endocrine pathways via multiple mechanisms making mixture effect more pronounced than individual. The EDCs acting on certain hormones via multiple mechanisms (central or peripheral) can be grouped for risk assessment of mixture of chemicals, according to their similar adverse outcomes.

Most of the EDCs have nonmonotonic dose-response curve which is the major drawback when establishing a relationship between the exposure kinetics and elicited response (Vandenberg et al., 2012; Beausoleil et al., 2013; Yang et al., 2016). Additional challenges like multiple mechanisms, delayed response (time lag between exposure to adverse outcomes), dynamic interaction involving crosstalk and common mechanisms, and transgenerational effect added more complexity in the quantitative risk assessment (Maffini et al., 2006; Matthiessen and Johnson, 2007; Rubin, 2011; Fowler et al., 2012).

However, understanding the molecular mechanism of interaction of chemicals with endogenous molecules or pathways can explain the variability among chemicals for the same adverse effect (Filby et al., 2007). For instance, BPA shows complex dose-response curve in concentration dependent model which could be explained by the fact that it alters the gene expression through genomic as well as nongenomic pathways (Takayanagi et al., 2006; Vandenberg et al., 2009; Vandenberg, 2014). Similarly, dioxin-like substances show dual response that can be explained by availability of endogenous hormone and their action. The potential dynamic interaction may lead to change in the response curve in case of mixture of chemical, which can be explained by understanding different types of mechanistic interactions like crosstalk or similar or dissimilar MOAs as it has been explained in this review. Similarly, understanding latency of exposure (i.e. lag time between exposure and response) is important as in the case of infertility disorder, which can only be detected after a certain age though exposure occurs at early stage of life.

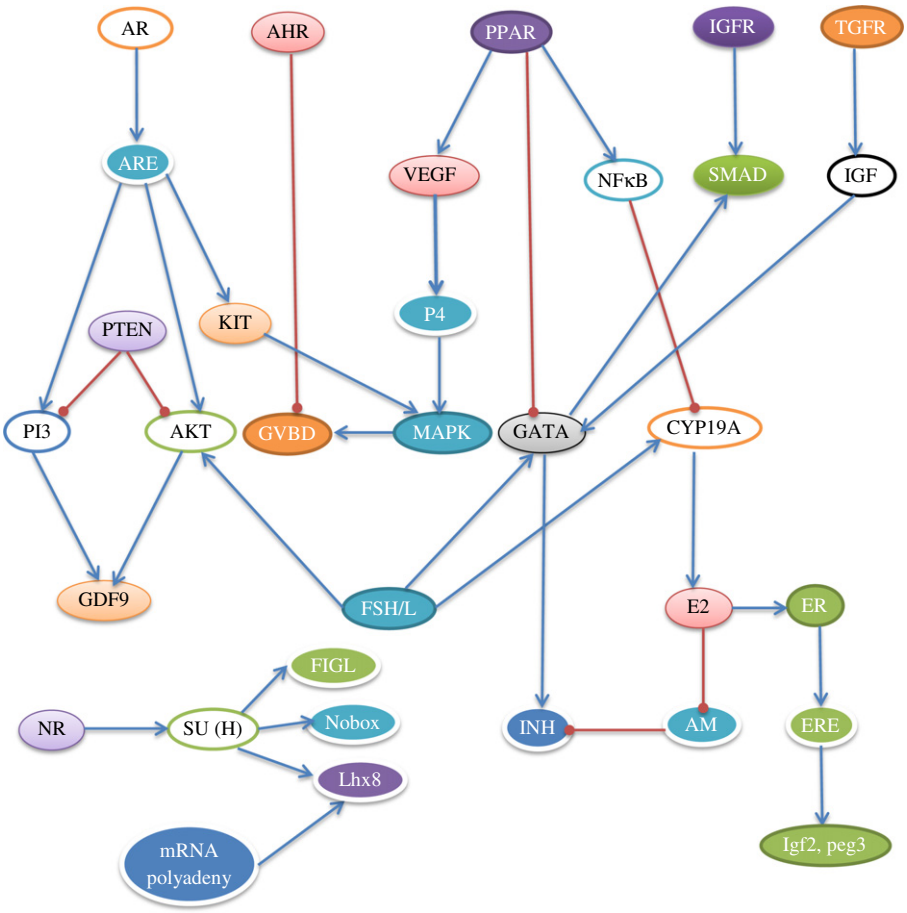

Fig. 6. Signaling pathway for life stage development of germ cell to zygote. The figure depicts the different signaling pathways' initiation via binding of endogenous molecule with receptors, which leads to inhibitory and stimulatory effects on signaling molecule following physiological demand for the development of germ cell into mature oocyte.

Lots of experiments have been done on individual EDCs but it is very hard to find mixture level studies. Selecting chemicals and then optimizing the dose for a selected mixture for carrying animal experiment is another difficult task. To know the potency of individual chemical in mixture due to their complex interaction behavior at different levels, requires large combinatorial experimental design. Normally this kind

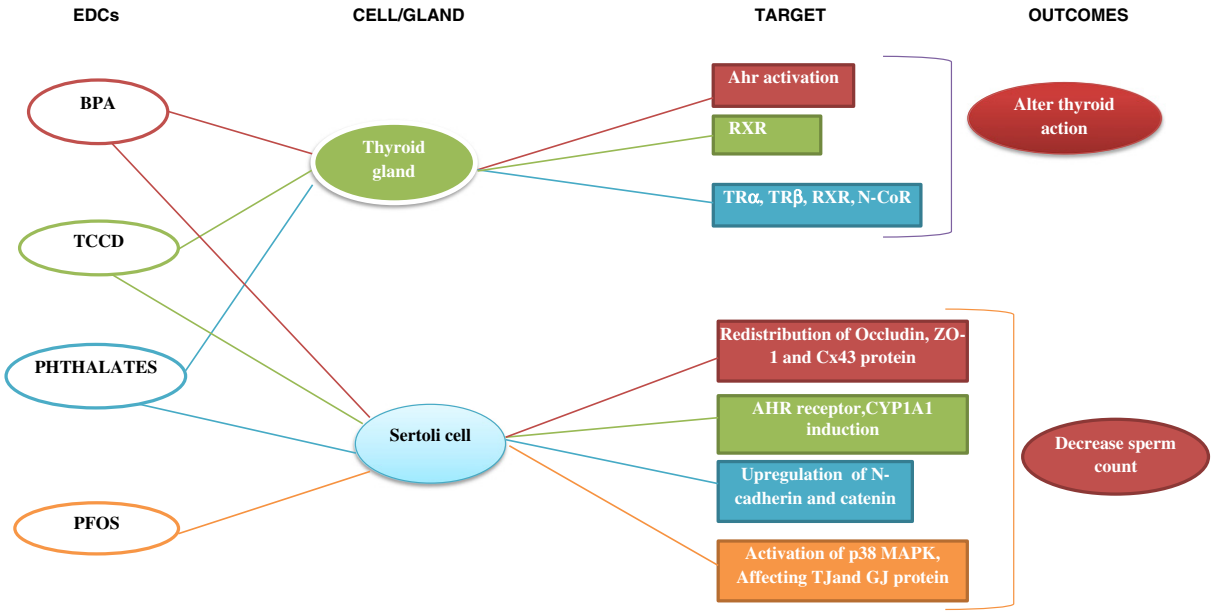

Fig. 7. Endocrine disruptor's classification on the basis of mode of action for selected chemicals (BPA, TCDD, phthalates and PFOS), with different targets on thyroid and Sertoli cell with common adverse effect in respective cell.

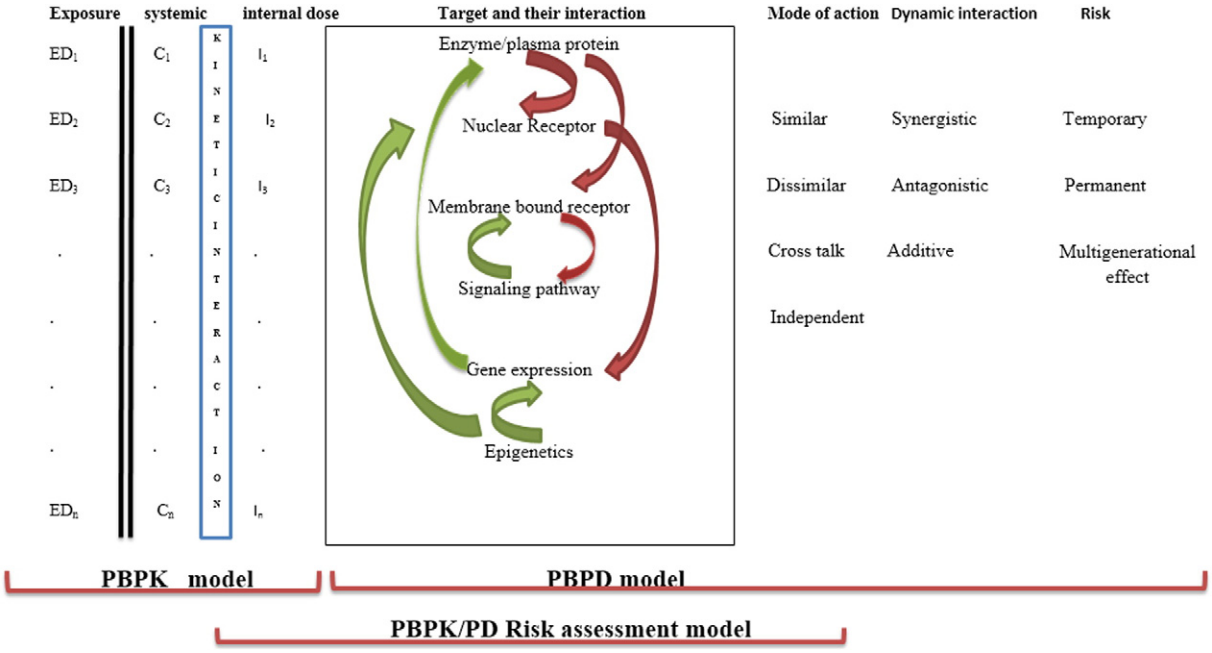

Fig. 8. Conceptual model of PBPK/PD in assessing risk for chemical mixture (ED-endocrine disruptor exposure, C-concentration of ED in systemic circulation, I-concentration of ED in target organ or tissue, DI-dynamic interaction). PBPK usually well describes the time course of tissue level exposure of chemicals relating environmental exposure by including their absorption, distribution, metabolism and excretion. At the cellular level, the interaction of chemicals with endogenous biomolecules and their pathways which are interrelated with each other results in initiation of an event that could lead to adverse outcomes which can be describe by PBPD model. The integrated PBPK/PD can describe the kinetic as well as dynamic interaction of EDCs giving time course effect of chemicals.

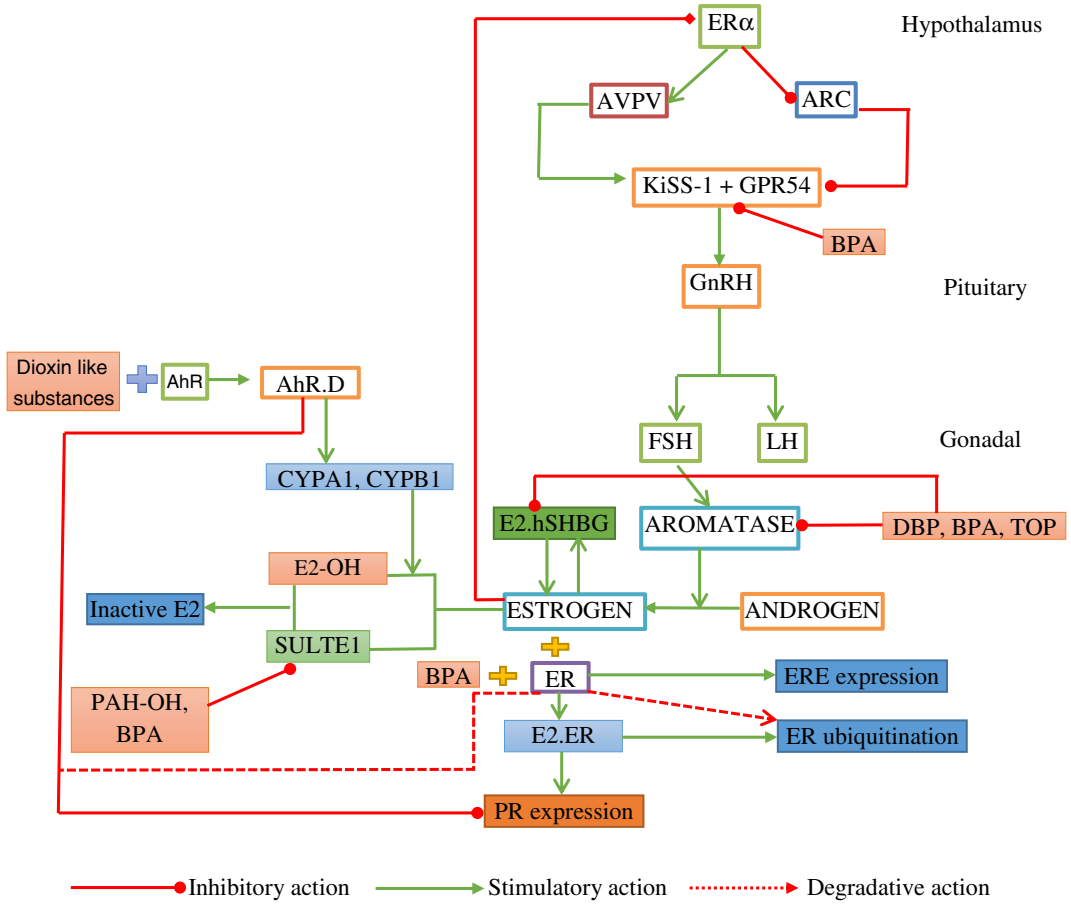

Fig. 9. Schematic model for studying mixture effect in dynamic level. This figure contains the hypothetical mixture model of characterizing risk through detailed understanding of mode of chemicals' interaction with different biological components of the HPG pathways describing multiple mechanisms.

of experiment requires a large number of animals which will be against the current ethical guideline of risk assessment (EU, 2010). However, tremendous development in in-vitro and in-silico techniques and emerging areas like omics, generating lots of toxicological data leads to new era of quantitative risk assessment (Knudsen et al., 2015).

Incorporation of individual mechanism of chemicals into mixture model provides a platform for assessment of combined risk produced by mixture of chemicals. Understanding individual mechanism and implementing those mechanisms in system based approach will help us in the development of mixture model. This will provide better understanding of the risk produced by chemical mixture exposure and it will further assist in designing animal experiment and optimization of dose which will reduce the use of animals. The European Union (2011) suggested concentration addition method for cumulative risk assessment of chemicals with similar or dissimilar mechanisms of action by considering their common adverse outcomes. But response addition method for a common adverse effect is still not recommended.

Categorization of chemicals in the same group according to similar adverse outcomes, accounting both similar as well as dissimilar mechanisms (crosstalk) of action may provide a sound basis for studying mixture toxicology. Based on this grouping strategy, addressing both kinetic and dynamic interactions of mixture and establishing a relationship between pharmacokinetic-pharmacodynamic-altered molecular events will give a better model to correlate the environment exposure with adverse outcomes. Finally, integrating individual mode of action of each chemical by the help of mathematics equation into advanced tools such as PBPK/PD would enable the simultaneous assessment of EDC mixtures correlating concentration in various biological matrixes (blood, tissue, urine) with various end points (endocrine diseases). It will also help in finding the toxic equivalent dose of chemicals eliciting similar adverse effects. Similarly, timing and duration of exposure are important factors which need to be considered while assessing the risk. Integrating physiology of the human body at different life stages and respective modes of action of EDCs will help in building life stage dynamic models. For example, dividing life stage into prenatal-postnatal-puberty-menopause and incorporating susceptible gene or receptor or protein at different life stages targeted by EDCs and physiological data provide a model able to predict the risk of infertility in females by exposure to these chemicals in different stages of life.

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