Article

Toxicology and Industrial Health

Toxicology and Industrial Health
1–13

DOI: 10.1177/0748233719898989
journals.sagepub.com/home/tih
SAGE

Wnt pathway: A mechanism worth considering in endocrine disrupting chemical action

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Abstract

Endocrine disrupting chemicals (EDCs) are defined as exogenous substances that can alter the development and functioning of the endocrine system. The Wnt signaling pathway is an evolutionarily conserved pathway consisting of proteins that transmit cell-to-cell receptors through cell surface receptors, regulating important aspects of cell migration, polarity, neural formation, and organogenesis, which determines the fate of the cell during embryonic development. Although the effects of EDCs have been studied in terms of many molecular mechanisms; because of its critical role in embryogenesis, the Wnt pathway is of special interest in EDC exposure. This review provides information about the effects of EDC exposure on the Wnt/β-catenin pathway focusing on studies on bisphenol A, di-(2-ethylhexyl) phthalate, diethylstilbestrol, cadmium, and 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Keywords

Endocrine disrupting chemical, Wnt signaling pathway, bisphenol A, phthalate

Received 4 March 2019; Revised 19 November 2019; Accepted 13 December 2019

Introduction

Signaling pathways and molecules that control important events in embryogenesis are of great importance in terms of biology of development. Over the last 20–30 years, various receptor superfamilies including bone morphogenetic proteins, fibroblast growth factors, WNTs, and their mechanisms of action were identified. The name WNT was formed by combining the names of *wingless* gene in *Drosophila* with *integrated* or *int-1* genes that are vertebrate homologs. These signaling pathways are often associated with diseases, particularly with endocrine diseases and cancer, reinforcing the notion that these diseases are related to impaired developmental processes (Komiya and Habas, 2008; Logan and Nusse, 2004).

The Wnt signaling pathway is an evolutionarily conserved pathway that consists of proteins that transmit cell-to-cell signals through cell surface receptors, regulating important aspects of embryonic development including cell migration, polarity, neural formation, and organogenesis (Willert and Nusse, 2012).

WNTs are secreted glycoproteins and include 19 proteins associated with the regulation, function, and biological consequences of signal transduction in humans (Komiya and Habas, 2008). Three Wnt signaling pathways have been identified, a canonical or Wnt/β-catenin pathway, a noncanonic planar cell polarization pathway, and a noncanonic Wnt/calcium pathway (Clevers and Nusse, 2012; Kuldeep and Gosens, 2016; Swarup and Verheyen, 2012; Willert and Nusse, 2012).

β-catenin is the central mediator of the canonical pathway and can either interact with cadherins at the cell membrane to control cellular adhesion or

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translocate to the nucleus, where it functions as a transcriptional coactivator. In the inactive state, cytosolic β-catenin is bound to a multiprotein destruction complex consisting of AXIN, adenomatous polyposis coli (APC), casein kinase 1α (CK1α), and glycogen synthase kinase 3β (GSK3β) (Narasipura et al., 2012). CK1α-regulated phosphorylation followed by GSK3β-regulated phosphorylation destines β-catenin for ubiquitination by β-transducing repeat-containing protein and degradation via the proteasomal pathway (Aberle et al., 1997; Narasipura et al., 2012; Seidensticker and Behrens, 2000). When a WNT ligand interacts with its receptor at the plasma membrane, the destruction complex is destabilized and β-catenin is translocated into the nucleus to associate with the DNA-binding proteins that perceive particular sequence designs in promoters and enhancers of target genes. Translocation of β-catenin into the nucleus leads to the activation of target genes through the actions of specific domains and several transcriptional coactivators (Cadigan and Waterman, 2012; Mosimann et al., 2009). There are different transcription factors that mediate the activation of Wnt targets genes by β-catenin. T cell factor/lymphoid enhancer factor (TCF/LEF) nuclear mediators are most closely associated with Wnt/β-catenin action. In the absence of Wnt/β-catenin signaling, TCF/LEF inhibits transcription; however, TCF/LEF becomes an activator when associated with β-catenin (Cadigan and Waterman, 2012; Filali et al., 2002; Ikeda et al., 1998). LEF1 is a downstream effector of this pathway and has been suggested to be a new indicator of cancer due to phthalate exposure through the activation of Wnt-responsive genes for the cell cycle and survival (Yang et al., 2015).

Endocrine disrupting chemicals (EDCs) are defined as exogenous substances that can alter the development and functioning of the endocrine system. In particular, bis(2-ethylhexyl) phthalate (DEHP) and bisphenol A (BPA) pose great risks to public and occupational health. Moreover, as the production and the utilization of EDCs increased in different technological processes, health risks associated with occupational exposure have raised new challenges (Fucic et al., 2018). These chemicals are found in the composition of plastic containers, bottles, baby bottles, toys, creams, and even drugs, so most people are exposed to these chemicals in their lives without knowing. EDCs may be pro-estrogenic in some tissues and anti-estrogenic in others by binding to nuclear estrogen receptors (ERs) and altering gene expression. Their high affinity binding to membrane receptors allows them to be harmful even at subnanomolar concentrations. It has been shown that the effects of exposure to EDCs during embryonic period may have more serious consequences later in life. Although the government authorities mention the low likelihood of exposure to toxic substances through food and cosmetics, the increase in cancer incidence including breast, testicular germ cell, and prostate cancer in recent years can be attributed to a quiet and deeply progressive outcome of EDC exposure (Akyuz et al., 2011, Alonso-Magdalena et al., 2010; Chen et al., 2014, Diamanti-Kandarakis et al., 2009).

EDC exposure is related to the impairment of the reproductive functions and other hormonally regulated metabolic processes and Wnt signaling pathway regulates major aspects of embryonic development. Although several mechanisms have been proposed on the detrimental effects of EDC exposure, the relationship between EDC exposure and Wnt pathway in the embryonic period is not adequately addressed. Therefore in this narrative literature review, we aimed to evaluate the current knowledge on the role of Wnt/β-catenin pathway in the mechanism of action of EDC, focusing on BPA, phthalates, diethylstilbestrol (DES), 2,3,7,8-tetrachlorodibenzo-p-dioxin, and cadmium.

Canonical or Wnt/β-catenin pathway

The Wnt family of signal proteins is involved in different developmental processes during embryogenesis and is associated with tissue homeostasis in adults (Komiya and Habas, 2008). Wnt signals are pleiotropic (acting in many different ways), affecting mitogenic stimulation, as well as cell fate and differentiation (Kuldeep and Gosens, 2016). WNT proteins are released from the surface of signaling cells or are secreted by these cells and bind to the frizzled (Fz)/low density lipoprotein receptor-related protein complex to exert effects on target cells (Logan and Nusse, 2004). The Wnt signal transduction model is schematically illustrated in Figure 1.

These receptors send signals to a number of intracellular proteins including disheveled (DSH), GSK-3β, AXIN, APC, and transcriptional regulator β-catenin. GSK-3/APC/AXIN complex controls the proteasome-mediated degradation of β-catenin to keep cytoplasmic β-catenin levels low (Clevers and Nusse, 2012). Wnt signals lead to inhibition of this degradation pathway and to the subsequent accumulation of β-catenin in the cytoplasm and nucleus (Swarup and Verheyen, 2012).

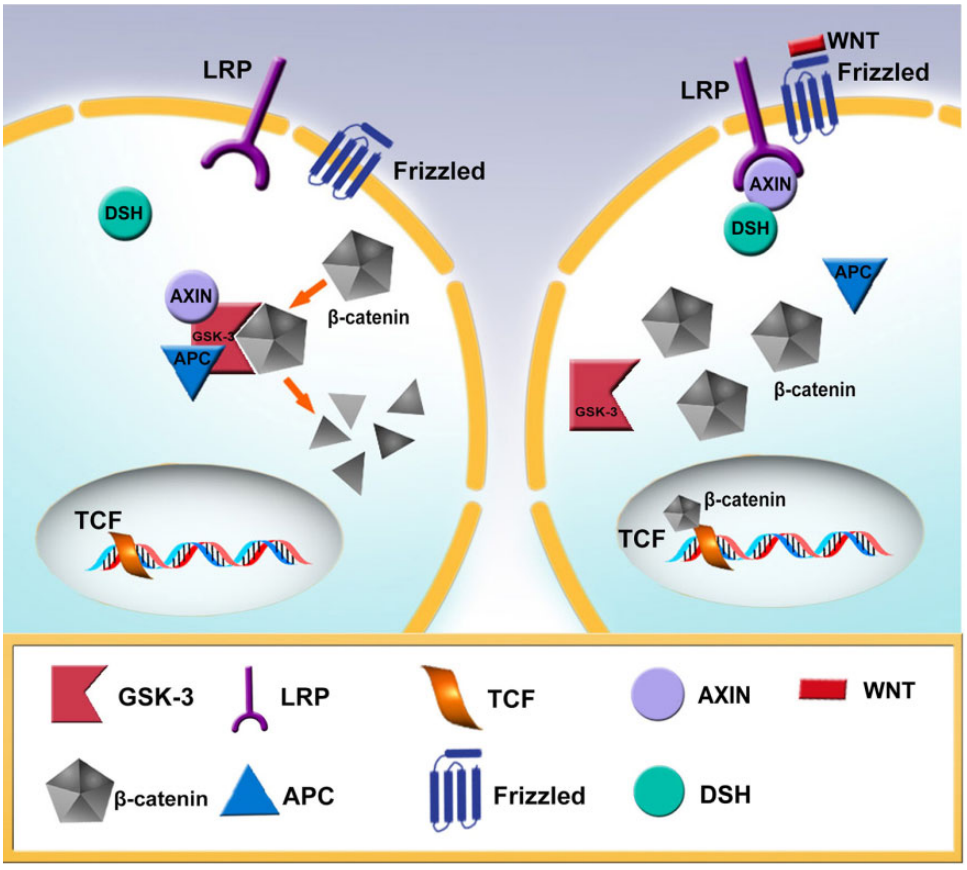

Figure 1. Canonical Wnt signaling pathway. In the absence of a Wnt signal (panel on the left), β-catenin is degraded by AXIN, APC, and GSK-3 interactions. When the Wnt proteins bind to the frizzled/LRP receptor complex on the cell surface (the right panel), DSH and AXIN interact with the signal transmitted to them (hyphens). As a result, the destruction of β-catenin is inhibited and β-catenin accumulates in the nucleus and cytoplasm. The β-catenin then interacts with the TCF to control transcription. AXIN, APC, and GSK3 are defined as negative regulators of this pathway as DSH, β-catenin, and TCF are defined as positive regulators. APC: adenomatous polyposis coli; GSK-3: glycogen synthase kinase 3; DSH: disheveled; TCF: lymphoid enhancer factor.

β-catenin in the nucleus combines with transcription factors, in particular the factor 1/T cell-specific transcription factor (lymphoid enhancer-binding factor 1/T cell-specific transcription factor, LEF/TCF) that bind the lymphoid enhancer to promote transcription. Many *wnt* gene targets have been recognized, including members of the Wnt signaling pathway, which provide feedback control to suppress the Wnt signal (Clevers and Nusse, 2012; Kuldeep and Gosens, 2016; Logan and Nusse, 2004; Swarup and Verheyen, 2012).

Effects of EDCs on Wnt pathway

Bisphenol A

BPA is a synthetic compound that belongs to the diphenylmethane derivatives and bisphenols groups. It has been used commercially since 1957. BPA has been identified as a possible threat to fetuses, infants, and young children and oral ingestion is the major exposure route to BPA through contaminated food and water by leaching from plastic food and beverage container materials (Goodson et al., 2002; Yang et al., 2015).

Since BPA is a chemical that can interact with hormone receptors, in animal studies, BPA exposure has been associated with low sperm count, hormonal changes, prostate enlargement, abnormalities in egg chromosome number, and precancerous changes in the reproductive system. BPA exposure has also been associated with obesity and insulin resistance (Vom Saal et al., 2007). In the 2003–2004 National Health and Nutrition Examination Survey (NHANES III) 93% of urine samples has been found to contain

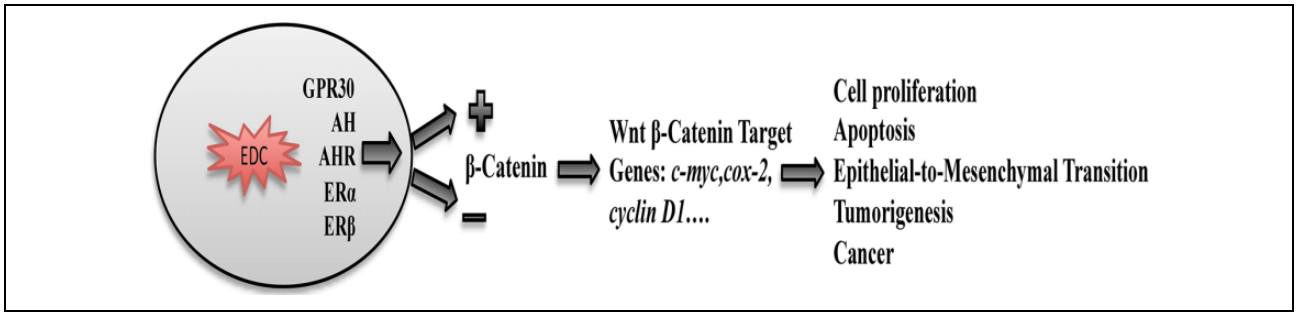

Figure 2. EDCs can interact with estrogen receptors (ERα, ERβ, and G protein-coupled estrogen receptor-GPR30), AH, and AHR to affect cell proliferation, apoptosis, epithelial-to-mesenchymal transition, tumorigenesis and cancer through altered intracellular β-catenin levels. EDC: endocrine disrupting chemical; AH: androgen receptor; ARH: aryl hydrocarbon receptor.

detectable levels of BPA and the highest level was found in the 6–12 years age group (Calafat et al., 2008). BPA was also detected in the blood of pregnant women, amniotic fluid, umbilical cord blood, placenta, newborn blood, and breast milk at levels determined to cause damage to experimental animals (Rubin and Soto, 2009). In other studies BPA has been shown to stimulate prostate cancer cells, create breast tissue changes similar to early stage breast cancer in mice and humans, affect brain and male and female reproductive system development in mice, and increase body weight after perinatal exposure and adipocyte differentiation (Vom Saal et al., 2007; Yang et al., 2015). It was found to be associated with lipid accumulation, glucose transport and release of adiponectin, diabetes mellitus in laboratory animals, early puberty, and neurological problems (Calafat et al., 2008).

EDCs can interact with different receptors to affect cell proliferation, apoptosis, epithelial-to-mesenchymal transition, tumorigenesis, and cancer through altered intracellular β-catenin levels (Figure 2). Wnt/β-catenin target genes mediate tumorigenesis and cancer development (Arend et al., 2013). Aberrant Wnt signaling has been observed prominently in colorectal cancer but also in many more cancer entities (Zhan et al., 2017). Although BPA has no structural homology with 17β-estradiol (E2), because of its phenolic structure, it has a similar structure to DES, the synthetic estrogen known to cause cancer (Kurosawa et al., 2002). Kurosawa et al. (2002) aimed to identify the estrogenic effect of BPA using luciferase assay on human ERα cDNA or ERβ cDNA transfected different cell lines. They reported that BPA acted as an estrogen agonist via ERβ but acted both as an agonist and antagonist via ERα in some cell types and concluded that ER subtype and the tissue affected the activity of BPA. For that reason BPA has long been suspected to have the potential to induce carcinogenesis (Keri et al., 2007; Konieczna et al., 2015).

Hui et al. (2018) exposed human ovarian adenocarcinoma SKOV3 cells to BPA and evaluated the effects of BPA on nuclear translocation of β-catenin and the global gene expression profile. They reported that nanomolar dose BPA caused significant β-catenin translocation to the nucleus, indicating that environmentally relevant doses of BPA exposure activated the canonical Wnt/β-catenin signaling pathway in ovarian carcinoma cells. It was concluded that BPA altered the gene expression profile, supported epithelial to mesenchymal transition events through canonical Wnt signaling pathway of ovarian cancer.

The *C-MYC* proto-oncogene (*MYC*) is a Wnt/β-catenin target gene, and its activation and overexpression has been associated with different human cancers and promoting tumorigenesis (Casey et al., 2016). Environmentally relevant doses of BPA has been shown to have genotoxic effects on mammary cell, increase *MYC* expression, and ROS (Pfeifer et al., 2015). Our group has shown that BPA increases oxidative stress and activates Wnt/β-catenin pathway in zebrafish embryos as indicated by the increased expression of the target gene *c-myc* as well as *wnt3a* (Üstündağ et al., 2017a,b). We have also investigated the relation between Wnt signaling, apoptosis, and proliferation in BPA exposed zebrafish embryos. We reported that BPA exposure led to increased vitellogenin levels, apoptosis, and *gsk3*β expressions in zebrafish embryos (Üstündağ et al., 2017b). Similar to the results of our study, WNT3a has been reported to induce pro-apoptotic changes in the intrinsic

apoptotic pathway, including BCL2L11, BBC3, and MCL1 (Zimmerman et al., 2013).

Aberrant β-catenin expression is a key marker of Wnt-signaling activation and has been reported in male mouse reproductive cells by Fang et al. (2015). In that study Fang et al. (2015) evaluated the toxicological effects of prenatal to postnatal BPA exposure on the reproductive system of Institute of Cancer Research (ICR) male murine pups by evaluating the association between Wnt signaling and testis development. The expressions of β-catenin and DKK-1 were determined by immunohistochemical and western blot methods in the testicular tissues of the 6-week-old male mice. In the BPA treated groups, significant decreases were observed in the murine pup number and in the testicular viscera coefficient of the male mice although the male/female ratio did not change. The control group exhibited normal testicular tissue morphology, whereas irregular seminiferous tubules of the testicular tissue and tube cell wall layers were observed in the BPA-treated groups. They showed that β-catenin and DKK-1 levels were significantly increased after BPA treatment, in a dose-dependent manner, suggesting the role of β-catenin and DKK-1 in BPA induced pathogenesis in male mouse reproductive cells. As an inhibitory molecule, DKK-1 is involved in embryonic development and plays an important inhibitory role in Wnt signaling pathway. Increased β-catenin levels in this study indicate the inhibitory effect of BPA on β-catenin degradation (Kong and Zhang, 2009; Ye et al., 2011). On the other hand, the association of Wnt/β-catenin signaling pathway and BPA-induced inhibition of male mouse reproductive cell growth and development remains to be further elucidated (Fang et al., 2015).

Chen et al. (2015) conducted a two-generation study to examine the reproductive effects of long-term exposure to low concentrations of BPA (1 nM) in zebrafish and reported a female-biased sex ratio in both F1 and F2 adult population, decreased sperm density and quality. Significant activation of non-canonical Wnt/planar cell polarity and Wnt/calcium signaling pathways have been reported in F2 male gonads with dysregulated mitochondrial biogenesis.

BPA mediates effects on reproduction through modulation of the Wnt pathway. *WNT* family genes have important functions in the development of female reproductive tract (Yin and Ma, 2005). *HOX* genes are defined as a subset of homeobox genes, which determine regions of the body plan along the head-tail axis of animals in embryogenesis. HOX proteins ensure that correct structures form in correct places in the body. Wnt signaling pathway has been shown to control *HOX* gene expression (Maloof et al., 1999). *HOXA13*, *WNT4*, and *WNT5A* have been shown to be differentially regulated genes sensitive to BPA exposure in late gestation. These genes play important roles in urogenital tract development and function in humans. *WNT4* has been shown to be upregulated in the BPA-exposed rhesus macaque fetal uterus and progesterone signaling has been suggested to be an upstream regulator of the differentially expressed genes (Calhoun et al., 2014).

Wnt/β-catenin signaling pathway regulates neurogenesis at different points such as proliferation of neural stem cells (NSCs) and neuronal differentiation. BPA has been shown to inhibit the Wnt pathway and lead to the consecutive depletion of β-catenin by different studies. Studies that reported inhibited Wnt pathway due to BPA exposure have focused mainly on DKK which is one of the most potent intracellular inhibitors of Wnt-signaling and β-catenin (Krause et al., 2014). A study showed that prenatal and early postnatal low-dose BPA treatment suppressed Wnt/β-catenin pathway in the rat and impaired NSC proliferation and differentiation (Tiwari et al., 2015). In the same study, it was reported that BPA enhanced Wnt inhibitory molecules DKK-1 and WIF-1 leading to reduced WNT levels and alterations in Wnt pathway. Normally inside the nucleus, β-catenin interacts with TCF/LEF promoter complex and activates the Wnt target genes such as cyclin D1 which regulates the proliferation and differentiation of NSC. However, in the case of BPA exposure, decreased WNT levels lead to decreased β-catenin levels and inhibited NSC proliferation and differentiation. Furthermore, in the same study, the activation of Wnt/β-catenin signaling pathway has been shown to decrease BPA-induced inhibition of neurogenesis *in vitro*. Accordingly, it was concluded that BPA inhibited neurogenesis through Wnt/β-catenin pathway inhibition both *in vitro* and *in vivo*.

In another study, Tiwari et al. (2016) investigated the neuroprotective effect of curcumin against BPA-induced neurogenesis inhibition. They reported that curcumin prevented BPA-induced decrease in NSC proliferation and neuronal differentiation and reduced neurodegeneration by activating Wnt pathway genes/proteins, which were reduced due to BPA exposure in the hippocampus. The protective effects of curcumin were attributed to the inhibition of DKK-1 in NSC culture treated with BPA. In the same study, curcumin

significantly reversed BPA-induced effects including increase in β-catenin phosphorylation, decreased GSK-3β levels, and β-catenin nuclear translocation. It was concluded that curcumin exerted neuroprotection against BPA-induced impaired neurogenesis by the activation of the Wnt/β-catenin signaling pathway.

Leem et al. (2017) evaluated BPA-induced cytotoxicity focusing on oxidative stress and β-catenin signaling in bone mesenchymal stem cells (BMSCs). In this study, BPA while increasing superoxide anion levels, inhibited nuclear β-catenin accumulation and expression of the β-catenin/LEF pathway-dependent target cyclin D1. Accordingly it was concluded that BPA exposure in hBMSCs caused disturbance in β-catenin signaling through a superoxide anion overload.

The Wnt signaling pathway, specifically the canonical one, has important functions in dendrite growth and synapse formation during embryonic development (Koles and Budnik, 2012). Liu et al. (2015) aimed to investigate if Wnt signaling was associated with BPA induced deterioration of dendritic spine formation in the hippocampal CA1 area in male Sprague-Dawley rat pups. They reported increased β-catenin phosphorylation levels after BPA treatment and suggested that BPA contributed to β-catenin degradation, which may disrupt spine formation directly or indirectly by inhibiting the expressions of downstream molecules. Moreover, BPA exposure reduced *wnt7a* expressions compared with the control group. Based on these results, it was concluded that Wnt signaling pathway played an important role in BPA induced memory deficits.

Phthalates DEHP

DEHP is a diester of phthalic acid that is widely used as plasticizer in the production of polyvinyl chloride. Worldwide three billion kilograms of DEHPs are produced annually. DEHP has been defined as a potential endocrine disruptor and therefore its environmental exposure has been an important concern especially in terms of reproductive system, development, obesity, cardiotoxicity, and cancer (Sharman et al., 1994).

DEHP serves to soften plastics and give flexibility. It has recently been reported that endocrine disruptive substances such as phthalate (and antimony) may migrate from polyethylene terephthalate bottles, in daily use conditions (Sax, 2010). The risk of migration increases with the increase in ambient temperature and the prolonged storage period. As a potential endocrine disruptor, DEHP has been related to reproductive toxicity mainly in testis by inhibiting the action of testosterone and also with cardiovascular diseases and cancer (Yang et al., 2015). Phthalates have been shown to cause adiposity and insulin resistance, decrease anogenital distance in male infants, levels of sex hormone, and affected male reproductive system in animal studies as a result of utero and lactational exposure. Male neurological development has also been reported to be impaired due to prenatal exposure (Sax, 2010; Tanner et al., 2011). DEHP, which constitutes 65% of all phthalate production, is classified as Group 3 in terms of carcinogenic effects (Tanner et al., 2011). DEHP was banned in Sweden in 2000 and in 2009 in the United States in children under 3 years of age (Tanner et al., 2011). Phthalate metabolites have also been related to obesity and insulin resistance (Desvergne et al., 2009).

Wnt/β-catenin signaling pathway is necessary for early teleost development to establish the dorsal-ventral axis. Fairbairn et al. (2012) investigated the morphological abnormalities due to the disruption of axis determination by environmental contaminants in zebrafish embryos. They suggested that commercial GSK-3β inhibitors and dibutyl phthalate induced an increase in nuclear β-catenin levels throughout the embryo.

Wnt/β-catenin pathway promotes bone formation and suppresses bone resorption (Baron and Kneissel, 2013). Cheon et al. (2016) evaluated the effects of parenteral exposure to DEHP on the microstructure of bone and Wnt signaling pathway in F2 female mice. In this study, pregnant mice (F0) were exposed to DEHP during pregnancy and lactation and microstructure of the tibial head and microarray analysis on ovary cells from F2 female siblings of 17–18 weeks of age were evaluated. Proliferative changes were reported in trabecular bone in the DEHP treated F2 siblings by micro-CT analysis and β-catenin was upregulated in groups after perinatal DEHP exposure.

On the other hand, *in utero* exposure to dibutyl phthalate affected genital tubercle development, down-regulated Wnt/β-catenin pathway, and decreased β-catenin expression in the genital tubercle of F1 male rat (Zhang et al., 2011).

Yang et al. (2015) suggested lymphoid enhancer-binding factor 1 (LEF1) to be a new indicator of cancer due to phthalate exposure. Although LEF1 by itself has no transcriptional activation potential, when

in association with β-catenin, LEF1 can activate many Wnt-responsive genes including those that are responsible for the cell cycle and survival (Schepers and Clevers, 2012; Singhi et al., 2014).

Our group has shown that DEHP exposure led to increased mRNA levels of *gsk3*β in zebrafish embryos (Üstündağ et al., 2017b). We have also investigated the relationship between oxidant-antioxidant status and the Wnt/β-catenin target proto-oncogene *c-myc* expression in DEHP (2.5 μg/L) exposed zebrafish embryos. We have reported increased lipid peroxidation and increased *c-myc* expression in DEHP exposed group (Üstündağ et al., 2017a).

Diethylstilbestrol

DES is a synthetic estrogen that was recommended for estrogen deficiency in women between the 1940s and 1980s (Hao et al., 2012). On the other hand, studies have shown long-term endocrine disrupting effects of DES exposure. Risk of breast cancer has been reported in DES exposed mothers and various reproductive health risks have been reported in their daughters and sons (Giusti et al., 1995; Hao et al., 2012; Palmer et al., 2009).

As a synthetic estrogen, in the developing fetus, DES can easily diffuse through the placental barrier and bind ERs (Kitajewski and Sassoon, 2000). Neonatal DES exposure in mice may cause multiple female reproductive tract patterning defects such as hypoplasia, stratification of luminal epithelium, disorganized smooth muscle, and reduced endometrial glands (Hayashi et al., 2011; Yoshida et al., 1999). The possible mechanisms have been explained as interaction of DES with estrogen receptor alpha (ESR1) and consequent hyperstimulation of ESR1 signaling resulting in abnormal uterine differentiation (Hayashi et al., 2011).

HOX genes regulate developmental axis in early embryogenesis and control the specification of individual regions of the female reproductive tract (Du and Taylor, 2016). *HOXA-10* and *HOXA-11* are expressed in endometrial glands and stroma during the estrous/menstrual cycle and are crucial for embryo implantation (Du and Taylor, 2016; Taylor et al., 1999).

During critical periods of reproductive tract patterning DES inhibited *Hox* and *Wnt* in mice, two gene families normally controlling developmental processes. These genes were not inhibited in ESR1-knockout mice, indicating the cross talk between this receptor and Hox and Wnt pathways (Couse et al., 2001; Hayashi et al., 2011; Ma et al., 1998; Miller et al., 1998). Moreover, *Hoxa10*, *Hoxa11*, *Wnt5a*, and *Wnt7a* mutations in mouse showed the need for these genes during postnatal uterine development (Hayashi et al., 2011).

Wnt7A is needed for the proper hox gene expression in the female reproductive tract and estrogenic hormones have been shown to inhibit *Wnt7A* expression as well as *Hoxa* genes (Kitajewski and Sassoon, 2000). *Wnt7a* is expressed in the female reproductive tract and serious changes were reported in the morphology, cytodifferentiation, and gene expression of the *Wnt7a* mutant mice (Miller and Sassoon, 1998). *Wnt7a* is involved in the DES response as evidenced by the close correlation between DES exposed phenotypes and the phenotype of the *Wnt7a* mutant female reproductive tract (Kitajewski and Sassoon, 2000; Parr and McMahon, 1998).

In another study to determine if *Wnt7a* is involved in the DES induced phenotypes, *Wnt7a* expression was compared between newborn DES-exposed and control uteri (Miller and Sassoon, 1998). *Wnt7a* was found to be expressed in the epithelium of the control uterus but *Wnt7a* transcript levels decreased in the DES-treated uteri at birth and returned to high levels 5 days after birth (Kitajewski and Sassoon, 2000; Miller and Sassoon, 1998). On the other hand, although *Wnt7a* levels returned to normal 5 days after birth, the uterine epithelium was changed and presented an abnormal thickened and stratified appearance (Kitajewski and Sassoon, 2000; Miller and Sassoon, 1998).

Hayashi et al. (2011) evaluated the effects of DES exposure on *Wnt* and *Fzd* gene expression in the mouse uterus and the function of *Wnt11* in postnatal mouse uterine development and function. They reported that in the neonatal mice, *Wnt4*, *Wnt5a*, and *Wnt16* were located in the endometrial stroma, whereas *Wnt7a*, *Wnt7b*, *Wnt11*, *Fzd6*, and *Fzd10* were located in the uterine epithelia. Inhibited endometrial gland development due to DES exposure was associated with decreased *Wnt4*, *Wnt5a*, *Wnt7a*, *Wnt11*, *Wnt16*, and *Fzd10* expressions. However endometrial adenogenesis and expressions of other Wnt genes were not affected in *Wnt11* null allele neonatal uterus, suggesting a lesser role for this gene in uterine development.

Benson et al. (1996) also evaluated the effects of DES on the reproductive tract of female mouse and

found that *Hoxa-10* expression was altered in mullerian duct of DES-exposed female offspring. *Hoxa-10* repression in reproductive tract is closely related to Wnt protein signaling. Accordingly studies conducted in the mouse uterus have demonstrated altered expressions of chromatin-modifying proteins and members of Wnt signaling pathway in DES exposure (Hayashi et al., 2011; Jefferson et al., 2013).

Cadmium

Cadmium (Cd^{2+}) is a trace element and a toxic pollutant with diverse toxic effects. Cadmium is a well known EDC affecting the synthesis and/or regulation of several hormones (Darbre, 2006; Henson and Chedrese, 2004).

Being absorbed from cigarette smoke, food, water, and air contamination cadmium exerts many harmful effects in both humans and animals including nephrotoxicity, carcinogenicity, teratogenicity, and endocrine disrupting effects. Cadmium toxicity has been related to cell proliferation, differentiation, and apoptosis at the molecular level (Branca et al., 2018; Rani et al., 2014). Cadmium and cadmium compounds are defined as Group 1 human carcinogens supported by recent epidemiologic evidence showing that cadmium induces cancer in many organs in humans (Hu et al., 2002; International Agency for Research on Cancer, 1993; Pesch et al., 2000).

Chakraborty et al. (2010a) reported that cadmium induced Wnt signaling in kidney proximal tubule cells and suggested that cadmium may induce carcinogenesis of these cells by increasing Wnt pathway-mediated proliferation and survival of pre-neoplastic cells.

In another study, Chakraborty et al. (2010b) showed that the upregulation of Wnt signaling components by cadmium was supported by increased expression of Wnt target genes including cell proliferation and survival genes *c-myc*, *cyclin D1*, and the multidrug transporter P-glycoprotein ABCB1B that induce malignancy. It was suggested that Wnt signaling regulated the cadmium induced changes of renal epithelial tissue characteristic of fibrosis and cancer.

Wnt/β-catenin pathway has also been investigated in nasopharyngeal carcinoma cell lines exposed to cadmium. In this study chronic low-dose Cadmium enhanced malignant progression, including more proliferative and aggressive characteristics through the activation of the Wnt/β-catenin pathway and DNA methylation (Peng et al., 2019).

In a recent study, cadmium has been shown to activate the non-canonical Wnt signaling pathway and impair hematopoietic stem cells (HSCs) function by promoting myelopoiesis while suppressing lymphopoiesis in C57BL/6 mice. Cadmium decreased the number of lymphocytes (B cells and T cells) and increased the number of myeloid cells (monocytes and neutrophils) in the peripheral bloods of mice and activated CDC42 of the noncanonical Wnt signaling pathway a protein whose role is to impair HSC function (Zhao et al., 2018).

2,3,7,8-Tetrachlorodibenzo-p-dioxin

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is an important environmental toxicant and endocrine disruptor. Numerous human and animal studies have shown the relationship between this EDC and many diseases including endometriosis, and cancer as well as processes including embryonic development, and regeneration (Bruner-Tran et al., 2016; Bruner-Tran and Osteen, 2011; Igarashi et al., 2005; Heindel, 2006; Yang and Foster, 1997).

Many tissues express aryl hydrocarbon receptor (AHR) during embryonic development and in adulthood which is activated by ligand binding (Schneider et al., 2014). AHR is able to bind hundreds of different chemical compounds including anthropogenic xenobiotics including TCDD. TCDD can trigger the activation of AHR signaling and therefore, exposure to TCDD during embryogenesis can have teratogenic consequences (Denison and Nagy, 2003; Schneider et al., 2014).

Both Wnt signaling and AHR signaling have very important roles in development and disease, and as discussed by Schneider et al., there is possibility that the AHR and Wnt might regulate each other as each pathway is activated by ligand-receptor binding events leading to substantial change to the transcriptome. Activated, AHR has been shown to interact with androgen receptor (AR), ESR1, or β-catenin leading to ubiquitination and, eventually, degradation of these proteins (Ohtake et al., 2007). Therefore, when activated AHR can inhibit AR, ESR1, and β-catenin expression without changing their transcriptional activity (Schneider et al., 2014).

On the other hand, studies have shown that in zebrafish, exposure to TCDD after fin amputation impaired regeneration, and in TCDD-exposed larval fish, the transcription of multiple Wnt signaling

regulators were altered, including RSPO1, which was upregulated (Mathew et al., 2008).

In another study when human prostate cancer cell line was exposed to the AHR agonists TCDD and/or benzo[a]pyrene (BaP), WNT5A expression was induced and mRNA levels of *FZD1*, *FZD3*, and *LEF1* were increased (Hrubá et al., 2011).

On the other hand, harmful effects of TCDD exposure leading to the downregulation of canonical Wnt signaling have also been reported. TCDD exposure inhibited GSK3B phosphorylation increasing active GSK3B pool and decreased *ctnnb1* expression (Xu et al., 2013). Although there are many studies about AHR and Wnt signaling pathways, their interaction has been a very new subject with limited data available (Schneider et al., 2014).

Conclusion

EDC exposure is an important public and occupational health problem. Detailed description of the molecular mechanisms of EDC action is necessary to identify the occupational health risks, surveillance, and exposure prevention. Moreover, EDC exposure in the embryonal period can lead to serious problems in future life. Given the effects of EDCs on embryonic development, and the key role of the Wnt pathway in that process, it is perhaps not surprising that these compounds would also modulate Wnt signaling. Therefore, the mechanism underlying the alterations in Wnt/β-catenin signaling pathway in EDC toxicity is a critical subject that remains to be further elucidated for the development of personalized protection from EDC exposure.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

Aberle H, Bauer A, Stappert J, et al. (1997) β-catenin is a target for the ubiquitin proteasome pathway. *EMBO J* 16: 3797–3804.

Akyuz S, Yarat A and Egil E (2011) Dental materials containing bisphenol-A: current approach. *Clinical and Experimental Health Sciences* 1: 190–195.

Alonso-Magdalena P, Vieira E, Soriano S, et al. (2010) Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environmental Health Perspectives* 118: 1243.

Arend RC, Londono-Joshi AI, Straughn JM, et al. (2013) The Wnt/beta-catenin pathway in ovarian cancer: a review. *Gynecologic Oncology* 131: 772–779.

Baron R and Kneissel M (2013) WNT signaling in bone homeostasis and disease: from human mutations to treatments. *Nature Medicine* 19: 179–192.

Benson GV, Lim H, Paria BC, et al. (1996) Mechanisms of reduced fertility in Hoxa-10 mutant mice: uterine homeosis and loss of maternal Hoxa-10 expression. *Development* 122: 2687–2696.

Branca JJV, Morucci G and Pacini A (2018) Cadmium-induced neurotoxicity: still much ado. *Neural Regeneration Research* 13: 1879.

Bruner-Tran KL and Osteen KG (2011) Developmental exposure to TCDD reduces fertility and negatively affects pregnancy outcomes across multiple generations. *Reproductive Toxicology* 31: 344–350.

Bruner-Tran KL, Gnecco J, Ding T, et al. (2016) Exposure to the environmental endocrine disruptor TCDD and human reproductive dysfunction: translating lessons from murine models. *Reproductive Toxicology* 68: 59–71.

Cadigan KM and Waterman ML (2012) TCF/LEFs and Wnt signaling in the nucleus. *Cold Spring Harbor Perspectives in Biology* 4(11): a007906.

Calafat AM, Ye X, Wong LY, et al. (2008) Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. *Environmental Health Perspectives* 116: 39–44.

Calhoun KC, Padilla-Banks E, Jefferson WN, et al. (2014) Bisphenol A exposure alters developmental gene expression in the fetal rhesus macaque uterus. *PLoS One* 23: e85894.

Casey SC, Tong L, Li Y, et al. (2016) MYC regulates the anti-tumor immune response through CD47 and PD-L1. *Science* 352(6282): 227–231.

Chakraborty PK, Lee WK, Molitor M, et al. (2010) Cadmium induces Wnt signaling to upregulate proliferation and survival genes in sub-confluent kidney proximal tubule cells. *Molecular Cancer* 9: 102.

Chakrabortya PK, Scharner B, Jurasov J, et al. (2010) Chronic cadmium exposure induces transcriptional activation of the Wnt pathway and upregulation of

epithelial-to-mesenchymal transition markers in mouse kidney. *Toxicology Letters* 198(1): 69–76.

Chen J, Xiao Y, Gai Z, et al. (2015) Reproductive toxicity of low level bisphenol A exposures in a two-generation zebrafish assay: evidence of male-specific effects. *Aquatic Toxicology* 169: 204–214.

Chen X, Xu S, Tan T, et al. (2014) Toxicity and estrogenic endocrine disrupting activity of phthalates and their mixtures. *International Journal of Environmental Research and Public Health* 11(3): 3156–3168.

Cheon KY, Kil KH, Choi JI, et al. (2016) Parenteral exposure to DEHP and its effect on the microstructure of bone and Wnt signaling pathway in F2 female mice. *BioChip Journal* 10(3): 233–240.

Clevers H and Nusse R (2012) Wnt/β-catenin signaling and disease. *Cell* 8: 1192–1205.

Couse JF, Dixon D, Yates M, et al. (2001) Estrogen receptor-alpha knockout mice exhibit resistance to the developmental effects of neonatal diethylstilbestrol exposure on the female reproductive tract. *Developmental Biology* 238: 224–238.

Darbre PD (2006) Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. *Journal of Applied Toxicology* 26(3): 191–197.

Denison MS and Nagy SR (2003) Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annual Review of Pharmacology and Toxicology* 43: 309–334.

Desvergne B, Feige JN and Casals-Casas C (2009) PPAR-mediated activity of phthalates: a link to the obesity epidemic? *Molecular Cell Endocrinology* 25: 43–48.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. (2009) Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocrinolgy Reviews* 30(4): 293–342.

Du H and Taylor HS (2016) The role of hox genes in female reproductive tract development, adult function, and fertility. *Cold Spring Harbor Perspectives in Medicine* 6(1): a023002.

Fairbairn EA, Bonthius J and Cherr GN (2012) Polycyclic aromatic hydrocarbons and dibutyl phthalate disrupt dorsal-ventral axis determination via the Wnt/β-catenin signaling pathway in zebrafish embryos. *Aquatic Toxicology* 15: 188–196.

Fang Z, Liu X, Yang X, et al. (2015) Effects of Wnt/β-catenin signaling on bisphenol A exposure in male mouse reproductive cells. *Molecular Medicine Reports* 12: 5561–5567.

Filali M, Cheng N, Abbott D, et al. (2002) Wnt-3A/beta-catenin signaling induces transcription from the LEF-1 promoter. *Journal of Biological Chemistry* 277(36): 33398–33410.

Fucic A, Galea KS, Duca RC, et al. (2018) Potential health risk of endocrine disruptors in construction sector and plastics industry: a new paradigm in occupational health. *International Journal of Environmental Research and Public Health* 15(6): 1229.

Giusti RM, Iwamoto K and Hatch EE (1995) Diethylstilbestrol revisited: a review of the long-term health effects. *Annals of Internal Medicine* 122: 778–788.

Goodson A, Summerfield W and Cooper I (2002) Survey of bisphenol A and bisphenol F in canned foods. *Food Additives & Contaminants* 19: 796–802.

Hao CJ, Cheng XJ, Xia HF, et al. (2012) The endocrine disruptor diethylstilbestrol induces adipocyte differentiation and promotes obesity in mice. *Toxicology and Applied Pharmacology* 263: 102–110.

Heindel JJ (2006) Role of exposure to environmental chemicals in the developmental basis of reproductive disease and dysfunction. *Seminars in Reproductive Medicine* 24: 168–177.

Hayashi K, Yoshioka S, Reardon SN, et al. (2011) WNTs in the neonatal mouse uterus: potential regulation of endometrial gland development. *Biology of Reproduction* 84: 308–319.

Henson MC and Chedrese PJ (2004) Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. *Experimental Biology and Medicine* 229: 383–392.

Hrubá E, Vondráček J, Líbalová H, et al. (2011) Gene expression changes in human prostate carcinoma cells exposed to genotoxic and nongenotoxic aryl hydrocarbon receptor ligands. *Toxicology Letters* 10: 178–188.

Hu J, Mao Y and White K (2002) Renal cell carcinoma and occupational exposure to chemicals in Canada. *Occupational Medicine* 52: 157–164.

Hui L, Li H, Lu G, et al. (2018) Low dose of bisphenol A modulates ovarian cancer gene expression profile and promotes epithelial to mesenchymal transition via canonical wnt pathway. *Toxicological Sciences* 1: 527–538.

Igarashi TM, Bruner-Tran KL, Yeaman GR, et al. (2005) Reduced expression of progesterone receptor-B in the endometrium of women with endometriosis and in cocultures of endometrial cells exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fertility and Sterility* 84(1): 67–74.

Ikeda S, Kishida S, Yamamoto H, et al. (1998) Axin, a negative regulator of the Wnt signaling pathway, forms a complex with GSK-3β and β-catenin and promotes GSK-3β-dependent phosphorylation of β-catenin. *EMBO Journal* 17: 1371–1384.

International Agency for Research on Cancer (1993) Beryllium, cadmium, mercury, and exposures in the glass. Apresentado em: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Beryllium, Lyon, 1993. *IARC Monographs on the Evaluation of Carcinogenic Risks to Human* 58: 1–415.

Jefferson WN, Chevalier DM, Phelps JY, et al. (2013) Persistently altered epigenetic marks in the mouse uterus after neonatal estrogen exposure. *Molecular Endocrinology* 27: 1666–1677.

Keri RA, Ho SM, Hunt PA, et al. (2007) An evaluation of evidence for the carcinogenic activity of bisphenol A. *Reproductive Toxicology* 24: 240–252.

Kitajewski J and Sassoon D (2000) The emergence of molecular gynecology: homeobox and Wnt genes in the female reproductive tract. *Bioessays* 22(10): 902–1010.

Koles K and Budnik V (2012) Wnt signaling in neuromuscular junction development. *Cold Spring Harbor Perspectives Biology* 4(6): a008045.

Komiya Y and Habas R (2008) Wnt signal transduction pathways. *Organogenesis* 4(2): 68–75.

Kong XB and Zhang C (2009) Dickkopf (Dkk) 1 promotes the differentiation of mouse embryonic stem cells toward neuroectoderm. *In Vitro Cell Developmental Biology Animal* 45: 185–193.

Konieczna A, Rutkowska A and Rachoń D (2015) Health risk of exposure to Bisphenol A (BPA). *Roczniki Państwowego Zakładu Higieny* 66(1): 5–11.

Krause U, Ryan DM, Clough BH, et al. (2014) An unexpected role for a Wnt-inhibitor: Dickkopf-1 triggers a novel cancer survival mechanism through modulation of aldehyde-dehydrogenase-1 activity. *Cell Death and Disease* 27(5): e1093.

Kuldeep K and Gosens R (2016) WNT-5A: signaling and functions in health and disease. *Cellular and Molecular Life Sciences* 73: 567–587.

Kurosawa T, Hiroi H, Tsutsumi O, et al. (2002) The activity of bisphenol A depends on both the estrogen receptor subtype and the cell type. *Endocrine Journal* 49: 465–471.

Leem Y, Oh S, Kang H, et al. (2017) BPA-toxicity via superoxide anion overload and a deficit in β-catenin signaling in human bone mesenchymal stem cells. *Environmental Toxicology* 32: 344–352.

Liu ZH, Yang Y, Ge MM, et al. (2015) Bisphenol-A exposure alters memory consolidation and hippocampal CA1 spine formation through Wnt signaling in vivo and in vitro. *Toxicological Research* 4(3): 686–694.

Logan CY and Nusse R (2004) The Wnt signaling pathway in development and disease. *Annual Review of Cell and Developmental Biology* 20: 781–810.

Ma L, Benson GV, Li.m H, et al. (1998) Abdominal B (AbdB) Hoxa genes: regulation in adult uterus by estrogen and progesterone and repression in mullerian duct by the synthetic estrogen diethylstilbestrol (DES). *Developmental Biology* 197: 141–154

Maloof JN, Whangbo J, Harris JM, et al. (1999) A Wnt signaling pathway controls hox gene expression and neuroblast migration in *C. elegans*. *Development* 1999 126(1): 37–49.

Mathew LK, Sengupta SS, Ladu J, et al. (2008) Crosstalk between AHR and Wnt signaling through R-Spondin1 impairs tissue regeneration in zebrafish. *FASEB Journal* 22(8): 3087–3096.

Miller C, Degenhardt K and Sassoon DA (1998) Fetal exposure to DES results in deregulation of Wnt7a during uterine morphogenesis. *Nature Genetics* 20: 228–230.

Miller C and Sassoon DA (1998) Wnt-7a maintains appropriate uterine patterning during the development of the mouse female reproductive tract. *Development* 125: 3201–3211.

Miller CK and Sassoon DA (1998) Fetal exposure to DES results in deregulation of Wnt-7a during a critical period of uterine morphogenesis. *Nature Genetics* 20: 228–230.

Mosimann C, Hausmann G and Basler K (2009) β-Catenin hits chromatin: regulation of Wnt target gene activation. *Nature Reviews* 10: 276–286.

Narasipura SD, Henderson LJ, Fu SW, et al. (2012) Role of β-catenin and TCF/LEF family members in transcriptional activity of HIV in astrocytes. *Journal of Virology* 86(4): 1911–1921.

Ohtake F, Baba A, Takada I, et al. (2007) Dioxin receptor is a ligand-dependent E3 ubiquitin ligase. *Nature* 446: 562–566.

Palmer JR, Herbst AL, Noller KL, et al. (2009) Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environmental Health* 8(1): 37.

Parr B and McMahon A (1998) Sexually dimorphic development of the mammalian reproductive tract requires Wnt-7a. *Nature* 395: 707–710.

Peng L, Huang YT, Zhang F, et al. (2019) Chronic cadmium exposure aggravates malignant phenotypes of nasopharyngeal carcinoma by activating the Wnt/β-catenin signaling pathway via hypermethylation of the casein kinase 1α promoter. *Cancer Management and Research* 11: 81.

Pesch B, Haerting J, Ranft U, et al. (2000) Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC

Study Group. Multicenter urothelial and renal cancer study. *International Journal of Epidemiology* 29: 1014–1024.

Pfeifer D, Chung YM and Hu MC (2015) Effects of low-dose bisphenol A on DNA damage and proliferation of breast cells: the role of c-Myc. *Environmental Health Perspectives* 123(12): 1271–1279.

Rani A, Kumar A, Lal A, et al. (2014) Cellular mechanisms of cadmium-induced toxicity: a review. *International Journal of Environmental Health Research* 24(4): 378–399.

Rubin BS and Soto AM (2009) Bisphenol A: perinatal exposure and body weight. *Molecular and Cellular Endocrinology* 304: 55–62.

Sax L (2010) Polyethylene terephthalate may yield endocrine disruptors. *Environmental Health Perspectives* 118(4): 445–448.

Schepers A and Clevers H (2012) Wnt signaling, stem cells, and cancer of the gastrointestinal tract. *Cold Spring Harbor Perspectives Biology* 4(4): a007989.

Schneider AJ, Branam AM and Peterson RE (2014) Intersection of AHR and Wnt signaling in development, health, and disease. *International Journal of Molecular Sciences* 15(10): 17852–17885.

Seidensticker MJ and Behrens J (2000) Biochemical interactions in the wnt pathway. *Biochimica et Biophysica Acta - Molecular Cell Research* 1495(2): 168–182.

Sharman M, Read WA, Castle L, et al. (1994) Levels of di-(2-ethylhexyl) phthalate and total phthalate esters in milk, cream, butter and cheese. *Food Additives and Contaminants* 11(3): 375–385.

Singhi AD, Lilo M, Hruban RH, et al. (2014) Overexpression of lymphoid enhancer-binding factor 1 (LEF1) in solid-pseudopapillary neoplasms of the pancreas. *Modern Pathology* 27(10): 1355–1363.

Swarup S and Verheyen EM (2012) Wnt/wingless signaling in drosophila. *Cold Spring Harbor Perspectives in Biology* 4(6): a007930.

Tanner CM, Kamel F, Ross GW, et al. (2011) Rotenone, paraquat, and Parkinson's disease. *Environmental Health Perspectives* 119: 866.

Taylor HS, Igarashi P, Olive D, et al. (1999) Sex steroids mediate HOXA11 expression in the human peri-implantation endometrium. *Journal of Clinical Endocrinology & Metabolism* 84: 1129 – 1135.

Tiwari SK, Agarwal S, Seth B, et al. (2015) Inhibitory effects of bisphenol-A on neural stem cells proliferation and differentiation in the rat brain are dependent on Wnt/β-catenin pathway. *Molecular Neurobiology* 52(3): 1735–1757.

Tiwari SK, Agarwal S, Tripathi A, et al. (2016) Bisphenol-A mediated inhibition of hippocampal neurogenesis attenuated by curcumin via canonical Wnt pathway. *Molecular Neurobiology* 53(5): 3010–3029.

Üstündağ ÜV, Ünal İ, Ates PS, et al. (2017a) Oxidant-antioxidant status and c-myc expression in BPA and DEHP-exposed zebrafish embryos. *European Journal of Biology* 76: 26–30.

Üstündağ ÜV, Ünal İ, Ateş PS, et al. (2017b) Bisphenol A and di(2-ethylhexyl) phthalate exert divergent effects on apoptosis and the Wnt/β-catenin pathway in zebrafish embryos: a possible mechanism of endocrine disrupting chemical action. *Toxicology and Industrial Health* 33(12): 901–910.

Vom Saal FS, Akingbemi BT, Belcher SM, et al. (2007) Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. *Reproductive Toxicology* 24(2): 131.

Willert K and Nusse R (2012) Wnt proteins. *Cold Spring Harbor Perspectives in Biology* 4(9): a007864.

Xu G, Zhou Q, Wan C, et al. (2013) 2,3,7,8-TCDD induces neurotoxicity and neuronal apoptosis in the rat brain cortex and pc12 cell line through the down-regulation of the Wnt/β-catenin signaling pathway. *Neurotoxicology* 37: 63–73.

Yang JZ and Foster WG (1997) Continuous exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin inhibits the growth of surgically induced endometriosis in the ovariectomized mouse treated with high dose estradiol. *Toxicology and Industrial Health* 13(1): 15–25.

Yang O, Kim HL, Weon JI, et al. (2015) Endocrine-disrupting chemicals: review of toxicological mechanisms using molecular pathway analysis. *Journal of Cancer Prevention* 20(1): 12–24.

Ye S, Wang J, Yang S, et al. (2011) Specific inhibitory protein Dkk-1 blocking Wnt/β-catenin signaling pathway improve protective effect on the extracellular matrix. *Journal of Huazhong University of Science and Technology Medical Sciences* 31: 657–662.

Yin Y and Ma L (2005) Development of the mammalian female reproductive tract. *Journal of Biochemistry* 137: 677–683.

Yoshida A, Newbold RR and Dixon D (1999) Effects of neonatal diethylstilbestrol (DES) exposure on morphology and growth patterns of endometrial epithelial cells in CD-1 mice. *Toxicologic Pathology* 27: 325–333.

Zhan T, Rindtorff N and Boutros M (2017) Wnt signaling in cancer. *Oncogene* 36: 1461–1473.

Zhang LF, Qin C, Wei YF, et al. (2011) Differential expression of the Wnt/β-catenin pathway in the genital tubercle (GT) of fetal male rat following maternal exposure to di-n-butyl phthalate (DBP). *Systems Biology in Reproductive Medicine* 57: 244–250.

Zhao Y, Li Q, Yang Z, et al. (2018) Cadmium activates non-canonical Wnt signaling to impair hematopoietic stem cell function in mice. *Toxicological Sciences* 165(1): 254–266.

Zimmerman ZF, Kulikauskas RM, Bomsztyk K, et al. (2013) Activation of Wnt/β-catenin signaling increases apoptosis in melanoma cells treated with trail. *PLOS ONE* 8(7): e69593.