

Endocrine Disrupting Chemicals: Epigenetic Relevance and Mechanisms

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Abstract

Genetics alone cannot thoroughly expound the environmental impact on the molecular complexity of the endocrine system. Epigenetic-induced alteration in gene expression has emerged as a way in which environmental compounds may exert endocrine effects. The environmental compounds that interfere with normal endocrine signaling are one of the largest classes of toxicants we are exposed to, on a daily basis. Epigenetic mechanisms, mainly the methylation of DNA and the modification of histones, lead to differentiated activation and deactivation of genome domains creating phenotype plasticity and divergent endocrine function among populations and individuals, as well. The issues examined in the present review are related to environmental epigenetics, and more precisely, the epigenetic-mediated modulation and relevance of endocrine disrupting chemicals, focusing on three broad aspects: 1) persistence of EDs, 2) their major hormonal effects and 3) the potential of compounds previously considered as endocrine disruptors to induce epigenetic effects. Evidence suggests that environmental exposures notably impact expression of endocrine-related genes and, thus, affect clinical endocrine outcomes.

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Introduction

There are plenty definitions that attempt to explain what an "Endocrine disruptor" (ED) is. The United States Environmental Protection Agency (US EPA), the World Health Organisation (WHO), the European Union (EU), a joint expert group formed by representatives of the German Bundesamt fuer Risikobewertung (BfR) and health authorities in the United Kingdom (UK-BfR) have proposed similar definitions all of which are considered as appropriate [1]. However, the definition provided [1] for endocrine disrupting chemicals (EDCs) by the US EPA is the most suitable to convey their essence in this review as it highlights their role in interfering with natural homeostasis and developmental processes-related hormones, affecting their behaviour or production.

The mammalian endocrine system consists of a number of distinct hormonal systems including hormones derived from the thyroid gland or other organs such as pancreas, or even brain. Hormonal activity should not necessarily be considered as beneficial or harmful. Their biological contribution can be neutral, as well [1]. Hormonal activity is a significant health risk only when resulting in adverse outcomes such as carcinogenicity or reproductive and developmental defects [1].

EDs steroid function and their androgenic, estrogenic and antiandrogenic activity has been investigated further than their ability to disrupt signaling pathways regulated by hormones of a different nature such as peptide hormones [2]. Endocrine activity is partly epigenome-shaped, and exposure to EDs is a key factor for this procedure [3]. EDs can modulate the direction of epigenetic regulation through their effects i.e., indirect, direct or metabolites; in some cases, EDs can also act transgenerationally [2].

EDs can act on the epigenome in various ways [4]. They can alter histone-modifying enzymes' level of expression or catalytic power [5], affecting consequently the entire endocrine system. The transcription of genes and the arrangement of DNA in chromatin compacts can be regulated by the interaction of histone modifying enzymes with nuclear steroid receptors [5]. Such an interaction is the expression of the target genes of histone demethylases, through the involvement of these

enzymes in protein clusters and, more importantly, with androgen receptors (AR) [5].

Genistein is a well-studied phytoestrogen and its impact on DNA methyltransferases (DNMTs) has been found to be among its epigenome modifying abilities [5,6]. Diethylstilbestrol (DES), a synthetic estrogen, and bisphenol A (BPA), a plasticizer, can both alter DNA methylation in animals [2,4]. Polybrominated diphenyl ethers (PBDEs) are fire retardants that affect hippocampal neurons reducing global DNA methylation [7-9]. Dioxins, such as 2,3,7,8-Tetrachlorodibenzo-pdioxin (TCDD), act on preimplantation embryos by altering the DNA methylation of imprinted genes *H19/insulin like growth factor 2 (IGF2)* [10-12]. Moreover, TCDD can slightly affect microRNA (miRNA) levels in the liver of adult rodents [5]. miRNAs are molecules that exert epigenetic regulation by regulating gene expression [13]. For instance, epigenetic regulation of ITGB4 by miR-21 is a key event in colorectal cancer [14]; other important miRNAs in this malignancy include miR-15a-5p [15], miR-16 [16], miR-24-3p [17], miR-28-5p [18], miR-34a [19], miR-96 [20], miR-182 [21], and miR-224 [22]. Several other miRNAs that regulate gene expression have been described as important epigenetic regulators [23-25].

Polychlorinated biphenyls (PCBs), which have a number of uses such as [26] in capacitors and in engines and are widely spread in the environment [27], can lead to irreversible DNA methylation [28]. Perfluorooctane sulfonate (PFOS) and perfluorooctanesulfonic acid (PFOA), which were the dominant and most frequently detected perfluorinated compounds (PFCs) in home dust [29], can induce *glutathione S-transferase Pi (GSTP)* aberrant methylation [30]. Heavy metals, such as arsenic (As), can differentially alter DNA methylation status in specific genes of white blood cells and it to this mechanism that Arsenic's toxicity may be attributed [31]. Polycyclic aromatic hydrocarbons (PAHs) have been found to increase asthma risk in children, which has been related to deviating methylation of the *acyl-CoA synthetase long-chain family member 3 (ACSL3)* and *Interferon gamma (IFNG)* [2,32,33]. Dichlorodiphenyltrichloroethane (DDT) has a long history as an ED. The compound was once

used randomly as an insecticide in the agricultural sectors and it has been found to cause hypomethylation in the young hypothalamus of male rats [34]. Vinclozolin (Vz), a fungicide, exerts antiandrogenic activity, and by modifying the methylation status in the sperm of animals' first generation it induces adult-beginning diseases that can last, trans-generationally, until the F3 generation [5,35].

Many genes are known to be hormonally regulated, including the family of kallikrein-related peptidases (KLKs) [36,37], such as *KLK1*, *KLK2* [38], *KLK5*, *KLK6*, *KLK7*, *KLK8*, *KLK9* [39], *KLK10* [40], *KLK11*, and *KLK12* [41]. Many of these genes are also important cancer and/or leukemia biomarkers [42-49]. Other genes that are similarly regulated include members of the BCL2 family [50,51], such as *BCL2* [52], *BAX* [53,54], and *BCL2L12* [55-59], which has been shown to produce many alternative splice variants, using classical molecular cloning techniques and next-generation sequencing (NGS) [60,61]. NGS is a very powerful methodology that can reveal the depth of genomes and transcriptomes [62]. Epigenetically regulated transcription factors [63] such as *HIF1* [64] and *STAT3* [65], as well as other genes, including *DDC* [66,67], *PA28γ* [68], *PIK3CA* [69], *NBS1* [70], and *PD-L1* [71].

Genistein

Persistence

Soy products are foods with high phytoestrogen content and are substantial components of vegetarian diets [72,73]. The name phytoestrogen is derived from the Greek word "phyto" which means "plant", and the word "estrogen" which is the hormone that regulates fertility in female mammals [74]. Isoflavones are the major class of phytoestrogens found in soy and genistein is the most abundant isoflavone [75]. Genistein (4Y,5,7-dihydroxyisoflavone) belongs to the aglycone subgroup of isoflavones [75] and it was first isolated in 1899 by "Genista tinctoria". Genistein is identical with prunetol and its chemical synthesis took place in 1928 [76]. Therefore, human beings can be exposed to these compounds through their diet, both during their adult life [77] and *in utero* development [78] as well as during infancy via breast milk [79]. More specifically, the concentration of genistein as a form of glycosidic conjugate in soy food ranges from 0.2 to 1

mg/g [76].

Genistein is found in a number of leguminous plant foods. Phytoestrogens are found in high amounts in soybeans, flaxseed, alfalfa and other edible plants. First of all, soybeans contain high protein levels and the greatest amount of genistein. It can also be found in small amounts in garbanzo beans. Variable amounts of genistein are present in soy protein isolates (SPI), soy milk, soy flour, textured soy protein, tempeh, tofu, and miso. 53% soy protein is found in soy flour while 50-70% soy protein can be found in soy-made meat substitutes such as sausages, hot dogs, hamburgers, meatballs and meat loafs. Other sources of soy protein are SPI, used in infant formulas, sports drinks, energy bars and may contain 90% soy protein [80].

There is a thriving market promoting soy and soy-based foods and formulas addressed to infants. These foods have extremely high circulating levels of genistein indicating the absorption of genistein from soy formulas [81].

Isoflavones in adults vary depending both on ethnicity and diet. Vegetarian women have the highest level of serum genistein while for Asian women the level is slightly lower. Non vegetarian women's serum genistein is considerably lower than the previous groups [77].

Regarding its chemical structure, genistein resembles stereochemically human endogenous estrogen (E2) [82,83]. The distance between OH groups on the opposite sides of genistein and E2 molecules is similar and this fact makes the compound capable of binding to estrogen receptor (ER) subtypes a and b [80].

Hormonal effect

These compounds have structures similar to mammalian estrogens and display both estrogenic and anti-estrogenic effects. Soy isoflavones are able to bind to the ER and induce estrogen-like effects both *in vivo* in animals as well as in humans. Moreover, it can be applied *in vitro* in cell cultures. Compared to animal estrogens, phytoestrogens are relatively weak but the relative estrogenic potency is dependent on the type of hormonal activity measurement, dosage, animal species, route of administration and on the duration and timing [84]. Thus, ingestion of soy isoflavones in high levels

may result in variable, both positive and negative, biological responses in humans and animals [85].

Epigenetic effects

Anti-proliferation factor 3 (BTG3)

Genistein contributes to protection against the development of cancer. Through the demethylation of genes p16, O-6-methylguanine-DNA methyltransferase (MGMT), GSTP1, retinoic acid receptor beta (RARβ) and mutL homolog 1 (hMLH1), that exert tumour suppressor function, genistein inhibits angiogenesis and proliferation, two major cellular processes. Rajvir Dahiya and his colleagues have found that genistein affects various miRs, such as miR-1260b, causing histone modification and demethylation of DNA and, consequently, upregulating secreted frizzled related protein 1 (SFRP1) and SMAD4 in Pca cells [86,87].

Shahana Majid et al., demonstrated a new role for genistein in prostate cancer. BTG3 is a potential tumour suppressor gene that is downregulated in prostate malignancy. Genistein has been found to reactivate the hypermethylated BTG3 gene by the demethylation of its promoter. More specifically, it prompts the demethylation of CpGs, the decrease of DNMT, the inhibition of the activity of methyl-CpG binding domain protein 2 (MBD2) and subsequent induction of prior silenced BTG3 gene [88,89].

hTERT (human telomerase reverse transcriptase) promoter

A possible mechanism that regulates gene transcription is the methylation of DNA and the acetylation of histones [90,91]. Treatment with genistein prompts the hypomethylation of hTERT in the E2F-1 sites of recognition [89]. Studies have shown that telomerase activity can be suppressed by genistein as a result of transcriptional regulation of hTERT [44]. Moreover, hTERT promoter can be restructured in the presence of genistein in the chromatin level in MCF-7 cell lines [92].

The evidenced hypomethylation in the E2F-1 sites leads to increased attachment of the repressor to this binding site, suggesting a cooperation between genetics and epigenetics in the modulation of hTERT transcription when this phytoestrogen compound is present [89].

Thus, genistein could be combined with an epigenetic

modulator in order to reach its full epigenetic potential in controlling telomerase's action in breast malignant cells [89].

Nsbp1 (nucleosomal binding protein 1)

Neonatal exposure in DES/Genistein evokes an adult-onset modification in uterine epigenome. Nsbp1 contribution in chromatin restructure and transcriptional function accompanied with the evidence that Nsbp1 transcription is defined by an epigenetic mechanism mediated by estrogen signals, encourages the theory of Nsbp1 participation in tumorigenesis after neonatal exposure to DES/genistein [93].

Normally, in mice without genistein-treatment, Nsbp1 expression is weak prior to puberty. Estrogenic hormones, more specifically estradiol, cause the silence of Nsbp1. However, neonatal exposure to genistein and the co-occurrence of ovarian hormones cause Nsbp1 to get expressed actively throughout life. Neonatal genistein/DES treatment is evidenced to result in promoter hypomethylation of Nsbp1. Consequently, through a mechanism that possibly prevents the silencing of Nsbp1, uterine cancer incidence could increase at some point afterwards [93].

DES

Persistence

In 1938, a nonsteroidal estrogen, called DES, was synthesized in the United States to prevent miscarriage and other pregnancy complications. It was used as an estrogen for decades and its effects continue to be evident [94]. DES was administered to women all around the world in nonstandardized quantities and forms such as pills and liquid creams. Many women were unaware that they were taking DES in the U.S., Europe, and Australia [95,96]. Although DES has not been prescribed for women during pregnancy in the USA for 40 years, adverse outcomes continue to occur in women exposed in utero. Given the above, continued monitoring for established and unexpected adverse outcomes seems prudent [96].

DES was used until 1971- in which year the Herbst paper appeared in the medical literature and the U.S. Food and Drug Administration (FDA) issued a warning about the [32] relationship between the development of adenocarcinoma and the use of DES in

pregnancy in adolescent girls and young women whose mothers had taken DES while they were pregnant. Moreover, DES had been widely used in agriculture to chemically castrate male chickens and increase weight gain in cattle. In addition, until the 1970s when the effects of DES on female offspring were reported, its use in the sheep and cattle industry was prominent. Thus, DES could be characterized as an environmental estrogen [97].

Despite the information that DES was a human carcinogen operating through a previously unknown mechanism, it continued to be used in clinical trials. DES reduces testosterone levels facilitating the treatment of advanced prostate cancer. Moreover, it is used in the treatment of postmenopausal breast cancer [97,98].

Hormonal effect

As a xenoestrogen, DES has a similar receptor affinity to the naturally occurring estrogen (estradiol) activating the ER-alpha (ER α). It has a significant oral activity as an estrogenic substance and invokes a strong hormonal response equivalent to an injected dose of the steroidal estradiol-17 β [99]. DES is a lipid soluble, well absorbable compound that reaches a peak concentration within 20–40 min following the oral administration [100]. DES contributes to the prevention of miscarriages as well as bleeding resulting from preterm labor and gestation [98,101]. DES metabolism may proceed via two routes. One route can produce hormonally inactive metabolites such as β -di- enestrol. The other pathway could produce compounds, such as DES- epoxide, which still retain a considerable amount of estrogenic activity. Evidence for such a bilateral metabolism of certain substances has been documented [99]. If DES undergoes such metabolism, then large doses or repeated ingestion could produce compounds in the body that are hormonally active and/or carcinogenic. It has a half-life of 3–6 h and is primarily excreted in urine [100].

Epigenetic effects

miR-9-3

In breast cancer, a miRNA gene, MIR-9-3, is usually hypermethylated. miR-9-3 is an apoptosis modulator. Consequently, the silencing of the gene through an epigenetic mechanism could lead to the proliferation of cancer cells [102]. One study indicated

that breast progenitor cells' exposure to DES could cause this epigenetic repression. DES downregulates the target miRNA, namely miR-9-3 through both genomic and nongenomic pathways resulting in mediation of gene transcription. Continuation of this signaling could leave a mark able to be inherited through remodeling of chromatin and subsequent DNA methylation in the promoter region of this miRNA [102].

Hoxa10

Hoxa10 gene expression can be modified by deviant DNA methylation after in utero DES exposure. DES, through a molecular mechanism that includes gene methylation, induces developmental changes in the programming of the reproductive tract [103]. DNA methylation caused by persistent administration of DES *in utero* can lead to permanent changes in Hox genes expression. The mechanism of the above mentioned epigenetic effect includes DES-mediated up-regulation of DNMTs [103].

Nsbp1

There is the so called 'second hit model' which is concerned with the impact of neonatal DES exposure to uterine adenocarcinoma development in adulthood [104]. Under normal circumstances, *Nsbp1* acts in the uterus only during the period of development. The first hit is neonatal exposure to DES which causes hypo or hypermethylation in a treatment-specific way that results in altered *Nsbp1* expression in prepuberty. Prepubertal ovariectomy on mice has been found to lead to the establishment of these methylation patterns through aging. The secondary hit results in elevated *Nsbp1* expression, not only before puberty, which is related to the development of uterine adenocarcinoma. This hit involves additional estradiol presence during puberty which causes *Nsbp1* promoter to shift to hypomethylated condition in the models which were estrogen exposed immediately after birth. It seems that there are underlying epigenetic events that are yet to be revealed by future trigger points [104].

HOTAIR

Estradiol modulates the transcription of HOTAIR. This antisense transcript participates in silencing of genes and plays an important role in breast cancer. More specifically, it has been reported that in breast cancer cell lines the administration of BPA and DES

prompts the expression of this long non-coding RNA. HOTAIR expression is upregulated in rat mammary glands upon treatment with BPA and DES, as well. According to Luciferase assay, the promoter EREs of HOTAIR (to a greater extent ERE2 and ERE3) are triggered by DES and BPA, suggesting their potential involvement in endocrine disruption mediated via BPA and DES. The attachment of the MLL family of histone methylases and ERs (MLL1 and MLL3) to HOTAIR promoter EREs induced by BPA and DES causes chromatin modification (H3K4-trimethylation, histone acetylation), which is crucial for gene activation. ERs knockdown leads to decreased DES and BPA mediated HOTAIR expression. In summary, it is demonstrated that HOTAIR expression is epigenetically induced by DES and BPA, without the presence of estrogen being necessary [104,105].

BPA

Persistence

Bisphenols (BPs) constitute a broad group of chemicals. BPA (2,2-bis-(4-hydroxyphenyl)propane;) is largely used as a monomer in the production of polycarbonates (PC), of epoxy resins and as an additive in other polymeric materials [106,107]. Each year the atmospheric burden of BPA is estimated to be 100 tons [108,109].

Epoxy resins mark the introduction of BPA to mainstream production. They were initially applied in food and drink industry to protect the products from the metal packaging since epoxy resins have been used as internal protective coatings in cans for food and beverages and in drinking water storage tanks. BPA is used to make polycarbonate plastics, such as baby bottles [108,110], and has plenty more applications in electronic devices and even in dentistry for sealants [108,111,112]. Increased exposure to BPA may be caused, inter alia, by environmental pollution e.g. dust, air, drinking water, surface water, wastewater, leachate from landfills [113-119].

According to existing studies, the route of human exposure to polycarbonate plastics is through epoxy resins and other substances related to foods and drinks [116,120,121]. Indeed, canned food is responsible for 10-40% of BPA intake as indicated by one risk assessment study [106,121]. Following the worldwide

intensive discussion triggered by toxicological findings, alternative options have been provided to replace this chemical. BPA substitutes, though, have been proved to induce delayed toxicity [106]. There is a huge amount of information about BPA biological effects. However, there have been discrepancies in outcomes among the various studies, so investigation of the issue is still in progress [122].

Hormonal effect

BPA is a chemical acting as a xenoestrogen [123]. It binds to ERs [124] exhibiting a 10-fold higher affinity to ERb than to ERa [123]. The endocrine disrupting properties of BPA were discovered in pursuit of synthetic estrogens by Dodds et al. [125]. However, as indicated by the same authors, DES, which had already been synthesized, had a much stronger estrogenic potential than BPA which was defined as weak [106]. Despite its environmental tenuous estrogenic activity there is not a safety threshold preventing cellular response stimulation, even in BPA concentrations lower than the ones required so that attachment to the ERs is achieved [126]. Thus, classical ER-dependent nuclear pathways is only one of the ways through which BPA elicits its effects [122].

Epigenetic effects

Intracisternal A particle retrotransposon (IAP) upstream of the Agouti gene

BPA applied *in utero* or neonatally affects body weight, increases susceptibility to prostate and breast cancer and prompts changes in the reproductive function. BPA affects, to a greater extent, epigenetic mechanisms in early development i.e., stem cell stage. There is evidence supporting the enhancement of yellow coat colour of *viable yellow agouti (Avy)* in mouse offspring, after maternal exposure to BPA [127]. The change in progeny coat color was induced by reduced methylation of CpGs (cytosine-guanine dinucleotide) in Agouti gene and, more specifically, upstream of this gene originating from an intracisternal A particle retrotransposon [127].

PDE4D4 (Phosphodiesterase type 4 variant 4)

PDE4D4, which plays a regulatory role in cyclic adenosine monophosphate breakdown, was analyzed in detail to determine its epigenetic response to estrogen

exposure neonatally. 5'-flanking CpG Island of *PDE4D4* was the methylating target of BPA and estradiol [107]. This specific methylation complex is generally required for epigenetic modulation. However, of great significance is the fact that the relationship between methylation level and gene expression is inversely correlated in the tissues of prostate. Thus, the progressive hypermethylation of *PDE4D4* promoter in physiological aging prostates results in decreased gene expression. Interestingly, animals exposed neonatally to estradiol or BPA maintain a hypomethylated status, thus engendering increased *PDE4D4* expression throughout life. Cell line studies have confirmed the model of transcriptional modulation and methylation of *PDE4D4* where NbE-1 cells, which normally originate from immortalized epithelial ones, show reduced expression of the gene when *PDE4D4* is hypermethylated. On the other hand, AIT cells, which are tumorigenic and originate from dorsal prostate, exhibit hypomethylating status. To sum up, there is a possible contribution of prostate's epigenome in epithelial cell conversion [107].

PBDEs

Persistence

PBDEs are widely used as additives to plastics, furniture, textiles, electric cable insulation, water and sewage pipes, office equipment and electronic devices and for fire retardancy reasons i.e., to prevent and retard the spread of fire [128]. Therefore, PBDEs move relatively easily from these items into the environment [129]. They can be found in house and office air and dust, in dryer lint, and in air intake filters [27]. Their presence has been evidenced in landfills, sewage treatment plants, in the manufacture and recycling procedures of PBDEs [130,131]. Developing countries carry the heavy burden of e-waste recycling collected from industrialized countries [132]. Human beings and wildlife have been widely affected from PBDE production. Infant and toddler bodies contain three to nine times more PBDEs compared to adults because of maternal milk consumption and dust inhalation. North America is heavily burdened with PBDEs compared to Asia and Europe. The most abundant congener are tetra-BDE or BDE-47, hexa-BDE or BDE-153, and deca-BDE or BDE-209. They can enter human bodies via many

routes. Human beings can be exposed to PBDEs through ingestion, food chain or dust and inhalation [27,133].

Regarding their chemical structure, PBDEs have two phenyl rings linked by an ether bond. The position and number of the bromine atoms results in 209 possible compounds, referred to as PBDE congeners. Technical PBDE products are produced by brominating diphenyl ether when a catalyst is present [134,135].

Hormonal effect

In humans, exposure to PBDEs can lead to disturbances in thyroid hormones. The associations appear to be life stage and dose dependent. It has been suggested that PBDEs possibly exhibit hyperthyroid effects [136]. Nonetheless, among Canadian women aged 30–51 years, higher levels of exposure were associated with elevated prevalence of hypothyroidism [137]. According to a study among US women, those with the highest levels of exposure to PBDEs were more likely to report a previous diagnosis of thyroid disease. This association though, was stronger among postmenopausal women [138]. The mechanisms of PBDE toxicity are complex and have not been fully resolved. PBDEs' toxic effects are possibly mediated through some nuclear hormone receptor pathways, in particular the pathways involving thyroid hormone receptor (TR), ER and aryl hydrocarbon receptor (AhR), AR and progesterone receptor (PR) [139].

Epigenetic effects

Hippocampal neurons from neonatal rat- Global DNA methylation levels

Darnerud and his colleagues have reported that PBDE-209 increases the incidence of hepatocellular carcinomas [9]. Studies have indicated that PBDE-209 can affect global DNA methylation decreasing their level. Moreover, it may affect secondary messengers and cause oxidative stress. These actions are potential causal factors inducing PBDE-209 neurotoxicity. Researchers concerned with the interaction between discrete levels of PBDE-209 and hippocampal neurons have reported that rats exposed neonatally to PBDE-209 could differ in cell's apoptotic rate and viability, oxidative stress, global methylation levels and molecular signaling and intracellular second messenger. More specifically, PBDE-209 could decrease global levels of gene DNA methylation, especially in the 10 and 30 g/ml groups.

However global levels of gene DNA methylation were increased when the concentration of PBDE-209 was elevated [9]. This result may be attributed to DNMT adaptability. Decreased global gene DNA methylation caused by PBDE-209 might be a cause of carcinomas [138].

TNF α

Tumor necrosis factor alpha (TNF α) is a gene involved in inflammations and its methylation status gets affected by exposure to environmental PBDEs, even perinatally [140]. Maternal exposure to PBDE47 results in CpG site promoter methylation of this proinflammatory gene, according to the evidence provided by the Boston Birth Cohort (BBC). Measurement of PBDE levels in a number of paired samples in maternal blood and cord blood at birth has demonstrated alteration in *TNF α* promoter methylation [140]. As indicated, immune system's functions can also be affected by exposure to PBDE [141-143]. *TNF α* , a cytokine, originates from macrophages, fibroblasts, B and T cells and is involved in immune-related diseases [144-146] and cancer, as well [147]. PBDEs are a potential causal factor of ectopic *TNF α* gene expression in the progeny. *TNF α* promoter in girls is more susceptible to hypomethylation after maternal exposure to this endocrine disruptor. Thus, *TNF α* hypomethylated status is inversely correlated with cord blood *TNF α* protein quantities i.e., they increase. In total, there is evidence that the progeny's immunological reaction could be epigenetically reprogrammed through *in utero* PBDE exposure.

MECP2 (epigenetic factor methyl-CpG binding protein 2)

Autism is a neurodevelopmental disorder which could be caused by a combination of external factors and genetic susceptibilities. Rett syndrome (RTT) shares autistic traits, and the MECP2 factor plays a regulatory role in the epigenome of this X-linked autism spectrum disorder (ASD) [148]. A pattern of 'two hits' was suggested to explore the interplay between a single -BDE-47 exposure and a specific gene-MECP2. MECP2 transcription leads to a protein that recognizes DNA methylation and is recruited to regulate neuronal function and maturation [149-151]. More specifically, mutations in MECP2 cause RTT [152]. Daily perinatal

exposure of mutant *Mecp2*308/1 dams to BDE-47 caused DNA hypomethylation in the progeny brain accompanied by decreased gregariousness following a motive that was independent from genotype. In addition, the exposure adversely affected the survival of the offspring and the knowledge acquisition process of fully developed females. Nonetheless, MECP2 mutation in the offspring of perinatally exposed dams led to a reversion of learning abilities which were accompanied by higher levels of DNMT3a. These results demonstrate a complex epigenetic and behavioral interaction [148].

TCDD

Persistence

TCDD, a potent environmental toxicant, evokes adverse health effects in a pattern defined by the gender, the tissue, the life stage and the species. It also prompts modification in the transduction of estrogen signals. Adverse health effects include hepatotoxicity, teratogenicity, cancer, severe anorexia-like wasting. It could even lead to death [153-157]. Dioxin adverse health effects are induced by AHR [158]. TCDD has strictly non-commercial use, occurring as a contaminant in specific chlorophenoxy acid and chlorophenols herbicides [159]. Moreover, TCDD can originate from combustion incidences and, to a greater extent, it may be formed when specific metal catalysts, such as copper, are present [160,161]. Some of the largest TCDD production facilities include waste disposal burning, manufacture of metals, and natural fuels or wood combustion [162].

Dioxins, like other chlorinated forms, accumulate in food source sequences (bioaccumulation) [160]. TCDD and structurally related halogenated aromatic compounds are industrial chemicals and combustion byproducts that have been identified in fish, wildlife, humans, and throughout the environment [163]. Because of the long biological half-life and the low water solubility of dioxins, food chain is susceptible to water derived accumulation of high quantities of TCDD [164].

Hormonal effect

TCDD is degeneration resilient and lipophilic, and its properties make it able to accumulate in the adipose tissue, as well [11]. TCDD has both estrogen agonist and antagonist activity. Characteristically, in

females it exerts AHR-dependent antiestrogenic effects in their reproductive tract, such as restrained estrogen-induced elevation in uterine weight, gene expression reactions and DNA composition [10]. TCDD, also, promotes estrogen-like effects. More specifically, it increases the ER DNA-binding potential without the presence of estrogen in the uterus of the rodent being required [165]. Additionally, TCDD administration to MCF-7 exerts estrogen-like cell cycle phase conversion and impacts on mitogenic activity [10]. TCDD also prompts tumors which are estrogen-dependent [166] and enhances endometriosis in TCDD-charged women and model organisms [167-170].

Epigenetic effects

H19 and Igf2

TCDD-exposed preimplantation embryos were transferred to unexposed recipients (mice). On Embryonic Day 14, the aforementioned TCDD exposed fetuses gained less weight than the unexposed controls. The levels of expression of the imprinted genes *Igf2* (insulin-like growth factor 2 gene) and *H19* decreased after preimplantation embryos' exposure to TCDD. It is evidenced that in the imprint region *H19/Igf2*, the methylation was increased in TCDD exposed fetuses and embryos compared to the controls. Moreover, TCDD caused an elevation in methyltransferase activity. Thus, exposure to the environmental toxicant TCDD at the preimplantation stage affects imprinted genes altering their DNA methylation state, influences their expression level in early development, and the altered methylation status is maintained throughout the fetal stage [171].

AHR

TCDD possibly mediates in the development of endometriosis. This endocrine disruptor could participate in transcription activities at variable levels, even in the epigenetic one [172]. More specifically, it could act in an epigenetic fashion, modifying consequently the normal processes induced by AHR pathways. This could affect the reproductive machinery both by altering the homeostasis of the peritoneal microenvironment, and provoking progesterone resistance [172].

PR

It has also been reported that progesterone sensitivity can be debilitated by TCDD as it prompts

epigenetic alterations with the contribution of toxicant-exerted inflammatory processes [173]. The methylation level in PR gene of female mice uterine samples was analyzed. The results showed that PR was partially methylated in 60% of the F1 female extracted tissues (*in utero* exposure to TCDD). Similar tissues of controlled mice were largely unmethylated. F3 females had also methylated PR in 40% of these animals [173]. Thus, silencing PR with epigenetic mechanisms induced by TCDD exposure could be the potential causal factor in inheritable infertility phenotype as well as an associated risk factor of spontaneous preterm birth (sPTB) in mice [174]. There is an obvious correlation between hypermethylation reported in these specific mice and the infertility rates in F1 and F3 mice which had earlier been examined [174].

Sperm DNA methylation

Recent studies demonstrate that TCDD exposure leads to stable and heritable changes in sperm DNA methylation in male rats [175]. The methylation changes induced by TCDD are likely to be tissue specific, or limited to specific genes [176]. Hanlon et al. (2003) [177] also reported inhibited adipogenesis in 3T3-L1 cells with TCDD exposure, suggesting a mechanism of suppression of peroxisome proliferator-activated receptor-gamma1 (PPARc1) through an AHR dependent process, even though no changes in global methylation status were observed.

PCBs

Persistence

PCBs were initially synthesized in the 1930s to be used as lubricants in capacitors and adaptors and, also, as pesticides, hydraulic fluids or plasticizers [178,179]. PCB production has been forbidden since 1970 but they still are a crucial health risk factor for the public since they are still persistent and widely dispersed in the environment, as well as in the food chain [180,181]. The main sources of dispersion are degenerating structures and waste disposals, as well as the simultaneous PCB production through industrial activities such as paint pigments [182].

So far, 209 possible congeners of PCBs with different biological activities have been recorded. These congeners could be categorized into dioxin- and non-dioxin-like, DL and NDL respectively, depending on

their molecular structure. Both of these types are abundant in the environment. DL PCBs activate AHR by attaching to it, just like dioxins do, whereas the so called NDL PCBs elicit minor AHR activity [178]. Evidence indicates NDL PCBs dominance upon DL PCBs as an environmental burden and in human tissues [183,184]. There is evidence about the involvement of the AHR [178,185] as well as other receptors in supporting the role of PCBs as EDs and interfering with calcium homeostatic mechanisms [186,187]. Several adverse health effects in both human beings and animals, such as birth weight reduction, disruption of reproductive system development, immune dysfunction, and altered brain development, have been correlated with exposure to PCBs during intrauterine life [188-192].

Hormonal effect

PCBs are organic chlorine compounds, highly lipophilic and chemically stable. They undergo limited catabolism after absorption and accumulate in the liver and adipose tissues. In addition, PCBs and their metabolites are easily transferred to the fetus through the placenta [193,194]. Thus, PCB exposure in gestation could be considered as inheritable [135,195-197]. Thyroid effects may be congener- or metabolite-dependent [135]. PCBs can disturb the homeostatic control of the thyroid system through a number of levels, in a pattern that can be characterized as congener-dependent. Each PCB metabolite plays a distinct role [135]. There are studies suggesting that PCBs are inversely correlated to thyroid hormones amount. A few studies suggest a neutral relationship between thyroid hormones and increased plasma PCB with a non obvious interplay [198]. Other studies suggest that serum PCBs and thyroid hormone levels change in the same direction [199,200].

Epigenetic effects

Irreversible DNA methylation

PCBs lead to toxicity in fetals when exposed prenatally and predispose children to poor health. When fetal cells get exposed to PCBs during the period of pregnancy they become susceptible to cytotoxic effects as well as genotoxic ones. Cell lines were examined at specific time points during a period of time, in order for global methylation levels and other cellular processes to be evaluated in response to PCB administration [201].

For 120 days, sheep embryonic fibroblasts (SEF) as well as amniocytes (SA) were exposed to limited quantities of PCBs. Fetal cells got hypermethylated by PCBs. The hypermethylation, though, was irreversible even when blocking the administration of Aroclor 1254 (A1254 is a commercial mixture of PCBs) to these cells. Global genome methylation in SEF in response to PCB treatment remained high even after discontinuation of PCB use in the 60th day, for up to one month. This indicates that fetal cell exposure to PCBs prompts irreversible epigenetic changes that could follow and affect growth process until adulthood [3,28].

DNMTs

PCBs can modify epigenetic mechanisms [3,5]. Prenatal exposure to PCB compounds decreases DNMT expression and activity in the liver of the offspring [202].

Jarid1b

It has been reported that exposure to reconstituted PCB compounds during gestation prompts Jarid1b expression (a demethylase) as well as Sirtuin1 (SIRT1) (a deacetylase) [5]. Thus, a decrease in their target protein forms in progeny's liver is demonstrated. The animals exposed themselves exhibited a reduced AR gene expression [4].

Altered Global DNA Methylation

Developing brain DNA methylation potentially contributes in developmental PCB-mediated neurotoxicity. DNMT activity is decreased in mouse preimplantation blastocytes [203] and exposure to PCB 153, an NDL congener, leads to decreased global methylation of DNA in N2A cells [179]. PCB 153 is a potential epigenetic disruptive factor only when applied to mouse cells since DNA in response to this congener was unaffected on human neuroblastoma cells [176]. It is, therefore, suggested that DNA methylation status is differentially affected by NDLS and DLs. More specifically, according to a Swedish study [204], DL PCBs shift the balance toward DNA hypermethylation whereas, as observed in Korean and Inuit studies [205,206], NDL PCBs favor DNA hypomethylation.

PFOA

Persistence

PFOA is one of the principal PFCs that are widely used in industrial and everyday consumer products

including textile coatings, flame retardants, surfactants, food packaging items and lubricants [207]. Moreover, PFOA is derived from the degradation of different fluoropolymers and is not further degenerated from environmental and metabolic breakdown. The United States general population was found to have average serum PFOA concentrations approximately 4 ng/mL [208]. In occupationally exposed populations, concentrations may range from 428 to 12,000 ng/mL [209]. PFOA is a persistent pollutant, thus, it can gather in tissues via multiple exposure routes [30]. PFOA can be found in liver, milk and serum [210-212]. It is also likely to be detected in blood, primarily, and in the kidney and liver as well, according to studies on monkeys and rats. Liver is a significant target organ [213-215]. As PFOA is widely spread and chemically stable several concerns have been raised with regard to the recorded PFOA accumulation recorded in aquatic and terrestrial biota, human serum as well as its environmental persistence [216-218].

Hormonal effect

Estrogenic signaling probably induces PFOA mediated tumor development in trouts in a peroxisome proliferation independent manner [208]. PFOA can cause hepatocarcinogenesis postinitiation to the rainbow trout model, even though this model is peroxisome proliferation insensitive. The molecular profiling of trout liver showed estrogenic gene marks which exhibited an important relation with E2. This mechanism is a distinct one for PFOA mediated cancer development. Thus, tumorigenesis is not attributed to the PFOA's role as a PPAR α agonist or as PP [207].

Epigenetic effects

Cord serum global DNA hypomethylation

There has been one epidemiological study evaluating associations between PFAAs and the methylation of DNA. Environmental exposures lead to aberrant methylation motives in circulating fetal DNA. Prenatal exposure to perfluoroalkyl chemicals, such as PFOA, is likely to induce global DNA hypomethylation in cord serum [219]. A study on newborns reported a negative association between PFOA concentrations in cord blood and total methylated cytosine in DNA isolated from cord serum while no such association was observed with PFOS.

GSTP

PFOA prompts GSTP altered methylation. It is known that GSTP is hypomethylated in the disease-free tissue. On the other hand, it is transcriptionally silenced and hypermethylated in human liver and prostate cancer cells as well as in leukemia cells [220-223]. Hypermethylation is also common in myelodysplastic syndromes [224,225]. The necessary genes for xenobiotic detoxification in L02 cells have a lack of transcription even though they are derived from a normal cell lineage, similar to immortalized human hepatocyte IHH1 cells [30,226]. In these L02 cells, however, an epigenetic level detoxification response was shown where GSTP promoter region methylation could be elevated from PFOA, whereas global DNA genome methylation remained unchanged [30]. The reports in gene-specific as well as global methylation in the specific study are contrasting [227-229].

GSTP promoter contains two SP1 (specificity protein 1) TF binding recognition sites that are very important cis-elements as they are required for the basal activity of the gene [230]. In the aforementioned L02 model, GSTP promoter CpGs were completely methylated with the exception of the seriate sites region from -152 until -124. Subsequent PFOA treatment prompts CpGs to be further methylated. SP1 binding can be perturbed by cytosine methylation at the recognition sites [220,231]. This indicates that SP1 binding may have a protectful role for CpG sites preventing methylation processes during development [220,232]. PFOA modified the status of methylation in these sites regardless of the protection provided to SP1.

DNMT3A is the potential basal contributor to GSTP excessive hypermethylation since DNMT3B and DNMT1 mRNA transcript levels have been found to be unchanged [233,234]. Thus, it is suggested that PFOA may affect GSTP SP1 sites and through DNMT3A expression alter DNA methylation. However, further investigation should follow to determine this detoxification response pathway [30].

As

Persistence

As is tasteless, odorless, colorless and even at high concentrations, human exposure to it is not easily avoided [235]. It is a widely distributed metalloid,

occurring in rock, soil, water and air. As contamination of the environment from both natural and anthropogenic sources is a major environmental concern due to its persistence and carcinogenic effects on living organisms. Exposure of the general population occurs mainly through oral ingestion via water and food, while occupational exposure to As occurs in workers in the paint, ceramics, pesticide, insecticide, and wood preservatives industry [236]. People can be exposed to it through ingestion of As while dermal As exposure is through contaminated soil. Another route of exposure is the inhalation of suspended arsenical dusts in the air [237,238]. It can be consumed through vegetables and crops which have taken up the As from contaminated soil and irrigation water. As is all over the environment. Once it is present in the environment, it can easily spread from soil to water and vice versa and then to plants, from air to soil through dust and atmospheric deposition and from air to surface and via precipitation to groundwater [239].

The presence of As in surface soils is either natural or artificial. Anthropogenic activities e.g. mining and metallurgical activities affect the toxic heavy metal content of agricultural soils. Artificial presence refers to the introduction of As by herbicides and long term watering with As burdened irrigation waters. Natural presence refers to As already present within the soils [240].

Hormonal effect

As activates or inhibits responses, maintaining, probably, the same action mechanism. In low doses As effect is stimulatory. In rat hepatoma cells (EDR3) 0.05–1 μM (6–120 ppb) of As, with the mediation of glycocorticoid receptor (GR), was found to induce gene activation of both the endogenous tyrosine aminotransferase (TAT) and other reporter genes [241,242]. At higher concentrations (1–3 μM), As effects became inhibitory for GR-mediated transcription. In EDR3 hepatoma cells, when As concentrations ranged from 0.045 to 2.7 μM , a similar biphasic response was observed for the mineralocorticoid receptor (MR), AR, and PR [243].

In the same way, in the NT2 human embryonic carcinoma cells and in the GH3 rat pituitary tumor cells a biphasic response was revealed similar to the one

observed for steroid receptors, on genomic-mediated induction by the retinoic acid receptor RAR and the TR [244].

Breast cancer MCF-7 cell line was used to explore As impact on ER [242]. As levels (0.25–3 μM), which are normally non-cytotoxic for cells, led to an important inhibition of genomic activation mediated by estradiol, whereas low levels of exposure exhibited no induction effect [244]. Similar results were also obtained in an in vivo study with administration of non-cytotoxic concentrations (1–50 $\mu\text{M}/\text{kg}$) of NaAsO₂ to chicken embryos, where Davey et al. showed a significant inhibition of ER-dependent gene transcription of the 17 β -estradiol (E2)-inducible vitellogenin II gene.

Concerning to estrogenic effect and inhibition of spermatogenesis, As inhibits estradiol binding, possibly by activating ER α through the construction of a high-affinity cluster with the receptor's hormone binding site. It was shown that in utero As exposure leads to marked alterations in gene expression in fetal liver involving a complex interplay between steroid metabolism and estrogen signaling pathways [245]. Overexpression of these estrogen-linked genes, such as X-inactive specific transcript (Xist), Anterior gradient protein 2 homolog (Agr2), Tff1, C-reactive protein (CRP)-ductin, ghrelin and obestatin prepropeptide (Ghrl), keratin 1-19 (Krt1-19), and cytochrome P450 (Cyp2a4,) are indicative of endocrine disruption effects of inorganic As at an early life stage [242].

After reporting spermatogenic degeneration in animals treated with estradiol, Jana et al. (2006) [246] suggested that an estrogen-type mechanism of action may be responsible for As-related reproductive toxicity. The results were repeated in a study conducted on human cancer cells of breast (MCF-7) that were exposed to 0.1, 1, 5, or 10 μM of sodium arsenite [247]. Interestingly enough, the arsenite-mediated effects included decreased expression of ER α and increased PR expression, like estradiol does. In addition, inhibition of arsenite estrogen-like activity was observed when an antiestrogen was present, suggesting that ER α is the target receptor. A marked effect was arsenite's ability to activate ER α even at low concentrations (1 nM).

In a study conducted by Jana et al., male Sprague Dawley rats were administered 5 mg/kg sodium

arsenite in drinking water for 6 d/wk, for 4 wk. The findings showed an alteration in the reproductive activity of the treated animals and, more specifically, reduction in testicular mass and decrease in plasma concentrations of testosterone and gonadotropin [246]. In vivo studies investigating the As effect on the male reproductive system reported sperm toxicity, inhibition of testicular androgenesis, and reduction in testicular and accessory sex organ weights. Sarkar et al. (2003) [248] administered sodium arsenite to male Wistar rats at variable doses and in the 5- and 6-mg/kg groups was evidenced important decreases in the internal reproductive organs' weights, in the epididymal spermatozoa, and in concentrations of Follicle-stimulating hormone (FSH), Luteinizing hormone-LH, and testosterone. A similar study has reported a significant reduction in testicular weight, sperm count and motility, and testicular enzymatic activities [249]. The aforementioned study of Jana et al. gave similar results [246].

Epigenetic effects

Phospholipase A2 (PLA2G2C)

PLA2G2C expression leads to a phospholipase, an enzyme participating in phospholipids' hydrolysis and their conversion into lysophospholipids and fatty acids [31]. These lipid mediators' roles in inflammation, cell growth, and cell death, [250] make them potentially important for cancer progression [31,251]. As is an established skin carcinogen and overexpression of Cyclooxygenase-2 (COX2) is associated with As exposure [252-254]. Interestingly enough, it has been shown that skin carcinogens induce A2 phospholipases (e.g., light ultraviolet B, phorbol ester) which eventually exert synthesis of prostaglandin via COX2 resulting in skin carcinogenesis [255,256].

The methylation levels seemed to increase at cg04605617 (chr1: 20,501,558) corresponding to higher As exposure. This locus of PLA2G2C is in its first exon. This locus have been mildly associated with elevated PLA2G2C gene expression. PLA2G2C locus methylation was the determining locus that was correlated with both blood and urinary As concentrations compared to other genes examined [31].

SQSTM1

SQSTM1 is involved in a variety of diseases such as cancer, neurodegenerative diseases, insulin resistance and obesity [257]. In vitro evidence indicates that As induces the factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway prompting, consequently, a skin carcinogenesis mechanism [258,259]. Higher As administration has been correlated with reduced methylation at the locus cg01225779 in the SQSTM1 5' untranslated region (UTR) [31]. This is a locus of the SQSTM1 gene that has been involved in many diseases such as cancer, obesity, insulin resistance, and neurodegenerative diseases [257]. SQSTM1 is translated to a protein that is ubiquitin binding and modulates the activity of kappa-B nuclear factor (NF-κB) signaling pathway [257].

SLC4A4

SLC4A4 expression leads to a sodium bicarbonate cotransporter that participates in the modulation of bicarbonate absorption and secretion and intracellular pH as well. SLC4A4 is, also, associated with decreased body weight/size and abnormal ion homeostasis in mice. Gene mutations of SLC4A4 are related to hypertension [260], a health outcome that has been associated with exposure to As [261]. Higher As was associated with reduced levels of methylation at locus cg06121226. This locus is inside SLC4A4 body and was determinedly correlated with elevated SLC4A4 gene expression [31].

IGH

Serum immunoglobulins appear to be increased under the presence of As [262], which may induce skin carcinogenesis [263]. The heavy locus of immunoglobulin contains diversity (D), variable (V), constant (C), joining (J) immunoglobulin segments and lymphoma has been correlated with translocations in the specific region [264]. Increased methylation at cg13651690 locus was observed in response to higher As exposure. This locus is inside Immunoglobulin heavy locus IGH body [31]. Additionally, in response to water contamination with As, an important replication of the locus was demonstrated.

Polycyclic aromatic hydrocarbons (PAHs)

Persistence

PAH are pervasive in our environment and are widely distributed all over atmosphere [265]. PAHs is a

group of compounds containing a high number of chemicals ubiquitously distributed. The physicochemical properties of PAHs make them highly mobile in the environment, allowing them to distribute across air, soil, and water bodies where their presence is ubiquitous [266,267]. PAHs are genotoxicants and carcinogens and, therefore, pose a serious threat to the health and well-being of humans [268]. Interestingly enough, PAHs have traditionally been examined for their genotoxic damage potential while their ability to cause epigenetic transformations has been widely ignored [269]. PAHs are released into the environment from both natural and anthropogenic sources [270]. Combustion of organic materials causes the widespread occurrence of PAHs. Incomplete burning of fuels, garbage, or other organic substances such as tobacco and plant material are some of PAHs sources [271]. Likewise, volcanic eruptions and conflagrations can equally contribute to environmental PAH burden [271]. A risk evaluation of the group of children is of high priority since they constitute a susceptible population, in part because they tend to have higher PAH exposure due to behavioral patterns such as hand-to-mouth behavior, time spent outside in contact with soil and dust, and higher inhalation rate per bodyweight unit [272].

Regarding their chemical structure, PAHs consist of 2 to 7 fused aromatic rings [273,274]. They are made of hydrogen and carbon formed into up to seven fused or condensed aromatic ring forms [275]. PAHs' molecular weight is positively correlated with their carcinogenic potential and negatively correlated with their acute toxicity potency. The most potent PAH carcinogens have been identified to include benzo[a]anthracene, benzo[a]pyrene (B[a]P), and dibenz[ah]anthracene [274,276,277]. PAHs are highly lipophilic and, therefore, miscible in organic solvents.

Hormonal effect

PAHs are considered as EDs because they mimick endogenous hormones, interfering consequently with the organisms' homeostasis. Schraplau et al., 2015 [277] isolated hepatocytes from male Wistar rats exposed to B[a]P for 72 h and examined them for thyroid hormone activity and related RNA expression profiles. It was demonstrated that B[a]P reduces the metabolic rate by breaking down thyroid hormone. It is

indicated that B[a]P exposure inhibits steroidogenesis [278].

Moreover, PAHs are either estrogenic or anti-estrogenic depending on the types and locations of the samples. However, the mechanisms responsible for their activities still remain unclear. The analyses of specific PAHs lead to several possibilities such as a direct interaction between PAHs and ERs (estrogenic), AHR-mediated suppression of estrogenic activity (anti-estrogenic), and modulation of estrogen or other signaling pathways (estrogenic or anti-estrogenic) [279].

Epigenetic effects

ACSL3

PAH exposure transplacentally can possibly cause methylation in ACSL3 5'CGI of umbilical cord's blood cell [32]. ACSL3 encodes enzymes fundamental in fatty acid metabolic activities [280]. There is a lack of biomarkers enhancing the theory that asthma induction can be affected by transplacental exposure to PAHs. However, there is some preliminary evidence supporting this relationship [281]. Prenatal monitoring of exposure to airborne PAH was completed for each mother participating in the study in person. The gene ACSL3 showed the highest concordance between the methylation level and the level of its expression. Consequently, ACSL3 was further examined and a significant positive correlation between the methylation status and maternal exposure to airborne PAH was shown [32].

IFN γ

IFN γ is a well known asthma-related gene. The gene methylation status is affected in umbilical cord blood cell in response to maternal PAH exposures [33]. Interestingly enough, in vitro studies on BaP impact, a PAH prototype, on lung cancer and Jurkat T lines, showed induction of IFN γ promoter hypermethylation [282] and decreased IFN γ expression. Cord blood cells' exposure to PAH also prompted the methylation of IFN γ promoter in the offspring of exposed women. An alteration in the methylation status in specific CpG sites of the IFN γ promoter sequence is a potential indicator of exposures to environmental pollutants [33].

Foxp3

PAH exposure results in altered methylation of

the Foxp3 promoter region [283] which was later associated with cellular functional changes, and an increase in total plasma immunoglobulin E (IgE) levels and impaired Treg function [284]. Asthma is associated with impaired function of regulatory T cells (Tregs). These cells maintain tolerance in healthy individuals by exerting suppressive effects on a variety of immune cells involved in allergic disease progression, including activated T cells, eosinophils, basophils, antigen-presenting cells, and mast cells [285].

PPAR γ peroxisome proliferator-activated receptor (PPAR γ)

Perinatal exposure to PAHs can lead to persistent alterations in fat mass, body weight and in the size of adipose cells of F1 and F2 generations [286]. The expression of PPAR γ gene and other adipogenic ones was inversely correlated with the methylation levels of the genes [287]. There are increasing reports of PAH exposure both direct and indirect through airborne particles that support a relationship between the pollutant and modified DNA methylation [288,289].

DDT

Persistence

Anopheles mosquitoes are a public health hazard in tropical and subtropical areas since they can cause malaria [290]. Thus, their eradication has been a main goal in these areas. Initially, DDT was used for insect elimination [291]. However, DDT's hazardous nature was demonstrated by its significant adverse effects in living organisms [292,293]. Interestingly, DDT compound levels throughout the environment and DDT accumulation in living organisms follow a causal relationship that is, also, statistically significant [294].

DDT is an issue still relevant for many reasons. First of all, DDT was widely used in the past affecting persistently women's health by increasing the risk of breast cancer, even in contemporary society as the generation of women born during this period of extreme DDT use is alive [295]. It is worth noting that DDT still remains a controversial issue since it is still in use for malaria control in both Asia and Africa in accordance with WHO recommendations [296,297]. Moreover, DDT is persistent in the natural environment so people worldwide continue to be exposed to it, as indicated by clinically relevant levels in animal tissues and soil [298].

Africa, Mexico and China [299,300] are the most susceptible regions since fundamental principles like disposal, storage, and safe use are not always applied, thus [301], prompting human exposure and environmental contamination. Furthermore, we should bear in mind that DDT detrimental health effects are here to stay since climate change supports the expansion of malaria vectors [302].

Hormonal effect

The increase in reports of abnormalities in male sex development in wildlife and humans coincided with the introduction of "estrogenic" chemicals, such as DDT, into the environment. This, probably, reflects the AR-mediated antiandrogenic function of DDT metabolite dichlorodiphenyldichloroethylene (p,p'-DDE) [302,303].

p,p'-DDE-induced sex development abnormalities in males may be AR-mediated. Although ER is considered to induce these phenotypic alterations, AR-mediated events are also consistent with inhibition. p,p'-DDE has a slight ability to attach to the ER, nonetheless it has been found to restrain androgen attachment to the AR, androgen induced transcription and androgen action in growth stages of male rats [303].

The male reproductive system is susceptible to the antagonistic effects of DDT metabolite as p,p'-DDE prompts inhibition of AR-androgen binding and subsequent inhibition of transcriptional activity. AR transcriptional activity in cell culture requires a lower concentration of p,p'-DDE compared to the levels that accumulate in the environment, and more specifically, in areas where DDT remains in use or is present in contaminated ecosystems. In the mid-1960s, period during which DDT was widely used, p,p'-DDE levels were found in tissues from stillborn infants suggesting a way of transplacental route. Indeed, in vitro rat model confirmed the risk of perinatal exposure of infants [304,305].

Epigenetic effects

DNA hypomethylation in the young hypothalamus

Along a period of a month, DDT was administered by gavage to male young rats at doses of 0, 0.006, 0.06, 0.6, 6, and 60 mg/kg/day. According to Shutoh Y et al., a low dose of DDT (0.06 mg/kg/day) is considered to be hormetic. It can induce transcriptional

down-regulation and DNA hypomethylation in the young hypothalamus [34].

DDT transgenerational actions

Epigenetic mediated transgenerational inheritance caused by environmental factors, potentially contributes to obesity induction as well as other associated diseases [306]. As shown in an in vivo study, exposure of rats to DDT can lead to obesity and altered DNA methylation up to F3 generation. More specifically, sperm DNA methylation was modified in *Tubb3*, *Carm1m* and *Slc4a4* in a statistically significant relation to the control lineage. The epigenetic transmission was derived from both gender germlines [306].

Inverse DNA methylation

DDT was inversely associated with global methylation levels in a study conducted on humans [206]. Inverse correlations between percent 5-methylcytosine and many of the persistent organic pollutant (POP) concentrations were measured and linear regressions, adjusting for cigarette smoking and age, showed statistically significant inverse linear relationships mainly for the Alu assay for p,p'-DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane), p,p'-DDE [1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene;], and other POPs and PCBs [206].

Vz

Persistence

Fungicides have a variety of applications such as on landscapes, golf courses, industrial activities, lawn turf, and woody ornamentals; thus, they can be readily spread to water supplies [307]. Vz (RS)-3-(3,5-Dichlorophenyl)-5-methyl-5-vinylloxazolidine-2,4-dione is a systemic dicarboximide fungicide effective in the control of diseases by inhibiting spore germination caused by *Botrytis cinerea*, *Sclerotinia sclerotiorum*, and *Monilinia* spp. Dicarboximide fungicides have been widely used in Europe to protect grapes, fruits, vegetables, hops, ornamental plants, and turf from fungi damage [308]. In the United States, Vz is registered for use on several fruits and vegetables, ornamental plants, and turfgrass. Vz is not persistent in the field but is rather degraded to several metabolites in the soil and/or within the plants themselves [308]. After application, DDTs are readily accessible to living organisms and untreated foods since their distribution is induced by

volatilization and air circulation [309]. Tap water cannot eliminate human exposure to DDT since it cannot remove it from produces [158].

Hormonal effect

Vz is an environmental compound acting as an anti-androgen. Anti-androgens exhibit a mechanism which is determined by interaction with the hormone receptor [158,310]. Two Vz metabolites can be totally attached to monkeys, rats and humans, as well as AR [311]. The effects of antiandrogens to sexual development are serious and can even affect male reproductive system by inducing hypospadias, a situation where the urinary opening is not at the appropriate location of the penis [312-316].

Vz and its active metabolites, M1 and M2, principally bind competitively to AR, thereby antagonizing the binding of natural androgens to the receptor [310,317,318]. Reduced anogenital distance, nipple retention, hypospadias, cryptorchidism, decreased sex accessory gland growth, induction of prostate inflammation and reduced sperm production at adulthood are abnormalities of androgen-regulated sexual differentiation in male offspring caused by administration of Vz to pregnant rats [318-320].

Epigenetic effects

Transgenerational Actions and DNA methylation on imprinted genes

Transgenerational inheritance of acquired traits can be derived either from a chromosomal or from an epigenetic modification. A brief prenatal exposure to vinclozolin or methoxychlor (which is an estrogenic chemical) during the sex determination stage has been found to cause adult decreased spermatogenic capacity and elevated infertility until up to the fourth generation. These effects were correlated with modified DNA methylation in germ line [308].

The transgenerational actions of Vz appear to involve an epigenetic (i.e. DNA methylation) reprogramming of the male germ line [308]. A study in an outbred strain of mice also showed that gestational exposure to parental oral Vz produces a reduction in sperm count and sperm head abnormalities [321]. Furthermore, it has been suggested that the detrimental transgenerational Vz effects on the reproductive system of males are induced by imprinting defects [321]. More

specifically, in vivo studies examined the methylation status of paternally and maternally imprinted genes after prenatal exposure to Vz. The results demonstrated altered DNA imprinting pattern in two paternal imprinted genes (Gtl2 and H19) and three maternal ones (Peg3, Peg1 and Snrpn) in the offsprings [321].

Conclusion

This review has made an attempt to describe emerging pollutants in the environment, EDCs, the major endocrine effects of these compounds and their relevance to epigenetics. People often ignore EDs and, also, the effects of EDs are not readily discerned. The report of EDs and their potential epigenetic actions has not been completed yet. There is an increasing production of chemicals that probably mediate epigenetic mechanisms to disrupt endocrine system's function. As far as we know, even though epigenetic mechanisms induced by the EDs may differ, DNA methylation is the most common, due to its heritable nature, stability, and ease of measurement. EDs might disturb endocrine mechanisms working in an epigenetic fashion and by mediating nuclear receptors. Further studies are required to explore the procedure by which EDs are capable of altering the epigenome.

List of abbreviations

A1254, Aroclor 1254; ACSL, acyl-CoA synthetase long-chain; ACSL3, acyl-CoA synthetase long-chain family member 3; ACSL3, acyl -CoA synthetase long -chain family member 3; Agr2, Anterior gradient protein 2; AHR, aryl hydrocarbon receptor; AIT, Dorsal prostate tumor derived cell line; AR, androgen receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; As, Arsenic; Avy, Agouti viable yellow; Avy, Viable yellow Agouti; B[a]P, benzo[a]pyrene; BBC, Boston Birth Cohort; BDE-47, 2,2'- ,4,4' Tetrabromodiphenyl ether; BfR, Bundesamt für Risikobewertung; BPA, Bisphenol A; BPs, Bisphenols; C, Constant; cAMP, Cyclic adenosine monophosphate; COX, Cyclooxygenase 2 ; COX2, cyclooxygenase -2; CRP , C -reactive protein; Cyp2a4, cytochrome P450; D, diversity; DDE, Dichlorodiphenyldichloroethylene; DDT, Dichlorodiphenyltrichloroethane; DES, diethylstilbestrol; DL, dioxin -like; DL, dioxine -like; DMDs, differentially methylated domains; DNMT, DNA methyltransferase; E2, endogenous estrogen; ED, Endocrine disruptor; EDC, Endocrine disrupting

chemical; EDCs, Endocrine disrupting chemicals; EPA, US Environmental Protection Agency; ER, estrogen receptor; EU, European Union; FDA, Food and Drug Administration; FSH, Follicle -stimulating hormone; Ghr, ghrelin and obestatin prepropeptide; GR, glucocorticoid receptor; GSTP, Glutathione S -transferase Pi; HAT, histone acetyltransferase; hMLH1, human mutL homolog 1; hTERT, human telomerase reverse transcriptase; IAP, intracisternal A particle; IFN γ , interferon gamma; IgE, immunoglobulin E; IGF, insulin like growth factor 2; Krt1 -19, keratin 1 -19; LH, Luteinizing hormone; MBD2, Methyl -CpG P168 Binding Domain Protein 2; MCF7, Michigan Cancer Foundation-7 human breast cancer cells; MCF-7, Michigan Cancer Foundation -7; MECP2, methyl -CpG binding protein 2; MeDIP, methylated DNA immunoprecipitation ; MGMT, O6 methylguanine methyltransferase; miRNAs, microRNAs; MR, mineralocorticoid receptor; N2a, Neuro2a cells; NBE1, normal prostate epithelial; ND, non -dioxin like; NGS, next-generation sequencing; NF- κ B, nuclear factor kappa -b; NF- κ B, nuclear factor kappa light chain enhancer of B cells; NR, nuclear hormone receptor; NSBP1, nucleosomal binding protein 1; PAHs, Polycyclic aromatic hydrocarbons; PBDEs, Polybrominated diphenyl ethers; PC, polycarbonates; Pca, Prostate Cancer; PCBs, Polychlorinated biphenyls; PDE4D4, Phosphodiesterase type 4 variant; Peg3, paternally expressed 3; PFCs, perfluorinated compounds; PFOA, Perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PLA2G2C, Phospholipase A2; POPs, Persistent organic pollutants ; PPAR γ 1, peroxisome proliferator -activated receptor -gamma 1; PR, progesterone receptor; RAR β , Retinoic Acid receptor beta; RTT, Rett syndrome; SA, Sheep Amniocytes; SEF, Sheep embryonic fibroblasts; SEF, Sheep Embryonic fibroblast; SFRP1, Secreted frizzled -related protein 1; SIRT1, Sirtuin 1; Snrpn, small nuclear ribonucleoprotein polypeptide N ; SP1, specificity protein 1; SPI, Soy protein isolates; sPTB, spontaneous preterm birth; TAT, tyrosine aminotransferase; TCDD, 2,3,7,8 -Tetrachlorodibenzo -p -dioxin; TCDD, 2, 2 7, 8 tetrachlorodibenzo -p -dioxin; TFs, transcription factors; TFs , transcription factors; Th2, T helper cell type 2; TNF α , tumor necrosis factor alpha; TR, thyroid hormone receptor; Tregs, regulatory T cells; Tubb3 , tubulin beta 3; UCWBC, umbilical cord white blood cell; UK-BfR, United Kingdom Bundesamt für Risikobewertung; UTR,

untranslated region; V, variable; VZ, vinclozolin; Xist, X - inactive specific transcript.

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