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Bisphenol-A and other Plastics: Review of Endocrine Disrupting Effects on Prostate Cancer

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Abstract: *Bisphenol-A (BPA) is widely spread among the endocrine-disrupting chemicals (EDCs). Different hormone derivates or various organochlorinated pesticides are industrial human-made "plastics." EDCs are ubiquitary used in the modern world, and their impact on human health has been intensively studied in the last decades. BPA is used as a representative model for endocrine disruption mechanisms; it represents a critical element of producing polycarbonate plastics and epoxy resins, necessary for the manufacture of beverage or food containers, various personal-care products or dental industry products. Environmental exposure to BPA or other EDCs has resulted in functional or morphological drastically alterations of the genital tract or mammary gland that lead to earlier onset of different diseases, reduce fertility, or inducing prostate cancer. All the above have been observed via multiple in vitro analyses on human cells or in vitro analyses on animal models, especially rats. BPA causes prostate cancer through a sum o mechanisms. It increases the activation of various signaling pathways (Erk or Akt kinase), steroidal receptors recruiting chromatin, derived activity of different histone-modifying enzymes, transcription of various androgen receptor mutants detected in prostate cancer or acting via a pro-inflammatory mechanism that leads to prostate cancer progression once installed. Other EDCs such as different dioxins, cadmium, or inorganic arsenic are also incriminating in the neoplastic transformation of the prostate. This review aims to evaluate the current knowledge on this topic. Most of the authors agree on the carcinogenetic effects of these compounds. Extensive in vivo research on humans is imperative for a better and more accurate understanding of "plastics" impact.*

Keywords*: Bisphenol-A, BPA, polycarbonate plastics, EDCs, dioxins, prostate cancer*

1. Introduction

Plastics represent a crucial element in modern life routine, technology, industry, agriculture, and medicine, including public health. Because of their resistance to physical, chemical, and biological degradation, our society depends heavily on plastic, especially in the health care sector. The versatility of this material serves as an essential characteristic of this chemical compound, and combined with its reduced manufacture cost, they implemented its mass production as the main constituent in disposable single-use medical products that are hygienic and functional. Our modern society relies massively on plastic; thus, its value for the community has been profoundly studied by various authors [1]. Due to the widespread usage of plastics and particular to the various additive indispensable in the manufacturing process, plastics are considered an environmental pollution risk and a potential human health threat. As this material is about to expose, some compounds are comprehensively accepted as a health risk, while others are subjects of intense controversy, further studies are required to conclude.

Beginning with Leo Baekeland's bakelite patent in 1906, "the material of a thousand uses," progressively resided in everything that was put on the market, from couches to phones, and jewelry to home appliances. Starting from 1950, when approximately 2 million tonnes of plastics were produced

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per year, the latest statistics from 2015 admitted an annual production and consumption of nearly 380 million tones (Figure 1). However, the historical overall plastic production exceeds 7.8 billion tonnes of plastic (Figure 2), representing roughly more than 1 tonne of plastic per person on the current world population [2].

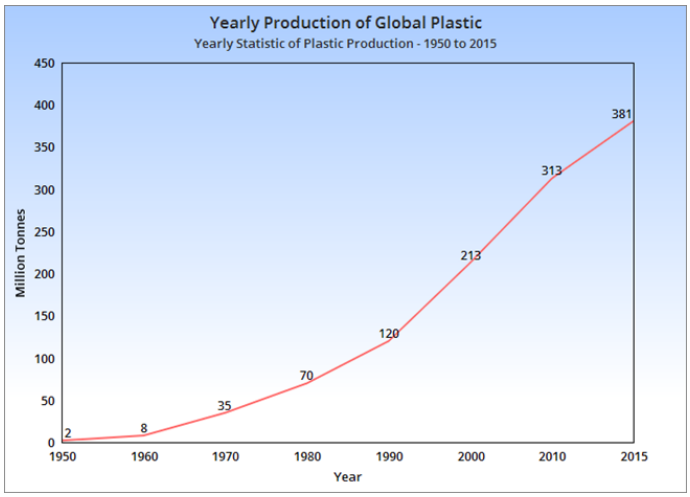

Figure 1. Yearly plastic production from 1950 to 2015 [2]

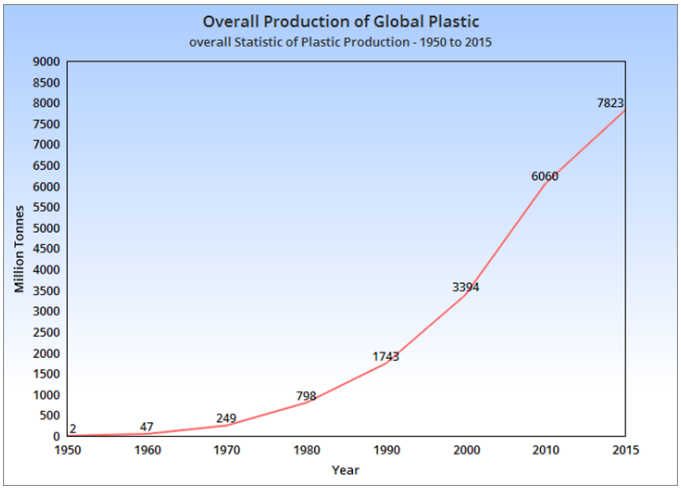

Figure 2. Overall plastic production from 1950 to 2015 [2]

Endocrine-disrupting chemicals (EDCs) are both natural or synthetic human-made “plastics”, ubiquitary spread in the environment, that have the capability inside the body to determine alterations of the known regulatory endocrine systems through multiple mechanisms, generally by blocking or mimicking endogenous hormones [3]. Although most mechanisms of action of these “potentially harmful” [4] compounds are not truly understood, the biological significance of these EDC exposures is accepted to be significant. Some of the main functions of synthetic EDCs are as plasticizers and pesticides, as follows: Bisphenol-A (BPA) - plasticizer (compound used in the production of plastic components in order to keep them pliable), Diethylstilbestrol (DES) - pharmaceutical (a chemical used in medical treatments or administered for medical purposes), 4-n-Nonylphenol and 4-tert-Octylphenol - surfactants (product capable of reducing surface tensions of a liquid; a wetting agent), Propanil - contact herbicide (a chemical used to destroy plants), Tributyltin (TBT) - biocide (represents a toxic compound for micro-organisms) and Tetrabromobisphenol-A - flame retardant (chemicals added to materials in order to make them resistant to catching flame) [5]. Even if it is demonstrated that adults exposed to these substances have essential consequences, exposure in fetal or early life occurs in a more severe

outcome that persists through life [6].

The ways these substances enter the body vary depending on the nature and usage of each EDCs. Some of them are contained in personal hygiene products like deodorants or from food or other beverage packages. Other pollute streams in the nearby of manufacturing plants, leaking into drinking water and sewages. The phytoestrogens represent the most important class of natural estrogenic endocrine-disrupting chemicals [7]. Different fruits, soy-rich foods, or selected nuts contain high levels of isoflavones (e.g. daidzein or genistein), and also, these compounds are increasingly consumed as supra-dietary supplements [8]. Other phytoestrogens are represented by resveratrol (contained in peanuts and red grapes), or enterodiol and lignans enterolactone, which are formed in the gut after the fermentation of plant-based precursor [9]. EDCs exert their effects through various mechanisms of action. These substances are characterized by the ability to bind different hormone receptors and nuclear receptors associated with varying sex hormones and other compounds of the endocrine system. Considering these capabilities, they can act as agonists or antagonists, altering the response of genetic elements, blocking real hormones to bind its receptors, or even mimics the action of natural endogenous hormone and over-activate self-receptors [10,11].

Various chronic diseases have been correlated with rising consumption of different plastic products, and especially the link between BPA and other hormone-related cancer have been intensively described [12]. The central characteristics of these diseases are the long-term duration and lengthy progression, representing a significant cause of mortality – approximately 60% of all deaths. Correlations between various human disorders and the consumption of plastic products are described in **Table 1**. However, further research is needed to assess all mechanisms of action against multiple health systems, considering the limited data on this matter.

Table 1. Epidemiological studies of the connection between BPA and other plastic products and various health disturbances [12]

Disease	Action	Year of evidence
Cancer	Risk of endometrial hyperplasia, endometrial, prostate, and breast malignancy	2004 [13] 2009 [14]
Diabetes type 2	Disorder of glucose metabolism	2011 [15,16]
Cardiovascular diseases	Increasing prevalence of severe coronary artery stenoses	2008 [17]
Autoimmune disease	Disorder of healthy immune system functions	2011 [18]
Respiratory diseases	Increasing the rate of asthma in the pediatric population	2012 [19]
Obesity	Changes in the differentiation of adipocytes leading to obesity	2011 [20] 2013 [21]
Reproductive disorders	Risk of sexual dysfunctions in males and females	2010 [22] 2004 [23]
Chronic kidney disease	Disorder of the renal function contributing more rapidly to dialyzes	2013 [24]
Executive disorders	Impairment in locomotor development in the pediatric population	2011 [25]

There are plenty of varieties of EDCs available worldwide today, and their alteration to biota represents an essential area of interest for researchers. The xenoestrogen Bisphenol-A (BPA), is the EDCs' family most thoroughly studied compound. BPA is an organic synthetic chemical first developed by the Russian chemist Aleksandr P. Dianin back in 1891 as a synthetic estrogen. The product was promising to have the same effect as estrone in stimulating the female reproductive system in laboratory experiments in the 1930s and later representing an essential production compound of polycarbonate

plastic and epoxy resins [26]. BPA is ubiquitary spread in industry and daily use products such as plastic water bottles, baby bottles, reusable food containers, papers, cardboards, polyvinyl chloride stretch films, and epoxy resins coating inside food cans. Considering that BPA can be leaked in human habitat, contaminating water and food, this compound has come under scrutiny regarding a potential environmental pollutant. The concern is justified by the finding of large amounts (higher than 1mg/kg) in food samples, like fruits and vegetables, potentially as a result of water irrigation devices, which are also plastic-based. Also, exposure to BPA is achievable through inhalation, dietary intake, oral or dermal contact [27]. Bisphenol-A has been detected in the urine of more than 90% of the US population [28].

Exposure to this compound is demonstrated starting from intrauterine life. The human fetus is exposed to it through maternal transmission and also in the neonatal period by ingesting maternal milk, infant formulas, or tinned food. Experiments on rats determined that individuals exposed prenatally to relatively low doses of this chemical manifest increased incidence of benign lesions such as benign prostatic hyperplasia and neoplastic forms – prostate cancer [29].

2. Bisphenol-A effects on human health

2.1. BPA: Androgen and Estrogen Receptor Pathway Disruptor

Disruption of the endocrine system by the action of various EDCs exposure has been linked to a higher incidence of different cancers [30,31]. This class of potent chemical compounds is associated with carcinomas in both male and female reproductive systems [32]. Various studies have linked exposure to different EDCs, especially BPA, to the formation of breast or prostate cancer, considering their action on either the androgenic or estrogenic pathway [33]. In vivo and in vitro, experimental models have shown that significant exposure to BPA could be connected to prostate carcinogenesis, potentially disrupting cancer cell proliferation [34].

In rats treated with BPA, prostate cancer tissues had differentially methylated regions connected to cancer pathways [35]. Furthermore, as in other types of cancer, in individuals exposed to BPA, prostate cancer cells have been related to histone post-transitional modifications, chromatin remodeling, or tumor-suppressor genes with actions in multiple pathways including cell cycle control, invasion, hormonal response or DNA damage repair [36]. The presence of the androgen receptor characterizes more than 70% of all primary breast cancer tissues [37]. This is connected to a favorable prognosis for low pathological grading, small tumor volume, and prolonged patient survival time [38].

Models on animals have shown that androgen receptor agonist (5α-dihydroxytestosterone) DHT acts as a suppressor on rats' mammary cell proliferation, while androgen antagonist – Flutamide enhance rat mammary gland cell proliferation [39]. Extensive research shows that BPA is an androgen receptor antagonist, considering that BPA dose-dependently acts as a suppressor for transcription activity induced by DHT [40]. Even more, BPA can influence the androgen receptor's operation and function by making changes in androgen receptor transcriptional activation and nuclear translocation, since Bisphenol-A can cause a dispersed distribution of androgen receptor between the cytoplasmic and nuclear compartments in the presence of testosterone [41].

2.2. Pro-inflammatory Mechanisms Triggered by BPA

BPA has a vital role in inflammation by targeting murine microglial BV2 cells and by targeting pathways of mitogen-activated protein - MAPK. Immunofluorescence studies, Western Blot, and expression analysis studies indicated that Bisphenol-A is implicated in murine BV2 cells by upregulated Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) which could be reversed by using specific estrogen receptor antagonist [32]. Furthermore, the c-Jun N-terminal protein kinase (JNK) inhibitor exhibit anti-inflammatory properties on Bisphenol-A-elicited cytokine response, demonstrated that c-Jun N-terminal kinase pathway plays an essential role in downstream inflammation signaling. NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), a crucial inflammatory transcription factor, has clearly shown a specific activation in this study [42]. This data indicates the pro-inflammatory role of BPA in microglial cells and considering its' role in the central nervous system. It might trigger a

neurodegenerative response progression to Parkinson's disease or Alzheimer's disease in adult life.

2.3. DNA Damage Induced by BPA

New studies suggest that a low dosage of BPA can cause DNA damage in mammary gland cancer cells and produce damage to the geometry of neoplastic tissue [43]. Single-cell gel electrophoresis and immunostaining indicated an upregulated c-Myc and other important proteins and produced cell proliferation among estrogen receptor α (ER-α) negative breast cells. Suppressing c-Myc gene via siRNA (Small interfering RNAs) inhibition proves that DNA (deoxyribonucleic acid) damaging effects can be reduced in the presence of a low dose of BPA. Thus c-Myc plays a key role in controlling down-stream action of DNA damage induced by a small dose of BPA [43].

The most dangerous and challenging to repair among all breaks in DNA chains are double-strand breaks (DSBs), and these are probably the most common defects in the presence of BPA among mammary gland cells and prostate cells [44]. Other studies suggest that not only DNA damage in normal mammary gland epithelial cells are performed by BPA, but also DNA methylation in breast cells at BPA dose of only 10^{-5} - 10^{-6} M can cause the formation of more than 75% fewer tubules in collagen. Considering these relatively low concentrations, the upregulation of DNA repair genes like BRCA1/2, RAD51, BARD1, CtIP, or BRCC3 has been demonstrated and the downregulation of essential apoptotic genes PDCD5 and BCL2L11. Thus even small quantities of BPA could delay apoptosis in abnormal cells and increase DNA damage, resulting in prolonged survival of these cells [45].

3. Bisphenol-A role in prostate cancer

In the male population, second to lung cancer, prostate cancer is the most common malignancy worldwide, counting over 1.2 million new cases and being responsible for over 350.000 deaths annually, representing approximately 4% of all deaths in the male population in 2018 [46]. The mortality and incidence of prostate cancer are related to increasing age, 66 years old represented the average age of the diagnosed patient [47], African-American being more predisposed to this neoplasia and at younger generations [48]. Many other different risk factors are related to prostate cancer, such as genetics, diet, infection, but also excessive hormone therapy, including androgens. In recent years, other risk factors were trying to be discovered, with the main focus on endocrine-disrupting chemicals, especially its leading wide-spread representative - BPA.

The main actions of androgens on prostate tissue are represented by controlling functional activities and normal growth [49]. They exerting their main biological effects through the androgen receptor (AR) [50]; the mechanism of action of ADT (androgen deprivation therapy) is to ablate the function of AR [51]. Androgen receptor is part of the nuclear receptor superfamily and has the primary role as a ligand-dependent transcription factor. Before ligand activation, the AR is present in the cell, but it is kept inactivated by the inhibitory heat stock proteins.

Testosterone is considered to be the most important androgen receptor ligand. The enzyme 5-α-reductase converts testosterone into dihydrotestosterone (DHT) in healthy prostatic cells or cancerous cells (adenocarcinoma) [52]. The testosterone metabolite, DHT is a ligand that has a high affinity for the androgen receptor, and this binding actions as stimulation for displacement the stock heat proteins, rapid translocation to the nucleus, and receptor homodimerization. The androgen receptor, which is activated than binds to DNA sequence – androgen-responsive elements (AREs) and has a role in recruiting other co-activators initialing gene transcription [50]. Once the transcription is realized, the androgen receptor exhibits multiple roles, such as cellular proliferation, secretion, and differentiation. Due to the close relationship between the androgen receptor actions and prostate cancer cell proliferation, the gene that is most characterized by androgen receptor target – prostatic-specific antigen (PSA) is widely clinically utilized in prostate cancer screening and follow-up of the disease [53]. Thus it's generally accepted that the androgen receptor function is the critical element in prostate cancer development and progression.

For extracapsular and metastatic disease, androgen deprivation therapy acts by blocking the activity of the androgen receptor activity by preventing the ligand synthesis or by acting directly as an androgen

receptor antagonist [54,55]. ADT acts at the cellular level through multiple events by programming cell death and cell cycle arrest. These actions are clinically significant by reducing the PSA serum levels and engaging tumor remission, although, after a while, recurrence of ADT-resistance tumors is frequent [56]. The rise in ADT-resistance can be attributed to restoring the activity of the androgen receptor activity (elevated PSA levels) and continuing tumor growth [57]. Extensive research had tried to determine the main mechanisms of androgen receptor reactivation and ADT-resistance. It was described at least four key pathways [58]:

- The androgen-receptor ligand activator is considered to occur by inducing cytokine pathways and growth factors such as IL-6, EGF, IGF, KGF;
- The overexpression of the androgen receptor activators was described and is thought that androgen-receptor co-activators can induce deregulation to sensitize to low ligand concentration;
- The androgen-receptor can be overexpressed or amplified in recurrent tumors by boosting basal activity to determine a biological response;
- The androgen deprivation therapy is considered to select the mutations that the binding domain of the androgen receptor ligand that pursuit conformation changes of the central area to allow activation by other hormones such as estrogen, progesterone, or cortisol [59,60].

Recent papers demonstrated that different mutations of the androgen-receptor are causes of ADT-resistant tumors, and the same mutations successfully convert androgen-receptor antagonists to agonists like flutamide [61,62].

Considering the potent role of BPA mutagen activation of the androgen receptor and the progression of prostate cancer, it is necessary to underline the molecular BPA action. It is considered to be a different prostatic response to BPA than it is comparing to DHT, such as distinctions in ligand binding, the intensity of proliferation response, or multiple ligand-induced kinetics of androgen receptor recruitment to different regions of regulatory genes [63]. Furthermore, it is well known that different ligands control target gene specificity at nuclear receptor sites. Despite the fact that multiple in vitro analyses demonstrated the direct binding and activation of mutated androgen receptor by BPA, it is also known that BPA can induce activation of ERα and ERß, receptors expressed in multiple prostate cancer cell line (e.g. adenocarcinoma cell line). Although cellular proliferation induced by BPA is dependent on activation of the androgen receptor, blocking its function, using androgen receptor antagonist (e.g. casodex) reverse of BPA effects on tumor cell proliferation [64].

Recent studies demonstrate by gene expression analyses how physiologically relevant, low-level, and a proliferation-inducing BPA doses and DHT result in elicit overlapping with specific transcriptional roles in prostate cancer cells by expressing the so-called mutation: AR-T877A [65]. Previous data similarly concluded that distinct androgen receptor ligand and receptor activation alter the specific targeted gene, suggesting a different mechanism of BPA from DHT in promoting prostate cancer cell proliferation [66]. Studies indicated that cell exposure to BPA in genes expressing these mutations result in dramatic down-regulation of ERß expression. In contrast, DHT was observed to produce modest changes in this receptor subtype dynamics.

Different studies on estrogen/testosterone ratio (E/T), both circulating and intraprostatic, showed that E/T is more elevated in men over 65 years old. Also, estrogen receptor expression is increased in the stromal compartment [67]. The result of higher sex hormone-binding globulin levels and reduced testosterone production by testis are directly connected with lower bioavailable testosterone and higher concentrations of circulated estrogens, which leads to increasing the E/T ratio [68]. The estrogenic prostrate stimulation in older men can also lead to the reactivation of prostate growth and neoplastic transformation [69]. Different studies state that interference in hormonal balance in the elderly by BPA and other endocrine disruptors can determine increasing incidence in both benign lesions (benign prostatic hyperplasia) and cancerous lesions (prostate adenocarcinoma).

Exposure to BPA during pregnancy on animal models can induce a multifocal inflammation located at the ventral or posterolateral of the prostate. It can determine the appearance of atypical cells associated with papillary intraepithelial neoplasia (PIN) of the prostrate – the precursor lesion for prostate cancer.

Also, some authors reported the presence of folded acinar epithelium, less reticular fibers as a response to the inflammatory infiltrate, rearrangement of periacinar stroma, and collagen accumulation. The same rats that were exposed to BPA presented elevated levels of estrogen receptors and androgen receptors comparing to control rats [70].

Recent studies on human stem cells derived from the prostate of a young patient, with normal health, expressing estrogen receptor and GPR30 (G protein-coupled estrogen receptor) also demonstrated that at normal, physiological concentration of blood BPA, similar to estradiol, can increase maintenance and self-renewal of stem-like nature at dose-dependent concentrations and determine rapid phosphorylation of p-Erk and p-Akt [71]. Studies on human patients suggested that men presenting prostate cancer have higher levels of BPA detected in urine, comparing to the control group, concluding that urinary BPA values play a prognostic role for prostate cancer [72].

Adduct formation of DNA was suggested as a potential effect of BPA, but these toxic properties may require significantly high doses of exposure. In rat embryonic cells, DNA adduct formation was initiated by BPA in a dose-dependent manner [73], changes were associated with the presence of cellular transformation and aneuploidy. Other studies suggest that BPA physiologically exposure can determine K-Ras mutation and considerable changes in the synthesis of DNA, representing an accurate indicator of the connection between BPA and genetic alteration and cancer development [74]. The carcinogenetic properties of this chemical compound are shared by multiple derivates of BPA, as studies demonstrate [73]. BPA transforms, through oxidation, into quinone derivates; that form DNA adducts both in vitro and on an animal model. These data reveal that changes of EDCs may disturb their bioavailability. Furthermore, BPA can suffer a nitrosylation process, which also determines DNA adduct mutations [75].

DHT is significantly more potent compared to testosterone, as an agonist of the androgen receptor. The strength is a consequence of aromatase function, an enzyme that realizes the aromatization process of androgens, an essential step in estrogens biosynthesis [76]. The adult male rats exposed to BPA were demonstrated to determine modifications in actions of 5α-reductase and aromatase. BPA administration on short-time period was shown to determine a decrease of protein levels and mRNA for 5α-reductase R1 and R2, but increasing levels of 5α-reductase R3, a suggested biomarker for prostate cancer, inducing an essential reduction of testosterone levels and high estradiol levels in animals exposed to BPA, resulting in a higher serum E/T ratio [77]. Moreover, exposing fetal rats to reduced doses of BPA was shown to increase the levels of estrogen and CYP19A1 (aromatase) actions in the animal urogenital sinus. This represents the start point of development during embryogenesis, and also increasing steroidogenic enzymes like Cyp11a1, Cyp17a1 and Cyp11b1 and increasing factors with key roles in determining future sex like Amhr2, Gata4, Nr5a1 or Nr0b1 [78].

Multiple studies demonstrated that exposure to BPA in early life could cause different epigenetic alterations in the prostate. Even low doses of BPA or estrogen in the developmental period causes the methylation of the same gene, demonstrating similar involving pathways in prostate carcinogenesis. These epigenetic alterations determine an increasing incidence in prostate cancer lesions in elderly males, suggesting fetal BPA exposure implication in the development of neoplastic modification [79]. Also, due to early exposure, DNA methylation processes may be the epigenetic causes that are associated with high cancer susceptibility in adult prostate [35]. Both estradiol and BPA can interfere with modifying histone expression enzymes like deacetylase SIRT1 and methyltransferase SET8. Vital elements in transforming the prostate cancer cells due to gene expression [80].

A recent paper suggests that BPA is not only involved in the occurrence of prostate cancer but also invasion and migration of prostate cancer cells. Pretreatment of a specific derived cell line from metastatic lymph node (LNCaP) with environmental doses of BPA was shown to determine robust cell migration. Treatment with this chemical compound can promote store-operated calcium entry amplification, in invasive prostate cancer cells and androgen-dependent LNCaP, mostly due to ion channel protein modulation, involved in neoplastic cell migration. The androgen receptor does not necessarily mediate the BPA effect on these channel protein alterations; as a consequence, those same actions are determined in androgen-independent androgen receptor PC-3 cells [81].

4. Other EDCs in prostate cancer

In humans, a direct link between prenatal or postnatal exposure to EDCs and increasing incidence of prostate cancer is mostly offered by epidemiology studies or in vitro research on neoplastic cell lines [82]. Also, in vivo animal models have recently been used, suggesting relations between EDCs and neoplasia such as susceptibility, carcinogenesis, and occurrence of prostate cancer. Except for the most common environmental compound of this class – BPA, there are many other ubiquitaries found in the modern world.

Dioxins, or polychlorinated biphenyls (dl-PCBs), polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzo-p-dioxins (PCDDs) are an essential class of chemical compounds, characterized by high persistence and lipophilicity, ubiquitous in the modern environment. Extensive research demonstrated their part in different pathological processes such as immunotoxicity, endocrinopathy, neurotoxicity, and carcinogenicity [83]. They appear to have considerable effects on human health, such as cancer, reproductive effects, growth retardation in fetuses, thyroid deficiency, neurodevelopment dysfunctions, or immune dysfunctions [84]. Accumulated dioxins in female bodies were demonstrated to pass via transplacental or lactation routes to babies [85,86]. The most toxic dioxin is considered to be 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It is well known the connection between changes in the expression of genes that are induced by TCDD, initiated by an attachment to aryl hydrocarbon receptor, which crosstalks the estrogen receptor [87]. The activation of the aryl hydrocarbon receptor leads to the inhibition of the estrogen receptor activity by multiple mechanisms [88]. Also, there was found an inverse relationship between serum estrogen and TCDD levels in chemical workers [89]. Related to the prostate, time of exposure seems to be essential; several studies revealed that exposure of adults to TCDD appears to have a protective role for developing BPH [90], whereas exposure during fetal time seems to be directly connected to developing BPH in adulthood [91].

Moreover, TCDD's role on prostate cancer is unclear, multiple research resulting in contradictory results, a recent paper stating that this chemical compound increase tumor-free survival in rats while developing prostate cancer. At the same time, aryl hydrocarbon receptor activation has a positive impact on lymph node metastasis [91]. Further studies are expected.

PCB-153 or Polychlorinated biphenyl-153, another dioxin compound, seems to be connected to the occurrence of low-grade prostate cancer, a recent South American study suggested [92]. On the other hand, other European research has shown that environmental doses of PCB-153 are linked to the occurrence of high-grade prostate cancer, and no connection with a medium grade or low-grade prostate cancer. Also, it is shown that markers related to prostate neoplasia were increased, such as MMP2/9, Snail, or Slug, suggesting its role in the appearance of prostate cancer [93].

Cadmium is considered to be a human carcinogen by the American National Toxicology Program and International Agency for Research on Cancer. It is known that cadmium acts as a ligand to the estrogen receptor and mimics the estrogen functions. It has a proliferative role to the human prostate tissue in vitro through a mechanism dependent on the estrogen receptor [94]. Also, for cadmium, there is contradictory research in literature. At the same time, some authors suggest that there is no connection between exposure to this chemical compound and the increasing incidence of prostate cancer; others think that it can be a link between them [95]. Considering that it can accumulate in human organisms, further studies are necessary to analyze the connection with prostate cancer incidence in males with occupational exposure.

Inorganic arsenic is another chemical compound, widely spread in the modern world, with carcinogenetic properties through endocrine disruption mechanism. It has been associated with prostate cancer since the 1980s [96], and since then, more research on this topic has been conducted [97]. Objectively, it has been stated that this compound interacts with estrogen receptor functions and activates multiple estrogen-regulated genes, thus resulting in an endocrine-disrupting action [98]. Considering the above, recent paper presented a study demonstrating that through Ras-MAPK pathways can promote in vitro malignant transformation on prostate cells and modifying them into an androgen-independent status [99].

5. Conclusions

Based on the latest literature regarding the effect of EDCs on human health, we highlight these conclusions.

The vast majority of cited authors suggested a particular connection between humans' exposure to multiple chemical compounds and increasing incidence of different neoplasia via endocrine disrupting mechanisms.

BPA's action on prostate tissue follows multiple pathways. Reprogramming stem cells via estrogen-like activity leads in elderly males to an increasing incidence of both benign lesions such as benign prostatic hyperplasia or precancerous or cancerous lesions like a PIN or even prostate cancer. Effects probably determined by the estrogen-like characteristics of this compound. That can be realized by increasing the activation of various signaling pathways (Erk or Akt kinase), steroidal receptors recruiting chromatin, or deviated activity of different histone-modifying enzymes (LSD/KDM lysine-demethylase). Also, studies have shown that BPA can determine transcription of various androgen receptor mutants, which are detected in prostate cancer (the most important AR-R877A), that increase cell growth at higher concentrations, demonstrating to be a key element in prostate cancer development and the occurrence of hormone-independent phenotype. Moreover, it was observed a pro-inflammatory effect of BPA that can lead to the progression of prostate cancer. The effects of other compounds acting via an endocrine-disrupting mechanism, such as dioxins (TCDD, PCB-153, Cadmium, or Inorganic arsenic), are quite inconclusive studies, highlighting that some of them can also be involved in the occurrence of prostate cancer, while others have a protective role.

Altogether, most studies in the literature are conducted on either in vivo analyses on human prostate cancer cells or in vitro experiences on animal models, most frequently rats, thus the need for more in vivo analyses on humans is imperative for a better and more accurate understanding of all chemical and biochemical mechanisms of action of this wide-spread "plastics" that represent a threat on human health.

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