International Journal of
Molecular Sciences

Review

Potential Mechanisms of Bisphenol A (BPA) Contributing to Human Disease

Ilaria Cimmino †, Francesca Fiory †, Giuseppe Perruolo, Claudia Miele, Francesco Beguinot, Pietro Formisano * and Francesco Oriente

Department of Translational Medicine, Federico II University of Naples and URT "Genomic of Diabetes" of Institute of Experimental Endocrinology and Oncology, National Council of Research (CNR), 80131 Naples, Italy; ilaria.cimmino@unina.it (I.C.); francesca.fiory@unina.it (F.F.); giuseppe.perruolo@unina.it (G.P.); c.miele@ieos.cnr.it (C.M.); beguino@unina.it (F.B.); foriente@unina.it (F.O.)
* Correspondence: fpietro@unina.it; Tel.: +39-081-7464450; Fax: +39-081-7464334
† These authors contributed equally to this work.

Received: 6 July 2020; Accepted: 7 August 2020; Published: 11 August 2020

Abstract: Bisphenol A (BPA) is an organic synthetic compound serving as a monomer to produce polycarbonate plastic, widely used in the packaging for food and drinks, medical devices, thermal paper, and dental materials. BPA can contaminate food, beverage, air, and soil. It accumulates in several human tissues and organs and is potentially harmful to human health through different molecular mechanisms. Due to its hormone-like properties, BPA may bind to estrogen receptors, thereby affecting both body weight and tumorigenesis. BPA may also affect metabolism and cancer progression, by interacting with GPR30, and may impair male reproductive function, by binding to androgen receptors. Several transcription factors, including PPARγ, C/EBP, Nrf2, HOX, and HAND2, are involved in BPA action on fat and liver homeostasis, the cardiovascular system, and cancer. Finally, epigenetic changes, such as DNA methylation, histones modification, and changes in microRNAs expression contribute to BPA pathological effects. This review aims to provide an extensive and comprehensive analysis of the most recent evidence about the potential mechanisms by which BPA affects human health.

Keywords: bisphenol A; receptors; transcription factors; epigenetics; metabolism; cancer

---

1. Introduction

Persistent organic pollutants (POPs) are organic compounds resistant to degradation and are able to bioaccumulate in the environment, affecting human health [1]. Today, as in the past, many POPs are used to produce fertilizers, pharmaceuticals, and pesticides. As a consequence, these chemicals have contaminated water, air, and soil, and high concentrations of POPs have been found in animal and human tissues, milk, and blood [2–4]. Bisphenol A (BPA) is an organic synthetic compound with a molecular weight of 228 Da and the chemical formula $(CH_3)_2C(C_6H_4OH)_2$. It is included in the group of diphenylmethane derivatives and bisphenols, with two hydroxyphenyl groups [5,6]. This chemical compound was firstly synthesized in 1891, by the Russian chemist Aleksandr P. Dianin, who combined phenol with acetone in the presence of an acid catalyst. In the 1950s, scientists discovered that the reaction of BPA with phosgene (carbonyl chloride) produced a clear hard resin known as polycarbonate, which became widely used in the packaging for food and drinks, safety and medical devices, thermal paper, and dental compounds [7–16]. BPA half-life is about 4.5 days in water and soil, while is less than one day in the air, because of the low volatility [17,18]. However, BPA presence in the air is due to the attachment to the solid particulates present in the atmosphere. Thus, the inclusion of BPA in the POPs category is controversial. Indeed, although not technically a persistent organic pollutant because of its short half-life, it is often grouped together with other POPs, as it can accumulate in human tissues and organs, and contribute to the pathogenesis of several diseases [6,19–21]. The first evidence for the mechanisms of action of BPA was obtained in 1936 by Dowds and Lawson who discovered its estrogenic properties in vivo [22]. In 1997, the involvement of estrogen receptors, ERα and β, in BPA action was described, while other mechanisms emerged later [23,24].

Several routes of exposure to BPA have been described, including the digestive system (ingestion), the vertical transmission (maternofetal), the respiratory system (inhalation), and the integumentary system (skin and eye contact) (Figure 1). BPA can be directly or indirectly released into the environment at any level of the life cycle of the product: production, consumption, or disposal [25].

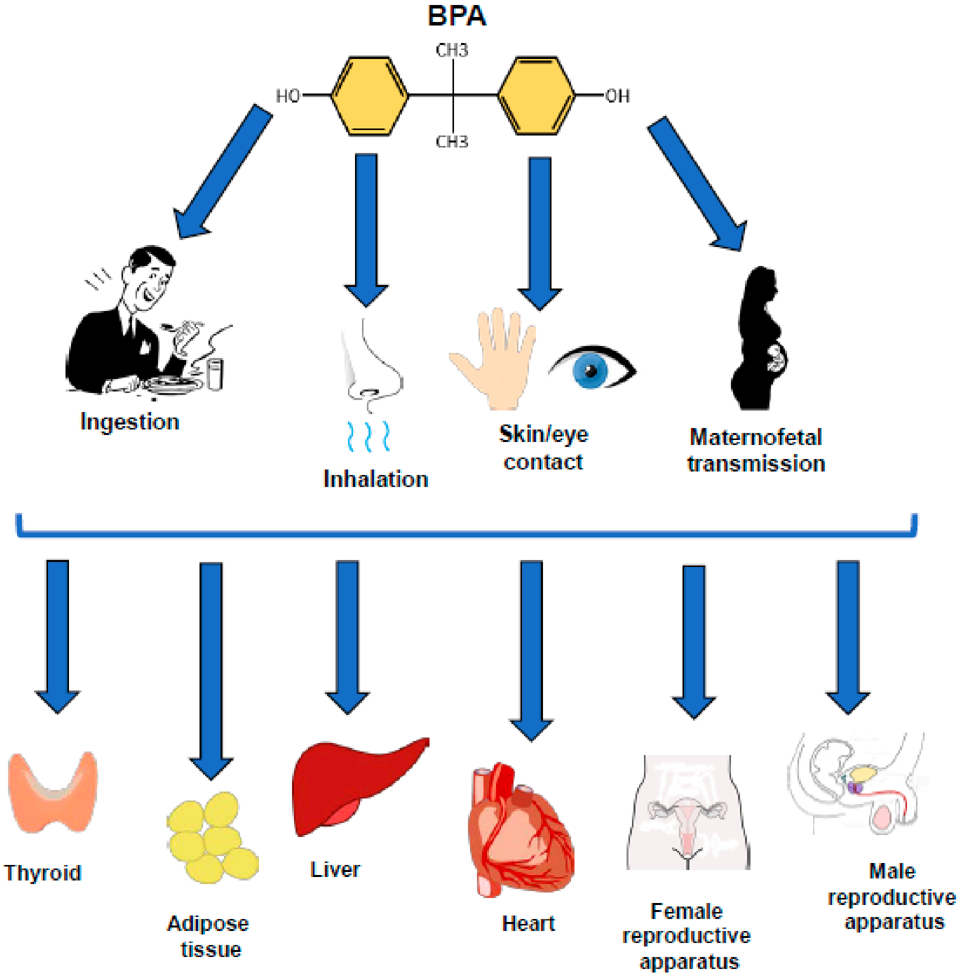

Figure 1. Potential BPA source and targets. BPA exposure sources include ingestion, maternofetal transmission, inhalation, skin, and eye contact. Once in the human body, BPA can negatively affect several targets, such as the thyroid, adipose tissue, liver, heart, female, and male reproductive apparatus. Images used to schematically represent anatomic parts and physiologic events were derived from openclipart.org and publicdomainvectors.org.

This compound can be found as colorless crystals or as powder and can be released by plastic products into foods and drinks as a result of heating and acid or basic conditions. Indeed, exposure of polycarbonate plastics to high temperatures, for example by heating food stored in packages or baby bottles, increases the rate of BPA transfer to human body. In addition, contact with acid or basic compounds and the presence of high levels of sodium chloride or vegetable oils cause an increase in the release of BPA from polymeric materials [26,27].

BPA is able to cross the placental barrier and has been detected in human maternal and fetal serum and the human placenta. Thus, BPA can find its way into tissues and fluids in the human womb [28–30]. Furthermore, BPA can be also absorbed by inhalation or by contact. For example, the thermal paper of the receipts may release this compound through contact with the epidermis [12]. Moreover, very high plasma and urine levels of BPA have been found in the cashiers, the latter being more in contact with the thermal paper [11,13–16]. Other routes of exposure are the discharges of municipal wastewater treatment plants, the combustion of domestic waste, and the degradation of plastic materials [21].

Recent metabolic and toxicokinetic studies have shown a rapid oral absorption of BPA. Once absorbed, this compound is conjugated in the liver with glucuronic acid. BPA glucuronate is sufficiently stable and represents a valid exposure biomarker [31]. Although some controversial evidence indicates that BPA is not toxic to human health [25,32], several recent studies highlight its harmful effects. Because of its lipophilic nature (logP of 3.4), BPA has the ability to accumulate in different human and animal tissues, compromising their physiological functions and exerting deleterious effects on health [21,33,34]. Indeed, studies performed in humans, rodents, and cellular cultures suggest that this compound may be obesogenic through different mechanisms. By modulating PPARs, BPA induces adipogenesis, stimulates lipid accumulation in adipose tissue and liver, and perturbs cytokines levels. Furthermore, data obtained in human and different cell lines show that BPA interferes with thyroid hormones synthesis, secretion, and signaling. Due to its anti-androgenic action, BPA works as an agonist on estrogen receptors and antagonist on androgen receptors [35]. Recently, it has been shown that BPA interferes with spermatogenesis and impairs male reproductive function. In parallel, sperm motility is negatively affected by BPA in human, mouse, bovine, chicken, and fish [36]. BPA exposure has been also associated with an increased risk for hypertension and cardiovascular disease in humans and rodents, although the mechanisms are still unclear [37] (Figure 1). Interestingly, BPA affects glucose metabolism, onset and progression of several tumors, and immune function by binding different receptors, modulating transcription factors, and inducing epigenetic changes [38,39]. Most of these results have been obtained in humans, rodents, and cellular cultures. The public concern about the potentially harmful health effects of BPA resulted in a ban on many plastic products, particularly those used for infants and young children [40].

In this review, we will discuss the main molecular mechanisms by which BPA mediates its deleterious effects.

2. BPA Interaction with Specific Receptors

BPA belongs to the endocrine-disrupting class of compounds and exhibits hormone-like properties. Low doses of this compound induce adverse effects on reproduction and regulation of the immune system, hormone-dependent cancers, and metabolism [41]. Both in vitro and in vivo data have shown that BPA can bind several nuclear receptors, such as estrogen receptors (ERα and β), GPR30, androgen receptor (AR), thyroid hormone receptors (TRα and β), estrogen-related receptor gamma (ERRγ) and glucocorticoid receptor (GR) [23,41–43]. All these receptors may contribute to the adverse effect of BPA in human diseases.

2.1. Estrogen Receptors

Estrogens are involved in different physiological processes, including growth, development, and homeostasis of several tissues, through the binding and the activation of classical estrogen receptors, ERα and ERβ. These molecules are encoded by two separate genes located on human chromosome 6 and 14, respectively [44,45]. Besides estrogens, ERα and ERβ can bind a wide range of compounds with different structures, including BPA, which exhibit different binding preferences and relative binding affinity for both ER subtypes and ERs of different species [46,47].

BPA acts like estradiol, stimulating different cell responses, although its affinity for the estrogen receptor is lower and its activity is approximately 10,000 to 100,000 times weaker compared to the natural hormone 17 beta estradiol (E2) [46,48]. Indeed, Delfosse et al. investigated the interaction between BPA and ERα, demonstrating that this compound binds ERα through 42 van der Waals interactions, instead of the 51 involved in E2-ERα binding [6]. Another key point is the concentration of BPA able to exert significant effects. Surprisingly, BPA features a stronger estrogen-like activity at nanomolar doses than at micromolar doses [49–51].

In vitro studies have demonstrated similarities between the action of estrogen and BPA on the gene expression of adipogenic transcription factors [52]. In addition, both BPA and E2 have been reported to inhibit adiponectin secretion from human adipocytes in a non-monotonic dose-dependent manner [53]. BPA may affect body weight, too. Indeed Rubin et al. reported sex- and dose-dependent body weight differences in mice after early postnatal exposure to endocrine disruptors. Tissue-specific alterations in ER expression may further modulate the BPA effect on body weight [54].

BPA binding to estrogen receptors plays an important role also in tumorigenesis. In particular, BPA-ER interaction increases proliferation and migration of several ovarian cancer cell lines through a pathway involving Stat3 and ERK1/2 [55]. A wide variety of studies demonstrated that nanomolar doses of BPA significantly increase the proliferation of ER-positive and ER-negative breast cancer cells [56]. Moreover, Dairekee and co-workers reported that BPA inhibits the pro-apoptotic effects of the rapamycin suppressing signaling pathway mediated by p53 and BAX in human breast epithelial cells [57].

2.2. *GPR30*

In contrast to nuclear receptors genomic signaling, it has been recently proposed that the adverse effects of low dose BPA on human health could be mediated by membrane receptors in a non-genomic way in order to produce fast biological responses on specific cellular targets. In particular, the signaling pathway that involves GPR30, a non-classical ER, plays a key role in the deleterious effects of low dose BPA [50,58,59].

GPR30 is a seven-transmembrane domain receptor, firstly identified as an orphan member of the G-protein coupled receptor family in the late 1990s [42,60–62]. GPR30 mRNA is expressed in several tissues (e.g., placenta, lung, liver, prostate, ovary, placenta, and endothelium), with different expression patterns [42,61,62]. GPR30 mediates some rapid biological events elicited by E2 through the activation of different pathways, including generation of the second messengers Ca^{2+}, cAMP, and NO, as well as activation of tyrosine kinase receptors, such as EGFR and IGF-1R, and induction of kinases like PI 3-kinase, PKB, and ERK family members [63–69].

Interestingly, Revnkar et al. have demonstrated that E2 affinity to GPR30 is 10-fold lower than ERα, while BPA affinity to GPR30 is about 50-fold higher than ERα [70,71].

The role of GPR30 in BPA-mediated detrimental effects on metabolism has been clearly demonstrated. Indeed, Wang et al. have indicated that GPR30 knockout (GPRKO) female mice are protected from high-fat diet (HFD)-induced obesity, blood glucose intolerance, and insulin resistance [72]. In parallel, Garcia-Arevalo et al. shed light on BPA interference with glucose metabolism, showing that BPA exposure causes impaired glucose tolerance, body weight gain, and reduced insulin secretion in mice [73,74]. We have recently demonstrated that low dose BPA increases GPR30 and the production of specific inflammatory proteins, including IL8, IL6, and MCP1α, both in cultured mature adipocytes and in stromal-vascular fraction cells isolated from mammary human adipose tissue biopsies [26].

GPR30 is widely expressed in different cell types and cancer cell lines and is overexpressed in endometrial, breast, and ovarian cancers [75,76]. Dong and collaborators have demonstrated that BPA, through GPR30, increases ERK1/2 phosphorylation and triggers a rapid biological response in both ER-positive and negative breast cancer cells [77]. In a mouse spermatocyte-derived cell line, GC-2 cells, low doses of BPA bind to GPR30 and activate the EGFR-MAPK pathway, with consequent activation of the c-Fos gene and inhibition of cell-cycle gene Cyclin D1 [78]. In males, GPR30 has been found to be particularly overexpressed in human seminoma tumors, the most frequent testicular germ cell tumor. Interestingly, the BPA-GPR30 complex induces testicular seminoma cell proliferation in vitro, and incubation with G15, a GPR30 antagonist, reverts this effect [79].

2.3. Androgen Receptor

Growing evidence supports the anti-androgen effect of BPA [80–82]. BPA is able to compete with 5α-dihydrotestosterone (DHT) for binding to androgen receptors (ARs). Several in silico studies have reported the ability of BPA to bind multiple sites on the AR surface through hydrophobic interactions [83,84]. The BPA-AR pathway is associated with adverse effects on spermatogenesis, steroidogenesis, atrophy of the testes, and alteration of adult sperm parameters, such as sperm count, motility, and density both in experimental animals and in humans [43,85]. These findings provide evidence that BPA induces several defects in the embryo, during postnatal and pubertal periods and adulthood. Indeed, this compound affects the hypothalamic-pituitary-testicular function by modulating androgen and estrogen synthesis as well as expression and activity of the respective receptors. The anti-androgenic effects on male reproductive function may be mediated by different mechanisms that involve receptor stabilization, dissociation of the heat shock protein 90, and nuclear translocation [86]. BPA's ability to impair male reproductive function in humans has been evidenced by epidemiological studies. Li et al. demonstrated that men exposed daily to BPA show lower sexual function such as erectile and orgasmic function, sexual desire, reduced libido, and erectile ejaculatory difficulties compared to controls [87]. These defects are paralleled by higher BPA levels in urine and plasma samples [88].

2.4. Other Receptor Targets of BPA Action

The estrogen-related receptors (ERRs) belong to a family of orphan nuclear receptors that includes (ERRα, β, and γ) [89]. Although these receptors share a relevant homology with ER, they do not directly bind estradiol. Differently, BPA can interact with these receptors, despite its estrogen-like activity. In particular, several studies demonstrated a strong affinity of ERRγ to BPA even at nanomolar concentrations [90–92]. ERRγ is constitutively active and owns a ligand-independent transcriptional activity [93]. However, Zhang and co-workers have demonstrated that low doses BPA could trigger the expression of the MMP2-mediated pathway and the invasion of triple-negative breast cancer through ERRγ [94]. In addition, the silencing of ERRγ attenuated BPA-induced proliferation of breast cancer cells [56].

It has been demonstrated that BPA can interact with the glucocorticoid receptor (GR) with lower affinity, compared to cortisol or dexamethasone. According to Atlas et al., BPA could not be considered a full GR agonist but has a synergistic effect on adipogenesis [95].

Interestingly, human urinary BPA levels have been associated with higher T3 and lower TSH circulating levels [96]. Thus, since BPA displays structural similarities with T3 [97], the interaction between BPA and the thyroid hormone receptor (TR) has been investigated. In particular, BPA has been shown to bind TR, exerting both agonist and antagonist effects, and to directly affect thyroid function by increasing the expression of several genes involved in thyroid cell proliferation and activity [98]. Anyway, more data are needed to further clarify the effect of BPA exposure on the thyroid hormones' pathway.

3. BPA Regulation of Transcription Factors

Growing evidence has shown the involvement of several transcription factors (TFs) in BPA action. In particular, some experimental evidence shows that induction of adipogenic TFs, such as PPARγ, C/EBPs, and Nrf2, plays a key role in the BPA "obesogenic effect". Other studies suggest an important role of HOX family members and HAND2 protein in BPA-mediated detrimental effects.

3.1. PPARγ

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily with a wide range of biological effects on metabolism, whole-body energy homeostasis, adipogenesis, cellular proliferation, differentiation, and immune response. This receptor family is comprised of three different subtypes (PPARα, β/δ, γ), all of which are important regulators of lipid and glucose metabolism in many different tissues including skeletal muscle, liver, adipose tissue, and gut. PPARγ activity is governed by the binding of small lipophilic ligands, mainly fatty acids, derived from nutrition or metabolism. Several studies suggest that BPA can modulate adipogenesis by inducing PPARγ, although the underlying molecular mechanisms are still unclear. Somm et al. indicate that both male and female pups prenatally exposed to low dose BPA (70 μg/kg/day) are overweight. However, at weaning, after postnatal BPA exposure via milk during lactation, only females show an increase in body weight, and this effect is associated with adipocyte hypertrophy and overexpression of proadipogenic transcription factors, such as PPARγ [99]. These results underline the importance of gender in PPARγ induction by BPA. In agreement, gestational BPA exposure enhances PPARγ expression in preadipocytes isolated from female, but not from male, sheep progeny [100].

Interestingly, PPARγ mediates BPA effects not only in adipose tissue but also in the liver. García-Arevalo et al. described that a subcutaneous injection of 10 μg/kg/day of BPA in mice upregulates the PPARγ gene in the liver and causes fasting hyperglycemia, glucose intolerance, and high levels of non-esterified fatty acids [73]. Similarly, Biasotto et al. indicated that administration of 5 μg/kg increases total body weight, fat mass, and hepatic PPARγ expression [101]. On the contrary, several conflicting results about the effect of BPA on PPARγ have been obtained in cellular cultures. According to Ariemma et al. and Biasotto et al. both low (0.1–1 nM) and high (80 μM) doses of BPA increased PPARγ in murine 3T3-L1 cells [101,102]. In contrast, Atlas et al. noted no differences in PPARγ 1 and PPARγ 2 expression in the same cells in response to BPA exposure [95].

In human cells, evidence in unclear. In adult human preadipocytes and in freshly cultured omental adipose tissue from children donors, BPA significantly increases PPARγ expression when used at different concentrations [103,104]. In contrast, PPARγ does not emerge as an essential mediator of BPA action in human adipose-derived stem cells [103]. The reason for these apparent discrepancies is still unknown but could be attributed to the different types of cell cultures and experimental procedures.

3.2. C/EBP

The CCAAT/enhancer-binding proteins (C/EBPs) encompass a family of six transcription factors with structural and functional homologies, but with different tissue specificity and transactivating ability.

C/EBPα was the first member cloned. Expression patterns of C/EBPα mRNA are similar in the mouse and human with measurable levels in liver, fat, intestine, lung, adrenal, peripheral blood mononuclear cells, and placenta. Similar to PPARγ, the role of C/EBPα as a mediator of BPA effects is currently under debate. Indeed, while Somm et al. have observed an increase of C/EBPα expression in adipocytes from BPA-exposed female rats [99], Atlas et al. did not find any effect of BPA on this transcription factor in 3T3-L1 cells [95]. Very recently, Salehpour et al. have described that BPA-induced triglyceride accumulation in human adipose-derived mesenchymal stem cells may be related not only to the upregulation of PPARγ and C/EBPα but also to the increase of C/EBPβ gene expression, suggesting that other members of the C/EBP family may be involved in the metabolic damage caused by BPA [105].

BPA exposure has been associated with liver dysfunction and diseases. De Benedictis et al. have shown that in fetal livers from female but not from male mice fed a diet supplemented with 25 mg BPA/kg, the level of C/EBPα, which is essential for hepatocyte maturation, is downregulated by 50% compared to the control animals. The authors conclude that in mice, BPA disrupts fetal liver maturation in a sex-specific manner and hypothesize that the decrease in C/EBPα may be responsible for the altered expression of albumin, alpha-fetoprotein, and glycogen synthase [106].

3.3. NRF2

Nuclear factor erythroid-2-related factor 2 (Nrf2) is a basic leucine zipper transcription factor that protects against oxidative damage by regulating the expression of antioxidant proteins [107]. Jiang et al. have shown that Nrf2$^{-/-}$ mice suffer from severe pathological renal alterations after treatment with pristane, a saturated terpenoid alkane inducing autoimmune diseases in rodents. Accordingly, an increased Nrf2 level can improve these alterations and protect from lupus nephritis [108]. Interestingly, a study by Dong et al. indicates that oral BPA administration to lupus-prone MRL/lpr mice decreases Nrf2 expression in renal tissue exacerbating lupus nephritis [109]. Thus, Nrf2 seems to play a protective role in BPA-induced renal damage. However, unlike the kidneys, Nrf2 impairs liver function [110]. Indeed, in the liver of leptin-deficient mice, constitutive activation of Nrf2 downregulates Kelch-like ECH-associated protein 1 (Keap1), increasing lipid accumulation [111]. Similarly, BPA induces Nrf2 via Keap1 inactivation in a human hepatoma cell line [112]. The possible association between BPA and Nrf2 has been further analyzed by Shimpi et al., who indicate that BPA (25 µg/kg/day) administration to pregnant CD-1 mice induces Nrf2 expression and its recruitment to the Srebp-1c promoter causing hepatic lipid deposition [113].

3.4. HOX

Hox genes are a group of related genes that encode for transcription factors characterized by a well-conserved DNA sequence known as the homeobox, of which the term "Hox" was originally a contraction. Thirty-nine HOX genes which are located in four clusters (A–D) have been found in humans and rodents. Hox genes are expressed during embryogenesis and early development, where they act as master transcriptional regulators. In adults, they are mainly involved in the maintenance of the normal phenotype [114,115]. Among the HOX genes, HOXA9, HOXA10, HOXA11, and HOXA13 are expressed in the female reproductive system, while HOXB9 and HOXC6 are involved in the development of the mammary gland [116,117]. Their misregulation may have deleterious effects. In particular, HOXA10 is important for normal decidualization and pregnancy; deregulation of its expression has been associated with several pathological conditions, including ectopic pregnancy, PCOS, endometriosis, hydrosalpinx, and improper implantation [118]. Elevated levels of HOXA10 in the uterine stromal cells of female pups exposed in utero to BPA (0.5 mg/kg–1.0 mg/kg) may mediate the decidualization defects [118].

Similar to HOXA10, HOXB9 and HOXC6 also play a physiological role in mammary gland development and are also overexpressed in several tumors, including breast cancer [119–121]. Several authors indicate that BPA increases HOXB9 and HOXC6 expression both in cultured human breast cancer cells (MCF7) and in the mammary glands of ovariectomized rats (25 µg/kg), suggesting these transcription factors as mediators of BPA harmful effects in breast tumor [122,123].

3.5. HAND2

Heart- and neural crest derivatives-expressed protein 2 (HAND2) is a basic helix-loop-helix transcription factor, involved in the establishment of a proper implantation environment for pregnancy. Li et al. have demonstrated that chronic exposure of female mice to BPA (60 or 600 µg/kg/day) decreases HAND2 expression in uterine stroma, affecting embryo implantation and formation of the decidua during early phases of pregnancy [124]. HAND2 is also involved in the development of ventricular chambers and in cardiac morphogenesis [125]. Its overexpression is associated with an excessive proliferation of cardiac progenitor cells, leading to enlargement of the heart and increased size of the outflow tract [126]. Interestingly, emerging evidence indicates an association between cardiovascular diseases and BPA, also due to the presence of several BPA target receptors in the cardiac tissue [127]. In addition, more recent data suggest an important role of BPA in impairing the differentiation of some cardiac progenitors [128–130]. In particular, Lombò et al. have shown that more than 30% of zebrafish embryos exposed to BPA (4000 µg/L) display cardiac edema, defects in looping and ballooning, blood accumulation, and elongation of heart chambers. Moreover, BPA significantly increases ERβ expression and H3K9 and H4K12 histone acetylation which may be, in turn, responsible for HAND2 upregulation and the higher percentage of heart malformations [130]. Thus, HAND2 represents a key regulator of several organs, including the uterus and heart, and impairment of its expression by BPA through genetic and epigenetic mechanisms may cause reproductive and cardiac disorders.

4. BPA-Regulated Epigenetic Mechanisms

Epigenetic changes are mitotically heritable chemical modifications able to affect chromatin three-dimensional conformation and, consequently, gene expression. Environmental factors such as nutritional agents and xenobiotic contaminants modulate epigenetic patterns, influencing DNA methylation of the CpG dinucleotides, post-translational chemical modifications of histone tails, and small non-coding RNA levels.

The first evidence that BPA may modulate DNA methylation came in 2006 when neonatal exposure to a low environmentally relevant dose of BPA was shown to increase the susceptibility of rats to neoplastic prostatic lesions, inducing early and prolonged phosphodiesterase type 4 variant 4 (PDE4D4) gene hypomethylation and elevated expression [131]. Similarly, Dolinoy et al. found that prenatal exposure of Agouti mice to BPA leads to a shift in the coat color phenotype of genetically identical individuals of the offspring. This phenomenon is due to a BPA-induced reduction in methylation of nine CpG sites located in an intracisternal A particle retrotransposon upstream of the agouti gene [132]. Later, BPA epigenetic effects have been characterized by dose-response experiments supplementing the maternal diet with three different amounts of BPA and using the yellow agouti gene as epigenetic biosensor [133]. Further studies have evidenced the relevance of the prenatal window for BPA-induced epigenomic changes. Indeed, in CD-1 mice, BPA is able to decrease the methylation of the HOXA10 gene when intraperitoneally injected in utero, deregulating the programmed gene expression during development and affecting embryo viability. In contrast, adult mice exposed to the same amount of BPA did not modify the HOXA10 methylation pattern [134]. Methylation is not the only BPA-induced epigenetic modification. Several reports show the ability of BPA to specifically interfere with the expression of multiple microRNAs (miRNAs). This is not surprising since BPA is an estrogen mimic. In this regard, it may be involved in miRNA processing and in direct regulation of specific miRNAs owing to estrogen response elements (EREs) in their promoters [135]. The impact of in utero BPA exposure on histone chemical modifications has been explored too but in less detail. It is known that BPA prenatal exposure upregulates the expression of the histone methyltransferase Enhancer of Zeste Homolog 2 (EZH2), increasing trimethylation of histone 3 (H3) at lysine 27 (H3K27me3) in the mammary gland, which represents a marker of transcriptional activation typical of breast cancer cells [136]. Moreover, BPA exposure induces histone H3K4 trimethylation at the transcriptional initiation site of the alpha-lactalbumin gene, enhancing its expression [137].

4.1. BPA-Induced Epigenetic Modifications in Metabolism

The discovery that BPA is epigenetically toxic further encouraged the study of the etiology of several complex diseases, such as type 2 diabetes (T2D), obesity, and cancer. Indeed, several metabolic pathways are significantly modified by BPA action on the epigenome. In sheep fetal ovaries, the expression of miRNAs is altered by prenatal BPA, affecting insulin homeostasis and 15 of the differentially expressed miRNAs that are potentially involved in the regulation of genes related to insulin signaling [138]. Moreover, the utilization of genome-wide analysis together with in-depth quantitative site-specific CpG methylation has allowed one to discover and validate modifications in DNA methylation patterns in the BPA-treated mouse liver and to identify cancer- and metabolism-related pathways [139]. Ma et al. have observed that BPA administration to pregnant Wistar rats results in increased insulin resistance and reduced hepatic glycogen storage in the offspring. In parallel, DNA methyltransferase 3B mRNA is overexpressed, and hepatic global DNA methylation is decreased. In contrast, promoter hypermethylation of hepatic glucokinase (Gck) and a concomitant decreased gene expression of this enzyme has been noted, leading to diminished glycogen synthesis. These data support the key role of BPA-induced epigenetic changes in fetal reprogramming in the pathogenesis of metabolic disorders [140]. However, there are also contrasting data published by van Esterik et al. showing that perinatal BPA exposure does not influence DNA methylation in the liver. According to the authors, discordant results are probably due to species, strain, and tissue used, discrepancies in BPA dose and administration method, and background diet and/or other unidentified factors [141]. Anyway, BPA ability to impair glucose homeostasis and hepatic Gck promoter methylation in F2 offspring through maternal exposure has been also investigated in Sprague–Dawley (S–D) rats by Li et al. [142]. These authors show that BPA-treated F2 offspring feature significantly higher glucose intolerance and insulin resistance and decreased Gck protein and mRNA levels, compared to the untreated control. Accordingly, the impaired methylated status of Gck promoter in the liver of BPA-treated F2 offspring and in the sperm of F1 generation confirms that oral BPA administration during gestation and lactation worsens the risk of T2D and its progression in the F2 generation. Thus, BPA-induced epigenetic changes allow the transmission of alterations of glucose metabolism through generations [142]. Other evidence indicates that BPA-induced epigenetic changes may affect the expression of genes relevant for hepatic function. Indeed, upon 10 months exposure to BPA, CD-1 mice feature a decrease of DNA methyltransferase levels, accompanied by hypomethylation and overexpression of genes involved in lipid synthesis, such as Srebf1 and Srebf2. From the metabolic point of view, BPA-treated mice are characterized by obesity and by anomalies of glucose and lipid metabolism, such as increased fasting blood glucose and serum insulin and significant hepatic accumulation of triglycerides and cholesterol [143]. Triglycerides accumulation promotes the development of non-alcoholic fatty liver disease (NAFLD). Interestingly, male C57BL/6 mice exposed to BPA by oral gavage for 90 days display a NAFLD-like phenotype paralleled by reduced expression of miR-192, responsible for the upregulation of Srebf1 and, in turn, of several genes involved in de novo lipogenesis. In these mice, exposure to BPA impairs hepatic insulin signaling and induces systemic insulin resistance [144]. Moreover, in male S–D rats, early-life BPA exposure contributes to the development of NAFLD in adulthood and exacerbates the deleterious long-term effects of a post-weaning high fat diet. The proposed mechanism includes the induction of DNA hypermethylation within the Carnitine palmitoyltransferase 1a (Cpt1a) gene, encoding the enzyme regulating the transport of long-chain fatty acids into the mitochondria for β-oxidation [145]. Hypermethylation, in turn, leads to the down-regulation of Cpt1a expression and to a consequent accumulation of free fatty acids. Interestingly, BPA affects liver homeostasis through histones modifications, too. Indeed, it modifies several histone marks, including H3Me2K4, in histone tails within the Cpt1a gene, thus reducing the binding of several transcription factors to the Cpt1a gene. These alterations are paralleled by the reduction in expression levels of Kmt2c, which methylates and activates H3Me2K4 [146].

However, the BPA impact on lipid metabolism has been further clarified by studies performed on adipose tissue, which plays an undeniable key role in the pathogenesis of insulin resistance and T2D. Several studies performed in animal and cellular models highlighted BPA contribution to the development of obesity, probably due to its dose-related enhancing effect on adipocyte differentiation observed in 3T3-L1 cells. At the molecular level, BPA (80 μM) significantly increases global DNA methylation in 3T3-L1 cells [147]. Further studies performed in murine preadipocytes have pointed out the key role of miR-21-a-5p, whose levels are decreased by BPA exposure. It has been shown that that miR-21-a-5p interferes with MKK3/p38/MAPK, blocking BPA induced adipocytes differentiation. Interestingly, miR-21-a-5p overexpression mitigates BPA obesogenic effect in vivo [147]. In humans, prenatal BPA exposure seems to favor overweight phenotype in children, modifying methylation of CpG sites, including one hypo-methylated CpG in the promoter of the mesoderm-specific transcript gene (MEST) encoding an obesity-related member of the α/β hydrolase fold family [148].

Beside affecting insulin resistance and obesity, BPA action on DNA methylation deeply affects T2D pathogenesis and progression impacting on beta cells function. There is a lot of evidence that, when F0 pregnant S–D rats are exposed to BPA during gestation and lactation, sperm of adult F1 male rats and islets of male F2 offspring feature Igf2 hypermethylation and decreased expression. These molecular alterations in male F2 offspring are paralleled by impaired glucose tolerance and beta-cell dysfunction [149]. BPAs impact on specific miRNAs expression plays an emerging role in beta-cell dysfunction, too. In particular, miR-338 has been identified for its involvement in beta-cells response to BPA. Indeed, in vitro studies performed in primary islets treated for 48 h with BPA have revealed that islets are unable to compensate for long-term effects of BPA toxicity, featuring reduced glucose-stimulated insulin secretion and downregulation of Pdx1 expression. Interestingly, the authors show that Pdx1 serves as a target of miR-338 and that long-term BPA treatment upregulates miR-338 levels, determining a decrease in Pdx-1 expression and subsequently, a lack of compensatory insulin secretion [150]. Other studies have evidenced the ability of BPA to affect glucose metabolism modifying histone code. Indeed, maternal exposure to BPA significantly reduces pancreatic beta-cell mass and Pdx1 expression levels at birth and at gestational day 15.5. Decreased expression of Pdx1 is paralleled by histones H3 and H4 deacetylation, by demethylation H3K4 and by methylation of H3K9. These alterations of histone code at the promoter of Pdx1 lead to a compact chromatin structure and are conserved in adult life together with glucose intolerance [151].

4.2. BPA-Induced Epigenetic Modifications in Cancer

BPA induced epigenetic changes can make a decisive contribution to the pathogenesis of hormone-dependent cancer, such as breast and prostate cancer [152]. Dhimolea et al. have found that in utero, BPA exposure is accompanied by relevant transcriptional changes and genome-wide epigenetic modifications in the Wistar–Furth rat mammary gland from the end of exposure to adulthood [137]. In humans, BPA modifies the morphogenesis of the fetal mammary gland in females and induces gynecomastia in males [153]. Interestingly, low dose BPA exposure during the early stages of mammary gland development increases the risk of breast cancer in adult animals [154,155]. In vitro studies have shown that BPA exposure increases the proliferation of the human breast cancer cell line [51]. Some of the first evidence that BPA-induced epigenetic changes affect breast cancer pathogenesis was provided by the finding that treatment of MCF-7 cells with BPA increases mRNA and protein expression of EZH2, a histone methyltransferase linked to breast cancer risk. In parallel, histone H3 trimethylation is increased upon BPA incubation. Similar results about BPA induction of EZH2 expression have been obtained in mammary tissue of BPA-exposed mice [136,156]. Similarly, in MCF-7 cells and in mammary glands of S–D rats, expression of HOXC6, commonly upregulated in breast tumor tissue, increases upon BPA incubation by enhancing H3K4me3, histone acetylation and recruitment of RNA polymerase II [123]. Besides histones modifications, BPA-induced alterations of DNA methylation are involved in breast cancer pathogenesis. In human primary breast epithelial cells, low dose BPA leads to hypermethylation and silencing of lysosomal associated membrane protein 3 (LAMP3) gene [157], whose overexpression is usually linked to cancer invasiveness [158]. DNA methylation of BRCA-1 and p16 INK4 is also increased in human mammary epithelial cells treated with low dose BPA [159]. The procarcinogenic effect of BPA is supported by its ability to deregulate the expression of non-coding RNAs. BPA enhancing effect on the proliferation of MCF-7 cells is paralleled by the overexpression of oncogenic miR-21, miR-19a, and miR-19b [160] and by the silencing of miR-19 downstream targets, such as PTEN [161]. Moreover, in human placental cell lines treatment with BPA induces miR-146a upregulation, linked to the development of triple-negative breast cancer [162].

Prostate carcinogenesis is also affected by BPA exposure in both rats [163] and humans [164]. Genome-wide DNA methylation analysis in rodent models has shown that neonatal exposure to BPA induces permanent differential methylation in 86 genes, and increases susceptibility to prostate cancer [165]. At the molecular level, BPA increases prostate stem-progenitor cell self-renewal and upregulates the expression of genes connected to human prostate cancer in a dose-dependent manner. Dose-specific changes in the DNA methylation of genes such as Creb3L4, Tpd52, Pitx3, Paqr4, and Sox2 have been indeed observed upon postnatal BPA exposure in male neonatal S–D rats [166]. A whole-genome microarray performed in healthy primary human prostate epithelial cells has shown that BPA treatment affects the expression of genes relevant for cancer development and progression in prostate cells, involved in pathways modulating angiogenesis, cell proliferation, cell cycle, DNA replication and repair, metabolism, inflammation, and immune response pathways. In parallel, BPA deregulates the expression of transcripts relevant to epigenetic changes, such as histone and DNA methylation modifying enzymes [167]. Similar results have been obtained by Fatma Karaman et al. who performed PCR arrays in the human prostate adenocarcinoma PC-3 cell line to investigate the transcriptional profiling of chromatin-modifying enzymes and DNA methylation levels of tumor suppressor genes including p16, Cyclin D2, and Rassf1. In particular, chromatin immunoprecipitation experiments have evidenced a BPA-induced specific histone modification affecting chromatin accessibility of p16. Taken together, these results have pointed out the functional role of BPA-induced epigenetic signatures, suggesting that both DNA methylation and histone modifications play a functional role in carcinogenesis and could represent molecular biomarkers of BPA-induced prostate cancer progression [168].

5. Conclusions

Most of the world population is still widely exposed to BPA, due to its large use in the production of polycarbonate plastic and to its release into foods and beverages. It is nowadays quite clear that BPA is a major risk factor for endocrine, immune, and oncological diseases. Indeed, this chemical has been now included in the list of banned substances in several products, such as cosmetics or baby bottles. However, several contrasting results about the toxic effects of BPA have been described. Discrepancies in the results may be due to the use of a wide range of BPA concentrations as well as to the different experimental models [169]. Hence, the interpretation of the results of toxicological and epidemiological studies about the effects of BPA has been complicated by the use of non-oral routes of administration in many experimental conditions, different doses, absence of dose-response relationships, or small numbers of test animals. In parallel, many efforts have been performed in order to elucidate the molecular mechanisms through which this compound acts. The integration of the knowledge about the BPA molecular pathways with epidemiology could certainly improve the comprehension of the toxic effects of BPA on human health.

As summarized in this review article, a growing body of evidence indicates that BPA action is initiated through binding to relatively specific hormone receptors, including sex hormone receptors (ERs and ARs) and thyroid hormone receptors, thereby directly regulating gene expression. Nonetheless, rapid non-genomic actions may be mediated by the membrane-associated ERs and/or GPR30, which in turn may elicit signal transduction pathways, finally recruiting key transcription factors involved in growth and differentiation as well as in energy and nutrient metabolism. Most intriguingly, all the upstream pathways may contribute to stable and inheritable modifications, by regulating epigenetic enzymes, which may also sustain earlier exposure to BPA [170] Figure 2.

Other chemicals including bisphenol S (BPS) and bisphenol F (BPF) have been evaluated as an alternative to BPA, without reaching encouraging results [171,172]. For instance, very recent studies indicate that BPS is as effective as BPA in promoting certain types of breast cancer, and even more harmful to the reproductive system [173]. In more detail, BPS stimulates the proliferation of breast cancer cells modulating cyclin D and E levels through ER-dependent signaling. In parallel, BPS increases the expression of genes involved in cellular attachment, adhesion, and migration inducing epigenetic and transcriptional modifications [174]. Thus, BPS is likely worthy of the same legal restriction as BPA [173].

Therefore, to date, the best practice to reduce the harmful effects of BPA is still the precaution of limiting the consumption of plastic materials and promoting the use of BPA-free products.

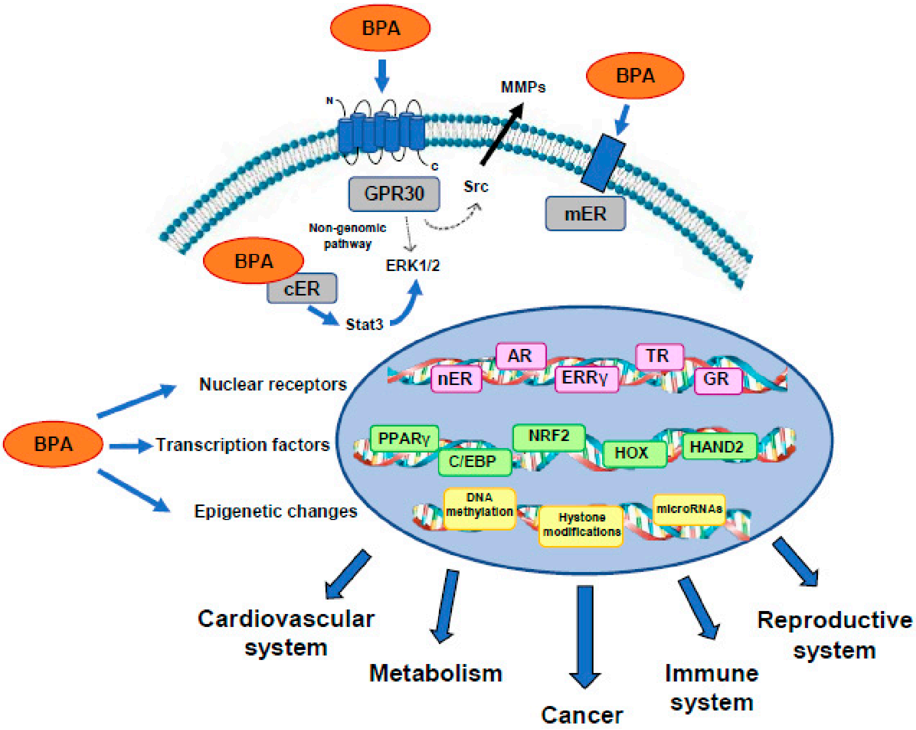

Figure 2. A potential integrative model of BPA molecular mechanisms. BPA exerts its deleterious effects on the cardiovascular system, metabolism, cancer, and immune and reproductive systems, by activating specific receptors, inducing transcription factors, and through epigenetic modifications.

Author Contributions: I.C. and F.F., prepared the first draft of the manuscript; G.P. and C.M. were involved in the literature search; F.B. and P.F. critically revised the manuscript. P.F. and F.O. supervised the work and wrote the final version of the article. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by Associazione Italiana per la Ricerca sul Cancro: IG-19001 Regione Campania: POR Campania FESR "Coepica".

Acknowledgments: Ilaria Cimmino and Francesca Fiory equally contributed to this work. This research was funded in part by Associazione Italiana per la Ricerca sul Cancro (AIRC grant IG-19001) and by Regione Campania (POR Campania FESR "Coepica").

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AR	Androgen receptors
BPA	Bisphenol A
C/EBPs	CCAAT/enhancer-binding proteins
cER	Cytosolic estrogen receptors
CREB3L4	CAMP responsive element binding protein 3 like 4
Cpt1a	Carnitine palmitoyltransferase 1a
E2	17 beta estradiol
EGFR	Estrogen growth factor receptor
ER	Estrogen receptors
ERE	Estrogen response elements
ERK	Extracellular receptor kinase
ERRγ	Estrogen-related receptor gamma
EZH2	Enhancer of Zeste homolog 2
Gck	Glucokinase
GPR30	G protein-coupled receptor 30 G protein-coupled receptor 30
GR	Glucocorticoid receptor

H3	Histone 3
HAND2	Heart- and neural crest derivatives-expressed protein 2
HFD	High fat diet
IL	Interleukin
HOX	Homeobox proteins
IGF	Insulin-like growth factor
IGFR	Insulin-like growth factor receptor
Keap1	Kelch-like ECH-associated protein
LAMP3	Lysosomal associated membrane protein 3
MAPK	Mitogen-activated protein kinase
mER	Membrane estrogen receptors
MEST	Mesoderm-specific transcript
NAFLD	Non-alcoholic fatty liver disease
nER	Nuclear estrogen receptors
NO	Nitric oxide
Nrf2	Nuclear factor erythroid-2-related factor 2
PPAR	Peroxisome proliferator-activated receptor
PAQR	Progestin and AdipoQ receptor family member 4
PCOS	Polycystic ovary syndrome
PDE4D4	Phosphodiesterase type 4 variant4
PDX1	Pancreatic and duodenal homeobox 1
PI3K	Phosphoinositide 3-kinases
Pitx3	Pituitary homeobox 3
PKB	Protein kinase B
POPs	Persistent organic pollutants
PR	Progesterone receptor
Sox2	SRY-box transcription factor 2
Srebf	Sterol regulatory element-binding transcription factor 1
STAT	Signal transducer and activator of transcription
T2D	Type 2 diabetes
T3	Triiodothyronine
TF	Transcription factor
TH	Thyroid hormone
TR	Thyroid receptor
TSH	Thyroid stimulating hormone

References

1. Alharbi, O.M.L.; Basheer, A.A.; Khattab, R.A.; Ali, I. Health and environmental effects of persistent organic pollutants. *J. Mol. Liq.* **2018**, *263*, 442–453. [CrossRef]
2. Ross, P.S.; Birnbaum, L.S. Integrated Human and Ecological Risk Assessment: A Case Study of Persistent Organic Pollutants (POPs) in Humans and Wildlife. *Hum. Ecol. Risk Assess.* **2003**, *9*, 303–324. [CrossRef]
3. Croes, K.; Colles, A.; Koppen, G.; Govarts, E.; Bruckers, L.; Van de Mieroop, E.; Nelen, V.; Covaci, A.; Dirtu, A.C.; Thomsen, C.; et al. Persistent organic pollutants (POPs) in human milk: A biomonitoring study in rural areas of Flanders (Belgium). *Chemosphere* **2012**, *89*, 988–994. [CrossRef] [PubMed]
4. Wilhelm, M.; Ewers, U.; Schulz, C. Revised and new reference values for some persistent organic pollutants (POPs) in blood for human biomonitoring in environmental medicine. *Int. J. Hyg. Environ. Health* **2003**, *206*, 223–229. [CrossRef]
5. Li, L.; Wang, Q.; Zhang, Y.; Niu, Y.; Yao, X.; Liu, H. The molecular mechanism of bisphenol A (BPA) as an endocrine disruptor by interacting with nuclear receptors: Insights from molecular dynamics (MD) simulations. *PLoS ONE* **2015**, *10*, e0120330. [CrossRef]
6. Delfosse, V.; Grimaldi, M.; Pons, J.L.; Boulahtouf, A.; le Maire, A.; Cavailles, V.; Labesse, G.; Bourguet, W.; Balaguer, P. Structural and mechanistic insights into bisphenols action provide guidelines for risk assessment and discovery of bisphenol A substitutes. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 14930–14935. [CrossRef]

7. Eladak, S.; Grisin, T.; Moison, D.; Guerquin, M.J.; N'Tumba-Byn, T.; Pozzi-Gaudin, S.; Benachi, A.; Livera, G.; Rouiller-Fabre, V.; Habert, R. A new chapter in the bisphenol A story: Bisphenol S and bisphenol F are not safe alternatives to this compound. *Fertil. Steril.* **2015**, *103*, 11–21. [CrossRef]
8. Tyl, R.W. Abbreviated assessment of bisphenol A toxicology literature. *Semin. Fetal. Neonatal. Med.* **2014**, *19*, 195–202. [CrossRef]
9. Huo, X.; Chen, D.; He, Y.; Zhu, W.; Zhou, W.; Zhang, J. Bisphenol-A and Female Infertility: A Possible Role of Gene-Environment Interactions. *Int. J. Environ. Res. Public Health* **2015**, *12*, 11101–11116. [CrossRef]
10. Takahashi, Y.; Shirai, A.; Segawa, T.; Takahashi, T.; Sakakibara, K. Why does a color developing phenomenon occur on thermal paper comprising of a fluoran dye and a color developer molecule? *Bull Chem. Soc. Jpn.* **2002**, *75*, 2225–2231. [CrossRef]
11. Mendum, T.; Stoler, E.; VanBenschoten, H.; Warner, J.C. Concentration of bisphenol A in thermal paper. *Green Chem. Let. Rev.* **2011**, *4*, 81–86. [CrossRef]
12. Hormann, A.M.; Vom Saal, F.S.; Nagel, S.C.; Stahlhut, R.W.; Moyer, C.L.; Ellersieck, M.R.; Welshons, W.V.; Toutain, P.L.; Taylor, J.A. Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). *PLoS ONE* **2014**, *9*, e110509. [CrossRef] [PubMed]
13. Ndaw, S.; Remy, A.; Jargot, D.; Robert, A. Occupational exposure of cashiers to Bisphenol A via thermal paper: Urinary biomonitoring study. *Int. Arch. Occup. Environ. Health* **2016**, *89*, 935–946. [CrossRef] [PubMed]
14. Biedermann, S.; Tschudin, P.; Grob, K. Transfer of bisphenol A from thermal printer paper to the skin. *Anal. Bioanal. Chem.* **2010**, *398*, 571–576. [CrossRef]
15. Liao, C.; Kannan, K. Widespread occurrence of bisphenol A in paper and paper products: Implications for human exposure. *Environ. Sci. Technol.* **2011**, *45*, 9372–9379. [CrossRef]
16. Liao, C.; Liu, F.; Kannan, K. Bisphenol s, a new bisphenol analogue, in paper products and currency bills and its association with bisphenol a residues. *Environ. Sci. Technol.* **2012**, *46*, 6515–6522. [CrossRef]
17. Abraham, C.; Cho, J.H. Inflammatory bowel disease. *N. Engl. J. Med.* **2009**, *361*, 2066–2078. [CrossRef]
18. Cousins, I.T.; Staples, C.A.; Clecka, G.M.; Mackay, D. A Multimedia Assessment of the Environmental Fate of Bisphenol, A. *Hum. Ecol. Risk Assess.* **2002**, *8*, 1107–1135. [CrossRef]
19. Haffner, D.; Schecter, A. Persistent Organic Pollutants (POPs): A Primer for Practicing Clinicians. *Curr. Environ. Health Rep.* **2014**, *1*, 123–131. [CrossRef]
20. Corrales, J.; Kristofco, L.A.; Steele, W.B.; Yates, B.S.; Breed, C.S.; Williams, E.S.; Brooks, B.W. Global Assessment of Bisphenol A in the Environment: Review and Analysis of Its Occurrence and Bioaccumulation. *Dose Response* **2015**, *13*, 1559325815598308. [CrossRef]
21. Valentino, R.; D'Esposito, V.; Ariemma, F.; Cimmino, I.; Beguinot, F.; Formisano, P. Bisphenol A environmental exposure and the detrimental effects on human metabolic health: Is it necessary to revise the risk assessment in vulnerable population? *J. Endocrinol. Investig.* **2016**, *39*, 259–263. [CrossRef] [PubMed]
22. Dodds, E.C.; Lawson, W. Synthetic, oestrogenic agents without the phenanthrene nucleus. *Nature* **1936**, *137*, 996. [CrossRef]
23. Kuiper, G.G.; Carlsson, B.; Grandien, K.; Enmark, E.; Haggblad, J.; Nilsson, S.; Gustafsson, J.A. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology* **1997**, *138*, 863–870. [CrossRef] [PubMed]
24. Mileva, G.; Baker, S.L.; Konkle, A.T.; Bielajew, C. Bisphenol-A: Epigenetic reprogramming and effects on reproduction and behavior. *Int. J. Environ. Res. Public Health* **2014**, *11*, 7537–7561. [CrossRef]
25. Almeida, S.; Raposo, A.; Almeida-González, M.; Carrascosa, C. Bisphenol A: Food Exposure and Impact on Human Health. *Compr. Rev. Food. Sci. Food Saf.* **2018**, *17*, 1503–1517. [CrossRef]
26. Cimmino, I.; Oriente, F.; D'Esposito, V.; Liguoro, D.; Liguoro, P.; Ambrosio, M.R.; Cabaro, S.; D'Andrea, F.; Beguinot, F.; Formisano, P.; et al. Low Dose Bisphenol-A Regulates Inflammatory Cytokines through GPR30 in Mammary Adipose Cells. *J. Mol. Endocrinol.* **2019**, *63*, 273–283. [CrossRef]
27. Vandenberg, L.N.; Hauser, R.; Marcus, M.; Olea, N.; Welshons, W.V. Human exposure to bisphenol A (BPA). *Reprod. Toxicol.* **2007**, *24*, 139–177. [CrossRef]
28. Ziv-Gal, A.; Flaws, J.A. Evidence for bisphenol A-induced female infertility: A review (2007–2016). *Fertil. Steril.* **2016**, *106*, 827–856. [CrossRef]
29. Ekbom, A. Growing evidence that several human cancers may originate in utero. *Semin. Cancer Biol.* **1998**, *8*, 237–244. [CrossRef]

30. Margel, D.; Fleshner, N.E. Oral contraceptive use is associated with prostate cancer: An ecological study. *BMJ Open* **2011**, *1*, e000311. [CrossRef]
31. Andra, S.S.; Austin, C.; Yang, J.; Patel, D.; Arora, M. Recent advances in simultaneous analysis of bisphenol A and its conjugates in human matrices: Exposure biomarker perspectives. *Sci. Total Environ.* **2016**, *572*, 770–781. [CrossRef] [PubMed]
32. Vom Saal, F.S.; Hughes, C. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. *Environ. Health Perspect.* **2005**, *113*, 926–933. [CrossRef] [PubMed]
33. Mathieu-Denoncourt, J.; Wallace, S.J.; de Solla, S.R.; Langlois, V.S. Influence of Lipophilicity on the Toxicity of Bisphenol A and Phthalates to Aquatic Organisms. *Bull. Environ. Contam. Toxicol.* **2016**, *97*, 4–10. [CrossRef] [PubMed]
34. Healy, B.F.; English, K.R.; Jagals, P.; Sly, P.D. Bisphenol A exposure pathways in early childhood: Reviewing the need for improved risk assessment models. *J. Expo. Sci. Environ. Epidemiol.* **2015**, *25*, 544–556. [CrossRef] [PubMed]
35. Rotondo, E.; Chiarelli, F. Endocrine-Disrupting Chemicals and Insulin Resistance in Children. *Biomedicines* **2020**, *8*, 137. [CrossRef]
36. Castellini, C.; Totaro, M.; Parisi, A.; D'Andrea, S.; Lucente, L.; Cordeschi, G.; Francavilla, S.; Francavilla, F.; Barbonetti, A. Bisphenol A and Male Fertility: Myths and Realities. *Front. Endocrinol. (Lausanne)* **2020**, *11*, 353. [CrossRef]
37. Wehbe, Z.; Nasser, S.A.; El-Yazbi, A.; Nasreddine, S.; Eid, A.H. Estrogen and Bisphenol A in Hypertension. *Curr. Hypertens. Rep.* **2020**, *22*, 23. [CrossRef]
38. Provvisiero, D.P.; Pivonello, C.; Muscogiuri, G.; Negri, M.; de Angelis, C.; Simeoli, C.; Pivonello, R.; Colao, A. Influence of Bisphenol A on Type 2 Diabetes Mellitus. *Int. J. Environ. Res. Public Health* **2016**, *13*, 989. [CrossRef]
39. Xu, J.; Huang, G.; Guo, T.L. Developmental Bisphenol A Exposure Modulates Immune-Related Diseases. *Toxics* **2016**, *4*, 23. [CrossRef]
40. Chapin, R.E.; Adams, J.; Boekelheide, K.; Gray, L.E., Jr.; Hayward, S.W.; Lees, P.S.; McIntyre, B.S.; Portier, K.M.; Schnorr, T.M.; Selevan, S.G.; et al. NTP-CERHR expert panel report on the reproductive and developmental toxicity of bisphenol A. *Birth. Defects. Res. B Dev. Reprod. Toxicol.* **2008**, *83*, 157–395. [CrossRef]
41. Nohynek, G.J.; Borgert, C.J.; Dietrich, D.; Rozman, K.K. Endocrine disruption: Fact or urban legend? *Toxicol. Lett.* **2013**, *223*, 295–305. [CrossRef] [PubMed]
42. Carmeci, C.; Thompson, D.A.; Ring, H.Z.; Francke, U.; Weigel, R.J. Identification of a gene (GPR30) with homology to the G-protein-coupled receptor superfamily associated with estrogen receptor expression in breast cancer. *Genomics* **1997**, *45*, 607–617. [CrossRef] [PubMed]
43. Wang, H.; Ding, Z.; Shi, Q.M.; Ge, X.; Wang, H.X.; Li, M.X.; Chen, G.; Wang, Q.; Ju, Q.; Zhang, J.P.; et al. Anti-androgenic mechanisms of Bisphenol A involve androgen receptor signaling pathway. *Toxicology* **2017**, *387*, 10–16. [CrossRef] [PubMed]
44. Enmark, E.; Pelto-Huikko, M.; Grandien, K.; Lagercrantz, S.; Lagercrantz, J.; Fried, G.; Nordenskjold, M.; Gustafsson, J.A. Human estrogen receptor beta-gene structure, chromosomal localization, and expression pattern. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 4258–4265. [CrossRef] [PubMed]
45. Menasce, L.P.; White, G.R.; Harrison, C.J.; Boyle, J.M. Localization of the estrogen receptor locus (ESR) to chromosome 6q25.1 by FISH and a simple post-FISH banding technique. *Genomics* **1993**, *17*, 263–265. [CrossRef]
46. Kuiper, G.G.; Lemmen, J.G.; Carlsson, B.; Corton, J.C.; Safe, S.H.; van der Saag, P.T.; van der Burg, B.; Gustafsson, J.A. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology* **1998**, *139*, 4252–4263. [CrossRef]
47. Matthews, J.; Celius, T.; Halgren, R.; Zacharewski, T. Differential estrogen receptor binding of estrogenic substances: A species comparison. *J. Steroid. Biochem. Mol. Biol.* **2000**, *74*, 223–234. [CrossRef]
48. Acconcia, F.; Pallottini, V.; Marino, M. Molecular Mechanisms of Action of BPA. *Dose Response* **2015**, *13*, 1559325815610582. [CrossRef]
49. Angle, B.M.; Do, R.P.; Ponzi, D.; Stahlhut, R.W.; Drury, B.E.; Nagel, S.C.; Welshons, W.V.; Besch-Williford, C.L.; Palanza, P.; Parmigiani, S.; et al. Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): Evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. *Reprod. Toxicol.* **2013**, *42*, 256–268. [CrossRef]

50. Nadal, A.; Ropero, A.B.; Laribi, O.; Maillet, M.; Fuentes, E.; Soria, B. Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor alpha and estrogen receptor beta. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 11603–11608. [CrossRef]
51. Wetherill, Y.B.; Akingbemi, B.T.; Kanno, J.; McLachlan, J.A.; Nadal, A.; Sonnenschein, C.; Watson, C.S.; Zoeller, R.T.; Belcher, S.M. In vitro molecular mechanisms of bisphenol A action. *Reprod. Toxicol.* **2007**, *24*, 178–198. [CrossRef] [PubMed]
52. Phrakonkham, P.; Viengchareun, S.; Belloir, C.; Lombes, M.; Artur, Y.; Canivenc-Lavier, M.C. Dietary xenoestrogens differentially impair 3T3-L1 preadipocyte differentiation and persistently affect leptin synthesis. *J. Steroid. Biochem. Mol. Biol.* **2008**, *110*, 95–103. [CrossRef] [PubMed]
53. Ben-Jonathan, N.; Hugo, E.R.; Brandebourg, T.D. Effects of bisphenol A on adipokine release from human adipose tissue: Implications for the metabolic syndrome. *Mol. Cell. Endocrinol.* **2009**, *304*, 49–54. [CrossRef] [PubMed]
54. Rubin, B.S.; Paranjpe, M.; DaFonte, T.; Schaeberle, C.; Soto, A.M.; Obin, M.; Greenberg, A.S. Perinatal BPA exposure alters body weight and composition in a dose specific and sex specific manner: The addition of peripubertal exposure exacerbates adverse effects in female mice. *Reprod. Toxicol.* **2017**, *68*, 130–144. [CrossRef]
55. Ptak, A.; Gregoraszczuk, E.L. Bisphenol A induces leptin receptor expression, creating more binding sites for leptin, and activates the JAK/Stat, MAPK/ERK and PI3K/Akt signalling pathways in human ovarian cancer cell. *Toxicol. Lett.* **2012**, *210*, 332–337. [CrossRef]
56. Song, H.; Zhang, T.; Yang, P.; Li, M.; Yang, Y.; Wang, Y.; Du, J.; Pan, K.; Zhang, K. Low doses of bisphenol A stimulate the proliferation of breast cancer cells via ERK1/2/ERRγ signals. *Toxicol. In Vitro* **2015**, *30*, 521–528. [CrossRef]
57. Dairkee, S.H.; Luciani-Torres, M.G.; Moore, D.H.; Goodson, W.H. Bisphenol-A-induced inactivation of the p53 axis underlying deregulation of proliferation kinetics, and cell death in non-malignant human breast epithelial cells. *Carcinogenesis* **2013**, *34*, 703–712. [CrossRef]
58. Alonso-Magdalena, P.; Laribi, O.; Ropero, A.B.; Fuentes, E.; Ripoll, C.; Soria, B.; Nadal, A. Low doses of bisphenol A and diethylstilbestrol impair Ca^{2+} signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ. Health Perspect.* **2005**, *113*, 969–977. [CrossRef]
59. Noguchi, S.; Nakatsuka, M.; Asagiri, K.; Habara, T.; Takata, M.; Konishi, H.; Kudo, T. Bisphenol A stimulates NO synthesis through a non-genomic estrogen receptor-mediated mechanism in mouse endothelial cells. *Toxicol. Lett.* **2002**, *135*, 95–101. [CrossRef]
60. O'Dowd, B.F.; Nguyen, T.; Marchese, A.; Cheng, R.; Lynch, K.R.; Heng, H.H.; Kolakowski, L.F., Jr.; George, S.R. Discovery of three novel G-protein-coupled receptor genes. *Genomics* **1998**, *47*, 310–313. [CrossRef]
61. Owman, C.; Blay, P.; Nilsson, C.; Lolait, S.J. Cloning of human cDNA encoding a novel heptahelix receptor expressed in Burkitt's lymphoma and widely distributed in brain and peripheral tissues. *Biochem. Biophys. Res. Commun.* **1996**, *228*, 285–292. [CrossRef] [PubMed]
62. Takada, Y.; Kato, C.; Kondo, S.; Korenaga, R.; Ando, J. Cloning of cDNAs encoding G protein-coupled receptor expressed in human endothelial cells exposed to fluid shear stress. *Biochem. Biophys. Res. Commun.* **1997**, *240*, 737–741. [CrossRef]
63. Pietras, R.J.; Marquez-Garban, D.C. Membrane-associated estrogen receptor signaling pathways in human cancers. *Clin. Cancer Res.* **2007**, *13*, 4672–4676. [CrossRef] [PubMed]
64. Ho, K.J.; Liao, J.K. Non-nuclear actions of estrogen: New targets for prevention and treatment of cardiovascular disease. *Mol. Interv.* **2002**, *2*, 219–228. [CrossRef]
65. Kelly, M.J.; Levin, E.R. Rapid actions of plasma membrane estrogen receptors. *Trends Endocrinol. Metab.* **2001**, *12*, 152–156. [CrossRef]
66. Levin, E.R. Cell localization, physiology, and nongenomic actions of estrogen receptors. *J. Appl. Physiol.* **2001**, *91*, 1860–1867. [CrossRef] [PubMed]
67. Levin, E.R. Cellular functions of plasma membrane estrogen receptors. *Steroids* **2002**, *67*, 471–475. [CrossRef]
68. Razandi, M.; Pedram, A.; Park, S.T.; Levin, E.R. Proximal events in signaling by plasma membrane estrogen receptors. *J. Biol. Chem.* **2003**, *278*, 2701–2712. [CrossRef]
69. Prossnitz, E.R.; Maggiolini, M. Mechanisms of estrogen signaling and gene expression via GPR30. *Mol. Cell Endocrinol.* **2009**, *308*, 32–38. [CrossRef]

70. Revankar, C.M.; Mitchell, H.D.; Field, A.S.; Burai, R.; Corona, C.; Ramesh, C.; Sklar, L.A.; Arterburn, J.B.; Prossnitz, E.R. Synthetic estrogen derivatives demonstrate the functionality of intracellular GPR30. *ACS Chem. Biol.* **2007**, *2*, 536–544. [CrossRef]
71. Thomas, P.; Dong, J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. *J. Steroid. Biochem. Mol. Biol.* **2006**, *102*, 175–179. [CrossRef] [PubMed]
72. Wang, A.; Luo, J.; Moore, W.; Alkhalidy, H.; Wu, L.; Zhang, J.; Zhen, W.; Wang, Y.; Clegg, D.J.; Bin, X.; et al. GPR30 regulates diet-induced adiposity in female mice and adipogenesis in vitro. *Sci. Rep.* **2016**, *6*, 34302. [CrossRef] [PubMed]
73. Garcia-Arevalo, M.; Alonso-Magdalena, P.; Rebelo Dos Santos, J.; Quesada, I.; Carneiro, E.M.; Nadal, A. Exposure to bisphenol-A during pregnancy partially mimics the effects of a high-fat diet altering glucose homeostasis and gene expression in adult male mice. *PLoS ONE* **2014**, *9*, e100214. [CrossRef] [PubMed]
74. Moon, M.K.; Jeong, I.K.; Jung Oh, T.; Ahn, H.Y.; Kim, H.H.; Park, Y.J.; Jang, H.C.; Park, K.S. Long-term oral exposure to bisphenol A induces glucose intolerance and insulin resistance. *J. Endocrinol.* **2015**, *226*, 35–42. [CrossRef]
75. Filardo, E.J.; Graeber, C.T.; Quinn, J.A.; Resnick, M.B.; Giri, D.; DeLellis, R.A.; Steinhoff, M.M.; Sabo, E. Distribution of GPR30, a seven membrane-spanning estrogen receptor, in primary breast cancer and its association with clinicopathologic determinants of tumor progression. *Clin. Cancer Res.* **2006**, *12*, 6359–6366. [CrossRef]
76. Smith, H.O.; Arias-Pulido, H.; Kuo, D.Y.; Howard, T.; Qualls, C.R.; Lee, S.J.; Verschraegen, C.F.; Hathaway, H.J.; Joste, N.E.; Prossnitz, E.R. GPR30 predicts poor survival for ovarian cancer. *Gynecol. Oncol.* **2009**, *114*, 465–471. [CrossRef]
77. Dong, S.; Terasaka, S.; Kiyama, R. Bisphenol A induces a rapid activation of Erk1/2 through GPR30 in human breast cancer cells. *Environ. Pollut.* **2011**, *159*, 212–218. [CrossRef]
78. Wang, C.; Zhang, J.; Li, Q.; Zhang, T.; Deng, Z.; Lian, J.; Jia, D.; Li, R.; Zheng, T.; Ding, X.; et al. Low concentration of BPA induces mice spermatocytes apoptosis via GPR30. *Oncotarget* **2017**, *8*, 49005–49015. [CrossRef]
79. Chevalier, N.; Bouskine, A.; Fenichel, P. Bisphenol A promotes testicular seminoma cell proliferation through GPER/GPR30. *Int. J. Cancer* **2012**, *130*, 241–242. [CrossRef]
80. Kojima, H.; Takeuchi, S.; Sanoh, S.; Okuda, K.; Kitamura, S.; Uramaru, N.; Sugihara, K.; Yoshinari, K. Profiling of bisphenol A and eight its analogues on transcriptional activity via human nuclear receptors. *Toxicology* **2019**, *413*, 48–55. [CrossRef]
81. Molina-Molina, J.M.; Amaya, E.; Grimaldi, M.; Saenz, J.M.; Real, M.; Fernandez, M.F.; Balaguer, P.; Olea, N. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. *Toxicol. Appl. Pharmacol.* **2013**, *272*, 127–136. [CrossRef] [PubMed]
82. Sohoni, P.; Sumpter, J.P. Several environmental oestrogens are also anti-androgens. *J. Endocrinol.* **1998**, *158*, 327–339. [CrossRef] [PubMed]
83. Fang, H.; Tong, W.; Branham, W.S.; Moland, C.L.; Dial, S.L.; Hong, H.; Xie, Q.; Perkins, R.; Owens, W.; Sheehan, D.M. Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. *Chem. Res. Toxicol.* **2003**, *16*, 1338–1358. [CrossRef] [PubMed]
84. Perera, L.; Li, Y.; Coons, L.A.; Houtman, R.; Van Beuningen, R.; Goodwin, B.; Auerbach, S.S.; Teng, C.T. Binding of bisphenol A, bisphenol AF, and bisphenol S on the androgen receptor: Coregulator recruitment and stimulation of potential interaction sites. *Toxicol. In Vitro* **2017**, *44*, 287–302. [CrossRef] [PubMed]
85. Manfo, F.P.; Jubendradass, R.; Nantia, E.A.; Moundipa, P.F.; Mathur, P.P. Adverse effects of bisphenol A on male reproductive function. *Rev. Environ. Contam. Toxicol.* **2014**, *228*, 57–82. [CrossRef] [PubMed]
86. Huang, X.; Cang, X.; Liu, J. Molecular mechanism of Bisphenol A on androgen receptor antagonism. *Toxicol. In Vitro* **2019**, *61*, 104621. [CrossRef]
87. Li, D.; Zhou, Z.; Qing, D.; He, Y.; Wu, T.; Miao, M.; Wang, J.; Weng, X.; Ferber, J.R.; Herrinton, L.J.; et al. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. *Hum. Reprod.* **2010**, *25*, 519–527. [CrossRef]
88. Vitku, J.; Sosvorova, L.; Chlupacova, T.; Hampl, R.; Hill, M.; Sobotka, V.; Heracek, J.; Bicikova, M.; Starka, L. Differences in bisphenol A and estrogen levels in the plasma and seminal plasma of men with different degrees of infertility. *Physiol. Res.* **2015**, *64*, S303–S311. [CrossRef]

89. Ascenzi, P.; Bocedi, A.; Marino, M. Structure-function relationship of estrogen receptor alpha and beta: Impact on human health. *Mol. Asp. Med.* **2006**, *27*, 299–402. [CrossRef]
90. Takayanagi, S.; Tokunaga, T.; Liu, X.; Okada, H.; Matsushima, A.; Shimohigashi, Y. Endocrine disruptor bisphenol A strongly binds to human estrogen-related receptor gamma (ERRgamma) with high constitutive activity. *Toxicol. Lett.* **2006**, *167*, 95–105. [CrossRef]
91. Tohme, M.; Prud'homme, S.M.; Boulahtouf, A.; Samarut, E.; Brunet, F.; Bernard, L.; Bourguet, W.; Gibert, Y.; Balaguer, P.; Laudet, V. Estrogen-related receptor gamma is an in vivo receptor of bisphenol A. *FASEB J.* **2014**, *28*, 3124–3133. [CrossRef] [PubMed]
92. Liu, X.; Matsushima, A.; Shimohigashi, M.; Shimohigashi, Y. A characteristic back support structure in the bisphenol A-binding pocket in the human nuclear receptor ERRγ. *PLoS ONE* **2014**, *9*, e101252. [CrossRef] [PubMed]
93. Ranhotra, H.S. The mammalian orphan nuclear receptors: Orphans as cellular guardians. *J. Recept. Signal Transduct. Res.* **2011**, *31*, 20–25. [CrossRef] [PubMed]
94. Zhang, X.L.; Liu, N.; Weng, S.F.; Wang, H.S. Bisphenol A Increases the Migration and Invasion of Triple-Negative Breast Cancer Cells via Oestrogen-related Receptor Gamma. *Basic Clin. Pharmacol. Toxicol.* **2016**, *119*, 389–395. [CrossRef]
95. Atlas, E.; Pope, L.; Wade, M.G.; Kawata, A.; Boudreau, A.; Boucher, J.G. Bisphenol A increases aP2 expression in 3T3L1 by enhancing the transcriptional activity of nuclear receptors at the promoter. *Adipocyte* **2014**, *3*, 170–179. [CrossRef]
96. Meeker, J.D.; Calafat, A.M.; Hauser, R. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. *Environ. Sci. Technol.* **2010**, *44*, 1458–1463. [CrossRef]
97. Sun, H.; Shen, O.X.; Wang, X.R.; Zhou, L.; Zhen, S.Q.; Chen, X.D. Anti-thyroid hormone activity of bisphenol A, tetrabromobisphenol A and tetrachlorobisphenol A in an improved reporter gene assay. *Toxicol. In Vitro* **2009**, *23*, 950–954. [CrossRef]
98. Gorini, F.; Bustaffa, E.; Coi, A.; Iervasi, G.; Bianchi, F. Bisphenols as Environmental Triggers of Thyroid Dysfunction: Clues and Evidence. *Int. J. Environ. Res. Public Health* **2020**, *17*, 2654. [CrossRef]
99. Somm, E.; Schwitzgebel, V.M.; Toulotte, A.; Cederroth, C.R.; Combescure, C.; Nef, S.; Aubert, M.L.; Huppi, P.S. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ. Health Perspect.* **2009**, *117*, 1549–1555. [CrossRef]
100. Pu, Y.; Gingrich, J.D.; Steibel, J.P.; Veiga-Lopez, A. Sex-Specific Modulation of Fetal Adipogenesis by Gestational Bisphenol A and Bisphenol S Exposure. *Endocrinology* **2017**, *158*, 3844–3858. [CrossRef]
101. Biasiotto, G.; Zanella, I.; Masserdotti, A.; Pedrazzani, R.; Papa, M.; Caimi, L.; Di Lorenzo, D. Municipal wastewater affects adipose deposition in male mice and increases 3T3-L1 cell differentiation. *Toxicol. Appl. Pharmacol.* **2016**, *297*, 32–40. [CrossRef] [PubMed]
102. Ariemma, F.; D'Esposito, V.; Liguoro, D.; Oriente, F.; Cabaro, S.; Liotti, A.; Cimmino, I.; Longo, M.; Beguinot, F.; Formisano, P.; et al. Low-Dose Bisphenol-A Impairs Adipogenesis and Generates Dysfunctional 3T3-L1 Adipocytes. *PLoS ONE* **2016**, *11*, e0150762. [CrossRef] [PubMed]
103. Boucher, J.G.; Gagne, R.; Rowan-Carroll, A.; Boudreau, A.; Yauk, C.L.; Atlas, E. Bisphenol A and Bisphenol S Induce Distinct Transcriptional Profiles in Differentiating Human Primary Preadipocytes. *PLoS ONE* **2016**, *11*, e0163318. [CrossRef] [PubMed]
104. Wang, J.; Sun, B.; Hou, M.; Pan, X.; Li, X. The environmental obesogen bisphenol A promotes adipogenesis by increasing the amount of 11beta-hydroxysteroid dehydrogenase type 1 in the adipose tissue of children. *Int. J. Obes. (Lond.)* **2013**, *37*, 999–1005. [CrossRef] [PubMed]
105. Salehpour, A.; Shidfar, F.; Hedayati, M.; Neshatbini Tehrani, A.; Farshad, A.A.; Mohammadi, S. Bisphenol A enhances adipogenic signaling pathways in human mesenchymal stem cells. *Genes Environ.* **2020**, *42*, 13. [CrossRef]
106. DeBenedictis, B.; Guan, H.; Yang, K. Prenatal Exposure to Bisphenol A Disrupts Mouse Fetal Liver Maturation in a Sex-Specific Manner. *J. Cell Biochem.* **2016**, *117*, 344–350. [CrossRef]
107. Ma, Q. Role of nrf2 in oxidative stress and toxicity. *Annu. Rev. Pharmacol. Toxicol.* **2013**, *53*, 401–426. [CrossRef]
108. Jiang, T.; Tian, F.; Zheng, H.; Whitman, S.A.; Lin, Y.; Zhang, Z.; Zhang, N.; Zhang, D.D. Nrf2 suppresses lupus nephritis through inhibition of oxidative injury and the NF-κB-mediated inflammatory response. *Kidney Int.* **2014**, *85*, 333–343. [CrossRef]

109. Dong, Y.; Zhang, Z.; Liu, H.; Jia, L.; Qin, M.; Wang, X. Exacerbating lupus nephritis following BPA exposure is associated with abnormal autophagy in MRL/lpr mice. *Am. J. Transl. Res.* **2020**, *12*, 649–659.
110. Xu, D.; Xu, M.; Jeong, S.; Qian, Y.; Wu, H.; Xia, Q.; Kong, X. The Role of Nrf2 in Liver Disease: Novel Molecular Mechanisms and Therapeutic Approaches. *Front. Pharmacol.* **2018**, *9*, 1428. [CrossRef]
111. Xu, J.; Donepudi, A.C.; More, V.R.; Kulkarni, S.R.; Li, L.; Guo, L.; Yan, B.; Chatterjee, T.; Weintraub, N.; Slitt, A.L. Deficiency in Nrf2 transcription factor decreases adipose tissue mass and hepatic lipid accumulation in leptin-deficient mice. *Obesity* **2015**, *23*, 335–344. [CrossRef] [PubMed]
112. Nakamura, M.; Yamanaka, H.; Oguro, A.; Imaoka, S. Bisphenol A induces Nrf2-dependent drug-metabolizing enzymes through nitrosylation of Keap1. *Drug Metab. Pharmacokinet.* **2018**, *33*, 194–202. [CrossRef] [PubMed]
113. Shimpi, P.C.; More, V.R.; Paranjpe, M.; Donepudi, A.C.; Goodrich, J.M.; Dolinoy, D.C.; Rubin, B.; Slitt, A.L. Hepatic Lipid Accumulation and Nrf2 Expression following Perinatal and Peripubertal Exposure to Bisphenol A in a Mouse Model of Nonalcoholic Liver Disease. *Environ. Health Perspect.* **2017**, *125*, 087005. [CrossRef] [PubMed]
114. Lappin, T.R.; Grier, D.G.; Thompson, A.; Halliday, H.L. HOX genes: Seductive science, mysterious mechanisms. *Ulster. Med. J.* **2006**, *75*, 23–31.
115. Featherstone, M. HOX proteins and their co-factors in transcriptional regulation. *Adv. Develop. Biol. Biochem.* **2003**, *13*, 1–42. [CrossRef]
116. Taylor, H.S.; Vanden Heuvel, G.B.; Igarashi, P. A conserved Hox axis in the mouse and human female reproductive system: Late establishment and persistent adult expression of the Hoxa cluster genes. *Biol. Reprod.* **1997**, *57*, 1338–1345. [CrossRef]
117. Chen, F.; Capecchi, M.R. Paralogous mouse Hox genes, Hoxa9, Hoxb9, and Hoxd9, function together to control development of the mammary gland in response to pregnancy. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 541–546. [CrossRef]
118. Smith, C.C.; Taylor, H.S. Xenoestrogen exposure imprints expression of genes (Hoxa10) required for normal uterine development. *FASEB J.* **2007**, *21*, 239–246. [CrossRef]
119. Hayashida, T.; Takahashi, F.; Chiba, N.; Brachtel, E.; Takahashi, M.; Godin-Heymann, N.; Gross, K.W.; Vivanco, M.; Wijendran, V.; Shioda, T.; et al. HOXB9, a gene overexpressed in breast cancer, promotes tumorigenicity and lung metastasis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 1100–1105. [CrossRef]
120. Bodey, B.; Bodey, B., Jr.; Siegel, S.E.; Kaiser, H.E. Immunocytochemical detection of the homeobox B3, B4, and C6 gene products in breast carcinomas. *Anticancer Res.* **2000**, *20*, 3281–3286.
121. Castronovo, V.; Kusaka, M.; Chariot, A.; Gielen, J.; Sobel, M. Homeobox genes: Potential candidates for the transcriptional control of the transformed and invasive phenotype. *Biochem. Pharmacol.* **1994**, *47*, 137–143. [CrossRef]
122. Deb, P.; Bhan, A.; Hussain, I.; Ansari, K.I.; Bobzean, S.A.; Pandita, T.K.; Perrotti, L.I.; Mandal, S.S. Endocrine disrupting chemical, bisphenol-A, induces breast cancer associated gene HOXB9 expression in vitro and in vivo. *Gene* **2016**, *590*, 234–243. [CrossRef] [PubMed]
123. Hussain, I.; Bhan, A.; Ansari, K.I.; Deb, P.; Bobzean, S.A.; Perrotti, L.I.; Mandal, S.S. Bisphenol-A induces expression of HOXC6, an estrogen-regulated homeobox-containing gene associated with breast cancer. *Biochim. Biophys. Acta* **2015**, *1849*, 697–708. [CrossRef] [PubMed]
124. Li, Q.; Davila, J.; Kannan, A.; Flaws, J.A.; Bagchi, M.K.; Bagchi, I.C. Chronic Exposure to Bisphenol A Affects Uterine Function During Early Pregnancy in Mice. *Endocrinology* **2016**, *157*, 1764–1774. [CrossRef] [PubMed]
125. McFadden, D.G.; Barbosa, A.C.; Richardson, J.A.; Schneider, M.D.; Srivastava, D.; Olson, E.N. The Hand1 and Hand2 transcription factors regulate expansion of the embryonic cardiac ventricles in a gene dosage-dependent manner. *Development* **2005**, *132*, 189–201. [CrossRef] [PubMed]
126. Schindler, Y.L.; Garske, K.M.; Wang, J.; Firulli, B.A.; Firulli, A.B.; Poss, K.D.; Yelon, D. Hand2 elevates cardiomyocyte production during zebrafish heart development and regeneration. *Development* **2014**, *141*, 3112–3122. [CrossRef]
127. Moreman, J.; Lee, O.; Trznadel, M.; David, A.; Kudoh, T.; Tyler, C.R. Acute Toxicity, Teratogenic, and Estrogenic Effects of Bisphenol A and Its Alternative Replacements Bisphenol S, Bisphenol F, and Bisphenol AF in Zebrafish Embryo-Larvae. *Environ. Sci. Technol.* **2017**, *51*, 12796–12805. [CrossRef]
128. Bakkers, J. Zebrafish as a model to study cardiac development and human cardiac disease. *Cardiovasc. Res.* **2011**, *91*, 279–288. [CrossRef]
129. Stainier, D.Y. Zebrafish genetics and vertebrate heart formation. *Nat. Rev. Genet.* **2001**, *2*, 39–48. [CrossRef]

130. Lombo, M.; Gonzalez-Rojo, S.; Fernandez-Diez, C.; Herraez, M.P. Cardiogenesis impairment promoted by bisphenol A exposure is successfully counteracted by epigallocatechin gallate. *Environ. Pollut.* **2019**, *246*, 1008–1019. [CrossRef]
131. Ho, S.M.; Tang, W.Y.; Belmonte de Frausto, J.; Prins, G.S. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. *Cancer Res.* **2006**, *66*, 5624–5632. [CrossRef] [PubMed]
132. Dolinoy, D.C.; Huang, D.; Jirtle, R.L. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 13056–13061. [CrossRef] [PubMed]
133. Anderson, O.S.; Nahar, M.S.; Faulk, C.; Jones, T.R.; Liao, C.; Kannan, K.; Weinhouse, C.; Rozek, L.S.; Dolinoy, D.C. Epigenetic responses following maternal dietary exposure to physiologically relevant levels of bisphenol A. *Environ. Mol. Mutagen.* **2012**, *53*, 334–342. [CrossRef] [PubMed]
134. Bromer, J.G.; Zhou, Y.; Taylor, M.B.; Doherty, L.; Taylor, H.S. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. *FASEB J.* **2010**, *24*, 2273–2280. [CrossRef]
135. Klinge, C.M. Estrogen Regulation of MicroRNA Expression. *Curr. Genom.* **2009**, *10*, 169–183. [CrossRef]
136. Doherty, L.F.; Bromer, J.G.; Zhou, Y.; Aldad, T.S.; Taylor, H.S. In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: An epigenetic mechanism linking endocrine disruptors to breast cancer. *Horm. Cancer* **2010**, *1*, 146–155. [CrossRef]
137. Dhimolea, E.; Wadia, P.R.; Murray, T.J.; Settles, M.L.; Treitman, J.D.; Sonnenschein, C.; Shioda, T.; Soto, A.M. Prenatal exposure to BPA alters the epigenome of the rat mammary gland and increases the propensity to neoplastic development. *PLoS ONE* **2014**, *9*, e99800. [CrossRef]
138. Veiga-Lopez, A.; Luense, L.J.; Christenson, L.K.; Padmanabhan, V. Developmental programming: Gestational bisphenol-A treatment alters trajectory of fetal ovarian gene expression. *Endocrinology* **2013**, *154*, 1873–1884. [CrossRef]
139. Kim, J.H.; Sartor, M.A.; Rozek, L.S.; Faulk, C.; Anderson, O.S.; Jones, T.R.; Nahar, M.S.; Dolinoy, D.C. Perinatal bisphenol A exposure promotes dose-dependent alterations of the mouse methylome. *BMC Genom.* **2014**, *15*, 30. [CrossRef]
140. Ma, Y.; Xia, W.; Wang, D.Q.; Wan, Y.J.; Xu, B.; Chen, X.; Li, Y.Y.; Xu, S.Q. Hepatic DNA methylation modifications in early development of rats resulting from perinatal BPA exposure contribute to insulin resistance in adulthood. *Diabetologia* **2013**, *56*, 2059–2067. [CrossRef]
141. Van Esterik, J.C.; Vitins, A.P.; Hodemaekers, H.M.; Kamstra, J.H.; Legler, J.; Pennings, J.L.; Steegenga, W.T.; Lute, C.; Jelinek, J.; Issa, J.P.; et al. Liver DNA methylation analysis in adult female C57BL/6JxFVB mice following perinatal exposure to bisphenol A. *Toxicol. Lett.* **2015**, *232*, 293–300. [CrossRef] [PubMed]
142. Li, G.; Chang, H.; Xia, W.; Mao, Z.; Li, Y.; Xu, S. F0 maternal BPA exposure induced glucose intolerance of F2 generation through DNA methylation change in Gck. *Toxicol. Lett.* **2014**, *228*, 192–199. [CrossRef] [PubMed]
143. Ke, Z.H.; Pan, J.X.; Jin, L.Y.; Xu, H.Y.; Yu, T.T.; Ullah, K.; Rahman, T.U.; Ren, J.; Cheng, Y.; Dong, X.Y.; et al. Bisphenol A Exposure May Induce Hepatic Lipid Accumulation via Reprogramming the DNA Methylation Patterns of Genes Involved in Lipid Metabolism. *Sci. Rep.* **2016**, *6*, 31331. [CrossRef] [PubMed]
144. Lin, Y.; Ding, D.; Huang, Q.; Liu, Q.; Lu, H.; Lu, Y.; Chi, Y.; Sun, X.; Ye, G.; Zhu, H.; et al. Downregulation of miR-192 causes hepatic steatosis and lipid accumulation by inducing SREBF1: Novel mechanism for bisphenol A-triggered non-alcoholic fatty liver disease. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2017**, *1862*, 869–882. [CrossRef] [PubMed]
145. Nakamura, M.T.; Yudell, B.E.; Loor, J.J. Regulation of energy metabolism by long-chain fatty acids. *Prog. Lipid Res.* **2014**, *53*, 124–144. [CrossRef]
146. Strakovsky, R.S.; Wang, H.; Engeseth, N.J.; Flaws, J.A.; Helferich, W.G.; Pan, Y.X.; Lezmi, S. Developmental bisphenol A (BPA) exposure leads to sex-specific modification of hepatic gene expression and epigenome at birth that may exacerbate high-fat diet-induced hepatic steatosis. *Toxicol. Appl. Pharmacol.* **2015**, *284*, 101–112. [CrossRef]
147. Bastos Sales, L.; Kamstra, J.H.; Cenijn, P.H.; van Rijt, L.S.; Hamers, T.; Legler, J. Effects of endocrine disrupting chemicals on in vitro global DNA methylation and adipocyte differentiation. *Toxicol. In Vitro* **2013**, *27*, 1634–1643. [CrossRef]

148. Junge, K.M.; Leppert, B.; Jahreis, S.; Wissenbach, D.K.; Feltens, R.; Grutzmann, K.; Thurmann, L.; Bauer, T.; Ishaque, N.; Schick, M.; et al. MEST mediates the impact of prenatal bisphenol A exposure on long-term body weight development. *Clin. Epigenet.* **2018**, *10*, 58. [CrossRef]
149. Mao, Z.; Xia, W.; Chang, H.; Huo, W.; Li, Y.; Xu, S. Paternal BPA exposure in early life alters Igf2 epigenetic status in sperm and induces pancreatic impairment in rat offspring. *Toxicol. Lett.* **2015**, *238*, 30–38. [CrossRef]
150. Wei, J.; Ding, D.; Wang, T.; Liu, Q.; Lin, Y. MiR-338 controls BPA-triggered pancreatic islet insulin secretory dysfunction from compensation to decompensation by targeting Pdx-1. *FASEB J.* **2017**, *31*, 5184–5195. [CrossRef]
151. Chang, H.; Wang, D.; Xia, W.; Pan, X.; Huo, W.; Xu, S.; Li, Y. Epigenetic disruption and glucose homeostasis changes following low-dose maternal bisphenol A exposure. *Toxicol. Res.* **2016**, *5*, 1400–1409. [CrossRef] [PubMed]
152. Shafei, A.; Ramzy, M.M.; Hegazy, A.I.; Husseny, A.K.; El-Hadary, U.G.; Taha, M.M.; Mosa, A.A. The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer. *Gene* **2018**, *647*, 235–243. [CrossRef] [PubMed]
153. Vandenberg, L.N.; Schaeberle, C.M.; Rubin, B.S.; Sonnenschein, C.; Soto, A.M. The male mammary gland: A target for the xenoestrogen bisphenol A. *Reprod. Toxicol.* **2013**, *37*, 15–23. [CrossRef] [PubMed]
154. Durando, M.; Kass, L.; Piva, J.; Sonnenschein, C.; Soto, A.M.; Luque, E.H.; Munoz-de-Toro, M. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. *Environ. Health Perspect.* **2007**, *115*, 80–86. [CrossRef] [PubMed]
155. Murray, T.J.; Maffini, M.V.; Ucci, A.A.; Sonnenschein, C.; Soto, A.M. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. *Reprod. Toxicol.* **2007**, *23*, 383–390. [CrossRef] [PubMed]
156. Bhan, A.; Hussain, I.; Ansari, K.I.; Bobzean, S.A.; Perrotti, L.I.; Mandal, S.S. Histone methyltransferase EZH2 is transcriptionally induced by estradiol as well as estrogenic endocrine disruptors bisphenol-A and diethylstilbestrol. *J. Mol. Biol.* **2014**, *426*, 3426–3441. [CrossRef]
157. Weng, Y.I.; Hsu, P.Y.; Liyanarachchi, S.; Liu, J.; Deatherage, D.E.; Huang, Y.W.; Zuo, T.; Rodriguez, B.; Lin, C.H.; Cheng, A.L.; et al. Epigenetic influences of low-dose bisphenol A in primary human breast epithelial cells. *Toxicol. Appl. Pharmacol.* **2010**, *248*, 111–121. [CrossRef]
158. Kanao, H.; Enomoto, T.; Kimura, T.; Fujita, M.; Nakashima, R.; Ueda, Y.; Ueno, Y.; Miyatake, T.; Yoshizaki, T.; Buzard, G.S.; et al. Overexpression of LAMP3/TSC403/DC-LAMP promotes metastasis in uterine cervical cancer. *Cancer Res.* **2005**, *65*, 8640–8645. [CrossRef]
159. Qin, X.Y.; Fukuda, T.; Yang, L.; Zaha, H.; Akanuma, H.; Zeng, Q.; Yoshinaga, J.; Sone, H. Effects of bisphenol A exposure on the proliferation and senescence of normal human mammary epithelial cells. *Cancer Biol. Ther.* **2012**, *13*, 296–306. [CrossRef]
160. Tilghman, S.L.; Bratton, M.R.; Segar, H.C.; Martin, E.C.; Rhodes, L.V.; Li, M.; McLachlan, J.A.; Wiese, T.E.; Nephew, K.P.; Burow, M.E. Endocrine disruptor regulation of microRNA expression in breast carcinoma cells. *PLoS ONE* **2012**, *7*, e32754. [CrossRef]
161. Li, X.; Xie, W.; Xie, C.; Huang, C.; Zhu, J.; Liang, Z.; Deng, F.; Zhu, M.; Zhu, W.; Wu, R.; et al. Curcumin modulates miR-19/PTEN/AKT/p53 axis to suppress bisphenol A-induced MCF-7 breast cancer cell proliferation. *Phytother. Res.* **2014**, *28*, 1553–1560. [CrossRef] [PubMed]
162. Avissar-Whiting, M.; Veiga, K.R.; Uhl, K.M.; Maccani, M.A.; Gagne, L.A.; Moen, E.L.; Marsit, C.J. Bisphenol A exposure leads to specific microRNA alterations in placental cells. *Reprod. Toxicol.* **2010**, *29*, 401–406. [CrossRef] [PubMed]
163. Prins, G.S.; Ye, S.H.; Birch, L.; Ho, S.M.; Kannan, K. Serum bisphenol A pharmacokinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague-Dawley rats. *Reprod. Toxicol.* **2011**, *31*, 1–9. [CrossRef] [PubMed]
164. Prins, G.S.; Hu, W.Y.; Shi, G.B.; Hu, D.P.; Majumdar, S.; Li, G.; Huang, K.; Nelles, J.L.; Ho, S.M.; Walker, C.L.; et al. Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostate epithelium. *Endocrinology* **2014**, *155*, 805–817. [CrossRef]
165. Cheong, A.; Zhang, X.; Cheung, Y.Y.; Tang, W.Y.; Chen, J.; Ye, S.H.; Medvedovic, M.; Leung, Y.K.; Prins, G.S.; Ho, S.M. DNA methylome changes by estradiol benzoate and bisphenol A links early-life environmental exposures to prostate cancer risk. *Epigenetics* **2016**, *11*, 674–689. [CrossRef]

166. Prins, G.S.; Ye, S.H.; Birch, L.; Zhang, X.; Cheong, A.; Lin, H.; Calderon-Gierszal, E.; Groen, J.; Hu, W.Y.; Ho, S.M.; et al. Prostate Cancer Risk and DNA Methylation Signatures in Aging Rats following Developmental BPA Exposure: A Dose-Response Analysis. *Environ. Health Perspect.* **2017**, *125*, 077007. [CrossRef]
167. Renaud, L.; Huff, M.; da Silveira, W.A.; Angert, M.; Haas, M.; Hardiman, G. Genome-Wide Analysis of Low Dose Bisphenol-A (BPA) Exposure in Human Prostate Cells. *Curr. Genom.* **2019**, *20*, 260–274. [CrossRef]
168. Fatma Karaman, E.; Caglayan, M.; Sancar-Bas, S.; Ozal-Coskun, C.; Arda-Pirincci, P.; Ozden, S. Global and region-specific post-transcriptional and post-translational modifications of bisphenol A in human prostate cancer cells. *Environ. Pollut.* **2019**, *255*, 113318. [CrossRef]
169. Vandenberg, L.N.; Maffini, M.V.; Sonnenschein, C.; Rubin, B.S.; Soto, A.M. Bisphenol-A and the great divide: A review of controversies in the field of endocrine disruption. *Endocr. Rev.* **2009**, *30*, 75–95. [CrossRef]
170. Singh, S.; Li, S.S. Epigenetic effects of environmental chemicals bisphenol A and phthalates. *Int. J. Mol. Sci.* **2012**, *13*, 10143–10153. [CrossRef]
171. FitzGerald, R.; Hank, V.L.; Civitella, C.; Castoldi, A.F.; Bernasconi, G. Assessment of new information on Bisphenol S (BPS) submitted in response to the Decision [1] under REACH Regulation (EC) No. 1907/2006. *EFSA* **2020**, *17*, 1844e. [CrossRef]
172. Moon, M.K. Concern about the Safety of Bisphenol A Substitutes. *Diabetes Metab. J.* **2019**, *43*, 46–48. [CrossRef] [PubMed]
173. Thoene, M.; Dzika, E.; Gonkowski, S.; Wojtkiewicz, J. Bisphenol S in Food Causes Hormonal and Obesogenic Effects Comparable to or Worse than Bisphenol A: A Literature Review. *Nutrients* **2020**, *12*, 532. [CrossRef] [PubMed]
174. Jung, N.; Maguer-Satta, V.; Guyot, B. Early Steps of Mammary Stem Cell Transformation by Exogenous Signals; Effects of Bisphenol Endocrine Disrupting Chemicals and Bone Morphogenetic Proteins. *Cancers* **2019**, *11*, 1351. [CrossRef] [PubMed]