Chapter

Perspective Chapter: Bisphenols as Endocrine Disruptor – A Crosstalk Between Toll-Like Receptor Signaling and Innate Immune Function

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Abstract

Bisphenols are widely used in the manufacture of polycarbonate plastics and epoxy resins, among other commercial applications. This has resulted in widespread environmental contamination and chronic human exposure. Bisphenol A (BPA), initially synthesized as a synthetic estrogen, can disrupt endocrine activity despite having a weak binding affinity for estrogen receptors when compared to endogenous estrogens. Concern over health effects associated with BPA has led to the introduction of substitutes such as bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF) that are touted to be "safer", but they retain key molecular components that underlie their endocrine activity. Specifically, the conserved diphenolic framework is characterized by two para-phenolic rings with hydroxyl group spacing similar to that of natural hormones. This chapter investigates the chemistry, sources, environmental persistence, and exposure pathways of BPA and its analogues, and explores how their structural properties drive endocrine and immune system disruption due to their interference with nuclear- (i.e., thyroid hormone receptors, estrogen receptors) and toll-like receptor (TLR)-mediated signaling to alter endocrine and immune function.

Keywords: biphenols, endocrine disruptors, toll-like receptors, NF-kB, MAPK, estrogen receptor, inflammation

1. Introduction

Bisphenols (BPs), such as Bisphenol A (BPA), are organic synthetic chemicals initially produced to serve as synthetic estrogen. However, since BPA did not bind to the estrogen receptor (ER) as strongly as natural estrogens, it was largely forgotten as a potential pharmaceutical [1]. In the 1950s, BPA was repurposed and commercialized for the manufacture of epoxy resins used as the lining of food cans and piping materials. Polycarbonate plastics are also produced by polymerizing BPA [2].

With the scale of BPA production in the United States reaching billions of pounds by the early 2000s [3], the sheer volume in circulation increases the probability of environmental leakage, making widespread contamination inevitable. Multiple biomonitoring studies have demonstrated the presence of BPA in biological samples [4], raising concerns about the long-term health effects of BPA exposure. Because BPA is not permanently bound to the polymers it is used to manufacture, it can slowly leach from consumer products into foodstuffs, water, or soils, accumulating in biological systems [5]. Due to extensive evidence linking BPA to detrimental health effects [6, 7], other BPA analogues, such as BPF, BPS, and BPAF, were introduced as "safer" substitutes. Nevertheless, structural similarities shared among all BPs pose them to act as potential endocrine disruptors [8].

The endocrine system is composed of ductless glands, including the hypothalamus, pituitary, pineal, thyroid, parathyroid, and adrenal glands, as well as the pancreas. Collectively, these organs regulate a wide range of physiological activities via endocrine signaling pathways that are dependent on receptor binding. Any disruption of normal endocrine function can lead to a myriad of pathophysiological and developmental disorders [9, 10].

The thyroid hormones (TH), thyroxine (T4) and triiodothyronine (T3), bind to nuclear thyroid receptors (TRs) to regulate gene transcription. While BPA can interfere by acting as a receptor antagonist to displace T3 (the predominant bioactive thyroid hormone) and disrupt the recruitment of coactivators [11], emerging evidence indicates that BPF and BPS can also disrupt thyroid hormone signaling via altered TR-regulated transcription [12–14].

BPs also interfere with estrogen receptor-mediated signaling. Estrogens are steroid hormones that regulate numerous physiological processes but are especially important for female reproductive function as well as normal sexual development. Estrogens are produced mostly in the ovary, and their effects are mediated by cytosolic estrogen receptors (ERα, ERβ). In each case, the ligand-estrogen receptor complex functions as a transcription factor to modulate the expression of estrogen-responsive genes. BPs can bind to ERs, albeit with weak affinity, to dysregulate normal ER-mediated functions, but in a receptor-specific context [15]. For example, BPA, BPF, and BPS exhibit estrogenic activity, with BPS showing preferential activation toward ERβ [16], while BPA acts as an antagonist toward ERβ [15]. BPF acts as a partial ERα and ERβ agonist [17]. BPAF can bind both ERs and has an antagonistic effect toward ERβ [18].

Innate immune cells, such as macrophages and neutrophils, can also be disrupted by BPs. In the case of neutrophils, activation requires a two-step process whereby they are primed by early inflammatory mediators, such as cytokines and pathogen-associated molecular patterns (PAMPs). Once primed, they show enhanced responsiveness, characterized by activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the enzyme complex responsible for generating reactive oxygen species (ROS) used to destroy bacteria and viruses [19, 20]. Macrophages also recognize PAMPs to produce proinflammatory cytokines, among other receptor-mediated responses. In each case, PAMPs serve as ligands for toll-like receptors (TLRs), with neutrophils and macrophages also expressing active TRs and ERs to contribute to the inflammatory response [21, 22].

2. Bisphenols: chemistry, sources, and exposure

2.1 Chemical structure, synthesis, and structural properties of BPA, BPS, BPF, and BPAF

Bisphenols are industrial chemical compounds used as monomers in the manufacturing of polymers such as polycarbonate and epoxy resins [15]. They are characterized by the presence of two phenolic rings connected by a central bridging group. Production involves acid- or base-catalyzed condensation reactions with phenolic substrates and small carbonyl or sulfonyl molecules to form stable -C–C-, -C–O-, or -C–S- bonds, giving rise to specific analogues (**Figure 1**). The defining diphenylmethane scaffold, consisting of two aromatic phenyl rings connected through a central bridging carbon, is the core architecture that influences the biological behavior of BPs. Moreover, phenolic hydroxyl groups located at the para positions of each ring are essential for ER binding as they mimic the hydrogen-bonding pattern of E2 within the ERα ligand-binding pocket. Ultimately, the distance and orientation of the phenol rings determine whether a bound BP stabilizes the receptor in its agonist configuration or disrupts helix-12 positioning to produce antagonism. In addition, substituents on the central carbon can strongly modulate receptor activity. Smaller groups (such as BPA's methyl groups) allow partial agonism, whereas longer or cyclic alkyl chains increase steric bulk and induce antagonism [23]. Ultimately, the identity of the bridging unit and the catalyst system used define the final BP structure and directly influence its polarity, rigidity, thermal stability, and reactivity.

The fundamental method for synthesizing BPA is the acid-catalyzed condensation of phenol with acetone, which forms its characteristic 2,2-bis (4-hydroxyphenyl) propane structure and results in the formation of an isopropylidene bridge linking the phenolic rings [24]. BPF is synthesized through the condensation of phenol with formaldehyde; because it lacks methyl groups, it has a less bulky central linkage, a lower molecular weight, and a higher polarity compared to BPA [24, 25]. Differences in polarity influence how BPs partition into lipid membranes, how they interact with biomolecules such as binding proteins, and

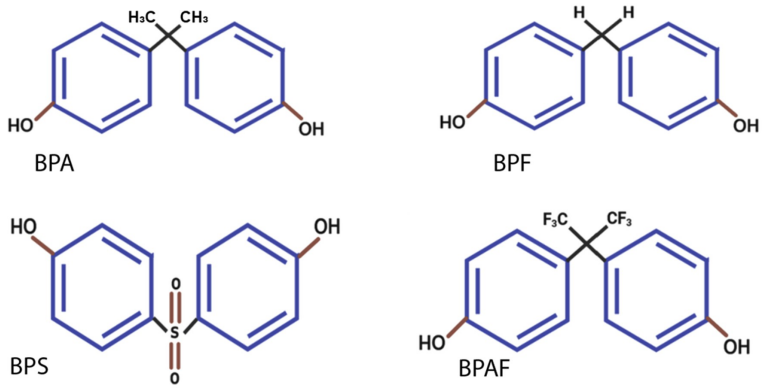

Figure 1.
Chemical structures of bisphenol A (BPA) and selected structural analogues, illustrating differences in the central bridging group and substituent chemistry.

their metabolic conversion via xenobiotic pathways, contributing to differences in diffusion behavior and persistence [25]. BPS is formed by the reaction of phenol with sulfonyl reagents to introduce a sulfone (-SO2-) bridge. The strong electron-withdrawing potential of the sulfone group increases the polarity of BPS and confers high thermal stability, resistance to degradation, and strong absorption behavior [24, 26]. BPAF is produced by the hydrogen fluoride-catalyzed condensation of phenol with hexafluoroacetone, yielding a fluorinated bridging group that enhances its chemical stability [24].

2.2 Human and environmental exposure

An early health-related effect of BPA was discovered in 1998 when Patricia Hunt noticed chromosomal errors in the ovaries of mice kept in BPA-containing polycarbonate cages that were not present when mice were housed in BPA-free cages, suggesting that BPA could disrupt fetal development [27]. Since then, the deleterious effects of BPA on reproductive and metabolic function have become well-known [28].

In humans, the short half-life of BPA (<6 hr) and its extensive first-phase glucuronidation suggest that BPA should not persist in humans [29], but real-world analysis contradicts this view. Virtually all individuals tested have detectable amounts of BPA in urine, although it remains below safe exposure levels [30]. Similar findings are true for BPA analogues, with BPS detection exceeding 70% of samples [28]. Notably, individuals living near BPAF manufacturing facilities in China exhibited detectable levels of multiple BPs, including BPA, BPF, BPAF, and BPS [31].

In humans, foodstuffs are responsible for >90% of BPA exposure due to the widespread use of BPA-containing food packages, where its release occurs as a result of high temperatures or changes in pH [5]. In addition, BPA, BPF, and BPS are detected in indoor dust, with BPA accounting for approximately 60–65% of the total. The median estimated daily intake (EDI) via dust is highest in toddlers due to their lower body weight. Nevertheless, indoor dust accounts for less than 2% of overall BPA ingestion [32]. BPA is also widely detected in surface waters as well as sediment samples [33, 34]. Transdermal exposure, mostly through skin contact with thermal receipts, is another source of BPA transference in humans [35]. While BPA and its analogues share common structural features such as aromatic rings and hydrophobicity, the specific contribution of these features to their environmental fate and persistence remains incompletely defined [29, 36].

3. Endocrine pathways targeted by bisphenols

3.1 Thyroid hormone signaling

Structural similarities shared by BPA, BPF, BPS, and BPAF with natural ligands allow BPs to exert its disruptive effects by interfering with normal receptor-mediated signaling. Thyroid hormones (triiodothyronine, T3; thyroxine, T4) play important roles in growth, development, and organismal metabolism and signal through each of the two TR isoforms (TRα, TRβ). Each is localized to the nucleus to function as a transcriptional repressor. Upon TH binding, corepressors are released

from the individual TRs, leading to the subsequent recruitment of coactivators to initiate gene expression [37].

BPA primarily acts as a TR antagonist. High-resolution crystal analyses reveal that both TRα and TRβ bind T3 deeply within a hydrophobic pocket [38, 39] occupied by T3's aromatic rings. Additionally, the hydroxyl group and amino-acid side chains form specific hydrogen bonds and electrostatic contacts with key residues to stabilize T3 binding and enable normal receptor activation [38]. Although the exact mechanism remains unknown, BPA acts as a TR antagonist, presumably due to structural features that allow it to occupy the ligand-binding domain (LBD). In a competitive binding assay, BPA displaced radiolabeled T3 from the endogenous TR with a Ki of ~ 200 μM, which is consistent with low-affinity occupancy of the ligand-binding pocket. Functionally, BPA inhibited T3-induced transcription through recruitment of corepressors while blocking coactivators [11]. Meanwhile, BPF, BPS, and BPAF each disrupted TH signaling in GH3 cells, as indicated by increased cell proliferation in the absence of T3 [40]. Finally, BPA can disrupt TH transport by displacing T4 from the TH-binding protein transthyretin, thereby affecting its delivery to hormone-responsive tissues [41].

3.2 Estrogen and ER signaling BPS interference

Estrogens are ubiquitously produced steroid hormones, with the ovary serving as the primary source in vertebrates. The most relevant physiological estrogens in females are: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4), with E2 being the most potent. Collectively, estrogens control multiple aspects of reproduction and sexual development, as well as bone density, nervous system function, cholesterol mobilization, and inflammatory response. Estrogens exert their effects through each of two nuclear receptors (ERα, ERβ) to regulate gene transcription. In either case, estrogens bind the receptor in the cytoplasm, leading to conformational changes and the subsequent translocation of the estrogen-ER complex to the nucleus, where it binds the DNA at specific estrogen response elements (ERE) [42].

Since BPA shares structural similarities with endogenous estrogens, it can occupy the LBD of the ER, but with approximately 1000–2000-fold lower affinity [43]. Ultimately, the functional effects of BPA binding are shaped by the estrogen receptor subtype. Although the DNA-binding domains of ERα and ERβ are similar, animal models have shown structural differences in their ligand-binding and regulatory regions. These differences are likely to result in distinct conformational responses upon ligand binding, determining whether it acts as an agonist or antagonist [44].

Mechanistic review of *in vitro* and *in vivo* studies examining BPA and its analogues has shown that all can modulate estrogen signaling but differ markedly in their potency, the receptor subtype targeted, and functional efficacy. *In vitro*, BPA can bind both receptor subtypes but shows preferential activity toward ERα, where it induces an agonist effect; binding to ERβ brings an antagonistic effect [15]. BPF shows relatively greater activity toward ERβ over ERα, while BPS has less estrogenic activity than both BPA and BPF [45]. *In vivo*, BPA and BPF have comparable agonistic activity, with BPS acting as a weaker, partial estrogen receptor agonist [45]. BPAF has a strong and selective interaction with both ERs, functioning as an ERα agonist and an ERβ antagonist [18].

4. Toll-like receptor signaling pathways overview

4.1 Toll-like receptor (TLR) signaling pathways

Beyond nuclear hormone receptors, there is evidence that BPA can modulate innate immune signaling, particularly that mediated by TLRs [21, 46]. TLRs exist as both transmembrane and endosomal receptors and are critical components of the innate immune system, acting as pattern recognition receptors (PRRs) for pathogen-derived molecular patterns generally called PAMPs or for host-derived damage-associated molecular patterns (DAMPs) that result from tissue injury. Conserved molecular structures serve as ligands for TLRs [47]. Upon ligand binding, TLRs initiate signaling cascades to trigger pro-inflammatory cytokine production, antimicrobial responses, and activation of transcription factors such as NF-κB and interferon-regulatory factors (IRFs). In general, NF-κB is a key regulator of immune and inflammatory responses. Moreover, individual TLRs often bind specific PAMPs/DAMPs. For example, TLR4 is a transmembrane TLR that is particularly responsive to bacterial lipopolysaccharide (LPS), while endosomal TLRs (such as TLR7) recognize viral nucleic acids and degraded microbial DNA [48]. Given the tightly regulated transcriptional activity of the NF-κB pathway, any dysregulation by environmental chemicals such as BPA can lead to inflammatory and immune disorders [48]. Modeling BPA-TLR interactions *in silico* suggests BPA can bind the ectodomains of multiple cell-surface TLRs [46].

4.2 Hormonal regulation of TLR signaling

Thyroid hormones regulate innate immunity through multiple converging pathways that interface with TLR-driven inflammation, as well as TR-mediated cytoplasmic pathways, including mechanisms that inhibit NF-κB activity. For example, in chronic kidney disease (CKD), renal fibrosis progresses more rapidly with a loss of macrophage TRα activation due to increased pro-inflammatory cytokine production and enhanced nuclear translocation of NF-κB p65 [49]. THs can also directly regulate TLR expression and downstream signaling. For example, acute T3 administration increases Kupffer-cell–derived oxidative stress via a robust activation of NF-κB activity independent of classic thyroid response elements [50]. Likewise, elevated T3 levels upregulate TLR4s expression in B-cells and mononuclear cells and activate the MyD88–NF-κB pathway, emphasizing that excessive TH signaling amplifies TLR4-driven immune activation [51]. TRα is also required for normal TH metabolic adaptation that occurs following TLR4 activation. In wild-type mice, LPS-induced activation of TLR4 suppresses circulating T3/T4 while altering the expression of deiodinases to modify tissue-level TH availability; this response was blunted in TRα-deficient mice [52].

TLR-mediated pathways are also influenced by estrogens. For example, TLR3-induced cytokine and chemokine production is suppressed by ER-mediated signaling [53], although this may depend on cell type, as well as dose and context, such as infectious disease [54–56]. For instance, when infected with the opportunistic pathogenic yeast *Candida albicans* during estrus, the surge of E2 limits IL-23 secretion and the TH-17 response [57, 58]. Similarly, E2 treatments increase renal bacterial burden during a uropathogenic *Escherichia coli* infection [59] and lead to increased susceptibility to *Listeria monocytogenes* [60]. On the other hand, E2 reduces

morbidity in an influenza A virus (IAV) infection model by reshaping chemokine profiles and enhancing neutrophil recruitment, in addition to altering antiviral killer T-cell responses [61].

Beyond receptor-level interactions, estrogens also regulate inflammatory signaling at the chromatin level in a way that intersects functionally with TLR-driven NF-κB activity. In rat aortic smooth muscle, E2 significantly enhances IκBα mRNA and protein resynthesis, thereby accelerating the negative-feedback loop that restrains NF-κB activation [62], in addition to reducing NF-κB p65 binding to inflammatory gene promoter regions [63]. Estrogens can also modulate the degree of histone acetylation [62, 64] and DNA methylation to block RNA polymerase II binding [65].

5. Crosstalk between bisphenols, endocrine signaling, and TLR activation (immune system)

In addition to regulating reproductive and metabolic function, T3/T4 and E2 can alter immune function via signaling through TRs and ERs. Consequently, any compound capable of altering normal TH or estrogen signaling has the potential to reshape the inflammatory response [66].

Macrophages play a central role in host defense, immune regulation, and tissue homeostasis [67] and are a direct target of TH signaling via TRβ1-mediated T3-dependent signaling to promote monocyte-to-macrophage differentiation, enhance chemotaxis, phagocytosis, and cytokine production, and a shift toward an activated M1 phenotype. In hypothyroidism, the normal maturation of macrophages is impaired, and there is an exaggerated inflammatory response [68]. Hence, BPs could interfere with TH-dependent signaling to disrupt macrophage-mediated inflammation [11, 69]. In addition to expressing TR isoforms, macrophages differentially express deiodinases to locally regulate the availability of bioactive TH [70, 71], which can be disrupted by BPA [71, 72] and other BPs [12, 73, 74].

The ERK pathway plays a crucial role in various cellular processes, including cell cycle progression, cell survival, and differentiation, with AKT serving to regulate metabolism and cellular transformation. AKT also plays a major role in innate immunity [75]. Importantly, T3 can activate both the ERK and AKT pathways while suppressing p38 MAPK activity and reducing NF-kB activation [76].

BPs can interfere with the LBD of both TRα and TRβ, acting as agonists in the absence of T3 while shifting toward antagonist activity when T3 is present by blocking T3-dependent signaling [77]. Ultimately, because macrophage differentiation and inflammatory output depend on a tightly regulated intracellular T3 level [68], the disruption of a normal T3-TR interaction could interrupt normal macrophage function. Supporting this notion, zebrafish embryo-larval studies demonstrate that BPA, BPF, and BPS each elevate T3 levels while altering the transcription of genes involved in thyroid development and hormone metabolism [14, 78].

Immune interplay is not limited to TH. ER expression on macrophages is well-documented and plays a critical role in immune regulation [79, 80]. For example, pretreatment of human monocyte-derived macrophages with E2 restores M2-associated markers and suppresses M1-associated cytokines. It can also inhibit NF-kB phosphorylation to attenuate inflammatory signaling. In postmenopausal women, there is reduced M2 polarization, consistent with estrogen deficiency shifting

macrophage function toward a pro-inflammatory phenotype [81], while E2 treatment of peritoneal macrophages and human peripheral blood monocytes significantly reduces multiple pro-inflammatory cytokines while simultaneously increasing anti-inflammatory mediators. TLR2 expression was also suppressed in conjunction with the downregulation of key regulators of the NF-κB pathway [82]. Finally, E2 treatment helps protect primary human monocyte-derived macrophages against HIV infection by inducing a strong antiviral state [83].

Helper T-cells can differentiate into subtypes responsible for orchestrating specific immune responses. Specifically, Th1, as well as Th17 cells, are characterized by a pro-inflammatory response, while Th2 cells are associated with humoral immunity [84]. High physiological levels of estrogens, such as those seen during pregnancy, shift away from Th1-type responses toward a Th2-dominant profile [85] via differential regulation of interleukin-2 (IL-2)-mediated signaling [86] and reduced IL-2 gene expression [85]. This suggests that endocrine-disrupting chemicals, such as BPs, could interfere with normal macrophage function [18, 43, 45]. Notably, BPA directly modulates inflammatory signaling through coordinated activation of MAPK-dependent pathways and NF-κB-mediated gene expression to increase the expression of pro-inflammatory cytokines [87]. Pharmacological inhibition of MAPK signaling or interfering with normal ER activity significantly attenuates the effect of BPA [88]. Moreover, E2 and TNF-α have a synergistic effect on the transcription of ER-responsive genes in MCF-7 cancer cells [89]. The expression of inducible nitric oxide synthase (iNOS) in macrophages is also under the control of NF-κB, and not surprisingly, BPA can suppress nitric oxide production [90]. The degree to which these effects are observed, however, varies with macrophage polarization state (i.e., M1 versus M2) [91].

Furthermore, ER-mediated gene expression and pro-inflammatory NF-κB signaling intersect at the transcriptional level. Specifically, activation of TLR4 and subsequent MyD88-dependent NF-κB nuclear translocation and pro-inflammatory gene transcription require co-activators such as CBP/P300 [92], which are utilized by ERs to regulate estrogen-responsive gene expression [93]. This same mechanism is used by BPA to induce estrogen-responsive gene expression [94, 95]. Hence, if coactivator availability is compromised by BPA sequestration, the degree of ER-mediated suppression of NF-κB transcriptional activation at inflammatory promoters of immune cells could be compromised [87].

Neutrophils are first responders to sites of inflammation, with a relatively short half-life [96], that rely on rapid TH-driven metabolic and signaling adjustments downstream of TR binding, as well as uptake via TH transporters and bioavailability due to differential deiodinase activity [97, 98]. In hyperthyroid individuals, elevated TH levels enhance ROS generation and other antimicrobial defenses by neutrophils, which is reversible when TH levels return to normal [97, 99, 100] and this results from TLR-mediated priming [101].

Likewise, an estrogenic regulatory interplay extends to neutrophils since they express both ERα and ERβ, but in a sex-dependent manner. Specifically, both ERα and ERβ expression are increased during high-estrogen phases in premenopausal women, whereas elevated estrogen levels selectively up-regulate ERα only in men. In addition, E2 treatment enhances neuronal nitric oxide synthase (nNOS) expression and plays a role in neutrophil tracking [102]. Hence, environmental estrogens such as BPs could interact with neutrophil ERs to alter activation thresholds and inflammatory responses [15, 43, 102]. Consistent with this notion,

neutrophils exposed to BPA, BPS, and their glucuronidated metabolites reprogram their glycolytic machinery and exhibit reduced CXCL8/IL-8 secretion, despite viability, phagocytosis, and superoxide production being largely intact [103]. In zebrafish, BPA, BPF, and BPS each significantly reduce neutrophil numbers during early growth and development. Interestingly, the effects of BPA and BPF were nearly identical, consistent with their shared diphenolic structure and overlapping estrogenic activity, while the effect of BPS was even greater. Interestingly, BPAF, despite its high estrogenic potency, did not significantly affect neutrophil numbers, suggesting differential receptor interactions or downstream signaling selectivity [104].

6. Comparison with BPA substitutes (BPS, BPF, BPAF)

6.1 Comparative hormonal activity of BPA and its analogues

Comparative analyses of BPA and its analogues demonstrate that chemical substitution does not alter endocrine activity but rather preserves or even enhances the effects [28].

6.2 Comparative analysis of bisphenol analogues: Structural determinant of estrogenic activity

Structure-activity analyses among BPs reveal that molecular structure is a key determinant of estrogenic activity. Structurally, BPA consists of two para-substituted phenol rings, each containing a hydroxyl group (-OH) in the para position, that are linked by a central sp3 carbon bearing two methyl groups (-C(CH3)2-) (**Figure 1**). This structure gives BPA planar aromatic domains, a hydrophobic core, and two hydrogen-bond-donating hydroxyl groups with a distance similar to that of endogenous steroid hormones. In addition, the fully aromatic phenyl rings effectively mimic the aromatic A-ring of E2, allowing BPA to engage similar surfaces within the ER-LBD. Despite lacking the rigid steroid core of E2, the isopropylidene bridge provides a hydrophobic central scaffold to position the phenolic rings correctly in 3D space [105, 106]. Accordingly, structurally related BP analogues (e.g., BPF) that preserve the core diphenolic structure of BPA, while differing in the nature of the central bridge, are predicted to retain similar estrogen receptor-interacting features based on quantitative structure-activity relationship (QSAR) principles [107].

Building on the conserved diphenolic ring architecture of BPA and BPF, BPS introduces a sulfone-linked scaffold that retains the phenol hydroxyl positioning needed for receptor binding while altering molecular rigidity and polarity. Extending this structure-activity relationship further, BPAF introduces fluorinated CF3 substituents that alter the electronic and steric properties of the BP backbone while preserving the diphenolic spacing [18, 24, 26].

7. Conclusion

Bisphenols are a class of environmental chemicals whose physiological activity is driven by structural similarities with endogenous hormones that allow them to

interact with nuclear hormone receptors, such as ERs and TRs, despite differences in binding affinity and receptor conformation relative to natural ligands. Ultimately, these interactions are sufficient to disrupt normal endocrine signaling by altering receptor activation, coactivator recruitment, and transcriptional regulation of hormone-responsive genes [90, 91, 95]. The presence of functional ERs and TRs in macrophages and neutrophils, in conjunction with BP-mediated regulation of TLR-mediated signaling pathways and subsequent effects on NF-κB and MAPK signaling, means that BPs can significantly modulate more than the well-characterized endocrine disruption of reproductive and metabolic pathways [88], underscoring that BP exposure represents a system-level endocrine and immunological challenge, with implications that extend beyond classical hormonal signaling to include innate immune modulation.

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