

Review

Beyond Degradation Efficiency: Toxicological Profile of Bisphenol Transformation Products in Nanomaterial-Based Advanced Oxidation Processes

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Abstract

Bisphenols are a family of synthetic endocrine-disrupting compounds commonly found in water systems, where they persist because of the limitations of conventional wastewater treatment. Nanomaterial-based Advanced Oxidation Processes (AOPs) have been widely studied as promising approaches for bisphenol degradation, achieving high removal efficiencies by generating reactive oxygen species (ROS). However, incomplete mineralization frequently leads to the formation of transformation products, which may have toxicological characteristics that differ significantly from those of the parent compounds. This review focuses on the toxicity of the degradation products generated during the nanomaterial-based AOP treatment of bisphenol A (BPA), bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF). Evidence from ecotoxicological, phytotoxicological, cytotoxic, genotoxic, neuroactive, and endocrine disruption studies shows that some intermediates may display toxicity equal to or exceeding that of the parent compounds, particularly during intermediate treatment stages. The influence of operational parameters such as catalyst type, ROS composition, irradiation conditions, and treatment duration on transformation product (TP) formation and toxicity evolution was further investigated. These findings suggest that removing the parent compound is not enough to guarantee the environmental safety of treated effluents and stress the importance of including a comprehensive toxicological assessment when evaluating advanced water treatment technologies.

Keywords: AOPs; bisphenols; byproducts; photocatalysis; toxicity; transformation products

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1. Introduction

The bisphenol family includes synthetic organic compounds extensively used in the manufacture of plastics, food packaging materials, epoxy resins, and thermal papers, among others [1,2]. The most widely produced and studied compound, owing to its extensive industrial use and documented endocrine-disrupting activity, is bisphenol A (BPA) [3]. The increasing awareness of BPA's adverse health effects has led to increasing regulatory restrictions worldwide [4]. Consequently, BPA has been progressively replaced by structurally related analogs, such as bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF). However, studies have shown that these substitutes exhibit

toxicological properties comparable to or even more severe than those of BPA [5]. Bisphenols constantly enter water environments through industrial discharge, domestic wastewater, landfill runoff, and wastewater treatment plant outputs [6]. This raises serious concerns for both the environment and public health [7]. Traditional methods often cannot fully eliminate these lasting micropollutants. As a result, they are commonly found in surface waters, sediments, groundwater, and drinking-water sources [8].

To tackle these challenges, Advanced Oxidation Processes (AOPs) have emerged as promising technologies for the degradation of persistent organic pollutants [9,10]. Nanomaterial-based AOPs have gained significant interest because of their high catalytic activity, tunable physicochemical properties, and enhanced ability to generate reactive oxygen species (ROS). Semiconductor nanomaterials (such as TiO_2 , BiVO_4 , WO_3 , ZnO , BiFeO_3) and graphitic carbon nitride ($\text{g-C}_3\text{N}_4$) have been widely studied as photocatalysts for bisphenol degradation, while magnetic carbon-based nanomaterials (such as FeCo/N -doped carbon nanosheets) have also demonstrated strong catalytic activity for bisphenol degradation as they can be easily separated from aqueous media facilitating catalyst recovery and reuse [11–14].

Although high degradation rates are often achieved, research has shown that the incomplete oxidation of bisphenols may generate transformation products that exhibit substantial toxicological activity [15]. In many cases, the identified transformation products displayed toxicity levels equal to or even greater than those of the parent compounds prior to complete mineralization. Therefore, pollutant removal alone is insufficient to guarantee treatment safety [16]. This literature review investigates the toxicity of transformation products generated during the nanomaterial-based AOP treatment of bisphenols. The focus is directed toward degradation pathways, formation mechanisms of the transformation products, and their ecotoxicological, genotoxic, cytotoxic, phytotoxicological, neuroactive, and endocrine-disrupting effects. Furthermore, this review discusses the operational parameters governing transformation product (TP) formation and highlights the need to incorporate toxicological assessments into the evaluation and optimization of advanced water treatment technologies.

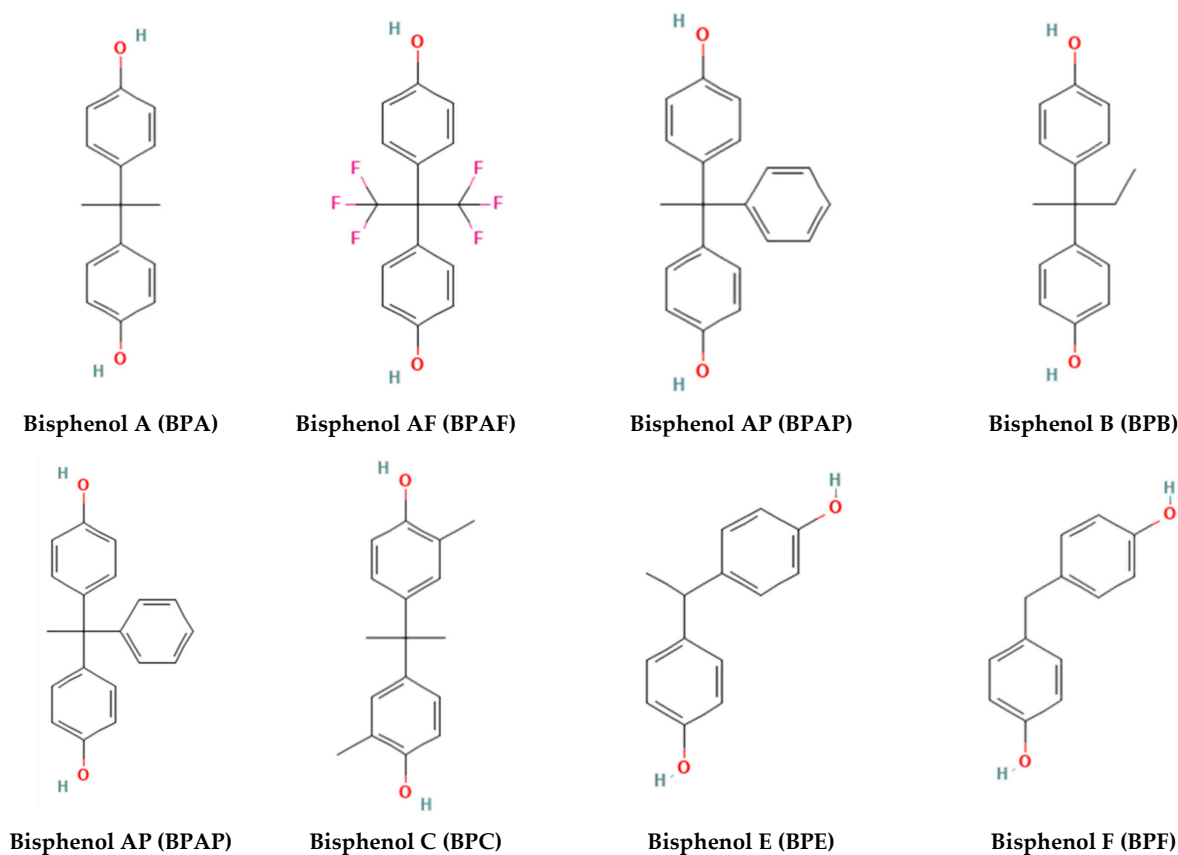
2. Background

2.1. Scope and Literature Selection

This narrative review presents a literature search conducted in Scopus, covering publications from 2010 to June 2026. The following search terms were combined: bisphenol, BPA, BPS, BPF, BPAF, advanced oxidation, photocatalysis, persulfate, nanomaterial, transformation product, degradation by-product, toxicity, ecotoxicity and endocrine disruption. Studies were included when they (i) concerned at least one bisphenol congener, (ii) applied a nanomaterial-based advanced oxidation process, and (iii) reported either the identification of transformation products or a toxicological assessment of the treated solution. Studies addressing degradation efficiency alone, without transformation product identification or toxicological evaluation, were excluded, as were studies concerning biological treatment or adsorptive removal, which fall outside the oxidative scope of this review. A small number of works on co-exposure toxicology and fungal biodegradation were retained as explicitly identified points of comparison. Of the 121 records initially retrieved, 19 met the inclusion criteria and are discussed here. Reference lists of the retained articles were additionally screened manually to identify further relevant studies. Finally, approximately two-thirds of the studied literature (spanning the period 2010–2026) was published within the last two years, reflecting the deliberate emphasis of this review on the most recent developments in the field.

2.2. Bisphenols: Structure, Usage, and Environmental Occurrence

Bisphenols are synthetic organic compounds sharing a common structure comprising two phenolic rings linked by a central bridge [17]. BPA is the most extensively produced member of this family and is primarily used in the manufacture of polycarbonate plastics and epoxy resins [18–20]. Approximately 70% of its global production is allocated to polycarbonate manufacturing, and nearly 20% is used for epoxy resin production [21]. Thus, BPA-containing products are ubiquitous in our daily lives. As concerns regarding the risks of BPA have grown, regulatory agencies have gradually restricted its use. The European Union banned BPA in baby bottles in 2011 and extended restrictions to food-contact materials from 2024 [22]. These regulations have led to the industrial substitution of BPA with analogues such as BPF, BPS, and BPAF. However, these replacement compounds are poorly regulated despite evidence of their significant endocrine-disrupting activity and widespread environmental occurrence [23]. The chemical structures of BPA and of its most frequently detected analogues are shown in Figure 1.



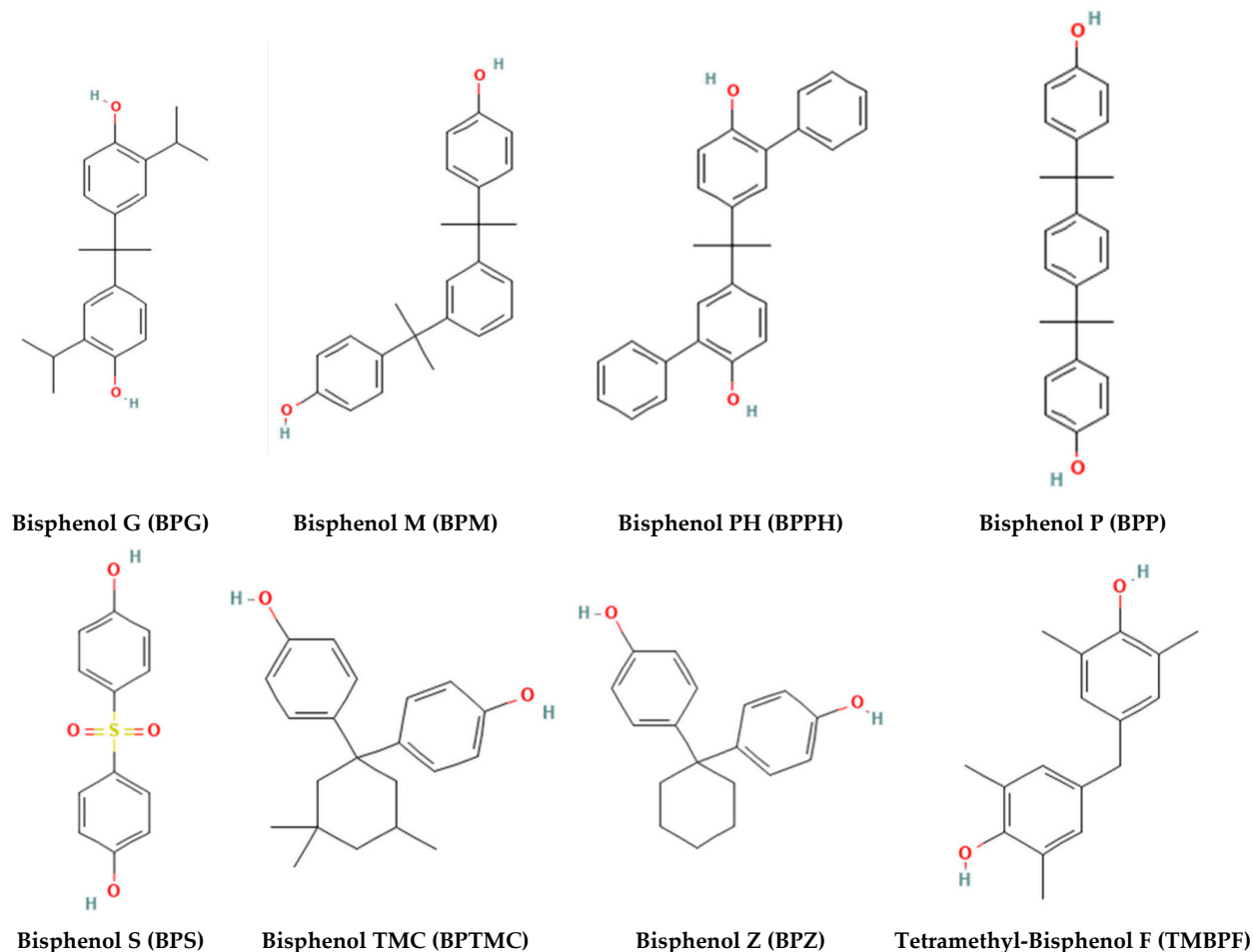


Figure 1. Chemical structures of BPA and its principal analogues. Structure depictions obtained from the PubChem database (National Library of Medicine, NIH); compounds selected based on the occurrence data reported in [10].

Bisphenols are classified as endocrine-disrupting chemicals (EDCs) as they are capable of interfering with hormonal signaling pathways even at very low concentrations [21]. Exposure to these compounds has been linked to reproductive toxicity, neurotoxicity, immune dysfunction, developmental abnormalities, metabolic disruption, and an increased risk of hormone-dependent cancers [24]. BPA has been reported to induce adverse biological effects at concentrations as low as 0.23 ng/L, while biomonitoring studies have detected BPA in the urine of over 90% of tested individuals [25]. Notably, BPAF and BPF have been reported to have stronger endocrine-disrupting potentials than BPA [26]. The principal adverse effects associated with human exposure to bisphenols are summarized in Figure 2.

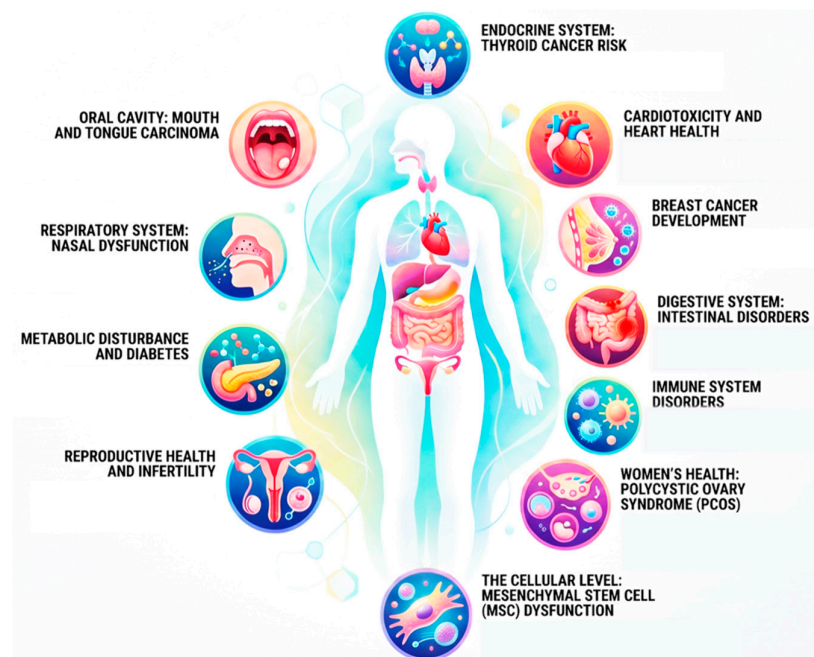


Figure 2. Effects of Bisphenols in human health.

Bisphenols enter the environment mainly via industrial wastewater discharge, municipal wastewater treatment plant effluents, landfill leachates, and plastic material degradation [27,28]. Conventional wastewater treatment systems frequently fail to completely remove these compounds, leading to their accumulation and persistence in aquatic environments. The half-life of BPA in surface waters can vary from several days to several months depending on environmental conditions, while BPS concentrations in aquatic systems have been reported at levels exceeding 1600 ng/L [28]. The main routes by which bisphenol analogues enter and are subsequently distributed within environmental compartments are illustrated in Figure 3.

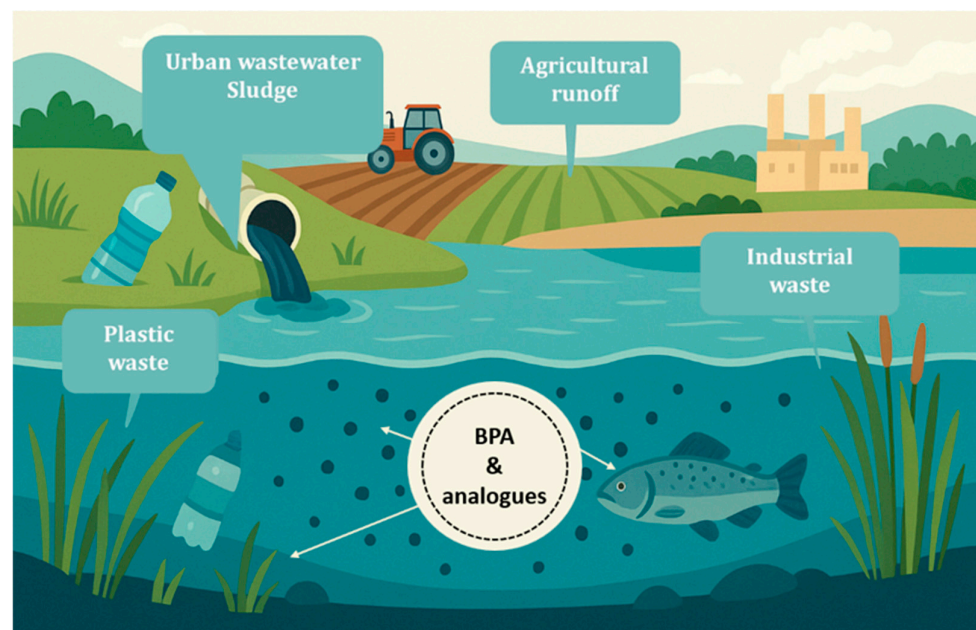


Figure 3. Environmental contamination due to bisphenol analogues.

Despite sharing a common bisphenolic scaffold, BPA and its structural analogues exhibit markedly divergent toxicological profiles, determined primarily by the nature of the central bridging group; these differences are compared systematically in Table 1, while the corresponding physicochemical, industrial, regulatory and environmental characteristics are provided in Table S1 of the Supplementary Materials. BPA, bearing two methyl groups at the central carbon, serves as the reference compound, with molecular targets enriched in oxidative stress responses, mitochondrial dysfunction and cell proliferation pathways [1,29]. Replacement of these methyl groups by hydrogen atoms in BPF increases conformational flexibility and confers stronger estrogen receptor binding than BPA itself, whereas substitution of the central carbon by a sulfone group in BPS confers exceptional thermal and chemical stability, slower biodegradation and the highest aquatic toxicity among the congeners examined [29]. BPAF, in which six fluorine atoms are introduced onto the central isopropylidene group, achieves the highest lipophilicity and nuclear receptor binding affinity of the group, with its $-CF_3$ substituents shifting protein interactions from hydrogen bonding towards halogen bonding [29]. These structural distinctions have divergent downstream consequences: BPS preferentially disrupts ribosomal pathways and PI3K-Akt signaling, while BPA and BPB modulate mitochondrial and epigenetic targets, respectively [1], and BPAF alone among the analogues has been associated with increased childhood myopia risk, mediated in part through changes in placental DNA methylation [30]. Molecular docking and molecular dynamic analyses corroborate these inter-congener differences, with all analogues binding the constitutive androstane receptor with higher affinity than BPA [31]; the corresponding quantitative descriptors are available in the cited primary literature and are not reproduced here. Collectively, these findings challenge the assumption that bisphenol analogues are toxicologically interchangeable and underscore the necessity of evaluating each congener individually when assessing the hazards posed by AOP-derived transformation products.

Table 1. Comparative overview of bisphenol A and its principal industrial substitutes: environmental occurrence, endocrine-disrupting potential, reported toxicological effects and behavior under advanced oxidation treatment.

Property	Bisphenol A (BPA)	Bisphenol S (BPS)	Bisphenol F (BPF)	Bisphenol AF (BPAF)
Environmental occurrence and persistence	Half-life in surface waters ranging from days to months [25,28].	Reported in aquatic systems at concentrations exceeding 1600 ng/L [28]	Widespread environmental occurrence reported	[23]
Endocrine-disrupting potential	Reference compound; well-established ER agonist; adverse effects reported at concentrations as low as 0.23 ng/L [25]	Highest environmental toxicity among the analogues assessed by aquatic bioassays [28]	Greater conformational flexibility gives stronger ER binding affinity and more potent endocrine activity than BPA [26,29]	Highest lipophilicity and nuclear receptor binding affinity of the group; $-CF_3$ substituents shift protein interaction from hydrogen to halogen bonding [26,29]
Principal molecular targets	Oxidative stress responses, mitochondrial dysfunction and cell proliferation pathways [1,29]	Ribosomal pathways and PI3K-Akt signalling [1]	Estrogen receptor-mediated pathways [29]	RXRA (halogen-bonding contacts only); RMSD 2.6–3.5 Å; MM-GBSA -34.32 kcal/mol [29]

Reported toxicological effects	U-shaped association between urinary levels and cancer mortality risk in epidemiological cohorts [29]	Highest aquatic toxicity among the congeners examined [29]	Endocrine disruption exceeding that of BPA [26]	Decreased spherical equivalent and increased childhood myopia risk, partially mediated by placental DNA methylation at TDRD3 (27.6% of total effect) and MROH1 [1]
Behavior under AOP treatment	Degrades via hydroxylation, β -scission and ring opening (Section 3.1)	Sulfone bridge resists β -scission; degradation proceeds through radical coupling to dimeric products [5].	Degradation proceeds through oxidation, decarboxylation and demethylation [13]	Degradation initiated by defluorination and phenolic group removal [13]

Conclusively, the widespread occurrence of bisphenols in aquatic matrices, their incomplete removal by conventional treatment, and the pronounced toxicological heterogeneity among congeners provide the rationale for applying advanced oxidation processes to this class of contaminants. At the same time, they explain why degradation efficiency alone is an insufficient performance criterion: because each congener presents a different preferred site of radical attack, the transformation products generated during treatment—and the hazard associated with them—cannot be inferred from the behavior of the parent compound. This consideration motivates the toxicity-centered perspective adopted throughout the remainder of this review.

2.3. Nanomaterial-Based Advanced Oxidation Processes for Bisphenol Degradation

Advanced Oxidation Processes rely on the generation of highly reactive oxygen species capable of degrading persistent organic contaminants into smaller molecules or mineralizing them completely to CO₂ and H₂O [32,33]. Among the main ROS generated in AOPs are hydroxyl radicals ($\cdot\text{OH}$), sulfate radicals ($\text{SO}_4\cdot^-$), superoxide radicals ($\cdot\text{O}_2^-$), and singlet oxygen ($^1\text{O}_2$) [34,35].

2.3.1. Photocatalytic Systems

Among the various AOPs investigated for bisphenol degradation, nanomaterial-based photocatalytic systems have been proven effective due to their tunable electronic properties, improved light absorption capabilities, enhanced catalytic efficiency and high specific surface area. Semiconductor nanomaterials such as TiO₂, ZnO, BiVO₄, BiFeO₃, WO₃, and graphitic carbon nitride (g-C₃N₄) have received considerable research attention [5,11,13,36,37]. Briefly, regarding the mechanism, when the photocatalyst absorbs light energy equal to or greater than its bandgap, electrons are excited from the valence band (VB) to the conduction band (CB), generating electron-hole pairs [38]. These charge carriers participate in oxidation and reduction reactions with water and dissolved oxygen, producing ROS that can attack and degrade bisphenol molecules. To improve photocatalytic performance under visible light irradiation and reduce electron-hole recombination, various structural modifications have been developed, including heterojunction construction, oxygen vacancy engineering, metal and non-metal doping, incorporation of carbonaceous materials [39]. Briefly, absorption of photons of energy equal to or exceeding the bandgap promotes electrons from the valence to the conduction band, and the resulting charge carriers react with water and dissolved oxygen to yield the ROS responsible for bisphenol degradation; this mechanism is well documented elsewhere and is not reproduced here. Because the nature of the ROS generated—rather

than the identity of the catalyst itself—ultimately governs which transformation products are formed and how their toxicity evolves, the catalyst classes considered in this review are presented in Figure 4 together with their dominant reactive oxygen species, the structural classes of transformation products they generate and the associated toxicological outcome.

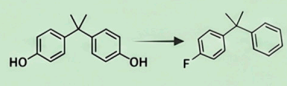
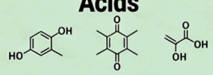
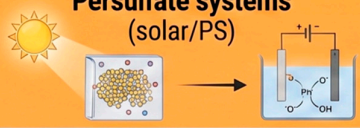
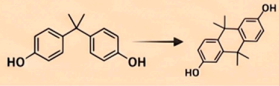
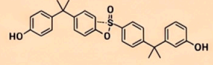
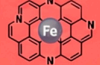
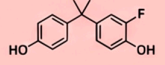
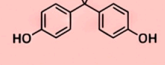
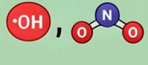
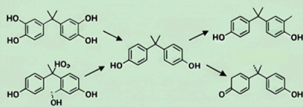
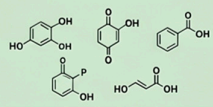
Catalyst Class	Dominant ROS	Degradation route	TP Class	Toxicity
Metal-oxides $(\alpha\text{-Fe}_2\text{O}_3/\text{ZnO}, \text{BiVO}_4, \text{TiO}_2 \text{ hybrids})$ 	$\bullet\text{OH}$ & $\text{O}_2^{\bullet-}$ 	Non-selective ring attack 	Hydroxylated, Quinones, Organic Acids 	
Persulfate systems (solar/PS) 	$\text{SO}_4^{\bullet-}$ 	Single-electron oxidation & dimer coupling 	Dimers 	
Single-atom catalysts $(\text{Fe-SAC@P/g-C}_6\text{N}_4)$ 	$\bullet\text{OH} + {}^1\text{O}_2$ 	Selective oxidation (intact core) 	Partially oxidized 	
Matrix-mediated (nitrite/DOM) 	$\bullet\text{OH}, \bullet\text{NO}_2$ 	Mixed pathways 	Mixed TPs 	

Figure 4. Relationship between the dominant reactive oxygen species, the prevailing degradation route, the structural class of transformation products formed, and the associated toxicological outcome during nanomaterial-based advanced oxidation of bisphenols.

MOF-derived heterostructures, such as $\alpha\text{-Fe}_2\text{O}_3/\text{ZnO}$ composites and noble metal deposition, exhibit enhanced visible-light absorption, increased charge separation efficiency, and superior photocatalytic activity compared to pristine semiconductors [37].

2.3.2. Persulfate-Based AOPs

Persulfate-based AOPs constitute another significant class of nanomaterial-assisted oxidation systems. In these systems, persulfate salts are activated by UV radiation, transition metals, heat, or nanocatalysts to generate sulfate radicals with high oxidation potentials. Solar-assisted persulfate activation has gained increasing interest owing to its reduced energy demand and potential applicability under environmentally relevant conditions [5].

2.3.3. Comparative Evaluation of Nanomaterial-Based Systems

The catalyst families reviewed above present distinct and complementary limitations. TiO_2 remains the most chemically stable and the least expensive option, but its band gap of approximately 3.2 eV confines activation to the ultraviolet region and restricts solar efficiency. ZnO offers comparable oxidative power under UV irradiation yet is subject to photocorrosion and consequent release of Zn^{2+} into the treated water so that catalyst degradation and effluent toxicity are directly coupled. Graphitic carbon nitride is visible-light-active and, being metal-free, presents no leaching risk but suffers from rapid charge-carrier recombination and a low specific surface area that limit its intrinsic activity. BiVO_4

absorbs efficiently in the visible region while remaining constrained by poor charge transport, which is why the vacancy-engineered and heterojunction variants discussed above have been developed. Iron-based and single-atom catalysts achieve high oxidative activity but operate within a narrower pH window and require verification of residual iron in the treated effluent. Reusability differs correspondingly: catalysts recovered by filtration or centrifugation typically show progressive activity loss through surface fouling by adsorbed intermediates, whereas magnetically separable composites such as FeCo/N-doped carbon nanosheets [12] can be recovered externally and retain their activity over repeated cycles more reliably. Most importantly for the present review, the selectivity of a catalyst cannot be dissociated from its safety profile: systems favoring non-selective hydroxyl radical attack proceed more readily to ring opening, whereas the selective, non-radical pathways increasingly pursued for their oxidant efficiency tend to leave structurally intact, partially oxidized intermediates whose biological activity may exceed that of the parent compound. Although nanomaterial-based AOPs often achieve high degradation rates for parent bisphenol compounds, complete mineralization is not always achieved under real-world conditions.

2.3.4. Formation and Environmental Relevance of Transformation Products

Numerous intermediate transformation products are generated during degradation. The structure, persistence, and toxicity of these TPs strongly depend on the type of nanocatalyst, irradiation conditions, dominant ROS, and molecular structure of the target bisphenol analog [13]. Notably, studies suggest that several degradation intermediates may exhibit considerable biological activity and, in some cases, toxicity that exceeds that of the parent compounds. Consequently, a comprehensive toxicological assessment is necessary to ensure the environmental safety of nanomaterial-based AOPs for water treatment. The nanomaterial-based systems reviewed in the following sections, together with the reactive oxygen species involved, the analytical approaches applied to TP identification and the toxicological assessments performed, are summarized in Table 2; the corresponding quantitative data, complete transformation-product lists and catalyst stability information are provided in Table S2 of the Supplementary Materials.

Table 2. Nanomaterial-based advanced oxidation systems applied to bisphenol degradation, grouped by catalyst class: dominant reactive oxygen species, analytical approach to transformation-product identification, principal structural class of transformation products, extent of mineralization and toxicological outcome.

Parent Compound	AOP System/Catalyst	Dominant ROS	TP Identification	Principal TP Structural Class	Mineralization	Toxicological Outcome	Ref.
<i>Heterogeneous semiconductor and heterojunction photocatalysts</i>							
BPA (with 4-tBP, 4-tOP)	α -Fe ₂ O ₃ /ZnO heterojunction (MIO@ZO), MOF-235(Fe)-derived	·OH	GC-MS	Quinone and alkylphenol intermediates → short-chain acids	● 36.8%	↓ Progressive detoxification (YES < LOD; V. fischeri 59 → 31%)	[37]
BPA, BPAF, BPF	C-doped, O-vacancy-modified BiVO ₄ (BVO-3), visible light	·OH	LC-MS	Hydroxylated monomers → ring-opening → short-chain acids	n.r.	↓ Congener-dependent: detoxification for BPA; transient neuroactivity for BPF/BPAF (BPF-P3, BPF-P5)	[13]
BPA	TiO ₂ -metalloporphyrin (ZnTCPP) hybrid, visible light	O ₂ ^{·−} , ·OH	LC-HRMS	Hydroxylated and ring-contracted monomers	n.r.	↑ Predicted (ECOSAR): several TPs with activity ≥ parent	[15]
<i>Single-atom and carbon-nitride catalysts</i>							
BPA	Fe single-atom catalyst on P-doped g-C ₃ N ₄ +peroxyacetic acid, visible light	·OH+ ¹ O ₂ (parallel routes)	LC-MS+Fu-kui indices	Hydroxylated monomer → aromatic acids → small carboxylic acids	● 64.5%	↑ In silico (TEST): low LC ₅₀ /mutagenicity flags for P2, P3, P6, P9, P11	[40]
<i>Homogeneous radical-oxidant and matrix-mediated systems (no solid catalyst)</i>							
BPS	Solar-activated persulfate (solar/PS)	SO ₄ ^{·−}	LC-TOF-MS	Phenoxy-coupled dimers (ether, biphenyl linkages)+ring-opening products	n.r.	↑ Confirmed: 50% root/46% shoot inhibition (<i>S. saccharatum</i>); dimers identified as drivers	[5]
BPA	UVA photolysis in artificial snow, nitrite photosensitization	·OH, ·NO ₂	HPLC-HRMS	Hydroxylated, ring-opening and mono-/di-nitrated products	n.a.	n.a. Not assessed experimentally; nitroaromatic TPs of recognized concern	[41]

Mineralization: ● > 60% TOC removal; ● 30–60%; n.r. not reported; n.a. not applicable. Toxicological outcome: ↑ toxicity of the treated mixture equal to or greater than that of the parent compound; ↓ transient increase at intermediate treatment stages followed by decline; ↓ progressive detoxification; n.a. not assessed. Color coding follows that of Table 3. Because the reviewed studies differ in congener, matrix, catalyst loading, irradiation source and exposure protocol, mineralization and toxicity are reported here as qualitative descriptors; the corresponding quantitative values, complete transformation-product lists with *m/z*, toxicity assessment protocols and catalyst stability data are provided in Table S2.

Table 3. Toxicity endpoints for bisphenol analogues and their transformation products.

Compound	Ecotoxicity	Phytotoxicity	Cytotoxicity	Genotoxicity	Neurotoxicity	Endocrine Disruption	Study
BPS	■	■	■	■	■	■	[2]
BPA	■	■	■	■	■	■	[6]
BPAF	■	■	■	■	■	■	[6]
BPF	■	■	■	■	■	■	[6]
BPA	■	■	■	■	■	■	[20]
BPA	■	■	■	■	■	■	[23]
BPA	■	■	■	■	■	■	[22]

■ TPs more toxic than parent ■ Transient toxicity increase ■ Progressive detoxification ■ Not assessed

3. Toxicological Assessment of Transformation Products

3.1. Identification and Characterization of Transformation Products

The identification of TPs generated during the AOP-based treatment of bisphenols is essential before any toxicological evaluation can be conducted. The type and distribution of TPs generated are largely determined by the molecular structure of the parent compound, the type of catalyst employed, and the dominant reactive species involved in the degradation process.

The accurate identification of these TPs is based on high-resolution analytical approaches and *in silico* tools, allowing for suspect and non-target screening of degradation mixtures. Thus, tentative structure elucidation is feasible thanks to accurate mass measurements, isotopic patterns, and fragmentation spectra provided by LC–HRMS, since reference standards are not always available for every possible intermediate [42,43]. Furthermore, for smaller, more volatile fragments, such as low-molecular-weight organic acids and phenolic derivatives produced at later stages, gas chromatography–mass spectrometry (GC–MS) may be a suitable technique. Apart from attribution to spectra, computational approaches such as Fukui function calculations are gaining ground to predict the most electrophilically or nucleophilically reactive sites within the bisphenol molecule, guiding the rational proposal of degradation pathways consistent with the detected mass fragments.

For BPS, Lalas et al. [5] detected five transformation products during solar-activated persulfate (solar/PS) treatment using LC–TOF–MS. The main degradation route involved radical formation and subsequent coupling reactions, leading to the formation of dimeric structures containing ether and biphenyl linkages (TP1 and TP2), as shown in Figure 5a. Secondary pathways included aromatic ring opening, generating lower-molecular-weight intermediates (TP3 and TP4), and detachment of one aromatic ring, yielding 4-phenol-sulfonic acid (TP5). These dimeric products are of particular toxicological concern because of their increased molecular complexity and structural similarity to the parent compound.

Tian et al. [40] also examined BPA degradation using Fe single-atom catalysts anchored on phosphorus-doped g-C₃N₄ (Fe-SACs@P/g-C₃N₄) combined with peroxyacetic acid (PAA) activation under visible light (Figure 5b). Two distinct degradation routes were proposed based on LC–MS analysis and Fukui function calculations. Pathway 1 involves the initial hydroxyl radical attack at susceptible carbon sites, producing hydroxylated BPA (P1, *m/z* = 243), followed by successive oxidation, aromatic ring cleavage, and C–C bond breaking to generate aromatic acids (P5–P7) and small-molecule carboxylic

acids (P8). Pathway 2 involved direct electron transfer between BPA and singlet oxygen ($^1\text{O}_2$), producing β -scission products (P9, $m/z = 135$) and further dehydrogenation to form unsaturated compounds (P11 and P12). Additional small-molecule organic acids (P13–P15) were detected before complete mineralization to CO_2 and H_2O .

The degradation pathway of BPAF differs considerably from that of BPA because of the presence of fluorinated substituents. BPAF ($m/z = 336$) initially underwent oxidative removal of a phenolic group and two fluorine atoms, yielding BPAF-P1 ($m/z = 236$), followed by successive defluorination and demethylation reactions, generating BPAF-P2 ($m/z = 218$) and BPAF-P3 ($m/z = 118$). An alternative route included cleavage of the phenol groups at both ends of the molecule, yielding BPAF-P4 ($m/z = 148$), which subsequently lost hydroxyl groups and underwent defluorination, leading to the formation of BPAF-P5, P6, and P7.

For BPF, degradation began with oxidation to BPF-P1 ($m/z = 266$), which then underwent decarboxylation to BPF-P2 ($m/z = 224$), and further loss of carboxyl and methyl groups to form BPF-P3 ($m/z = 148$). This intermediate was subsequently transformed through dehydroxylation and demethylation reactions into BPF-P4 ($m/z = 118$) and BPF-P5 ($m/z = 122$), eventually leading to complete mineralization of the compound.

In the photocatalytic degradation of a mixture of BPA, 4-tert-butylphenol (4tBP), and 4-tert-octylphenol (4tOP) using a MOF235(Fe)-derived $\alpha\text{-Fe}_2\text{O}_3/\text{ZnO}$ heterostructured photocatalyst (MIO@ZO), Quero-Jiménez et al. [37] detected several intermediate TPs by GC-MS analysis (Figure 5c), including oxalic acid, acetic acid, ethane-1,2-diol and 2-hydroxyacetic acid as final low-molecular-weight products, while toxic aromatic compounds such as 2,4-di-tert-butylphenol and 1,3-di-tert-butylbenzene were detected at intermediate degradation stages.

Frassati et al. [41] studied the photodegradation of BPA in artificial snow under UVA irradiation in the presence of various photosensitizers. As shown in Figure 5d, 13 transformation products were identified by HPLC-HRMS, including hydroxylated BPA derivatives (compounds 1–4), oxidized and ring-opening products (compounds 5–9), and nitrated compounds (compounds 10–13) generated in the presence of nitrite as a photosensitizer. Particularly noteworthy were the mono- and di-nitrated forms of BPA (compounds 10 and 11) and the nitrophenol derivatives (compounds 12 and 13). These nitroaromatic compounds have important environmental implications, as reactions of $\cdot\text{NO}_2$ with aromatic organic compounds can produce products with substantially higher toxicity than the starting substances. Several of these photoproducts were also detected in real Alpine snow samples, suggesting that BPA photodegradation and the associated formation of potentially toxic TPs may occur under natural environmental conditions.

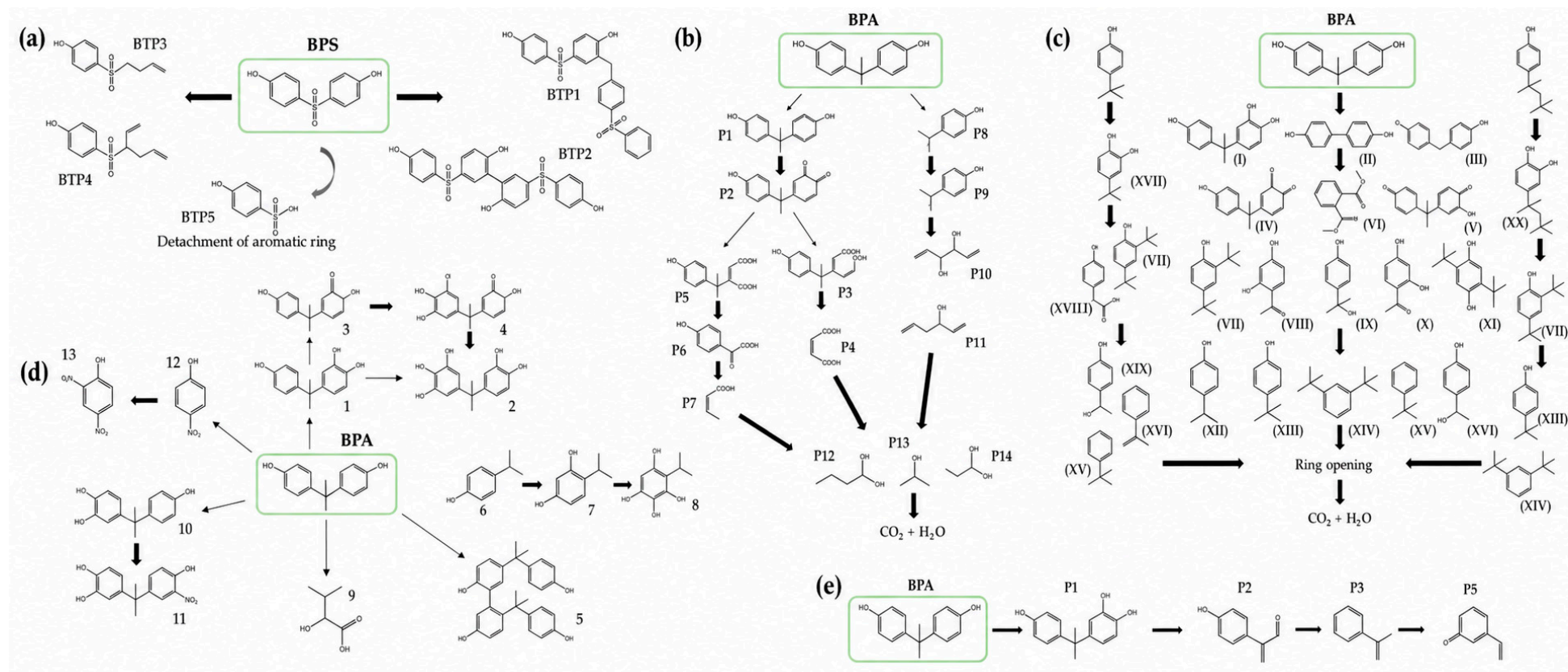


Figure 5. Different degradation pathways of bisphenol analogues that lead to toxic transformation products, redrawn by the authors based on the mechanistic data reported in the cited sources: **(a)** Degradation of BPS during solar/PS treatment [5]. **(b)** Degradation of BPA utilizing Fe-SACs@P/g-C₃N₄ as photocatalyst under visible light [40]. **(c)** Photocatalytic degradation of a mixture of BPA, 4-tert-butylphenol (4tBP), and 4-tert-octylphenol (4tOP) [37]. **(d)** BPA photodegradation under UVA irradiation utilizing different photosensitizers [41]. **(e)** Degradation of BPA during photocatalysis with BVO-3 [13].

Jiang et al. [13] investigated the degradation pathway of BPA using a carbon-doped, oxygen-vacancy-modified BiVO₄ photocatalyst (BVO-3) under visible-light irradiation. As shown in Figure 5e, BPA first underwent hydroxylation to generate a monohydroxylated intermediate (BPA-P1, $m/z = 244$), followed by carbon chain cleavage and oxidation to produce BPA-P2 ($m/z = 148$). Subsequent dehydroxylation and demethylation reactions successively generated BPA-P3 ($m/z = 118$) and BPA-P4 ($m/z = 104$), before aromatic ring-opening cleavage produced the small-molecule acid BPA-P5 ($m/z = 62$), ultimately leading to complete mineralization.

The transformation products discussed above have been identified with markedly differing degrees of analytical confidence, a consideration that is rarely made explicit in the primary literature. Within the framework proposed by Schymanski et al., the majority of the structures reviewed here correspond to level 3 (tentative candidate), being assigned on the basis of accurate mass, isotopic pattern and fragmentation behavior, occasionally supported by *in silico* fragment prediction. Level 1 confirmation against authentic reference standards is reported only for a small minority of products, principally those which are themselves commercially available compounds, such as 4-isopropenylphenol, hydroquinone and 4-hydroxyacetophenone. This distinction is not merely formal. Isomeric hydroxylation products are indistinguishable by accurate mass alone, yet the position of hydroxylation determines whether an *ortho*- or *para*-dehydroxylated moiety capable of oxidation to the corresponding quinone is generated—precisely the structural feature underlying the redox-cycling behavior of BPA 3,4-quinone [37]. Identification confidence therefore conditions the toxicological interpretation directly, and reporting of the confidence level attained should be regarded as a minimum requirement rather than an optional refinement.

Workflow design imposes a second, related constraint. Most of the studies reviewed employ suspect screening against pre-compiled lists of anticipated oxidation products, an approach that is efficient for the hydroxylated and ring-opening intermediates expected from radical attack but structurally conservative by construction: products arising from unanticipated pathways, such as the nitrated derivatives reported by Frassati et al. [41] or the dimeric coupling products characteristic of sulfate-radical systems [5], are recovered only where a genuine non-target workflow is applied. A third constraint is instrumental. Reversed-phase LC–HRMS in negative electrospray mode is well suited to the phenolic parent compounds and their early oxidation products, but the low-molecular-weight carboxylic acids formed after ring opening are poorly retained on C18 stationary phases and ionize inefficiently, so the final stages of the degradation sequence are systematically under-characterized unless complementary GC–MS, HILIC or ion-chromatographic separation is employed. Taken together, these three constraints imply that the transformation products reported in the literature are biased towards the intermediate stages of degradation—which is also, as Section 3.3 indicates, the stage at which toxicity most frequently reaches its maximum.

Assessment of mineralization is similarly incomplete, since scarce studies reviewed here report TOC removal alongside parent compound degradation or mineralization kinetics, and none reports a closed carbon balance. Where both parameters are available, TOC removal consistently lags well behind the disappearance of the parent compound, confirming that the oxidative sequence terminates in accumulated intermediates rather than in complete conversion to CO₂ and water within the treatment times applied. This discrepancy is of direct toxicological relevance: a system reporting near-complete degradation of the parent bisphenol may simultaneously retain the greater part of the initial organic carbon in the form of transformation products of unknown hazard. We therefore consider the routine reporting of TOC removal and, where feasible, of a carbon balance to

be a necessary complement to degradation efficiency in the evaluation of nanomaterial-based AOPs.

3.2. Common Transformation Products and Structural Convergence Across Bisphenol Degradation Pathways

Across the studies reviewed in Section 3.1, five mechanistic families account for essentially all of the transformation products reported: hydroxylation of the aromatic rings, radical coupling and dimerization, β -scission of the central bridging group, dealkylation and defluorination, and aromatic ring opening, leading ultimately to mineralization. The intermediates arising from these routes recur across different parent congeners and different AOP systems and are considered below in terms of structural class rather than individual study. A comparison of the transformation products reported in the reviewed literature revealed several recurring structural patterns and common intermediates, regardless of the bisphenol analog or AOP system employed in the respective study. Such a recurring pattern indicates that certain degradation pathways are thermodynamically or kinetically favored under oxidative conditions and that specific intermediate structures could serve as universal indicators of bisphenol degradation.

The intermediate most frequently reported across all BPA degradation studies is the monohydroxylated BPA derivative ($m/z \approx 244$), identified by Jiang et al. [13], Tian et al. [40], Frassati et al. [41], and Quero-Jiménez et al. [37]. This compound results from the initial electrophilic attack of hydroxyl radicals on the electron-rich aromatic rings of BPA, representing the first step of oxidative degradation regardless of whether the system is photocatalytic, persulfate-based, or photochemical. Its widespread detection across different reaction matrices—including aqueous solution, treated wastewater, and even snow—underscores its environmental significance and suggests that monohydroxylated BPA is a ubiquitous early-stage transformation product of BPA degradation.

Particularly striking is the recurrence of intermediates with $m/z \approx 148$ and $m/z \approx 118$ across the structurally distinct bisphenol analogs. The $m/z \approx 148$ fragment was identified during the degradation of BPA [6], BPAF (as BPAF-P4), and BPF (as BPF-P3), whereas the $m/z \approx 118$ fragment appeared in BPA (as BPA-P3), BPAF (as BPAF-P3), and BPF (as BPF-P4). These common intermediates are likely generated by the cleavage of the central C-C bond connecting the two phenolic rings, representing a common fragmentation pathway across the bisphenol family. The structural similarity of these fragments across different parent compounds points to the central bridging group as a favored site for oxidative attack and to the fact that the resulting phenolic fragments follow similar subsequent transformation routes regardless of the specific substituents present on the parent molecule.

Quinone and carbonyl-containing intermediates constitute another recurrent and toxicologically important class of TPs. BPA 3,4-quinone was identified by both Quero-Jiménez et al. [37] and Tian et al. [40], and quinone-like structures were also implicated in the elevated toxicity of BPF intermediates P3 and P5 reported by Jiang et al. [6]. Quinones are electrophilic compounds capable of forming covalent adducts with DNA and cellular proteins, and their generation during AOP treatment raises concern regarding genotoxicity. The transient accumulation of these structures during intermediate degradation stages—before eventual ring-opening and mineralization—could account for the toxicity peaks often reported in bioassays conducted at intermediate treatment time points.

The formation of nitroaromatic compounds during BPA photodegradation in the presence of nitrite, as reported by Frassati et al. [41], is particularly notable with environmental implications. Mono- and di-nitrated BPA derivatives (compounds 10 and 11) were detected both in artificial snow experiments and in real Alpine snow samples. These compounds were predicted to exhibit higher aquatic toxicity than that of the parent BPA,

particularly toward fish and green algae. The environmental relevance of this pathway is not limited to engineered treatment systems, as nitrite is a naturally occurring photosensitizer in surface waters and snowpacks. Consequently, BPA photodegradation in natural environmental matrices can give rise to nitroaromatic products with greater toxicological significance than those produced under controlled AOP conditions.

Finally, low-molecular-weight organic acids were consistently identified across all reviewed studies—including oxalic acid, acetic acid, 2-hydroxyacetic acid, and glycolic acid—as terminal degradation products preceding complete mineralization to CO₂ and H₂O. These compounds generally exhibit low aquatic toxicity and are not considered environmentally hazardous at the concentrations generated during AOP treatment. Therefore, their formation can be regarded as a favorable sign of treatment progress toward the complete mineralization of the pulp tissue. However, the persistence of certain small-molecule intermediates, particularly carboxylic acids that are resistant to further oxidation, may limit the achievable mineralization efficiency under practical operating conditions and should be considered when designing and optimizing AOP treatment systems.

3.3. Toxicity of Transformation Products

3.3.1. Ecotoxicity

The ecotoxicological evaluation of bisphenol degradation TPs has been carried out through both computational QSAR-based approaches and experimental bioassays involving aquatic organisms.

For BPS, Lalas et al. [5] used the ECOSAR model (v2.2, US EPA) to predict the toxicity of five identified transformation products in fish, *Daphnia magna*, and green algae. The findings showed that several TPs exhibited higher predicted toxicity than the parent BPS compound. Specifically, TP1 and TP2, the dimeric products formed through radical coupling reactions, exhibited acute toxicity toward fish and green algae and were classified as chronically very toxic to green algae, with Chronic Values (ChV) of 0.745 and 0.714 mg L⁻¹, respectively. Although TP3 and TP4 were generally less acutely toxic, they demonstrated considerable chronic toxicity toward *Daphnia* and green algae. Notably, TP5 was found to be non-harmful to all tested species, suggesting that if the solar/PS process is carried out for a sufficient duration, it can lead to the formation of non-toxic transformation products. These findings were further corroborated by Shah et al. [44], who reported higher inhibition in *Vibrio fischeri* bioassays during the first 30 min of UVC/persulfate treatment of BPS, followed by a reduction to levels comparable to those of BPS alone, indicating the initial formation of more toxic products that are subsequently degraded.

Jiang et al. [13] assessed the predicted ecotoxicity of the identified intermediates of BPA, BPAF, and BPF using the ECOSAR program. For BPA, all detected intermediates, except BPA-P3, exhibited lower toxicity than the parent compound toward fish, *Daphnia*, and green algae, suggesting that the photocatalytic process generally results in progressive detoxification of the parent compound. In contrast, all detected BPAF degradation products were predicted to be less toxic than the parent BPAF. For BPF, intermediates P3 and P5 were predicted to exhibit higher toxicity than the parent BPF compound, showing that some degradation routes may produce more hazardous products than the original contaminant.

Quero-Jiménez et al. [37] identified toxic intermediates including BPA 3,4-quinone and 2,4-di-tert-butylphenol in the degradation of BPA using the MIO@ZO heterostructured photocatalyst through ECOSAR predictions. These compounds were classified as toxic or very toxic to fish, *Daphnia*, and green algae at both acute and chronic exposure levels, confirming that incomplete mineralization can result in the persistence of ecotoxicologically relevant TPs in treated effluents.

Frassati et al. [41] assessed the aquatic toxicity of BPA photodegradation products in snow using ECOSAR software (version v2.2). The results indicated that the toxicity of several identified photoproducts was similar to that of BPA at different trophic levels, and some were even less toxic. However, compounds 8, 10, and 11 were predicted to be more toxic than BPA, particularly in fish and green algae. Compounds 10 and 11, which are nitrated BPA derivatives, were photoproducts in irradiated real snow samples, raising environmental concerns regarding BPA photodegradation in natural snowpacks and the subsequent release of toxic photoproducts into water bodies upon snow melting.

Collectively, these findings demonstrate that degradation efficiency alone cannot adequately describe the environmental safety of treated effluents, as certain transformation products may exhibit toxicity levels equal to or exceeding those of the parent compounds, particularly during the intermediate treatment stages.

All in all, the ecotoxicological data indicate that acute lethality endpoints are the least sensitive indicators of treatment success: in several systems the treated solution satisfied acute criteria, while chronic and sublethal endpoints continued to register effects. The reliance on a small number of standard test organisms also limits the extent to which these results can be extrapolated to receiving ecosystems.

3.3.2. Phytotoxicity

The phytotoxic effects of bisphenol degradation mixtures were investigated using seed germination and plant growth assays. Lalas et al. [5] evaluated the phytotoxicity of BPS and its transformation products generated during solar/PS treatment using three seed species: *Sorghum saccharatum*, *Lepidium sativum*, and *Brassica nigra*. BPS alone exhibited an inhibitory effect on root and shoot growth, as well as on germination rate, across all tested species. Importantly, phytotoxicity did not decrease monotonically with the treatment duration. A pronounced phytotoxic effect was observed for *Sorghum saccharatum*, with the highest root and shoot inhibition recorded after 120 min of treatment at 50% and 46%, respectively. For *Brassica nigra*, root inhibition was observed at 120 and 240 min of treatment (36% and 38%, respectively), whereas shoot inhibition reached 50% after 60 min. These results suggest a transient accumulation of toxic TPs during oxidation, leading to temporary increases in phytotoxicity before attenuation.

In contrast, *Lepidium sativum* showed a reduction in phytotoxic effects throughout the treatment process, with all treated samples being notably less phytotoxic than those treated with BPS alone, indicating greater tolerance to the mixture of BPS and its transformation products. These species-specific differences highlight the importance of employing multiple bioassay systems when evaluating the phytotoxicological safety of AOP-treated effluents, as conclusions drawn from a single species may not adequately reflect the overall biological risk.

Phytotoxicity endpoints proved to be among the most sensitive to the transient accumulation of dimeric intermediates, yet they remain the least frequently applied across the reviewed literature. Their capacity to detect hazards that aquatic assays did not register arguments for their systematic inclusion rather than their present use as an optional complement.

3.3.3. Neurotoxicity and Behavioral Effects

Recent studies have highlighted the potential neuroactive effects of residual degradation products of bisphenol. Jiang et al. [13] conducted behavioral assays using *Zebrafish larvae* to evaluate locomotor responses following exposure to degradation solutions of BPA, BPAF, and BPF at different treatment time points.

For BPA, *larvae* exposed to the original BPA solution exhibited significantly reduced swimming activity compared with that of the blank control group. Although total

swimming distance in the 90-min degradation group returned to normal levels, *larvae* showed increased locomotor activity under light stimulation compared to the blank group, suggesting that residual degradation products may exert potential neuroactive effects despite apparent detoxification according to standard viability endpoints.

A similar behavioral pattern was observed after BPAF exposure. Locomotor activity was significantly inhibited in *larvae* in the BPAF and BPAF-45 exposure groups, whereas those in the 90-min degradation group recovered and displayed slightly higher activity than the blank group, again suggesting the potential neuroactive effects of residual degradation products.

For BPF, the swimming activity of larvae in the BPF and BPF-45 exposure groups was significantly inhibited, while that in the 90-min degradation group returned to normal, indicating elimination of neuroactive effects following prolonged treatment.

These findings emphasize the importance of incorporating sublethal behavioral endpoints into toxicological assessments of AOP-treated effluents, as conventional viability-based assays may underestimate the residual biological effects of degradation TPs on fish.

Behavioral endpoints consistently detected residual effects at treatment stages at which viability-based assays indicated complete detoxification and did so with divergent outcomes among congeners treated under identical conditions. This dissociation between survival and function is the clearest available evidence that apparent detoxification cannot be established from lethality data alone.

3.3.4. Cytotoxicity

While comprehensive cytotoxicity data for bisphenol degradation mixtures remain limited, available evidence indicates that certain transformation products may retain or transiently enhance cellular toxicity during advanced oxidation process (AOP) treatments. The identification of reactive intermediates, such as BPA 3,4-quinone, during BPA degradation using the MIO@ZO photocatalyst by Quero-Jiménez et al. [37] is particularly relevant in this context. BPA 3,4-quinone has been previously reported to exhibit genotoxic properties, and its formation during photocatalytic treatment represents a potential cytotoxic hazard that must be considered when evaluating treatment safety.

The in vitro toxicity assessment conducted using the *Vibrio fischeri* bioluminescence inhibition test demonstrated a reduction in bioluminescence suppression from 59% at the start of the process to 31% following 330 min of photocatalytic treatment with MIO@ZO, classifying the final effluent as moderately toxic. This persistent moderate toxicity was attributed to the presence of residual aromatic intermediates, including 1,3-di-tert-butylbenzene and 2,4-di-tert-butylphenol, which were not fully mineralized under the experimental conditions employed.

Beyond the cytotoxic effects reported for photocatalytic and persulfate-based transformation products, recent studies have examined bisphenol-induced cytotoxicity through complementary co-exposure and biodegradation lenses. Nanoplastics co-exposed with BPA or BPS have been shown to induce significant cytotoxic and genotoxic damage in human hepatocellular carcinoma (HepG2) cells, with BPA alone also showing significant cytotoxicity after prolonged (72 h) exposure [45]. Similarly, chronic co-exposure of BPA with a second hepatotoxic agent (alcohol) has been shown to synergistically increase apoptosis, oxidative stress and DNA damage in hepatic cells compared to BPA alone [46], highlighting the context-dependent nature of BPA cytotoxicity which may also extend to bisphenol transformation product mixtures generated during incomplete AOP treatment.

However, not all degradation pathways generate cytotoxic TPs. *Neopestalotiopsis formicarum*, an endophytic fungus, was found to biodegrade BPA, and the process achieved complete BPA removal. The fermentation filtrates showed low cytotoxicity to mammalian

fibroblasts [45], highlighting that the toxicological consequences of BPA degradation are profoundly affected by the specific transformation pathway and not just by removal efficiency.

Cytotoxicity assays provide mechanistic resolution unavailable from whole-organism endpoints, but their results are strongly dependent on the cell line selected and on exposure duration, and no two of the reviewed studies employed comparable protocols. Cross-study comparison of cytotoxic potency is therefore not possible on the present evidence base.

3.3.5. Genotoxicity and Mutagenicity

The genotoxic and mutagenic potential of bisphenol degradation TP_s is a growing concern. Tian et al. [40] used TEST software version 4.2.1 (Toxicity Estimation Software Tool) to predict both the acute toxicity (LC₅₀) and the mutagenic potential of BPA and its degradation products as separate endpoints. With respect to acute toxicity, BPA itself showed relatively low predicted LC₅₀ values, indicating high acute lethality, while several intermediates displayed progressively higher LC₅₀ values, consistent with gradual detoxification along the degradation sequence. Mutagenicity was evaluated separately, as a binary Ames-model prediction, and is reported here independently of the LC₅₀ values. Intermediates P2, P3, P6, P9 and P11 were flagged as potentially mutagenic irrespective of their predicted acute toxicity, demonstrating that the two endpoints do not covary: a transformation product may be less acutely lethal than its parent compound while simultaneously presenting a greater genotoxic hazard. This dissociation reinforces the argument that acute lethality alone is an inadequate criterion for judging the safety of AOP-treated effluents. Mutagenicity assessment similarly revealed transient increases for intermediates P2, P6, P9, and P11, likely attributed to quinone–DNA adduct formation and oxidative stress. However, the mutagenic activity declined toward negative values as mineralization proceeded, with the final small-molecule products (P12–P15) falling within the non-harmful range. These findings confirm that the Fe-SACs@P/g-C₃N₄+PAA+light system not only rapidly degrades BPA but also progressively reduces the genotoxic risk of transformation products, supporting the environmental safety of the proposed treatment approach.

Additionally, the formation of electrophilic intermediates, such as quinones and partially oxidized aromatic structures, during BPA photodegradation, as identified by Quero-Jiménez et al. [37] and Frassati et al. [41], underscores the importance of integrating genotoxicity screening into the evaluation of AOP performance.

Comet assay studies further support the genotoxicity of bisphenols, demonstrating that BPA and BPS induce DNA strand breaks in human hepatocellular cells within hours of exposure and that co-exposure to nanoplastics further modulates this genotoxic response in a dose- and time-dependent manner [46]. The results confirm the genotoxic potential of bisphenols in human cell models and further support the use of comet assay endpoints in addition to the already discussed ECOSAR- and TEST-based predictions.

Genotoxic and mutagenic endpoints diverge systematically from acute toxicity: intermediates predicted to be less acutely lethal than the parent compound were repeatedly flagged as potentially mutagenic. Since these endpoints are assessed almost exclusively *in silico* across the reviewed literature, and experimental confirmation is largely absent, this represents one of the least secure areas of the current evidence base.

3.3.6. Endocrine Disruption Potential

Assessing endocrine-disrupting activity is essential because bisphenols and many of their degradation intermediates retain phenolic structures capable of interacting with hormone receptors. Quero-Jiménez et al. [37] evaluated the estrogenic activity of effluents

generated during the photocatalytic degradation of a BPA, 4tBP, and 4tOP mixture using the Yeast Estrogen Screen (YES) assay. The initial estrogenic activity of the EDC mixture was $1228.01 \pm 9.99 \text{ ng L}^{-1}$ expressed as estradiol equivalents (E2-EQ). Following photocatalytic treatment with the MIO@ZO photocatalyst, the estrogenic response decreased to below the detection limit ($\text{LOD} = 640.1 \text{ ng L}^{-1}$), confirming the absence of estrogenic TPs at the end of the treatment process. These results demonstrate that the heterostructured photocatalyst was effective in eliminating estrogenic activity, despite achieving only partial mineralization (36.76% total organic carbon (TOC) removal).

In contrast, photolysis alone achieved only a 34.26% reduction in estrogenic activity, underscoring the superior performance of the photocatalytic system in eliminating endocrine-disrupting potential. Regarding BPA analogs, Jiang et al. [6] confirmed that BPAF and BPF exhibit stronger endocrine-disrupting potential than BPA itself and that their degradation intermediates may retain key estrogenic structural features during early degradation stages, contributing to the transient toxicity enhancement observed in zebrafish embryo assays.

Endocrine endpoints were the most consistently improved by treatment among all those reviewed, with estrogenic activity reduced below detection in the best-performing system. This nevertheless coincided with only partial mineralization, confirming that the loss of receptor-mediated activity does not imply the removal of the organic load.

3.3.7. In Vivo Toxicity Assessment

In vivo toxicity assays provide biologically relevant validation of ecotoxicological risks that may not be captured by computational predictions. Jiang et al. [13] conducted acute toxicity tests on zebrafish embryos to evaluate the toxicity evolution of BPA, BPAF, and BPF during photocatalytic degradation.

Exposure to the original BPA solution resulted in significantly inhibited embryonic development, with a survival rate of only 68%. As degradation progressed, toxicity decreased substantially: the 45-min degradation solution showed a markedly increased hatching and survival rate exceeding 90%, while both hatching and survival rates returned to 100% in the 90-min degradation group, comparable to the blank control.

For BPAF, both the original solution and the 45-min degradation solution caused severe embryonic abnormalities, including reduced hatching rates (70% in the BPAF group and even lower in the BPAF-45 group), pericardial edema, spinal deformities, and tail curvature. Notably, the 45-min degradation solution was more toxic than the original BPAF solution, confirming the generation of more toxic intermediates during the initial degradation stage. After 90 min of treatment, embryo hatching and survival rates returned to levels comparable to those of the blank control group.

Similar results were observed for BPF. Both the original BPF solution and the 45-min degradation solution caused embryonic malformations, with a hatching rate of only 70% in the BPF group and an even lower rate in the BPF-45 group, confirming increased toxicity during the initial degradation stage. After 90 min, the embryo hatching and survival rates returned to the control levels.

Quero-Jiménez et al. [37] evaluated the chronic toxicity of *Ceriodaphnia dubia*. Exposure to the BPA, 4tBP, and 4tOP mixture resulted in an LC_{50} of 2.59 mg L^{-1} . At the end of the photolysis and ZnO photocatalytic processes, higher toxicity was observed (LC_{50} values of 0.83 and 0.60 mg L^{-1} , respectively), indicating the formation of toxic TPs. In contrast, treatment with MIO@ZO resulted in only a slight increase in toxicity (LC_{50} of 2.32 mg L^{-1}), suggesting reduced formation of toxic TPs due to enhanced mineralization.

The in vivo data reproduce, at the organism level, the non-monotonic pattern observed across the other endpoints: developmental effects intensified during the intermediate treatment stage before returning to control levels. Because these studies sampled

only two treatment intervals, the true position and magnitude of the toxicity maximum remain undetermined.

In a nutshell, the toxicity data reviewed above resist quantitative comparison: the studies differ in test organism, exposure duration, endpoint definition and treatment stage sampled, and only one of the works reviewed reports any measure of uncertainty (Tables 3 and 4). A consistent qualitative pattern nevertheless emerges—toxicity does not decrease monotonically with treatment time. In most of the systems reviewed, an intermediate stage can be identified at which the treated solution is as toxic as, or more toxic than, the untreated one, with the maximum typically coinciding with the accumulation of hydroxylated and dimeric intermediates and preceding aromatic ring opening. A second recurring observation is the divergence between *in silico* predictions and experimental bioassays, which agree on the direction of the effect considerably more often than on its magnitude. The principal knowledge gap is therefore not the absence of toxicity data but the absence of harmonized, time-resolved testing protocols that would allow results obtained with different AOP systems to be compared on a common basis.

Table 4. Detailed experimental parameters, AOP systems, dominant ROS, toxicity assessment methods, and principal transformation products for bisphenol degradation studies.

Compound	Endpoint	AOP System	Dominant ROS	Assessment Method (Species/System)	Exposure	Value	Principal TPs (Increased Toxicity)	Study
BPS	Phytotoxicity	Solar-activated persulfate (solar/PS)	SO ₄ ^{•−}	Seed germination/growth bioassay (Sorghum saccharatum)	120 min	50% root/46% shoot inhibition	TP1, TP2 (dimeric products)	[5]
BPS	Phytotoxicity	Solar-activated persulfate (solar/PS)	SO ₄ ^{•−}	Seed germination/growth bioassay (Brassica nigra)	120–240 min	36–38% root; 50% shoot (60 min)	TP1, TP2 (dimeric products)	[5]
BPS	Ecotoxicity	Solar-activated persulfate (solar/PS)	SO ₄ ^{•−}	ECOSAR (QSAR); fish, Daphnia magna, green algae	—	ChV 0.745/0.714 mg/L (green algae)	TP1, TP2 (dimeric products)	[5]
BPA	Endocrine disruption	Photocatalysis (MIO@ZO/α-Fe ₂ O ₃ -ZnO)	•OH	Yeast Estrogen Screen (YES) assay	Initial vs. treated	1228.01 → <640.1 ng/L (LOD), U = ±9.99 ng/L	BPA 3,4-quinone; 2,4-di-tert-butylphenol	[37]
BPA	Cytotoxicity	Photocatalysis (MIO@ZO/α-Fe ₂ O ₃ -ZnO)	•OH	Vibrio fischeri bioluminescence inhibition	330 min	59% → 31% inhibition	BPA 3,4-quinone; 2,4-di-tert-butylphenol	[37]
BPA	Cyto-/Genotoxicity	N/A (co-exposure toxicology, not AOP)	N/A	Comet assay; HepG2 cells	72 h	Significant increase (qualitative)	Not TP-specific (parent BPA+nanoplastic co-exposure)	[46]

BPA	Genotoxi- city/Muta- genicity	Photocatalytic PAA acti- vation (Fe-SACs@P/g- C3N4+PAA+light)	$\cdot\text{OH}/^1\text{O}_2$	TEST software (in silico QSAR)	—	Low LC50 (qualita- tive)	P2, P3, P6, P9, P11 [40]
BPA/BPA F/BPF	Neurotoxi- city	Photocatalysis (C,O-va- cancy modified BiVO ₄)	$\cdot\text{OH}$	Behavioral assay; zebrafish larvae	45/90 min	Altered lo- comotor ac- tivity; 70% hatching (BPAF/BPF)	BPF-P3, BPF-P5 [13]
BPA	Cytotoxi- city (detox case)	N/A (fungal biodegrada- tion, not AOP)	N/A	Fibroblast cytotoxi- city assay	—	Low cyto- toxicity (qualita- tive)	None identified (detoxify- ing path- way) [45]

4. Toxicity of Transformation Products Versus That of Parent Compounds

4.1. Reported Toxicity Outcomes Across Treatment Systems

A key finding from the reviewed studies is that the degradation of parent bisphenol compounds does not always translate into the detoxification of treated effluents. In numerous cases, the intermediate transformation products generated during AOP treatment exhibited toxicity levels comparable to or even greater than those of the original contaminants. Table 3 summarizes the toxicity endpoints evaluated for each bisphenol compound in these studies.

As explained in the legend, red cells indicate that the transformation products were predicted or experimentally confirmed to be more toxic than the parent compound. Amber cells denote cases in which a transient toxicity increase was observed during the intermediate degradation stages, followed by an eventual reduction. The green cells indicate progressive detoxification during treatment. Gray cells indicate that the corresponding toxicity endpoints were not assessed in the respective studies.

Table 4 complements the qualitative heatmap overview in Table 3 by providing the underlying AOP system, dominant reactive oxygen species (ROS), toxicity assessment method, test species/system, exposure duration, endpoint value, reported uncertainty, and principal transformation products (TPs) associated with increased toxicity for each cited study. Where the cited source reported only qualitative findings or the study did not involve an AOP/ROS-based mechanism, this is indicated accordingly.

This phenomenon is particularly evident during intermediate treatment stages, where partially oxidized aromatic structures accumulate before complete mineralization. Hydroxylated derivatives, quinone-like compounds, dimeric products, partially defluorinated intermediates, and nitroaromatic compounds frequently retain biologically active functional groups that can interact with cellular targets and endocrine receptors.

The differences in the evolution of toxicity among BPA, BPF, BPS, and BPAF highlight the importance of molecular structure in determining degradation behavior and TP toxicity. BPA generally undergoes progressive detoxification during treatment, whereas BPAF and BPF often produce highly reactive intermediates associated with transient toxicity enhancement. BPS degradation is associated with the formation of dimeric products with substantial ecotoxicological potentials. Furthermore, BPA photodegradation in environmental matrices, such as snow, can generate nitroaromatic compounds with toxicity exceeding that of the parent compound, highlighting the relevance of considering photochemical transformation pathways beyond those occurring in engineered treatment systems.

The use of multiple toxicity assessment tools—including ECOSAR, TEST software, zebrafish embryo bioassays, *Vibrio fischeri* inhibition tests, *Ceriodaphnia dubia* chronic toxicity tests, and YES assays—has proven essential for capturing the full spectrum of biological risks associated with bisphenol degradation TPs. Collectively, these findings demonstrate that treatment performance should not be evaluated exclusively based on pollutant removal efficiency. Instead, a comprehensive assessment of degradation TPs and residual toxicity is required to ensure the environmental safety of the treated effluents.

4.2. Comparative Synthesis

Which catalysts generate the safest transformation products?

The evidence compiled in Tables 2 and 4 does not yet support a ranking of individual catalysts, since no two studies apply the same catalyst to the same congener under comparable conditions. A structural tendency is nevertheless apparent: systems that promote rapid, non-selective attack on the aromatic ring and proceed to ring opening are associated with progressive detoxification, whereas systems relying on selective one-electron oxidation tend to accumulate structurally intact intermediates. The α -Fe₂O₃/ZnO heterojunction of Quero-Jiménez et al. [37] reduced estrogenic activity below the limit of detection and lowered *Vibrio fischeri* inhibition from 59% to 31%, whereas the solar/persulfate treatment of BPS reported by Lalas et al. [5] generated dimeric transformation products more phytotoxic than the parent compound. Whether this reflects a property of the catalyst or of the oxidant cannot be resolved from the present literature, and this constitutes a specific priority for future work.

Therefore, it should be clarified which reactive oxygen species are associated with lower residual toxicity. This distinction is more consistent across the reviewed studies than the catalyst-based one. Hydroxyl-radical-dominated systems, in which ·OH adds non-selectively to the electron-rich aromatic rings, most frequently proceed through hydroxylated intermediates to ring-opening products and short-chain acids and are the systems in which detoxification is most often reported. Sulfate-radical systems, by contrast, favor one-electron oxidation to phenoxyl radicals, whose subsequent coupling yields the dimeric products identified as the principal toxicity drivers in BPS treatment [5]. Singlet-oxygen-assisted systems occupy an intermediate position, with Tian et al. [42] reporting several intermediates predicted to be mutagenic. The dominant ROS therefore appears to be a more reliable predictor of toxicological outcome than either the catalyst identity or the degradation efficiency. These relationships between the dominant reactive oxygen species, the degradation route followed, the structural class of transformation products generated, and the resulting toxicological outcome during nanomaterial-based advanced oxidation of bisphenols are summarized in Figure 4.

Hydroxyl-radical-dominated systems proceed through non-selective ring attack towards ring-opening products and progressive detoxification; sulfate-radical systems favor one-electron oxidation to phenoxyl radicals and subsequent coupling to dimeric products of increased toxicity; singlet-oxygen-assisted pathways yield structurally intact, partially oxidized intermediates that may retain or exceed the biological activity of the parent compound. Chloride and nitrate present in the water matrix redirect all three routes towards halogenated and nitrated transformation products, respectively.

Which operational parameters most strongly influence detoxification?

Treatment time emerges as the single most influential parameter, not because longer treatment is invariably safer but because toxicity does not evolve monotonically. In the majority of the systems reviewed, an intermediate stage can be identified at which the treated solution is as toxic as, or more toxic than, the untreated one, with the maximum typically coinciding with the accumulation of hydroxylated and dimeric intermediates

and preceding ring opening. Water matrix composition ranks second, since chloride and nitrate redirect the degradation route towards halogenated and nitrated products respectively [43], while oxidant dose and pH act principally by modulating the relative contribution of the dominant ROS.

Are toxicity trends consistent among BPA, BPF, BPS and BPAF?

They are not, and the assumption of interchangeability among congeners is not supported by the reviewed evidence. The clearest demonstration is provided by Jiang et al. [13], who treated all four compounds under identical photocatalytic conditions: after 90 min, BPF-derived solutions restored normal locomotor activity in zebrafish larvae, whereas BPA- and BPAF-derived solutions produced hyperactivity relative to the control, indicating residual neuroactive products despite apparent detoxification by conventional viability endpoints. BPS is the most consistent outlier, since its sulfonyl bridge resists the β -scission that governs BPA degradation and directs the reaction instead towards radical coupling and dimerization. Divergent behavior among congeners is therefore the expectation rather than the exception, and toxicological conclusions drawn for BPA cannot be extrapolated to its substitutes.

5. Parameters Influencing TP Formation and Toxicity

The formation and toxicity of degradation TPs during nanomaterial-based AOP treatment depends on various operational and physicochemical factors.

The type of nanocatalyst is a key factor in shaping the ROS generation pathway and degradation mechanism. Semiconductor band structure, surface area, crystallinity, heterojunction formation, and defect engineering strongly influence charge separation efficiency and ROS production.

Reaction conditions such as pH, catalyst dosage, pollutant concentration, irradiation intensity, and dissolved oxygen concentration also have a significant effect on degradation kinetics and intermediate formation. In persulfate-based systems, the activation method and sulfate radical generation efficiency are the key parameters.

Overall, these catalyst-dependent ROS generation pathways affect both the degradation kinetics of bisphenol compounds and the specific transformation routes followed; the latter determine the structural nature, and therefore the toxicity, of the resulting intermediates [11,44]. Catalysts favoring non-selective radical attack (e.g., $\cdot\text{OH}$ -dominated systems) generally promote extensive ring opening and faster detoxification, whereas catalysts relying on more selective, non-radical pathways (e.g., singlet oxygen) can leave partially oxidized, structurally intact intermediates with enhanced biological activity [33]. This contrast is illustrated by the systems reviewed here: the $\cdot\text{OH}$ -dominated $\alpha\text{-Fe}_2\text{O}_3/\text{ZnO}$ photocatalyst reported by Quero-Jiménez et al. [37] achieved progressive detoxification across both the Yeast Estrogen Screen and the *Vibrio fischeri* assay, whereas the $^1\text{O}_2$ -assisted Fe-SACs@P/g- C_3N_4 system of Tian et al. [40] generated several intermediates predicted to be mutagenic. The dominant ROS therefore emerges as a more informative predictor of toxicological outcome than the degradation efficiency alone.

Treatment duration plays a particularly important role because the toxicity evolution during degradation is highly dynamic. Intermediate treatment stages often coincide with peak toxicity levels due to the accumulation of partially oxidized products, whereas prolonged treatment tends to favor detoxification and mineralization [44].

The composition of the water matrix modifies degradation pathways and TP profiles through radical scavenging and through interactions with dissolved organic matter and inorganic ions. Natural organic matter competes with the target pollutants for ROS and can itself act as a precursor of additional oxidation by-products. Bicarbonate converts hydroxyl and sulfate radicals into carbonate radicals, which exhibit lower reactivity but

markedly higher selectivity towards electron-rich aromatic moieties; degradation therefore becomes slower but more targeted, altering the resulting TP distribution rather than simply suppressing it. Chloride similarly scavenges $\cdot\text{OH}$ and $\text{SO}_4\cdot^-$ to yield chlorine-derived radical species ($\text{Cl}\cdot$, $\text{Cl}_2\cdot^-$, $\text{ClOH}\cdot$), which are additionally capable of generating chlorinated transformation products that are typically more persistent and more toxic than the parent bisphenol—an outcome that is particularly relevant when treated effluents are subsequently chlorinated. Nitrate plays a dual role, acting both as a $\cdot\text{OH}$ source under UV photolysis and as a precursor of reactive nitrogen species that promote the formation of nitrated TPs; this pathway was directly observed by Frassati et al. [41], who identified mono- and di-nitrated BPA derivatives and nitrophenol products in the presence of nitrite. Moreover, co-existing organic and inorganic contaminants in real wastewater compete for both active sites and ROS, further reducing treatment efficiency and complicating TP prediction relative to idealized laboratory conditions. As a consequence, the degradation behavior observed in ultrapure water can deviate considerably from that observed in real wastewater matrices, and toxicity assessments performed exclusively in simplified matrices may substantially misrepresent the hazard associated with full-scale treatment.

6. Conclusions and Future Perspectives

Nanomaterial-based Advanced Oxidation Processes have proven to be highly effective for degrading bisphenols and other persistent organic pollutants, with semiconductor nanomaterials and heterostructured photocatalysts considerably boosting the generation of reactive oxygen species under both artificial and solar irradiation.

However, the reviewed literature shows that degradation efficiency alone cannot serve as a reliable indicator of environmental safety in the long term. Incomplete mineralization often produces transformation products that display considerable ecotoxicological, cytotoxic, neuroactive, and endocrine-disrupting effects, with several intermediates showing toxicity equal to or exceeding that of the parent compounds, particularly during intermediate treatment stages. This transient toxicity enhancement highlights the dynamic nature of degradation pathways and the need to monitor toxicity evolution throughout treatment rather than relying solely on final degradation percentages.

The toxicity evolution observed during treatment depends strongly on the bisphenol structure, degradation pathway, catalyst properties, dominant ROS, and operational conditions. The integration of computational predictions (e.g., ECOSAR, TEST) with experimental bioassays has proven to be essential for comprehensive safety assessment, as discrepancies between predicted and biologically observed toxicity show that depending on a single evaluation method is insufficient. According to conventional viability endpoints, endocrine-disrupting activity and subtle neurobehavioral effects may persist even after apparent detoxification.

Several practical gaps still limit the translation of nanomaterial-based AOPs to real-world use. Computational tools such as ECOSAR and TEST do not always agree with experimental bioassays, so no single method can yet reliably predict TP hazard on its own. The wide range of species, exposure durations and endpoints used across studies also makes direct comparison difficult and complicates the establishment of common safety benchmarks. Most systems, moreover, have been validated only in simplified, single-contaminant matrices, while catalyst stability, reusability and scale-up economics remain largely unaddressed. The risk of secondary pollution deserves particular emphasis: ZnO-based photocatalysts, among the most widely reported for bisphenol degradation, are prone to photocorrosion and release Zn^{2+} into the treated effluent, so the catalyst itself may become a source of toxicity independent of the transformation products formed. These systems consequently need to be evaluated as an integrated whole, in which degradation efficiency, transformation product hazard, catalyst durability and residual metal release

are assessed together rather than in isolation. Future research should therefore focus on: (i) chronic toxicity and behavioral assays alongside acute viability testing; (ii) identification of transformation products in real wastewater matrices; (iii) evaluation of endocrine activity throughout treatment; and (iv) development of environmentally sustainable nanocatalysts—addressing concerns such as nanoparticle release and metal leaching—able to achieve complete mineralization while reducing toxic TP formation.

Beyond the assays applied in the studies reviewed here, several approaches now established in regulatory toxicology remain essentially unexploited for AOP-treated effluents. Transcriptomic and metabolomic profiling would allow the sublethal, mechanism-level effects suggested by the behavioral findings discussed in Section 3.3.3 to be characterized directly, rather than inferred from apical endpoints. The adverse outcome pathway framework offers a means of linking the molecular initiating events associated with specific transformation product structures—for instance quinone formation and consequent oxidative stress—to the population-level outcomes measured in ecotoxicological assays and would provide a mechanistic basis for the currently empirical correspondence between predicted and observed toxicity. Machine-learning models trained on curated transformation product datasets represent a natural extension of the QSAR tools already applied in this field and may prove better suited to the structurally unusual intermediates for which ECOSAR and TEST were not parameterized—a limitation that plausibly underlies the divergence between predicted and experimentally measured toxicity noted repeatedly in the studies reviewed. None of these approaches has yet been applied to bisphenol transformation products generated by nanomaterial-based advanced oxidation, and their adoption would constitute a significant advance in the toxicological evaluation of such systems.

On the basis of the limitations identified throughout this review, we propose a minimum framework for the toxicological assessment of effluents treated by nanomaterial-based AOPs. Such assessments should, at a minimum: (i) sample toxicity at no fewer than three treatment intervals, including at least one intermediate stage, since the evidence reviewed here demonstrates that toxicity does not evolve monotonically and that a single terminal measurement will systematically overlook the transient maximum; (ii) employ a battery of assays spanning at least two trophic levels, complemented by at least one sublethal or mechanistic endpoint, given the repeated demonstration that behavioral and endocrine effects persist beyond the point of apparent detoxification by viability-based criteria; (iii) report the confidence level attained for every proposed transformation product structure, using an established framework such as that of Schymanski et al., since isomeric intermediates indistinguishable by accurate mass may differ substantially in hazard; (iv) report TOC removal alongside parent compound degradation so that the fraction of organic carbon persisting as transformation products is made explicit; (v) report replicate number and a measure of uncertainty for every toxicological endpoint value, a requirement met by only one of the studies reviewed here; (vi) include at least one experiment in an environmentally realistic matrix, given the documented capacity of chloride, nitrate and dissolved organic matter to redirect degradation towards halogenated and nitrated products; and (vii) quantify residual catalyst-derived metals in the treated effluent, since the catalyst may itself contribute to the toxicity attributed to the transformation products. Widespread adoption of these requirements would permit the quantitative cross-study comparison that the present literature does not yet support.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/app16157620/s1>, Table S1: Comparative overview of bisphenol A and its principal industrial substitutes: structural characteristics, applications, regulatory status, environmental occurrence, endocrine-disrupting potential, reported toxicological effects and

behavior under advanced oxidation treatment; Table S2: Nanomaterial-based advanced oxidation systems applied to bisphenol degradation: catalyst, dominant reactive oxygen species, analytical approach to transformation product identification, principal transformation products, extent of mineralization, and toxicological assessment performed.

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Abbreviations

The following abbreviations are used in this manuscript:

AOPs	Advanced Oxidation Processes
BP	Bisphenol
ECOSAR	Ecological Structure Activity Relationships
ROS	Reactive oxygen species
TEST	Toxicity Estimation Software Tool
TP	Transformation product

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