Ann Ist Super Sanità 2026 | Vol. 62, No. 3: 267-276
DOI: 10.4415/ANN_26_03_09

Bisphenol S-induced inflammation: a comparative insight on inflammatory pathway activation in zebrafish and rodent models

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Abstract

Background. Bisphenol S (BPS) is a widespread BPA substitute with emerging immunotoxicity; this review synthesizes zebrafish and rodent experimental evidence to clarify BPS-induced inflammation.

Methods. Narrative synthesis of experimental studies in zebrafish and rodent models, focusing on molecular pathways, organ-level effects, and exposure timing.

Results. Across models, BPS consistently activates an oxidative stress-mediated NF-κB axis with increased ROS, lipid peroxidation, and upregulation of TNF-α, IL-1β, and IL-6; chronic and developmental low-to-moderate exposures produced stronger inflammatory phenotypes than acute high doses.

Conclusions. Convergent mechanistic and pathological findings strengthen the weight of evidence for BPS immunotoxicity and support targeted monitoring and controls; key research gaps include inflammasome activation, receptor mechanisms, sex differences, mixture effects, epigenetic regulation, and standardization.

Key words

- bisphenol S
- inflammation
- inflammatory pathway
- rodent
- zebrafish

INTRODUCTION

Bisphenol S (BPS) is a widely used substitute for bisphenol A (BPA) analogues in consumer and industrial products such as polycarbonate plastics, epoxy resins, and thermal papers. BPA is a non-perennial anthropogenic compound widely used in recent decades as a primary plastic material for various applications such as food packaging, personal care products, household items, and medical devices [1]. BPA has been recognized as an Endocrine Disruptor Chemical (EDC) that alters endocrine function by imitating, inhibiting, or modifying hormone production, transport, metabolism, and receptor binding [2]. BPA has been banned in consumer products, including all baby bottle production, in the EU and Malaysia since 2012, and the ban has expanded to all materials used in food contact applications in 2024.

BPS, also known as 4,4'-sulphonyldiphenol, is a primary substitute for BPA, sharing a similar chemical structure with BPA, including two phenol groups connected by a sulphonyl group [3]. Despite being introduced as a safer alternative, BPS has become ubiquitous in the environment and in human populations. Several studies have reported that BPS has been detected in surface water, sewage, and sediment samples globally, indicating widespread environmental pollution [4, 5]. As a result, biomonitoring data show that BPS is detected in the urine in most people, including 89.4% of adults in the US, and broad detection across Asian and European cohorts [6]. Temporary trends suggest that BPA levels are gradually stabilising or declining as a result of global BPA ban regulations. In contrast, BPS concentrations in human samples are gradually increasing, raising serious concerns about the potential health consequences, which may be comparable to or worse than those of BPA. Various consumer products, particularly food and beverage packaging, primarily expose

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people to BPS. Furthermore, thermal paper, such as receipts, is a major source of exposure. High levels of BPS were detected in fractional urinary excretion, reaching up to 92% in men and 72% in women [7].

Inflammation represents an essential biological response to harmful stimuli, but its dysregulation is a major cause of disease. Acute inflammation serves as a protective, short-term response to injury or infection, while chronic inflammation indicates a prolonged, low-level condition marker due to ongoing immune activation and tissue damage [8]. Recent research has focused on the recognition of systemic chronic inflammation as a fundamental mechanism in the pathogenesis of major noncommunicable diseases, including cardiovascular disease, type 2 diabetes, obesity, neurodegenerative disorders, and cancer [9]. Pathological processes are mediated by critical intracellular signalling pathways, particularly the Nuclear Factor kappa-B (NF-κB) pathway, the Mitogen-Activated Protein Kinase (MAPK) cascade, and the NLRP3 inflammasome [10]. These pathways regulated the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [8].

Well established toxicological evidence links that environmental pollution can act as an endocrine-disrupting chemical (EDC), potentially altering the homeostasis balance between pro-inflammatory and anti-inflammatory signals [1]. The relationship between environmental toxicants is increasingly linked to the induction of sterile inflammation, establishing a mechanistic connection between chemical exposure and the risks associated with chronic diseases [2]. Although BPS has been extensively studied for its ability to induce inflammation via oxidative stress and receptor-mediated pathways, its inflammatory capacity remains poorly understood despite its structural similarities. It is scientifically conceivable that BPS may cause a comparable or different inflammatory response due to its similar phenol groups responsible for receptor binding. Therefore, an extensive assessment of its immunotoxicity potential is required.

A cross-species comparative approach would allow for a thorough examination of the mechanisms of BPS-induced inflammation, providing valuable translational insight. Animal models allow for controlled dosing and exposure timing, which aids in the identification of thresholds and chronic effects relevant to environmental and human exposure [11]. Monitoring and comparing BPS-induced inflammation in different animal models is critical for understanding its health effects and causes, as well as applying the findings to human health. This phenomenon is due to variations in BPS sensitivity, immune response, and metabolic processing among species. By comparing animal model studies, we can determine which findings are likely to be applicable to humans, and some models can highlight different mechanistic diversity, such as gut microbiome involvement, while others focus on immune cell activation or organ-specific damage, providing a comprehensive view of BPS toxicity.

This narrative review provides a novel comparative synthesis of BPS-induced inflammatory pathways in zebrafish and rodent models. By exploring the underexplored existing literature to identify conserved mechanisms, model-specific responses, and gaps for human risk assessment. Databases consulted included PubMed, Web of Science, and Scopus. Search terms combined "bisphenol S" OR "BPS" with "inflammation" OR "inflammatory pathway" AND "zebrafish" OR "*Danio rerio*" OR "rodent" OR "mouse" OR "rat". Studies from 2015 to 2025 were included if they reported BPS-induced inflammation in these models with mechanistic data. Exclusion: non-English paper, review without primary data, non-peer-reviewed sources.

INFLAMMATORY PATHWAYS OVERVIEW

The molecular landscape of BPS toxicity involves a complex network of signaling cascades that bridge initial chemical exposure to systemic pathology. As illustrated in *Figure 1*, BPS-induced inflammation is characterized by the integrated activation of the NF-κB pathway, the MAPK cascade, and the NLRP3 inflammasome, all of which are modulated by upstream sensors like TLR4 and metabolic regulators such as PPARγ.

The primary regulator of the inflammatory response is the NF-κB signalling pathway. Under normal physiological conditions, NF-κB is sequestered in the cytoplasm by the inhibitory protein IκB. *Figure 2* illustrates a detailed schematic representation of canonical NF-κB activation sequence following BPS-induced ROS/TLR4 signaling. Research has shown that upon BPS exposure, IkB undergoes rapid phosphorylation and degradation, facilitating the translocation of the active p65/p50 NF-κB complex into the nucleus [12]. Upon entering the nucleus, this complex binds to specific DNA promoter regions, leading to the transcription of a diverse array of pro-inflammatory genes. These genes include cytokines like TNF-α, IL-6, and IL-1β, which are recognised as key biomarkers of BPS immunotoxicity [13]. This pathway acts as a central convergence point for BPS toxicity, integrating signals from oxidative stress and upstream receptors in the chain, initiating a systemic inflammatory response.

The Mitogen-Activated Protein Kinase (MAPK) cascade exhibits a significant relationship with NF-κB. This pathway serves as a crucial mechanism for the signal transduction pathway that responds to external stressors outside the cells. Exposure to BPS has been proved to activate essential MAPK subfamilies, particularly ERK1/2, JNK, and p38 [13]. The activation of the phosphorylation process in response to Reactive Oxygen Species (ROS) via BPS or receptor binding. This pathway functions as an essential signal transducer, converting stress signals from outside the cell, which are frequently caused by BPS-induced ROS, into a response inside the cell that increases cytokine production and influences cell fate, shifting the equilibrium towards survival and apoptotic cell death [14]. The MAPK pathway is an important mechanism that acts as an amplifier of inflammatory signals, bridging the gap between initial chemical toxicant exposure and the cellular stress response.

The activation of the NLRP3 inflammasome, a multiprotein intracellular complex that serves as a sensor for "danger" signals, represents a distinctive and significant component of BPS-induced inflammation. The expo-

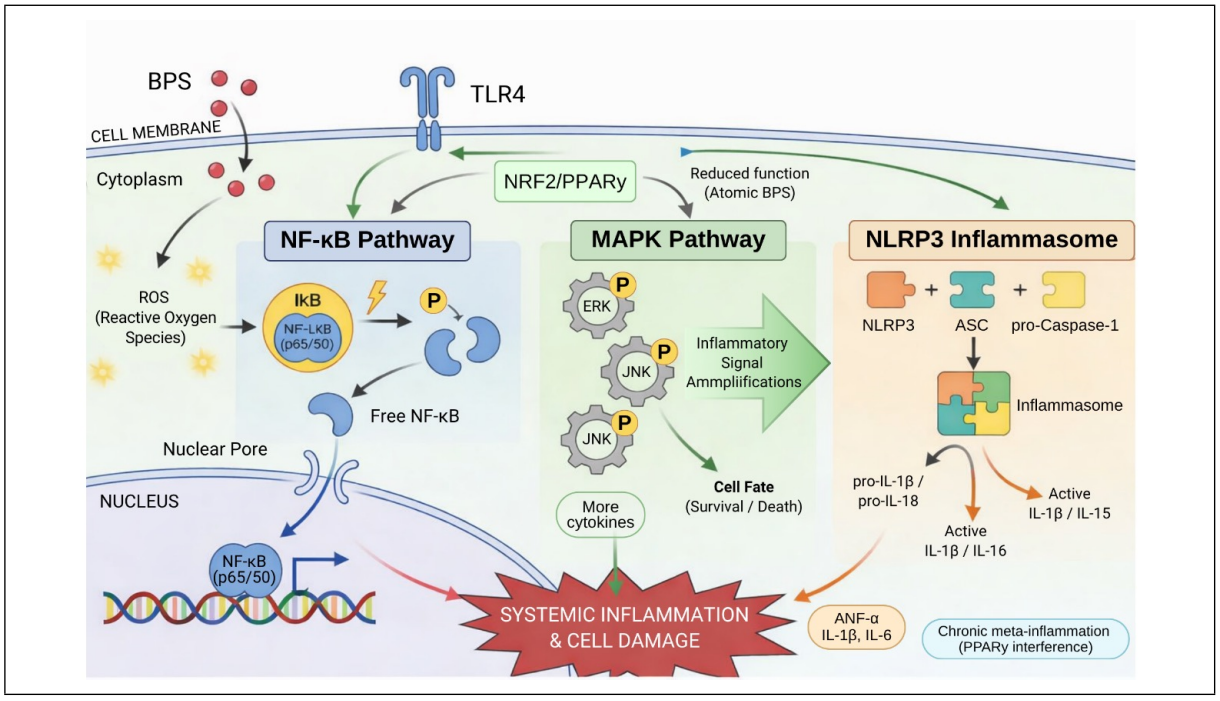

Figure 1
Overview of BPS-induced pathways (NF-κB, MAPK, NLRP3, upstream TLR4/Nrf2/PPARγ) leading to cytokine production, cell death, and chronic meta-inflammation.

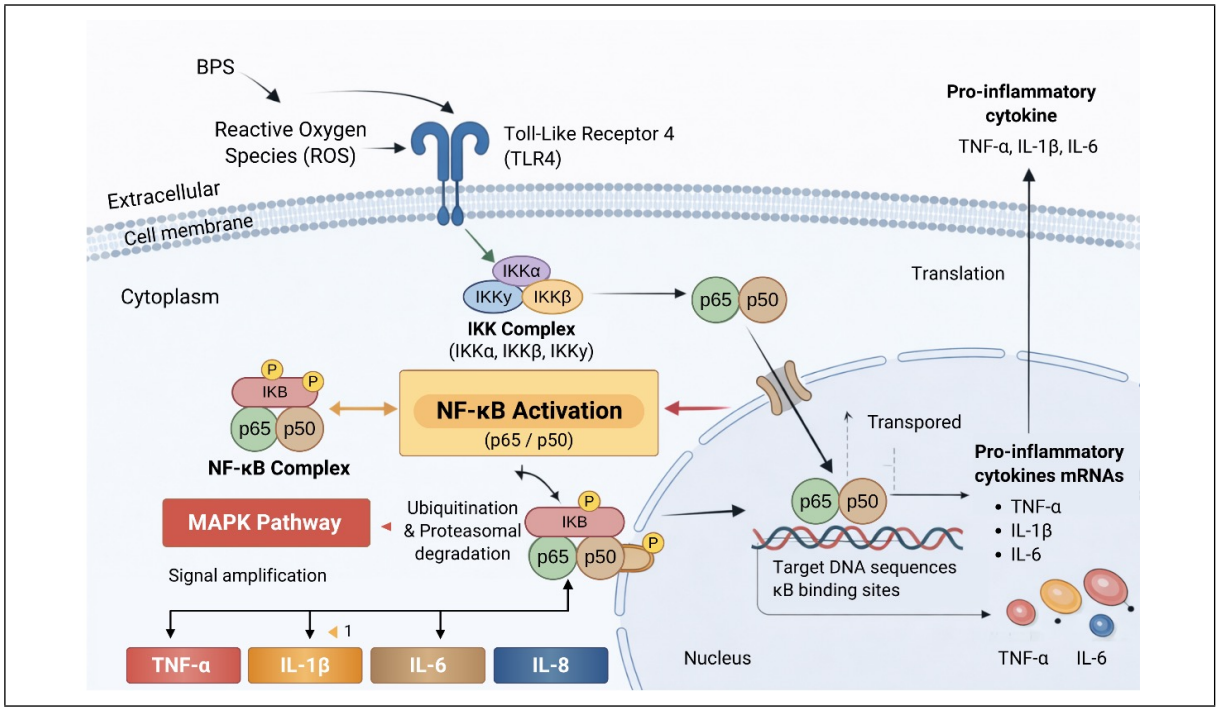

Figure 2
Schematic representation of the canonical NF-κB activation pathway. This Figure illustrates BPS-induced ROS/TLR4 signaling leading to IkB degradation, p65/p50 nuclear translocation, and cytokine (TNF-α, IL-1β, IL-6) transcription conserved across models.

sure of BPS triggers the formation of a complex comprising NLRP3, ASC, and pro-caspase-1 and serves as a molecular mechanism responsible for processing and releasing the inflammatory cytokines IL-1β and IL-18 [15]. This pathway is particularly significant because it leads to pro-apoptosis, which is a form of programmed cell death that induces significant inflammation [2]. The activation of the NLRP3 inflammasome suggests that BPS may induce sterile inflammation, leading to tissue injury even in the absence of pathogens.

The upstream sensor frequently initiates or modifies the activation of these key pathways. Toll-Like Receptor 4 (TLR4), which is conventionally recognised as a sensor for bacterial endotoxins, may undergo aberrant activation due to cellular damage signals caused by BPS. This activation triggers a signalling cascade that directly interacts with NF-κB and MAPK pathways [16]. Simultaneously, BPS interferes with the Nrf2/Keap1 pathway, which is the cell's main mechanism for protecting cells against oxidative stress. The initial activation of Nrf2 is a protective response designed to neutralise ROS created by BPS. However, when this pathway is chronically dysregulated, it may lead to persistent oxidative stress and inflammation. Finally, BPS interferes with PPARγ signalling, a nuclear receptor pathway that links lipid metabolism with inflammation [17]. By disrupting PPARγ activity, BPS can cause "meta-inflammation", a chronic low-grade inflammatory state linked to metabolic disorders such as obesity and fatty liver disease.

ANIMAL MODELS IN BPS-INDUCED/EXPOSED INFLAMMATION

Zebrafish and rodents were chosen as complementary vertebrate models to capture both mechanistic detail and systemic complexity of BPS-induced inflammation. zebrafish enable high-resolution, real-time analysis of innate immune cell dynamics and early-life responses under controlled waterborne exposure, but underdeveloped adaptive immunity, and lack complex mammalian organs. While rodents provide insights into organ-specific chronic pathology, adaptive immunity, and dose-dependent systemic effects relevant to human exposure scenarios.

ZEBRAFISH MODEL

Zebrafish (*Danio rerio*) have emerged as a popular vertebrate model for studying inflammation, including the effects of toxicants such as BPS, due to their high genetic and physiological similarities to mammals. Over 70% of human genes have a zebrafish counterpart, and more than 80% of genes associated with human disease are conserved [18]. This indicates many essential inflammatory pathways and immune cell types are shared between zebrafish and mammals. This significant degree of conservation is also observed in the innate immune system. Zebrafish macrophages, neutrophils, and various inflammatory mediators and receptors are similar to those found in humans [19].

Zebrafish offer practical and mechanistic advantages for BPS studies. Zebrafish larvae are transparent, facilitating real-time imaging of leukocyte recruitment, barrier damage, and tissue regeneration at single-cell resolution with fluorescent reporter lines for neutrophils, macrophages, NF-κB activity, inflammasomes, and cytokines [20]. High reproductive rate, low cost, rapid development, and compatibility with microinjection or waterborne exposure make them a valuable model for studying both the mechanisms of inflammation and the effects of environmental toxicants like BPS. However, differences in immune response and susceptibility to specific inflammatory triggers exist due to evolutionary divergence, and certain aspects of adaptive immunity are less developed compared to mammals [19].

RODENT MODEL (MICE AND RATS)

Rodent models, primarily *Mus musculus* (mice) and *Rattus norvegicus* (rats), serve as the essential foundation for *in vivo* studies of BPS-induced inflammation due to the substantial similarities in the genomes of about 85% of the immune, endocrine, and metabolic systems with humans [21]. Both rats and mice allow regulated oral, inhalation, or parenteral exposure to BPS with precise doses and defined life stages, enabling investigation of acute and chronic low-dose effects on specific organs such as the gastrointestinal tract, liver, kidneys, lungs, brain, heart, and reproductive tissues.

Mice, is a widely used mammalian model for studying inflammation caused by environmental toxicants. This advantage stems from their unique characteristics, small size, rapid reproductive rate, and extensive genetic information readily available for research. Various knockout and transgenic lines, including NF-κB reporters, cytokine knockouts, AhR, PPARγ, and microbiota-manipulated lines [22]. This enables the examination of particular BPS-sensitive inflammatory pathways within specific cells or organs. Common strains include C57BL/6, widely used in immunology and metabolism research; BALB/c, preferred for Th2-biased and allergy or asthma models; and outbred Swiss mice, typically used in general toxicology and reproductive studies [23]. These strains facilitate the alignment of the strain background with specific inflammatory phenotype under investigation.

Rats provide larger organ dimensions and improved sampling capabilities for biochemical, histological, and haemodynamic endpoints, which are advantageous for evaluation of organ-level inflammatory injuries associated with BPS, such as effects on the liver, kidney, cardiovascular system, and neuroinflammatory responses [24]. The Wistar and Sprague-Dawley rat strains possess comprehensive historical information on systemic inflammation, organ weights, and clinical chemistry, making them ideal for evaluating BPS-induced injuries in the liver, kidneys, and cardiovascular system.

COMPARATIVE RESULTS OF MODEL-SPECIFIC PATTERNS AND MECHANISTIC CONVERGENCE

The research articles listed in *Table 1* and *Table 2* of the matrix were published over the past five years, with some studies extending back a decade. This selection offers a broad perspective on the effects of BPS on inflammation across widely used vertebrate models, including zebrafish and rodents. It highlights how each model contributes to a deeper understanding of BPS's impact on inflammation at various developmental stages and within different experimental contexts.

CONSERVED INFLAMMATORY MECHANISMS ACROSS MODELS

Across zebrafish and rodent models, BPS consistently activates an oxidative stress driven from the NF-κB axis with upregulated ROS and classical pro-inflammatory

Table 1
Matrix of rodent BPS-induced toxicity in inflammation

Author(s)	Rodent species/ strain	Age/sex	Dose exposure	Route	Duration	Organ/ System	Inflammatory pathway/ biomarker (findings)	Key inflammatory pathway	Remarks on biomarkers
[8]	Mice C57BL/6	Male (6-7 weeks)	0, 100, 1000 µg/ kg bw/day	Daily oral gavage	3 months	Colon/ intestine	↑macrophage (F4/80+), ↑TUNEL apoptosis, ↑IL-18, ↓Reg3b/Reg3g	NF-kB	BPS caused crypt distortion, increased macrophage infiltration, apoptosis, pro-inflammatory IL-8, and changes in barrier genes.
[17]	Mice C57BL/6	Both (12 weeks)	25 µg/kg/ day	Oral gavage in drinking water	12 weeks	Heart	↑TNF-α, ↑IL-6, ↑CD11c	NF-kB PPARγ	BPS + high-fat diet increases cardiac pro-inflammatory cytokines, leading to chronic low-grade cardiac inflammation.
[26]	Mice C57BL/6	Female (6-7 weeks)	0, 0.05, 5 mg/kg/ day	Daily oral gavage	4 weeks	Colon	↑TNFα, ↑IL1β, ↑IL6, ↓IL10, ↑NFκB p65, ↓ZO1, ↓Claudin1, gut dysbiosis	NF-kB	BPS includes colonic injury with increased pro-inflammatory cytokine gene expression. NF-kB activation reduces anti-inflammatory IL-10.
[29]	Mice C57BL/6	Both (12-24 weeks)	25-30 µg/ kg/day	Oral gavage in drinking water	12 weeks	Kidney	↑AhR, ↑NFκB, ↑CD31, no change in IL6	NF-kB	BPS increases NF-kB and AhR expression in renal tubules and CD31 in glomeruli. NF-kB is linked to inflammatory signaling despite unchanged IL-6 levels.
[30]	Rat	Female pregnant	12 µg/kg/ day	Daily oral gavage in olive oil	3 weeks before GD 0	Brain	↑NF-κB, ↑p53, ↓Bcl2, ↓NeuN, ↓Ki67, ↑GFAP, ↑βamyloid, ↓NO	NF-kB	BPA exposure in the perinatal period activates NF-kB and p53, reducing anti-apoptotic proteins. GFAP and β-amyloid produce striatal neuroinflammation
[31]	ICR Mice	Male adult (6 weeks)	0, 5, 50, 500 mg/ kg/day	Daily oral gavage	90 days	Heart	↑P-NFκB (Pp65), ↑ROS	NF-kB	BPS induces oxidative stress. Increased P-NF-kB and ROS indicate activation of NF-kB inflammatory signaling.
[34]	Mice C3H/HeJ	Male (6-11 weeks)	0.04, 0.4, 4 µg/kg/ day	Oral gavage in drinking water	6 weeks	Lungs	↑IL-5, ↑IL-13, ↑IL-33, ↑CCL11/ eotaxin, ↑OVA-IgE, ↑OVA-IgG1	Indirect NF-kB (Th2 cytokines mediated)	BPS + allergic asthma increase pulmonary inflammation, Th2 cytokines/chemokines.
[35]	Long-Evant rat	Male (21 days)	5 and 20 mg/kg	Daily oral gavage in drinking water	14 days	Liver	↓ROS, no changes in caspase-3, IL-1	NA	No detectable pro-inflammatory or pro-apoptotic liver response compare to control.
[36]	Sprague Dawley rat	Male (8 weeks)	0, 0.05, 20 mg/kg	Daily oral gavage	4 weeks	Intestine	↑pp38 and ↑pERK (MAPKs),	MAPK	BPS damaged intestinal epithelium and increased inflammatory cytokines. Activation of p38 and ERK MAPK leads to impaired sperm quality.
[37]	Mice C57BL/6J	Pregnant female	1.5 mg/kg/ day	Oral gavage in drinking water	GD 0 - PND 21	Colon	NA	Other (intestinal immune)	BPS causes persistent intestinal inflammation in F1 and F2 male gut. F3 reduces gut inflammation.
[38]	Mice C57BL/6J	Both (8 weeks)	4 µg/kg/ day	Oral gavage by dams	GD 0 – PND 28	Spinal cord (CNS)	↑ inflammatory cell infiltration and glial activation in spinal cord	Other (CNS neuro-inflammation)	BPS shows neurodegeneration with milder inflammatory marker changes.
[39]	Mice C3H/ HeN	Pregnant female	5 or 50 µg/ kg bw/day	Daily oral gavage	GD 15 – PND 21	Intestine	↑ fecal lipocalin	Other (Barrier-linked inflammation)	Perinatal BPS exposure alters intestinal immune function in offspring and increases fecal inflammatory lipocalin. Low-grade inflammation.
[44]	ICR Mice	Female (4 weeks)	1 mg/kg/ bw/day	Daily oral gavage in corn oil	4 weeks	Gut and ovary	↑Lymphocyte infiltration, ↑IL-6,	Other (microbiota-intestinal inflammation)	BPS reshaped the gut microbiota, increased intestinal permeability, and altered the inflammatory, impairing oocyte quality.
[45]	Mice C57BL/6J	Male (8 weeks)	50 mg/kg/ day	Daily oral gavage	6 weeks	Liver	↑IL1β, ↑TNFα, ALT, ↑AST; ↑MDA, ↓SOD	PPARγ	BPS caused lipid accumulation & elevated IL-1β and TNF-α, oxidative stress and histologic inflammatory cell infiltration.

BPS: bisphenol S; GD: gestational day; PND: postnatal day; NA: not available; ICR: Institute of Cancer Research; CNS: Central Nervous System; ROS: Reactive Oxygen Species; MDA: malondialdehyde.

Table 2
Matrix of zebrafish BPS-exposed toxicity in inflammation

Author(s)	Fish species/ strain	Age/sex	BPS dose exposure	Route	Duration	Organ/ System	Inflammatory pathway/ biomarker (findings)	Key inflammatory pathway	Remarks on biomarkers
[25]	Zebrafish (*Danio rerio*)	Adult (5 months)	1, 10, 100, 1000 µg/L	water exposure	14 days	Intestine	↑MDA, ↑8OHdG, ↑IL1β, ↑TNFα	PPARγ	BPS increased intestinal oxidative damage and pro-inflammatory cytokines. Altered PPAR signalling and other metabolic pathways, and disrupted gut microbial.
[27]	Zebrafish (*Danio rerio*)	Embryo	1, 10, 100 mg/L	semi-static exposure	3 hpf-120 dpf	Liver	↑IL-1β, ↑TNFα, ↑NF-κB, ↑IKK	NF-kB	BPS exposure drove progression from steatosis to steatohepatitis. Marked with IL-1β, TNF-α, and NF-κB indicates chronic hepatic inflammation driven by lipotoxicity.
[33]	Zebrafish (*Danio rerio*)	Juvenile (2hpf-3dpf)	1, 10, 100 µg/L	water exposure	2hpf-3dpf	Brain	↑Microglia & macrophages, ↑ROS, ↓SOD, ↓CAT, ↑apoptotic cells, ↑caspase8/9/3a/3b mRNA	Other (lipid neuro-inflammation)	BPS reduces brain lipid, increases microglial, increases oxidative stress, and causes neuroinflammatory/ apoptotic changes
[43]	Zebrafish (*Danio rerio*)	Larvae	8.13 mg/L	water exposure	4 hpf – 120 hpf	Immune system	↑IL-6, ↑TNF-α, activation of IKBKB	NF-kB	BPS enhances inflammation via IKBKB and modulates Ptgs2a (COX-2), Nos2a, and antioxidant genes.

BPS: bisphenol S; Hpf: hour after fertilisation; dpf: day after fertilisation.

cytokines like TNF-α, IL-1β and IL-6 across liver, intestine, kidney, heart, brain, and immune tissues [25]. *Figure 3* visually summarizes the conserved oxidative stress NF-κB axis and highlights model-specific organ manifestations in zebrafish and rodent studies. In C57BL/6 mice, colonic exposure models and high-fat diet sensitized cardiac models show increased TNF-α, IL-1β, and IL-6, alongside activation of NF-κB-p65 and barrier disruption, resulting in a pattern of low-grade chronic inflammation in the gut and heart [17, 26]. In zebrafish studies from *Table 2*, prolonged exposure of waterborne BPS results in increased expression of IL-1β and TNF-α

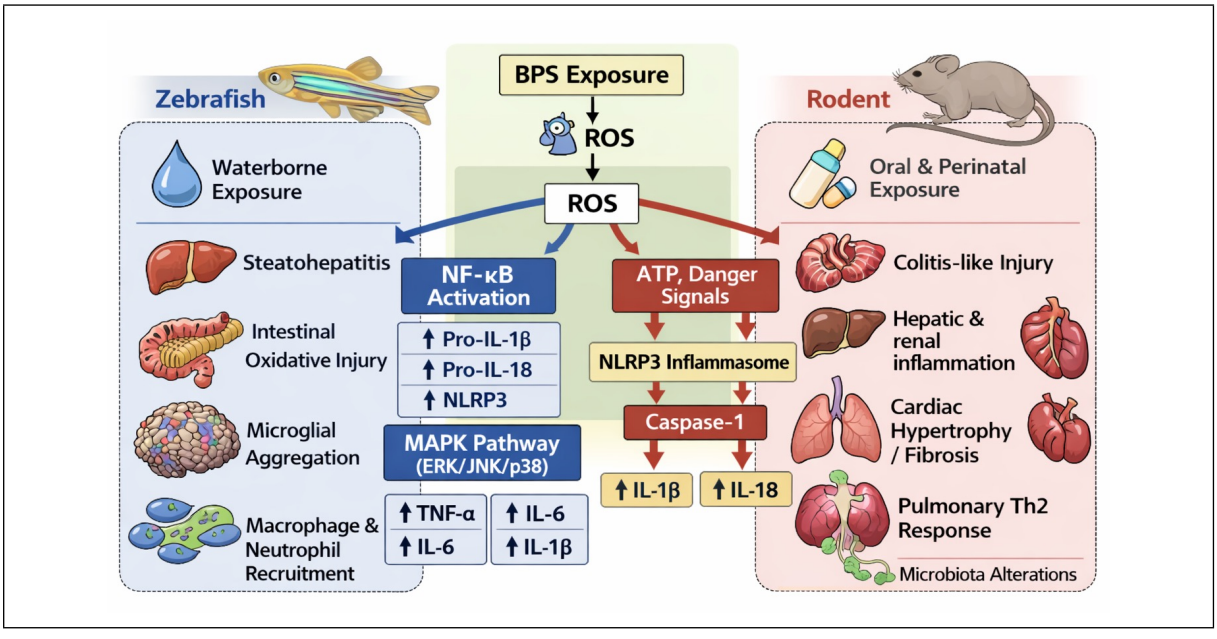

Figure 3
Conserved and model-specific inflammatory responses to BPS. Oxidative stress activates NF-κB with MAPK and NLRP3 branches, producing TNF-α, IL-1β, IL-6, and IL-18. Zebrafish (left): waterborne exposure causes hepatic, intestinal, and neural inflammation. Rodents (right): oral/perinatal exposure leads to gut, hepatic, cardiac, pulmonary, and neuroinflammatory outcomes.

as well as NF-κB and IKK, thereby promoting the progression from steatosis to steatohepatitis [27]. Comparable responses associated with NF-κB signaling have been documented in zebrafish models of immunity and intestinal function, demonstrating that BPS promotes intestinal injury or neuroinflammation. Rodent model studied by the [28-31] reveal a consistent pattern involving the colon, heart, kidneys, and liver show elevated levels of TNF-α, IL-1β, and IL-6, along with nuclear NF-κB or phospho-p65 and an indicator of oxidative damage, ROS, MDA, and SOD/CAT activity, which reduces antioxidant enzyme activity. This suggests a conserved relationship between redox imbalance and NF-κB-mediated cytokine production across both species.

Chronic or developmental exposure to low-to-moderate doses of BPS more consistently induces inflammatory phenotypes compared to rapid high-dose exposure. Research involving zebrafish and the application of semi-static waterborne protocols from early developmental phases to the juvenile or adult stage (30-120 days) reveals a significant oocyte-dependent activation of IL-1β, TNF-α, and NF-κB. This activation has been linked with notable histological steatohepatitis and immune-organ injury [25, 32, 33]. Meanwhile, in rodent studies, the administration of several μg–mg/kg/day through drinking or feeding for 4-12 weeks consistently results in elevated levels of cytokines in tissues, activation of the NF-κB signaling pathway, and histological evidence of inflammation in various organs including the colon [26], liver [20], kidneys [29], lungs [34], and heart [17]. Conversely, shorter rat studies (14-28 days) yield more inconsistent results, with some indicating oxidative alterations but exhibiting limited classical inflammatory markers [35, 36] Furthermore, perinatal exposure to BPS via dams has a high potential to induce latent or sex-dependent inflammatory responses in the intestines and Central Nervous System (CNS) of adult offspring [37-39].

Cross-species evidence suggests that BPS induces oxidative stress by increasing ROS and MDA levels and decreasing antioxidant enzyme activity, thereby activating the NF-κB pathway. In some models, interact with PPARγ, AhR, or other metabolic/xenobiotic pathways to drive organ-specific inflammatory response [25, 29, 32, 40]. Although affected organs may differ between models, for example, zebrafish are primarily in the liver, intestine, and brain, whereas rodents are primarily in the gut, liver, kidney, lung, heart, and central nervous system. The current combination of ROS upregulation, NF-κB activation, and pro-inflammatory cytokine upregulation is a common inflammatory mechanism of BPS toxicity seen in rodent and zebrafish studies.

Across zebrafish and rodent studies, the exposure route influences the inflammatory outcomes observed in each model. Although there is currently no information on internal BPS concentrations, zebrafish are frequently immersed in water from embryogenesis, resulting in whole body absorption and simultaneous exposure to the liver, gut, and brain [41]. Meanwhile, rodent studies employ BPS doses between mg/kg/day over several weeks to months through oral administration, similarly mimicking possible BPS exposure in the daily human lifestyle when drinking water or food [42]. These methodologies more accurately replicate human consumption and allow for organ-specific exposure scenarios such as increased cardiac, hepatic, or renal inflammation caused by chronic BPS exposure and lifestyle. The perinatal mouse and rat models add complications because the subject mother is exposed to BPS during pregnancy and lactation. The offspring are indirectly exposed to BPS doses through the placenta and milk, which is important for programming effects but complicates precise dose-response interpretation.

MODEL-SPECIFIC INFLAMMATORY RESPONSES

Zebrafish research focusses on early developmental and organ-specific innate inflammation, making use of transparent larvae and whole organism exposure. Chronic waterborne BPS exposure in zebrafish leads to hepatic IL-1β/TNF-α upregulation, NF-κB or PPARγ involvement, acute protein induction, and intestinal oxidative injury under standardised exposure and genetic background [25]. Further research on the brain reveals that environmental BPS reduces key phospholipids (PC, LPC) and causes microglial aggregation, ROS, and neural apoptosis. This suggests that BPS causes inflammation through lipid changes, which provides greater clarity in zebrafish than traditional models. Research on transgenic zebrafish shows that BPS induces macrophages and neutrophils and elevates ROS and malondialdehyde (MDA), indicating innate immunotoxicity and mixture effects at the LC50-based concentration [43].

Rodent studies, on the other hand, show more complex inflammatory responses involving multiple organs and potentially influenced by external factors such as sex and diet. For instance, chronic oral BPS administration in the gastrointestinal tract alters the gut microbiota, which can cause colitis-like manifestations, including crypt distortion, macrophage accumulation, epithelial apoptosis, and increased IL-18, suggesting that the microbiota influences the response to BPS-induced inflammation [28, 44]. Perinatal BPS exposure induces sex-specific intestinal/metabolic inflammation in F1-F3 offspring [37, 38]. Additionally, perinatal exposure in the Experimental Autoimmune Encephalomyelitis (EAE) model of multiple sclerosis appears to accelerate disease onset and worsen neurodegeneration in adult males [38]. Administration of low-dose BPS in conjunction with a high-fat diet leads to cardiac hypertrophy, fibrosis, and upregulation of TNF-α, IL-1β, and IL-6 in the left ventricle [17] . In obese mice, AhR and NF-κB are activated within renal tubules and glomeruli, resulting in the upregulation of CD31 and subsequent structural damage to the kidney. This is frequently accompanied by relatively minor changes in classical cytokines [29]. Variations in rodent observation significantly reflect the differences in strain, sex, nutrition, co-exposure, and developmental stage, in contrast to the more uniform inflammatory responses reported in standard zebrafish larval and juvenile.

In addition to differences in exposure route, the biomarker panels used across studies also vary between

models. Zebrafish studies often use nominal water concentration exposure and heavily rely on mRNA profiles of IL-1β, TNF-α, IL-6, NF-κB, and PPARγ-associated genes, oxidative stress indicators, including ROS, MDA, and antioxidant enzymes, acute-phase proteins, and immune cell or microglia images [25]. Rodent studies typically use dosages ranging from µg to mg/kg/day, including tissue and serum cytokines, immune cell markers, histopathological evaluations, functional outcomes, and protein pathways like NF-κB, AhR, P-NF-κB, or tight junction components. A study conducted by Liu *et al.* [35] on Long Evans rat hepatocellular shows that minimal and brief exposure to BPS can reduce ROS levels without increasing inflammatory markers. This demonstrates how time and exposure degree have a significant impact on the biomarker profile. These methodological differences highlight the need for more standardised internal dose measurement and a minimal overlapping panel of cytokines and pathway markers to improve quantitative cross-model synthesis.

KNOWLEDGE GAPS AND UNDEREXPLORED AREAS

Despite strong evidence supporting the involvement of oxidative stress and NF-κB pathways, several inflammatory mechanisms in BPS toxicology remain poorly understood. The activation of the NLRP3 inflammasome, detailed TLR4 signalling, and Nrf2/AhR crosstalk have been investigated in a small number of rodent studies, specifically in kidney, liver, and reproductive contexts. However, these mechanisms are still significantly underexplored in zebrafish and extrahepatic tissues [29, 36]. The role of PPARγ mediated meta-inflammation has been relatively described in hepatic endpoints within both zebrafish and rodent models [32, 45]. However, its implications in cardiovascular, renal, and CNS models remain 6, limiting researchers' ability to understand the specific contributions of various pathways in different organs. Zhu *et al.* [36] documented the involvement of MAPK cascades p38 and ERK in testicular inflammation in rats exposed to BPS, but no systematic evaluation was conducted in other rodent organs or fish inflammatory responses.

Limited research has systematically compared males and females within identical frameworks, but available evidence suggests a sex-dependent effect. For example, perinatal exposure to BPS causes more intestinal inflammation in F1-F2 males than females across generations [37], enhance CNS autoimmune damage in male but not female EAE offspring [38], and show different fecal lipocalin and immune skewing patterns between sexes in perinatal immune studies [39]. This study looks into the effects of real-world BPS exposure scenarios, such as low-dose BPS combined with other toxicants, an unhealthy diet or lifestyle, and long-term environmental exposure. Wang *et al.* [25] and Su *et al.* [43] found that BPS exposure with a high-fat diet causes additive immunotoxicity and synergistic oxidative stress in zebrafish larvae, as well as NF-κB-mediated neuroinflammation in the rat brain [30]. However, the majority of rodent studies evaluate BPS in isolation, leaving significant uncertainty about the relevance of experimental findings to chronic, multi-pollutant human exposure scenarios. Similarly, Brulport *et al.* [37] and Bonaldo *et al.* [38] have documented a transgenerational inflammatory program following perinatal BPS in the mouse intestine and CNS, respectively, whereas the epigenetic mechanisms of microbiota inheritance and the persistence of inflammatory phenotypes beyond F2 are poorly understood.

CONCLUSION

This review demonstrates that bisphenol S-induced inflammation operates through a conserved oxidative stress-NF-κB axis across evolutionarily divergent animal models. The organ-specific inflammatory manifestations reflect differences in anatomical complexity and immune architecture between fish and mammals. The complementary strengths of zebrafish and rodent systems, namely transparency and mechanistic clarity in fish versus systemic integration and adaptive immunity in rodents, provide powerful tools for understanding how chronic BPS exposure disrupts inflammatory homeostasis. Evidence suggests that low-dose, persistent environmental exposure to BPS can activate inflammatory signalling pathways, disrupt epithelial barriers, alter gut microbiota, and cause transgenerational immune dysfunction, implicating BPS in the pathogenesis of chronic inflammatory diseases. However, the current evidence base is limited by incomplete mechanistic coverage, insufficient standardization of exposure design and biomarker reporting, and a lack of consistent sex-specific and life-stage-specific analyses, which reduces cross-study comparability and translational confidence. In particular, pathways such as NLRP3 inflammasome activation, TLR4 signaling, Nrf2/AhR crosstalk, and PPARγ-mediated inflammatory regulation remain underexplored in a comparative framework. Future research should therefore prioritize standardized internal dose assessment, harmonized biomarker panels across models, and systematic inclusion of both sexes and multiple developmental windows. In addition, studies investigating combined exposures, dietary or metabolic co-stressors, epigenetic regulation, microbiota-mediated effects, and transgenerational outcomes are needed to better reflect real-world exposure scenarios. Such efforts will strengthen the mechanistic interpretation of BPS immunotoxicity and improve its relevance for human health risk assessment and regulatory decision-making.

Acknowledgments

The Authors would like to thank all staff and contributors at the Faculty of Health Sciences, Optometry, and Visual Sciences Research Groups (iROViS), UiTM Selangor, Puncak Alam Campus, for their assistance, supervision, and insightful suggestions in preparing this article. WNIWA, RD, FNZ, NZA, DAFA, and EK also acknowledge their membership of the Optometry and Visual Science Research Group (iROViS), UiTM Selangor, for their contribution to this study. Thank you to the Tun Abdul Razak Library (PTAR) at UiTM for creating a suitable online database platform for this review.

Authors' contributions

RD designed, administered, and supervised this study; WNIWA, NZA and DAFA conducted sampling and statistical analysis; RD, FNZ, FP and EK provided resources for this study and were responsible for the formal analysis; WNIWA, RD, FNZ, NZA, DAFA, RR, and EK participated in writing original draft, writing-review & editing.

Disclaimer statement

The Authors used ChatGPT, Grammarly, and QuillBot to improve the readability and language of this review. The Authors declare that all Figures are original and were prepared by the Authors. AI-assisted drafting tools were used in part, with subsequent verification and editing performed in BioRender. Final Figures were validated for accuracy by the Authors. The Authors used these tools to review and edit the content as needed, and they accept full responsibility for the content of the published article.

Conflicts of interest statement

The Authors declare no conflict of interest.

Received on 23 December 2025.
Accepted on 27 May 2026.

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