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Current Insights into Bisphenol F-induced Liver Toxicity: A Review of Animal Study Evidence

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Abstract: Bisphenol F (BPF), widely used as a replacement for Bisphenol A (BPA), exhibits comparable or greater hepatotoxic potential. This review synthesises evidence from 2015 to 2025 on the molecular, cellular, and physiological effects of BPF in animal models, with emphasis on zebrafish due to their translational relevance in toxicology. BPF exposure induces dose-dependent liver injury, characterised by steatosis, fibrosis, vacuolation, and inflammation. BPF disrupts lipid metabolism, induces oxidative stress, and compromises mitochondrial function, effects that mirror or exceed those of BPA. Despite growing evidence, data remain limited regarding chronic exposure, sex-specific susceptibility, and post-exposure recovery. These findings highlight the need for advanced mechanistic and cross-species studies to clarify BPF's toxicological profile and support the development of safer bisphenol alternatives.

Keywords: Bisphenol F (BPF); hepatotoxicity; animal models; endocrine-disrupting chemicals (EDCs); oxidative stress.

1. Introduction

Bisphenol A (BPA; 2,2-bis(4-hydroxyphenyl) propane) is one of the most widely produced industrial chemicals, used in the manufacture of polycarbonate plastics and epoxy resins for various consumer products [1, 2]. BPA is prevalent in the environment due to its extensive use, and human exposure occurs via both dietary and non-dietary pathways [3]. Structurally similar compounds, such as bisphenol-F (BPF), have been increasingly used as alternatives in these materials. These compounds share a common structure with two hydroxyphenyl groups and are collectively termed bisphenol analogues, as illustrated in Figure 1.

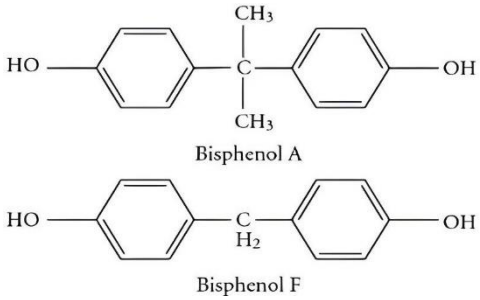

Figure 1. Chemical structures of BPA and BPF. Adapted from [4].

Sixteen bisphenol analogues are currently used in industrial applications. Among them, BPF, Bisphenol S (BPS), and Bisphenol AF (BPAF) are common structural substitutes increasingly used in products labelled as "BPA-free" [1,5]. Evidence suggests that these analogues may exhibit toxicity levels comparable to or exceeding those of BPA [6]. BPF (4,4′-methylene-diphenol) is a principal replacement for BPA in the production of polycarbonate plastics and epoxy resins [7, 8]. It is incorporated into coatings, adhesives, water pipes, dental materials, and food packaging, and has also been identified as a natural compound in mustard [9].

BPF is increasingly used as a structural analogue and industrial replacement for BPA following extensive evidence of BPA-induced toxicity [6]. BPF is incorporated into a wide range of consumer and industrial materials, including food packaging, thermal papers, and epoxy resins [10]. Both BPA and its analogues are frequently detected in environmental matrices and human biological fluids, with accumulating evidence associating these compounds with acute toxicity, endocrine disruption, neurotoxicity, and organ-specific injury [11,12]. Consuming food and beverages contaminated with these compounds can harm human health, particularly the liver [13]. Although BPF is marketed as a safer alternative to BPA, emerging evidence indicates that it may exhibit comparable or even greater toxicological effects, particularly affecting metabolic and endocrine functions, including liver health [14,15]. The liver, a critical organ for detoxification and metabolic regulation, is highly susceptible to endocrine-disrupting chemicals (EDCs), such as BPF, which can interfere with hepatic function and contribute to metabolic disorders. Numerous studies have investigated the toxicity of BPF on the liver. These studies have comprehensively examined the mixture effects of BPF and its analogues on various organisms' livers, including mice [14], rats [16, 17], zebrafish [18], marine medaka [19], and Labeo rohita [20], which generates extensive data resources for studying the effects of BPF mixtures on the liver. Given the growing prevalence of BPF exposure and its potential health risks, an urgent comprehensive evaluation of its hepatotoxic effects is needed. This narrative review synthesises current evidence from 2015 to 2025, focusing on the molecular, cellular, and physiological impacts of BPF on the liver and discussing underlying mechanisms and potential therapeutic interventions.

BPF has been detected in human urine, blood, and breast milk, confirming widespread exposure. Yet, its long-term health effects, particularly on the liver, a key organ in xenobiotic metabolism, remain poorly understood, with evidence linking prolonged exposure to oxidative stress, inflammation, lipid accumulation, and endocrine disruption [21,22]. These perturbations, particularly the accumulation of lipid droplets (LDs), contribute to NAFLD-like pathological changes that may progress to more severe hepatic conditions, including steatohepatitis, fibrosis, and hepatocellular carcinoma [18]. Understanding these mechanisms is essential for shaping evidence-based regulations and developing safer alternatives. Based on Figure 2, BPF-containing products are widespread, including personal care products (PCPs),

food containers, dust, and thermal papers. This extensive distribution raises concerns about continuous human exposure through multiple pathways.

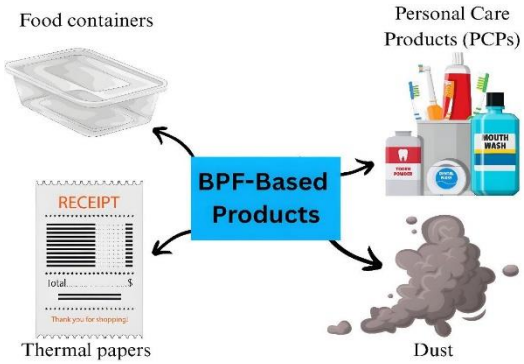

Figure 2. BPF-based products.

This review emphasises liver toxicity, as the liver serves as the primary site for xenobiotic metabolism and detoxification [23]. There is increasing evidence that BPF exposure elicits hepatic alterations comparable to those induced by BPA. It explores key themes, including BPF's mechanisms of hepatic toxicity, such as oxidative stress and mitochondrial dysfunction [22], its role in promoting liver inflammation and fibrosis via cytokine dysregulation [15], and its contribution to metabolic disturbances, including insulin resistance and lipid metabolism dysregulation [24]. Additionally, this narrative review discusses gaps in current research and future directions for mitigating BPF-associated health risks. By consolidating findings from in vitro, animal, and epidemiological studies, it aims to provide a critical update on BPF's hepatotoxic potential and offer insights for researchers and clinicians.

2. Materials and Methods

A targeted search was conducted in PubMed, Web of Science, Scopus, Google Scholar, and ScienceDirect using Boolean operators ("AND", "OR") with keywords such as "Bisphenol F", "BPF", "liver", and "toxicity". The search covered studies published between 2015 and 2025. Studies were included if they examined molecular, cellular, or physiological liver effects of BPF in in vitro or in vivo models, while reviews and studies without liver-related outcomes were excluded. A total of approximately 50 studies were identified, but only 33 met the inclusion criteria and were selected for detailed analysis.

3. Results and Discussion

3.1. Hepatic histological changes.

The liver, the most significant internal organ in the body, performs numerous vital functions, including breaking down and removing toxins, producing proteins, and regulating blood sugar levels to maintain balance [13]. Recent studies identify the liver as a primary target organ for bisphenols, with emerging evidence showing that BPF disrupts hepatic metabolic processes. Prior research demonstrated that BPF markedly increased plasma and hepatic levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in male mice, confirming its hepatotoxic potential and ability to impair liver function [16]. Experimental studies across multiple animal models have demonstrated that BPF exposure induces direct hepatotoxic effects, evidenced by histological alterations in liver tissue under both acute and chronic exposure conditions (Table 1). A previous study reported that histological examination

of liver tissue stained with H&E revealed no significant changes in hepatocyte steatosis or lipid droplet accumulation in mice treated with BPF at doses of 100 and 1000 μg/kg body weight/day for 3 months. Despite the lack of visible alterations in liver morphology at these doses, Nile red staining of AML12 liver cells exposed to 100 μM BPF revealed clear lipid accumulation, indicating that BPF can induce hepatic lipid deposition at the cellular level. These findings suggest that while conventional histological staining may not detect early-stage changes, BPF exposure at both in vivo and in vitro levels may still disrupt hepatic lipid metabolism, potentially leading to metabolic disturbances before structural liver damage becomes apparent [24]. Furthermore, another study using zebrafish demonstrated that Masson staining of liver sections revealed BPF-induced hepatic fibrosis in all treatment groups (0.5, 5.0, and 50 μg/L), with dose-dependent increases in the area of fibrosis measured at [3073 (ns), 8552 ($p<0.01$), and 11,971 ($p<0.01$) μm^2/section, respectively]. Controls exhibited minimal fibrosis (only one sample at 1419.6 μm^2). Meanwhile, HE staining further revealed concentration-dependent hepatocyte vacuolation across all BPF exposures, with increasing severity indicating the development of steatosis [18]. Moreover, in another study using Long Evans rats, the animals were randomly assigned to three groups: a control group (non-treated), a low-dose BPF group receiving 0.0365 mg/kg body weight/day (LBPF), and a high-dose BPF group receiving 3.65 g/kg body weight/day (HBPF). The results demonstrated that exposure to BPF led to elevated levels of nitrosative stress markers and pro-inflammatory cytokines, indicating an inflammatory response. There was a significant activation of the NLRP3 inflammasome in the liver tissues of both lactating dams and postnatal day 6 (PND6) offspring [25]. These observations suggest that BPF exposure can induce hepatic inflammation, potentially contributing to the onset or progression of liver disease.

3.2. Metabolic disruptions.

BPF exposure has increasingly been implicated in disrupting hepatic metabolic pathways, particularly those governing lipid and amino acid metabolism, which are central to maintaining liver function and systemic metabolic homeostasis [16]. BPF exposure in *Labeo rohita* fish led to notable alterations in lipid profiles, including an increase in hepatic triglyceride accumulation, a hallmark of steatosis that signals impaired lipid regulation [20]. This dysregulation likely arises from BPF-induced changes in the expression of key genes and enzymes involved in lipogenesis and fatty acid oxidation. Further supporting this, a study demonstrated that, in rodent models, BPF exposure affects amino acid metabolism by altering the concentration and utilisation of essential amino acids, thereby impairing protein synthesis and mitochondrial energy production [26]. These metabolic disturbances are corroborated by enzymatic analyses showing downregulation of β-oxidation enzymes crucial for fatty acid catabolism and concurrent upregulation of lipogenic enzymes, which together shift the hepatic metabolism toward lipid accumulation [14]. Comparative studies between BPF and BPA suggest that although both compounds share structural similarities and toxicological profiles, BPF might exert a more profound impact on glucose and lipid metabolism in specific biological contexts. For instance, BPF has been linked with heightened insulin resistance, disrupted glucose homeostasis, and hyperglycemia in animal studies, underscoring its diabetogenic potential [27]. Despite these findings, significant gaps persist in the understanding of the precise dose-response relationships, long-term metabolic outcomes, and potential interspecies variability in BPF toxicity. Future studies must integrate omics-based approaches and human-

relevant models to identify reliable biomarkers of BPF-induced metabolic dysfunction and clarify its risk profile under environmentally relevant exposure scenarios.

3.3. Oxidative stress and mitochondrial dysfunction.

Oxidative stress and mitochondrial dysfunction are critical, interconnected pathways through which BPF induces hepatotoxicity. BPF exposure markedly elevates reactive oxygen species (ROS) and promotes lipid peroxidation, as shown in *Labeo rohita*, where chronic exposure caused oxidative damage to hepatocyte membranes and compromised cellular integrity [20]. Mitochondria, being both a primary source and target of ROS, are particularly vulnerable. Rodent studies reveal that BPF disrupts mitochondrial membrane potential, reduces ATP synthesis, and impairs overall bioenergetic function [24]. This dysfunction amplifies ROS production, creating a vicious cycle of oxidative injury and apoptosis. Compared to BPA, BPF may exert stronger oxidative and mitochondrial effects due to its greater lipophilicity, facilitating deeper integration into mitochondrial membranes and structural disruption [28]. However, the molecular signalling pathways underlying these effects, such as Nrf2/Keap1, MAPK, and regulators of mitochondrial biogenesis, remain poorly characterised [10]. Further research using omics-based and mechanistic approaches is crucial to clarify these mechanisms, as summarized in Table 2, and to develop antioxidant or mitochondrial-protective strategies to mitigate BPF-induced liver damage [18].

3.4. Inflammatory responses.

BPF exposure has been increasingly associated with the modulation of hepatic inflammatory responses, a key contributor to liver pathology, including fibrosis and chronic liver disease. Evidence from recent studies reveals that BPF can upregulate pro-inflammatory cytokines and activate signalling pathways that sustain chronic inflammation in hepatic tissues [29]. Furthermore, BPF treatment in *Labeo rohita* fish significantly elevated the levels of key pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), both of which are known to play pivotal roles in initiating and perpetuating hepatic inflammation [20]. This cytokine upregulation can lead to immune cell infiltration and hepatic stellate cell activation, ultimately contributing to fibrosis. Other studies suggest that bioactive lipids, such as lysophosphatidylcholine (LPC), play key roles as signalling molecules in regulating inflammation [30]. They also affect several cellular processes, including cancer growth, immune responses, and the control of metabolic disorders. Furthermore, in vitro studies have shown that BPF activates the PI3K-AKT signalling pathway in macrophages, leading to increased glycolytic flux and enhanced cytokine secretion, a phenomenon consistent with the metabolic reprogramming observed in activated immune cells [26].

Table 1. Summary of selected studies on the effect of BPF-induced liver histological changes.

No	Type of animal	Dose/ concentration	Vehicles	Mode of administration	Duration of treatment	Histology results	Reference
1	Zebrafish	0.5, 5.0, 50 µg/L/day	Water	Waterborne exposure	180 days	Masson's staining showed dose-dependen liver fibrosis, significant at 5.0 and 50 µg/L BPF. (3073 ($p > 0.05$), 8552 ($p < 0.01$) and 11,971 ($p < 0.01$) µm2/section) H&E staining showed dose-dependent hepatocyte vacuolation, indicating steatosis.	[18]
		0.5 µg/L	Water	Waterborne exposure	60 days	BPF exposure caused lipid buildup (Oil Red O staining), confirming steatosis ($p >$	[15]

No	Type of animal	Dose/ concentration	Vehicles	Mode of administration	Duration of treatment	Histology results	Reference
						0.05)	
		1, 10, 100 µg/L	Water	Waterborne exposure	30 days	Exposure to 1 and 100 µg/L BPF caused vacuolation($p < 0.05$)	[31]
		80, 160, 800 µg/L	Water	Waterborne exposure	13 days	BPF caused liver damage, shown by increased lipid Peroxidation. ($p < 0.05$)	[22]
2	Marine Medaka	0.05, 0.5, and 5 µM	water	Waterborne exposure	72 hours	No histologically detectable changes in lipid droplets formation or hepatocyte morphology	[19]
		200 µg/L	Water	Waterborne exposure	70 days	Increased vacuole formation in the livers of both male and female fish as compared to the control group ($p < 0.05$, $p < 0.01$, $p < 0.001$) Eosinophilic bodies were present in the livers of female fish only.	[28]
3	ICR mice	100 ng/g bw/day	Corn oil	Oral	14 days	BPF exposure led to lipid accumulation in hepatocytes. ($p < 0.05$)	[14]
		100 ng/g bw/ day	Corn oil	Oral	21 days	BPF exposure did not induce histological disruptions in the liver	[27]
4	C57BL/6 mice	100 and 1000 µg/kg bw/day	Corn oil	Oral	3 months	H&E showed no steatosis, but Nile Red revealed BPF-induced hepatic lipid accumulation. ($p < 0.05$).	[24]
		0.05, 0.2, and 0.5 mg/kg/b.w/da y	Corn oil	Oral	30 days	Severe mitochondrial damage: fragmentation (prominent), crest loss, swelling, cavitation. ($p < 0.05$).	[10]
		0.05 and 5 mg/kg b.w./day	Water	Oral	48 days	Reduced presence of lipid droplets in liver cells, as indicated by decreased Oil Red O staining. ($p < 0.05$).	[16]
		100 µg/kg	Olive oil	Oral	5 months	Nile Red staining showed lipid buildup in liver cells, indicating steatosis. ($p < 0.05$).	[32]
5	BALB/c mice	5, 10, or 20 mg/kg of bw/day	Corn oil	Oral	14 days	Biochemical markers (↑ LDH) suggest subcellular injury. Hepatocyte damage (vacuolization, membrane disruption). ($p < 0.05$).	[33]
6	Long-Evans rats	0.0365 and 3.65 mg/kg b.w/day	Corn oil	Oral	60 days	Mitochondrial swelling and fragmentation, Inflammatory cell infiltration. Statistical significance was determined by one-way ANOVA. ($p < 0.05$; $p < 0.01$; $p < 0.001$; $p < 0.0001$ compared to control group. $p < 0.05$; $p < 0.01$; LBPF vs. HBPF).	[25]
7	Rainbow Trout	0, 15.63, 31.25, 62.50, 125, 250, and 500 µM	N/A	N/A	24 hours	BPF-exposed hepatocytes (500 µM) exhibited degeneration. ($p < 0.05$)	[34]
8	*Labeo rohita*	600, 1200, and 1800µg/L	Water	Waterborne expo-sure	21 days	Degenerative nuclei, necrotic cells, damaged central veins, disrupted sinusoids, and clustered nuclei formation. ($p < 0.05$)	[20]

Note: Data derived from in vivo animal studies involving zebrafish, Marine Medaka, and mice exposed to BPF through waterborne or oral administration. Histological alterations were assessed using Masson's trichrome, H&E, and Nile Red staining. Quantitative values, where reported, are expressed as the means ± SEMs, $p < 0.05$ considered statistically significant. b.w., body weight; N/A: Non-Applicable; H&E, Hematoxylin and Eosin; LBPF, low-dose BPF; HBPF, high-dose BPF; LDH, Lactate Dehydrogenase.

This shift to glycolysis, often termed the "Warburg effect" in immune cells, supports sustained inflammatory responses and tissue damage. BPF exposure has been linked to greater activation of the NLRP3 inflammasome, a key sensor of cellular stress and damage that drives IL-1β maturation and secretion, further amplifying the inflammatory milieu in liver tissue [25].

Although progress has been made, the precise mechanisms through which BPF influences immune pathways remain unclear. Future research should use targeted, unbiased methods to identify key receptors and transcription factors, such as NF-κB, STAT3, and inflammasome components, and to assess the long-term effects of chronic BPF exposure on liver inflammation, particularly in human-relevant models. Clarifying these mechanisms could guide therapies to reduce BPF-induced liver damage.

Table 2. Summary of selected studies on the mechanism of BPF-induced liver damage.

No	Type of animal	Dose/ concentration	Vehicles	Mode of administration	Duration of treatment	Mechanism	Reference
1	Zebrafish	0.5, 5.0, 50 µg/L/day	Water	Waterborne exposure	180 days	Mitochondrial Dysfunction Metabolic disruption	[18]
		0.5 µg/L	Water	Waterborne exposure	60 days	Inflammatory dysregulation Metabolic disruption	[15]
		1, 10, 100 µg/L	Water	Waterborne exposure	30 days	Metabolic disruption	[31]
		80, 160, 800 µg/L	Water	Waterborne exposure	13 days	Oxidative Stress Metabolic disruption	[22]
2	Marine Medaka	0.05, 0.5, and 5 µM	water	Waterborne exposure	72 hours	Metabolic disruption	[19]
		200 µg/L	Water	Waterborne exposure	70 days	Metabolic disruption	[28]
3	ICR mice	100 ng/g bw/day	Corn oil	Oral	14 days	Oxidative Stress Metabolism Disruption	[14]
		100 ng/g bw/ day	Corn oil	Oral	21 days	Metabolic disruption	[27]
4	C57BL/6 mice	100 and 1000 µg/kg bw/day	Corn oil	Oral	3 months	Metabolic disruption	[24]
		0.05, 0.2, and 0.5 mg/kg/b.w/day	Corn oil	Oral	30 days	Oxidative Stress Metabolism Disruption Mitochondrial Dysfunction	[10]
		0.05 and 5 mg/kg b.w./day	Water	Oral	48 days	Metabolic disruption	[16]
		100 µg/kg	Olive oil	Oral	5 months	Oxidative stress Metabolic disruption	[32]
5	BALB/c mice	5, 10, or 20 mg/kg of bw/day	Corn oil	Oral	14 days	Metabolic disruption	[33]
6	Long-Evans rats	0.0365 and 3.65 mg/kg b.w/day	Corn oil	Oral	60 days	Inflammatory dysregulation	[25]
7	Rainbow Trout	0, 15.63, 31.25, 62.50, 125, 250, and 500 µM	N/A	N/A	24 hours	Oxidative stress and antioxidant disruption	[34]
8	*Labeo rohita*	600, 1200, and 1800 µg/L	Water	Waterborne exposure	21 days	Oxidative stress and antioxidant disruption Metabolic disruption	[20]

Note: Data derived from in vivo animal studies involving zebrafish, Marine Medaka, mice, rats, and other fish species exposed to BPF through waterborne or oral routes. Mechanistic parameters such as oxidative stress, mitochondrial dysfunction, and metabolic disruption are reported with the means ± SEMs, $p < 0.05$ indicating statistically significant effects. b.w., body weight; N/A, Non-Applicable.

Table 1 summarises selected studies that investigated the histological effects of BPF exposure on the liver across different animal models, including zebrafish, marine Medaka, and mice. The results consistently demonstrate that BPF exposure can induce notable hepatic alterations depending on dose and exposure duration. In zebrafish, long-term waterborne exposure resulted in dose-dependent liver fibrosis and hepatocyte vacuolation, indicating steatosis and early signs of liver injury. Similarly, exposure to higher concentrations of BPF caused lipid accumulation and increased lipid peroxidation, confirming hepatocellular damage. Marine Medaka exhibited vacuole formation and eosinophilic bodies, particularly in females,

after prolonged exposure, whereas lower doses showed minimal histological disruption. In mammalian models, such as ICR mice, oral administration of BPF led to lipid accumulation in hepatocytes, although some studies reported no visible histological changes at comparable exposure levels. These findings indicate that BPF can disrupt liver architecture via mechanisms such as lipid accumulation, fibrosis, and cellular vacuolation, which differ among species and are influenced by exposure concentration and duration.

Table 2 summarises the proposed mechanisms underlying BPF-induced liver damage, as reported in various in vivo studies using zebrafish, Medaka, mice, rats, and other fish species. The most commonly identified mechanisms include oxidative stress, mitochondrial dysfunction, metabolic disruption, and inflammatory responses. Zebrafish exposed to BPF exhibited mitochondrial impairment and elevated production of inflammatory mediators, consistent with disrupted cellular energy metabolism. Similar patterns were observed in mice and fish, where oxidative stress led to an imbalance between pro-oxidant and antioxidant systems, contributing to hepatocellular injury. Long-term oral exposure in rodent models revealed metabolic disturbances that may affect lipid and glucose regulation, while other studies identified inflammatory pathways as a key contributor to liver dysfunction. These findings indicate that BPF-induced hepatotoxicity is multifactorial, primarily involving oxidative and metabolic stress pathways that compromise liver integrity and function across aquatic and mammalian species.

The toxicological impacts of BPF on hepatic health have been increasingly scrutinised, particularly using zebrafish models, which offer a cost-effective, genetically tractable system for toxicological screening. Evidence synthesised from recent studies reveals a convergence in findings regarding histopathological damage, mechanisms of oxidative stress, mitochondrial disruption, and metabolic dysregulation. Nevertheless, nuanced differences across species, exposure durations, and methodologies provide a complex picture that warrants critical analysis.

3.5. Comparative Perspectives on Histomorphological Alterations.

Multiple zebrafish studies, including those by [15,18,31], consistently reported dose-dependent hepatocyte vacuolation, steatosis, and fibrosis. These pathological features, visualised using H&E and Masson's trichrome staining, indicate hepatocellular lipid accumulation and fibrogenesis, suggesting a direct correlation between BPF concentration and liver damage. In contrast, marine Medaka showed no detectable liver damage even at comparable exposure levels and durations, highlighting interspecies variability in hepatic sensitivity [28]. Similar inconsistencies are observed in rodent models. For instance, no significant hepatic histological changes were found in ICR mice in an earlier study [27], whereas a subsequent study reported lipid accumulation [14], underscoring the potential influence of exposure duration and animal strain on outcomes. These discrepancies emphasise the need for standardised dosing protocols and multi-species comparisons in toxicological assessments.

3.6. Mechanistic Insights and Converging Pathways.

Zebrafish studies reveal three primary mechanistic pathways of BPF-induced hepatotoxicity: oxidative stress, mitochondrial dysfunction, and metabolic disruption. It has been shown that BPF increases lipid peroxidation, a marker of oxidative damage. This was

demonstrated in prior research [22]. Mitochondrial impairment has also been linked to downstream metabolic consequences, as supported by experimental findings [15,18]. These results are consistent with rodent studies, which report mitochondrial swelling and disrupted energy metabolism [10, 32]. Despite similarities in mechanistic pathways, some species appear more resilient to certain BPF doses. For example, lipid accumulation was detectable by Nile Red staining, whereas conventional H&E histology failed to detect steatosis in C57BL/6 mice [24]. This highlights the importance of complementary imaging techniques for mechanistic clarity. Inflammatory mediator upregulation has also been identified as a significant hepatotoxic mechanism in other species [20,25]. These findings suggest that inflammation may be an underexplored component in zebrafish models, indicating a need for further investigation using molecular markers of inflammation.

3.7. Consistency and Gaps in the Literature.

A comparative review of hepatic outcomes across various aquatic and terrestrial models reveals a largely consistent picture of BPF-induced hepatotoxicity, albeit with some variability across species and methodologies. Lipid droplet formation has been observed in both zebrafish and rainbow trout, reflecting BPF's lipogenic effects across aquatic species [15,34]. Similar outcomes have been reported in mouse models, further suggesting that these effects are conserved across vertebrates [10, 32]. However, other studies failed to detect lipid changes in Medaka, cautioning against overgeneralising findings across species [27]. Additionally, the dose-response relationship remains ambiguous. While some studies demonstrated low-dose effects, such as those observed at 0.5 µg/L in zebrafish [15], other models required higher concentrations to elicit comparable hepatic responses [20]. These discrepancies highlight the non-monotonic nature of endocrine-disrupting chemicals (EDCs) like BPF, which do not always follow linear dose-response patterns.

3.8. Implications for Future Research.

The synthesis of existing literature indicates several pressing research needs. First, future studies should incorporate multi-omics approaches (e.g., transcriptomics, proteomics) in zebrafish to delineate the molecular pathways underlying histological changes. Transcriptomic profiling, for example, could reveal early biomarkers of mitochondrial stress or lipid metabolism dysregulation, offering mechanistic insights beyond what histology alone can provide. Second, zebrafish embryos and juveniles should be studied alongside adults to better understand the developmental windows of vulnerability. This recommendation is informed by findings from rodent models demonstrating age-dependent sensitivity to BPF exposure [33]. Third, although zebrafish present numerous experimental advantages, cross-validation with mammalian models remains essential. Aligning findings from zebrafish with those observed in murine models such as BALB/c mice and Long Evans rats would strengthen translational relevance in regulatory toxicology contexts [25, 33]. Lastly, future research should explore the potential reversibility of BPF-induced liver damage. As most current studies focus on acute or subchronic exposure paradigms, there is a critical need for longitudinal designs that assess recovery following exposure cessation to better establish no-observed-adverse-effect levels (NO-AELs).

3.9. Practical Applications and Regulatory Considerations.

The compiled evidence positions BPF as a hepatotoxic compound with mechanistic profiles overlapping those of its precursor, BPA. However, regulatory agencies have yet to reach consensus on BPF safety thresholds. Zebrafish studies, particularly those indicating hepatotoxicity at environmentally relevant doses [15], show the need for a precautionary approach in environmental and occupational health guidelines. In environmental contexts, monitoring aquatic ecosystems for BPF contamination is imperative, given its relevance to waterborne exposure. For biomedical and consumer product applications, manufacturers should consider safer bisphenol alternatives, supported by thorough preclinical evaluations using sensitive in vivo models such as zebrafish.

3.10 Future Work.

While zebrafish studies have elucidated critical aspects of BPF-induced hepatotoxicity, several limitations persist in the current body of research. Most investigations focus on acute or sub-chronic exposures, with limited exploration of chronic and developmental effects across life stages [22, 31]. Future research should examine the long-term impacts of BPF using multi-generational zebrafish models to assess transgenerational epigenetic modifications and cumulative liver damage. Furthermore, mechanistic studies often rely on general markers of oxidative stress and lipid accumulation, rather than leveraging advanced high-throughput omics techniques [18]. Incorporating metabolomics and transcriptomics could help unravel gene-environment interactions and identify early biomarkers of hepatotoxicity [10, 32]. Sex-specific differences, an important determinant in liver responses to toxicants, are underreported in zebrafish studies, despite rodent data suggesting divergent hepatic outcomes between males and females [28, 33]. By stratifying zebrafish results by sex, we can enhance the translational value of findings for human health risk assessments. In addition, co-exposure studies are lacking. Because aquatic organisms are seldom exposed to isolated contaminants in their natural habitats, it is crucial to examine the interactions between BPF and other endocrine disruptors or environmental stressors to achieve ecological accuracy [20,25]. Finally, the reversibility of BPF-induced liver damage remains largely unexplored. Post-exposure recovery studies are needed to determine whether hepatic impairments persist after exposure cessation, which is critical for establishing safe exposure thresholds [14,24]. Expanding on these directions will improve the ecological and human health relevance of zebrafish-based BPF toxicology research.

4. Conclusions

This review emphasises that BPF, despite being promoted as a safer alternative to BPA, inflicts considerable toxic effects on the liver, including steatosis, fibrosis, oxidative stress, and mitochondrial dysfunction, which are comparable to or exceed those induced by BPA. However, variations in species response, exposure duration, and concentration limit the direct translation of these findings to humans. These insights underscore the urgent need for long-term, multi-species studies and stronger regulatory evaluations to ensure the safe use of BPF in consumer and industrial products.

Author Contributions

Conceptualization, R.D.; methodology, R.D.; investigation, D.A.F.A. and N.Z.A.; formal analysis, R.D., F.N.Z., and S.A.R.; resources, R.D., F.N.Z., and S.A.R.; writing—original draft preparation, D.A., R.D., F.N.Z., and S.A.R.; writing—review and editing, D.A., R.D., F.N.Z., and S.A.R.; supervision, R.D.; project administration, R.D. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ALT	Alanine Aminotransferase
AML12	Alpha Mouse Liver 12
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BALB/c	Bagg Albino
BPA	Bisphenol A
BPF	Bisphenol F
BPS	Bisphenol S
B.W	Body Weight
EDCs	Endocrine-Disrupting Chemicals

HBPF	High-Dose BPF
H&E	Hematoxylin And Eosin
ICR	Institute of Cancer Research
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
Keap1	Kelch-like ECH-associated protein 1
LBPF	Low-Dose BPF
LDs	Lipid Droplets
LDH	Lactate Dehydrogenase
LPC	Lysophosphatidylcholine
MAPK	Mitogen-Activated Protein Kinase
N/A	Non-Applicable
NAFLD	Non-Alcoholic Fatty Liver Disease
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells
NLRP3	NOD-, LRR-, And Pyrin Domain-Containing Protein 3
NOAELs	No-Observed-Adverse-Effect Levels
Nrf2	Nuclear factor erythroid 2-related factor 2
PCPs	Personal Care Products
PI3K-AKT	Phosphatidylinositol 3-Kinase - Protein Kinase B
PND6	Postnatal Day 6
ROS	Reactive Oxygen Species
STAT3	Signal Transducer and Activator of Transcription 3

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