Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 13, Issue 1, 2023, 75
https://doi.org/10.33263/BRIAC131.075

A Systematic Review of the Effects of Bisphenol Analogs on Embryonic Development and Cytoskeletal Organization of Zebrafish (*Danio rerio*) Embryos

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Received: 26.11.2021; Accepted: 30.12.2021; Published: 6.02.2022

Abstract: Recent research has raised concerns about widespread exposure to chemicals that resemble bisphenol A (BPA) structurally or functionally. Because of the strict regulations governing production and use, various bisphenol analogs to replace BPA have increased. Some analogs have been reported to have disruptive physiological and endocrine effects. This study focuses on the impact of bisphenol A analogs on zebrafish embryos. The effect of bisphenol analogs is a major concern, prompting researchers to conduct numerous related studies. Regrettably, previous research has not focused on embryonic health. A systematic search strategy based on the RepOrting Standards for Systematic Evidence Syntheses (ROSES) guidelines was used. Three central journal repositories were used: Scopus, Web of Science, and ScienceDirect. Thirteen articles were discovered through search efforts and will be thoroughly examined. Bisphenol analogs were unearthed to have similar adverse effects on embryonic health as bisphenol-A. This study clarified how bisphenol A analogs affect embryonic development and cytoskeletal organization in the zebrafish model by disrupting the endocrine, cardiovascular, nervous, reproductive, and other systems. To thoroughly investigate these issues, more research on each source, metabolic pathway, exposure mechanisms, and effects on organisms is required.

Keywords: Bisphenol analogs; zebrafish; embryonic development; cytoskeletal; ROSES.

1. Introduction

Consumers worldwide are unwittingly exposed to BPA every day through food and beverage containers, personal care products, medical supplies, and other products. Studies have suggested that BPA might be harmful to human health because of its ability to disrupt normal

biological processes, impact endocrine functions, interrupt normal behavioral states, cause DNA damage and alter epigenome profiling [1–7]. According to recent estimates by Costa *et al*. (2020), 359 million tons of plastics produced worldwide, of which 40% were meant for packaging, and 100 tons of BPA per year may end up in the environment due to plastic degradation, resulting in concentrations of between 5 to 21ug/L in environmental water [8]. Studies reported that higher concentrations of BPA were observed near wastewater treatment plants or landfills [3,9–11]. BPA pollution leaches into rivers and seas, probably due to the migration of plastic containers from the industrial rubbish heap [10,12–14]

BPA and its action as an endocrine-disrupting chemical (EDC) are now increasingly linked to many chronic diseases and disorders [15–18]. Canada, the USA, and France have banned BPA in infant products, particularly polycarbonate feeding bottles, food containers, and beverage packaging. Because of BPA's adverse effects and usage restrictions, industries are looking for alternatives to BPA. Due to public concern, some industries have gradually replaced BPA with other bisphenol analogs. Such alternatives include bisphenol monomers which are bisphenol AF (BPAF), bisphenol S (BPS), bisphenol B (BPB), bisphenol AP (BPAP), bisphenol Z (BPZ), and bisphenol F (BPF) [19–22]. BPAF is used to produce electronic devices and plastic fibers [23,24]. BPS, BPZ, BPF, BPB, and BPAP are used in food packaging, canned foods, soft drinks, and thermal paper [3]. The general rationale for choosing alternative chemicals to replace BPA is that those chemicals are less toxic and less harmful than BPA. Unfortunately, the chemicals used to replace BPA have not been adequately tested, and some have even worse effects than BPA. The phenomenon is more of significant concern because the chemicals used in manufacturing products are not thoroughly studied before being marketed to the public.

Recently, many studies reported that the bisphenol analogs possess the similar endocrine-disrupting activity and cause harmful effects to humans and animals [25–28]. Some other studies have confirmed the detrimental effects of bisphenol analogs exposures on the development of germ cells, fertility, neurobehavioral, hormones, genes, and proteins [7,29–33]. Animals used to study the adverse effects of bisphenol analogs are rats, mice, frogs, fishes, and zebrafish. However, to date, most studies focused on animals in the growing or adult stages. Studies in the early stages of embryonic development remain scarce and limited, especially in zebrafish embryos.

Zebrafish were chosen as the main discussion topic due to their unique characteristics as a model species. Recent research shows that zebrafish (*Danio rerio*) are widely used in drug, toxicology, and many other fields [34–36]. Zebrafish are very robust and easy to maintain. The zebrafish eggs are fertilized and grown outside the mother, and their early development makes them a good model organism. Thirdly, zebrafish are incredibly fertile, producing hundreds of eggs per breeding cycle, making them ideal for high-throughput drug screening [37,38]. Other models, like mice, develop internally, restricting visual investigation. On top of that, humans share 70% of their genes with zebrafish and 84 percent of disease-related genes [37,39,40]. The zebrafish genome has been fully sequenced. Over 140,000 genes have been mutated, and their role in development and disease is critical. They also generate rapidly in short generation time, speeding up the overall experimental process [41,42].

The systematic collection of research evidence on bisphenol analogs' effects on zebrafish embryo development is expected to address the problems caused by bisphenol adverse impact on communities' concerns today. This review is critical because existing works do not explain how bisphenol analogs affect the body. A systematic approach can describe the

study forms and depth of research on fetal development. Moreover, this review can help researchers understand the harmful effects of bisphenol analogs on humans and animals. The study is essential to raise community awareness of the risks of bisphenol analogs on public health. The main research question is: How do bisphenol analogs affect zebrafish embryonic development and cytoskeletal organization? The effects of bisphenol analogs on embryonic development will be emphasized, and the adverse effects on the body system will be detailed more systematically using a formulation of research questions, identification, screening, eligibility, quality appraisal, and data analysis. A systematic searching strategy of systematic environmental reviews and systematic maps was conducted following the RepOrting Standards for Systematic Evidence Syntheses (ROSES) guidelines [43].

2. Methodology

2.1. Review protocol (ROSES).

ROSES or RepOrting Standards for Systematic Evidence Syntheses is a pro forma and flow diagram explicitly designed for systematic reviews and systematic maps in conservation and environmental management. ROSES aims to prompt researchers to ensure they offer the right information with the correct detail level [43]. Based on the ROSES protocol, we started by formulating appropriate research questions for the review using a specific research question development tool (RQDT). We then explain the systematic searching strategy, consisting of three sub-processes: identification, screening (inclusion and exclusion criteria), and eligibility. Then, we appraise the quality of the selected articles, whereby we explain the strategy applied to ensure the quality of the articles to be reviewed. Lastly, we explain how the data were abstracted for the review and how the extracted data were analyzed, appraised, and validated.

2.2. Formulation of the research question.

The formulation of the research question for this study was based on PICOS, a tool that assists authors in developing a relevant research question for the review. PICOS is based on five main concepts: Population, Intervention, Comparison, Outcome, and Setting [44]. The five main aspects, namely zebrafish (Population), bisphenol analogs (Intervention/Treatment), development of embryos (Comparison), cytoskeletal organization (Outcome), and treatment (Setting), were included in this review as shown in Table 1. The main aspects then guide the authors to formulate their main research question: What are the effects of bisphenol analogs on zebrafish embryonic development and cytoskeletal organization?

Table 1. The use of PICOS in formulating the research question.

Concepts	**Population**	**Intervention**	**Comparison**	**Outcome**	**Setting**
Aspects	*Zebrafish*	*Bisphenol analogs*	*Development of embryos*	*Cytoskeletal organization*	*Treatment*
Research Question (RQ)	RQ: What are the effects of bisphenol analogs on embryonic development and cytoskeletal organization of zebrafish embryos?				

2.3. Systematic searching strategies.

There are three main processes in the systematic searching strategies: identification, screening, and eligibility [45] (refer to Figure 1).

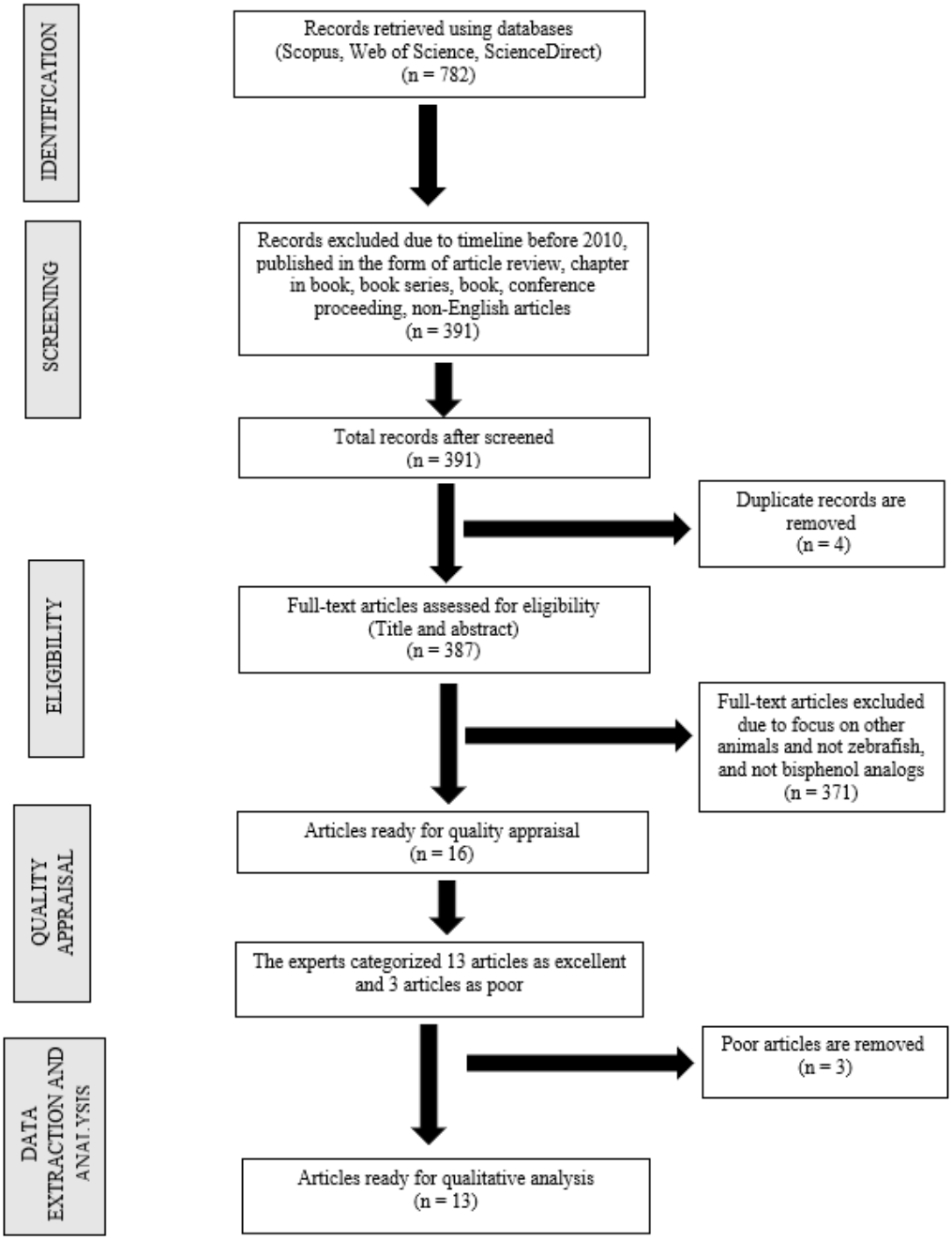

Figure 1. The flow diagram.

2.3.1. Identification.

Identification is a searching process that explores synonyms, related terms, and variations for the main keywords: zebrafish embryos, bisphenol analogs, embryonic development, and cytoskeletal organization. The process provides more options for the selected database in scrutinizing more related articles for the review. The keywords are developed based on the research question, as suggested by Tawfik *et al.*, 2019 [46]. Online thesaurus, past studies, expert panels, and suggested keywords by Scopus were used to identify the right keywords during the identification process. The search strings were developed using keywords such as Bisphenol analog, embryo development, zebrafish, and cytoskeletal organization. The strings developing process relies on the Boolean operator (AND, OR), phrase searching, truncation, wild card, and field code function.

A single database is insufficient to retrieve all systematic review references [47]. Therefore, the three primary databases, namely Web of Science (WoS), Scopus, and ScienceDirect, were used in this study (Table 2). WoS and Scopus are two world-leading and competing citation databases. According to Zhu and Liu (2019), researchers from more knowledge domains use WoS and Scopus for academic research, such as health/medical science-related domains and the traditional Information Science and Library Science fields. Other than that, a large share of WoS- and Scopus-related papers are associated with meta-analysis and bibliometric-related studies [48]. These two databases were selected because they are the leading databases in a systematic literature review due to several advantages: advanced searching functions, comprehensiveness (indexing more than 5000 publishers), control of the quality, and multidisciplinary focus, including environment management related studies [49,50]. The third database, namely ScienceDirect, was selected as an additional database. ScienceDirect is a full-text scientific database that provides an extensive bibliographic database of scientific and medical publications. It hosts over 18 million pieces of content from more than 4,000 academic and peer-reviewed journals, more than 11,000 books, and 30,000 e-books. Other than that, it offers more than 9.5 million articles and book chapters [51].

In total, 782 articles were retrieved from the three databases in the first stage of the systematic review process.

Table 2. The search strings.

Database	Search strings
Scopus	TITLE-ABS-KEY (("Bisphenol*" OR "Bisphenol analog*" OR "Bisphenol substitute*" OR "Bisphenol agent*" OR "phenol derivative*" OR "phenol*") AND ("embryogenesis" OR "embryo* development") AND ("cytoskelet*" OR "organi*ation" OR "orientat*" OR "malformation*" OR "disrupt*") AND ("zebrafish*" OR "Danio rerio" OR "embryo*" OR "larva*" OR "eleutheroembryo*"))
Web of Science	TS=(("Bisphenol*" OR "Bisphenol analog*" OR "Bisphenol substitute*" OR "Bisphenol agent*" OR "phenol derivative*" OR "phenol*") AND ("embryogenesis" OR "embryo* development") AND ("cytoskelet*" OR "organi*ation" OR "orientat*" OR "malformation*" OR "disrupt*") AND ("zebrafish*" OR "Danio rerio" OR "embryo*" OR "larva*" OR "eleutheroembryo*"))
ScienceDirect	(("Bisphenol analogs" OR "Bisphenol substitutes" OR "Bisphenol agents") AND ("embryogenesis" OR "embryo development") AND ("cytoskeletal malformation" OR "disruption") AND ("zebrafish" OR "Danio rerio"))

2.3.2. Screening.

The searching process in the three databases resulted in 782 articles. The articles were selected by choosing the criteria for articles in selection panels, which is done automatically based on the sorting and refine functions available in the database. In the screening process, the research question was referred to in determining the selection criteria mentioned by Kitchenham & Charters, 2007 [52]. Only research articles published in English were selected as a primary database. Non-English articles were not chosen for this study to avoid misinterpretation during the review and limitations of relevant sources from team members who spoke other native languages [53,54]. Eleven years (2010-2020) were set for the timeline for this review. The setting is based on the 'study's maturity as projected by the multiplication of the number of published articles related to the study starting from 2010 [55]. The document type, article review, book chapter, book series, and conference proceedings were excluded in this review.

Moreover, to ensure the quality and accuracy of the articles for review, only articles that used zebrafish or zebrafish embryos and were treated with bisphenol analogs are included (Table 3). As a result, 391 articles were excluded from the searching process as they did not fit

the inclusion criteria, and four duplicated articles were removed. The remaining 387 articles were advanced to proceed for the third review process, namely eligibility.

Table 3. The inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Timeline	2010-2020	<2010
Document type	Articles journal	Article review, chapter in the book, book series, conference proceeding
Language	English	Non-English
Animal use	Zebrafish, zebrafish embryo	Non-zebrafish
Chemical use	Bisphenol analogs	Non-bisphenol analogs or other chemicals

2.3.3. Eligibility.

Eligibility is fundamental to the systematic review process and should be given priority in 'authors' reports [56]. The eligibility screening step involves monitoring the titles, abstracts, and the 'articles' main contents. We manually examined and verified that the remaining retrieved articles are aligned with the inclusion criteria. We did this process by reading the 'articles' titles and abstracts to accomplish the 'study's objective. At this stage, 371 articles were excluded due to focusing on other animals and not focusing on zebrafish, and focusing on other chemicals rather than bisphenol analogs. Overall, there were only 16 articles ready for quality appraisal.

2.4. Quality appraisal.

A review process relies upon a systematic review team's skills and composition to make judgments and appraise the quality of the final articles. The quality appraisal process is essential to evaluate the studies' quality by thoroughly synthesizing the data to avoid low-quality articles that may lead to inaccurate conclusions and bias [57]. This review followed and adapted the quality appraisal questions proposed by Alsolai and Roper (2019). The quality assessment's main objective is to evaluate and select studies that answer the research question and support a more detailed analysis of inclusion and exclusion criteria. The remaining articles were presented to at least two experts for quality assessment by scoring each question: 1 represents. Yes, 0.5 represents Partly, and 0 represents No. For the articles to be included in the review, the articles will be given scores ranked by the experts according to four categories: excellent ($13.5 \leq$ scores ≤ 15), good ($9.5 \leq$ scores ≤ 13), fair ($5 \leq$ scores ≤ 9), and fail ($0 \leq$ scores ≤ 4.5) [58]. Only articles ranked as excellent and good will be analyzed at the final stage of review after discussing any disagreement during scoring with the experts. Finally, the experts categorized 13 articles as excellent and fulfilled the review criteria, while three articles were low and excluded from the study (Table 4).

Table 4. Quality assessment result.

Articles	Questions															Total Score	Rating
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
[77]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	*1*	*0.5*	*1*	*1*	*1*	*0.5*	***13.5***	***Excellent***
[76]	*1*	*1*	*0.5*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	***14.5***	***Excellent***
[72]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	*1*	*1*	*1*	*0.5*	***14***	***Excellent***
[68]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	***14.5***	***Excellent***
[75]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	***14.5***	***Excellent***
[65]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	***14.5***	***Excellent***
[71]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	***15***	***Excellent***
[74]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	***15***	***Excellent***
[66]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	***15***	***Excellent***
[67]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0*	***14***	***Excellent***
[69]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	***15***	***Excellent***
[70]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	***15***	***Excellent***
[73]	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*0.5*	***14.5***	***Excellent***

2.5. Data extraction and analysis.

The final process of the review is data extraction and analysis. The integrative review has been selected to synthesize and analyze the final articles in this section. An integrative review is a constant method and design in comparing and identifying patterns of the extracted data (quantitative and qualitative) and transforming the data into systematic categories, variations, themes, and relationships [59]. Additionally, in considering the needs of scientific evidence in healthcare and practice-based knowledge, the integrative review is used as a tool to synthesize the data. It includes a systematic and rigorous approach to the process, particularly data analysis, to reduce biases and errors. It will also allow the reader to assess the review results [60] critically.

The thematic analysis was selected as it is considered the most suitable synthesizing mixed-method research design for the review [61–63]. Theme identification is one of the most fundamental tasks in the final review process. As a result, the present review selected all 13 articles for the thematic analysis. We selected the articles through thorough reading processes, particularly in abstract, results, and discussions. All the information found was extracted into a table based on the research questions and the objective. We completed the thematic analysis by identifying all the themes and sub-themes.

Each pattern, theme, similarities, relationship, cluster, and group within the articles were pinpointed and pooled together in a group [64]. Before finalizing the themes and sub-themes, we discussed and brainstormed the 'findings' patterns, resolved any inconsistencies or queries, generated ideas on the final data, and established themes and sub-themes. In this study, five main themes and 30 sub-themes were recognized and finalized (Table 5). Three experts in qualitative research, reproductive health, and zebrafish research were appointed to examine the final data to validate the final themes and sub-themes. The validation process was done to ensure the selected themes and sub-themes' precision, relevancies, and suitability. Finally, the modifications were made based on the validation feedback from the experts.

Table 5. The main themes and sub-themes.

Main themes	Sub-themes	Authors												
		Norman Halden *et al.* (2010) [77]	Kinch *et al.* (2015) [76]	McCormick etal. (2010) [72]	Weiler & Ramakrishnan *et al.* (2019) [68]	Coumailleau *et al.* (2020) [75]	Wei *et al.* (2018) [65]	Mi *et al.* (2020) [71]	Yuan *et al.* (2019) [74]	Lee at al. (2020) [66]	Qiu *et al.* (2016) [67]	Mu *et al.* (2018) [69]	Yang *et al.* (2017) [70]	Y.Yang *et al.* (2020) [73]
Effects on the endocrine system	Disruption of T3, T4						√			√	√			
	Inhibition of GnRH				√									
	Increased estrogenic activity				√						√	√	√	
	Inhibition of testosterone level and androgenic activity												√	
Effects on the cardiovascular system	Decreased heart rate			√				√				√		
	Impeding cardiac looping							√						
	Decreased cardiac contractility							√						
	Alteration of cardiac-related genes							√						
	Pericardial edema			√								√		√
	Hemorrhage			√										
	Retarded cardiac morphogenesis							√						
Effects on the nervous system	Spine edema and deformities											√		
	CNS cell apoptosis								√					
	Reduced locomotor activity					√			√					

Main themes	Sub-themes	Authors												
		Norman Halden *et al.* (2010) [77]	Kinch *et al.* (2015) [76]	McCormick etal. (2010) [72]	Weiler & Ramakrishnan *et al.* (2019) [68]	Coumailleau *et al.* (2020) [75]	Wei *et al.* (2018) [65]	Mi *et al.* (2020) [71]	Yuan *et al.* (2019) [74]	Lee at al. (2020) [66]	Qiu *et al.* (2016) [67]	Mu *et al.* (2018) [69]	Yang *et al.* (2017) [70]	Y.Yang *et al.* (2020) [73]
	Altered brain development		√			√			√					
	Neuroinflammation								√					
	Altered genes and proteins								√		√			
Effects on the reproductive parameters / success	Yolk sac edema	√										√		√
	Modification of gonads (testis and ovary)	√											√	√
	Reduced survival rate	√											√	
	Embryo death													√
	Hatching delay						√					√	√	√
	Reduced egg number												√	
	Growth retardation		√				√			√				√
	Fewer spermatid cysts	√												
Effects on other parts of body	Swim bladder inflation						√							
	Stripe hypopigmentation						√					√		
	Trunk Edema			√										
	Tail malformation			√			√					√		
	Eyes pigmentation											√		

3. Results

3.1. General findings and background of the selected articles.

Overall, 13 selected articles were obtained from the review process. Based on the thematic analysis, five main themes were recognized: effects on the endocrine system, effects on the cardiovascular system, effects on the nervous system, effects on the reproductive system, and effects on others or body defects. The general findings and background of the selected articles are summarized in Table 6. Further analysis of the themes was done to elaborate on the main themes that have been identified. As a result, 30 sub-themes were identified related to the main themes. Out of 13 selected articles, four studies were found using bisphenol F (BPF), four studies using bisphenol S (BPS), three studies were conducted on bisphenol AF (BPAF). Two studies were published in 2010, one in 2015, one in 2016, one in 2017, two in 2018, three in 2019, and three published in 2020. One study was conducted on each of the following analogs, namely bisphenol AP (BPAP), bisphenol B (BPB), fluorene-9-bisphenol (BHPF), 2,4,6-tribromophenol (TBP), and tetrabromophenol A (TBPA), respectively (Figure 2).

3.2. The themes and sub-themes.

3.2.1. Effects on the endocrine system.

The endocrine system regulates the release of hormones in our bodies. It is a chemical messenger system composed of feedback loops of hormones released into the bloodstream and affecting target organs. The feedback process will allow hormones to travel to other cells regulate mood, reproduction, growth and development, organ function, and metabolism. The endocrine system is affected by bisphenol analogs. Six studies focused on T3 and T4 hormones, one on GnRH inhibition, and four on increased estrogenic activity. Another study targeted testosterone and androgenic activity.

Table 6. Summary of general findings and background of the selected articles.

Authors	Type of bisphenol analogs	Sample	Concentration / Dosage	Exposure window	Duration of treatment/ exposure	Endpoint / Findings	Remarks
[77]	2,4,6-tribomophenol (TBP)	Mature Danio (male and female)	33, 330, and 3300 µg/g feed	Stainless steel net cages within 15-L glass aquaria	6 weeks parental exposure	Reduced the fertilization success, disturbed the gonad morphology, and increased yolk sac edema. Fewer spermatid cysts in males and increased atretic follicles and oocytes with decreased vitellogenesis in females.	Significant effects were observed at 3300 µg/g feed
[76]	Bisphenol S (BPS)	Larvae	0.0068 µM, 1,000-fold lower than the accepted human daily exposure	96-well plates	0–5 dpf	Caused later hyperactive behaviors and affects neurodevelopment. Increased locomotor bursting activity.	BPS influence hypothalamic development and act through AroB-mediated mechanism.
[72]	Tetrabromobisphenol A (TBBPA)	Larvae	TBBPA (0.75, 1.5, or 3 µM) / (0.4, 0.8, 1.6 mg/L)	Zebrafish embryos were exposed for 5 days in capped glass vials containing 1 mL of TBBPA	5 days	Developmental exposure to TBBPA results in a reduction in embryo survival. Alteration of proper MMP expression and activity.	TBBPA is more potent than BPA. TBBPA exposure results in reduced survival one-month post-exposure.
[68]	Bisphenol F (BPF)	Larvae	0.25, 0.5 and 1 µM BPF	Standard Petri-dishes containing 20 mL of embryo medium (EM)	3 dpf	BPF exposure reduced neural area at 2 dpf. Exposure to the higher BPF doses showed a reduction in TN-GnRH3 neuron area at 3 dpf	BPF affects the developing GnRH neural system via an estrogen-mediated pathway.
[75]	Bisphenol F (BPF) Bisphenol AF (BPAF) Bisphenol S (BPS) Bisphenol AP (BPAP)	Larvae	1 and 0.1 µM	Glass Petri dishes containing water	6 days	Exposure to the different bisphenol analogs accelerates the time of hatching of zebrafish embryos. The induction of AroB protein expression was also observed between the various bisphenols (BPAF>BPA>BPF>BPS).	Moderate doses of bisphenols trigger developmental defects, strong induction of AroB protein expression, and decreased locomotor activity.
[65]	Bisphenol S (BPS)	Larvae	1, 10, and 100 µg/L of BPS (environmentally relevant concentrations)	Glass beakers containing 1.5 L of BPS	120 days	Decreased levels of thyroxine (T4) in F0 females, Increased levels of 3,5,3'-triiodothyronine (T3) in F0 females and males TH content in eggs (F1) spawned by exposed F0 generation exhibited similar changes as the F0 females, with significant decreases in T4 and increases in T3, demonstrating excessive levels of maternal T3 in the offspring. Delayed embryonic development and hatching, swim bladder inflation defect, reduction in motility, developmental neurotoxicity, and lateral stripe hypopigmentation in non-exposed F1 embryos and larvae.	Transgenerational thyroid endocrine disruption induced by bisphenol S affects the early development of zebrafish offspring. BPS-induced maternal transfer of thyroid endocrine disruption.
[71]	Fluorene-9-bisphenol (BHPF)	Larvae	Series of BHPF concentrations 1 µM, 2 µM, 5 µM, 10 µM, and 20 µM.	6 well plates	72 dpf	BHPF exposure increased mortality, induced malformation, promoted apoptosis. BHPF exposure led to severe cardiotoxicity, which retarded cardiac morphogenesis and caused the failure of cardiac looping. The expression of cardiac development-related genes and transcriptional regulators was downregulated.	Acute BHPF exposure induced developmental abnormality, retarded cardiac morphogenesis, and injured cardiac contractility.
[74]	Bisphenol F (BPF)	Larvae	Solutions of 0.0005 (an environmentally relevant concentration), 0.5, and 5.0 mg/L BPF.	24-well plates	6 dpf	BPF induces significant neurotoxicity and apoptosis by inhibiting locomotion and peripheral motor neuron development. Both microglia and astrocyte were significantly activated by BPF, indicating the existence of neuroinflammatory response.	BPF lead to abnormal neural outcomes, induce neuroinflammation and CNS cell apoptosis even at environmentally relevant concentration.
[66]	Bisphenol AP (BPAP)	Larvae	0, 18.2, 43.4, and 105.9 µg/L BPAP	96-well plates	120 hpf	Decreased in T4 level at the maximum nonlethal concentration. BPAP did not cause significant changes in transcription and genes related to the TH system.	BPAP has weak or negligible potency regarding TH disruption
[67]	Bisphenol S (BPS)	Larvae	0.1, 1, 10, 100, and 1000 ——— g/L	Petri dishes	120 hpf	Low levels of BPS exposure during development led to advanced hatching time, increased numbers of GnRH3 neurons in both terminal nerve and hypothalamus, increased expression of reproduction-related genes, and a marker for synaptic transmission.	This study demonstrates that alternatives to BPA used in the manufacture of BPA-free products are not necessarily safer.
[69]	Bisphenol AF (BPAF) Bisphenol F (BPF) Bisphenol S (BPS)	Larvae	Exposed to solutions of bisphenol analogues at 5%, 25% and 50% of the LC50 concentration: 0.1, 0.5 and 1.0 mg/L for BPAF; 0.5, 2.5 and 5 mg/L for BPA; 1, 5 and 10 mg/L for BPF; and 2.5, 12.5 and 25 mg/L for BPS, respectively.	24-well plates	96 hpf	The lethality of bisphenol analogs decreased in the order of BPAF > BPA > BPF > BPS. BPAF and BPF significantly decreased heart rate hatching inhibition and caused teratogenic effects. The binding potentials of bisphenol analogs towards zfERs decreased in the following order: BPAF > BPA > BPF > BPS BPAF, BPA, and BPF significantly enhanced the protein levels of ERα along with the mRNA levels in zebrafish embryos.	BPAF showed the highest lethality, developmental effects, and estrogenic activity (both in silico and in vivo) followed by BPA and BPF. BPS showed the weakest toxicity and estrogenic activity.
[70]	Bisphenol B (BPB)	Larvae	0.01, 0.1, and 1 mg/L BPB.	10 L glass aquaria	6 dpf	BPB exposure (1 mg/L) could impair reproductive function decline the egg numbers, hatching rate, and survival rate. The homogenate T levels in male zebrafish decreased in a concentration-dependent manner, and the E2 level significantly increased when exposed to BPB. Hepatic vitellogenin (vtg) expression was upregulated in all exposure males, suggesting that BPB possesses estrogenic activity.	BPB can lead to adverse effects on the endocrine system of teleost fish and these effects were more prominent in males than in females.
[73]	Bisphenol AF (BPAF)	Larvae	0.05, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mg L-1 BPAF	The 24-well plates were filled with 2 mL per well fresh tested solutions	120 hpf	BPAF exposure delays embryo hatching and contributes to deformity and embryonic death. BPAF caused growth-retardation, delayed hatching, pericardial edema, yolk sac edema, non-inflated swimming bladder, and death.	BPAF exposure hazards the development of embryos and larvae. Waterborne BPAF exposure might pose serious risks to aquatic organisms and break the balance of aquatic ecosystem.

3.2.1.1. Disruption of T3 and T4.

The exposure of zebrafish embryos to bisphenol analogs was associated with thyroid hormone system disruption. Parental exposure to bisphenol analogs at environmentally relevant water concentrations affected embryos and offspring. Wei *et al*. (2018) discovered that bisphenol S-induced transgenerational thyroid endocrine disruption affects the early development of zebrafish offspring. They found that the T4 content of F1 eggs from all exposure groups was significantly decreased. Still, the T3 content was significantly increased compared to the T4 and T3 plasma levels in the maternal F0 groups [65].

Lee *et al*. (2020) found a 1.5-fold reduction in T4 levels in zebrafish larvae exposed to the highest BPAP concentration (105.9 g/L) [66]. In zebrafish, thyroid hormones are essential for development from the embryonic to the larval stage. In the developing zebrafish brain, BPS acts as a thyroid hormone antagonist, mediating the 'hormones' negative feedback effect on the pituitary gland and reproductive neuroendocrine system, according to Qui *et al*. (2016). This study shows that low-level BPS exposure on the thyroid hormone receptor pathway affects zebrafish embryonic development [67].

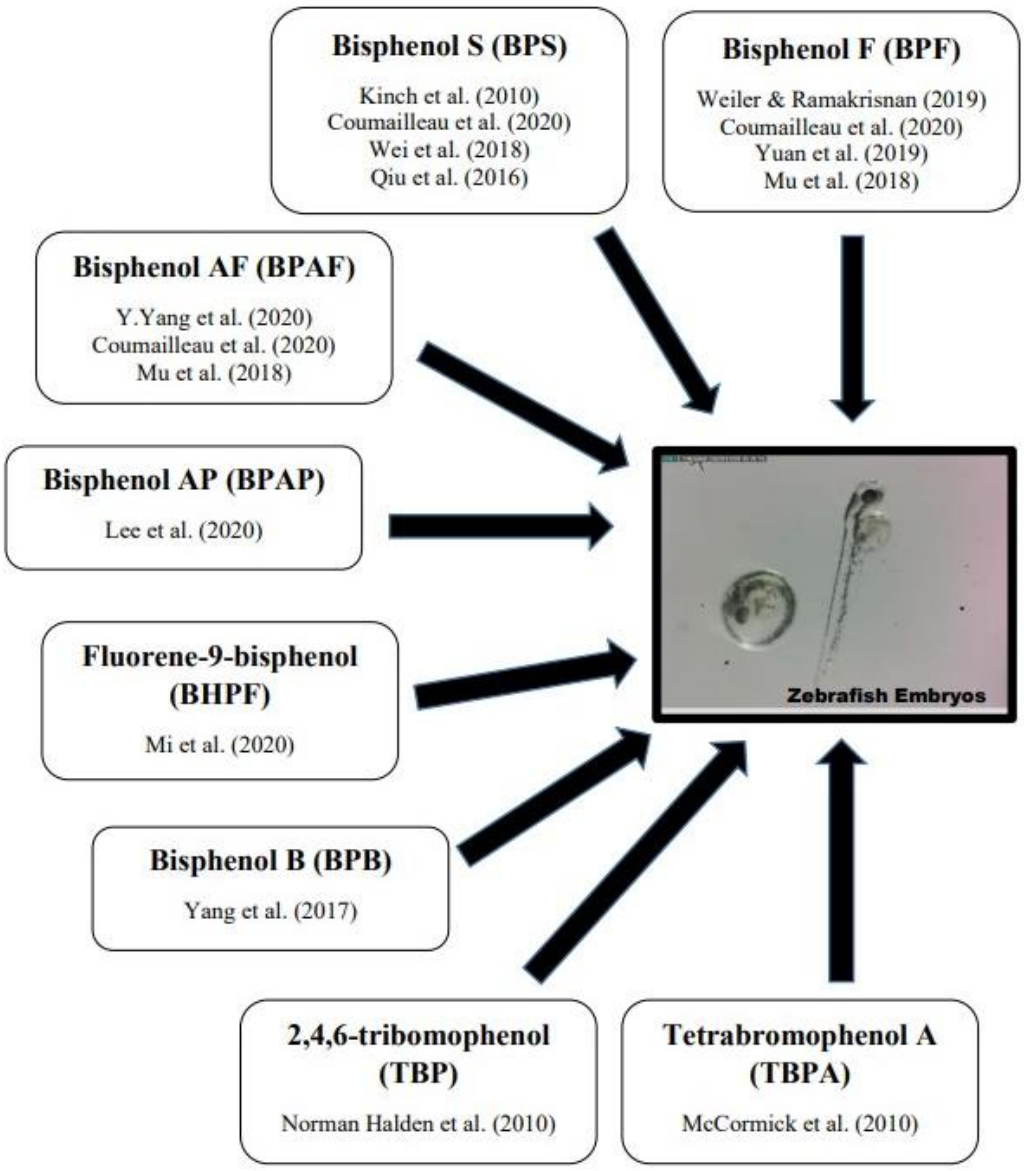

Figure 2. Types of bisphenol analogs (affecting zebrafish embryos) extracted from selected studies.

3.2.1.2. Inhibition of GnRH.

Gonadotropin hormone-releasing hormone (GnRH) is responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). GnRH neurons in the brain play a vital role as the primary controllers of reproduction and allied behavior in most vertebrates. Unfortunately, it is prone to endocrine disruption by bisphenols. As a result of this review, bisphenol analogs, namely BPF, affected the developing GnRH neural system via an estrogen-mediated pathway. They also found that at 0.25μM BPF exposure, TN-GnRH3 neurons showed significant reductions in the neural area [68]. Moreover, Qiu *et al*. (2016) found that BPS acts through multiple cellular pathways. Thus, it could potentially alter the hypothalamic-pituitary-gonadal axis by affecting the GnRH and Kiss systems and reducing GnRH3 neuron number and the expression levels of reproductive neuroendocrine-related genes early zebrafish development [67].

3.2.1.3. Increased estrogenic activity.

In the body, estrogen has several functions. Estrogen contributes to developing and maintaining the reproductive system, female characteristics, cognitive and bone health, cardiovascular function, and other vital bodily processes. The circulation of E2 into estrogen target tissues initiates estrogen action. They mimic human estrogen and affect the targeted organ after binding to the estrogen receptor. Weiler (2019) demonstrated that estradiol and BPF-treated embryos exhibited similar response patterns by portraying estradiol mimicked-doses. The higher doses of BPF mimicked the effects of higher doses of estradiol in both groups [68]. Qiu *et al*. (2016) reported that BPS acts through multiple cellular pathways, including an estrogenic pathway [67]. Mu *et al*. (2018) found that BPAF and BPF significantly upregulated the estrogen receptors' transcription levels and significantly enhanced the protein levels of ERα along with the mRNA levels of esr1, esr2a, esr2b, and vtg1 in zebrafish embryos. BPAF showed the highest estrogenic activity than BPF and BPS [69]. Lastly, Yang *et al*. (2017) reported exposure of male zebrafish to BPB significantly increased the concentration of 17β-estradiol [70].

3.2.1.4. Inhibition of testosterone level and androgenic activity.

Androgen hormones play a vital role in male traits and reproductive activity. Androgen levels vary depending on a 'person's sex, age, physical activity, and health. Excessive amounts of androgens result in hirsutism, acne, and balding, while low androgen levels can be a problem such as low libido, fatigue, bone loss, osteoporosis, and fractures. This review showed that a study by Yang *et al*. (2017) concluded that BPB significantly caused the decline of testosterone levels in males. Another study demonstrated the disruption of androgenic activity by upregulating the expression of Aromatase (cyp19). It is the critical enzyme to synthesize estrogen from testosterone when exposed to BPB [70].

3.2.2. Effects on the cardiovascular system.

The cardiovascular system comprises the heart and a network of closed vessels known as arteries, veins, and capillaries. The primary function of the heart and blood vessels is to transport oxygen, nutrients, and metabolic waste products. The cardiovascular system of zebrafish was disturbed by bisphenol analogs in this review. Seven sub-themes were identified, including decreased heart rate (3 studies), impeding cardiac looping (1 study), decreased cardiac

contractility (1 study), pericardial edema (3 studies), hemorrhage (1 study), and retarded cardiac morphogenesis (1 study).

3.2.2.1. Decreased heart rate.

The exposure of zebrafish embryos to bisphenol analogs decreased the embryos' heart rate [69,71,72]. A study by McCormick *et al*. (2010) demonstrated that exposure to tetrabromobisphenol A (TBBPA) (1.5 and 3 μM) at 48 hpf and 72 hpf caused significantly slower heartbeat as compared to control embryos [72]. In another study, Mi *et al*. (2020) found that the zebrafish 'embryos' heart rate reduced in 2 μM, 5 μM, and 10 μM BHPF-treated groups [71]. More importantly, Mu *et al*. (2018) showed that BPAF and BPF significantly reduced the embryonic heart rate at 48 hpf, and the level of reduction increased with increasing dosage [69].

3.2.2.2. Impeding cardiac looping.

Mi *et al*.'s (2020) study shows that exposure to bisphenol analogs impedes cardiac looping. They demonstrated that exposure of 2 μM, 5 μM, and 10 μM of BHPF increased sinus venous and bulbous arteriosus (SV-BA) distance, looped between two chambers, reduced cardiomyocytes, and significantly caused linearization ventricle and atrium. The results indicated that BHPF exposure could disturb cardiac looping [71].

3.2.2.3. Decreased cardiac contractility.

Exposure to bisphenol analogs contributed to the disruption of cardiac contractility. Mi *et al*. (2020) determined that BHPF exposure at 2μM, 5μM, and 10μM directly injured cardiac contractile function, including heart rate, stroke volume, and cardiac output as a fractional shortening ventricle compared to the control. The results indicated that BHPF exposure disturbed cardiac contractility in zebrafish embryos [71].

3.2.2.4. Alteration of cardiac-related genes.

The alteration of cardiac-related genes has been discovered by Mi *et al*. (2020), where the study demonstrated that BHPF exposure disturbed the expressions of critical transcriptional regulators relating to cardiac development such as nkx2.5, tbx5a, gata4, myh6, and myh7 was significantly down-regulated under BHPF exposure [71].

3.2.2.5. Pericardial edema.

Pericardial edema accumulates excess fluid in the sac-like structure surrounding the heart, impairs normal heart function, and results in death or heart failure. In this study, bisphenol analogs were found to contribute to zebrafish embryo pericardial edema [69,72,73]. TBBPA was proven to cause edema in the caudal region of zebrafish embryos at a concentration of 3 M [72]. Similarly, BPAF exposure at concentrations of 0.1, 0.5, and 1.0 mg/L was found to induce pericardial edema [69], whereas Y. Yang *et al*. (2020) demonstrated that BPAF exposure at concentrations of 1.0, 1.5, 2.0, 2.5, and 3.0 mgL^{-1} could contribute significantly to pericardial edema in zebrafish embryos [73].

3.2.2.6. Hemorrhage.

Bisphenol analogs can also cause hemorrhage and lesions in zebrafish embryos exposed for five days to 1 mL of TBBPA at varying concentrations (0.5, 0.75, 1, 1.5, or 3 μM), as McCormick *et al*. (2010) demonstrated [72]. TBBPA-induced hemorrhaging in developing zebrafish resulted in various developmental lesions in the embryos, including a delay in hatching, vascular lesions (edema and hemorrhage), tail and trunk lesions.

3.2.2.7. Retarded cardiac morphogenesis.

Mi *et al*. (2020) indicated that acute exposure to bisphenol analogs, namely fluorene-9-bisphenol retarded early development and disrupted cardiac morphogenesis in zebrafish. In the study, they found that a series of BHPF concentrations (1 μM, 2 μM, 5 μM, 10 μM, 20 μM) exposure led to cardiotoxicity and retarded cardiac morphogenesis in zebrafish embryos [71].

3.2.3. Effects on the nervous system.

Five studies examined the nervous system effects of bisphenol analogs. From the primary theme, we identified nine sub-themes: spine edema and deformities (1 study), CNS cell apoptosis (1 study), reduced locomotor activity (2 studies), altered brain development (3 studies), increased neuroinflammation (1 study), and altered genes and proteins expression (1 study).

3.2.3.1. Spine edema and deformities.

Spine edema can be caused by an acute spinal cord injury or neoplastic or inflammatory spinal canal lesions. According to this review, bisphenol analogs may cause spine edema and deformities. Mu *et al*. (2018) demonstrated that exposure to BPAF at concentrations of 0.02, 0.2, and 1.0 mg/L significantly induced teratogenic effects on zebrafish embryos, including spine edema and deformities [69].

3.2.3.2. CNS cell apoptosis.

According to Yuan *et al*. (2019), BPF could lead to abnormal neural outcomes during zebrafish early life stages by inducing neuroinflammation and CNS cell apoptosis even at environmentally relevant concentrations. Their study found that BPF could induce significant neurotoxicity toward zebrafish embryos by causing CNS cell apoptosis at an effective concentration of 0.0005 mg/L [74].

3.2.3.3. Reduced locomotor activity.

Additionally, it was discovered that bisphenol analogs affect the locomotor activities of zebrafish. Yuan *et al*. (2019) reported that at a low concentration of BPF, 0.0005 mg/L, the locomotor and moving activities of the zebrafish are disrupted [74]. Coumailleau *et al*. (2020) discovered a similar finding that six days of BPAF exposure significantly reduced locomotor activity [75].

3.2.3.4. Altered brain development.

Exposure to bisphenol analogs hampered brain development. Kinch *et al*. (2015) found that low-dose exposure to bisphenol S (0.0068 mM) affected neurogenesis in embryonic zebrafish [76]. Also, Coumailleau *et al*. (2020) showed that bisphenol analogs induce Aromatase B protein

expression in wild-type larval brains in a region-specific, concentration-dependent manner. They discovered high AroB-immunoreactive signal intensity and radial glial cell morphology in the POA of BPF and BPAF treated zebrafish larvae [75]. Yuan *et al*. (2019) found that BPF significantly inhibited peripheral motor neuron development at 72 hpf. BPF exposure significantly affected neuronal developmental processes and cell apoptosis pathways, according to their RNA-seq results [74].

3.2.3.5. Neuroinflammation.

BPF may cause abnormal neural outcomes in developing zebrafish by inducing neuroinflammation and CNS cell apoptosis via activation of astrocytes or microglia. The observed neurotoxicity is caused by astrocyte dysfunction after toxicant exposure. In this case, Yuan *et al*. (2019) found that BPF significantly activated microglia and astrocytes in the zebrafish brain, indicating a neuroinflammatory response. The study found that 0.0005 and 0.5 mg/L BPF increased Tnf levels, while 5.0 mg/L increased IL-6 and IL-1 transcription. BPF may cause neuroinflammation in zebrafish larvae by activating astrocytes and microglia [74].

3.2.3.6. Altered genes and proteins.

According to Yuan *et al*. (2019), the neural influences of BPF were derived from ER activation genes, namely ERα. They found 40 ER-embedded DNA sequences ranging from 239 to 590 bp in the control group and 96 peaks ranging from 241 to 991 bp in the 0.5 mg/L BPF-treated group, indicating that BPF altered the target gene profile of ER [74]. Similarly, BPF disrupts apoptosis-related pathways like FoxO and TGF- signaling. The FoxO signaling pathway was most affected by 0.0005 mg/L BPF. BPF exposure in zebrafish embryos disrupted the MAPK signaling pathway, leading to neurotoxicity, cognitive impairment, anxiety-like behavior, and apoptosis. Qiu *et al*. (2016) investigated those low levels of BPS exposure during development accelerated hatching time, increased GnRH3 neurons in the terminal nerve and hypothalamus, and increased expression of reproduction-related genes [67].

3.2.4. Effects on the reproductive parameters/success.

The primary function of the reproductive system is to ensure the survival of the species. A total of nine studies focused on the effects of bisphenol analogs on the reproductive parameters/success. The themes were categorized into eight sub-themes as follows: Modification of gonads (testis/ovary) (3 studies), reduce egg number (1 study), reduce spermatid cysts (1 study), yolk sac edema (3 studies), hatching delay (4 studies), growing retardation (4 studies), reduced survival rate (2 studies), and embryo death (2 studies).

3.2.4.1. Modification of gonads (testis/ovary).

BPAF exposure at various concentrations resulted in gonad modification in BPAF-exposed zebrafish embryos, according to Y.Yang *et al*. (2020) [73]. Yang *et al*. (2017) discovered that BPB altered the histology of the testis and ovary of zebrafish exposed to BPB [70]. TBP exposure at various concentrations, according to Norman Halden *et al*. (2010), significantly decreased vitellogenesis, altered gonad morphology, and increased the presence of atretic follicles and oocytes in female zebrafish [77]. Furthermore, Yang *et al*. (2017) found that hepatic vitellogenin expression was increased in all BPB-exposed males, implying that BPB has estrogenic activity [70].

3.2.4.2. Reduced egg number.

In this issue, Yang *et al*. (2017) found that BPB exposure at 1mg/L could decline the egg numbers, hatching rate, and survival rate. This finding is related to modifications of the BPB-exposed 'zebrafish's ovary [70].

3.2.4.3. Reduced spermatid cysts.

Reduction in spermatid cysts in males was found to be one of the negative impacts of bisphenol analogs. This issue was proven in the study on TBP exposure at concentrations of 33, 330, and 3300 µg/g via feed to adult male and female zebrafish. They reported that TBP significantly reduced spermatid cysts in males after six weeks of treatment [77].

3.2.4.4. Yolk sac edema.

According to Norman Halden *et al*. (2010), TBP causes yolk sac edema. They found that feeding adult male and female zebrafish TBP at 33, 330, and 3300 µg/g feed for six weeks altered gonad morphology and increased yolk-sac edema [77]. BPAF at 1.0 mg/L caused yolk sac edema, and the ratio and extent of deformity increased with BPAF concentration [69]. Y.Yang *et al*. (2020) found that BPAF exposure at concentrations of 0.05, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mgL^{-1} harmed zebrafish embryos and larvae development and contributed to yolk sac edema [73].

3.2.4.5. Hatching delay.

Four studies discussed hatching delay due to bisphenol analog exposure. Studies found that BPB exposure to zebrafish embryos could delay hatching [70,73]. BPAF and BPF at 5 and 10mg/L also inhibit zebrafish embryo hatching ratio, according to Mu *et al*. (2018). The offspring of maternal zebrafish exposed to BPS at various concentrations had delayed embryonic development and hatching [65].

3.2.4.6. Growth retardation.

The BPAF exposure resulted in growth-retardation in the exposed zebrafish embryos [73]. On another note, BPS was found to disturb the embryos' growing process via alteration on the expected developmental timing and improper fine-tuning of the brain [76]. Furthermore, maternal exposure to BPS resulted in growth retardation of non-exposed F1 embryos [65]. The growth retardation process was also studied by Lee *et al*. (2020), and they found that embryonic growth retardation occurred in the zebrafish embryos treated with BPAP [66].

3.2.4.7. Reduced survival rate.

According to Yang *et al*. (2017), exposing zebrafish embryos to BPB (1 mg/L) reduced their survival rate [70]. Another critical point to mention is that feeding TBP interferes with reproduction in zebrafish by lowering fertilization success and survival rate [77].

3.2.4.8. Embryo death.

Embryonic death is one of the effects of exposure to bisphenol analogs. Y.Yang *et al*. (2020) stated that BPAF exposure on zebrafish embryos could contribute to growth-retardation and embryonic death [73].

3.2.5. Effects on other parts of the body.

The effects of bisphenol analogs on different parts of the body were also investigated in this section. Five sub-themes were identified in this regard, namely swim bladder inflation (1 study), stripe hypopigmentation (2 studies), trunk edema (1 study), tail malformation (2 studies), and eye pigmentation (1 study).

3.2.5.1. Swim bladder inflation.

A study by Wei *et al*. (2018) highlighted the adverse effects on the early development of offspring induced by BPS at environmentally relevant concentrations (1, 10, and 100 μg/L) for 2 hours post-fertilization to 120 days post-fertilization. They reported that maternal exposure to BPS resulted in swim bladder inflation defects and developmental neurotoxicity in F1 generations [65].

3.2.5.2. Stripe hypopigmentation.

Bisphenol analogs were found to induce hypopigmentation in embryonic zebrafish. A study on BPS exposure at a concentration of 1, 10, and 100 μg/L to the maternal resulted in lateral stripe hypopigmentation in non-exposed F1 embryos and larvae [65]. On another note, exposure to BPAF at 0.02, 0.2, and 1.0 mg/L concentrations significantly induced lateral stripe hypopigmentation on zebrafish embryos [69].

3.2.5.3. Trunk edema

McCormick *et al*. (2010) studied zebrafish embryos exposed to TBBPA at varying concentrations (0.5, 0.75, 1, 1.5, or 3 μM) for five days. The results showed that TBBPA significantly induced developmental lesion and trunk edema on zebrafish embryos [72].

3.2.5.4. Tail malformation.

BPS was studied by Wei *et al*. (2018) on the early development of zebrafish offspring. They found BPS at environmentally relevant concentrations (1, 10, and 100 μg/L) can disrupt zebrafish offspring's tail formation [65]. In another study conducted on TBBPA, McCormick *et al*. (2010) reported that TBBPA caused tail malformation on zebrafish embryos at the varying concentrations of TBBPA (0.5, 0.75, 1, 1.5, or 3 μM) [72]. The case of tail malformation was also found by Mu *et al*. (2018) on the exposure of BPAF at concentrations of 0.02, 0.2, and 1.0 mg/L in zebrafish embryos [69].

3.2.5.5. Eyes pigmentation.

One significant adverse effect of bisphenol analogs on zebrafish embryos is pigmentation on the eyes or eye hypoplasia. It has been proven by the study of Mu *et al*. (2018) on the zebrafish embryos exposed to BPF at 5.0mg/L. They found that the 'embryos' eyes' pigmentations in the BPF-exposure groups were significantly reduced compared to the control group [69].

4. Discussion

According to the thematic analysis findings in this review, it was found that the reproductive system of zebrafish embryos is the most reportedly affected due to exposure to bisphenol analogs. Such reported effects were yolk sac edema [69,73,77], modification of testis

and ovary [66,70,73,77], reduced survival rate [70,77], embryo death [76,78], hatching delay [65,70,73,75,76], reduced egg number [70], growth retardation [65,66,68,73,76], atretic follicles [77], fewer spermatic cysts [77], and increased vitellogenesis [70,77]. The reproductive system is the principal target of bisphenol analogs' negative impacts due to the homeostasis of sex steroids and thyroid hormones. Hence, reproductive health, considered a continuum from gamete production and fertilization through intrauterine and post-natal development of progeny, is recognized as being especially vulnerable to endocrine disruption [79].

Bisphenol analogs potentially interfere with endogenous hormones' production, secretion, metabolism, transport, or peripheral action by binding to hormone receptors and transcription factors. Bisphenol analogs can mimic hormonal activity and prevent natural hormone binding to receptors [80]. Aside from that, bisphenol analogs may affect enzyme expression, metabolism pathways, plasmatic clearance or directly affect gene expression via epigenetic modifications without affecting nucleotide sequences [81]. In females, bisphenols may affect the oviduct, uterus, ovary, hypothalamus-pituitary-ovarian axis estrous cyclicity, and implantation in animal models [82]. Bisphenols can inhibit follicle growth, affecting folliculogenesis via estrogen receptors [83,84].

In atretic follicles, exposure to bisphenol analogs increased the expression of proapoptotic BCL2-associated X protein (Bax) to antiapoptotic Bcl2 and Trp53, causing follicle atresia and DNA damage in cells [85]. The conditions could be due to the persistence and bioaccumulation of the chemicals in the body following parental exposure before conception or maternal exposure during pregnancy [32,33]. Because embryos grow and develop rapidly, the increased cell division and differentiation rate may increase susceptibility to the adverse effects of exposures during critical developmental periods, leading to permanent structural and organ system deficits. Some chemicals, such as polychlorinated biphenyls and lead, persist in body tissues and thus expose embryos in the maternal reproductive system [11,30].

Machtinger *et al*. (2013) found that exposure to bisphenols interfered with normal egg development and maturation, reducing the number of mature eggs and increasing the number that degenerated or activated abnormally [86]. Our review found that bisphenol analogs reduce spermatic cysts and modify the testis [66,70,77]. Increased oxidative stress in male germ cells disrupts daily sperm production and damages DNA [87,88]. Recent research shows that bisphenols reduce sperm number, induce sperm apoptosis and oxidative stress, and alter seminiferous tubule morphology in animals [89,90]. Mentor *et al*. (2020) found that bisphenol analogs like BPAF, BPF, and BPS are embryotoxic and that BPAF may be causing estrogen-like effects that feminize males [91].

Bisphenol analogues harmed zebrafish embryo development such as inflation of the bladder (Wei *et al*., 2018), stripe hypopigmentation [65,69], trunk edema [72], tail malformation [65,69,72], and pigmentation of the eyes [69]. Inflated swim bladders cause malformations and affect fish's energy allocation, growth, and feed conversion [92–94]. The uninflated swim bladder can cause immobility and death by affecting the fish's body buoyancy [93,94]. In terms of stripe hypopigmentation, bisphenol analogs induced hypopigmentation in zebrafish embryos. According to Parichy (2003), pigment patterns in zebrafish are clues to development and behavior. The process involves changes in color pattern changes and metamorphosis of embryonic melanophores. This transformation consists of developing scales and adult fins in the zebrafish, changes to the gut, skeleton, sensory systems, and the larval fin fold [95]. Therefore, hypopigmentation patterns after exposure to bisphenol analogs are related to the negative signs of development and behavior [96–98].

According to Skold *et al*. (2015), pigmentation is related to hormonal regulation of physiological color change in fish eyes involving ACTH or MSH. The eyes will be the most affected by ACTH [99]. They have been shown to increase oxidative stress in animals and cells [2,88,100,101]. Takamiya *et al*. (2016) found that eye pigmentation may be linked to increased oxidative stress and eye diseases like cataract formation. During embryonic development, melanosomes in epithelial cells protect the lens from oxidative stress [102]. So, less pigmentation in the eyes means more bisphenol analogs in the system. In zebrafish embryos, bisphenol analogs cause trunk edema, which results in a shortening, curling, and clubbing of secondary lamellae with an increased number of mucous cells [103]. The excess fluid in the lungs may cause embryonic death, making the fish difficult to breathe. The embryo has a cardiac beat, fully formed body sections, and the tail is detached from the yolk. The endpoint of embryonic growth in zebrafish is when the tail completely separates from the yolk. Toxicology causes tail kinks and bends [35]. Other causes of zebrafish tail malformations include water toxicity and abnormal muscle fiber organization [104].

BPA analogs are likely to affect epigenetic mechanisms via methylation of CpG sites, histone modification, chromatin structure changes, and mitochondrial DNA (mtDNA) instability, resulting in interference with developmental processes [105,106]. Mitochondria are required for cell form and function because they generate energy via oxidative phosphorylation. It was also crucial for fatty acid oxidation, iron-sulfur synthesis, chemical signaling, and programmed cell death. Chemical perturbation in the mitochondria can impair mitochondrial activity, leading to mitochondrial dysfunction [107,108]. Recent research suggests that estrogenic properties of BPA analogs can impair mitochondrial patterning and biogenesis, alter cellular functions, cause DNA damage, disrupt spermatogenesis, promote obesity, congenital deformities, and the development of metabolic diseases [2,109].

Neuroinflammation is one of the most important targets of bisphenol neurotoxicity. According to research, exposure to bisphenol analogs such as BPS and BPAF can induce neuroinflammatory responses due to neuronal cell apoptosis [110,111]. Aside from that, early embryonic development exposure to bisphenols affects neurotransmission, including decreased acetylcholinesterase, disruption of the dopamine system, and dysregulation of genes related to 5-hydroxytryptamine. The exposure may result in neurological deficits such as anxiety-like behaviors, disruption of the neuroendocrine system, and changes in neurobehavioural responses [112–114]. Previous zebrafish research revealed that bisphenols might also disrupt hormonal levels such as sex hormones and thyroxine, which are mediated by estrogen receptors (ESRs) and thyroxine receptors (THRs) [115,116].

Research on the effects of bisphenols on the behavioral phenotype of aquatic animals is still limited and controversial. However, a recent study revealed that BPS and BPF exposure caused abnormal behavioral effects in zebrafish larvae, such as hyperactivity, increased locomotion with aggressive behavior, and erratic movements. These abnormal behavioral phenotypes may be caused by the activation of astrocytes or microglia in developing zebrafish, which causes changes in CNS volume and neuronal death [117,118]. Zhang *et al*. (2012) demonstrated that rapid activation of microglia causes the secretion and accumulation of proinflammatory factors such as cytokines, chemokines, and reactive oxygen species (ROS), which can cause neuronal damage and neurodegenerative disorders [119]. Furthermore, the effects on zebrafish larvae's behavioral phenotype, locomotion, and motility are strongly linked to motor neuron development. For example, Yuan *et al*. (2019) demonstrated that BPF exposure in zebrafish embryos affects motor neuron development at 72 hpf by inhibiting axon growth [98].

Another study discovered that exposure to bisphenols caused motor neuron degeneration, impaired motor function, and reduced motor axon length in zebrafish embryos at 48 hpf [120].

5. Recommendation

Our research revealed the detrimental effects of bisphenol analogs on zebrafish embryos and cytoskeletal, which may help fill future research gaps. Future studies should examine bisphenol analogs' effects on marine, freshwater, and aquatic species. Bisphenols in water can harm aquatic life and disrupt the ecosystem's balance. More research is required to understand bisphenol analogs' effects on products and potential animal hazards. The public should be aware of the risks of new bisphenol analogs, and future research must identify bisphenol analog toxicity mechanisms. Studies also focused on the eight bisphenols A analogs. Other bisphenol analogs such as bisphenol P (BPP), bisphenol E (BPE), and bisphenol Z (BPZ) require more investigation. The situation is grave because if even a small dose of bisphenol analogs harms the models, their use in consumer products should be prohibited. In the meantime, more research on bisphenol analogs' effects on males is needed, particularly in terms of reproductive system parameters. Knowing the adverse effects of bisphenol analogs on zebrafish embryo models, we hope researchers will continue to research the risks of using bisphenol analogs and educate the public about the dangers of using bisphenol analogs. Because manufacturers control product production, they should work together to ensure that consumer products are safe and free of bisphenol analogs. Mandatory testing ensures chemicals like bisphenol analogs are safe for consumers.

6. Conclusions

Finally, the recent systematic review on the effects of bisphenol analogs on embryonic development and cytoskeletal organization in zebrafish embryos adds to our knowledge of how bisphenol analogs disrupt biological systems in zebrafish embryos. Overall, five major themes representing the major body systems affected by bisphenol analog exposure were identified. The first theme refers to the endocrine system's effects, which focus on disrupting hormonal activities. Following that, the theme considers the impact of bisphenol analogs on the cardiovascular system, emphasizing cardiac toxicity and morphogenesis. The third theme focuses on the effects of bisphenol analogs on the nervous system, including significant deformities and malformations in the spine, nerve cells, neurogenesis, neuroinflammation, protein alterations, and genes. The fourth theme emphasizes the adverse effects of bisphenol analogs on the reproductive system. The final theme focuses on the effects of bisphenol analogs on other parts of the zebrafish, such as swim bladder inflation, stripe hypopigmentation, trunk edema, tail defects, and eye pigmentation.

Funding

This study was supported by research grant from Universiti Teknologi MARA (UiTM) Malaysia, specifically the Geran Penyelidikan Khas (GPK) Grant 600-RMC/GPK5/3 (213/2020).

Acknowledgments

The authors would like to express their gratitude to all staff and contributors from the Faculty of Health Sciences and Faculty of Pharmacy, UiTM Selangor, Puncak Alam Campus; the Faculty of Medicine, UiTM Selangor, Sg. Buloh Campus; the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia and the Livestock Science Research Centre, Malaysian Agricultural

Research and Development Institute (MARDI) for their kind assistance, helpful comments, and unwavering interest in completing this research. Thank you also to the Tun Abdul Razak Library (PTAR) UiTM for providing a solid online database for conducting this systematic review.

Conflicts of Interest

The authors declare no conflict of interest.

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