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A SYSTEMATIC REVIEW ON THE EFFECTS OF SHORT-TERM EXPOSURE TO BISPHENOL-A AND BISPHENOL-S DURING EMBRYONIC STAGES OF ZEBRAFISH (*Danio rerio*)

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Abstract

Bisphenol-A is a highly used industrial chemical and a pervasive environmental oestrogen. Therefore, bisphenol-S was introduced as a safe alternative, yet endocrine disruption properties have been reported. Therefore, the safety of bisphenol-S as a safe substitute of bisphenol-A has become questionable. Yet, the existing published literature on comparative assessment of bisphenol effects are not conclusive. Therefore, a systematic review was carried out to comprehend the relative effects of bisphenols, by comparing the growth-related effects of early-life exposure to bisphenol-A and bisphenol-S in the model organism, *Danio rerio* (Zebrafish). The review analysed the published research through Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy. The search was conducted in Research Gate, Pub Med, Google Scholar, and Science Direct databases for articles published from the start of database coverage until August 2021, searching for articles on survival and growth-related effects of bisphenols in embryonic stages of zebrafish. Out of 181 articles, only 7 articles became eligible for inclusion criteria of early life (embryo) short-term bisphenol exposure. In recruited articles, hatching rate, body length, locomotion, malformations and survival of zebrafish were analysed under bisphenol concentrations of 0.0001 mg/L to 100mg/L. Studies on hatching rate have reported that exposure to both types of bisphenols in the concentration range of 1-100 µg/L significantly increase the hatching rate in a comparable manner. One study has reported that bisphenol-S significantly decreases embryo survival in lower concentrations than bisphenol-A. Decreased body length under the concentration range of 0.1-100 µg/L were evident for both bisphenols in a comparable manner. Based on the systematic review, it can be concluded that acute exposure to bisphenol-A and bisphenol-S exert similar effects to zebrafish embryos. Therefore the claim on the bisphenol-S as a safe bisphenol-A substitute warrants further investigations.

Keywords: Bisphenol-A, Bisphenol-S, PRISMA analysis, Short-term exposure, Zebrafish

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Introduction

Bisphenol-A (BPA) was originally produced as a pharmaceutical chemical and later became a largely produced industrial chemical in the plastic industry worldwide (Vandenberg et al., 2010). BPA is popularly used for the manufacturing of polycarbonate plastics and epoxy resins including plastic water bottles, baby feeding bottles, dental sealants, thermal receipt paper, compact discs, electronic devises, automobile parts, flame retardants, eyeglass lenses, impact resistant safety equipment, numerous medical devices and inner coating of food cans (Cano-Nicolau et al., 2016; Ji et al., 2013; Mu et al., 2018). BPA has become a universal environmental contaminant due to its leaching from discarded plastic products, effluent discharge, and with the existing plastic waste management practices (Corrales et al., 2015). Terrestrial and aquatic ecosystems serve as major reservoirs of BPA imposing a great exposure risk to living organisms. Environmental monitoring studies around the world have reported circulating and tissue levels of BPA in all biota including fish, amphibians, mollusks, and invertebrates threating the aquatic ecosystem health (Corrales et al., 2015).

BPA is a xenoestrogen and an endocrine disruptor, which interferes with hormonal pathways leading to abnormalities of growth, development, physiology, and behaviour of living organisms (Richter et al., 2007; Xing et al, 2021). BPA alters cellular signalling pathways by binding to hormone receptors including estrogen, thyroid, androgen and aromatase (AROM) enzyme pathways (Baravalle et al., 2017). The phenolic structure of BPA has higher tendency to bind with estrogen receptors leading to changes on estrogen regulated-gene expression impacting numerous developmental and growth outcomes. BPA exposure during early life stages is considered critical as significant development and maturation of organ systems take place in organisms. Numerous studies have pointed out that BPA is linked with adverse health effects such as developmental, reproductive, behavioural, neurological and physiological abnormalities (Mu et al., 2018). Due to negative health effects of BPA on animals, humans and ecosystems, some countries have restricted BPA use and have introduced substitutes of BPA.

Bisphenol-S (BPS) is the most widely used BPA alternative and is used in the manufacturing processes of food and beverage industry, epoxy glues, paper currencies, luggage tags, food cartons, and thermal receipt paper (Wu et al., 2018). Global usage of BPS was approximately 185 thousand tonnes in 2023. Environmental retention of BPS is higher than BPA due to high thermal and light stability. Recent studies have revealed that BPS also has the ability to bind to estrogen and androgen receptors, thereby interferes with endocrine signalling pathways. Further, its presence has been reported in environmental screening and tissue biomonitoring studies making BPS to the list of “emerging environmental pollutants” (Wu et al., 2018; Zhao et al., 2021). Thereby BPS has also shown to cause adverse effects on reproductive, nervous, immune and endocrine systems in animals affecting the ecosystem health (Coumailleau et al., 2020).

In this context, safety of BPA substitution through BPS has been largely questioned. Lack of comparable and comprehensive studies have challenged researchers in comprehending the relative effects of BPA and its analogue BPS on ecosystem health. Therefore this study was aimed at analysing the biological effects of BPA and BPS on zebrafish embryos by carrying out a systematic review of published literature.

In systematic review existing research studies are set to a previously defined study criteria and sorted further by analysing its content thoroughly (Li et al., 2018; Ribeiro et al., 2019; Wassenaar et al., 2017). In the sorting process its validity and suitability to the research question is highly assessed. Qualitatively

synthesized conclusion is extracted by using the inclusion and exclusion criteria as the final outcome of systematic review. Results extracted from systematic reviews can be quantitatively analysed by recruiting statistical analysis tools (Wassenaar et al., 2017).

Systematic reviews in physiology and medicine often follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al, 2009). This approach involves four key steps: identification, screening, eligibility, and inclusion of relevant scientific literature. Articles that meet qualitative criteria are selected for analysis, while those deemed most appropriate are chosen for quantitative analysis (Li et al., 2018; Ribeiro et al., 2019).

Since early-life exposures are critical in organism's survival and growth, literature on early-life exposure effects on survival, hatching, locomotion and malformations were systematically reviewed to scrutinize the effects of BPA and BPS in the popular toxicology animal model of zebrafish (*Danio rerio*).

Methodology

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed in designing the systematic review and in analysing the published research data (Li et al., 2018). Peer-reviewed research articles were obtained from searching databases including Research Gate, Pub Med, Google Scholar, and Science Direct during the period from June to August 2021. Articles published from the start of database coverage until August 2021 were collected, screened and reviewed. The four sequential stops of PRISMA analysis were identification, screening, eligibility, and inclusion.

Literature searching process by using related terms, synonyms and variations as key words is called the identification. For the "Identification" process data base search was carried out using key words of BPA, BPS, Zebrafish, body weight, body length, survival, sex ratio, growth and swimming speed. Screening ensures the quality of the review by applying selected criteria such as removing duplicate articles and assessing articles by title and the abstract. Initial sorting of the collected articles was performed by removing duplicate articles. Suitable articles were selected by reading abstracts. Initially selected articles were further studied by reading the full text and articles meeting the exclusion criteria were carefully removed. Most qualitatively suitable and eligible articles were included for analysis (Li et al., 2018; Ribeiro et al., 2019).

Following inclusion and exclusion criteria were used in selecting articles for the study. Inclusion criteria: Research articles that reported on 1) early life stages; embryo, larvae, juvenile, of zebrafish (*Danio rerio*) wild type or ornamental type, 2) short term exposure (less than 7 days) 3) and growth-related outcomes such as body weight, body length, specific growth rate, condition factor, body mass index, sex ratio as well as swimming speed were included.
Exclusion criteria: Articles were excluded if 1) they were duplicate articles, 2) only BPA was tested, 3) zebrafish (*Danio rerio*) were not used as the model organism, 4) only the effect of stress, temperature or behaviour were tested, 5) only plasma/ serum analysis has been performed, 6) only genetic analysis was performed.

In the eligibility step, article content was manually verified for the content and irrelevant articles were excluded after reading full text. In inclusion, the most suitable data extracted from the articles were included to the final qualitative analysis. Articles that fulfil most of the criteria were included in this step. The quality

of selected data was assessed using the criteria for reporting and evaluating ecotoxicity data (CRED) using six categories for evaluation, including general information, test design, test substance, test organism, exposure conditions, and statistical methods (Moermond et al., 2015).

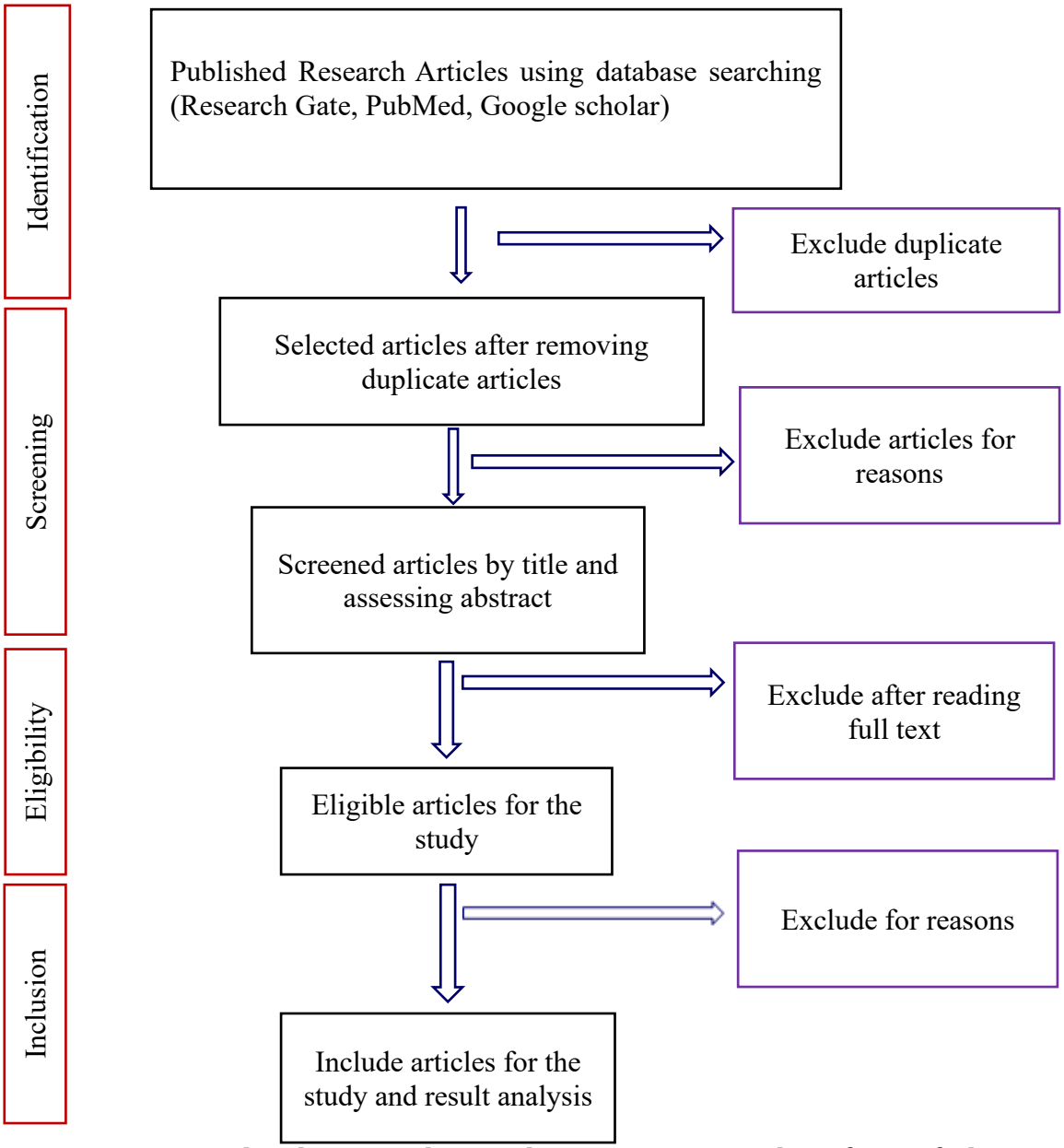

Figure 1: PRISMA Flow diagram indicating the recruitment procedure of scientific literature for systematic review and meta-analysis (Adopted from Moher et al, 2009).

Results

Research articles were searched using the keywords such as BPA, BPS, body weight, body length, sex ratio, and swimming speed. A total of 181 research articles were collected from Science direct (n =78), Research Gate (n =57), Google Scholar (n =32) and Pub Med (n = 14). After screening, 22 duplicate articles were removed. Ninety three articles were removed from the remaining 159 articles owing to exclusion criteria

such as use of other model organisms such as rat, mouse, carps and guppies, only BPA-treated articles, articles that investigated the other parameters such as serum parameters and other endocrine disruptors such as DDT (dichloro-diphenyl-trichloroethane) and unavailability of full papers as experimental design and results can't be obtained by reading the abstract alone. Remaining 66 articles were screened by reading the full text. At the eligibility step, 24 articles were selected and 42 articles were removed due to absence of growth-related outcomes and presenting of only genetic, behavioural, or histological studies. Remaining 24 articles were sorted according to the age structure such as early life stages (embryo, larvae and juveniles) and adult stages of zebrafish. Accordingly, 9 studies with adult stages were excluded and 15 articles encompassing early life stages were included. Subsequently exposure period of selected articles was classified into short term (less than a week) and long term (more than a week) exposures. Early life, long term exposures were reported in 4 articles while early life, long and short exposures were reported in 11 articles. All studies with only long term exposures (n=4) were excluded. Four of the short term exposure studies were excluded due to lack of both BPS and BPA treatments in the study design. After all, 7 articles met the eligibility criteria for the systematic review on impact of early life (embryo) short term BPS exposure (less than 7 days) on growth related outcomes in comparison to BPA. These 7 articles were used for the qualitative analysis presented in this paper.

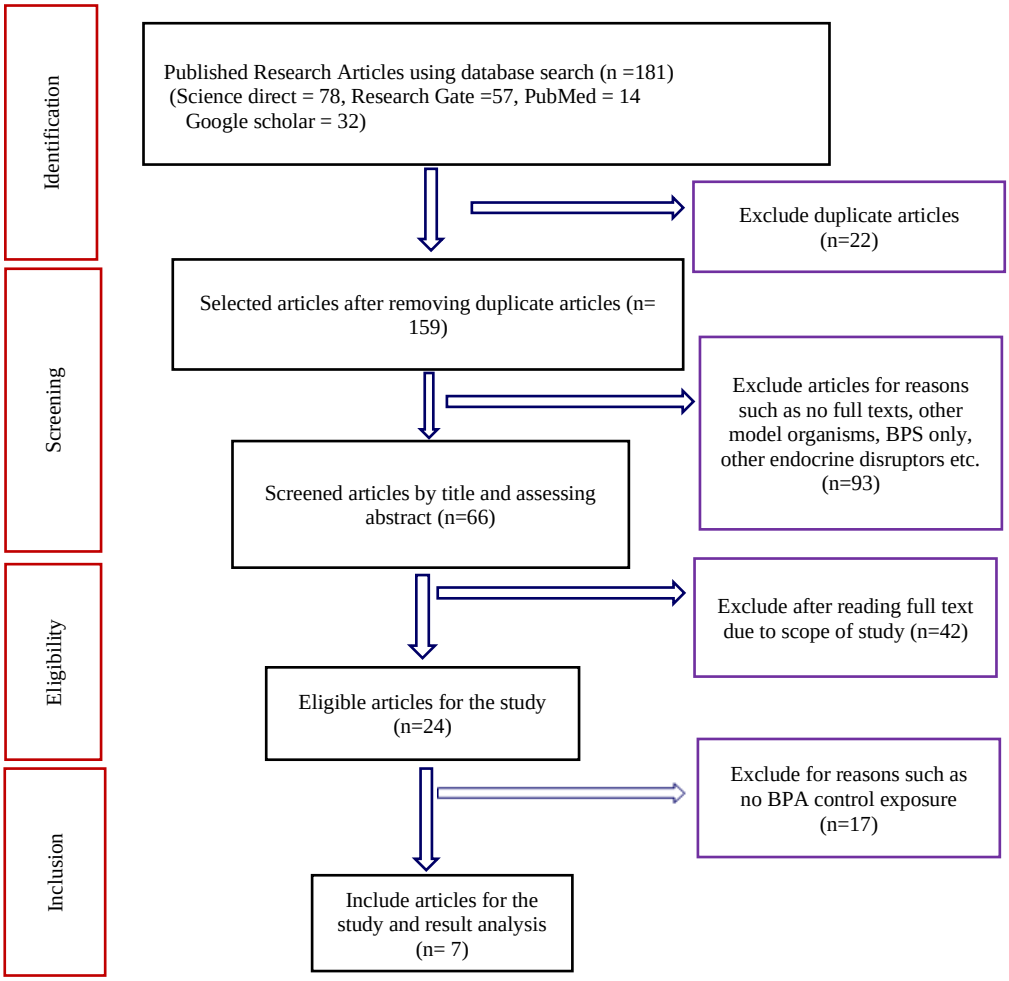

Figure 2: Flow diagram indicating the search strategy, inclusion and exclusion criteria of the scientific literature in this article.

The selected articles have investigated the growth-related effects such as body length increment, swimming performance, survival, and hatching rate of zebrafish embryos upon exposure to BPS and BPA for less than seven days. Different concentrations of BPS and BPA (0.0001mg/L to 100mg/L) have been used for the treatments, while 0.0.1% v/v DMSO (Dimethyl sulfoxide) has been used as the treatment control. The animal model used in four articles are wildtype, one study has used transgenic zebrafish lines while other two articles have used wild/transgenic fish. These studies were carried out in China, South Korea and United Kingdom during the period of 2017-2020 (Table 1). Hatching rate was investigated in five studies (Coumailleau et al., 2020; Lee et al.; 2019; Moreman et al., 2017; Qiu et al., 2018; Qiu et al., 2021) while three articles have investigated the length effects of zebrafish upon BPA and BPS exposure (Gyimah et al., 2021; Qiu et al., 2018; Qiu et al., 2021). Four articles have investigated fish locomotion (Coumaileau, et al., 2020; Gyimah et al.; 2021; Mu et al., 2018; Qiu et al., 2021;) while three articles have focussed on malformations (Gyimah, et al., 2021; Lee et al., 2019;Moreman, et al., 2017;). Significant effect on hatching rate (Coumailleua et al., 2020; Lee et al., 2019; Qiu et al., 2018; Qiu et al., 2021) was observed in four studies while two articles have observed significant effect on body length (Gyimah et al., 2021; Qiu et al 2021). One out of four articles have observed significant effect on locomotion (Gyimah et al., 2021). Significant malformations were identified in two articles (Gyimah et al., 2021; Moreman et al., 2017). Survival was also reported to be significantly affected in one investigated article (Lee et al., 2019).

Table 1: Summary of studies on short term exposure to BPS and BPA in early life stages of zebrafish (*Danio rerio*)

Author	Life cycle stage	Chemicals	Exposure period	Exposure concentrations	Effects/observations
(Gyimah et al., 2021)	Embryo	BPA, BPS	5 days	0.002, 0.004, 0.02 0.04, 0.2 mg/L (both BPA and BPS)	decreased length increased malformations increased locomotion (for both BPA and BPS)
(Moreman et al., 2017)	Embryo	BPA, BPS	5 days	[BPA]= 1, 2, 5, 10,12.5 mg/L [BPS]= 10, 20, 50, 100 mg/L	malformations (cardiac edema, spinal cord and tail) delayed hatching
(Lee et al., 2019)	Embryo	BPA, BPS	5 days	[BPA]= 0.08, 0.4, 2 mg/L [BPS]= 0.4, 2, 10, 50 mg/L	decreased survival delayed hatching increased malformations

(Mu et al., 2018)	Embryo	BPA, BPS	4 days	[BPA]= 0.5, 2.5, 5 mg/L [BPS]= 2.5, 12.5, 25	decrease in spontaneous movements
(Qiu et al., 2018)	Embryo	BPA, BPS	5 days	0.0001, 0.001, 0.01, 0.1, 1 mg/L (both BPA and BPS)	decreased body length increased hatching rate
(Qiu et al., 2021)	Embryo	BPA, BPS	5 days	0.001, 0.1 mg/L (both BPA and BPS)	increased hatching rate decreased body length decreased locomotion
(Coumailleau et al., 2020)	Embryo	BPA, BPS	6 days	0.02, 0.2 mg/L (both BPA and BPS)	increased hatching rate decreased locomotion

Table 2: Summary of studies that reported on statistically significant growth-related outcomes upon exposure to BPS and BPA in zebrafish (*Danio rerio*)

Articles	**Concentration of chemicals occurred significant effect**	**Significant outcomes**
(Qiu et al., 2018) (Qiu et al., 2021) (Coumailleau et al., 2020)	[BPA]= 0.001, 0.1 mg/L [BPS]= 0.2 mg/L	Increased hatching rate [BPS]= 0.001, 0.1 mg/L > 0.01%(v/v)DMSO [BPS]= 0.2 mg/L > 0.01%(v/v)DMSO [BPA]= 0.001, 0.1 m g/L > 0.01%(v/v)DMSO [BPA]= 0.2 mg/L > 0.01%(v/v)DMSO [BPS]= 0.001, 0.1mg/L= [BPA]= 0.001, 0.1 mg/L [BPS]= 0.2mg/L = [BPA]= 0.2mg/L
(Lee et al., 2019)	[BPA]=[BPS]= 10mg/L	Decreased hatching rate [BPS]= 10mg/L > 0.01%(v/v)DMSO [BPA]= 10mg/L > 0.01%(v/v)DMSO
(Lee et al., 2019)	[BPA]=10mg/L [BPS]= 2mg/L	Reduced survival [BPS]= 2mg/L > 0.01%(v/v)DMSO [BPA]= 10mg/L > 0.01%(v/v)DMSO
(Gyimah et al., 2021)	[BPA]= 0.06 to 0.2mg/L [BPS]= 0.06, 0.2 mg/L	Decreased body length [BPS]= 0.06, 0.2mg/L > 0.01%(v/v)DMSO

(Qiu et al., 2021)		[BPA]= 0.06, 0.2mg/L > 0.01%(v/v)DMSO [BPS]= 0.06, 0.2mg/L = [BPA]= 0.06, 0.2mg/L [BPA]= 0.1mg/L > 0.01%(v/v)DMSO [BPS]= 0.1 mg/L > 0.01%(v/v)DMSO
(Gyimah et al., 2021)	[BPA]= 0.06, 0.2 mg/L, [BPS] 0.06, 0.2 mg/L	Decreased swimming speed [BPS]= 0.06, 0.2mg/L > 0.01%(v/v)DMSO [BPA]= 0.06, 0.2mg/L > 0.01%(v/v)DMSO [BPS]= 0.06, 0.2mg/L = [BPA]= 0.06, 0.2mg/L
(Gyimah et al., 2021) (Moreman et al., 2017)	[BPA]= 0.06, 0.2, 2,10,12.5,50 mg/L [BPS]= 10,20,50,100,200 mg/L	Cardiac edema [BPA]= 0.06, 0.2mg/L > 0.01%(v/v)DMSO [BPA]= 2,10,12.5,50 mg/L> 0.01%(v/v)DMSO [BPS]= 10,20,50,100,200 mg/L > 0.01%(v/v)DMSO
(Gyimah et al., 2021) (Moreman et al., 2017)	[BPA]= 0.06, 0.2, 2mg/L [BPS]= 20,100,200 mg/L	Spinal and tail malformations [BPA]= 0.06, 0.2, 2mg/L > 0.01%(v/v)DMSO [BPS]= 20,100,200 mg/L > 0.01%(v/v)DMSO
(Moreman et al., 2017)	[BPA]= 2, 10, 12.5 mg/L [BPS]= 20, 100, 200 mg/L	Cranio-facial malformations [BPA]= 2, 10, 12.5 mg/L> 0.01%(v/v)DMSO [BPS]= 20, 100, 200 mg/L > 0.01%(v/v)DMSO
Lee *et al.*, 2019)	[BPA]= 0.4, 10 mg/L [BPS]= 0.4, 2, 10, 50 mg/L	Other different types of malformations [BPA]= 0.4, 10 mg/L > 0.01%(v/v)DMSO [BPS]= 0.4, 2, 10, 50 mg/L > 0.01%(v/v)DMSO

Of the studies included, only the studies in Table 2 have shown statistically significant differences for growth-related parameters.

Hatching rate: Significant increment in hatching rate was observed in three studies (Coumailleau et al., 2020; Qiu et al., 2018; Qiu et al., 2021). Hatching rate was increased significantly in a comparable manner under both bisphenols when compared to negative control, DMSO. BPA in concentrations upto 0.2 mg/L and BPS upto 0.2mg/L have shown the affect the hatching in similar manner. But in all the studies, hatching rate increment in BPS was not significantly different with corresponding concentrations of BPA. In

contrast, hatching rate was significantly decreased under 10mg/L of both bisphenols compared to treatment control of DMSO in the study carried out by Lee and colleagues (Lee et al., 2019).

Survival: Only one study that investigated on survival has reported on reduced survival under 10mg/L BPA and 2mg/L BPS when compared to DMSO control (Lee et al., 2019). As of the results BPS, even at low concentrations as 2mg/L reduces survival. However BPA-induced reduced survival has been observed with 10mg/L concentration (Lee et al., 2019).
Swimming speed: Swimming speed was decreased significantly when compared to DMSO, under both BPS and BPA exposure in the concentrations of 0.06- 0.2mg/L. There was no significant difference observed between BPS and BPA treatments (Gyimah et al., 2021).

Malformations: Two studies have investigated on malformations such as spinal, tail, craniofacial and cardiac edema (Gyimah et al., 2021; Moreman et al., 2017). Gyimah et al (2021) has observed cardiac edema and spinal malformations at significantly higher levels under both BPA and BPS treatments when compared to DMSO control (Gyimah et al., 2021). Second study has indicated significant cardiac edema in the concentrations of 10, 20, 50, 100, 200 mg/L of BPS and 2, 50, 10, 12.5 mg/L of BPA when compared to negative control (Moreman et al., 2017). Tail abnormalities have been observed in 20, 100, 200 mg/L BPS and 2mg/L of BPA than in the control. Significant cranio-facial abnormalities in concentrations of 2, 10, 12.5 mg/L BPA and 20, 100, 200 mg/L BPS have been observed compared to control (Moreman et al., 2017). Third study by Lee et al. (2019) has reported that both BPA and BPS exert abnormalities in a similar manner but significantly higher than negative control.

Body Length: Two studies (Gyimah et al., 2021; Qiu et al., 2021) which focused on length effects have reported that both types of bisphenols result in significant length decrease of zebrafish. However no statistical significance has been reported between BPA and BPS effects (Gyimah et al., 2021).

Discussion

Due to the endocrine disruption nature and the increasing human health and ecosystem health effects of BPA, BPS was introduced as a safe alternative to BPA (Chen et al., 2016; Eladak et al., 2015). BPS also leaches from plastic products acting as a synthetic estrogenic compound with higher thermal stability and lower photo degradability than BPA (Wu et al., 2018; Yamazaki et al., 2015). Due to these reasons, safety of BPS as a substitute for BPA has become highly controversial. Insufficient and limited number of comprehensive studies has become a challenge in understanding the relative safety of BPS in comparison with BPA. Therefore, this study was designed to evaluate the safety of BPS with respect to the BPA by analysing existing published literature. Popular toxicology animal model, zebrafish (*Danio rerio*) is most widely used in studies with environmental pollutants. Early life stages are more vulnerable for endocrine disruption as it's a critical period of development and growth. Therefore variables associated with growth and development such as length, swimming, malformations were selected for the study. During the systematic review the literature on short term (4 to 6 days) early life exposures of BPS with BPA treatments were qualitatively analysed. Studies encompassing acute and embryonic exposures with both BPS and BPA together with an appropriate control on wild or transgenic types of zebrafish were reviewed.

Environmentally-relevant low concentrations up to 2mg/L were used in two papers (Coumailleau et al. 2020; Gyimah et al. 2021), while other studies have used supra-environmental concentrations (Lee et al.

2019; Moreman et al. 2017). Even though both low and high concentrations led to observable adverse effects on embryos, the severity of effects such as malformations and reduced locomotion tends to increase with increasing exposure concentrations (Lee et al. 2019; Moreman et al. 2017). Several studies show a decrease in body length with BPA and BPS exposure, in lower concentrations such as 0. 2mg/L (Gyimah et al. 2021, Qiu et al. 2018; Qiu et al. 2021). These observations indicate a similar effect of these chemicals on inhibiting normal embryonic growth of zebrafish. Existing literature points out that both BPA and BPS interferes with hormone regulation, which is critical for growth and development even at the lowest concentrations. Therefore growth inhibition could be one of the earliest and most sensitive markers of BPA and BPS-induced toxicity. Some studies have detected malformations, like cardiac edema, and spinal cord and tail malformations (Moreman et al., 2017; Mu et al., 2018; Lee et al., 2019). These malformations were observed regardless of the differences in exposure concentrations of bisphenols and suggests that both BPA and BPS have teratogenic effects during embryonic development. The reduction in locomotion, as observed by Gyimah et al. (2021), Qiu et al. (2021) and Coumailleau et al. (2020) suggest neurotoxic effects of BPA and BPS. Bisphenols interfere with the development of the nervous system, potentially affecting motor neuron function and muscle development (Mu et al., 2018). The decrease in locomotion could be linked to oxidative stress, apoptosis, or disruptions in neurotransmitter systems, as suggested by other studies on BPA and BPS (David et al., 2017). Hence it could be stated that BPA and BPS might have long-lasting effects on neurological health.

An increase in hatching rates was observed (Coumailleau et al., 2020; Qiu et al., 2018; Qiu et al., 2021), it can be suggested that BPA and BPS may alter some developmental processes like hatching, growth and movement. Decrease in survival rates was observed with environmentally relevant higher concentrations (Lee et al., 2019). Early life bisphenol exposure was reported to cause decreased body length, increased malformations, reduced locomotion, increased hatching rates and decreased survival in zebrafish embryos (Coumailleau et al., 2020; Qiu et al., 2018; Qiu et al., 2021). It could be suggested that both BPA and BPS exert a multi-faceted toxic effects on developing embryos. In all the studies, it was observed that both BPA and BPS were exerting similar toxic effects, affecting body length, malformations, locomotion, and hatching rates. This finding challenges the claim on BPS as a safer BPA alternative.

Conclusion and recommendations

This review addresses varying BPA and BPS concentrations across studies, which link to growth related outcomes, hatching rates and survival of early life stages of zebrafish. In conclusion, the similarity in toxic effects of BPA and BPS imposed on early life stages of zebrafish model challenges the claim of BPS as a safe BPA substitute. We recommend comprehensive literature review incorporated with meta-analysis and encompassing of all life stages of *Danio rerio* to better comprehend the relative safety of BPA substitute, BPS.

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