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Johanna R. Rochester and Ashley L. Bolden

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Johanna R. Rochester and Ashley L. Bolden

The Endocrine Disruption Exchange (TEDX), Paonia, Colorado, USA

Address correspondence to Johanna R. Rochester, TEDX, P.O. Box 1407, Paonia, Colorado 81428 USA. Telephone: 970-527-4082. E-mail: johanna.rochester@gmail.com

Running title: Comparison of the hormonal activities of BPA substitutes

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Abstract

Background: Increasing concern over bisphenol A (BPA) as an endocrine disrupting chemical and its possible effects on human health have prompted the removal of BPA from consumer products, often labeled "BPA-free." Some of the chemical replacements however, are also bisphenols, and may have similar physiological effects in organisms. Bisphenol S (BPS) and bisphenol F (BPF) are two such BPA substitutes.

Objectives: This review was carried out to evaluate the physiological effects and endocrine activities of the BPA substitutes BPS and BPF. Further, we compared the hormonal potency of BPS and BPF to BPA.

Methods: We conducted a systematic review, based on the Office of Health Assessment and Translation (OHAT) protocol.

Results: We identified the body of literature-to-date, consisting of 32 studies (25 *in vitro* only, and seven *in vivo*). The majority of these studies examined the hormonal activities of BPS and BPF and found their potency to be in the same order of magnitude and of similar action to BPA (estrogenic, anti-estrogenic, androgenic, and anti-androgenic) *in vitro* and *in vivo*. BPS also has potencies similar to estradiol in membrane-mediated pathways, which are important for cellular actions like proliferation, differentiation, and death. BPS and BPF also showed other effects *in vitro* and *in vivo*, such as altered organ weights, reproductive endpoints, and enzyme expression.

Conclusions: Based on the current literature, BPS and BPF are as hormonally active as BPA, and have endocrine disrupting effects.

Introduction

There is increasing evidence that bisphenol A (BPA), used in plastics, receipts, food packaging, and other products, might be harmful to human health due to its actions as an endocrine disrupting chemical (EDC) (Bonefeld-Jorgensen et al. 2007; Richter et al. 2007b; Rochester 2013). Scientists, regulators, and the general public have raised concerns about the use of BPA, especially due to its ubiquitous nature and potential for continuous exposure (Vandenberg et al. 2012a). This has prompted industry to seek alternative chemicals. As manufacturers have begun to remove BPA from their products due to consumer concern, there has been a gradual shift to using bisphenol analogues. For the purpose of this paper, we chose to evaluate two of these analogues: bisphenol S (BPS) and bisphenol F (BPF) due to their widespread consumer and commercial use. BPS is used for a variety of industrial applications including as a wash fastening agent in cleaning products, an electroplating solvent, and a constituent of phenolic resin (Clark 2012). BPS is also used as a developer in thermal paper including products marketed as "BPA-free paper" (Liao et al. 2012c). BPF is used to make epoxy resins and coatings, especially for systems needing increased thickness and durability (i.e. high solid/high build systems), such as tank and pipe linings, industrial floors, road and bridge deck toppings, structural adhesives, grouts, coatings, and electrical varnishes (Fiege et al. 2000). BPF epoxy resins are also used for several consumer products such as lacquers, varnishes, liners, adhesives, plastics, water pipes, dental sealants, and food packaging (Office of Environmental Health Hazard Assessment 2012). BPS and BPF have been detected in many everyday products such as personal care products (e.g. body wash, hair care products, makeup, lotions, and toothpaste) (Liao and Kannan 2014), paper products (e.g. currency, flyers, tickets, mailing envelopes, and airplane boarding passes) (Liao et al. 2012c), and food (e.g. dairy products, meat and meat products, vegetables, canned foods, and

cereals) (Liao and Kannan 2013). BPS, BPF, and BPA have been detected in indoor dust at the following concentrations: BPS, 0.34 ug/g; BPF, 0.054 ug/g; BPA, 1.33 ug/g (Liao et al. 2012b). BPS and BPF have also been detected in surface water, sediment, and sewage effluent, generally at lower concentrations than BPA, but in the same order of magnitude (Fromme et al. 2002; Song et al. 2014; Yang et al. 2014). In humans, BPS and BPF have been detected in urine, at concentrations and frequencies comparable to BPA (Liao et al. 2012a; Zhou et al. 2014). In urine samples from 100 American, non-occupationally exposed adults, Liao et al. (2012a) found BPF in 55% of samples, at concentrations up to 212 ng/mL, and BPS in 78% of samples, at concentrations up to 12.3 ng/mL. BPA was found in 95% of the samples, with concentrations up to 37.7 ng/mL.

Ideally, substitutes used to replace a chemical of concern would be inert, or at least far less toxic than the original chemical(s). Unfortunately, many chemical replacements are untested before being placed on the market, and in some cases are similar enough to the original chemical to cause concern. For that reason, such chemical analogues should be evaluated before they are used as replacements for toxic chemicals. These chemicals may be just as harmful as the originals, or more so, and have been described as "regrettable substitutions," as is the case with several perfluorinated chemicals (Howard 2014), pesticides (Coggon 2002), and flame retardants (Bergman et al. 2012). In the case of BPS and BPF, these chemicals are structural analogs to BPA (Figure 1) thus their effects in physiological systems may be similar. BPA is a known endocrine disruptor based on *in vitro* (Wetherill et al. 2007) and animal laboratory studies (Richter et al. 2007a; Vandenberg 2014b), and exposures to environmental levels of BPA have been associated with adverse health outcomes in children and adults in over 75 human studies (Rochester 2013). In order to evaluate the endocrine disrupting properties of the BPA substitutes

BPS and BPF, we conducted a systematic review of the literature using the National Institute of Environmental Health Sciences' Office of Health Assessment and Translation (OHAT) systematic review protocol (National Toxicology Program 2013; Rooney et al. 2014). In this analysis we summarize *in vivo* and *in vitro* literature and compare the hormonal potency of BPS and BPF to BPA using the *in vitro* studies.

Literature Search and Review

A comprehensive literature search was performed in order to identify studies describing endocrine and other physiological effects of exposure to BPF and BPS. The search included all articles published and indexed for all years to June 2014. Electronic searches were performed in Web of Science (https://webofknowledge.com/) and Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) using CAS registry numbers and common names. See Table 1 for search logic.

For inclusion, the studies had to be primary literature and assess any *in vitro* or *in vivo* physiological effects of BPS or BPF exposure. Two independent reviewers screened all titles and abstracts for relevancy, using the software Distiller SR®, and resolved any conflicts or discrepancies. Data from the studies were extracted, and were crosschecked by the two reviewers. When needed, data were extracted from figures or graphs using the Universal Desktop Ruler® software, with measurements taken in triplicate by a single reviewer.

Study quality for *in vivo* studies was assessed using a protocol developed by OHAT. Briefly, Risk of Bias (RoB) in experimental methodology was assessed by answering 13 questions. The RoB questions covered biases in subject selection, protocol performance, attrition/exclusion of subjects, detection of outcomes, selective reporting of outcomes, and statistical methodology.

Questions were rated as "definitely low RoB," "probably low RoB," "probably high RoB," or "definitely high RoB" depending on standardized responses. See Figure 2 for the individual RoB questions. Next, 'key' study quality questions, identified *a priori*, were used to determine the initial quality of each study, then ratings of the remaining questions were used to determine the overall study quality: "low," "moderate," or "high". If any study received a "low" rating, it was removed from analysis. This protocol has been described in detail elsewhere (National Toxicology Program 2013; Rooney et al. 2014).

As specified in the OHAT protocol (National Toxicology Program 2013; Rooney et al. 2014), *in vitro* studies were not assessed for quality, but were used to support specific *in vivo* endpoints. For example, ER binding or activation studies support the biological plausibility of increased uterine growth, an *in vivo* estrogenic response. Where there were at least three *in vitro* studies, the strength of support was rated on the following factors: relevance of biological process or pathway to human disease, consistency across model systems (where there were more than two systems), physiological relevance of the dose concentration, potency (magnitude of response compared to positive control), dose-response (monotonic or non-monotonic), and publication bias. These factors were integrated for a final rating of "weak," "moderate," or "strong" *in vitro* support of the biological plausibility of *in vivo* observations, but were not used to exclude studies. *In vitro* observations that had less than three studies per endpoint, or did not relate to any observed *in vivo* endpoints, were described in the text.

Results

Our search identified 1,370 studies, a total of 32 studies (25 *in vitro* only and 7 *in vivo*) were identified as relevant for inclusion. Figure 2 shows the study quality ratings for the *in vivo*

studies. All studies were rated moderate quality or better, therefore no *in vivo* studies were removed due to low quality.

BPS

The current literature reporting the physiological effects of BPS exposure consists of four *in vivo* studies and 18 *in vitro* studies. *In vivo* studies are presented in Table 2. BPS exposure caused acute toxicity in *Daphnia magna* (Chen et al. 2002). In rats, Yamasaki et al. (2004), found that postnatal BPS exposure caused an induction of uterine growth, a marker of estrogen exposure (Owens and Ashby 2002), at the lowest and highest doses. The authors also found that BPS bound to the nuclear estrogen receptor (ER) at 0.0055% relative binding affinity (Yamasaki et al. 2004). Ji et al. (2013) studied BPS exposure in zebrafish and found decreases in gonad weight, alterations in plasma estrogen and testosterone, and disrupted reproduction (i.e. decreased egg production and hatchability, increased time to hatch, and increased embryo malformations). Another study in zebrafish showed that BPS exposure increased female to male sex ratio, decreased body length, altered testosterone, estradiol, and vitellogenin concentrations, and led to reproductive disruption (i.e. decreased egg production, increased time to hatch, and decreased sperm count) (Naderi et al. 2014).

In vitro data from 12 studies assessing estrogenicity provided strong evidence supporting the estrogenic responses in in vivo observations (Table 3). This was based on relevance of the endpoint to human health (e.g. interaction with human estrogen receptor [ERα] and G-protein coupled receptor 30 [GPR30]), consistent response across eight cell lines, and physiologically relevant concentrations assessed (μmol range) (Chen et al. 2002; Grignard et al. 2012; Hashimoto et al. 2001; Hashimoto and Nakamura 2000; Kitamura et al. 2005; Kuruto-Niwa et al.

2005; Molina-Molina et al. 2013; Rajasarkka et al. 2014; Rosenmai et al. 2014; Teng et al. 2013; Vinas and Watson 2013a, b). Several of these studies showed that BPS had weaker estrogenic potency than estradiol (E2), when assayed in nuclear receptor models (Chen et al. 2002; Grignard et al. 2012; Hashimoto et al. 2001; Hashimoto and Nakamura 2000; Kitamura et al. 2005; Kuruto-Niwa et al. 2005; Molina-Molina et al. 2013; Teng et al. 2013). However, two studies (Vinas and Watson 2013a, b) showed equivalent or greater estrogenic potency to E2 when assayed in membrane receptor models; BPS induced membrane receptor-mediated pathways typically upregulated by E2. Four studies showed that BPS bound to the ER in competitive binding assays (Grignard et al. 2012; Hashimoto et al. 2001; Molina-Molina et al. 2013; Yamasaki et al. 2004). There was also one study showing androgenic activity of BPS (Molina-Molina et al. 2013) and one study showing anti-androgenic activity (Kitamura et al. 2005). Additionally, in other in vitro experiments BPS exposure induced caspase-8 production, which indicates that BPS may alter cellular apoptotic and survival signaling (Salvesen and Walsh 2014; Vinas and Watson 2013a, b). BPS also had effects on hepatic cells (Peyre et al. 2014); it bound to serum albumins (Mathew et al. 2014), and it caused DNA damage (Fic et al. 2013; Hashimoto and Nakamura 2000; Lee et al. 2013).

BPF

Of the five *in vivo* studies, four showed that BPF exposure was estrogenic, androgenic and thyroidogenic (Table 2). Nineteen *in vitro* studies showed estrogenic, androgenic, and other physiological/biochemical effects (Table 3). BPF was acutely toxic in *Daphnia magna* (Chen et al. 2002). Two studies showed that BPF exposure induced uterine growth in rats, indicating estrogenic activity (Stroheker et al. 2003; Yamasaki et al. 2004). There were also two studies that showed evidence of androgenic activity: one study indicated that BPF increased the weight of the

testes (Higashihara et al. 2007), and the other showed a cumulative effect of BPF when co-administered with testosterone propionate that increased Cowper's gland weight (Yamasaki et al. 2003). The cumulative effect indicates BPF may augment other androgens, if indeed acting synergistically. BPF exposure also increased thyroid weight and altered thyroid hormone concentrations, as well as caused changes to hematological parameters and enzyme expression (Higashihara et al. 2007).

As shown in Table 3, *in vitro* data from 12 studies provided strong evidence that BPF had estrogenic activity, supporting *in vivo* observations. This rating was based on relevance to human health (MCF-7 and human ER), consistency across five cell models, and the use of relevant concentrations (μmol range) (Cabaton et al. 2009; Chen et al. 2002; Hashimoto et al. 2001; Hashimoto and Nakamura 2000; Kitamura et al. 2003; Kitamura et al. 2005; Molina-Molina et al. 2013; Perez et al. 1998; Pisapia et al. 2012; Rajasarkka et al. 2014; Rosenmai et al. 2014; Satoh et al. 2004). One study showed that BPF was not estrogenic in a yeast two-hybrid assay (Ogawa et al. 2006). One study indicated that BPF was anti-estrogenic (Stroheker et al. 2004). Moderate evidence from six studies showed that BPF was anti-androgenic based on relevance to human health (i.e. human androgen receptor [AR]), consistency across four cell models, and potency (i.e. within 100 orders of magnitude of positive control) (Cabaton et al. 2009; Kitamura et al. 2005; Molina-Molina et al. 2013; Rosenmai et al. 2014; Satoh et al. 2004; Stroheker et al. 2004). BPF also showed other *in vitro* effects such as cytotoxicity, cellular dysfunction, DNA damage, and chromosomal aberrations (Audebert et al. 2011; Cabaton et al. 2009; Lee et al. 2013; Nakagawa and Tayama 2000; Pisapia et al. 2012), and decreased adiponectin production and secretion *in vitro* (Kidani et al. 2010).

BPS and BPF potency compared to BPA

BPS and BPF are already being used as alternatives for BPA, thus it is important to understand whether or not these substitutes possess similar endocrine disruptive/active properties as BPA. Seventeen studies tested BPS and/or BPF as well as BPA in the same assays, allowing the potencies and mechanisms of action to be directly compared. Table 4 presents these results, comparing the hormonal potencies of BPF and/or BPS to BPA. The average and standard deviation of estrogenic potency for BPF as compared to BPA was 1.07 ± 1.20, with a range of 0.10 to 4.83. The average and standard deviation of estrogenic potency for BPS compared to BPA was 0.32 ± 0.28, with a range from 0.01 to 0.90. These results indicate that the potencies of BPS and BPF are in the same order of magnitude as the potency of BPA, and in the case of BPF, may be just as potent (or more potent) than BPA. Further, BPS and BPF have potencies in the same order of magnitude as BPA in regards to androgenic, anti-androgenic, anti-estrogenic, aryl hydrocarbon activity and inhibitory hormonal signaling in adipocytes (Table 4).

Rosenmai et al. (2014) employed several assays to assess steroidogenic activity, as well as teratogenicity, genotoxicity, carcinogenicity, and metabolic effects. Similar to the current evaluation, they found that BPS and BPF had similar estrogen receptor binding, estrogenic activity, and anti-androgenic activity as BPA, with BPS the least potent. However, BPS and BPF exhibited the greatest steroidogenic (i.e. progesterone) activity, increasing 17α-OH progesterone and progesterone levels, while BPA did not (Rosenmai et al. 2014). While the authors did not examine the mechanism of action of progesterone upregulation, previous work suggests a direct inhibition of the CYP17 lyase reaction, independent of estrogen receptor action (Zhang et al. 2011). Thus, BPA analogues may have additional disruptive effects that have not been detected with BPA.

Discussion

Although there are relatively few studies examining the hormonal actions of BPS and BPF (especially *in vivo*), the *in vitro* literature indicates that BPS and BPF have actions and potencies similar to BPA, and supports the biological plausibility of their hormonal activity *in vivo.* This is not surprising, as BPF and BPS are structural analogues of BPA and thus mechanisms of action would be expected to be similar. For example, BPF showed cumulative, possibly synergistic, actions *in vivo* when co-administered with an androgen (Yamasaki et al. 2003), and BPA has also been shown to have these types of effects when combined with other hormones or xenoestrogens (Kang et al. 2002; Silva et al. 2002). Particularly interesting is the fact that BPS seems to have similar actions on non-genomic signaling as BPA (Vinas and Watson 2013a, b). BPA is sometimes called a 'weak' estrogen, because of its relatively weak binding/activation of the nuclear receptors compared to E2, although this is not always the case (see Table 3, Kitamura et al. 2005; Perez et al. 1998; Pisapia et al. 2012). However, when the non-genomic estrogenic activity of BPA is measured, it is comparable, if not more potent, than E2. This potent, non-genomic estrogenic activity of BPA has been described in several experimental models (Alonso-Magdalena et al. 2008; Alonso-Magdalena et al. 2012 (review); Vinas and Watson 2013a, b; Watson et al. 2014). The potency of BPS in a non-genomic signaling assay was similar to BPA. In femtomolar to picomolar concentrations, BPS induced membrane ERalpha (mERα)-mediated pathways and actions: MAPK signaling, cell proliferation, and activation of caspase 8 (Vinas and Watson 2013a, b). These rapid, non-genomic pathways are important for optimal cell function, mediating proliferation and apoptosis (Vinas and Watson 2013a, b), as well as other actions, such as pancreatic cell function (Alonso-Magdalena et al. 2008) and estrogen-mediated brain function and behavior (Laredo et al. 2014; Moenter and Chu 2012).

BPS and BPF had potencies in the same order of magnitude as BPA. The issue of potency is complicated due to the fact that lowest observed effect levels depend on endpoint, receptor type, pathway, tissues, windows of exposure, etc. In general, BPS was slightly less potent than BPA. The average BPF potency was similar to BPA, with a fairly wide range of potencies. However, the implications of these differences are not clear. In regards to potency, it is not known whether a compound that is, for example, half as potent as BPA *in vitro* would have half the effect *in vivo*, especially since very little is known about the exposure and metabolism of BPS and BPF. Further, even if potencies of BPS and BPF are slightly less than BPA, it is unclear if these compounds are safer—many scientists have advocated a 'no-threshold' approach to endocrine disruption due to the fact that thresholds may change during development, or may be very difficult to assess (Munn and Goumenou 2013).

The metabolism and biological fate of BPS and BPF have not been well-studied, but experiments of BPF *in vitro* and *in vivo* indicate that BPF has similar metabolism and distribution as BPA. *In vitro,* BPA was metabolized by human and rat hepatic cells to many different metabolites, including the non-bioactive sulfate and glucuronide conjugates (Cabaton et al. 2008; Dumont et al. 2011). *In vivo*, BPF administered to pregnant rats via gavage resulted in the excretion of BPF and several metabolites in the urine, including the non-active sulfate conjugated BPF. Active BPF was also distributed to many tissues, including the uterus, placenta, amniotic fluid, and fetuses. The ratio of the active parent compound to the metabolites/conjugates was similar to that of BPA (Cabaton et al. 2006; Vandenberg et al. 2013b). The primary route of excretion for BPF appeared to be through the sulfatase conjugate, rather than the glucuronide conjugate (as with BPA). Cabaton et al. (2006) suggest this may be due to the fact that BPF glucuronide may be more easily deconjugated to its bioactive state and reabsorbed in large quantities, which also

appears to occur with BPA (Vandenberg et al. 2013b). No studies have assessed the metabolism of BPS, nor the bioactivity of the metabolites. Studies determining the metabolism of BPS and the bioactivity of metabolites from BPF and BPS are warranted.

The *in vivo* body of literature of the effects of BPS and BPF is scant, but it points to these chemicals as endocrine disruptors and reproductive toxicants. BPS induced uterine growth in rodents (indicative of estrogenic action), and disrupted reproduction in fish (Ji et al. 2013; Naderi et al. 2014; Yamasaki et al. 2004), and BPF also had uterotropic (estrogenic) effects in female rodents and gonadotropic (androgenic) effects in male rodents (Higashihara et al. 2007; Stroheker et al. 2003; Stroheker et al. 2004; Yamasaki et al. 2004). While most of the *in vitro* data supports estrogenic, and to some extent, anti-androgenic, actions of BPS and BPF (see Table 3), one *in vitro* study showed that BPS has androgenic activity similar to BPA (Molina-Molina et al. 2013). Thus, the *in vitro* data support the *in vivo* observations of hormonal and endocrine disruptive activity of these compounds.

Concern over the endocrine disruptive effects of BPA has resulted in hundreds of laboratory studies, including *in vitro* (Wetherill et al. 2007) and *in vivo* (Richter et al. 2007b; Vandenberg 2014b), studies identifying estrogenic and other effects. Although some regulators have rejected this body of literature because of a lack of standardized protocols, reviews of these studies have indicated strong methodologies and stringent laboratory practices, often of higher quality than studies employing "Good Laboratory Practices" (Myers et al. 2009). Many *in vivo* BPA studies demonstrate adverse outcomes at "low" (i.e. environmentally or physiologically relevant doses) (Vandenberg 2014a; Vandenberg et al. 2012b). Many studies also report that BPA has a non-linear, or non-monotonic, dose-response curve. Non-monotonic dose-responses (NMDRs) are

indicative of an endocrine-mediated response and are consistent with natural hormone responses (Vandenberg 2014b; Vandenberg et al. 2013a; Vandenberg et al. 2012b; Zoeller et al. 2012). Further, nearly 100 human studies describe the relationship between BPA and several endocrine related health impacts on reproduction, neurodevelopment, thyroid function, and metabolic health (Rochester 2013). Although, epidemiological studies are less controlled than laboratory animal experiments, making it difficult to show causation, they are important indicators of potential health effects (Diamanti-Kandarakis et al. 2009; Zoeller et al. 2012). Further, although BPA is quickly metabolized and excreted from the body (with a half life of about 6 hours (Dekant and Volkel 2008)), the fact that it is found in almost all humans sampled at any one time suggests the ubiquitous and constant nature of BPA exposure (Vandenberg et al. 2012a), which is disconcerting in light of the animal and human evidence of health effects. Many researchers have raised concern over this overwhelming evidence, and have called for stricter regulation of BPA (Vandenberg et al. 2012b; Vandenberg et al. 2009). Although this concern has prompted BPA to be phased out of certain products (FDA 2012), the structural analogue replacements may not be any safer.

Because BPS and BPF appear to have similar metabolism, potencies, and mechanisms of action *in vitro* as BPA, including hormonal actions beyond that of BPA, they may pose similar potential health hazards as BPA. Therefore, when evaluating the safety of compounds for consumer use, it may be prudent to consider entire classes as opposed to individual compounds. In addition, as other researchers have suggested (Vinas and Watson 2013a), future research efforts should focus on designing chemical substitutes that do not have similar biological or hormonal activity to BPA. Further, this review demonstrates that systematic reviews may be useful in the process of conducting safety evaluations of chemical classes. The use of the bisphenol class of compounds

as replacements for BPA in consumer products with high human contact should be implemented with caution.

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Table 1. BPS and BPF search logic.

	PubMed and Web of Science Search Logic
BPF	620-92-8[EC/RN] OR Bisphenol-F OR (bisphenol* AND BPF) OR Bis(4-hydroxyphenyl)methane OR Bis(p-hydroxyphenyl)methane OR Bis(4-hydroxyphenyl)-methane OR Bis(p-hydroxyphenyl)-methane OR p-(p-Hydroxybenzyl)phenol OR p-(p-Hydroxybenzyl)-phenol OR 4-(4-Hydroxybenzyl)phenol OR 4-(4-Hydroxybenzyl)-phenol OR "4,4'-Methylenebis(phenol)" OR "p,p'-Bis(hydroxyphenyl)methane" OR "p,p'-Bis(hydroxyphenyl)-methane" OR "4,4'-Bis(hydroxyphenyl)methane" OR "4,4'-Bis(hydroxyphenyl)-methane" OR "4,4'-Dihydroxydiphenylmethane" OR "4,4'-Dihydroxydiphenyl-methane" OR "4,4'-Methylenediphenol" OR "4,4'-Methylene-diphenol" OR "4,4'-Methylenebisphenol" OR "4,4'-Methylene-bisphenol"
BPS	80-09-1[EC/RN] OR bisphenol-s OR ((bisphenol OR bisphenols) AND BPS) OR bis(4-hydroxyphenyl)-sulfone OR bis(4-hydroxyphenyl)sulfone" OR bis(4-hydroxyphenyl)-sulphone OR bis(4-hydroxyphenyl)sulphone OR bis(p-hydroxyphenyl)-sulfone OR bis(p-hydroxyphenyl)sulfone OR bis(p-hydroxyphenyl)-sulphone OR bis(phydroxyphenyl)sulphone OR 4,4'-dihydroxydiphenyl-sulfone OR 4,4'-dihydroxydiphenylsulfone OR 4,4'-dihydroxydiphenyl-sulphone OR 4,4'-dihydroxydiphenylsulphone OR p,p'-dihydroxydiphenyl-sulfone OR p,p'-dihydroxydiphenylsulfone OR p,p'-dihydroxydiphenyl-sulphone OR p,p'-dihydroxydiphenylsulphone OR 4,4'-sulfonyldiphenol OR 4,4'-sulfphonyldiphenol OR p,p'-sulfonyldiphenol OR p,p-sulfphonyldiphenol OR 4,4'-sulfonylbisphenol OR 4,4'-sulfphonylbisphenol OR p,p'-sulfonylbisphenol OR p,p-sulfphonylbisphenol OR 4,4'-sulfonylbiphenol OR 4,4'-sulfphonylbiphenol OR p,p'-sulfonylbiphenol OR p,p'-sulfphonylbiphenol OR 4-hydroxyphenyl-sulfone OR 4-hydroxyphenylsulfone OR 4-hydroxyphenyl-sulphone OR 4-hydroxyphenylsulphone OR p-hydroxyphenyl-sulfone OR p-hydroxyphenylsulfone OR p-hydroxyphenyl-sulphone OR p-hydroxyphenylsulphone

Table 2. *In vivo* BPS and BPF hormonal/physiological effect studies.

Chemical	Study	Model	Exposure Duration	Age at Exposure	Route of Exposure	Doses	LOEL[a]	Results
BPS	Chen et al. 2002	D. magna	2 or 4 days	Juvenile	Culture	NA	NA	BPS was shown to be acutely toxic in Daphnia magna EC50 76 mg/L (24h) and EC50 55 mg/L (48h). BPS showed estrogenic activity and did not show mutagenic activity in vitro.
BPS	Yamasaki et al. 2004	Rat	3 days	20 days	Injection	0, 20, 100, 500 mg/kg/day	20 mg/kg	BPS exposure was shown to be estrogenic in rats via increases in uterine weight. BPS was also shown to bind the estrogen receptor.
BPS	Ji et al. 2013	D. rerio	21 days	3-5 months	Water	0, 0.5, 5, 50 µg/L	0.5 ug/L	BPS exposure in zebrafish showed decreases in gonad weight with respect to body weight in males and females. No changes were shown in liver or brain weight with respect to body weight. E2 levels were increased in males and in females, T levels were decreased in males, and E2/T ratios were increased in males and females. Reproduction was impaired as evidenced by decreased egg production and hatchability, and increased time to hatch and embryo malformation rates. Gene expression in the brain and gonads of several genes involved in the hypothalamic-pituitary-gonadal axis were altered in males and females.
BPS	Naderi et al. 2014	D. rerio	75 days	4-6 months	Water	0, 0.1, 1, 10, 100 µg/L	1 ug/L	BPS exposure in zebrafish showed decreases in body length and weight in males, increased female to male sex ratio, decreased gonad weight, increased liver weight, decreased T3 and T4, decreased T in males, increased E2 in males and females, and increased VTG in males and females. BPS also caused disrupted reproduction, with decreased number of eggs produced, decreased hatching rate, increased time to hatch, and decreased sperm count.
BPF	Chen et al. 2002							

BPF	Yamasaki et al. 2003	Rat	10 days	19 days	Gavage	0, 50, 200, 1000 mg/kg/day	100 mg/kg	BPF co-administered with TP increased the weight of the Cowper's gland. BPF alone and combined with TP decreased body weight.
BPF	Yamasaki et al. 2004	Rat	3 days	20 days	Injection	0, 100, 300, 1000 mg/kg/day	100 mg/kg	BPF induced uterine growth in immature rats. BPF was positive for relative binding affinity (E2).
BPF	Higashihara et al. 2007	Rat	28 days	8 weeks	Gavage	0, 20, 100, 500 mg/kg/day	20 mg/kg	There were decreases in body weight and food consumption in males and females treated with BPF. Hematological and biochemical parameters were altered, including decreased cholesterol and glucose in males and females. BPF treatment decreased T3 and increased T4 levels. BPF increased testes, liver, thyroid, brain, and kidney weights.
BPF	Stroheker et al. 2003	Rat	4 days	22 days	Gavage	0, 25, 50, 100, 200 mg/kg/day	100 mg/kg	BPF was shown to increase uterine weight in rats.

Abbreviations: BPS, bisphenol S; NA, not available; EC50, half maximal effective concentration; E2, 17β-estradiol; T, testosterone; T3, triiodothyronine; T4, thyroxin; VTG, vitellogenin; BPF, bisphenol F; TP, testosterone propionate.

[a]The dose at the endpoint of the lowest observed effect.

Table 3. Studies assessing BPS and activity *in vitro.*

Study	Chemical(s) Tested	Endpoint Measured	Chemical Concentrations Tested
Audebert et al. 2011	BPF	cytotoxicity; genotoxicity	1 to 100 µM
Cabaton et al. 2006	BPF/BPS	anti- androgenicity; estrogenicity; genotoxicity	10^{-11} to 10^{-5} M 36.4 to 170 µM
Chen et al. 2002	BPF/BPS	acute toxicity; estrogenicity	0.01 to 100 mg/L
Fic et al. 2013	BPF/BPS	cytotoxicity; genotoxicity; mutagenicity	12.5 to 100 µM 0.1 to 10 µM 4 to 500 µg/plate
Grignard et al. 2012	BPS	estrogenicity	10^{-12} to 10^{-4} M
Hashimoto and Nakamura 2000	BPF/BPS	estrogenicity	10^{-7} to 10^{-3} M
Hashimoto et al. 2001	BPF/BPS	estrogenicity	10^{-9} to 10^{-3} M
Kidani et al. 2010	BPF	adiponectin	80 µM
Kitamura et al. 2003	BPF	estrogenic; estrogen CBA	10^{-8} to 10^{-4} M
Kitamura et al. 2005	BPF/BPS	anti- androgenicity; estrogenicity	10^{-7} to 10^{-4} M
Kuruto-Niwa et al. 2005	BPS	estrogenicity	10^{-7} to 10^{-4} M
Lee et al. 2013	BPF/BPS	cytotoxicity; genotoxicity	10 to 250 µM
Mathew et al. 2014	BPS	serum albumin binding	0.2 to 4 µM
Molina-Molina et al. 2013	BPF/BPS	androgenicity; anti- androgenicity; estrogenicity; estrogen CBA	10^{-8} to 10^{-5} M
Nakagawa and Tayama 2000	BPF	cytotoxicity; mitochondrial function	0.25 to 1 mM
Ogawa et al. 2006	BPF	estrogenicity	10^{-7} to 10^{-3} M
Perez et al. 1998	BPF	estrogenicity	10^{-8} to 10^{-5} M
Peyre et al. 2014	BPS	hepatic cell function	1 to 500 µM
Pisapia et al. 2012	BPF	estrogenicity	10^{-7} to 10^{-5} M
Rajasarkka et al. 2014	BPF/BPS	BPA activity; estrogenicity	10^{-7} to 10^{-2} M
Rosenmai et al. 2014	BPF/BPS	anti- androgenicity; estrogenicity; steroidogenesis; AhR activity	0.0001 to 100 µM
Satoh et al. 2004	BPF	anti- androgenicity; cytotoxicity; estrogenicity; estrogen and androgen CBA	10^{-9} to 10^{-3} M
Stroheker et al. 2004	BPF	anti- androgenicity; anti-estrogenicity; estrogenicity; estrogen CBA	10^{-10} to 10^{-5} M
Teng et al. 2013	BPS	androgenicity; estrogenicity	10^{-13} to 10^{-4} M
Vinas and Watson 2013a	BPS	estrogenicity	10^{-15} to 10^{-7} M
Vinas and Watson 2013b	BPS	estrogenicity	10^{-14} M
Yamasaki et al. 2004	BPS	estrogen CBA	10^{-11} to 10^{-4} M

Abbreviations: BPS, Bisphenol S; BPF, Bisphenol F; CBA, Competitive binding assay.

Table 4. *In vitro* BPS and BPF hormonal activity compared to BPA.

Assay (Receptor Tested)	Chemical Potency vs. Positive Control (Control)	BPA Potency vs. Positive Control (Control)	Chemical Potency Compared to BPA Potency[a]	Reference
BPS, Estrogenic Activity				
MCF-7 GFP (ERα)	5.54E-06 (E2)	8.86E-06 (E2)	0.62	Kuruto-Niwa et al. 2005
E-Screen (ERα)	NA (E2)	NA (E2)	0.67	Hashimoto and Nakamura 2000
yeast 2-hybrid (ERα)	4.33E-06 (E2)	2.76E-5 (E2)	0.16	Hashimoto and Nakamura 2000
E-Screen (ERα)	NA (E2)	NA (E2)	0.90	Hashimoto et al. 2001
yeast 2-hybrid (ERα)	4.83E-06 (E2)	2.40E-5 (E2)	0.20	Hashimoto et al. 2001
yeast 2-hybrid (ERα)	NC (E2)	NC (E2)	0.10	Chen et al. 2002
MCF-7 Luc (ERα)	7.82E-06 (E2)	1.37E-05 (E2)	0.57	Kitamura et al. 2005
MELN (ERα)	9.76E-06 (E2)	1.77E-05 (E2)	0.55	Grignard et al. 2012
BG1Luc4E2 (ERα, ERβ)	2.52E-07 (E2)	3.14E-06 (E2)	0.08	Grignard et al. 2012
E-screen (ERα)	1.0E-06 (E2)	3.75E-05 (E2)	0.03	Molina-Molina et al. 2013
MELN (ERα)	NA (not reported)	NA (not reported)	0.04	Molina-Molina et al. 2013
HELN (ERα)	NA (not reported)	NA (not reported)	0.10	Molina-Molina et al. 2013
HELN (ERβ)	NA (not reported)	NA (not reported)	0.30	Molina-Molina et al. 2013
CV-1 Luc (ERα)	5.73E-05 (E2)	4.63E-4 (E2)	0.12	Teng et al. 2013
GH3/B6/F10 ERK (mER)	0.68 (E2)	1.56 (E2)	0.43	Vinas and Watson 2013a
GH3/B6/F10 ERK (mER)	1.36 (E2)	1.91 (E2)	0.71	Vinas and Watson 2013b
yeast bioreporter (ERα)	NA (not reported)	NA (not reported)	0.01	Rajasarkka et al. 2014
BG1Luc4E2 (ERα)	NC (E2)	NC (E2)	0.23	Rosenmai et al. 2014
BPS Average Estrogenic Potency Compared to BPA (mean ± SD)			**0.32 ± 0.28**	
BPS, Anti-Androgenic Activity				
NIH353 + DHT (AR)	0.18 (Flutamide)	0.58 (Flutamide)	0.25	Kitamura et al. 2005
BPS, Androgenic Activity				
MCF-7 AR1 (AR)	9.00E-07 (R1881)	2.25E-06 (R1881)	0.40	Molina-Molina et al. 2013
PALM (AR)	NA (not reported)	NA (not reported)	0.79	Molina-Molina et al. 2013
BPS, BPA Activity				
yeast bioreporter (BPAR)	2.50E-02 (BPA)	1.00 (BPA)	0.03	Rajasarkka et al. 2014
BPF, Estrogenic Activity				
E-Screen (ERα)	0.001(E2)	0.01 (E2)	0.10	Perez et al. 1998
E-Screen (ERα)	NA (E2)	NA (E2)	0.89	Hashimoto and Nakamura 2000
yeast 2-hybrid (ERα)	6.69E-05 (E2)	2.76E-05 (E2)	2.42	Hashimoto and Nakamura 2000
E-Screen (ERα)	NA (E2)	NA (E2)	0.99	Hashimoto et al. 2001
yeast 2-hybrid (ERα)	6.39E-5 (E2)	2.40E-5 (E2)	2.67	Hashimoto et al. 2001
yeast 2-hybrid (ERα)	NC (E2)	NC (E2)	0.79	Chen et al. 2002
E-Screen (ERα)	5.31E-05 (E2)	1.10E-05 (E2)	4.83	Stroheker et al. 2004
E-Screen (ERα)	4.67E-06 (E2)	7.78E-06 (E2)	0.60	Satoh et al. 2004
MVLN Luc (ERα)	5.86E-06 (E2)	1.17E-05 (E2)	0.50	Satoh et al. 2004
MCF-7 Luc (ERα)	8.6E-06 (E2)	1.37E-05(E2)	0.63	Kitamura et al. 2005
E-Screen (ERα)	0.55 (E2)	0.86 (E2)	0.64	Pisapia et al. 2012

Assay (Receptor Tested)	Chemical Potency vs. Positive Control (Control)	BPA Potency vs. Positive Control (Control)	Chemical Potency Compared to BPA Potency[a]	Reference
E-screen (ERα)	1.0E-05 (E2)	3.75E-05 (E2)	0.27	Rajasarkka et al. 2014
MELN (ERα)	NA (not reported)	NA (not reported)	0.48	Molina-Molina et al. 2013
HELN (ERα)	NA (not reported)	NA (not reported)	0.29	Molina-Molina et al. 2013
HELN (ERβ)	NA (not reported)	NA (not reported)	0.36	Molina-Molina et al. 2013
yeast bioreporter (ERα)	NA (not reported)	NA (not reported)	1	Rajasarkka et al. 2014
BG1Luc4E2 (ERα)	NC (E2)	NC (E2)	0.81	Rosenmai et al. 2014
BPF Average Estrogenic Potency Compared to BPA (mean ± SD)			**1.07 ± 1.20**	
BPF, Anti-Androgenic Activity				
MDA-MB453+DHT (AR)	NA (not reported)	NA (not reported)	0.78	Stroheker et al. 2004
AR-EcoScreen+DHT (AR)	0.03 (Cyproterone acetate)	0.06 (Cyproterone acetate)	0.52	Satoh et al. 2004
NIH353+DHT (AR)	0.21 (Flutamide)	0.58 (Flutamide)	0.36	Kitamura et al. 2005
PALM (AR)	NA (not reported)	NA (not reported)	0.13	Molina-Molina et al. 2013
CHO AR (AR)	NC (R1881)	NC (R1881)	0.94	Rosenmai et al. 2014
BPF Average anti-androgenic Potency Compared to BPA (mean ± SD)			**0.55 ± 0.32**	
BPF, Anti-Estrogenic Activity				
E-Screen+tamoxifin (ERα)	NA (not reported)	NA (not reported)	1.12	Stroheker et al. 2004
BPF, Adiponectin Secretion				
3T3-L1	NA (not reported)	NA (not reported)	0.56	Kidani et al. 2010
BPF, BPA Activity				
yeast bioreporter (BPAR)	2.50E-03 (BPA)	1.00 (BPA)	0.003	Rajasarkka et al. 2014
BPF, AhR Activity				
H4IIE/CALUX (AhR)	NC (TCDD)	NC (TCDD)	1.2	Rosenmai et al. 2014

Abbreviations: bisphenol S, BPS; bisphenol F, BPF; bisphenol A, BPA; ERα, estrogen receptor α; ERβ, estrogen receptor β; mER, membrane estrogen receptor; AR, androgen receptor; BPAR, BPA-targeted receptor; AhR, aryl hydrocarbon receptor; luc, Luciferase; GFP, green fluorescent protein; DHT, dihydrotestosterone; E2, 17-β estradiol; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; NA, not available; NC, not able to calculate from the data presented (e.g. the positive control values were not reported)

[a]Potencies were calculated by dividing the BPS or BPF potency by the BPA potency in the same study.

Figure Legends

Figure 1. Chemical structures of bisphenol A, bisphenol S, and bisphenol F.

Figure 2. Risk of Bias (RoB) ratings for BPS and BPF *in vivo* studies. ++, definitely low risk of bias, +, probably low risk of bias, -, probably high risk of bias, n/a, not applicable.

Figure 1.

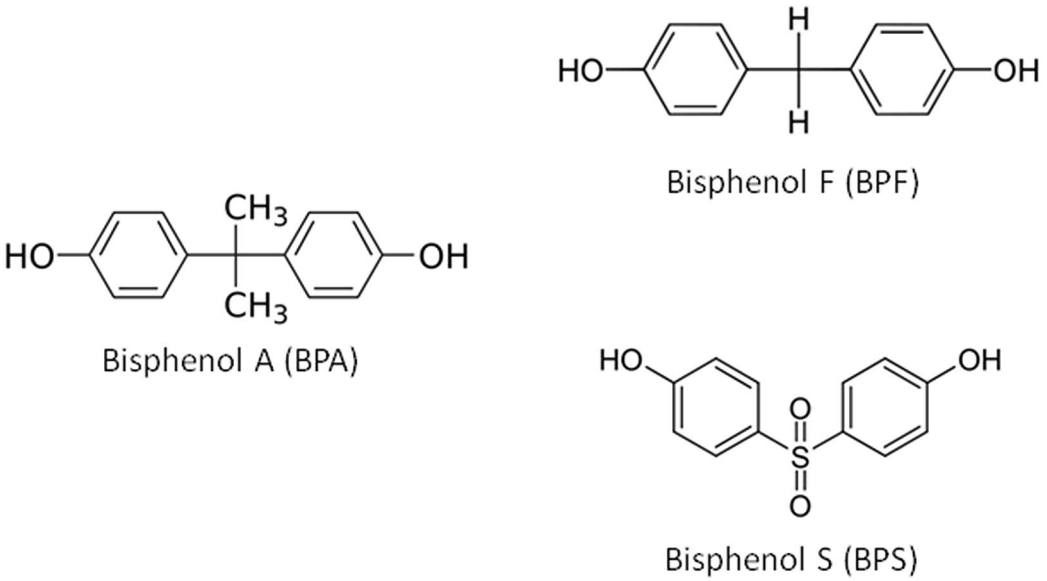
HO
OH
H
H
Bisphenol F (BPF)
HO
OH
CH3
CH3
Bisphenol A (BPA)
HO
OH
O
S
O
Bisphenol S (BPS)

Figure 2.

Source	Was treatment adequately randomized?	Was the allocation of treatment adequately concealed to researchers?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers rule out any impact from an unintended exposure that might bias results?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Did variation from the study protocol compromise the conclusions of the study?	Was the attrition rate low and/or similar across groups?	Were the outcome assessors blinded to the intervention or exposure status of participants?	Were confounding variables assessed consistently across groups using valid and reliable measures?	Can we be confident in the exposure assessment?	Can we be confident in outcome assessment?	Are the potential outcomes pre-specified and reported by the researchers?	Was an appropriate statistical approach used to analyze the data?
Yamasaki et al. 2004	+	+	+	-	++	+	+	-	-	+	++	++	+	-
Stroheker et al. 2003	+	+	+	-	+	+	+	-	-	+	+	++	++	-
Yamasaki et al. 2003	+	+	+	-	++	+	+	-	-	+	++	++	-	-
Higashihara et al. 2007	+	+	+	-	++	+	+	+	-	+	++	++	-	++
Chen et al. 2002	-	+	-	+	-	+	+	n/a	-	n/a	-	++	+	n/a
Ji et al. 2013	-	+	+	-	++	+	+	++	-	-	+	+	++	++
Naderi et al. 2014	+	+	+	-	-	+	+	+	-	+	+	++	++	++