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Food Packaging Forum

Dossier - Bisphenol S

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1 Physical and chemical properties

Bisphenol S (**BPS**; CAS 80-09-1; IUPAC name: 4,4'-sulfonyldiphenol) is an organic compound with two hydroxyphenyl groups connected by a sulfonyl group (1, Figure 1). It has the chemical formula $C_{12}H_{10}O_4S$. BPS is slightly soluble in benzene and dimethyl sulfoxide, soluble in ethanol and ether, but not in water [1]. Its calculated octanol/water partition coefficient (log K_{OW}) is 1.65, the experimentally determined log K_{OW} is 1.2 [2].

2 Production and use

BPS is the reaction product of two phenol molecules with one molecule of sulfuric acid. 2,4'-sulfonyldiphenol is often formed as side product [1]. BPS or its derivatives are used in the production of polyethersulfones (**4**), polysulfones (**5**) and epoxy resins (**6**) (Figure 1), water-soluble and thermosetting resins, heat-sensitive developers, photographic chemicals, polyphthalate carbonates, polymer modifiers and brominated flame retardants (as published on the homepage of the BPS manufacturer Konishi Chemical [3]). BPS continuously finds application in synthetic polymers such as poly(ethylene terephthalate) [5], poly(butylene terephthalate) [6], polyurethanes [7] and epoxy resins [8].

In 2000, the Scientific Committee on Food (SCF) stated that BPS is used as comonomer for kitchen utensils, mainly for repeated use [9]. Polyethersulfone is one of the materials replacing bisphenol A (BPA)-based polycarbonate in baby bottles [10]. BPS also substituted BPA in many thermal papers by now [11]. It was found in high concentrations in receipts (up to 22 mg/g) and also detected in recycled food carton and food packaging paper [11] and in the lining of cans [12].

3 Market data

For the year 2012, the U.S. Environmental Protection Agency (EPA) listed 8 manufacturers and/or importers of BPS registering a total volume between 454 and 4540 tons per year [13]. The European Chemicals Agency (ECHA) published a tonnage band for BPS of 1000 to 10000 tons per year. European registrants and suppliers were BASF (D), Brunschwig Chemie (NL), Lanxess (D), NetSun (NL), SCAS Europe (BEL), and Solvay Specialty Polymers (I) [14].

4 Current regulations

4.1 European Union

BPS is an authorized food contact material (FCM) according to Regulation EU 10/2011 and it is approved to be used as monomer for the production of plastics [15]. BPS has a Specific Migration Limit (SML) of 0.05 mg/kg food, which is 12 times lower than that of BPA [15]. In 2000, the SCF reported that no ADI or TDI could be established for BPS based on the toxicological data [9]. The SML was assigned on the basis of BPS' low migration rates assuming that the available toxicological data would result in a TDI leading to a higher SML. Thus, the SCF concluded that the maximum likely intakes arising from the uses of the additive are safe.

BPS was not listed in Annex I of a report published by EFSA's Scientific Cooperation Working Group (ESCO WG), which compiles non-plastic FCMs collected from EU member states and industry [16]. According to this list, no national regulations exist regarding the occurrence of BPS in non-plastic FCMs.

4.2 United States

In the U.S., BPS is listed as indirect food additive to be used as monomer in the production of polyethersulfone resins. Articles (partially) composed of polyethersulfone resins shall be intended for repeated use. More specific details regarding the composition and characteristics of polyethersulfone polymers, the migration of certain monomers and chemicals into food simulants and the manufacturing process were regulated in Title 21 of the Code of Federal Regulations (Sec. 177.2440). A specific migration limit for BPS was not set in this regulation.

The Toxic Substances Control Act (TSCA) requires manufacturers of BPS to report preliminary assessment information concerned with production, exposure, and use to EPA (40 C.F.R. §712.30) [17]. BPS is also included on the TSCA list that requires manufacturers to submit unpublished health and safety studies to EPA (40 C.F.R. §716.120)[18].

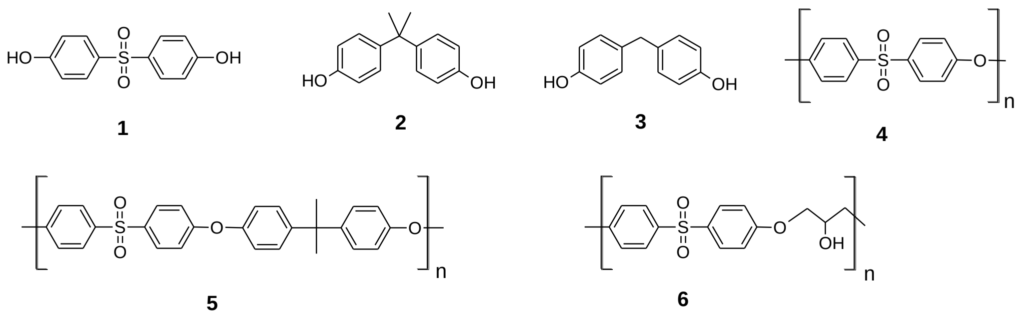

Figure 1: Chemical structures of bisphenol S (BPS) **1**, bisphenol A (BPA) **2**, bisphenol F (BPF) **3**, polyethersulfone **4**, polysulfone **5** and BPS-based epoxy resin **6**.

5 Toxicity of BPS

5.1 General toxicity

Investigations on the acute oral toxicity of BPS resulted in LD_{50} values in the range of several grams per kg body weight. This data was summarized on ECHA`s website [14] and in a draft report published by the EPA [19]. In Europe, the human toxicity and ecotoxicity of BPS was not classified yet according to the Dangerous Substances Directive 67/548/EEC or the CLP Regulation (EC) No. 1272/2008.

5.2 Genotoxicity

BPS had no mutagenic properties when it was tested *in vitro* with Ames *Salmonella typhimuricum*, *E. coli* and mouse lymphoma assays. BPS did not induce chromosomal aberrations *in vivo* and only one *in vitro* test gave ambiguous hints for genotoxicity according to the ECHA database [14]. In contrary, one recent, peer-reviewed study by Lee et al. showed evidence of genotoxicity caused by BPS in immunofluorescence and chromosomal aberration tests [20].

5.3 Endocrine disrupting properties

In vitro studies

In the beginning of this century Hashimoto and colleagues published first results on estrogenic activity of BPS in the E-screen assay [21, 22]. Low estrogenic activity was also confirmed in a yeast two-hybrid system [23]. The receptor binding affinity of BPS to the human estrogen receptor was published to be 0.0055% of E2 [24]. In 2004 and 2012, two further independent studies using different in vitro assays demonstrated comparable estrogenic potencies for BPA and BPS, which were both far lower than the binding affinity of E2 [25, 26]. In 2013, several *in vitro* studies were published indicating an endocrine disrupting potential of BPS: Four different endocrine receptors were targeted in the publication by Molina-Molina et al. including two human estrogen receptors (ER), the androgen receptor (AR), and the pregnane X receptor (PXR; a nuclear receptor that functions as a regulator of xenobiotic metabolism) [27]. The bioassay showed that BPS was an activator of both ERs, a weak antagonist of AR, but it did not interfere with PXR. These tests were performed at micromolar concentrations of BPS, which are unlikely to be found in food. In contrast, Viñas and Watson published a detailed paper on endocrine disrupting effects of BPS at femto- to picomolar concentrations [28]. Using rat pituitary cells, BPS interrupted membrane-initiated cell signaling, which is usually induced by the physiologic estrogen E2. The consequences were altered cell proliferation, cell death and prolactin release. The same researchers also investigated mixture effects of xenoestrogens at environmentally relevant concentrations using similar assays [29]. In combination with BPA and nonylphenol, BPS changed the endocrine responses differently and more dramatically. Furthermore, the mixtures also interfered with endogenous estrogen E2 and altered its effects.

In vivo studies

In 2004, Yamasaki and colleagues showed that three daily BPS doses of 20 and 500 mg/kg body weight/day significantly increased the uterus size of rats [24]. An *in vivo* study focusing on endocrine effects of BPS in zebrafish was published recently [30]. In adult zebrafish BPS caused reproductive dysfunction, altered plasma sex hormone levels and gene transcription in the hypothalamic-pituitary-gonad axis at concentrations $\geq$0.5 µg/L. When not only the parent fish, but also the eggs were continuously exposed to BPS, even less embryos hatched and the rate of malformation increased. The authors request further studies confirming the effects of BPS on sex hormone concentrations and elucidating the underlying mechanisms.

5.4 Reproductive and developmental toxicity

One study with limited documentation on the reproductive and developmental toxicity of BPS was cited on the ECHA website. BPS was judged to have moderate reproductive and developmental toxicity with No Observed Adverse Effect Levels (NOAELs) of 10 and 60 mg/kg body weight/day for parental and reproductive toxicity, respectively.

5.5 Repeated dose studies

ECHA included three repeated dose studies for BPS in their dossier [14]. A 13-days rat study from 1973 with limited documentation resulted in a NOAEL of 97 mg/kg body weight and day when nephrotoxicity was measured as endpoint. A NOAEL of 40 mg/kg body weight/day was determined for BPS from a 28-days subacute toxicity study with rats. A variety of treatment-related effects were seen at 200 and 1000 mg/kg body weight/day (decreased body weight gain, proteinuria, increased kidney weight, hyperplasia and necrosis in cecal mucosal epithelium). The results of the third study are not published yet in the database. Complementary, the EPA included two more repeated dose studies in their draft evaluation of printing ink alternatives and came to the conclusion that BPS has a high hazard potential [19]. Appleton paper, a manufacturer of thermal papers, suggested in a commenting letter to assign a moderate hazard potential based on the underlying studies [31].

6 Migration and exposure

Simoneau and colleagues investigated the migration of BPS and some of its derivatives from 30 different polyethersulfone (**4**) baby bottles [10]. No detectable amounts of BPS were found in any of the migration tests using 50% ethanol as food simulant (level of detection (LOD): 100 ng/kg; level of quantification (LOQ): 300 ng/kg). In a study by Gallart-Ayala et al., no migration of BPS from soft drinks purchased in Spanish supermarkets was detected (LOD: 5-25 ng/L; LOQ: 15-84 ng/L) [32]. In 2010, another Spanish study investigated the migration of bisphenols from epoxycoated cans into different foods [12]. BPS concentrations up to 170 and 35 ng/mL were found in

Table 1. Analyses of food samples from China and the U.S. regarding the bisphenol (BP) detection frequencies, mean concentrations and contributions to the total bisphenol concentration (ΣBP).

	289 food samples from China [2]				267 food samples from the U.S. [4]			
	BPS	BPA	BPF	ΣBP	BPS	BPA	BPF	ΣBP
Detection frequency (%)	22.5	60.9	19.4	77.5	20.9	56.9	10.1	74.5
Mean conc. (ng/g)	0.29	4.94	2.5	9.35	0.13	3.0	0.93	4.38
Contribution to ΣBP (%)	7.7	64	10	100	<10	42	17	100

the supernatants and solid food, respectively. These values partially exceeded the SML of 0.05 mg/kg food that was approved in 2011 by the European Commission [15]. BPS was also detected in more than 50% of the tested food cartons at concentrations up to 143 ng/g [11]. The concentrations and detection frequency of BPS in food contact paper were lower (detection rate: 8.3%, highest concentration: 12 ng/g).

In 2013, Liao and Kannan published studies analyzing the bisphenol contamination of food samples collected in China and the U.S. in the years 2010 and 2011. The analysis of 289 food samples from China showed that BPS was detected in 22.5% of the investigated samples with mean concentrations of 0.29 ng/g (Table 1) [2]. BPS contributed to 7.7% of the total exposure to bisphenols. Especially meat and meat products, fish, seafood, vegetables, cookies, snacks and condiments contained relatively high fractions of BPS. The analysis of 267 food samples collected in the U.S. showed that BPA and bisphenol F (BPF, **3**) accounted for 42 and 17%, respectively, of the total bisphenol concentration, whereas the contribution of BPS was less than 10% (Table 1) [4]. BPS was detected in 20.9% of all samples with a mean concentration of 0.13 ng/g. Also in the U.S. the highest BPS concentrations were measured in meat and meat products. When comparing the packaging material, canned foods had the highest mean concentration of bisphenols, whereas food packed in glass was least contaminated [2, 4]. Although the concentrations found in food in all studies cited in this paragraph do not reach the levels measured for BPA, these results provide clear evidence for the application of BPS in FCMs, e.g. in the coating of cans.

7 Biomonitoring

A first study on the occurrence of BPS in human urine from the U.S. and several Asian countries was published recently [33]. 42% of the Korean samples contained BPS, but it was ubiquitous in all samples from Japan and Vietnam wit 100% detection rates. The highest BPS concentrations were found in urine from Japan, followed by the U.S. and China. Samples from Vietnam, Kuwait, India, Malaysia and Korea contained lower BPS concentrations. Estimated daily intakes (EDIs) were calculated based on a simple pharmacokinetic approach assuming similar pharmacokinetics for BPS and BPA. According to this model, EDIs of BPS (mean values) were estimated to be 3.47, 1.48 and 0.707 µg/person/day for Japan, the U.S. and China, respectively. These data suggest widespread use of BPS as replacement for BPA in various applications such as FCMs and thermal paper receipts.

EDIs were also calculated based on bisphenol concentrations measured in food samples combined with estimated consumption patterns [2, 4]. According to this model, EDIs of BPS were predicted to be 9.55 and 1.31 ng/kg body weight/day for Chinese and U.S. American adults, respectively. Although the mean concentrations and detection frequencies for BPS did not differ very much in both studies (Table 1), the underlying exposure estimates for the Chinese and U.S. American populations are probably the reason for these different EDIs and might especially underestimate the U.S. American exposure.

Several bisphenol analogues were measured in sediment samples from industrialized areas in the U.S., Japan and Korea [34]. The highest BPS concentrations were found in Korea and reached almost 2 mg/g dry weight. BPA and BPF represented more than 90% of the total bisphenol concentrations in all sediments, but BPS concentrations increased in the sediment cores from Japan after 2001 indicating the replacement of other bisphenols by BPS.

It would be highly interesting to continue such exposure and biomonitoring studies in the coming years, because the levels of BPS might further increase due to the replacement of BPA with BPS in epoxy coatings, reusable plastics and thermal paper.

8 Environmental degradation and metabolism

BPS was not degraded by several bacterial strains that were known to metabolize other bisphenols under aerobic conditions [35-37]. In 2013, two independent research groups described the aerobic degradation of BPS by bacterial strains [38] and by a hydroponic system using a combination of reed and two bacterial strains [39], respectively. BPS was also metabolized under anaerobic conditions using pond sediment [37] and photocatalytically degraded under UV irradiation [40]. These results indicate a lower degradability of BPS than BPA.

To our knowledge, no data were published on the pharmacokinetics of BPS in test animals or humans.

Abbreviations

AR	Androgen Receptor
BP	Bisphenol
BPA	Bisphenol A
BPS	Bisphenol S
BPF	Bisphenol F
ECHA	European Chemicals Agency
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
ER	Estrogen Receptor
ESCO WG	EFSA Scientific Cooperation Working Group
E2	17β-Estradiol
FCM	Food Contact Material
LD_{50}	Lethal Dose, 50%
LOD	Level of Detection
LOQ	Level of Quantification
NOAEL	No Observed Adverse Effect Level
PXR	Pregnane X Receptor
SCF	Scientific Committee on Food
SML	Specific Migration Limit
TSCA	Toxic Substances Control Act

References

1. Ogata E, Oi F, Yanase N, et al. 2008. Process for producing high-purity 4,4'-dihydroxydiphenyl sulfone. US Patent. 7,456,321 B2.
2. Liao C, and Kannan K. 2013. A survey of bisphenol A and other bisphenol analogues in foodstuffs from nine cities in China. Food Addit Contam A.
3. Konishi Chemical Ind Co., LTD. 2010. Products - Bisphenol S. [http://www.konishi-chem.co.jp/product_e/biss.html]
4. Liao C, and Kannan K. 2013. Concentrations and profiles of bisphenol A and other bisphenol analogues in foodstuffs from the United States and their implications for human exposure. J Agric Food Chem. 61:4655-62.
5. Lotti N, Colonna M, Fiorini M, et al. 2013. Poly(ethylene terephthalate), modified with bisphenol S units, with increased glass transition temperature. J Appl Polym Sci. 128:416-23.
6. Lotti N, Colonna M, Fiorini M, et al. 2011. Poly(butylene terephthalate) modified with ethoxylated bisphenol S with increased glass transition temperature and improved thermal stability. Polymer. 52:904-11.
7. Liaw DJ, Huang CC, and Liaw BY. 1998. Synthesis and properties of polyurethanes based on bisphenol-S derivatives. Polymer. 39:3529-35.
8. Gao JG, and Li YF. 2000. Curing kinetics and thermal property characterization of a bisphenol-S epoxy resin and DDS system. Polym Int. 49:1590-5.
9. SCF. 2000. Opinion of the Scientific Committee on Food on the 10th additional list of monomers and additives for food contact materials. [http://ec.europa.eu/food/fs/sc/scf/out62_en.pdf]
10. Simoneau C, Valzacchi S, Morkunas V, et al. 2011. Comparison of migration from polyethersulphone and polycarbonate baby bottles. Food Addit Contam A. 28:1763-8.
11. Liao C, Liu F, and Kannan K. 2012. Bisphenol S, a new bisphenol analogue, in paper products and currency bills and its association with bisphenol a residues. Environ Sci Technol. 46:6515-22.
12. Viñas R, Campillo N, Martínez-Castillo N, et al. 2010. Comparison of two derivatization-based methods for solid-phase microextraction-gas chromatography-mass spectrometric determination of bisphenol A, bisphenol S and biphenol migrated from food cans. Anal Bioanal Chem. 397:115-25.
13. U.S. EPA. 2013. Chemical Data Access Tool (CDAT). [http://java.epa.gov/oppt_chemical_search/]
14. ECHA. Accession date: January 2014. Bisphenol S Registration data. [http://apps.echa.europa.eu/registered/data/dossiers/DISS-97d7311b-f959-040b-e044-00144f67d031/DISS-97d7311b-f959-040b-e044-00144f67d031_DISS-97d7311b-f959-040b-e044-00144f67d031.html]
15. European Commission. 2011. Commission regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Official Journal of the European Union.
16. EFSA. 2012. Report of ESCO WG on non-plastic Food Contact Materials. [http://www.efsa.europa.eu/en/supporting/doc/139e.pdf]
17. Protection of Environment. 40 C.F.R. §712.30 (1970). [http://www.ecfr.gov/cgi-bin/searchECFR?ob=r&idno=40&q1=712.30&rgn1=Section&op2=and&q2=&rgn2=Section&op3=and&q3=&rgn3=Section&SID=a0bd3d53ccb90cd3ce9aef1dbe334636]
18. Protection of Environment. 40 C.F.R. §716.120 (1970). [http://www.ecfr.gov/cgi-bin/searchECFR?ob=r&idno=40&q1=716.120&rgn1=Section&op2=and&q2=&rgn2=Section&op3=and&q3=&rgn3=Section&SID=a0bd3d53ccb90cd3ce9aef1dbe334636]
19. U.S. EPA. 2012. Bisphenol A alternatives in thermal paper - Draft for public comments. [http://www.epa.gov/dfe/pubs/projects/bpa/aa-for-bpa-full-version.pdf]
20. Lee S, Liu X, Takeda S, et al. 2013. Genotoxic potentials and related mechanisms of bisphenol A and other bisphenol compounds: a comparison study employing chicken DT40 cells. Chemosphere. 93:434-40.
21. Hashimoto Y, Moriguchi Y, Oshima H, et al. 2001. Measurement of estrogenic activity of chemicals for the development of new dental polymers. Toxicol In Vitro. 15:421-5.
22. Hashimoto Y, and Nakamura M. 2000. Estrogenic activity of dental materials and bisphenol-A related chemicals *in vitro*. Dent Mater J. 19:245-62.
23. Chen MY, Ike M, and Fujita M. 2002. Acute toxicity, mutagenicity, and estrogenicity of bisphenol-A and other bisphenols. Environ Toxicol. 17:80-6.
24. Yamasaki K, Noda S, Imatanaka N, et al. 2004. Comparative study of the uterotrophic potency of 14 chemicals in a uterotrophic assay and their receptor-binding affinity. Toxicol Lett. 146:111-20.
25. Grignard E, Lapenna S, and Bremer S. 2012. Weak estrogenic transcriptional activities of Bisphenol A and Bisphenol S. Toxicol In Vitro. 26:727-31.
26. Kuruto-Niwa R, Nozawa R, Miyakoshi T, et al. 2005. Estrogenic activity of alkylphenols, bisphenol S, and their chlorinated derivatives using a GFP expression system. Environ Toxicol Pharmacol. 19:121-30.
27. Molina-Molina JM, Amaya E, Grimaldi M, et al. 2013. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol Appl Pharmacol. 272:127-36.
28. Viñas R, and Watson CS. 2013. Bisphenol S disrupts estradiol-induced nongenomic signaling in a rat pituitary cell line: effects on cell functions. Environ Health Perspect. 121:352-8.
29. Viñas R, and Watson CS. 2013. Mixtures of xenoestrogens disrupt estradiol-induced non-genomic signaling and downstream functions in pituitary cells. Environ Health. 26:1-11.
30. Ji K, Hong S, Kho Y, et al. 2013. Effects of bisphenol S exposure on endocrine functions and reproduction of zebrafish. Environ Sci Technol. 47:8793-800.
31. U.S. EPA. 2012. Public comments - Bisphenol A alternatives in thermal paper, draft report. [http://www.epa.gov/dfe/pubs/projects/bpa/bpa-report-public-comments10-18-12.pdf]
32. Gallart-Ayala H, Moyano E, and Galceran MT. 2011. Analysis of bisphenols in soft drinks by on-line solid phase extraction fast liquid chromatography-tandem mass spectrometry. Anal Chim Acta. 683:227-33.
33. Liao C, Liu F, Alomirah H, et al. 2012. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. Environ Sci Technol. 46:6860-6.
34. Liao C, Liu F, Moon HB, et al. 2012. Bisphenol analogues in sediments from industrialized areas in the United States, Japan, and Korea: spatial and temporal distributions. Environ Sci Technol. 46:11558-65.
35. Danzl E, Sei K, Soda S, et al. 2009. Biodegradation of bisphenol A, bisphenol F and bisphenol S in seawater. Int J Environ Res Public Health. 6:1472-84.
36. Sakai K, Yamanaka H, Moriyoshi K, et al. 2007. Biodegradation of bisphenol A and related compounds by *Sphingomonas* sp. strain BP-7 isolated from seawater. Biosci Biotechnol Biochem. 71:51-7.
37. Ike M, Chen MY, Danzl E, et al. 2006. Biodegradation of a variety of bisphenols under aerobic and anaerobic conditions. Water Sci Technol. 53:153-9.
38. Ogata Y, Goda S, Toyama T, et al. 2012. The 4-tert-butylphenol-utilizing bacterium *Sphingobium fuliginis* OMI can degrade bisphenols via phenolic ring hydroxylation and meta-cleavage pathway. Environ Sci Technol. 47:1017-23.
39. Toyama T, Ojima T, Tanaka Y, et al. 2013. Sustainable biodegradation of phenolic endocrine-disrupting chemicals by *Phragmites australis*-rhizosphere bacteria association. Water Sci Technol. 68:522-9.
40. Cao GP, He RL, Cai ZW, et al. 2013. Photolysis of bisphenol S in aqueous solutions and the effects of different surfactants. React Kinet Mech Cat. 109:259-71.