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Bisphenol S instead of bisphenol A: a story of reproductive disruption by regretable substitution – a review

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ABSTRACT: A range of substances that are released into the environment, foodstuffs and drinking water as a result of human activity were originally considered relatively harmless, and it was only later that their adverse effects were discovered. In general the use of such substances is currently restricted, and they are often replaced by other substances. This applies also in the case of a range of endocrine disruptors. These substances have the capacity to disturb the balance of physiological functions of the organism on the level of hormonal regulation, and their pleiotropic spectrum of effects is very difficult to predict. Endocrine disruptors include the currently intensively studied bisphenol A (BPA), a prevalent environmental pollutant and contaminant of both water and foodstuffs. BPA has a significantly negative impact on human health, particularly on the regulation mechanisms of reproduction, and influences fertility. The ever increasingly stringent restriction of the industrial production of BPA is leading to its replacement with analogues, primarily with bisphenol S (BPS), which is not subject to these restrictions and whose impacts on the regulation of reproduction have not yet been exhaustively studied. However, the limited number of studies at disposal indicates that BPS may be at least as harmful as BPA. There is therefore a potential danger that the replacement of BPA with BPS will become one of the cases of regrettable substitution, in which the newly used substances manifest similar or even worse negative effects than the substances which they have replaced. The objective of this review is to draw attention to ill-advised replacements of endocrine disruptors with substances whose effects are not yet tested, and which may represent the same risks for the environment, for the reproduction of males and females, and for human health as have been demonstrated in the case of the originally used substances.

Keywords: human health; environment; endocrine disruptor; reproduction; oocyte; sperm

INTRODUCTION

Many substances have been introduced into use with great hopes, only for it to be demonstrated earlier or later that they are harmful to the environment and/or human health. Notorious cases include the mass use of DDT as an insecticide (http://apps.who.int/iris/handle/10665/40018), thalidomide

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as a drug for pregnant women (McBride 1961), or more recently neonicotinoid insecticides used for the protection of fields against seed-destroying insects (Blacquiere et al. 2012). Substances whose negative effects on the environment or human health were detected only after a long period of use also include endocrine disruptors (Damstra et al. 2002).

The detection of the negative effects of abundantly used substances leads to a dramatic restriction of their use and their substitution with other substances. In a range of cases this brings about a genuine improvement. For example, chromated copper arsenate (CCA) used for wood preservation was demonstrated to be a substance with carcinogenic effects, and as a result was replaced with alkaline copper quaternary (ACQ). ACQ does not contain arsenic or chrome, and although it is just as effective as CCA against wood destroying arthropods, its impacts on the environment and human health are fundamentally less serious (Landrigan et al. 2004).

On the other hand, we have been witnesses to substitutions of harmful substances which have later been shown to be highly problematic. For example, 2,3-butanedione, which occurs naturally in butter, has been produced synthetically and added to foods in order to impart a buttery flavour. When it was demonstrated that 2,3-butanedione damaged lung tissue, it was replaced by 2,3-pentanedione, which however was subsequently proven to have similar negative effects on lung tissue as 2,3-butanedione (Hubbs et al. 2012). There are far more similar examples of "regrettable substitutions" (Fahrenkamp-Uppenbrink 2015; Zimmerman and Anastas 2015). In these cases, negative impacts on reproduction are often subsequently detected. For example, in the case of pyrethroids, which replaced older insecticide agents such as organocholorines, organophosphates or carbamates, and which were considered harmless to mammals, negative impacts were demonstrated on the maturation of mammal oocytes (Petr et al. 2013).

From the perspective of reproductive risks, the substitution of bisphenol A (BPA), a widely used component of plastics and many other materials, with its analogue bisphenol S (BPS) appears to be potentially problematic. BPA has been proven to be a strong endocrine disruptor, and its use has been restricted. Many products are sold with a "BPA-free" guarantee. Because BPA is substituted in a range of cases by BPS, these products are not however "bisphenol-free" (Glausiusz 2014), and their use may be linked to significant reproductive risks. The aim of this review is to point to the replacement of BPA by BPS as a "regrettable substitution".

Endocrine disruptors

A less harmful substitute is currently searched for a number of substances that had previously been considered safe from a toxicological perspective and finally appeared to exert various negative effects on health. This category of compounds includes substances referred to summarily as endocrine disruptors (Clayton 2011). According to the US Environmental Protection Agency, endocrine disrupting chemicals (EDCs) are defined as "exogenous agent(s) that interfere(s) in synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes" (Diamanti-Kandarakis et al. 2009).

EDCs manifest a range of particular properties. Their hormone-like effects may be suppressed or may fade away entirely in the case that the concentration of EDCs is higher than the physiological level of their hormonal counterpart. This ability of agents to attain paradoxically stronger effects in low doses than in high ones (vom Saal and Welshons 2005) is termed the "low dose effect" (Grasselli et al. 2010; Vandenberg et al. 2012). The low dose hypothesis posits that exogenous chemicals that interact with hormone action can do so in a quite specific manner. In accordance with that, mentioned traditional toxicological endpoints are not capable to preclude adverse outcome, as EDCs act with dose responses, that are nonlinear and potentially non-monotonic (Vandenberg et al. 2012). In the case the relationship between dose and response is nonlinear, any prediction is even more complex. Therefore, the low dose definition was extended by the effects of non monotonic response curves. The mechanisms responsible for the non-linear effects are described in detail (Vandenberg et al. 2012), usually in connection with an interaction between a ligand (hormone or EDC) and a hormone receptor (Vandenberg 2014).

Non-linear dose-response patterns are commonly observed with endogenous and synthetic agonists (e.g. numerous drugs, hormones, peptides) that activate and inhibit receptor-mediated signal pathways that affect various biological functions

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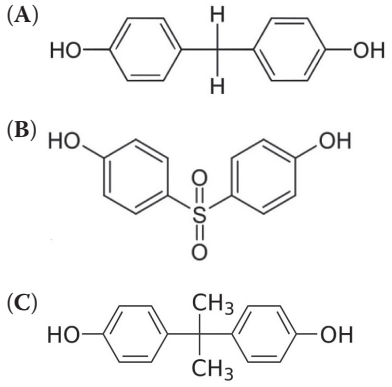

Figure 1. Chemical structure of bisphenol A (**A**), bisphenol S (**B**), bisphenol F (**C**)

(Calabrese and Baldwin 2001; Calabrese 2005). However, EDCs can also produce non monotonic dose responses in which the slope of the curve changes sign over the course of the dose-response (www.who.int/ceh/publications/endocrine/en/index.html) and low dose effects are described for the majority of EDCs (Birnbaum 2012; Vandenberg et al. 2012, 2013; Zoeller et al. 2012; Bergman et al. 2013).

The concept of endocrine-disrupting chemicals was proposed after these compounds had been observed to affect various reproductive functions in wildlife and humans (Colborn et al. 1993). The influence of several EDCs was demonstrated on the course of development of male gametes, sperm (Li et al. 2011; Knez et al. 2014) and female gametes, oocytes, as well as embryonic development of males and females (Mok-Lin et al. 2010; Xiao et al. 2011). Moreover, the effect of EDCs on the reproduction of adult individuals, including transgenerational inheritance, has been described (Susiarjo et al. 2015; Ziv-Gal et al. 2015). Therefore, reproductive functions represent crucial targets of the EDCs' negative effects. Recently intensively studied EDCs, interfering with the regulation of physiological reproductive processes, include bisphenols, a family of chemical compounds with two hydroxyphenyl functional groups (Figure 1).

Bisphenol A

An example of a widely used substance, in which endocrine-disrupting properties were detected only later, is bisphenol A (BPA, 4,4'-(propane-2,2-diyl)diphenol) (Vandenberg et al. 2009). BPA was first synthesized in 1891, and as early as in 1936 it was demonstrated that it imitates the activity of the hormone estradiol (Dodds and Lawson 1936). Despite a very strong estrogen activity, BPA has been commercially used since 1957, and despite the fact that its endocrine-disrupting activity was discovered (Krishnan et al. 1993), BPA has become a high production volume chemical (Wang et al. 2012). Worldwide annual production, which in the case of BPA reached 4.6 million t in 2012, is constantly increasing. Its production was estimated at 5.4 million t in 2015 (Merchant Research & Consulting, http://mcgroup.co.uk/researches/bisphenol-a-bpa).

BPA is present especially in polycarbonate plastics, epoxide resins, and several paper products (Ehrlich et al. 2014), and as a result it is used in a variety of commonly used consumer products such as thermal recipes, cosmetics, dental materials, medicinal tubes, utensils, toys, baby feeding bottles and dummies, etc. Heat, UV radiation, alkaline treatment or intensive washing causes a release of BPA monomer. It is estimated that the worldwide release of BPA into the environment is almost half million kg per year (Mileva et al. 2014).

BPA is released into the environment either directly from chemical, plastic coating, and staining manufacturers, from paper or material recycling companies, foundries which use BPA in casting sand, or indirectly leaching from plastic, paper, and waste in landfills (Yang et al. 2015). BPA passes into foodstuffs or water directly from the lining of food and beverage cans, where it is used as an ingredient in the plastic used to protect the food from direct contact with the can (Goodson et al. 2002; Vandenberg et al. 2009). The main path of human exposure is the consumption of such contaminated foodstuffs, drinking water or via dermal contact with thermal paper and cosmetics or inhalation (Miyamoto and Kotake 2005; Huang et al. 2012).

It is therefore not surprising that a range of studies have now demonstrated the presence of BPA in human tissue. Levels of BPA have been tested in various populations worldwide, and the presence of BPA was demonstrated in 92.6% of Americans (Wetherill et al. 2007) and 90% of Canadians (Bushnik et al. 2010). Levels of BPA have been demonstrated in various biological matrices, most frequently in urine (Casas et al. 2013; Salgueiro-Gonzalez et al. 2015), but also in blood serum. Within the human reproductive system, levels of BPA have been confirmed for example in testicle tissue, seminal plasma (Manfo et al. 2014), in ovarian follicular fluid (Ikezuki et al. 2002), mother's

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Table 1. Bisphenol A (BPA) levels in human fluids

Sample	Level of BPA	References
Blood (ng/ml)	12.4–14.4	Bushnik et al. (2010)
Maternal blood (ng/ml)	0.63–14.36	Yamada et al. (2002)
Fetal blood (ng/ml)	0.2–9.2	Schonfelder et al. (2002)
Urine (ng/ml)	0.02–21.0	Liao et al. (2012c)
Saliva (ng/ml)	0.3	Joskow et al. (2006)
Follicular fluid (ng/ml)	2.4 ± 0.8	Ikezuki et al. (2002)
Amniotic fluid (ng/ml)	1.1–8.3	Ikezuki et al. (2002)
Placental tissue (ng/g)	1.0–104.9	Schonfelder et al. (2002)
Breast milk (ng/ml)	0.5–1.3	Mendonca et al. (2014)
Semen plasma (pg/ml)	66 (fertile men) 132–179 (infertile men)	Vitku et al. (2015)

milk, fetal plasma (Shonfelder et al. 2002), amniotic fluid (Yamada et al. 2002; Edlow et al. 2012), and the placenta (Jimenez-Diaz et al. 2010; Cao et al. 2012) (Table 1). Several studies have demonstrated a direct correlation between exposure of the mother and the BPA level of the fetus (Ikezuki et al. 2002; Kuruto-Niwa et al. 2007). BPA may permeate the placenta and thus influence the development of the fetus (Edlow et al. 2012; Corbel et al. 2014). Newborns may then be further exposed to the effect of BPA during breastfeeding due to the presence of BPA in mother's milk (Mendonca et al. 2014).

The effects of BPA on humans are dependent not only on the dose, but also on the window of exposure. Exposure to BPA in the prenatal and neonatal period probably affects the human organism in the most receptive period (Fernandez et al. 2014).

Mechanism of BPA action

A typical feature of endocrine disruptors is their wide spectrum of outcomes (Figure 2). Combination of their action in various target systems in the organism is one of causes of their non-linear effects. In this respect, BPA acts as a typical endocrine disruptor with multi-level impacts (Khan and Ahmed 2015). Nongenomic effects of BPA have been described, thus influencing cellular signalling

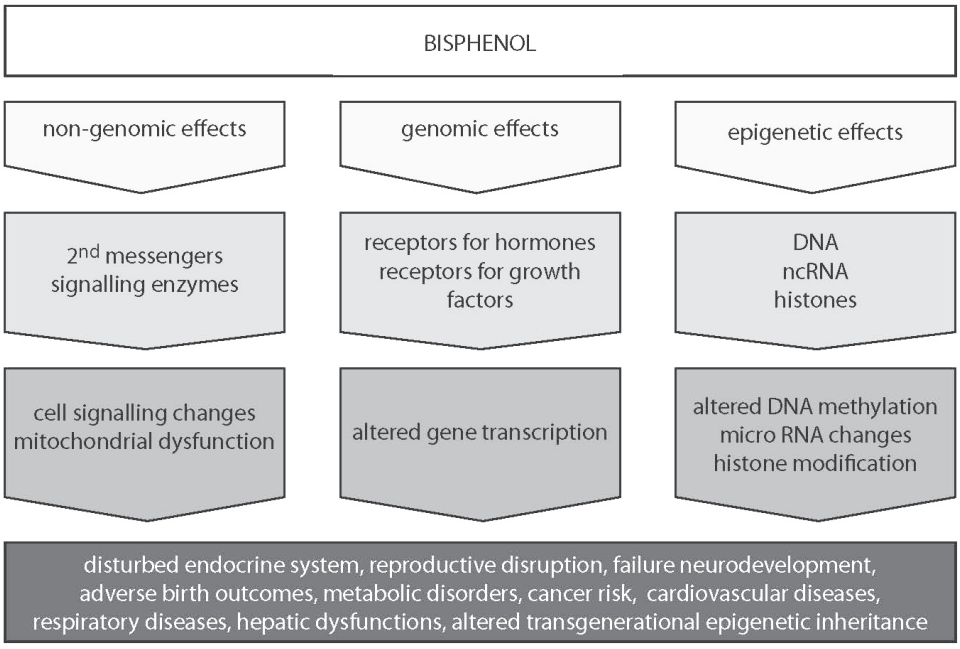

Figure 2. Possible mechanisms of bisphenol action and its potential impact on human health

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(Nakagawa and Tayama 2000), as well as genomic, which affect transcription regulation (Trapphoff et al. 2013), and also epigenetic, responsible for the methylation and acetylation of DNA and core histones (Bromer et al. 2010). It is precisely pronounced estrogen activity of BPA *in vitro* (vom Saal et al. 2007; Wetherill et al. 2007) and *in vivo* that contributes to its immense potential to afflict the hormonal system and act as an endocrine disruptor.

BPA inhibits the activity of natural endogenous estrogens and thus disrupts estrogen nuclear hormone receptor action (Kitamura et al. 2005; Wetherill et al. 2007; Grignard et al. 2012). BPA affects hormonal homeostasis, for example through bonding to the classic nuclear estrogen receptors α, β, γ (ERα, ERβ, ERγ), where it manifests a combination of agonistic and/or antagonistic actions in dependence on the target tissue, cell types, ER subtypes, and differential cofactors recruited by ER-ligand complexes (Kurosawa et al. 2002). BPA also bonds to non-classical membrane ERs and causes activation of the nuclear receptor gamma (Takayanagi et al. 2006; Matsushima et al. 2007).

BPA has been identified as an antagonist of androgen receptors (Kitamura et al. 2005; Wetherill et al. 2007; Vinggaard et al. 2008; Molina-Molina et al. 2013). Its anti-androgenic activity has been documented in several studies, but with changing values of the maximum inhibition concentration (Xu et al. 2005; Bonefeld-Jorgensen et al. 2007). In contrast with other known androgen receptor antagonists, BPA inhibits the effective nuclear translocation of the androgen receptors, and disrupts their function by means of a number of mechanisms (Teng et al. 2013). The endocrine-related BPA action mechanism also involves a reduction of aromatase expression (Zhang et al. 2011; Chen et al. 2014) and a decrease in aromatase activity *in vitro* (Bonefeld-Jorgensen et al. 2007). Within this context, it is of interest that a decline in the synthesis of testosterone and estradiol *in vivo* has been documented following exposure to BPA (Akingbemi et al. 2004).

The epigenetic mechanisms of the effect of BPA include the alteration of certain DNA methylation samples (Dolinoy et al. 2007; Susiarjo et al. 2013). Prenatal exposure to BPA alters the expression of genes coding individual subtypes of ERs in a sex- and brain region-specific manner (Kundakovic et al. 2013) and disrupts the normal development of the placenta (Susiarjo et al. 2013). As a result, it is possible that BPA predetermines the response to steroid hormones in the very early phase of development (Wilson and Sengoku 2013). It has been documented that BPA also disrupts the gene expression of the regulating factors that control the stability and flexibility of epigenetic regulation, and as a result has an adverse influence on the development of functions of the controlling organ of hormonal regulation, the hypothalamus (Warita et al. 2013). The impacts of these changes have transgenerational effects (Manikkam et al. 2013).

Further demonstrated actions of BPA in the organism include the bonding to the glucuronide receptor, suppression of the transcription receptor of the thyroid hormone, reduction of the transport of cholesterol via the mitochondrial membrane, increase of oxidation of fatty acids, stimulation of prolactin release (Machtinger and Orvieto 2014) or an agonistic effect on the human pregnane X receptor (Sui et al. 2012).

BPA and human health

With such a wide spectrum of effects, it is evident that BPA has a negative influence on human health. Frequently discussed themes include the possible association of BPA for example with obesity (Trasande et al. 2012), diabetes (Lang et al. 2008), neurobehavioural disorders (Jasarevic et al. 2011), cancer (Jenkins et al. 2011), hepatic (Peyre et al. 2014) and cardiovascular diseases, hypertension, and disorders of the thyroid gland function (Rochester 2013; Wang et al. 2013).

Especially in the area of reproduction in both animal models and in humans, a wide range of negative influences of BPA have been observed (Kwintkiewicz et al. 2010; Trapphoff et al. 2013; Zhang et al. 2014). BPA has varied and complex mechanisms of action that may interfere with normal reproductive development and functions. In both males and females, BPA interferes with hormonal regulation and influences the hypothalamic–pituitary–gonadal axis on all levels (Navarro et al. 2009; Patisaul et al. 2009; Xi et al. 2011).

Influences of BPA on reproduction of males

As a rule, endocrine-disrupting substances have pronounced impacts on the reproduction of both sexes. Several studies have shown detrimental effects of BPA on spermatogenesis and semen quality in fishes. The number of mature and im-

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mature spermatozoa was decreased and increased, respectively (Sohoni et al. 2001) and also the sperm motility and concentration were reduced (Lahnsteiner et al. 2005). There is a large evidence that BPA can induce sex reversal from male to female in aquatic animals. Changes in sex ratio were observed at zebrafish during embryonic development (Drastichova et al. 2005) and *Xenopus* larvae through metamorphosis (Kloas et al. 1999).

Experimental studies on the effects of BPA on the reproduction of male rodents have revealed an adverse influence on the development of testes (Vrooman et al. 2015) and on the spermatogenesis of adult individuals following prenatal *in utero* or early postnatal exposure. Exposure to BPA during the period of development of the testes is frequently linked to a range of negative effects in adult testes, e.g. decreased levels of testicular testosterone, decreased weights of the epididymis and seminal vesicles, a decrease in daily sperm production per gram testis, and increased weights of the prostate and preputial (Richter et al. 2007). Vrooman et al. (2015), with the help of transplantation of spermatogonia from the testes of mice exposed to the action of BPA into mice which were not exposed, demonstrated permanent damage to spermatogenesis. The influence of the exposure of adult rodents to BPA on the quality of sperm was also studied (Peretz et al. 2014).

Despite the differences in the experimental designs used, certain findings appear repeatedly, especially reduction in the number of sperm, reduction in the motility of sperm, increased amount of apoptotic cells in the seminiferous tubules, changes in the levels of hormones and steroid enzymes, and damage to the DNA of sperm (Peretz et al. 2014).

Contemporary studies confirm that rodents are not relevant for predicting the effect of low BPA concentrations on the endocrine function of human fetal testis (N'Tumba-Byn et al. 2012). In a comparative study by Maamar et al. (2015), the influence of BPA was studied both on rats and on human fetal testes, and it was determined that in both cases BPA had dose-dependent anti-androgenic effects. Nevertheless, the authors urge caution in interpreting the results obtained on rodents and their application in human medicine (Maamar et al. 2015).

Unfortunately, there is only a limited number of studies that have observed the influence of exposure to BPA on the quality of sperm in adult humans. In men exposed to BPA in the workplace and patients in reproduction centres, a higher level of BPA in urine was linked to a lower number, concentration, and motility of sperm (Knez et al. 2014; Lassen et al. 2014). Nevertheless, in a study conducted by Mendiola et al. (2010) on fertile men, the concentration of BPA in urine did not correlate with changes in semen parameters, despite the fact that a significant correlation was observed between the level of BPA in urine and the volume of seminal plasma or markers of free testosterone (Mendiola et al. 2010).

The following cohort study examined the relationship between the concentration of BPA in urine and the level of reproductive hormones and semen in a group of 308 young healthy men. It was determined that the concentration of BPA strictly correlates with higher levels of selected circulating reproductive hormones and reduced motility of sperm. The results indicated that the exposure to BPA on the level of environment has an anti-androgenic and/or anti-estrogenic effect due to the effect of BPA on the level of receptors. The anti-estrogenic effect on the level of the epididymis also explains the determined low mobility of the sperm (Lassen et al. 2014).

Influences of BPA on reproduction of females

BPA markedly influences not only the reproduction of males, but also the reproduction of females. In both *in vitro* and *in vivo* studies, the influence of BPA has been demonstrated on fertility, function of the womb i.e. formation of benign and malignant lesions (Newbold et al. 2009), disruption apoptosis of the uterine epithelium during estrus (Mendoza-Rodriguez et al. 2011), function of ovaries and quality of oocytes (Peretz et al. 2014), and defective folliculogenesis (Santamaria et al. 2016). In females it is precisely the ovaries that are the key organ responsible for reproductive and endocrine functions, and BPA is frequently indicated as an ovarian toxicant. BPA afflicts not only the overall morphology and weight of the ovaries (Suzuki et al. 2002; Santamaria et al. 2016) but also demonstrably reduces the quality of oocytes in both animal and human models (Machtinger and Orvieto 2014).

During the course of the maturation of mouse oocytes *in vitro* following treatment with BPA, changes were documented in the configuration of the meiotic spindle resulting in errors in chromosome segregation and hyperploidy frequencies in mouse

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oocytes (Hunt et al. 2003). Similary, it was reported that BPA exposure altered chromosome and spindle organization which resulted in hyperploidy of mouse oocytes during meiosis (Can et al. 2005) and it was also demonstrated that low BPA doses are related with aberration during meiotic prophase, including increased incidence of recombination (Susiarjo et al. 2007) and failure formation of primordial follicle by inhibiting meiotic progression of oocytes (Zhang et al. 2012). In contrast, Eichenlaub-Ritter and her colleagues found no evidence that low BPA doses increased hyperploidy at meiosis II. On the other hand they observed cell cycle delay and meiotic spindle abnormalities, changes in the distribution of pericentriolar material and chromosome alignment (Eichenlaub-Ritter et al. 2008). Exposure of mice, from mid-gestation to birth, causes synaptic abnormalities in oocytes and an increased amount of recombination between homologous chromosomes. It is also of interest that identical effects have been observed in homozygous mice with an intentionally disrupted gene coding the ERβ. In mouse oocytes, epigenetic changes have also been documented following cultivation of follicles in the presence of BPA, in which a disruption of the configuration of chromosomes took place, as well as disorders of meiosis caused by faulty genomic imprinting and altered posttranslational modification of histones (Trapphoff et al. 2013). Chronic exposure of oocytes was linked to an increased incidence of aberrant metaphases II and prematurely segregated chromatids (Pacchierotti et al. 2008).

Bovine oocytes cultivated in the presence of BPA have also manifested disorders of the meiotic spindle and the chromosomal configuration (Ferris et al. 2015). In Barbary Macaques, negative effects of BPA have been demonstrated in various stages of the oogenesis of developing ovaries. Oocytes in the prophase of meiosis and in fetal ovaries exhibited an increased number of recombination, and an increased number of abnormally formed follicles containing multiple oocytes was recorded in perinatal ovaries (Hunt et al. 2012).

Similary as in the aforementioned studies on rodents, cattle, and primates, an increased number of crossing over and degenerations in oocytes have been determined also in human oocytes cultivated *in vitro* in the presence of BPA (Brieno-Enriquez et al. 2011). In connected studies it has been demonstrated that the exposure of human oocytes to BPA is linked to up-regulation of genes involved in meiotic processes connected to double strand breaks repair progression (Brieno-Enriquez et al. 2012). A non-linear response to BPA doses on the incidence of MII oocytes with aligned chromosomes has also been determined (Machtinger et al. 2013). The changes which have been recorded in the development of oocytes exposed to bisphenol may lead to disorders in the development of embryos, fetal loss or genetic disorders (Rama Raju et al. 2007; Ye et al. 2007; Tomari et al. 2011). The result of maternal exposure to BPA may be the disruption of the entire oogenesis in the developing ovary (Susiarjo et al. 2007).

A number of cohort studies have been focused on groups of persons who undergo treatment for infertility through *in vitro* fertilization (IVF). The measured levels of BPA in these persons were examined in connection with the ovarian response, quality of embryos and implantation. A reduced ovarian response was linked to a reduced success rate of IVF (Mok-Lin et al. 2010). BPA also disrupted embryonal development of fish via delay hatching, yolk reabsorption, and larval growth of trouts (Aluru et al. 2010), moreover lethality in zebrafish larvae increased (Chan and Chan 2012).

There is only a limited number of studies which have observed the effects of BPA on the development and quality of mammalian blastocysts. Failure of embryonic development to mouse blastocyst stage has been demonstrated after exposure of females to BPA (Xiao et al. 2011). Disorder of implantation of mouse blastocysts was also demonstrated by Borman et al. (2015).

In human, Bloom et al. (2011) state a correlation between the concentration of BPA in the urine of men, though not in women, and a decline in the quality of embryos generated by IVF. By contrast, in a study performed by Knez et al. (2014), which confirms changes to the semen quality of men with a determined environmental level of BPA, undisrupted development of embryos into blastocysts is described. As against this finding, in women who have undergone IVF, a correlation has been demonstrated between the concentration of BPA in urine and a change to the formation of blastocysts, though a reduced quality of embryos was not recorded (Ehrlich et al. 2012).

The advent of BPS

The above-stated facts led to the necessity for stringent regulation of the use of BPA, and in a

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range of cases its substitution with another chemical. On the basis of the effects on human health and reproduction demonstrated with the help of standardized toxicological testing procedures, government agencies in the United States (the US Environmental Protection Agency, USEPA), Canada (Health Canada), and Europe (the European Food Safety Authority, EFSA) have established tolerable daily intake levels, ranging from 25 to 50 µg BPA/kg of body weight (BW) per day (Rochester 2013). With regard to the fact that several studies have demonstrated BPA low dose effects (Vandenberg et al. 2012), and that this possibility is unfortunately not taken into account in the approach of "traditional" toxicological studies, in which low doses are not generally subjected to examination (Vandenberg et al. 2012; Rochester 2013), scientists have expressed concerns that the "safe" cut-off set for BPA is too high (vom Saal and Hughes 2005). In 2010 the Canadian government prohibited the import, sale, and advertisement of baby feeding bottles containing BPA. The European Union responded with a prohibition of the manufacture of baby feeding bottles with BPA, which was passed in 2011 (Commission Directive 2011). The Food and Drug Administration (FDA) has indicated BPA as a "chemical of concern", and in July 2012 a blanket prohibition of BPA in baby feeding bottles and sippy cups was recommended (FDA 2011). However, new data and refined methodologies have led EFSA experts to considerably reduce the safe level of BPA from 50 µg/kg of BW/day to 4 µg/kg of BW/day (EFSA 2014).

With regard to these restrictions and societal pressures, manufacturers of plastics are now forced to seek an alternative product which can replace BPA. It is in the interest of chemical concerns that the substitute which replaces BPA is inert or at least far less toxic than BPA. Nevertheless, new chemicals introduced onto the market are frequently untested, and may be equally or more harmful than the originals, which are ultimately termed "regrettable substitutions" (Rochester and Bolden 2015), as has been the case of a number of perfluorinated chemicals (Howard 2014), pesticides (Coggon 2002), and self-extinguishing compounds (Bergman et al. 2012). Manufacturers seeking BPA alternatives have turned primarily to bisphenol S (BPS, 4,4'-sulfonyldiphenol) (see Figure 1), a structural analogue of BPA, to produce "BPA-free" products (Grignard et al. 2012; Barrett 2013). BPS is chemically more stable, worse in terms of biodegradability than BPA, and shows better dermal penetration than BPA (Ike et al. 2006; Danzl et al. 2009; Liao et al. 2012a, b). It is disconcerting that these properties may lead to a longer or higher body burden or bioavailability of BPS versus BPA (Helies-Toussaint et al. 2014). For these reasons, too, at present the replacement of BPA with BPS is considered a "regrettable substitution" (Fahrenkamp-Uppenbrink 2015; Zimmerman and Anastas 2015). With regard to the increase in production of BPS and the indispensability of bisphenols in the production of plastics, it is unfortunately possible to expect the same widespread use of BPS as in the case of BPA (Liao et al. 2012c). Now the presence of BPS can be expected in almost all the consumer goods here in which BPA was initially used (Mathew et al. 2014), for example as a wash fastening agent in clearing products, an electroplanting solvent, and a constituent of phenolic resins (Rochester and Bolden 2015).

One of the major industries that have replaced BPA due its high occurrence (~3–22 g/kg) is that of thermal paper (Mathew et al. 2014). In the USA, Korea, Vietnam, Japan, and China (Liao et al. 2012c), BPS has been detected in several different "BPA free" paper products, including receipts and paper money (Liao et al. 2012a). The presence of BPS has been determined in tinned foodstuffs (Vinas et al. 2010). The occurrence of BPS has also been determined in indoor dust (Liao et al. 2012b), in fluvial water (Ike et al. 2006), surface water, and waste waters (Song et al. 2014) (Table 2).

The main pathway to the human body is dermal, dust ingestion, and dietary exposures (Liao et al. 2012b). Unfortunately, for example thermal paper carries BPS into all recycled paper products, making dermal exposure inevitable. Massive exposure of the population to the effects of environmental BPS has been demonstrated in a number of different countries. Within the range of 0.02–21 ng/ml (0.8–84nM) it has been detected in human urine samples originating from seven Asian countries and the USA (Liao et al. 2012a) in 81% of analyzed samples. In the following study the presence of BPS in urine was demonstrated in residents living near a manufacturing plant in south China in a concentration of 0.029 ng/ml (Yang et al. 2015).

Biological effects of BPS

Although nowhere near as much information is available about BPS as about the endocrine-

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Table 2. Bisphenol S (BPS) levels in the personal care products and environment

Sample	Level of BPS	References
Canned food (ng/g)	8.9–17	Vinas et al. (2010)
Thermal paper (mg/g)	0.0000138–22.0	Liao et al. (2012c)
Tickets (μg/g)	0.183–5.93	Liao et al. (2012c)
Currency bills (μg/g)	0.00–6.26	Liao et al. (2012c)
Other paper product types (μg/g)	0.00–8.38	Liao et al. (2012c)
Indoor dust (μg/g)	0.34	Liao et al. (2012b)
Municipal sawage sludge (ng/g dry weight)	0.17–110.00	Song et al. (2014)
River water (ng/l)	0.29–18.99	Yang et al. (2014)

disrupting effects of BPS, the substitution of BPA with BPS is raising concerns. The limited number of studies available at the present time, dealing with the biological interactions of BPS with the organism, indicate that BPS is also capable of imitating properties of hormones, interacting with ER (Delfosse et al. 2012; Rosenmai et al. 2014; Le Fol et al. 2015), and direct binding to nuclear ERs (Yamasaki et al. 2004) and serum albumins (Mathew et al. 2014) has been confirmed.

Some *in vitro* studies have demonstrated a weaker estrogen activity of BPS than the activity manifested by estradiol (Kuruto-Niwa et al. 2010; Grignard et al. 2012; Molina-Molina et al. 2013; Rochester and Bolden 2015). By contrast, a study conducted by Vinas and Watson (2013a, b) demonstrated the same or higher estrogen effectiveness than estradiol, BPS was capable of stimulating the membrane receptor pathways ordinarily up-regulated by estradiol. After exposure to BPS there are also changes in the expression of aromatase, the key enzyme in the synthesis of estradiol (Kinch et al. 2015).

Like in the case of BPA, the androgenic activity of BPS was confirmed (Kitamura et al. 2005), and subsequently its anti-androgenic activity as well (Molina-Molina et al. 2013). These observations *in vitro* have also been confirmed by *in vivo* studies. Chen et al. (2002) described acute toxicity of BPS in *Daphnia magna* and at the same time also demonstrated estrogen activity of BPS *in vitro*. Yamasaki et al. (2004) documented estrogen activity of BPS *in vivo* in rats with the assistance of postnatal exposure to BPS, which in both low and high doses induced the growth of the womb (Owens and Ashby 2002). An *in vivo* study on the effect of BPS in zebrafish documented not only changes in the mass of the gonads and plasmatic levels of estrogen and testosterone, but also a marked disruption of reproduction. The study of Qiu and colleagues evaluated the impact of BPA and BPS on the reproductive neuroendocrine system during zebrafish embryonic development, and explored potential mechanisms of action associated with ER, thyroid hormone receptor, and enzyme aromatase pathways. All of these pathways were necessary to observe the full effects of BPS on the changes in gene expression in the reproductive neuroendocrine axis (Qiu et al. 2016). These data were substantiated by a decrease in egg production and hatchability and an increasing number of embryo malformations (Ji et al. 2013). These observations were later extended upon by increased time to hatch, reduced number of sperm, increasing number of female to male ratio, and changes in the levels of testosterone, estradiol, and vitellogenin (Naderi et al. 2014). In further experiments provided in cell cultures it has been demonstrated that BPS acts cytotoxically, genotoxically (Lee et al. 2013), and mutagenically (Fic et al. 2013).

The reason for these negative effects may be for example binding to serum albumins or DNA damage and subsequent influencing of several signal cascades anywhere within the organism (Lee et al. 2013; Mathew et al. 2014). Exposure to BPS disrupts cellular signalling in the apoptotic and survival pathways (Salvesen and Walsh 2014). Evidently, it is possible to expect the interference of BPS in signal pro-apoptotic pathways and signal cascades described also in gametes, leading to an altered cell cycle and cell death (Nevoral et al. 2013; Sedmikova et al. 2013). Further studies focused on the mechanism of BPS action are needed for a full understanding its negative effect on reproduction on the gamete level and cell cycle regulation.

In respect to previous regrettable substitution, another bisphenols, such as bisphenol F (BPF, bis(4-hydroxyphenyl)methane; see Figure 1), do

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not seem to be a suitable alternative. In addition to BPA and BPS, BPF has been described as endocrine disruptor as well (Perez et al. 1998). Surprisingly, natural presence of BPF has recently been observed in mustard and, therefore, it is a frequent compound of foodstuff (Zoller et al. 2016). Hence, BPF regulation is ambiguous for its chronical intake by a major part of human population (Dietrich and Hengstler 2016).

CONCLUSION

At present we are witnessing the substitution of BPA with BPS in a whole range of materials, and BPS is becoming a standard component of several products. BPS is a substance which is structurally very similar to BPA, it shows analogous effectiveness and mechanism of *in vitro* action. Biological changes occurring in the range of typical human exposures were documented at doses below those used in traditional toxicology. On the basis of the described comparisons, it is possible to expect that BPS, like BPA, is an endocrine disruptor, and that it may have similar targets and manner of action *in vivo* and may influence physiological processes on several levels. With regard to its slower degradation, BPS may act for a longer time in the organism and thus interfere with the regulation of reproduction of mammals in a yet more dangerous manner than has been demonstrated by a range of studies in the case of BPA.

The alarming results of the first reproduction studies on BPS have generated an acute need for a wider and at the same time more detailed assessment of the impacts of BPS, with emphasis on the area of reproduction of mammals, which is entirely lacking at present. Should this not materialize, due to the increasing industrial production of BPS caused by the need to replace BPA, unfortunately BPS may within the foreseeable future become just as great an environmental health risk as BPA. There is a need for very intensive research and subsequently also legislative measures in order to ensure that BPS will not become another "regrettable substitution" with pronounced negative impacts on the environment and on human health, including negative impacts on reproduction.

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