Abstract

The endocrine disrupting chemical bisphenol A (BPA) is widely used in the production of polycarbonate plastics and epoxy resins. The use of BPA-containing products in daily life makes exposure ubiquitous, and the potential human health risks of this chemical are a major public health concern. Although numerous in vitro and in vivo studies have been published on the effects of BPA on biological systems, there is controversy as to whether ordinary levels of exposure can have adverse effects in humans. However, the increasing incidence of developmental disorders is of concern, and accumulating evidence indicates that BPA has detrimental effects on neurological development. Other bisphenol analogues, used as substitutes for BPA, are also suspected of having a broad range of biological actions. The objective of this review is to summarize our current understanding of the neurobiological effects of BPA and its analogues, and to discuss preventive strategies from a public health perspective.

Key words: Bisphenol A, Epigenetics, Neurodevelopment

Introduction

Bisphenols (BPs) form a large family of chemicals that are utilized to produce polycarbonates and epoxy resins. The most widely used bisphenol is bisphenol A (2,2-bis-(4-hydroxyphenyl)propane; BPA). BPA is a major high-production chemical, with over 6 billion pounds produced each year and over 100 tons are estimated to be released into the atmosphere [1, 2]. BPA was first synthesized by Dianin as early as 1891. In the mid-1930s, Dodds et al. discovered the estrogenic properties of BPA during their pursuit of a synthetic estrogen [3]. However, these authors found that diethylstilbestrol (DES) was a far more potent estrogen using a classical estrogenic assay and concluded that the estrogenic potential of BPA was marginal.

Commercial production of BPA did not begin before the early 1950s, when the first epoxy resins were developed. To protect foods and drinks from direct contact with metals, epoxy resins are frequently used in the internal coating of food and beverage containers. BPA is a building block of polycarbonate plastics, including baby bottles [4]. BPA is also used for some dental sealants, carbonless paper for receipts, digital media (CDs and DVDs), electronic equipment, flooring, tableware, and reusable bottles [1, 5, 6]. A recent study reported that BPA was detectable in dust, air particles and water, making exposure widespread [7].

Previous studies have shown that BPA can leach from polycarbonate plastics, epoxy resins and other products in contact with foods and drinks, and as a result, routine oral ingestion of BPA is likely [1, 8-10]. Indeed, one risk assessment study suggested that canned food items contribute to 10–40% of the daily BPA intake [11]. Because of the potential health risk of BPA, the chemical has been replaced by alternatives. Ironically, these BPA substitutes have also been demonstrated to have detrimental effects on human health. For example, bisphenol F (BPF) and halogenated BPA, used in products for daily life, are suspected of having toxic effects on biological systems [12, 13].

Numerous studies on the biological effects of BPA have been published, and its potential human...
health hazards have been extensively summarized [1, 4]. Previous studies have linked BPA exposure to abnormalities of the reproductive system and a higher incidence of cardiovascular disease [14-17]. Along with recent increases in the prevalence of neurobehavioral disorders [18], evidence has been accumulating that BPA can perturb nervous system development. For example, elevated gestational urinary concentrations of BPA have been correlated with adverse behavioral outcomes in children [19-21]. However, many uncertainties remain and controversial discussions are still ongoing.

In this review, recent data on BPA exposure and the potential human health hazards are summarized, focusing on its neurological effects. Knowledge of the effects of other bisphenol analogues on the nervous system is also presented, followed by future directions for the preventive strategies to lessen the impact of these compounds, from a public health perspective.

**Human biomonitoring data of BPA**

Exposure data from the biomonitoring of BPA is essential for translating findings from animal studies to human health risk assessment. Although the biological half-life of BPA in humans is estimated to be less than 6 h [22], long-term daily intake of BPA can lead to steady-state BPA concentrations in human samples [23, 24]. Since 2007, a number of extensive reviews have been published on exposure assessment for BPA [10, 24-26]. Human BPA biomonitoring data has recently been reported [27, 28] and will not be described in detail. Here, brief summary of several key findings from BPA biomonitoring is presented.

Over 10 years ago, a report analyzed human serum samples, and BPA concentrations up to 1.49 ng/ml (6.5 nM) were found [29]. BPA has been found not only in adult serum, but also in maternal circulation [26, 30], amniotic and placental fluids [31-33], breast milk [34], and the urine of infants [35]. BPA levels in human amniotic fluid have been measured, and levels as high as 8.3 ng/ml (36 nM) have been reported [31]. BPA has also been detected in human neonatal blood and cord blood [10]. Indeed, it appears that the human placenta does not act as a barrier to BPA [32]. Abnormal exposure to compounds during critical periods of development can interfere with normal homeostasis and lead to long-term deleterious effects [1]. The fetal brain is especially vulnerable because of an immature xenobiotic-metabolizing system and a relatively permeable blood–brain barrier. Consequently, studies aimed at clarifying the effects of BPA exposure in human neonates and the development of preventive strategies are urgently needed.

Urinary BPA measurements are preferred for evaluating exposure levels because the chemical is concentrated in urine [24]. BPA-glucuronide, a major BPA metabolite in urine, is stable and serves as a useful biomarker of BPA exposure. Administered doses of BPA are completely recovered in urine as BPA-glucuronide within 42 h [36, 37]. Thus, the measurement of urinary concentrations of BPA-glucuronide or total BPA in urine is the most appropriate and feasible way to assess daily exposure in humans from all sources [24].

In 2005, the first study to measure total BPA concentrations in a reference population was reported from the Centers for Disease Control (CDC) [38]. BPA was detected in 95% of the urine samples analyzed, and concentrations up to 5.18 ng/ml (95th percentile) were reported. The CDC followed this study with a second one, examining spot urine samples from 2,517 Americans > 6 years of age in the 2003–2004 National Health and Nutrition Examination Survey (NHANES) [39]. BPA was detected in 92.6% of participants, with concentrations ranging from 0.4 to 149 ng/ml (with a geometric mean of 2.6 ng/ml urine). The geometric mean of BPA was 2.49 ng/ml for the period 2003–2004 and 1.79 ng/ml for the period 2005–2006 [15], suggesting that exposure levels may have declined recently.

Importantly, the geometric mean urinary concentration of BPA among premature infants undergoing intensive therapeutic medical intervention was one order of magnitude higher than in the general population (30.3 vs. 2.6 ng/ml urine) [35]. Such a high level of exposure may be due to the use of medical equipment, including medical tubes and bottles. While adults have a high capacity to rapidly metabolize and excrete BPA, the fetus and infant have lower hepatic levels of metabolizing enzymes, and thus are at greater risk from exposure to unconjugated BPA than the adult [40]. Therefore, BPA exposure in fetuses and neonates is of great concern because of the high sensitivity of developing organs. Indeed, the US Food and Drug Administration raised concerns over BPA exposure in fetuses, infants and young children [41]. To avoid potential hazards, Canada became the first country to declare BPA to be a toxic compound and required its removal from all infant formula bottles in 2010. BPA was also banned in infant formula bottles by the European Union in 2011 and by the United States in 2012. In France, the use of BPA in any food or beverage packaging was forbidden from January 2015 [42].

BPA concentrations in biological samples differ among published studies. One possible source of discrepancy may be differences in analytical methodology [24]. At present, the gold standard for measuring BPA is solid-phase extraction coupled with high performance chromatography-isotope dilution tandem
mass spectrometry with peak focusing [7]. The choice of equipment and containers used to collect and store samples is critical for the accurate assessment of BPA concentrations. A major concern is potential contamination of biological specimens by materials and processes, e.g., by dust containing BPA. In fact, contamination of reagents or solvents with BPA or leaching of BPA from materials used for sampling and sample storage have been reported [37, 43]. Therefore, a general problem with blood and urine BPA measurements is background contamination of samples, which may interfere with quantitation at low concentrations. Therefore, in future studies, to accurately evaluate the effects of BPA exposure in the general population, large sample size and accurate and sensitive assessment methods devoid of contamination from materials used for sampling and storage are required.

It has been reported that only about 10% of orally ingested BPA is bioavailable 20 to 30 minutes later [44]. Given the short half-life of orally ingested BPA and the high frequency of detection, continued exposure to human body may be present. The ubiquity of BPA-containing plastics makes human exposure nearly universal. A study of temporal variability found that a single spot urine sample had moderate sensitivity for predicting an individual’s tertiary BPA categorization [45]. Other studies have shown that urinary BPA concentrations can vary up to two orders of magnitude within a given day, making it difficult to eliminate exposure misclassification [46, 47]. Thus, multiple urine samples collected over an extended period of time are required for more accurately assessing long-term exposure. Indeed, reproducibility, estimated by the intraclass correlation coefficient, was reported to be only 0.32 for urinary BPA concentrations measured during pregnancy [48]. Braun et al. reported an even lower intraclass correlation coefficient of 0.11 for BPA across three urine samples collected during pregnancy, suggesting the need for repeated urinary BPA measurements during pregnancy for less biased exposure-response estimates [49]. This variability may be a limitation for large-scale epidemiological studies, because multiple sample collection is often not practical. Future studies should consider the importance of collecting multiple or integrated urinary concentration measurements to improve exposure estimation.

**Pleiotropic actions of BPA**

In this section, I summarize our current mechanistic understanding of the pleiotropic actions of BPA. BPA is a well-known xenoestrogen [50]. Biochemical assays have examined the kinetics of BPA binding to estrogen receptors (ERs) [51]. BPA was demonstrated to bind both ERα and ERβ, with approximately 10 times higher affinity for ERβ [50]. Although BPA was considered a weak environmental estrogen, results from several studies have revealed that BPA can stimulate cellular responses at very low concentrations, below the levels where BPA is expected to bind to the classical nuclear ERs [23]. Thus, it is improbable that BPA elicits its effects only through classical ER-dependent nuclear pathways.

Mounting evidence suggests a variety of pathways through which BPA can elicit cellular responses at very low concentrations and with the same or even higher efficiency than 17β-estradiol (E2) [52-55]. BPA has been shown to bind to a membrane-associated ER and produce non-genomic effects [56] with the same efficacy and potency as E2 [52, 54, 57]. Indeed, a recent report showed that BPA and E2 have an equimolar activational capacity for ER rapid signaling pathways in human prostaspheres [58]. However, despite this similarity, it has been reported that ligand-dependent differences exist in the ability of the ER to provoke different actions. For example, BPA and E2 induce distinct conformational changes in the tertiary structure of the ER after binding, and have a differential ability to recruit coactivator proteins [59]. Thus, binding affinities of xenoestrogens for ERs may not accurately predict ability to recruit coactivator proteins or subsequent action.

BPA has been reported to have the ability to modify the actions of physiologic estrogens. For example, BPA has a marked inhibitory effect on E2-induced extracellular-signal-regulated kinase (ERK) activity in rat pituitary cells. In these cells, BPA therefore acts as an antiestrogen, although the underlying molecular mechanisms remain to be clarified [60].

Molecular studies have revealed a variety of pathways through which BPA stimulates cellular responses at very low doses. BPA was reported to bind to the aryl hydrocarbon receptor [61] and to the thyroid hormone receptor [62], inhibiting the transcriptional activity induced by triiodothyronine (T3) [63]. A potent antiandrogenic activity of BPA, resulting from its ability to interfere with agonist binding to the androgen receptor, was also reported [64]. In addition, BPA has been found to act as a glucocorticoid receptor agonist [65] and impair insulin homeostasis [66]. BPA also activates the pregnane X receptor [67]. Thus, the net effect of BPA may result from multiple actions on different signaling pathways. The multitude of targets may underlie the pleiotropic effect of BPA on multiple biological systems.

Estrogen-related receptor γ (ERRγ) was identified as a BPA target receptor in 2006 [68]. Indeed, BPA binds very strongly to ERRγ, with a Kd of 5.5 nM
[68-70]. ERRγ is expressed very strongly in the mammalian brain during development [71]. ERRγ is a nuclear receptor whose natural ligand is not known, but is thought to play a role in the differentiation and maturation of the fetal brain [71]. If BPA can bind to ERRγ specifically, the physiological functions of ERRγ might be perturbed and neurodevelopmental disorders may ensue, especially when exposure occurs during the critical early periods of nervous system development.

**Effects of BPA on neurological systems**

Because of its impact on the endocrine system, BPA was initially examined for effects on sexual dysfunction, malformation, and cancers of reproductive origin. Recent population-based epidemiological studies have linked BPA to metabolic disorders, such as obesity and diabetes, and to cardiovascular disease [72, 73]. Along with the growth in the production of toxic chemicals, an increase in the prevalence of neurodevelopmental disorders has been observed over the past few decades. Evidence has been accumulating that environmental chemicals, including BPA, can cause neurodevelopmental disorders. Indeed, the National Toxicology Program (NTP) of the United States concluded that “there is some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to BPA”. Thus, neurological systems are considered important targets of BPA. In this section, I summarize recent advances in our understanding of the effects of BPA on neurological function.

A number of animal studies reported that BPA exposure during gestational period affects brain development and behaviors (Table 1). Perinatal or neonatal BPA exposure alters brain sexual differentiation [74, 75]. BPA can induce aggression, anxiety, cognitive deficits, and learning-memory impairment [76-80]. BPA can also influence the display of juvenile social behaviors in mice [81, 82]. Perinatal exposure to BPA increases anxiety-like behavior and elevates dopamine levels in male, but not female, mice [83]. BPA exposure in male rats during lactation is associated with hyperactivity and the degeneration of dopaminergic neurons [84]. BPA exposure during organogenesis and breastfeeding upregulates dopamine receptor function, whereas exposure at other gestational periods does not, suggesting the presence of critical developmental windows of BPA toxicity [85]. In both rodents and nonhuman primates, BPA has adverse effects on the brain even at relatively low exposure levels [86, 87].

| Animal                  | Major Effects                                                                 | References |
|-------------------------|-------------------------------------------------------------------------------|------------|
| Mice                    |                                                                               |            |
| 2 ng/g or 20 ng/g of body weight | Increased aggression in male mice                                              | Kawai et al. (2003) [76] |
| 25 ng/g/day             | Decreased number of tyrosine hydroxylase neurons                               | Suzuki et al. (2003) [143] |
| 20 ng/kg/day            | Perturbed differentiation and migration of neurons                            | Nakamura et al. (2006) [99] |
| 2 and 200 ng/kg/day     | Increased anxiety-like behavior in female mice                                 | Ryan et al. (2006) [144] |
| 30 ng/g diet            | Enhanced morphine-induced hyperlocomotion and rewarding effect                | Narita et al. (2006) [145] |
| 10 µg/kg/day            | Alterations in brain structure                                                | Palanza et al. (2008) [146] |
| 100 µg/kg/day           | Anxiolytic-like effect and induction of cognitive deficits                    | Tian et al. (2010) [79] |
| 50 mg/kg feed weight    | Impact on social behavior and anxiety                                         | Cox et al. (2010) [81] |
| 20 µg/kg/day            | Perturbation of neurotransmitter system                                       | Nakamura et al. (2010) [147] |
| 40 µg/kg/day            | Changes in nitric oxide production                                            | Martini et al. (2010) [148] |
| 50 mg/kg feed weight    | Perturbed spatial learning abilities and exploratory behaviors               | Jasarevic et al. (2011) [149] |
| 250 ng/kg/day           | Increased anxiety-like behavior in males                                      | Matsuda et al. (2012) [83] |
| 2 µg/kg/day             | Sex-specific epigenetic disruption in the brain                               | Kundakovic et al. (2013) [97] |
| 10 µg/kg/day            | Increased anxiety in females                                                  | Gioiosa et al. (2013) [150] |
| Rats                    |                                                                               |            |
| 1.5 mg/kg/day           | Disrupted sexual differentiation in the brain                                 | Kubo et al. (2001) [151] |
| 40 mg/kg/day            | Increased estrogen receptor expression in the medial preoptic nucleus        | Aloisi et al. (2001) [152] |
| 40 µg/kg/day            | Altered brain monoaminergic function                                          | Adriani et al. (2003) [153] |
| 100 µg/kg/day           | Changes in gender-dependent memory acquisition                               | Carr et al. (2003) [154] |
| 15 µg/kg/day            | Increased immobility in the forced swim test                                  | Fujimoto et al. (2006) [155] |
| 600 µg/kg/day           | Increased spontaneous motor activity                                          | Ishido et al. (2007) [84] |
| 50 µg/kg/day            | Increased anxiety and cognitive deficits                                      | Poimenova et al. (2010) [156] |
| 50 µg/kg                | Increased oxytocin-immunoreactive cell number in the female rat paraventricular nucleus | Adewale et al. (2011) [153] |
| 2 µg/kg/day             | Hyperactivity                                                                  | Ishido et al. (2011) [157] |
| 50 µg/kg/day            | Increased hyperactivity and decreased attention                               | Zhou et al. (2011) [158] |
| 24 µg/kg/day            | Enhanced short-term passive avoidance memory                                  | Xu et al. (2011) [159] |
| Other Species           |                                                                               |            |
| African green monkeys   | Perturbation of the synaptogenic effect of estradiol                         | Leranth et al. (2008) [86] |
| Cynomolgus monkeys      | Altered behavior and sexual differentiation                                  | Nakagami et al. (2009) [87] |
In humans, accumulating evidence suggests that early life exposure to BPA impacts neural development (Table 2). BPA exposure during gestation is associated with hyperactivity and aggression in 2-year-old girls [19] and with anxiety and depression in 3-year-old girls [20]. Importantly, childhood urinary BPA concentrations were less important predictors than gestational BPA exposure [20]. Perera et al. found that maternal urinary BPA concentrations during pregnancy were associated with increased aggressive behavior and emotional reactivity in boys between 3 and 5 years of age [88]. Harley et al. reported that prenatal urinary BPA concentrations were associated with increased internalizing problems in boys, but not girls [21]. However, some studies found no significant associations between gestational exposure to BPA and infant neurobehavioral measures [89]. Miodovnik et al. reported prenatal BPA exposure was not associated with childhood social impairment in 7- and 9-year-olds [90]. Although the source of these discrepancies remains obscure, low levels of exposure may be below a threshold at which neurobehavioral effects manifest. Alternatively, the discrepancies may reflect differences in study populations or methodology for exposure assessment. In addition, the behavioral effects of BPA exposure may manifest differentially depending on both child age and time of exposure. Recently, one human cell culture study showed that BPA significantly decreased potassium chloride cotransporter 2 (Kcc2) mRNA expression in developing cortical neurons, suggesting that BPA delays the perinatal chloride shift [91]. This may have relevance for our understanding of the mechanisms of BPA neurodevelopmental toxicity.

Intriguingly, BPA has sex-specific effects on the expression of behaviors associated with anxiety, activity and sociality [82, 92]. Many behaviors and neuroendocrine pathways are sexually dimorphic. Exposure to BPA that disrupts hormone function during critical periods of prenatal development may perturb sex-specific or hormonally regulated behaviors. Disruptions in behaviors may lead to reduced social adaptation and impaired responsiveness to environmental demands. Thus, the sex of the child may impact the association between prenatal BPA exposure and externalizing behaviors. Indeed, a sex-specific effect of perinatal BPA exposure on hypothalamic morphology was reported [93]. BPA exposure affects exploratory activity and behavior in females, but only minimally disrupts partner preference formation [94].

 Gonadal hormones are known to influence the sexual differentiation of the brain. Therefore, exposure to endocrine disrupters which affect gonadal hormone levels may contribute to sex-specific behavioral changes [95]. Galloway et al. found that urinary BPA was correlated with serum concentrations of total testosterone [96]. Thus, alterations in gonadal hormone levels provoked by BPA exposure may perturb sex-dependent neurobehaviors. Interestingly, a recent report showed that prenatal BPA treatment results in a sex-specific disruption of epigenetic pathways in the brain [97]. Future studies should examine whether males and females have differential levels of susceptibility to BPA at different periods of development.

The molecular mechanisms mediating the effects of BPA on the nervous system are beginning to be clarified. Disruption of maternal thyroid or gonadal hormones critical for normal development may underlie the effects of BPA. Chevrier et al. found that BPA exposure during pregnancy was associated with decreased total thyroxine (T4) in pregnant women and reduced thyroid stimulating hormone (TSH) in male neonates [98]. Furthermore, prenatal exposure to low doses of BPA in pregnant mice alters thyroid receptor expression in the fetal neocortex [99]. These findings suggest that perinatal hypothyroxinemia caused by BPA exposure during pregnancy may underlie some of the neurological deficits in offspring.

Early life exposure to BPA has been shown to affect the dopamine system [100]. Gestational exposure to BPA reduces the number of midbrain dopamine neurons in monkeys [101]. It has been reported that tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, is affected by BPA [84]. Thus, an alteration of the dopaminergic system may account for some of the neurological deficits associated with BPA exposure, such as anxiety-like behaviors [81, 83]. Additionally, developmental exposure to BPA alters the organization and function of the oxytocin (OT)/vasopressin (AVP) system [102, 103], and may

Table 2 Association Between Prenatal Exposure to BPA and Neurological Development (Human Studies)

| Subjects              | Major Findings                                           | References    |
|-----------------------|----------------------------------------------------------|---------------|
| Girls 2 years of age  | Increased hyperactivity and aggression scores            | Braun et al. (2009) [19] |
| Girls 3 years of age  | Association with worse behavior                          | Braun et al. (2011) [20] |
| Infants at 5 weeks    | No association with infant behavior                       | Yolton et al. (2011) [98] |
| Infants 7 and 9 years of age | No association with social impairment               | Miodovnik et al. (2011) [90] |
| Boys 3-5 years of age | Association with increased aggressive behavior and emotional reactivity | Perera et al. (2012) [88] |
| Boys 7 years of age   | Increased symptoms of depression and anxiety             | Harley et al. (2013) [21] |
| Infants 6-10 years of age | Increased behavior problems in boys but not girls     | Evans et al. (2014) [161] |
Bisphenol A analogues

Because of the biological effects of BPA, there has been a gradual shift to using bisphenol analogues. Several chemicals that are structurally similar to BPA are presently used in the manufacture of resins and plastics, as substitutes or replacements for BPA. The biological actions of bisphenol analogues are beginning to be clarified.

As described in the previous section, estrogens affect normal brain function and behavior [113, 114]. A study examined the estrogenic activity of BPA and related compounds using an estrogen response element reporter gene assay in MCF-7 human breast cancer cells [12]. Among the 19 BPA-related compounds tested, several, including tetrachlorobisphenol A (TCBPA), bisphenol AF (BPAF), bisphenol B (BPP), 2-(4-hydroxyphenyl)-2-phenylpropane (HP), 1,1-bis(4-hydroxyphenyl) cyclohexane) (BPCH), 4-hydroxydiphenyl-methane (HDM) and 3,3’-dimethyl-bisphenol A (DMBA), were found to have higher estrogenic activity than BPA [12]. Thus, these estrogenic BPs may cause neurodevelopmental disorders by disrupting ER-dependent pathways.

The production and use of (bis-(4-hydroxyphenyl)sulfone) (bisphenol S; BPS) has recently risen in many countries [115]. BPS contains two phenolic rings connected by sulfur and is more heat-stable than BPA [116]. It was introduced into consumer goods, such as canned foods and cash-register receipts. BPS is often used as a BPA alternative in “BPA-free” thermal printing paper. BPS has been found in thermal receipt papers at concentrations comparable to those of BPA [117]. Widespread exposure of the general population to BPS has been demonstrated in various countries. For example, BPS in the urine has been detected in 81% of 315 people sampled in American and Asian populations, with levels ranging from 0.02 to 21 ng/ml (0.8–84 nM) [118]. BPA and BPS are about the same size and have similar phenolic ring structures, and therefore, BPS has been suspected to function as a xenoestrogen [119]. Indeed, an assay for estrogenic activity showed that BPS has a weak estrogenic effect [120]. However, the cell biological effects of BPA and BPS appear to differ [121]. BPS, at low-dose ranges likely to be present in food items, appeared to interact predominantly with the cell-membrane ER and affect nongenomic signaling, leading to potential consequences for cell function [122]. A recent study showed that both BPS and BPA influence hypothalamic development [123]. Given the disrupting effects of BPS and its higher resistance to environmental degradation in comparison to BPA [124], the proposal to utilize BPS instead of BPA in various products should be viewed with caution.

Bisphenol AF (BPS), a fluorinated derivative of BPA, is used in polycarbonate copolymers in high-temperature composites, electronic materials, and specialty polymer applications [125]. BPSA binds to ERα more strongly than BPA and has a much higher affinity for ERα than ERRγ [70]. BPSA is a strong ligand for both ERα and ERβ, with a 3-fold greater preference for the latter [126]. However, interestingly, BPSA is a full agonist for ERα, but an antagonist for ERβ [125, 126]. Thus, BPSA perturbs physiological processes regulated by estrogen and may have significant adverse effects on the nervous system.

Bisphenol-A diglycidyl ether (BADGE) is an an-
alog of BPA that is used in manufacturing coating and resins, and can leach from packaging materials into food. BADGE induces adipogenesis in multipotent mesenchymal stromal stem cells, as well as in 3T3-L1 adipocytes at low nanomolar concentrations comparable to those observed in human biomonitoring [127]. The effects of BADGE appear to be mediated, at least in part, by peroxisome proliferator-activated receptor γ (PPARγ) [128, 129]. PPARγ is a member of the nuclear receptor superfamily and is involved in the pathogenesis of obesity and diabetes [130]. Interestingly, brain PPARγ regulates energy balance, and its activation may lead to hyperphagia and an increase in adipose tissue mass [131, 132]. Thus, BADGE may function as an obesogen via central nervous system.

Environmental as well as human exposure data indicate that halogenated BPs are emerging contaminants [133]. Analogs of BPA where the phenolic moieties are substituted with halogens (Br or Cl) are used as flame retardants. Approximately 200,000 tons of tetrabromobisphenol A (TBBPA) are produced annually, and used to protect computer boards and other electric equipment [133]. Tetrachlorobisphenol A (TCBPA) is also used as a flame retardant. The presence of TCBPA and other chlorinated analogs (mono-, di- and triCBPA) in environmental samples has been unequivocally demonstrated [134]. Their presence in human samples, including mother’s milk, has also been demonstrated [2, 135, 136]. Significant levels of TBBPA are found in human cord blood (200 pg/g fresh weight) and maternal milk (0.1–37.4 ng/g lipid weight), indicating both prenatal and postnatal exposure [135]. Not all halogenated BPA analogs are ER agonists. In general, the greater the number of bromine atoms, the weaker the ER agonism [129]. TCBPA and BPA display full agonistic activity towards ERα, with a 1,000 to 10,000-fold lower potency than E2 [128]. While these analogs show marginal estrogenicity in assays, they bind with stronger affinity to PPARγ than BPA [128, 129]. Thus, these halogenated BPA analogs may contribute to onset and disease progression via PPARγ, similar to BADGE.

Current knowledge on the biological and potential toxicological effects of BPA analogues, especially on the nervous system, is limited. Moreover, relatively little is known about the biological processing of BPA analogues or the bioactivity of their metabolites, and in vivo studies are lacking. Some BPA substitutes appear to be more resistant to environmental degradation than BPA [124, 137]. Thus, the use of BPA analogues should be carried out with caution, especially until effective risk assessment is conducted.

**Future perspectives**

Although numerous studies have been published on the effects of BPA on neurobiological functions, the underlying mechanisms remain unclear. BPA displays non-monotonic dose-response functions, and very different effects at environmentally relevant doses compared with higher exposures [4]. It is evident that BPA does not function solely as an estrogen mimic. Furthermore, it is unclear why BPA has such wide-ranging effects on neurobiological systems at low concentrations. Detailed mechanistic studies are needed to clarify the effects of chronic low-dose BPA exposure.

Alterations in gene expression induced by fetal exposure to BPA have been demonstrated, suggesting a role for epigenetic regulation, such as altered DNA methylation and miRNA expression [138-140]. The contribution of epigenetics to phenotype is an exciting research topic. Because of the relatively new understanding of the role of miRNAs in gene regulation, the direct targets of many specific miRNAs and their roles in early neurodevelopment are largely unknown. Nonetheless, altered miRNA expression may be a potential mechanism of BPA action, but needs further study.

Even low doses of BPA can trigger major neurological perturbations when exposure occurs during critical developmental windows [1, 141]. Timing of exposure is a key factor determining potential developmental and behavioral consequences. Understanding the factors impacting the neurotoxicity of BPs during pregnancy is essential for preventing the adverse neurological effects of these compounds. Studies are needed to more accurately determine the critical windows of developmental exposure, to clarify gender-specific effects and resolve the molecular and cell biological impact of these compounds. The general population may experience chronic low-dose exposures requiring improved biomarkers for detection of low-dose toxicity. This will be especially important for identifying sensitive subpopulations and for discriminating the effects of BPs from those of other environmental contaminants.

Despite widespread human exposure in developed countries, there are a limited number of epidemiological studies on the association of BPs with neurodevelopmental disorders. In particular, large-scale prospective studies are lacking to validate findings from animal studies. Future research should include prospective, longitudinal cohort studies in which exposure to BPs are assessed in relation to neurodevelopmental outcome. In the real world, environmental exposure is rarely due to a single chemical, but rather involve complex chemical mixtures. Indeed, a recent study found that BPA concentrations were correlated with other EDC metabolite concentrations (such as phthalates) in urine from the prenatal
stage up to 7 years of age [142]. Given the ubiquitous presence of BPs and other EDCs in the environment, it is not unexpected that they would be widely detectable in the general population. The effects of cumulative exposure on neurodevelopmental outcomes are a concern, which need to be investigated further. Despite the absence of epidemiological studies, concerns over adverse effects of BPA and its analogues are warranted given the unique vulnerability of the developing fetus and neonate. Thus, caution is recommended in the use of BP compounds, particularly until further data are obtained from risk assessment studies.

**Abbreviations**

BPs: bisphenols; BPA: bisphenol A; DES: diethylstilbestrol; E2: 17β estradiol; ER: estrogen receptor; ERR: estrogen-related receptor; PPAR: peroxisome proliferator-activated receptor

**Competing Interests**

The authors have declared that no competing interest exists.

**References**

1. Vandenberg LN, Maffini MV, Semmenschein C, et al. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. Endocr Rev. 2009; 30: 75-95.
2. Jimenez-Diaz I, Zafra-Gomez A, Ballesteros O, et al. Determination of Bisphenol A and its chlorinated derivatives in placental tissue samples by liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2010; 878: 3363-3369.
3. Dodds EC, Lawson W. Synthetic estrogenic agents without the phenanthrene nucleus. Nature. 1936; 137:996.
4. Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J Steroid Biochem Mol Biol. 2011; 127: 27-34.
5. Vogel SA. The politics of plastics: The making and unmaking of bisphenol-a: a safety”. Am J Public Health. 2009; 99 (Suppl 3): 5559-5569.
6. Bierderman S, Tschudin P, Grob K. Transfer of bisphenol A from thermal printer paper to the skin. Anal Bioanal Chem. 2010; 398:571-576.
7. Asimakopoulos AG, Thomaidis NS, Koupparis MA. Recent trends in biological dis-ruptive activity of bisphenol A and 19 related compounds. Toxicol Lett. 2012; 218:141-154.
8. Kang JH, Kondo F, Katayama Y. Human exposure to bisphenol A. Toxicology. 2006; 226: 79-89.
9. Wilson NK, Chuang JC, Morgan MK, et al. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. Environ Res. 2007; 103: 9-20.
10. Vandenberg LN, Hauser R, Marcus M, et al. Human exposure to bisphenol A (BPA). Reprod Toxicol. 2007; 24: 139-177.
11. Von Goetz N, Wormuth M, Scheringer M, et al. Bisphenol a: how the most relevant exposure sources contribute to total consumer exposure. Risk Anal. 2010; 30: 473-487.
12. Kitamura S, Suzuki T, Sanoh S, et al. Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds. Toxicol Sci. 2005; 84:249-259.
13. Delfosse V, Grimaldi M, Pons JL, et al. Structural and mechanistic insights into bisphenols action provide guidelines for risk assessment and discovery of bisphenol A substitutes. Proc Natl Acad Sci USA. 2012; 117:14930-14935.
14. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA. 2008; 300: 1303.
15. Melzer D, Rice NE, Lewis C, et al. Association of urinary bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation. 2012; 125:1482-1490.
16. Melzer D, Osborne NJ, Henley WE, et al. Urinary bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation. 2012; 125:1482-1490.
17. Melzer D, Gates P, Osborne NJ, et al. Urinary bisphenol A concentration and angiography-defined coronary artery stenosis. PLoS One. 2012; 7: e33784.
Variable urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections. Environ Health Perspect. 2011; 119: 983-988.

48. Snijder CA, Heederik D, Piek A, et al. Fetal growth and prenatal exposure to bisphenol A: the generation R study. Environ Health Perspect. 2013; 121: 393-398.

49. Jusko TA, Shaw PA, Snijder CA, et al. Reproducibility of urinary bisphenol A concentrations measured during pregnancy in the generation R study. J Expo Sci Environ Epidemiol. 2014; 24:532-536.

50. Braun JM, Kalkbrenner AE, Calafat AM, et al. Variability and predictors of urinary bisphenol A concentrations measured during pregnancy. Environ Health Perspect. 2011; 119: 131-137.

51. Kuiper GG, Lemmen JG, Carlsson B, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998; 139: 4252-4263.

52. Gould JC, Leonard LS, Maness SC, et al. Bisphenol A interacts with the estrogen receptor α in a distinct manner from estradiol. Mol Cell Endocrinol. 1998; 142: 203-214.

53. Alonso-Magdalena P, Laribi O, Roper AB, et al. Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. Environ Health Perspect. 2005; 113:969-977.

54. Alonso-Magdalena P, Morimoto S, Ripoll C, et al. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ Health Perspect. 2006; 114:106-112.

55. Hugo ER, Brandeberg TD, Woo JG, et al. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. Environ Health Perspect. 2008; 116:1642-1647.

56. Zolotukhina A, Y. H., Wang HS, et al. Ovariectomy of rapid estrogen-mediated extracellular signal-regulated kinase signaling in the rat cerebellar cortex: potent neurogenic agonist and endocrine disrupting activity of the xenobio- gen bisphenol A. Endocrinology. 2005; 146:5386-5396.

57. Wetherill YB, Akingbemi BT, Kanno J, et al. In vitro molecular mechanisms of bisphenol A action. Reprod Toxicol. 2007; 24: 178-198.

58. Wozniak AL, Bulayeeva NN, Watson CS. Xenooestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-alpha-mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. Environ Health Perspect. 2005; 113: 431-439.

59. Prins GS, Hu WY, Shi GB, et al. Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostatic epithelial xenografts. Endocrinology. 2010; 151:4046-4057.

60. Routledge EJ, White R, Parker MG, et al. Differential effects of xenoestrogens on maternal behavior and offspring sexual development. Reprod Toxicol. 2006; 22: 41-44.

61. Bonefeld-Jorgensen EC, Long MA, Hofmeister MV, et al. Endocrine-disrupting chemicals: tissue-specific isoforms are expressed during development and in the adult. Mol Cell Endocrinol. 1998; 142: 40-46.

62. Zsarnovszky A, Le HH, Wang HS, et al. Ontogeny of rapid estrogen-mediated neuroendocrine response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. Proc Natl Acad Sci USA. 2008; 105: 14187-14191.

63. Abramson E, Broussard A, Litosseliti G. Behavioural, endocrine, and metabolic consequences of in utero bisphenol A exposure in the rat. Neurotoxicology. 2012; 33: 1410-1419.

64. Snijder CA, Heederik D, Pierik FH, et al. Reproducibility of urinary bisphenol A concentrations measured during pregnancy in the generation R study. J Expo Sci Environ Epidemiol. 2014; 24:532-536.

65. Proc Natl Acad Sci USA. 2011; 108: 3267-3272.

66. Sui Y, Ai N, Park SH, et al. Bisphenol A and its analogues activate human estrogen-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development and in the adult. Mol Cell Endocrinol. 2000; 140: 382-386.

67. Shankar A, Teppala S. Relationship between urinary bisphenol A levels and diabetes mellitus. J Clin Endocrinol Metab. 2011; 96: 3822-3826.
Masujo Y, Ishido M. Neurotoxicity of endocrine disruptors: possible involvement in brain development and neurodegeneration. J Toxicol Environ Health B Crit Rev. 2011; 14: 346-349.

Elsworth JD, Jentsch JD, Vandervoort CA, et al. Prenatal exposure to bisphenol A impacts midbrain dopamine neurons and hippocampal spine synapses in non-human primates. Neurotoxicology. 2013; 35: 113-120.

Pataisal HB, Sullivan AW, Radford ME, et al. Anxiogenic effects of developmental and prenatal exposure are associated with gene expression changes in the juvenile rat amygdala and mitigated by soy. PLoS One. 2012; 7:e43890.

Adewale HB, Todd KL, Mickens JA, et al. The impact of neonatal bisphenol A exposure on sex-dimorphic hypothalamic nuclei in the female rat. Neurotoxicology. 2011; 32: 32-49.

Itoh K, Yai T, Fushiki S. Bisphenol A, an endocrine-disrupting chemical, and brain development. Neurotoxicology. 2012; 33: 447-457.

Wolstenholme JT, Rius A, le Maire A, Grimaldi M, et al. Comparison of two derivatization methods for bisphenol S in seawater. Int J Environ Res Public Health. 2009; 6: 1472-1484.

Liao C, Liu F, Alomirah H, et al. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. Environ Sci Technol. 2012; 46: 2329-2335.

Dolinsky DC, Huang D, little RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci USA. 2007; 104: 13056-13061.

Inadera H. Developmental origins of obesity and type 2 diabetes: molecular aspects and role of chemicals. Environ Health Prev Med. 2013; 18:185-197.

Yaoi T, Itoh K, Nakamura K, et al. Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. Biochem Biophys Res Commun. 2012; 415: 563-567.

Wenholme Gordon OS, Jones ET, et al. An expression microarray approach for the identification of metastable epitheliae in the mouse genome. Epigenetics. 2011; 6:1105-1113.

Kandakovic M, Champagne FA. Epigenetic perspective on the developmental neurotoxicity of bisphenol A. Brain Behav Immun. 2011; 25:1084-1093.

De Cock M, Maas YG, van de Bor M. Does prenatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. Acta Paediatrica. 2012; 101: 811-818.

Elshabbi M, Dalmass C, Koh YJ, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012; 5: 160-179.

Moenter SM, Chu Z. Rapid nongenomic effects of estradiol on gonadotropin-releasing hormone neurons. J Neuroendocrinol. 2012; 24: 117-121.

Laredo SA, Villalon Landeros R, Trauner BC. Rapid effects of estrogens on behavior: environmental modulation and molecular mechanisms. Front Neuroendocrinol. 2014; 35: 447-458.

Song S, Song M, Zeng L, et al. Occurrence and profiles of bisphenol analogues in water and sediment samples in China. Environ Sci Technol. 2010; 44:1024-1030.

Vinas P, Campillo N, Martinez-Castillo N, et al. Comparison of two derivatization-based methods for solid-phase microextraction-gas chromatography-mass spectrometric determination of bisphenol A, bisphenol S and bisphenol migrated from food cans. Anal Bioanal Chem. 2010; 397: 115-125.

Liao C, Liu F, Kannan K. Bisphenol S, a new bisphenol analogue, in paper products and currency bills and its association with bisphenol A residues. Environ Sci Technol.2012; 46: 6515-6522.

Liao C, Liu F, Alomirah H, et al. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. Environ Sci Technol. 2012; 46: 6860-6866.

Grignon E, Lapenna S, Bremer S. Weak estrogenic transcriptional activities of bisphenol A and bisphenol S. Toxicol In Vitro. 2012; 26:232-233.

Molina-Molina JM, Amaya E, Grimaldi M, et al. In vivo study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol Appl Pharmacol. 2013; 272:122-136.

Helleis-Toussaint C, Peyre L, Costanto C, et al. Bisphenol S a safe substitute for bisphenol A in terms of metabolic function? An in vitro study. Toxicol Appl Pharmacol. 2014; 280: 224-235.

Vinas R, Watson CS. Bisphenol S disrupts estradiol-induced nongenetic signaling in a rat pituitary cell line: effects on cell functions. Environ Health Perspect. 2013; 121: 352-358.

Kinch CD, Bhaizekeio K, Jeong JH, et al. Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish. Proc Natl Acad Sci USA. 2015; 112: 1475-1480.

Daneh E, Sei K, Soda S, et al. Biodegradation of bisphenol A, bisphenol F and bisphenol S in seawater. Int J Environ Res Public Health. 2009; 6: 1472-1484.

Li Y, Burns KA, Aray Y, et al. Differential estrogenic actions of endocrine-disrupting chemicals bisphenol A, bisphenol AF, and zearalenone through estrogen receptor α and β in vitro. Environ Health Perspect. 2012; 120:1029-1035.

Matsushita A, Liu X, Okada H, et al. Bisphenol AF is a full agonist for the estrogen receptor ERα but a high antagonist for ERβ. Environmental Health Perspectives. 2010; 118: 1267-1272.

Chamorro-Garcia R, Kirchner S, Li X, et al. Bisphenol A diglycidyl ether induces adipogenic differentiation of multipotent stromal stem cells through a peroxisome proliferator-activated receptor-gamma-independent mechanism. Environmental Health Perspectives. 2012; 120: 984-989.

Riu A, le Maire A, Grimaldi M, et al. Characterization of novel ligands of ERα, ERβ, and PPARγ: the case of halogenated ligands and their conjugated metabolites. Toxicol Sci. 2011; 122: 372-382.

Riu A, Grimaldi M, le Maire A, et al. Peroxisome proliferator-activated receptor-γ is a target for halogenated analogs of bisphenol A. Environ Health Per- spect. 2011; 119: 1227-1232.
157. Ishido M, Masuo Y, Terasaki M, et al. Rat hyperactivity by bisphenol A, but not by its derivatives, 3-hydroxybisphenol A or bisphenol A 3,4-quinone. Toxicol Lett. 2011; 206: 300-305.

158. Zhou R, Bai Y, Yang R, et al. Abnormal synaptic plasticity in basolateral amygdala may account for hyperactivity and attention-deficit in male rat exposed perinatally to low-dose bisphenol-A. Neuropharmacology. 2011; 60: 789-798.

159. Xu X, Li T, Lus Q, et al. Bisphenol-A rapidly enhanced passive avoidance memory and phosphorylation of NMDA receptor subunits in hippocampus of young rats. Toxicol Appl Pharmacol. 2011; 255:221-228.

160. Fujimoto T, Kubo K, Nishikawa Y, et al. Postnatal exposure to low-dose bisphenol A influences various emotional conditions. J Toxicol Sci. 2013; 38: 539-546.

161. Evans SF, Kobrosly RW, Barrett ES, et al. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. Neurotoxicology. 2014; 45: 91-99.