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Review

Bisphenol A: Human exposure and neurobehavior

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ABSTRACT

The effect of bisphenol A (BPA) exposure on human brain and behavior is a relatively new issue, and particular concerns have been raised about its potential impact on children. The primary objective of this review was to analyze the current state of knowledge on the association of environmental BPA exposure during pregnancy and/or childhood with child cognitive and/or behavior outcomes. All scientific publications until March 2015 that include examination of this relationship have been reviewed using the MEDLINE/PubMed database. Although research on this issue has not been abundant, an association with altered neurobehavior was reported by eight out of the twelve available articles, including aggressive behavior, attention deficit, hyperactivity disorder, depression and anxiety impairments, mostly in children exposed *in utero*, indicating disruption of the brain during this critical window of development. Despite the reduced number of studies and their heterogeneity, the results suggest that prenatal BPA exposure may have a negative impact on neurobehavioral functioning in children and that the effects may be sex-dependent. It is therefore necessary to be vigilant towards the potential adverse effects of ubiquitous low-level BPA exposure, although more studies in humans are required to convincingly confirm or rule out the association between BPA exposure and health. Meanwhile, it is desirable to inform women planning or undergoing pregnancy about measures to reduce or avoid exposure to BPA. We discuss some key aspects of the relationship between exposure and neurobehavioral outcomes.

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1. Introduction

Dodds and Lawson (1938) discovered the estrogenic properties of bisphenol A (BPA) while seeking estrogenic compounds without the phenanthrene nucleus. More than 50 years later, Krishnan et al. (1993) reported that leaching of this endocrine disrupting chemical (EDC) from polycarbonate flasks during autoclaving was responsible for the estrogenicity found in yeast culture medium. Over the subsequent two decades, there has been considerable research on the actions of BPA and its possible adverse effects on human health.

BPA is a monomer widely used in the production of epoxy resins and polycarbonate plastics, and several million tons are produced worldwide every year (Vogel, 2009). It is present in the epoxy resin that coats canned food and beverages (Bemrah et al., 2014; Brotons et al., 1995; Cao et al., 2009; Carwile et al., 2009; Vandenberg et al., 2007) and in polycarbonate plastic bottles, food containers, plastic plates and cups, dental sealants, water supply pipes, toys, thermal receipts, cigarette filters, and even medical equipment, including medical tubing and implant devices (Calafat et al., 2009; Duty et al., 2013; Ehrlich et al., 2014; Geens et al., 2012; Vandenberg et al., 2007; Welshons et al., 2006).

Biomonitoring studies indicate that human exposure to BPA is ubiquitous, with more than 90% of the population evidencing detectable levels of BPA in different biological matrices (usually measured in urine in the concentration range of nanograms per milliliter) (Becker et al., 2009; Calafat et al., 2008; Casas et al., 2013; Vandenberg et al., 2010). Food and beverages are thought to be among the main sources of exposure in the general population (Vandenberg et al., 2010; von Goetz et al., 2010), although aquatic, air, soil and dermal routes may also contribute to total human exposure (Michałowicz, 2014).

BPA is one of the most widely studied EDCs (Vandenberg et al., 2010), with varied and well-documented effects in animals and humans (Chapin et al., 2008; Rochester, 2013; vom Saal et al., 2007). BPA has been consistently detected in maternal blood, amniotic fluid, and fetal serum (Vandenberg et al., 2010). It has been found that BPA can cross the placenta and enter the fetus (Corbel et al., 2014; Edlow et al., 2012; Jiménez-Díaz et al., 2010; Tsutsumi, 2005). Neonates can also be exposed to BPA through maternal breast milk (Mendonca et al., 2014; Vandenberg et al., 2010). The effects of BPA in humans depend on the dose and timing, with the prenatal/neonatal period representing the most vulnerable window of exposure (Barker, 2007; Capra et al., 2013; Fernández et al., 2014; Vandenberg et al., 2009).

The human brain is a sexually dimorphic organ (MacLusky and Naftolin, 1981; Yang and Shah, 2014), and major morphological differences are shaped during prenatal development under the regulation of gonadal steroid hormones, especially estrogen and aromatizable androgens (Bao and Swaab, 2011; Berenbaum and Beltz, 2011; Cohen-Bendahan et al., 2005; Manson, 2008; Swaab, 2007). Therefore, the effects on human brain and behavior of EDCs in general and BPA in particular are of special interest. Animal studies have shown that exposure to low (environmentally relevant) doses of BPA during critical periods alter sex-specific structural and behavioral patterns, increasing, decreasing, or eliminating sex differences and thereby affecting the sexually dimorphic development of the brain (Bowman et al., 2014; Chen et al., 2014; Jašarević et al., 2011; Kubo et al., 2003; Tando et al., 2014) and altering steroid receptor levels (Cao et al., 2013; Rebuli et al., 2014). Experimental animals exposed to low BPA doses have also been found to display behavioral changes, including: hyperactivity (Anderson et al., 2013; Komada et al., 2014; Zhou et al., 2011), increased aggressiveness (Kawai et al., 2003; Patisaul and Bateman, 2008), greater anxiety (Luo et al., 2014; Tian et al., 2010; Xu et al., 2012), and modified socio-sexual behavior (Farabollini et al., 2002; Porrini et al., 2005). Low BPA doses can also alter the development of play behavior (Dessì-Fulgheri et al., 2002), spatial learning, and memory function (Carr et al., 2003; Eilam-Stock et al., 2012; Kuwahara et al., 2013; Wang et al., 2014) in animals. The finding that BPA exposure changes socio-sexual interactions in infant and juvenile nonhuman primates is of special interest (Nakagami et al., 2009; Negishi et al., 2014).

The effect of BPA exposure on human brain and behavior is a relatively new issue, and there is particular concern about the potential impact of BPA exposure on children (Colborn, 2004). The purpose of this study was to review available data on child BPA exposure and its relationship to neurodevelopment and behavioral outcomes.

2. Mechanisms of action and targets in the brain

BPA has varied and complex mechanisms of action that may interfere with normal brain and behavior development, evidencing a plausible causal link (Wolstenholme et al., 2011a). The main mechanisms that may be related to brain development are summarized below.

2.1. Endocrine-related BPA mechanisms

BPA binds to classical nuclear estrogen receptors (ERs) and exerts a mix of agonist and/or antagonist actions depending on the target tissues, cell types, ER subtypes, and differential cofactors recruited by ER-ligand complexes (Welshons et al., 2006). For example, depending on the tissue involved and the ER subtype, BPA acts as an agonist of ERβ receptors and as an agonist/antagonist of ERα (Kurosawa et al., 2002), with lower affinity for ER-α and ER-β in comparison to estradiol (Andersen et al., 1999; Perez et al., 1998). BPA has been reported to have an 80-fold greater affinity for ERγ, which is highly expressed in placenta and mammalian fetal brain, than for ERα, both *in vitro* (Matsushima et al., 2007; Takayanagi et al., 2006; Takeda et al., 2009) and *in vivo* (Tohmé et al., 2014). BPA can also bind to estrogen membrane receptors such as GPR30 (Thomas and Dong, 2006) and elicit nongenomic estrogenic actions in experimental models (Alonso-Magdalena et al., 2012; Watson et al., 2007), producing rapid responses to very low BPA concentrations from 10 fM to 10 nM (Wetherill et al., 2007; Zsarnovszky et al., 2005). Interestingly, a sexually differentiated pattern of GPR30 expression has been reported in some brain areas of hamsters (Canonaco et al., 2008).

BPA is also an antagonist of the androgen receptor (AR) (Molina-Molina et al., 2013; Wetherill et al., 2007). Its anti-androgenic activity has been described in several studies, with varying half maximal inhibitory concentration (IC_{50}) values (Bonefeld-Jørgensen et al., 2007; Roy et al., 2004; Xu et al., 2005). Whereas BPA has a half maximal effective concentration (EC_{50}) of 10–100 nM for the ERα, it has an IC_{50} of 1–2 μM against the AR (Teng et al., 2013). Unlike other known AR antagonists, BPA inhibits efficient nuclear translocation of the AR and interferes with its function *via* multiple mechanisms (Teng et al., 2013).

BPA can also bind to sex hormone-binding globulin (SHBG) (Déchaud et al., 1999), which may alter the androgen–estrogen balance (Takeuchi and Tsutsumi, 2002) and interfere with neuroendocrine regulation of the hypothalamus–pituitary-axis (Gore, 2010; Chen et al., 2014).

Endocrine-related BPA action mechanisms also involve the aryl hydrocarbon receptor (AhR), decreasing its activity *in vitro* (Bonefeld-Jørgensen et al., 2007) and, at extremely low doses (0.02 μg/kg/d), upregulating brain mRNA expression of this receptor *in vivo* (Nishizawa et al., 2005). BPA can also reduce aromatase activity *in vitro* (Bonefeld-Jørgensen et al., 2007) and the

synthesis of testosterone and estradiol *in vivo* (Akingbemi et al., 2004).

BPA binds to thyroid receptors (TRs), acting as an antagonist (Moriyama et al., 2002). *In vitro* studies have shown that BPA binds to both TR α and β subtypes, although with a relatively low affinity (Delfosse et al., 2014; Kitamura et al., 2005). Moreover, BPA can inhibit thyroid hormone sulfotransferase activity (Butt and Stapleton, 2013) and change the transcription and gene expression of TRs, both *in vitro* and in experimental models (Gentilcore et al., 2013; Sheng et al., 2012).

BPA has been found to alter glucocorticoid-regulated responses, affecting the sexual differentiation of brain and behavior in rodents (Poimenova et al., 2010), and it has also been proposed as a corticoid agonist (Prasanth et al., 2010). Finally, a recent animal study indicated that chronic perinatal exposure to low BPA concentrations can alter the basal and stress-induced activity of the hypothalamic–pituitary–adrenal axis in a sexually dimorphic manner, increasing susceptibility to stress- and anxiety-related disorders in later life (Panagiotidou et al., 2014).

2.2. Epigenetic effects of BPA

Epigenetic mechanisms of action of BPA include the alteration of some DNA methylation patterns (Dolinoy et al., 2007; Susiarjo et al., 2013). Studies in rodents found that prenatal BPA exposure alters the expression of genes encoding estrogen receptor subtypes (ERα, ERβ and ERγ) in a sex- and brain region-specific manner (Kundakovic et al., 2013) and disrupts normal placental development (Susiarjo et al., 2013). Hence, BPA may predetermine the response of certain brain areas to steroid hormones from a very early stage of development (Wilson and Sengoku, 2013). BPA was reported to impair gene expression of regulatory factors that provide stability and flexibility to epigenetic regulation, adversely affecting the normal development of hypothalamic functions (Warita et al., 2013). Although these changes affect gene expression without altering the underlying DNA, they are heritable and can exert trans-generational effects (Manikkam et al., 2013).

2.3. Synaptic effects

BPA exposure largely abolishes the synaptogenic response to estradiol in hippocampal and prefrontal spine synapses in both rat and non-human primate models (Leranth et al., 2008; MacLusky et al., 2005). This inhibitory effect, at environmentally relevant doses, appears to be mediated *via* membrane receptors in which rapid responses are elicited (Hajszan and Leranth, 2010). Thus, low BPA doses (40–400 μg/kg/d) altered synaptogenic remodeling in rats (MacLusky et al., 2005) and impacted on dopamine neurons and spine synapses in the hippocampus of *in utero* exposed non-human primates (Elsworth et al., 2013). As a consequence of this research, concerns have arisen about the effect of BPA exposure on infant human brain functioning and its cognitive and behavioral repercussions.

3. Methods

We reviewed all scientific publications up to March 2015 that addressed the association of human BPA exposure during pregnancy and/or childhood with infant cognitive and/or behavior outcomes. The MEDLINE/PubMed database was searched for publications written in English, using the key words "BPA", "Child" "Neurodevelopment", and "Behavior/Behaviour". References cited in the retrieved papers were also examined. We found twelve articles that met the search criteria and gathered the following data: (1) study design and population; (2) type and timing of exposure, (3) exposure assessment (direct assessment/proxy, spot, or repeated measurements), (4) evaluation of neurodevelopment evaluation (tests); and (5) statistical methods and adjustment for confounders.

4. Results

Up to March 2015, only twelve epidemiological studies explored the relationship between perinatal BPA exposure and neurobehavioral outcomes in childhood (Braun et al., 2009, 2011, 2014; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Maserejian et al., 2012a, 2012b; Miodovnik et al., 2011; Perera et al., 2012; Roen et al., 2015; Yolton et al., 2011). Eight of these studies reported a significant association between behavior and BPA exposure during childhood (Harley et al., 2013; Hong et al., 2013; Maserejian et al., 2012a; Roen et al., 2015) and, especially, *in utero* (Braun et al., 2009, 2011; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015). In the other four studies, no significant relationship was found between BPA exposure and neurodevelopment or behavioral outcomes (Braun et al., 2014; Maserejian et al., 2012b; Miodovnik et al., 2011; Yolton et al., 2011) (Table 1).

Within the Health Outcomes and Measures of the Environment (HOME) study, a prospective birth cohort in Cincinnati, Ohio (USA), Braun et al. (2009) recruited 249 mother–child pairs between 2003 and 2006, collecting maternal spot urine samples during pregnancy, at 16 and 26 wk of gestation, and at birth. The median concentration of total (free plus conjugated) BPA was 1.8 ng/ml (16 wk), 1.7 ng/ml (26 wk), and 1.3 ng/ml (at birth). The behavior of these infants was assessed at 2 yr of age using the Behavioral Assessment System for Children (BASC-2) completed by parents. After adjustment for confounders, linear regression models showed no association between prenatal BPA exposure and externalizing, internalizing, or Behavior Symptom Index (BSI) scores in the global sample. However, sex-stratified analyses revealed a positive and significant association in the girls, but not in the boys, between BPA levels (at 16 and 26 wk of gestation) and worse externalizing behavior ($\beta = 6.0$; 95%CI, 0.1–12.0; $p < 0.05$) and BSI scores ($\beta = 5.5$; 95% CI, 0.3–10.7). A stronger association was found with BPA levels at ≤16 wk than with those at 17–21 weeks.

The follow up of this birth cohort (Braun et al., 2011) continued with the collection of new spot urine samples from the children at 1, 2, and 3 yr of age between 2004 and 2009 (median value 4.1 ng/ml). At the age of 3 yr, the BASC-2 test was once more used to evaluate the children's behavior, and the Behavior Rating Inventory of Executive Function—Preschool (BRIEF—P) test was completed by the parents to assess executive function. Maternal total BPA concentrations during pregnancy (median 2 ng/ml) were again positively associated in the girls with higher BASC-2 scores for hyperactivity ($\beta = 9.1$; 95%CI, 3.1–15; $p < 0.05$), anxiety ($\beta = 12$; 95%CI, 4.7–20, $p < 0.05$), and depression ($\beta = 11$; 95%CI, 3.6–18; $p < 0.05$) and with lower BRIEF—P emotional control ($\beta = 9.1$; 95%CI, 2.8–15; $p < 0.05$) and inhibition ($\beta = 9.3$; 95%CI, 1.8–17) scores. In contrast, the BASC-2 hyperactivity score was negatively associated with maternal BPA in the boys ($\beta = -6.3$; 95%CI, −12 to −0.6; $p < 0.05$). No association was found between childhood total BPA exposure and neurobehavior.

Yolton et al. (2011) studied 350 mother–child pairs enrolled in the HOME cohort, evaluating the neurobehavior of the neonates at 5 wk of age using the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). Logistic regression models showed no significant associations between maternal BPA concentrations during pregnancy and neonate neurobehavior, although a trend was observed towards greater hypotonia with higher BPA concentrations at 16 wk of gestation (1.8 ng/ml of total BPA concentration).

Table 1
Human epidemiological studies linking bisphenol A (BPA) and children neurobehavior.

Authorship—Study design	Study population	Urine BPA concentration	Behavior evaluation	Neurobehavior effect
Braun et al. (2009) Prospective Birth Cohort (USA)	**HOME study:** 249 mother–child pairs Ethnicity: White (62%), Nonwhite (38%) Recruitment: March 2003–January 2006	**Maternal gestational Total BPA:** 16 wk: 1.8 ng/ml 26 wk: 1.7 ng/ml Birth*: 1.3 ng/ml (*samples collected within 24 h of parturition)	BASC-2 (at 2 years) By mothers	No association between BPA exposure and behavior in the all sample. After sex-stratified analyses, associations were found with externalizing behavior [β = 6.0; 95%CI, 0.1–12.0; $p < 0.05$] and BSI scores (β = 5.5; 95%CI, 0.3–10.7; $p < 0.05$), but only among girls. These associations were stronger when considered the earliest mean prenatal exposure (16 wk)
Braun et al. (2011) Prospective Birth Cohort (USA)	**HOME Study (follow up):** 244 mother–child pairs	**Maternal gestational Total BPA** (16 wk, 26 wk and birth): 2 ng/ml **Childhood Total BPA** (1, 2 and 3 years): 4.1 ng/ml	BASC-2 and BRIEF-P (at 3 years) By mothers	**Gestational BPA exposure**: **-Girls:** Positive associations were found: 1. BASC-2: Increased hyperactivity (β = 9.1; 95%CI, 3.1–15; $p < 0.05$), increased anxiety (β = 12; 95%CI, 4.7–20; $p < 0.05$) and depression (β = 11; 95%CI, 3.6–18; $p < 0.05$). Interestingly, at the same time hyperactivity decreased among boys (β = −6.3; 95%CI, −12 to −0.6; $p <$ 0.05). 2. BRIEF-P: Poorer emotional control (β = 9.1; 95%CI, 2.8–15; $p < 0.05$) and inhibition (β = 9.3; 95%CI, 1.8–17; $p < 0.05$) among girls. **Childhood BPA exposure**: No association was found
Braun et al. (2014) Prospective Birth Cohort (USA)	**HOME Study (follow up):** 175 mother–child pairs Boys (n = 95) Girls (n = 80)	**Maternal gestational Total BPA:** 2.1 ng/ml	SRS (at 4 years and 5 years) By mothers	**No association between BPA and SRS scores was observed.** They found a mean of 52 EDCs in the biological samples A semi-Bayesian hierarchical regression model showed a direct association between some EDCs and SRS scores (indicating more social problems), while others were inversely associated
Perera et al. (2012) Prospective Birth Cohort (USA)	**CCCEH Cohort** 198 mother–child pairs Ethnicity: Afro-American and Latina. Low income. Recruitment: 1998–2003	**Maternal gestational Total BPA:** (34 wk; range 24–40 wk): 1.96 ng/ml **Childhood Total BPA** (between 3 and 4 years): 3.94 ng/ml	CBCL (between 3–5 years) By mothers (oversaw by trained research workers)	**Gestational BPA exposure**: **- Boys**: Increased emotional reactivity (1.62 times greater; 95%CI, 1.13–2.32; $p < 0.008$) and aggressive behavior (1.29 times greater; 95%CI, 1.09–1.53; $p < 0.003$). **- Girls**: Decreased anxious/depressed (0.75 times as high; 95%CI, 0.57–0.99; $p < 0.04$), less aggressive (0.82 times as high; 95%CI, 0.7–0.97; $p < 0.017$). **Childhood BPA exposure**: Negative association was found for only the Emotionally Reactive scale within all children sample (0.76 times as high; 95%CI, 0.59–0.97; $p < 0.029$)
Roen et al. (2015)	**CCCEH Cohort (follow up):** 250 mother–child pairs	**Maternal gestational Total BPA:** (34 wk; 1.9 ng/ml) **Childhood Total BPA** (between 3 and 4 years): 3 ng/ml	CBCL (between 7–9 years) By mothers	**Gestational BPA exposure**: **- Boys:** Increased internalizing (β = 0.41; CI95%, 0.24–0.58; $p < 0.0001$) and externalizing (β = 0.40; CI95%, 0.24–0.56; $p < 0.0001$) problems. - **Girls:** the opposite trend was observed in internalizing composite score (β = −0.17; 95%CI, −0.33, −0.01; $p < 0.04$). **Childhood BPA exposure:** **- Boys:** fewer symptoms were seen among boys in both internalizing (β = −0.29; CI95%, −0.47, −0.11; $p < 0.002$) and externalizing (β = −0.37; CI95%, −0.54, −0.20; $p < 0.0001$) problems. **- Girls:** increased problems in both internalizing (β = 0.30; 95%CI, 0.14–0.45; $p < 0.0002$) and externalizing (β = 0.33; 95%CI, 0.17–0.5; $p < 0.0001$) symptoms.
Miodovnik et al. (2011) Prospective Birth Cohort (USA)	**Mount Sinai Children's Environmental Health Study** 137 mother–child pairs Multiethnic Recruitment: May 1998-July 2002	**Maternal gestational Total BPA:** (31 wk; range 25–40 wk): 1.2 ng/ml (Lot of participants near to LOD)	SRS By mothers (between 7 and 9 years)	**Gestational BPA exposure**: No association was found with gestational BPA exposure. However, when several outliers were removed (n = 128), they found statistically significant association with higher total SRS score

Table 1 (*Continued*)

Authorship—Study design	Study population	Urine BPA concentration	Behavior evaluation	Neurobehavior effect
Harley et al. (2013) Prospective Birth Cohort (USA)	**CHAMACOS Study** 292 mother–child pairs Ethnicity: Latina (99%) Low income. Recruitment: 1999–2000	**Maternal gestational Total BPA:** (13, 6 wk and 26, 4 wk): 1.1 ng/ml **Childhood Total BPA:** (at 5 years): 2.5 ng/ml	BASC-2 and CADS (at 7 years) By mothers and teachers CPT (at 9 years) Direct computerized test	**Gestational BPA exposure**: **- Boys:** higher BPA concentrations during pregnancy were associated with increased internalizing problems [mother report ($\beta = 1.8$; 95%CI, 0.3–3.3; $p < 0.05$)/teacher report ($\beta = 2.5$; 95%CI, 0.7–4.4; $p < 0.01$)], with increased symptoms of anxiety* and depression**, and increased aggressive behavior* in boys at 7 years of age, according to either or both mother and teacher report on BASC-2. Prenatal BPA concentrations were not associated with scores on CADS at 7 years. **- Girls:** No significant association was seen between prenatal BPA concentrations and behavior. However, for almost all scales, the point estimates showed trends towards decreased behavior problems. **Childhood BPA**: **- Boys:** BPA concentrations at age 5 were associated with increased internalizing scores ($\beta = 1.8$; 95%CI, 0.4–3.1; $p < 0.05$) and increased anxiety* on the BASC-2 and attention problems* on the BASC-2 and the CADS, at age 7 according to teacher report. No associations were seen with the maternal report. **- Girls**: associations were also found with both internalizing [teacher report ($\beta = 1.8$; 95%CI, 0.1–3.6; $p < 0.05$)] and externalizing (by mother and teacher report) problems, both in BASC-2 and CADS, including hyperactivity* and conduct problems**. **- All together**: All associations persisted and became more statistically significant. CPT scores were not associated with gestational or childhood BPA exposure. * $p < 0.05$ ** $p < 0.01$
Yolton et al. (2011) Prospective Birth Cohort (USA)	**HOME Study** 350 mother–child pairs Multiethnic Recruitment: March 2003-January 2006	**Maternal gestational Total BPA:** 16 wk: 1.8 ng/ml 26 wk: 1.7 ng/ml	NNNS (Neonates at 5 wk)	**Gestational BPA exposure**: No significant associations were found between BPA and behavior in neonates. Only a non-significant trend related to hypotonia was observed ($\beta = 0.170$; $p = 0.09$).
Hong et al., 2013 Cross-sectional study (Korea)	1008 children Ethnicity: Asiatic Recruitment: missing data	**Children Total BPA**: 1.32 μg/g of creatinine	CBCL LDES (at 8–11 years) By parents	**Childhood BPA**: BPA levels were positively associated with CBCL total score ($\beta = 0.85$; 95% CI, 0.26–1.44; $p = 0.00$) and negatively associated with LDES total score ($\beta = -1.90$; 95%CI, −3.5 to −0.30; $p = 0.02$). Further, CBCL anxiety/depression score ($\beta = 1.07$; 95%CI, 0.57–1.58; $p = 0.00$) and LDES listening score ($\beta = -0.81$; 95%CI, −1.27 to −0.34; $p = 0.00$) remained significant after correction for multiple comparisons
Evans et al. (2014) Prospective Birth Cohort (USA)	**Study for Future Families II** 176 mother–child pairs Multiethnic Recruitment: 2002–2005	**Maternal gestational Total BPA:** 26.6 wk: 1.1 ng/ml	CBCL (at 6–10.5 years) By parents	**Gestational BPA exposure**: **- Boys**: Prenatal BPA exposure was significantly associated with behavior problems in several domains, including externalizing composite scale [$\beta(p) = 0.27(0.006)$], anxiety [$\beta(p) = 0.15(0.04)$], aggressive behavior [$\beta(p) = 0.23(0.01)$], conduct disorder [$\beta(p) = 0.22(0.003)$], and oppositional/defiant behaviors [$\beta(p) = 0.20(0.008)$]. - **Girls:** No significant association was seen between prenatal BPA concentrations and any CBCL scores; however, the trend was toward negative BPA associations with behavior problems
Maserejian et al. (2012a) Randomized Clinical Safety Trial (USA) Maserejian et al. (2012b)	**NECAT:** **New England children's amalgam trial** 434 children Multiethnic recruitment: 1997–2005	Estimation of **cumulative exposure** from dental treatment (composite *vs.* amalgam material) establishing surface-years categories. 5 years follow-up	BASC-SR (self-reported) At ≥8 years CBCL (by parents) (at 6 to 10 years)	**Cumulative BPA exposure:** Higher exposure to bisGMA-based composite was associated with worse scores on three of the four BASC-SR scales: Emotional Symptoms ($\beta = 0.8$; $p = 0.003$), Clinical Maladjustment ($\beta = 0.7$; $p = 0.02$) and personal adjustment ($\beta = -0.8$; SE = 0.2; $p = = 0.002$). No associations were found to amalgam or urethane dimethacrylate-based composite. No associations were found for CBCL
	Secondary analysis 444 children	Idem	WISC-III WIAT WRAML WRAVMA COWAT	**Neuropsychological development:** Greater exposure to dental composite materials (containing bisGMA and TEGDMA) was not linked to any statistically significant association with neuropsychological scores through follow up. However, a trend was observed between worse scores and children with greater exposure

HOME (Health Outcomes and Measures of the Environment Study). CCCEH (Columbia Center for Children's Environmental Health). CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas). NECAT (New England Children's Amalgam Trial). BASC-2 (Behavioral Assessment System for Children). BSI (Behavioral Symptom Index). BRIEF-P (Behavior Rating Inventory of Executive Function Preschool Version). LOD (Limit of Detection). CBCL (Child Behavior Check List). SRS (Social Responsiveness Scale). CADS (Conner's ADHD/DSM-IV Scales). CPT (Connors' Continuous Performance Test). NNNS (Neonatal Intensive Care Unit Network Neurobehavioral Scale). LDES

Recently, within the HOME study, Braun et al. (2014) screened a large number of EDCs ($n = 70$) in relation to autistic behaviors. Blood and/or urine samples of mothers were analyzed during pregnancy and autistic behaviors were assessed when the children were 4 and 5 years old using the Social Responsiveness Scale (SRS). They found a mean of 52 EDCs in the biological samples. A semi-Bayesian hierarchical regression model showed a direct association between some EDCs and SRS scores (indicating more social problems), while others were inversely associated. BPA was not associated with SRS scores.

The Mount Sinai Children's Environmental Health Study is a prospective multiethnic birth cohort of primiparous women recruited between 1998 and 2002 (Miodovnik et al., 2011). Only one maternal urine sample was collected during pregnancy, between 25 and 40 wk of gestation (mean 31.2 wk), yielding a median total BPA concentration of 1.2 ng/ml. Between 7 and 9 yr of age, the social behavior of the children was reported by their mothers ($n = 137$) using the Social Responsiveness Scale (SRS), and the SRS scores were higher (worse) with greater BPA exposure *in utero*. According to multivariable adjusted linear regression models, the association between BPA exposure and SRS scores was not statistically significant ($\beta = 1.18$; 95%CI, −0.75, 3.11), although significance was reached after the removal of outliers ($\beta = 1.73$; 95%CI, 0.02, 3.45).

The Columbia Center for Children's Environmental Health (CCCEH) is a prospective cohort study of 198 mother–child pairs recruited between 1998 and 2003 (Perera et al., 2012). One spot urine sample was collected between 24 and 40 wk of pregnancy (mean 34 wk) and another from the children between 3 and 4 yr of age, finding geometric mean total BPA concentrations of 1.96 ng/ml and 3.94 ng/ml, respectively. At the age of 3–5 yr, the behavior of the children was reported by their mothers using the Child Behavior Check List (CBCL). Poisson and linear regression models showed an association between gestational BPA exposure (highest quartile *vs.* lowest three quartiles) and greater problems among the boys in emotionally reactive behavior (1.62-fold greater; 95%CI, 1.13–2.32; $p < 0.001$) and aggressive behavior (1.29-fold greater; 95%CI, 1.09–1.53; $p < 0.003$). Among the girls, higher BPA exposure was related to fewer problems in all areas, finding a statistically significant negative association with anxious/depressed behavior (0.75-fold higher; 95%CI, 0.57–0.99; $p < 0.04$) and aggressive behavior (0.82-fold higher; 95%CI, 0.7–0.97; $p < 0.02$). No significant relationship was found between childhood BPA exposure and behavior.

The follow up of this birth cohort (Roen et al., 2015) continued with the re-assessment of children' behavior at 7–9 years of age ($n = 250$). Among the boys ($n = 115$), higher gestational BPA concentration (upper tertile *vs.* lower two tertiles) was associated with increased internalizing ($\beta = 0.41$; 95%CI, 0.24–0.58; $p < 0.0001$) and externalizing ($\beta = 0.40$; 95%CI, 0.24–0.56; $p < 0.0001$) problems. Among the girls ($n = 135$), the opposite trend was observed in internalizing composite score ($\beta = -0.17$; 95%CI, −0.33, −0.01; $p < 0.04$). Moreover, among the girls, higher postnatal BPA concentrations were associated with increased problems in both internalizing ($\beta = 0.30$; 95%CI, 0.14–0.45; $p < 0.0002$) and externalizing ($\beta = 0.33$; 95%CI, 0.17–0.5; $p < 0.0001$) symptoms; while fewer symptoms were seen among the boys in both internalizing ($\beta = -0.29$; 95%CI, −0.47, −0.11; $p < 0.002$) and externalizing ($\beta = -0.37$; 95%CI, −0.54, −0.20; $p < 0.0001$) problems.

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS, USA) conducted a prospective cohort study of 292 mother–child pairs recruited between 1999 and 2000 on environmental factors and the growth and development of children (Harley et al., 2013). Two maternal urine samples were taken during pregnancy (mean of 13.6 and 26.4 wk) and one sample during childhood (at 5 yr of age), finding mean total BPA concentrations of 1.1 ng/ml during pregnancy and 2.3 ng/ml at 5 yr. At the age of 7 yr, the children's behavior was assessed with the BASC-2 and Conner's ADHD/DSM-IV Scale (CADS), which were both completed by the mothers and teachers; at the age of 9 yr, they were directly assessed using Conner's Continuous Performance Test (CPT). Multivariable linear regression models for the boys showed that each twofold rise in gestational total BPA concentration was significantly associated with an increase at the age of 7 yr in mother- and teacher-reported internalizing problems [mother's report ($\beta = 1.8$; 95%CI, 0.3–3.3; $p < 0.05$), teacher's report ($\beta = 2.5$; 95%CI, 0.7–4.4; $p < 0.01$)], symptoms of anxiety ($p < 0.05$) and depression ($p < 0.01$), externalizing problems, and aggressive behavior ($p < 0.05$). No associations were found between prenatal BPA concentrations and behavior at 7 yr in the girls, although there was a trend towards decreased behavior problems. Among the boys in the CHAMACOS cohort, childhood total BPA exposure was associated, as in the case of *in utero* exposure, with increases in teacher-reported BASC-2 internalizing ($\beta = 1.8$; 95%CI, 0.4–3.1; $p < 0.05$) and anxiety ($p < 0.05$) scores and BASC-2 and CADS attention problems ($p < 0.05$); no significant associations with mother-reported scores were observed. Among the girls, associations were also found with internalizing [teacher-reported ($\beta = 1.8$; 95%CI, 0.1–3.6; $p < 0.05$)] and externalizing (mother- and teacher-reported) problems in both BASC-2 and CADS tests, including hyperactivity ($p < 0.05$) and conduct problems ($p < 0.01$). When the entire sample was analyzed, these associations persisted and became more statistically significant. No association was found between *in utero* or childhood BPA exposure and CPT scores.

In a cross-sectional study of 1008 children aged between 8 and 11 yr old (mean of 9.05 ± 0.70 yr), total urinary BPA levels were measured (mean 1.32 μg/g) and the children's behavior was assessed by using the CBCL and the Learning Disabilities Evaluation Scale (LDES), completed by the parents (Hong et al., 2013). Multivariate linear regression adjusted models showed that urinary BPA concentrations were positively associated with the CBCL total problem score ($\beta = 0.85$; 95% CI, 0.26–1.44; $p = 0.001$; $R^2 = 0.20$) and negatively associated with the LDES score ($\beta = -1.90$; 95%CI, −3.5 to −0.30; $p = 0.02$; $R^2 = 0.20$). Linear association of anxiety/depression ($\beta = 1.07$; 95%CI, 0.57–1.58; $p = 0.001$) and LDES listening ($\beta = -0.81$; 95%CI, −1.27 to −0.34; $p = 0.001$) scores with the CBCL score remained significant after correction for multiple comparisons.

Maserejian et al. (2012a) studied 434 children (6 to 10 yr old at baseline) in the New England Children's Amalgam Trial (NECAT) between 1997 and 2005. They estimated cumulative exposure to BPA from bisphenol-A-glycidyl-methacrylate (bis-GMA)-based dental composite resins, measured by surface years (each treated surface weighted by no. yrs present in the mouth). The behavior of the children was evaluated with the BASC-SR (Self-reported) and CBCL (parent-reported) tests. Multivariate linear and logistic regression models evidenced an association between greater cumulative exposure to bisGMA and detrimental effects on psychosocial health. The children evidenced more anxiety, depression, social stress, and interpersonal-relation problems with increasing levels and duration of the exposure and were more likely to have clinically significant scores for total problem behaviors. Associations were stronger with posterior-occlusal chewing surfaces, where the degradation of composite is increased and the transfer of BPA derivatives is greater. In the same study population (NECAT), Maserejian et al. (2012b) also examined whether cumulative exposure to bisGMA composite materials was associated with neuropsychological development, finding small but non-significant adverse effects (*e.g.*, slightly lower scores in intelligence, achievement, and memory tests).

Within the Study for Future Families II (SFII), a prospective cohort study of mother–child pairs recruited between 2002 and 2005, maternal urine samples were collected during pregnancy at a mean of 26.6 wk of gestation (range 10–39 wk), yielding a median total BPA concentration of 1.1 ng/ml. Behavior was evaluated at 6–10.5 yr of age in 153 children with (parent-reported) CBCL test (Evans et al., 2014). Prenatal BPA exposure was significantly and positively associated with behavior problems among the boys in several domains, including externalizing composite scale [$\beta(p) = 0.27(0.006)$], anxiety [$\beta(p) = 0.15(0.04)$], aggressive behavior [$\beta(p) = 0.23(0.01)$], conduct disorder [$\beta(p) = 0.22(0.003)$], and oppositional/defiant behaviors [$\beta(p) = 0.20(0.008)$]; observing a significant interaction between BPA and sex for various behaviors. In contrast, a trend towards fewer problems with greater exposure was observed among the girls.

5. Discussion

Increasing attention has been paid over recent years to the impact of prenatal BPA exposure on child neurodevelopment, due to the ubiquitous presence of this EDC and the suspicion of brain and behavior effects based on results obtained in animal models. Only twelve studies on this issue have been published to date, eight of them reporting altered neurobehavior (*e.g.*, hyperactivity, aggressive behavior, anxiety, depression, attention problems, and/or other cognitive function impairments), especially in children exposed *in utero*, suggesting disruption of the brain during this critical window of development.

The greatest impediment to the comparative analysis of these studies is their heterogeneity. There are disparities in the study design, assessment of exposure (proxy of exposure *vs*. direct measurements in one or more biological samples), neurodevelopment evaluation (different tests, evaluation periods, and reporters), sample size, adjustment for potential confounders, and/or socio-demographic characteristics of the populations. These shortcomings limit the conclusions that can be drawn on the epidemiology of the potential health risks of BPA exposure on neurodevelopment. Therefore, it is necessary to critically evaluate the main aspects of the most comparable investigations, *i.e.*, those with direct measurements of BPA exposure, a prospective design, and behavior evaluation at a similar developmental period (Braun et al., 2009, 2011; Evans et al., 2014; Harley et al., 2013; Miodovnik et al., 2011; Perera et al., 2012; Roen et al., 2015). Braun et al. (2014) was also excluded, because the main objective of this study was to identify multiple gestational EDC exposure biomarkers and to develop statistical techniques that account for the complex EDC mixtures present in real life.

Among these seven more comparable investigations, six found significant associations between BPA exposure and adverse behavior effects (Braun et al., 2009, 2011; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015), while Miodovnik et al. (2011) found no relationship. We examined the results of these seven selected studies and discuss below some key aspects of the relationship between BPA exposure and the neurobehavior of children.

5.1. Timing of exposure

A stronger relationship between prenatal *vs.* childhood BPA exposure and adverse behavioral effects was observed in six out of the seven aforementioned studies. The fetal period is the most important stage of neurodevelopment, and hormones are key factors in numerous developmental events (Fowden and Forhead, 2009). Thus, sex steroids are crucial in the sexual differentiation of central nervous system structures that control neuroendocrine, behavioral, and cognitive functions (Bao and Swaab, 2011; Peper et al., 2011). Further, the period between weeks 8 and 24 of pregnancy has long been considered as the critical period for sexual differentiation of the human brain, especially at around 16 wk (Auyeung et al., 2009, 2013; Berenbaum and Beltz, 2011; Cohen-Bendahan et al., 2005; Manson, 2008). In this line, Braun et al. (2009), found that externalizing problems and anxious and depressed symptoms in children were more strongly associated with the total BPA concentration at 16 wk of gestation than at 26 wk or at the delivery (<24 h postpartum), indicating a possible critical window of exposure (Braun et al., 2009). Nevertheless, the majority of studies that found a significant association considered the gestational period as a whole, based on one or two urine samples collected during different trimesters.

Only two studies have reported relevant associations with postnatal BPA exposure (Harley et al., 2013; Roen et al., 2015), and further research is required to confirm or rule out its effects on later behavior.

The impact of EDC exposure on human health appears to depend strongly on its timing, and the effects of BPA exposure *in utero* differ from those of exposure during adulthood in both rats (Gore et al., 2014) and non-human primates (Elsworth et al., 2013). Embryos, fetuses, and neonates are highly sensitive to EDC exposure and suffer more severe adverse effects in comparison to adults (Fernández et al., 2014).

The endocrine disruption hypothesis fits well the paradigm of the fetal origin of disease, which suggests that interactions between the developing organism and the environment exert a major influence on the risk of disease in adulthood (Barker, 2007; Capra et al., 2013). Thus, developmental exposure to EDCs at low doses can result in functional changes in gene expression that do not produce a phenotypic change observable at birth but may increase the risk of dysfunction and disease later in life. Adverse effects may emerge during childhood and adolescence, given that health-disease represents a continuous spectrum of outcomes in response to risk factors (Vandenberg et al., 2010).

5.2. Neurodevelopment assessment

There is no consensus on the most appropriate and sensitive instruments for evaluating cognitive and behavioral problems in children at different ages (Myers et al., 2010). In the reviewed studies, behavior was assessed with multiple different tests completed by different reporters (parents and/or teachers), hampering comparison of the behavioral results. In addition, most of the scales considered only behavioral variables, and there has been very little evaluation of cognitive variables. Hence, there is a need to include cognitive measures in the assessment of BPA effects upon neurodevelopment, given that neuropsychological functions (working memory, behavioral inhibition, cognitive flexibility, reasoning, problem solving and planning) act together to control cognition and modulate complex behaviors (Diamond, 2013). It is also necessary to conduct longitudinal studies with multiple assessments during different developmental periods in order to further quantify the influence of BPA exposure on the mental and behavioral development of children and its long-term effects on their neurobehavioral functioning.

In the seven selected studies, the most frequently applied behavior tests were BASC-2 and CBCL. These two assessment tools showed a correlation of 0.35 to 0.76 for comparable sub-scales and 0.69 to 0.82 for the composite indices [internalizing, externalizing and total] (Myers et al., 2010). Consequently, differences in the scales applied may produce slight-to-moderate variations in behavioral results.

Among behavioral outcomes related to BPA exposure, externalizing composite scores have been found in three out of the six selected studies that showed a positive association (Braun et al.,

2009; Evans et al., 2014; Roen et al., 2015), including aggressive behavior (Evans et al., 2014; Harley et al., 2013; Perera et al. (2012); Roen et al., 2015), and rule-breaking behavior (Evans et al., 2014; Roen et al., 2015). Internalizing composite scores have been associated in Harley et al. (2013) and Roen et al. (2015), including anxiety/depression symptoms reported in four out of these six studies (Braun et al., 2011; Evans et al., 2014; Harley et al., 2013; Roen et al., 2015), emotional control/reactivity problems (Braun et al., 2011;Perera et al., 2012) and somatization (Braun et al., 2011; Roen et al., 2015).

5.3. Sex-dependent effects

Results of the selected studies also indicated that the impact of BPA exposure on neurobehavioral functioning may differ between boys and girls. Thus, in the cohort studied by Braun et al. (2009, 2011), girls were observed to be more susceptible to the impacts of prenatal BPA exposure than were the boys, with findings of increased hyperactivity, anxiety, depression, and somatization symptoms among girls. In contrast, several studies reported that *in utero* BPA exposure was associated with increased behavior problems in boys but with a trend towards decreased behavior problems in girls (Evans et al., 2014; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015).

An association with postnatal BPA exposure has been predominantly observed in girls rather than boys, indicating that sex-dependent effects may depend upon the developmental period in which exposure occurs. However, only two studies have addressed this issue (Harley et al., 2013; Roen et al., 2015), which requires further investigation.

The above discrepancies in results have been attributed to differences in the timing of exposure, in the neuropsycological tests used, or in the age of the children at assessment as well as to confounders (Perera et al., 2012; Roen et al., 2015; Rosenfeld and Trainor, 2014). With regard to the timing, Harley et al. (2013) and Braun et al. (2009) measured BPA exposure during a similar period (early to mid-pregnancy and observed different effects in boys and girls, respectively). Moreover, this gender discrepancy cannot be attributed to a difference in behavior assessment tools, because Harley et al. (2013) and Braun et al. (2009) both used the BASC-2 test. The age at assessment differed between the studies by Braun et al. (2009, 2011), 2–3 years of age, and those by Harley et al. (2013), Perera et al. (2012), Evans et al. (2014), and Roen et al. (2015), 3–10 years of age (Table 1). Various authors have pointed out that externalizing problems become more prevalent in boys at 5–7 years of age (Rosenfeld and Trainor, 2014), which may in part explain why associations in boys have largely been observed at an older age. Furthermore, the gender discrepancies observed do not appear to be related to factors such as ethnicity or socioeconomic status; thus, the populations studied by Evans et al. (2014) and Braun et al. (2009, 2011) shared similar sociodemographic characteristics.

The combined effects of exposure to mixtures of EDCs on neurodevelopment have been demonstrated both *in vivo* and *in vitro* (Cory-Slechta, 2005; He et al., 2009; Pellacani et al., 2014; Sobolewski et al., 2014; Tiffany-Castiglioni et al., 2006). In this line, a low-level mixture of EDCs recently demonstrated a sex-specific enhanced behavioral toxicity in rodents (Sobolewski et al., 2014). Humans are exposed to many EDCs from different sources (Michałowicz, 2014). Thus, Braun et al. (2014) reported that most pregnant women in the HOME cohort were exposed to a mean of 52 EDCs. A number of epidemiological studies have found that prenatal exposure to EDCs has a negative impact on neuropsychological development during the first years of life (Bellinger, 2013). However, the short- and long-term risks to humans derived from early exposure to environmentally relevant doses of complex mixtures remain unclear and represent an area of increasing concern (Vilahur et al., 2014). Our research group reported that boys appear to be more vulnerable to prenatal exposure to mixtures of xenoestrogens, while no significant associations were seen in girls, with regression coefficients in the opposite direction (Vilahur et al., 2014). The overall mixture of EDCs may affect the androgen/estrogen balance during a critical and sensitive window of neurodevelopment, thereby altering the dimorphic behaviors that characterize boys and girls, which may in part explain both the sex-discrepancy and the observation of opposite trends in males and females across studies.

Furthermore, mechanisms that underlie the neurodevelopmental toxicity and sex-specific effects of BPA are not fully understood. In experimental studies, Kundakovic et al. (2013) observed that *in utero* exposure to low BPA doses can induce an enduring epigenetic disruption of the brain that may permanently alter brain function and behavior in offspring, especially in relation to sexually dimorphic behaviors. This disruption is associated with long-term changes in ER-related gene expression and DNA methylation in the brain. Moreover, Miodovnik et al. (2012) found that specific polymorphisms in the maternal steroid pathway may be related to behavior problems in boys.

The biological plausibility of the adverse effects of BPA on the brain has been consistently reported in experimental models (Palanza et al., 2008; Wolstenholme et al., 2011a). Results obtained in animals (mostly rodents) have shown that low doses of BPA can disrupt the development of sexually dimorphic behaviors, including anxiety, social interaction, aggression, and spatial memory, and that this disruption has distinct effects on males and females (Adriani et al., 2003; Gioiosa et al., 2013; Palanza et al., 2008; Rubin et al., 2006; Rosenfeld, 2012; Wolstenholme et al., 2011a, 2011b). Notably, administration of low BPA doses (relevant to human exposure) to nonhuman primates abolished the synaptogenic response to estradiol (Leranth et al., 2008) and impacted on midbrain dopamine neurons and hippocampal spine synapses (Elsworth et al., 2013). Moreover, prenatal exposure to low BPA doses (10 μg/kg/d) altered male infant behavior towards the mother [male infants behaved as females] (Nakagami et al., 2009) and modified socio-sexual interactions in male juvenile primates, demasculinizing key sexually dimorphic behaviors (Negishi et al., 2014).

Research on the causal link between BPA and child neurodevelopment is highly challenging. The continual exposure of humans to low doses of BPA means that a scant number of individuals remain unexposed. Furthermore, some authors have concluded that it may never be possible to associate the exposure of a single EDC with a specific neurobehavioral endpoint, at least by using the conventional epidemiological model, due to the ubiquity of BPA, its varied mechanisms of action, the possibility of complex co-exposure effects in humans and living organisms (Braun et al., 2014; Katchy et al., 2014; Rajapakse et al., 2002; Sárria et al., 2011; Vilahur et al., 2014), the difficult characterization of long-term exposure to BPA, and the existence of critical windows of exposure (Colborn, 2004).

6. Conclusion and perspectives

In summary, the mechanisms of BPA action on the brain have been elucidated in experimental models, and the biological plausibility of its adverse cerebral effects has been demonstrated (Elsworth et al., 2013; Hajszan and Leranth, 2010; Nakagami et al., 2009; Negishi et al., 2014; Palanza et al., 2008; Wolstenholme et al., 2011a). The epidemiologic studies conducted to date point in the same worrying direction, suggesting that prenatal exposure to BPA (and possibly postnatal BPA exposure) may be related to increased neurobehavioral problems in children. Although the very

small number of human studies does not yet allow any conclusive link to be established, the results of our comparative analysis show that aggressive behavior and anxiety/depression symptoms are the problems most consistently associated with BPA exposure.

Understandably, there is special concern about the potential effect on the fetus and neonate brain, given their particular vulnerability to neurotoxicants and generally higher exposure to BPA in comparison to adults (Calafat et al., 2008; Mielke and Gundert-Remy, 2009). Moreover, the almost universal exposure of humans to BPA means that small changes in behavior at the individual level may have major social repercussions (Bellinger, 2004, 2007). The magnitude of the potential impact of BPA exposure represents a valuable research line that might lead to a reassessment of the risks for vulnerable populations (Chapin et al., 2008; vom Saal et al., 2007).

Many more studies in humans are required to clarify the relationship between BPA exposure and health. Nevertheless, there is a present need for vigilance in regard to the potential adverse effects of ubiquitous low-level BPA exposure, and it appears desirable to inform women planning or undergoing pregnancy about measures to reduce or avoid EDC exposure (Groff, 2010; Stotland et al., 2014).

7. Future actions

(a) *More prospective birth cohort studies are needed.* Vigilance is now essential in regard to the potential adverse effects of ubiquitous low-level BPA exposure.
(b) *Physicians, especially gynecologists and pediatricians, should be aware of the hazards of EDC exposure*, allowing them to make lifestyle recommendations for preventing and/or reducing exposure, especially in high-risk populations.
(c) *A new risk assessment is required in order to take account of increasing evidence of the deleterious effects of BPA on child behavior and cognition* (Chapin et al., 2008). It appears appropriate to follow the precautionary principle until more conclusive data are available on the exposure of fetuses and children to BPA.

Conflict of interest

The authors declare no conflict of interest.

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